STUDIES IN THE SYNTHESES

OF FURANOTERPENES

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OF FURANOTERPENES

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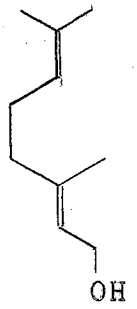
HISTORICAL AND INTRODUCTION

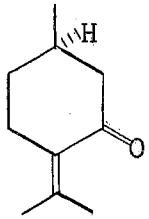
Introduction

Nature produces a large variety of chemical substances. Members of one group of naturally occurring compounds are called terpenes, and are usually produced by plants. Monoterpenes for example, may be found in essential oils which are derived by the steam distillation of plant material. These oils may contain other substances but nearly always contain one or more monoterpenes. In some cases, a single compound may comprise as much as 80-90% of the oil. Because a large number of compounds have been found to contain an integral number of C_5 isoprene units, the "isoprene rule" was formulated which states that terpenes are compounds with a carbon skeleton consisting of isoprene units usually linked in a regular head-to-tail fashion, or occasionally linked in an irregular sequence (1).

Members of the simplest class of terpenes, the monoterpenes, con-



I



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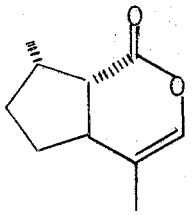
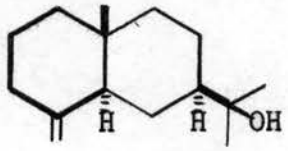


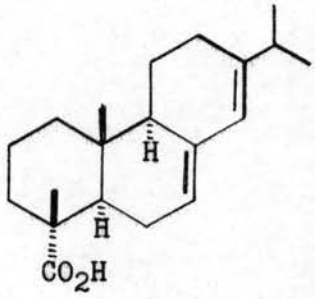
III

tain two isoprene units. This class may be illustrated by geraniol (I), and members of the p-menthane and cyclopentane groups, pulegone (II) and nepetalactone (III) respectively.

While monoterpenes contain ten carbon atoms, sesquiterpenes, diterpenes, and triterpenes contain fifteen, twenty, and thirty carbon atoms respectively. The sesquiterpene eudesmol (IV) and diterpene abietic acid (V) exemplify these types.

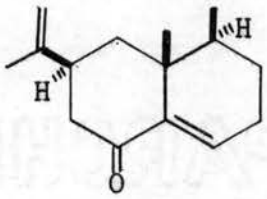


IV

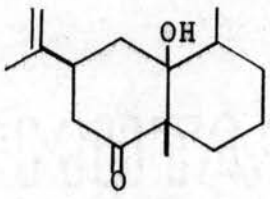


V

Although some compounds such as eremophilone (VI) are non-isoprenoid, they may still be classed as terpenes since their carbon skeleton may be rationalized by a simple rearrangement from some isoprenoid precursor. Such a precursor for eremophilone might be the eudesmol type compound VII.



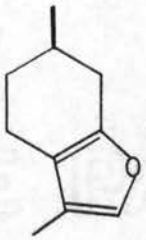
VI



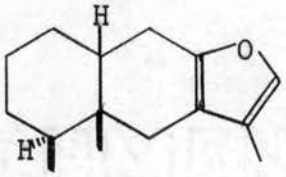
VII

Naturally occurring furans are rather common, particularly benzofurans. However, terpenes containing the furan system, referred to as "furanoterpenes", are not quite so common and are the subject of this thesis. As examples, menthofuran (VIII), furanoeremophilane (IX), and

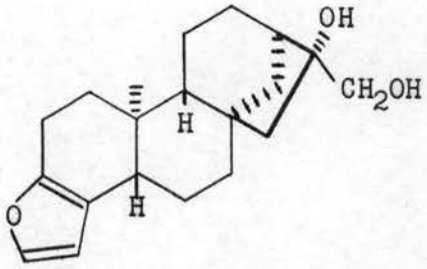
cafestol (X), might be cited as members of the furanoid mono-, sesqui-, and diterpene groups respectively.



VIII

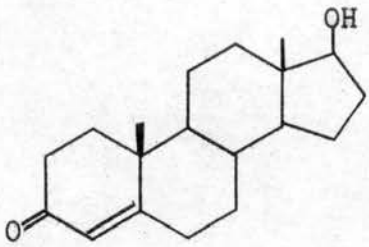


IX



X

Menthofuran has been the most thoroughly studied while furanoeremophilane and cafestol are unique in that they are non-isoprenoid.



XI

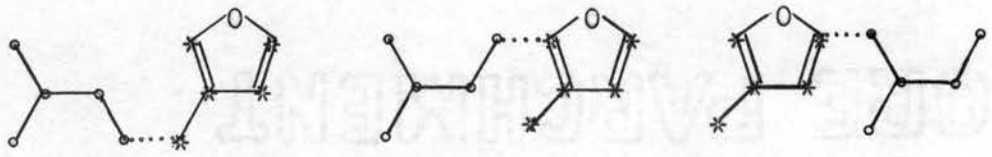
Cafestol has the additonal feature of being a member of a relatively small group of compounds having an absolute configuration at the bridgehead position opposite to that of the steroids. The steroid testosterone (XI) will serve for a comparison of that point.

Of the various furanoterpenes known, only the less structurally complicated have been synthesized and the knowledge gained from these syntheses will be reviewed.

As pointed out by Dean (2) the furanoterpenes may be divided into three patterns based on the isoprene unit as shown below, variations being the point of attachment of other isoprene units.

Although least common at the time of the review by Dean (2),

several furanoterpenes of the pattern C have recently been reported and will be the main subject of this thesis.



A B C

Literature Survey

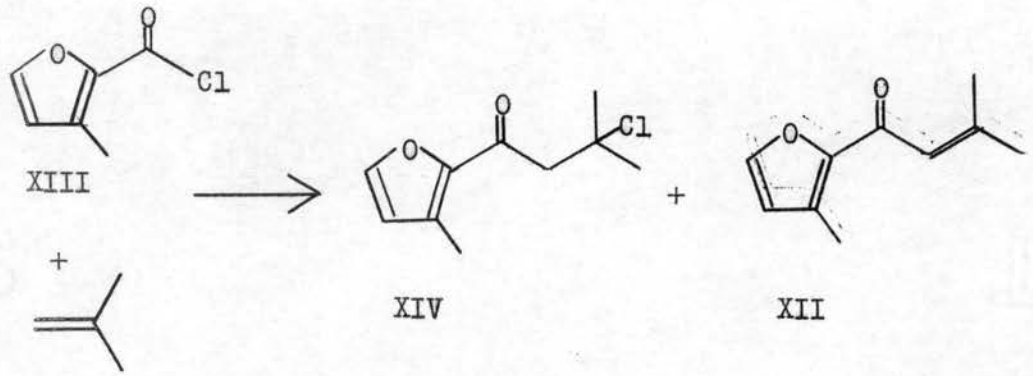
The literature covering naturally occurring furans has been reviewed recently by Dean (2). That review covers briefly the literature to 1961 concerning occurrence, structure elucidation, stereochemistry, and synthesis of furanoterpenes and some other furans which are not terpenoid. This section of the thesis is an attempt to bring the review by Dean up to date and cover most of the more recently reported furanoterpenes. The total synthesis of a furanoterpene will be the last facet of investigation to be discussed and those whose synthesis have been described by Dean (2) will not be discussed here. Also, biosyntheses will not be discussed.

Monoterpenes

β-Dehydroelsholtzione (XII), $C_{10}H_{12}O_2$.

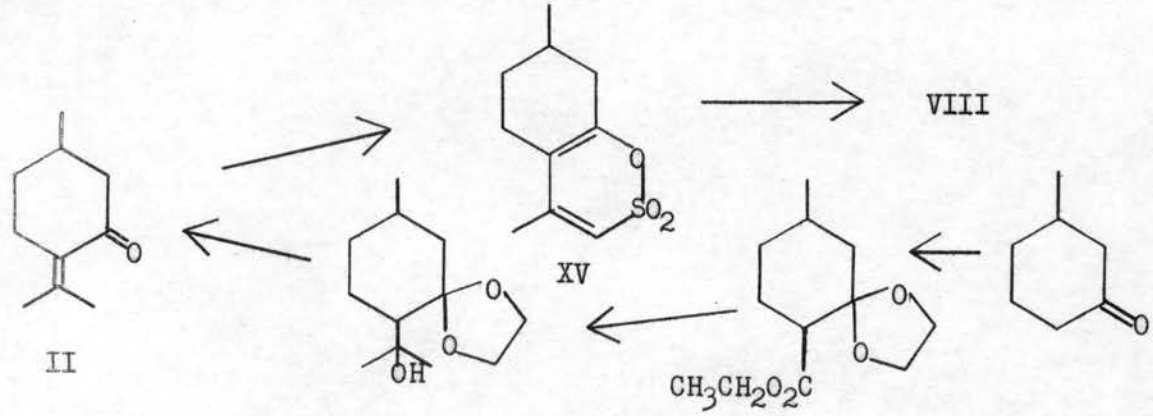
The synthesis of β-dehydroelsholtzione (XII) or naginata ketone was accomplished by the acylation of 2-methylpropene with the acid

chloride XIII (3). The chloroketone XIV could be further dehydrohalogenated to the desired product.



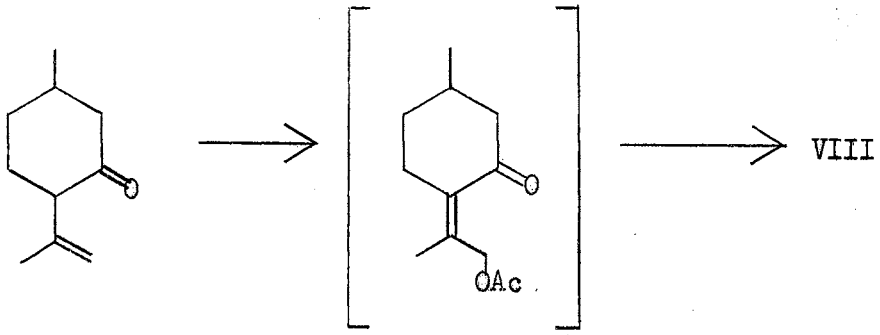
Menthofuran (VIII), $C_{10}H_{14}O$.

Although the conversion of pulegone (II) to menthofuran was reported by Treibs (4) in 1937, pulegone itself was only recently synthesized



in racemic form by the route shown (5,6). Also, later work by Treibs (7) resulting in another synthesis of menthofuran was not reported by Dean (2) but since it is pertinent to this study it will be discussed here.

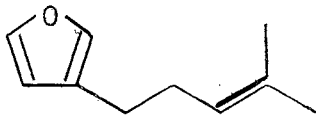
In a study of the reaction of mercuric acetate with ketones and olefins, Treibs (7) reported that upon treating isopulegone (XVI) with that reagent and then distilling the crude reaction mixture, menthofuran was formed along with other oxidation products. The keto-ester XVII was suggested as the probable intermediate.



XVI XVII

Perillene (XVIII), $C_{10}H_{14}O$.

The synthesis of perillene has not been reported (2).



XVIII

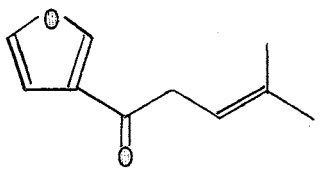
α-Clausenane, $C_{10}H_{12}O$.

Since the time of the review by Dean (2), no papers were found concerning the unknown structures of α-clausenane and other furans found in the essential oil of Clausena willdenovii.

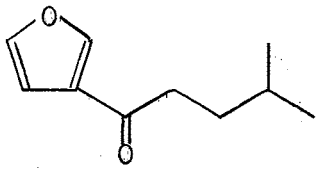
Egomaketone (XIX), $C_{10}H_{12}O$.

The occurrence in the essential oil of a variety of Perilla frutescens Brit. of egomaketone and its structure proof have recently been reported (8). The infrared spectrum of egomaketone showed it to contain a furan ring, a conjugated carbonyl, and a trisubstituted double bond. It was shown not to be perillaketone (XX) by mixed melt-

ing point of the 2,4-dinitrophenylhydrazone derivatives. Treatment of egomaketone with sodium and amyl nitrite gave β-furoic acid while hydro-



XIX



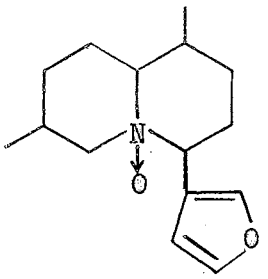
XX

genation with platinum catalyst gave perillaketone. The position of the double bond was shown by the formation of acetone (identified by its 2,4-dinitrophenylhydrazone derivative) upon oxidation with permanganate. Its synthesis has not been reported.

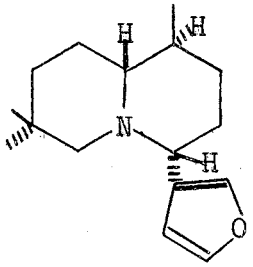
Sesquiterpenes

Nupharidine (XXI), $C_{15}H_{23}NO_2$.

Although a synthesis of d,l-deoxynupharidine (XXII) had been re-



XXI



XXII

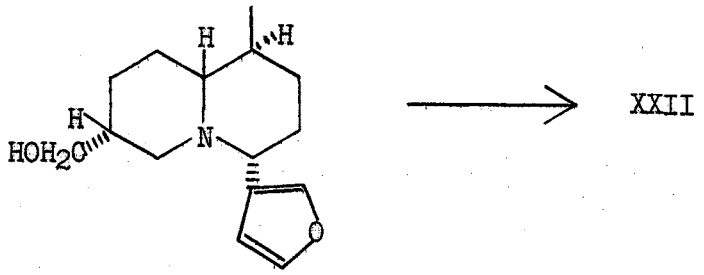
ported in 1959, it was later considered to be a mixture of diastereomers (9). The stereochemistry was not established until 1961 (10). The absolute configuration has recently been established as XXII by degrada-

tion to (S)-(-)-α-methyladipic acid by Kawaski (9) and confirmed by Arata (11).

Other syntheses have recently appeared, each involving a separation of the 4 d,l pairs formed (10,12).

Castoramine (XXIII), $C_{15}H_{23}NO_2$.

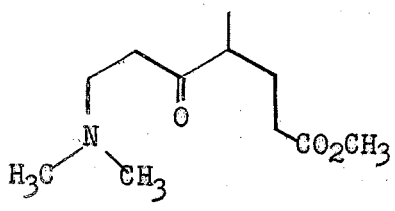
This sesquiterpene alkaloid, extracted from the scent glands of the beaver, has been shown to be of the same type as nupharidine (13). Although the conversion to deoxynupharidine (XXII) was made, it was not



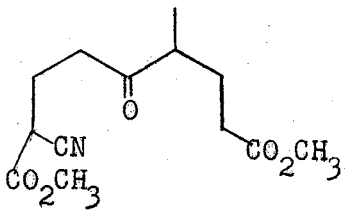
XXIII

known which methyl held the hydroxyl group. By a study of the hydrogen bonding in model compounds and then synthesizing the two possibilities, the structure was finally established as XXIII (14).

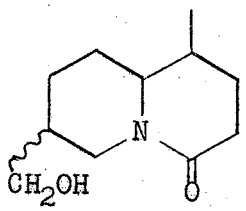
The synthesis of castoramine will exemplify the type of approach in-



XXIV



XXV



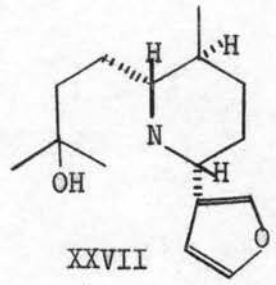
XXVI

volved in the synthesis of these furanoterpene alkaloids. This synthesis involved the dialkylation of ethyl acetoacetate followed by decarboxylation and then the Mannich reaction to give the keto-ester XXIV. Treatment of the amine salt with methyl cyanoacetate gave the nitrile XXV which was cyclized by catalytic reduction and then reduced to the lactam-alcohol XXVI. The reaction of this lactam-alcohol with 3-furyllithium gave an olefin which was hydrogenated to give a mixture of 4 d,l pairs from which d,l-castoramine was isolated (14).

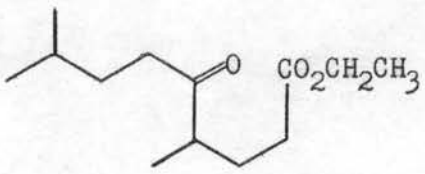
Nupharamine (XXVII), $C_{15}H_{23}NO_2$.

The stereochemistry of nupharamine was known since in the structure proof it was degraded to some of the same compounds obtained from degradations of nupharidine. The absolute configuration was recently determined by Kawaski (15) as XXVII by its conversion to 1-deoxynupharidine.

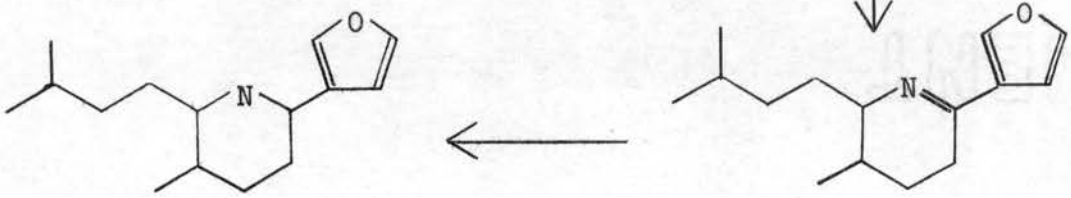
The snythesis of d,l-deoxynupharamine (XXVIII) was accomplished in



XXVII



XXIX

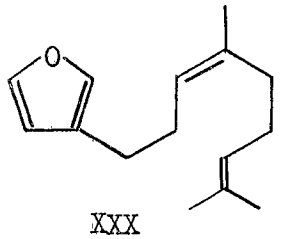


XXVIII

1963 by Arata (16) by a series of alkylations on ethyl acetoacetate to give the keto-ester XXIX. The oxime of XXIX was reduced, acylated with β-furoyl chloride and then cyclized to the tetrahydropyridine. Reduction gave d,l-deoxynupharamine and an isomer.

Dendrolasin (XXX), $C_{15}H_{22}O$.

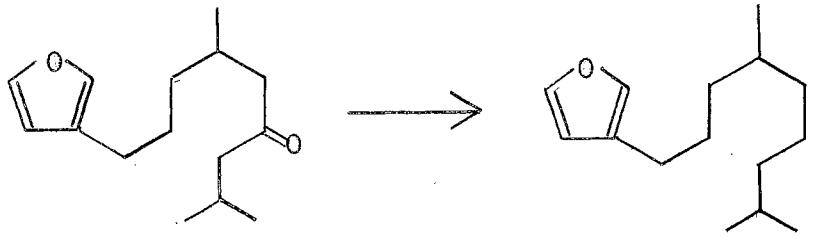
Although the synthesis of tetrahydrodendrolasin has been reported by Quilico, Grunager, and Piozzi (17), as part of the structure proof, a synthesis of the naturally occurring substance has not been reported (2).



XXX

8-(3-Furyl)-2,6-dimethyl-4-octanone (XXXI), $C_{15}H_{24}O_2$

Ogawa and Hirose (18) have recently reported the isolation of ketone XXXI from sweet potato fusel oil. Upon Wolff-Kishner reduction

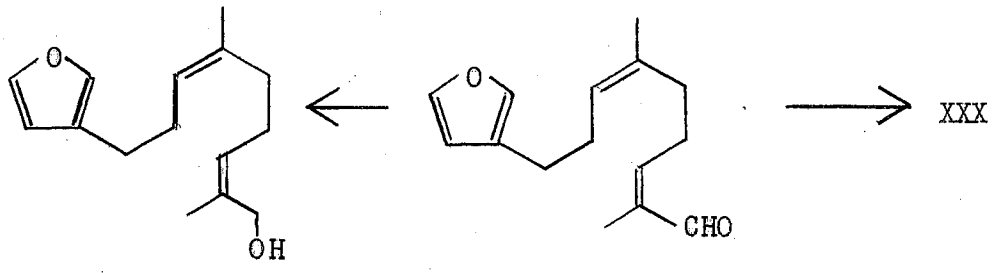


XXXI XXXII

it gave tetrahydrodendrolasin (XXXII), thereby defining its structure.

Torreyal (XXXIII), $C_{15}H_{20}O_2$, and Torreyol (XXXIV), $C_{15}H_{22}O_2$.

Recent investigations of the neutral volatile wood oil of Torreya nucifera Sieb. et Zucc. have revealed the presence of two new furano-



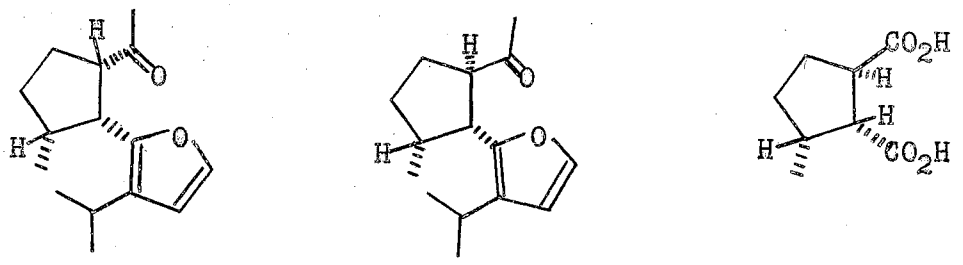
XXXIV XXXIII

terpenes, torreyal,and torreyol in addition to dendrolasin (XXX).

The structure of torreyal was determined by spectral data and ozonolysis. The structure was confirmed by Wolff-Kishner reduction of the semicarbazone to dendrolasin. Torreyol was found to be identical to the lithium aluminum hydride reduction product of torreyal, hence the structure XXXIV for torreyol (19).

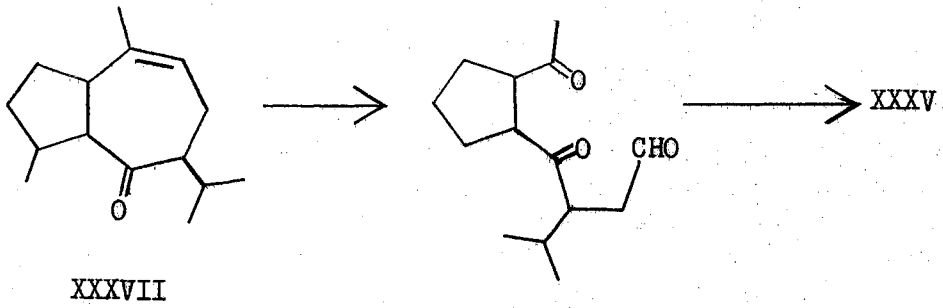
Pelargone (XXXV), $C_{15}H_{22}O_2$.

Pelargone A (XXXVa) has been isolated from the essential oil of



XXXVb XXXVa XXXVI

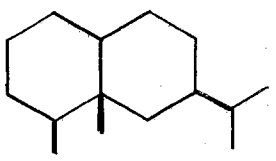
Geranium bourbon and has been degraded to 3-methylcyclopentane-1,2-dicarboxylic acid as part of the structure proof (20,21). Further proof of the stereochemistry and absolute configuration was provided when the acid was found to be identical to (-)-trans, cis-nepetic acid (XXXV) (22). Pelargone B is considered to be an epimer of pelargone A. The pelargones are not isoprenoid but might arise by oxidation of an appropriate sesquiterpene precursor such as XXXVII (18).



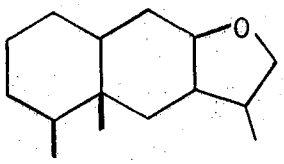
XXXVII

Furanoeremophilanes.

In a recent series of papers Sorm (23,24,25) has reported the isolation of a group of sesquiterpenes with the eremophilane skeleton XXXVIII and containing a fused furan ring. Although some of the structures are not proven, tentative ones have been assigned based on evidence obtained by their conversion to the tetrahydrofuran XXXIX.

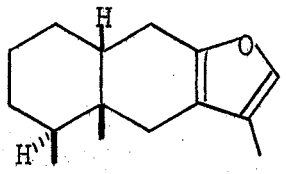


XXXVIII

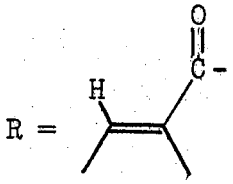


XXXIX

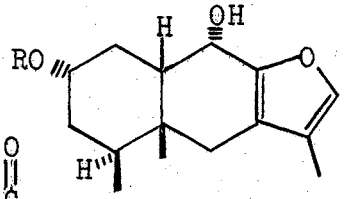
Furanoeremophilane (IX) has been characterized by Herout (26) and its stereochemistry and absolute configuration have been established by relation to other known compounds of the eremophilane type (27). Based on recent evidence, the structure XL has been suggested for furano-



IX

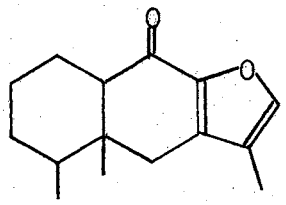


R =

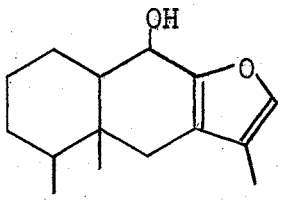


XL

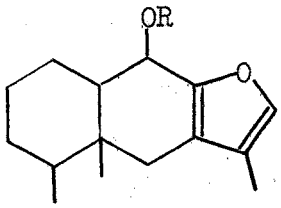
petasin (28). Tentative structures have been assigned to furanoeremophilone (XLI), petasalbin (XLII), albopetasin (XLIII), and albopetasol (XLIV) as shown (23).



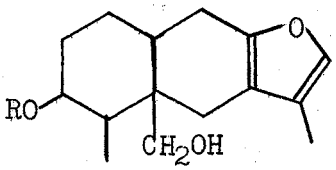
XLI



XLII



XLIII

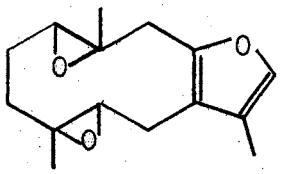


XLIV

None of the naturally occurring sesquiterpenes of the eremophilane skeleton have been synthesized (29).

Alexandrofuran (XLV), $C_{15}H_{20}O_3$.

Although no papers have appeared in print describing the isolation or chemical structure proof of alexandrofuran, its structural formula is available through a recently published volume by Djerassi,

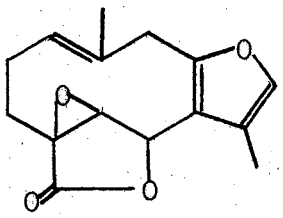


XLV

Williams, and Budzikiewiez (30) on the application of mass spectrometry to structural problems. Mass spectral analysis established the molecular formula and was helpful in the structure elucidation. Alexandrofuran is being investigated by Alpin and Halsall (31).

Linderane (XLVI), $C_{15}H_{16}O_4$.

Linderane and linderene (XLVII) are constituents of the root of Lindera strychnifolia. Their isolation was reported in 1925 by Kondo and Sanada (32). Only recently has linderane received much attention



XLVI

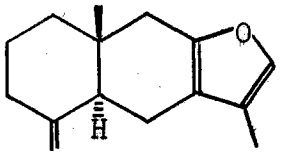
and the structure XLVI has recently been assigned by Takeda (33).

Linderane is claimed to be the first example of a sesquiterpene

containing both a ten-membered ring and a furan ring (33). Alexandrofuran is probably the second such example.

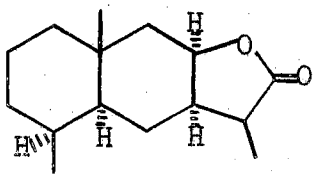
Atractylone (XLVIII), $C_{15}H_{20}O$.

Atractylone was isolated from the essential oil of the rhizomes of a species of Atractylodes japonica collected in Manchuria (34). The structure was recently reported (35,36).

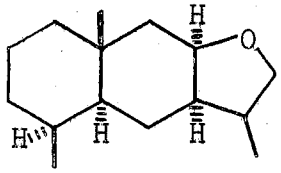


XLVIII

The compound was shown to have an exocyclic double bond by ozonolysis to give formaldehyde. The presence of a furan ring was indicated by chemical tests, spectroscopic data, and by formation of



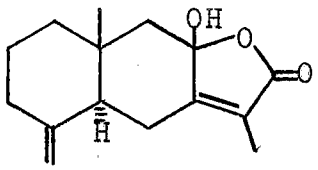
L



XLIX

a maleic anhydride adduct. Only one mole of hydrogen was absorbed over platinum oxide while three moles were taken up over palladium on carbon giving octahydrodeoxylinderene (XLIX). The stereochemistry of octahydrodeoxylinderene has recently been established by its synthesis from the known tetrahydroantolactone (L) (37). The structure XLVII was confirmed by its n.m.r. spectrum. Atractylone is easily air-

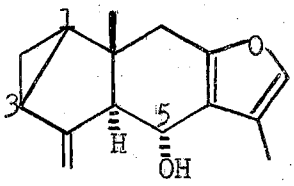
oxidized to the lactol LI. Menthofuran behaves in a similar manner (2).



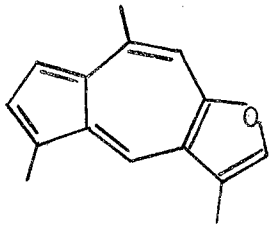
LI

Linderene (XLVII), $C_{15}H_{18}O_2$.

The structure for linderene has only recently been assigned by Takeda (37) on the basis of the structure given for octahydrodeoxylinderene (XLIX). Perhaps the experimental result which has been the



XLVII

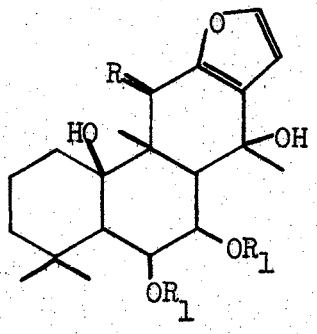


LII

most misleading since the very onset of investigation was that linderazulene (LII) was formed on dehydrogenation thereby indicating the incorrect carbon skeleton. Linderene was shown by n.m.r. to have a secondary hydroxyl group (which was previously considered to be tertiary) adjacent to a single proton, and a cyclopropane ring. Evidence from the n.m.r. spectrum of the dehydration product of octahydrolinderene allowed the position of the hydroxyl group to be assigned to C-5 and the cyclopropane then could only be at C-1 and C-3. From the chemistry of the alcohol and the coupling constant between the protons at C-5 and C-10, the hydroxyl was assigned the equatorial configuration.

α,β, and γ-Caesalpins.

The isolation of these three bitter constituents from the seeds of Caesalpin bonducella Flem was first reported in 1960 (38). The plant grows wild in the India-Pakistan area and the seed kernel is



LIII

R = O

R_1 = Ac

LIV

R = O

R_1 = H

LV

R = H, OH

R_1 = H

used locally for medicinal purposes.

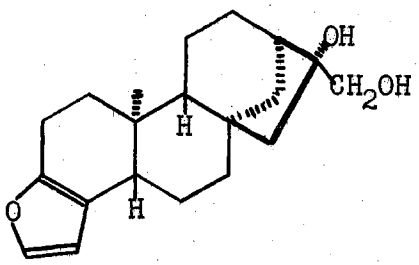
The structures for α-caesalpin (LIII) and β-caesalpin (LIV) and hydrolyzed γ-caesalpin (LV) have recently been assigned from the evidence obtained by sodium periodate oxidation of the γ-isomer. β-Caesalpin is obtained from α-caesalpin by hydrolysis and can be reacetylated to LIII. Treatment of α-caesalpin with lithium aluminum hydride gives hydrolyzed γ-caesalpin (LV). Thus, the location of the acetate in γ-caesalpin is not known (39,40).

Cafestol (X), $C_{20}H_{26}O_3$.

Since the time of the review by Dean (2) the stereochemistry and absolute configuration of cafestol have been determined to be as shown in X.

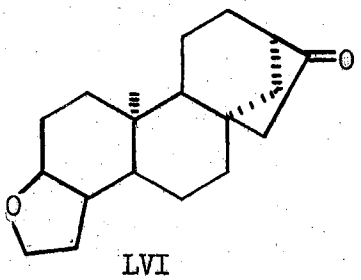
On the basis of optical rotatory dispersion measurements, the stereochemistry and absolute configuration of the A/B and C/D ring

junctures were correctly assigned as shown in X. The stereochemistry

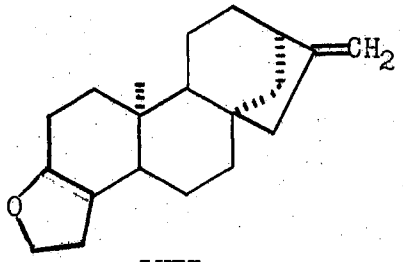


X

of the glycol grouping in the D ring was determined by conversion of cafestol to the ketone LVI, which was treated with the Wittig reagent to give the exo-methylene compound LVII. When LVII was treated with



LVI



LVII

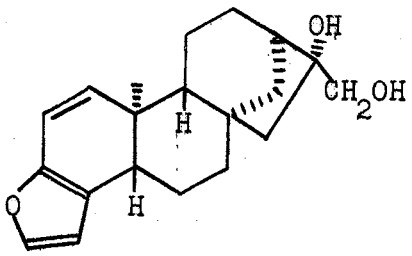
osmium tetroxide the glycol was obtained which was identical to that obtained from natural cafestol. The stereochemical requirements of the reaction allow the assignment of configuration as in X (41).

A recent x-ray analysis of a bromide derivative of cafestol indicates that the B/C ring juncture is trans as in X and firmly establishes the stereochemistry and absolute configuration of cafestol (42).

Kahweol (LVIII), $C_{20}H_{24}O_3$.

The diterpene kahweol has long been known to be similar to cafestol but with further unsaturation since hydrogenation of a mixture of the two gave pure cafestol (43). By quantitative hydrogenation it was shown that kahweol absorbed three moles of hydrogen while cafestol

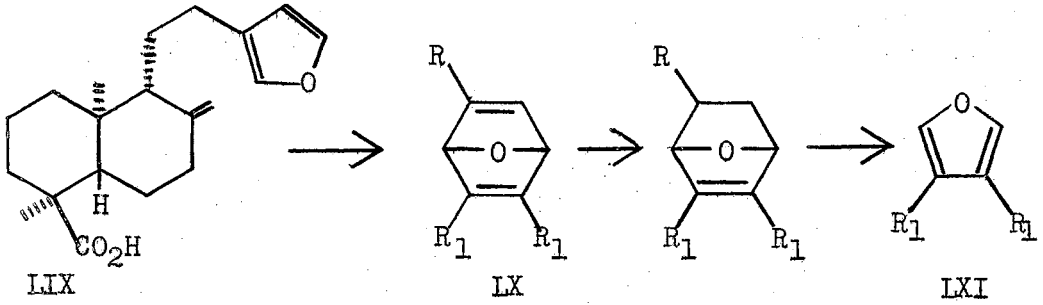
absorbed only two. On this basis and evidence obtained from the methanol adduct and spectroscopic and chemical properties, the structure LVIII has recently been established for kahweol (44).



LVIII

Polyalthic Acid (LIX), $C_{20}H_{28}O_3$.

This acid was isolated in nearly 1% yield from the stem bark of a large tree (Polyalthia fragrans Bth.) which grows on the west coast of India. Based on chemical and spectroscopic evidence the structure

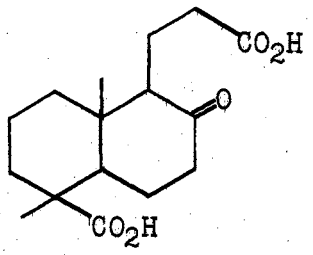


LIX LX LXI

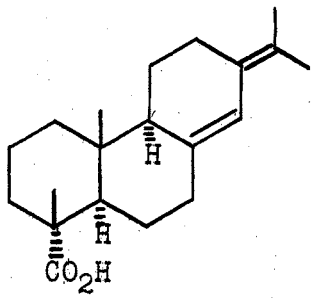
R_1 = $-CO_2CH_2CH_3$

LIX has been assigned to polyalthic acid (45). The presence of a β-substituted furan ring was confirmed by the Alder-Rickert degradation by reaction of the furan ring with diethyl acetylenedicarboxylate, hydrogenation of the adduct LX and then pyrolysis to give the retro Diels-Alder product diethyl furan-3,4-dicarboxylate (LXI). The nature of the carbon skeleton was shown by selenium dehydrogenation to 1,2,5-

trimethylnaphthalene while the tertiary carboxyl group was indicated by its chemistry which also suggested it to be equatorial. The



LXII



LXIII

structure was confirmed by degradation to the acid LXII, identical in all respects except for opposite sign of rotation to the corresponding acid obtained from the known neoabietic acid (LXIII). The stereochemistry and absolute configuration then must be that depicted by LIX. These points were confirmed by a similar comparison of two other sets of derivatives of polyalthic and neoabietic acids.

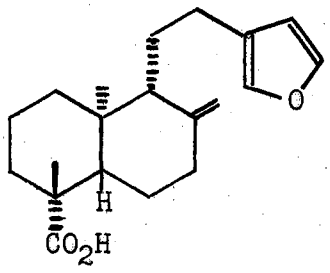
Daniellic Acid (LXIV), $C_{20}H_{28}O_3$.

Daniellic acid was recently isolated from the African copal tree, Daniellia oliveri (Caesalpineae) and its structure, stereochemistry, and absolute configuration have been reported (46). The structure elucidation was much the same as that of polyalthic acid.

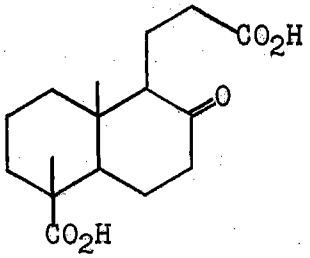
The difficulty in hydrolyzing the ester derivatives led to the conclusion that the carboxyl group was tertiary and axial. The structure proof was confirmed and the stereochemistry and absolute configuration were proven by comparison of the keto-acids LXV derived from daniellic acid and the known agathic acid (LXVI). The keto-acids were identical in all respects except their optical rotatory dispersion curves were opposite, thus establishing the antipodal relationship

depicted in LXIV.

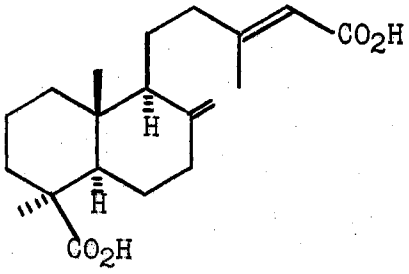
It might be noted that daniellic acid and polyalthic acid are identical except for the configuration of the carboxyl groups.



LXIV



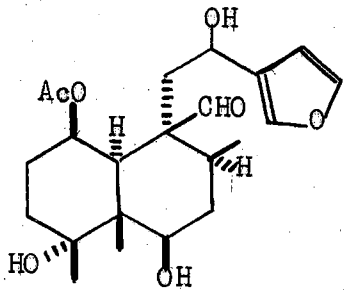
LXV



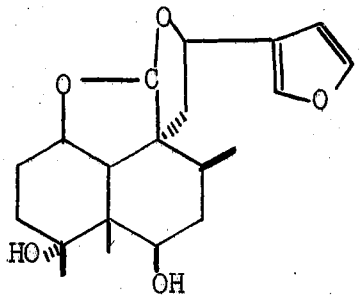
LXVI

Cascarillin (LXVII), $C_{22}H_{32}O_7$.

The bitter principle from the bark of Croton eleuteria was isolated long ago and was studied as early as 1896. With the aid of



LXVII

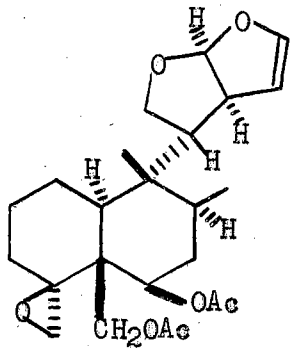


LXVIII

modern instrumental methods its molecular formula was correctly established as $C_{22}H_{32}O_7$. In addition to the spectroscopic evidence, degradative experiments gave information which allowed a tentative structure LXVII to be assigned (47).

Cascarillin is easily hydrolyzed to the alcohol which when treated with acid readily loses a molecule of water to give an acetal considered to be LXVIII. The stereochemistry was suggested on the basis

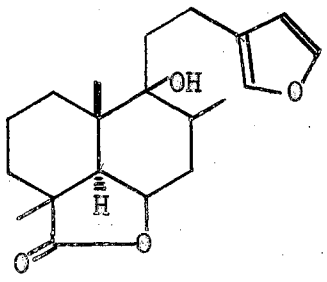
of a probable biogenetic pathway and its relationship to the known clerodin (LXIX).



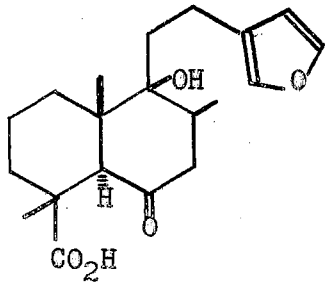
LXIX

Marrubin (LXX), $C_{20}H_{28}O_4$.

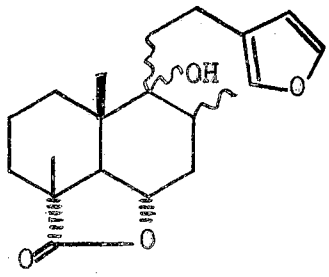
Although marrubin has been well studied there still remains some question as to its stereochemistry (48). The stereochemistry of the



LXX



LXXI



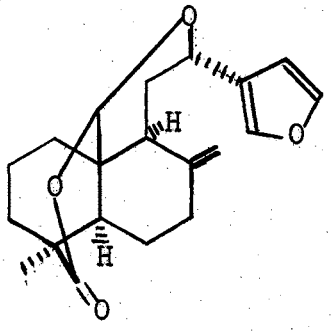
LXXII

A/B ring juncture had been agreed upon as in LXX (49). Based on the reduction of the keto-acid LXXI with lithium and liquid ammonia, and sodium borohydride, the configuration of the lactone ring was suggested as in LXXII. The remaining centers are still in dispute (48).

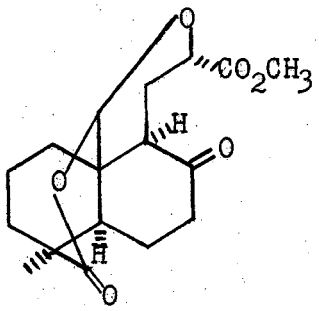
Sciadin (LXXIII), $C_{20}H_{24}O_4$.

From the wood of Sciadopitys verticillata Sieb. et Zucc. of Japan has been isolated a diterpenoid bitter principle named sciadin. Re-

cent investigations by Sumimoto (50) employing classical chemical degradations and an application of modern instrumental techniques have allowed the structure to be assigned.

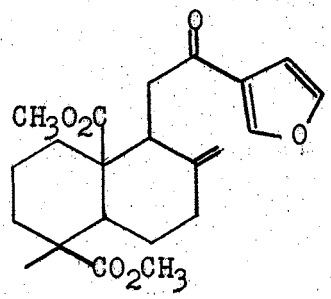


LXXIII

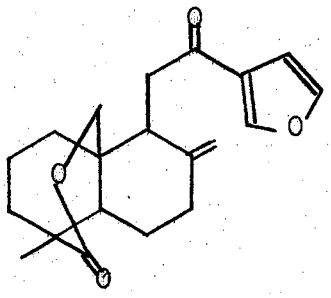


LXXIV

The evidence provided by optical rotatory dispersion measurements on the keto-ester LXXIV has allowed tentative assignments of



LXXV



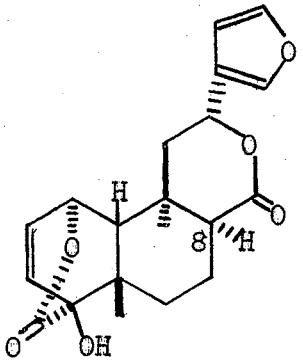
LXXVI

stereochemistry to be made.

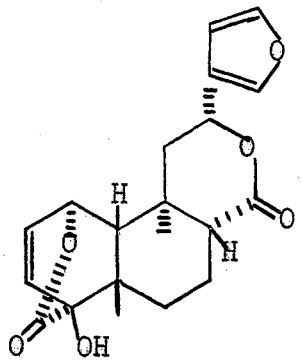
Two other diterpenes, dimethyl sciadinoate (LXXV) and sciadinone (LXXVI) have been isolated from the same source and related to sciadin (51). The interrelationships were performed by degradations of each to a common substance or transformations of one into the other.

The ozonolysis of sciadinone gave a diketone which was unchanged on base treatment thus confirming that the side chain was in the equatorial configuration, and confirming the tentative stereochemical assignments of LXXIII (52).

Columbin (LXXVII), $C_{20}H_{22}O_6$.

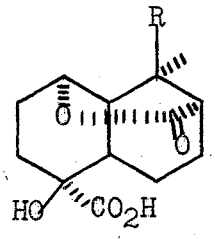


LXXVII



LXXIX

The most recent information leads to the stereochemistry depicted in LXXVII for columbin (53). This conclusion was based on the formation of an isolactone LXXVIII which could not be formed if the



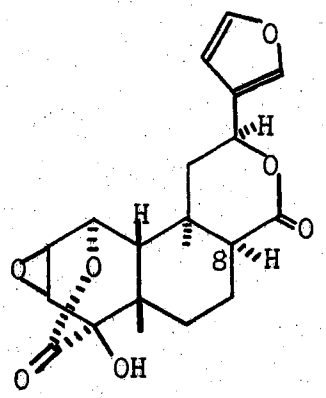
LXXVIII

A/B juncture were trans. The stereochemistry of the furan ring was determined by application of the Hudson-Klyne lactone rule (54). Treatment with base gives isocolumbin, (LXXIX) believed to be an epimer at C-8.

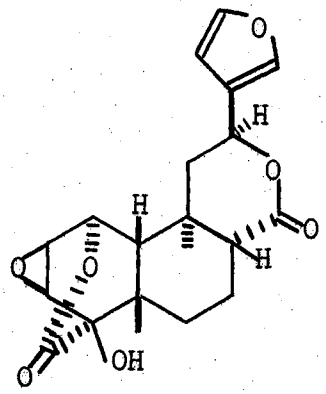
Palmarin (LXXX), $C_{20}H_{22}O_7$.

In two recent papers by Barton (55,56) the structures of palmarin, chasmanthin (LXXXI), jateorin (LXXXII), and isojateorin (LXXXIII) are discussed. The relationships of these compounds may best be shown by their interconversions by base treatment which is

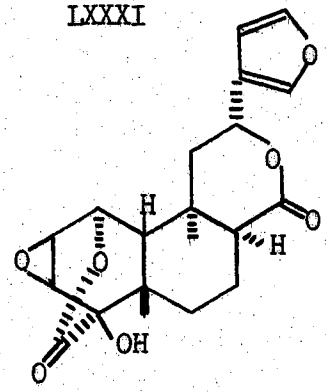
believed to result in epimerization at C-8 as with columbin.



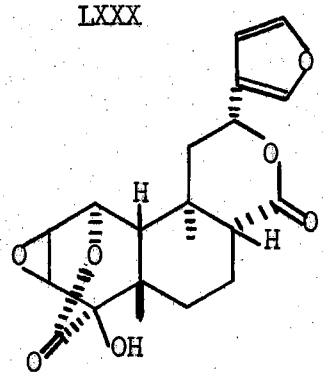
LXXXI



LXXX



LXXXII



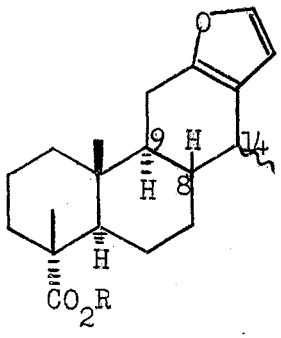
LXXXIII

Isojateorin and dihydroisocolumbin have been converted to a common derivative thereby showing that isojateorin is the epoxide of isocolumbin (56). If the stereochemical assignment of the furan ring of columbin is valid then these formulas should represent the compounds under discussion.

Methyl Vinhaticoate (LXXXIV), $C_{21}H_{30}O_3$ and Methyl Vouacapenate (LXXXV), $C_{21}H_{30}O_3$.

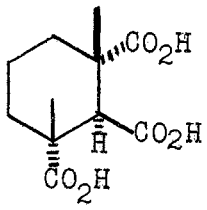
These diterpenes of the molecular formula $C_{21}H_{30}O_3$ are identical except for the configuration of the carboxyl group. This was shown by reduction of the carboxyl group in each of the two thereby giving the same gen-dimethyl compound. The stereochemistry of the A/B ring system of the acid LXXXVI has been shown to be trans and to have the same

absolute configuragion as abietic acid by oxidation to the tricarboxylic acid LXXXVIII, identical to that obtained from abietic acid (57). Cassamic acid, a diterpene alkaloid of similar structure, and LXXXVII have been interrelated by conversion to the same diacid LXXXIX

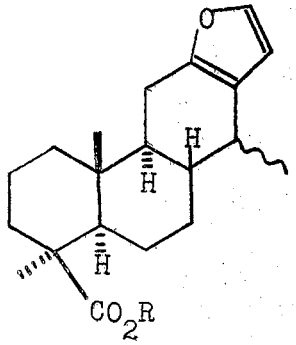


LXXXIV R = CH_3

LXXXVI R = H

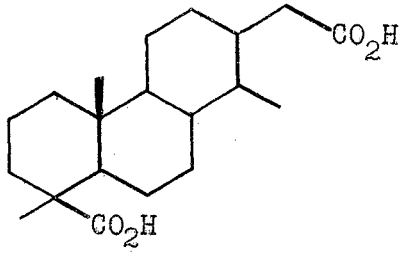


LXXXVIII



LXXXV R = CH_3

LXXXVII R = H



LXXXIX

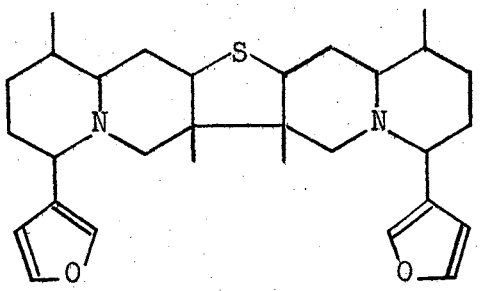
(58). Optical rotatory dispersion measurements on cassamic acid derivatives indicate a trans-anti-trans configuration for the A/B and B/C ring junctures allowing the hydrogens at C-8 and C-9 to be assigned the β and α configurations respectively as in LXXXV. These data are also consistent with a β methyl group at C-14 although this point has not been settled (58).

Triterpenes

Thiobinupharidine and Neothiobinupharidine (XC), $C_{30}H_{42}O_2N_2S$.

These triterpenes were first isolated in 1939 from the yellow lily and have recently been isolated by a new procedure based on chromatography (59). The relationship between these two new alka-

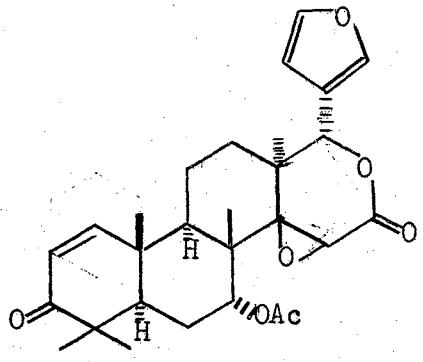
loids and deoxynupharidine was suspected on evidence from spectroscopic studies (59). The relationship with deoxynupharidine as well as the molecular formulas were confirmed from the mass spectral splitting patterns (60). Based on this evidence the tentative structure XC has been assigned to the two, one being a stereoisomer of the other (60).



XC

Gedunin (XCI), $C_{28}H_{34}O_7$.

This triterpene has been isolated from Entondrophragma angolense along with its dihydro derivative. Since gedunin exhibited reactions similar to those of limonol, whose structure and

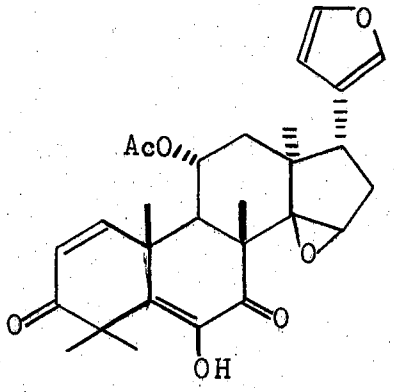


XCI

stereochemistry have been determined by x-ray analysis, a tentative structure XCI was assigned (61). An x-ray analysis of the iodoacetate confirmed the structure XCI assigned earlier (62).

Anthothecol (XCII), $C_{28}H_{32}O_7$.

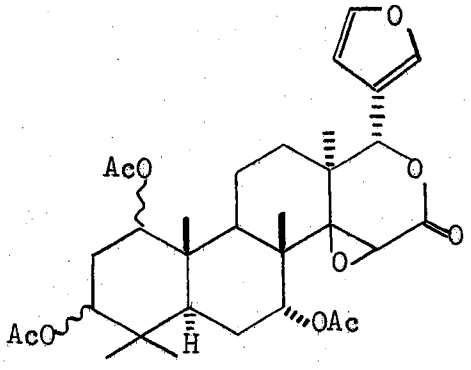
A series of new substances has been isolated from West African timbers, one of which is anthothecol, which has been assigned the tentative structure XCII on the basis of similarities with other members of the group (63).



XCII

Khivorin (XCIII), $C_{32}H_{42}O_{10}$.

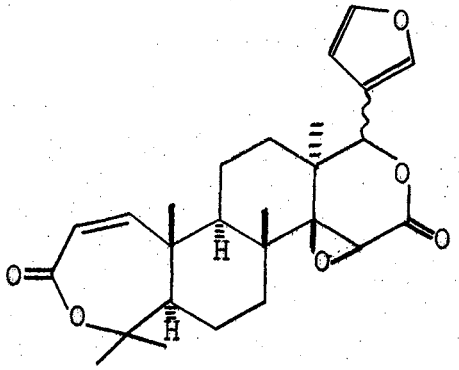
Another of the series isolated from West African timbers, khivorin, has been assigned the tentative structure XCIII with only the configuration of the acetates remaining undefined. The assignments were made on the basis of analogy to other members of this series (64).



XCIII

Obacunone (XCIV), $C_{26}H_{30}O_7$.

Based on a suspected relationship to limonin, Barton, Jager, Corey, and Arigoni and collaborators (65) proposed the structure XCIV for obacunone but did not indicate the stereochemistry.

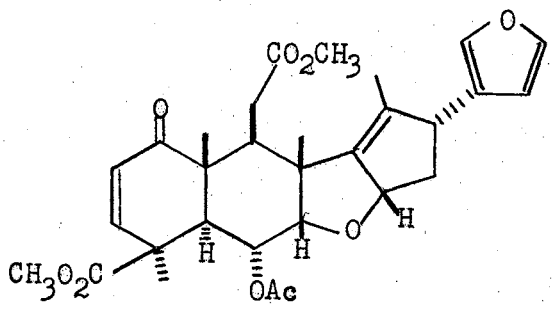


XCIV

Shortly thereafter, obacunone was related to limonin via a degradation product and the stereochemistry was suggested as shown in XCIV (66,67). Although the configuration of the furan ring has not been established it is suspected of being the same as in limonin.

Nimbin (XCV), $C_{30}H_{36}O_9$.

By a combination of chemical and instrumental methods the structure XCV has been proposed for nimbin (68). The stereochemis-



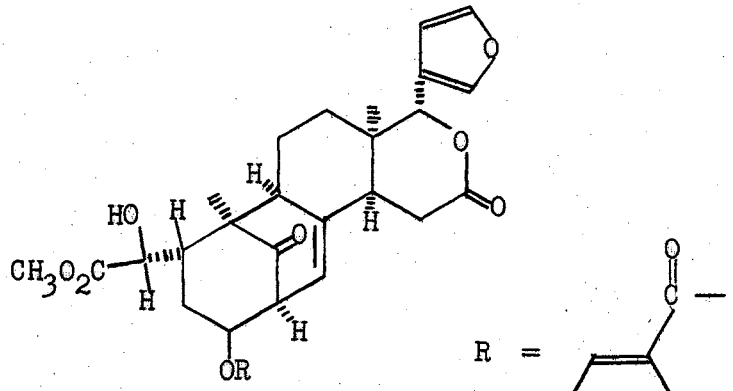
XCV

try and absolute configuration of nimbin has also been shown to be as

in XCV by n.m.r. and optical rotatory dispersion studies (69).

Swietenine (XCVI), $C_{32}H_{42}O_9$.

Two recent communications, one dealing with the x-ray analysis of

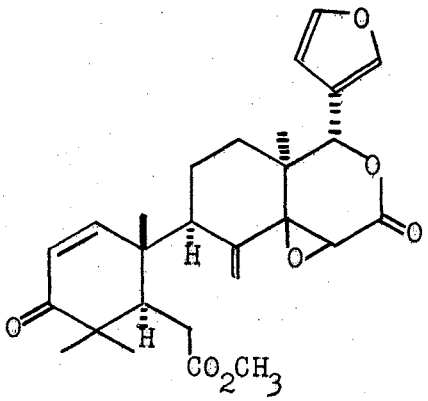


XCVI

a p-iodobenzoate derivative of swietenine, establish its structure and absolute stereochemistry as XCVI (70,71).

Andirobin (XCVII), $C_{27}H_{32}O_7$.

Andirobin, isolated from the seeds of Carapa guayanesis Aubl. (Meliaceae), was shown to have a molecular formula of $C_{22}H_{32}O_7$ by mass spectrometry. Its structure has recently been deduced as XCVII (72). In the same communication the stereochemistry was suggested on the basis of a biogenetic analogy with other compounds of similar structure.



XCVII

Review of the Syntheses Reported

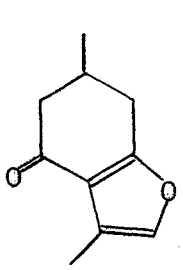
A review of the literature indicates that:

(1) All monoterpenes of known structure have been synthesized except for perillene and egomaketone (2).

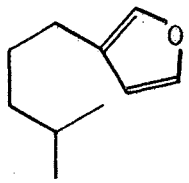
(2) The only furanosesquiterpenes which have been synthesized are tetrahydrodendrolasin, deoxynupharidine, castoramine, and deoxynupharamine.

(3) None of the furanoid di- or triterpenes have been synthesized (2).

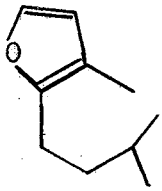
Almost all of the syntheses reported have involved the addition of a preformed furan ring somewhere in the synthetic route. The exceptions to this are the syntheses of menthofuran (VIII) and evodone (XCVIII) in which the appropriate functional groups were cyclized to form the furan ring. Also, these two furanoterpenes have been the only ones synthesized that may be classed as type C according to Dean (2). Of the compounds reported, all examples of type C have involved the furan ring as part of another ring.



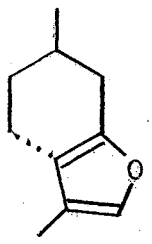
XCVIII



A



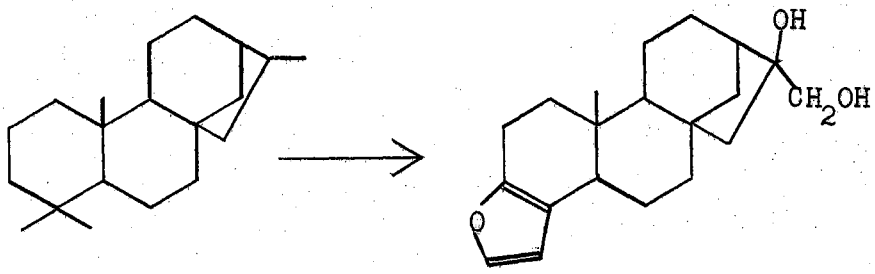
B



C

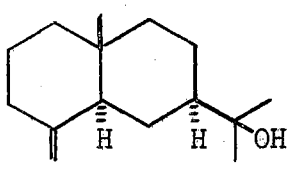
The two major groups of furanoterpenes are those corresponding to

type C where the furan system is part of another ring and those of type A where a monosubstituted furan ring is attached to the rest of the molecule. Although a few examples of type B are known, none of them involve the furan ring as part of another ring. The compounds cafestol (X) and methyl vouacapenate (LXXXV) for example, appear to be of type B but close examination will show them to be nonisoprenoid. They are considered to have isoprenoid precursors in which methyl migration has occurred in order to allow the furan ring to be formed as shown for cafestol.

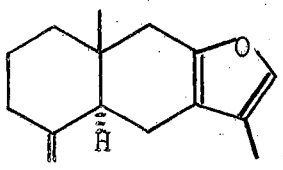


X

Terpenes are usually classed according to their carbon skeleton. For example, eudesmol (IV) has a eudalane skeleton and the corresponding furanoterpene, atractylone (XLVIII), obviously can be said to belong to the same class. Thus, there are several cases where the furanoter-



IV



XLVIII

pene is a member of a class of terpenes of well established carbon skeleton. Sometimes synthetic routes are already available which

lead to a particular skeleton or there may be available from natural sources sufficient amounts of some terpene which would be potentially useful in the synthesis of a particular furanoterpene.

As the complexity of the furanoterpene increases, the possibility exists that any furan ring introduced at an early state in the synthesis may not survive the many and varied chemical reactions that might be necessary to bring about construction of the rest of the molecule.

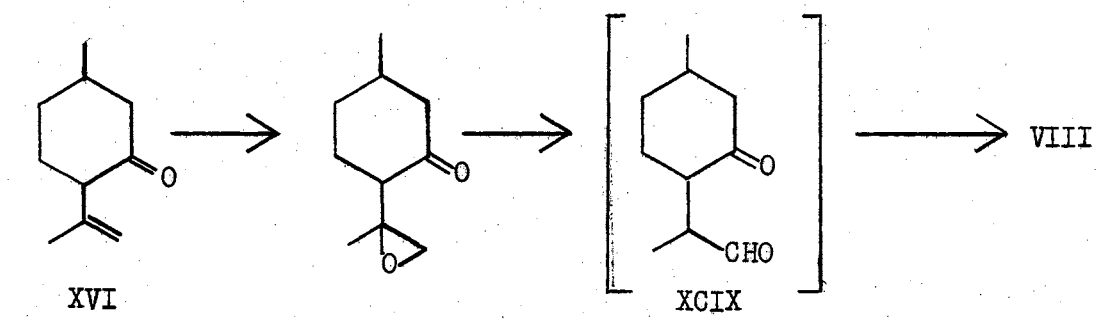
It seems clear that the approaches involved in the syntheses of type A and C furanoterpenes would be somewhat different. If this is true then only a review of the syntheses of type C furanoterpenes, namely, the syntheses of menthofuran and evodone, would be helpful in planning syntheses of other furanoterpenes of type C. Although most furanoterpenes are of type A, the number of examples of type C is now large enough to warrant some attention. The efforts of this thesis are directed to that end.

The problem seems to be resolved to the construction of a furan ring on another ring. Ideally, a number of methods should be available to allow the greatest flexibility in the synthesis of the rest of the molecule.

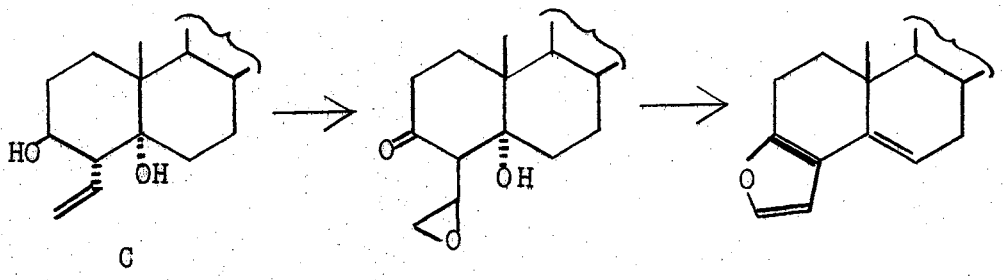
Much can be learned from a study of the syntheses of menthofuran and evodone, the only furanoterpenes of type C that have been synthesized. Between the two, almost every type of furan synthesis has been employed.

One of the oldest routes, the Paal-Knorr synthesis, involves the closure of 1,4-dicarbonyl compounds and has been employed by Fritel and Fetizon (73). Isopulegone (XVI) was converted by perbenzoic acid

into the epoxide which was then cyclized by hot acid to menthofuran in an overall yield of 13%. The dicarbonyl compound XCIX might have been an intermediate.



XVI XCIX



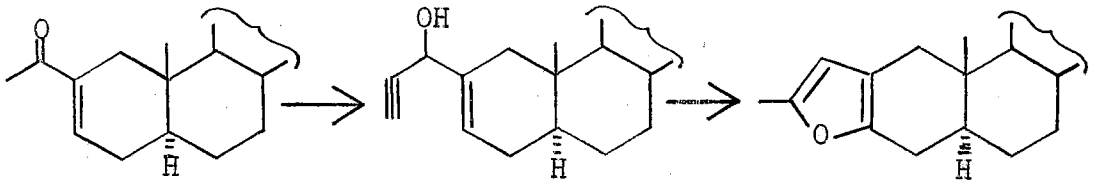
C

Examples of the Paal-Knorr synthesis have recently appeared in the steroid literature. Steroids could serve as effective models for the higher terpenes. Julia and Moutannier (74) have reported the formation of several steroid-furan derivatives analogous to cafestol and kahweol by the sequence indicated with a cholestane derivative C. The reported yields for the cholestane, androstane, and pregnane examples were greater than 65% in the last step.

A second example involved the sequence starting with the androstane derivative CI (75). The overall yield of 3.5% casts a doubt as to the suitability of such a reaction sequence in a synthetic route.

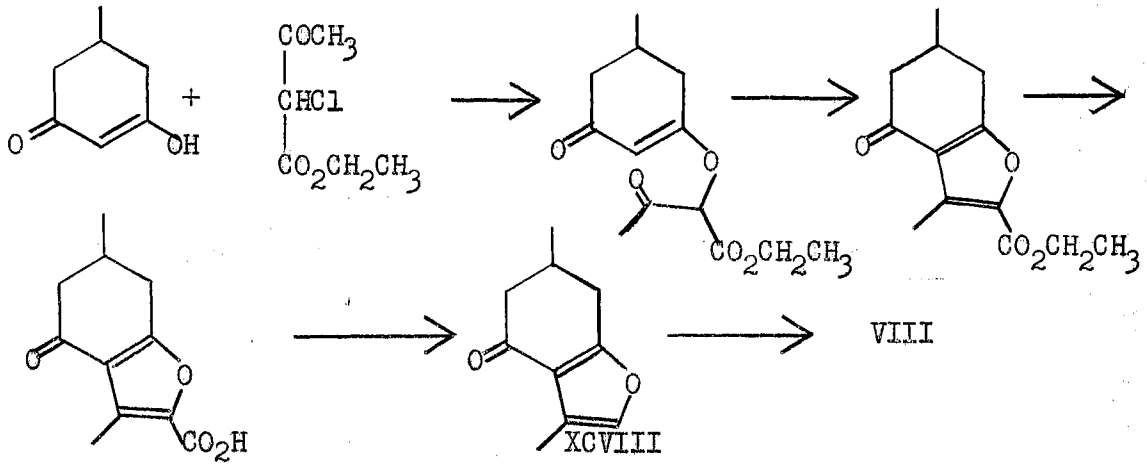
Recent examples of the formation of simple furans from masked 1,4-dicarbonyl compounds have appeared and good yields are reported

(76,77).



CI

Another well known synthesis of furans is the Feist-Bernary method which involves an α-halo-carbonyl compound and a β-keto-ester. The synthesis of d,l-evodone (XCVIII) exemplifies this method (78).

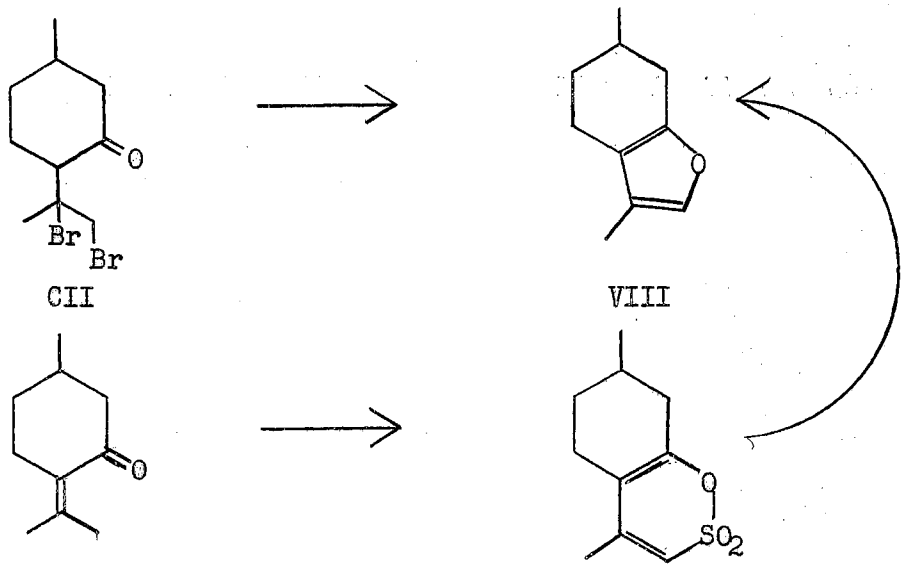


d,l-Menthofuran was obtained by Wolff-Kishner reduction of evodone. The inherent disadvantage in this method lies in the fact that either carbonyl may react. Hence, in an unsymmetrical molecule more than one product might be obtained.

Another base-catalyzed reaction resulting in the formation of menthofuran was reported by Wienhaus and Dewein (79). Isopulegone dibromide (CII) when treated with base gave menthofuran.

The reaction used by Treibs (4) in the first synthesis of menthofuran from pulegone (II) has been developed by Morel and Verkade (80,81,82) and found to be a general reaction for the conversion of α, β- or β, γ-unsaturated ketones into the δ-sultone.

Pyrolysis of the sultone gives the furan and sulfur dioxide in good yield.

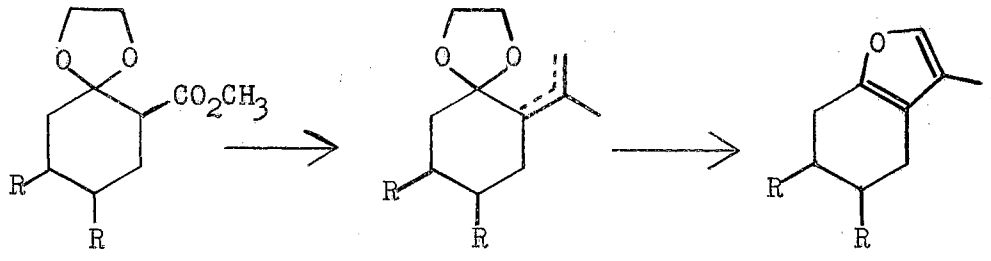


CII VIII

II XV

Finally, the reaction of isopulegone with mercuric acetate reported by Treibs (7) and discussed earlier in this chapter resulted in the formation of menthofuran.

Up to this time probably the best method used to introduce an isopropylidene, isopropyl or isopropenyl group adjacent to a carbonyl group has been the reaction of methylmagnesium iodide on a ketal-ester such as CIII. Since the isopropylidene, isopropyl, and isopropenyl groups are readily available by this route by



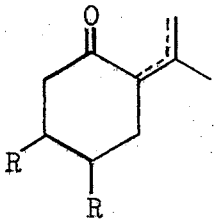
CIII CIV CV

varying the reaction sequence, the conversion of such a system as CIV into a furan ring is important.

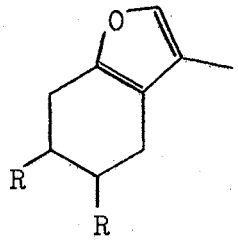
CHAPTER II

RESULTS AND DISCUSSION

The purpose of this study was to find several ways to effect the conversion of systems such as CIV into furan system CV.



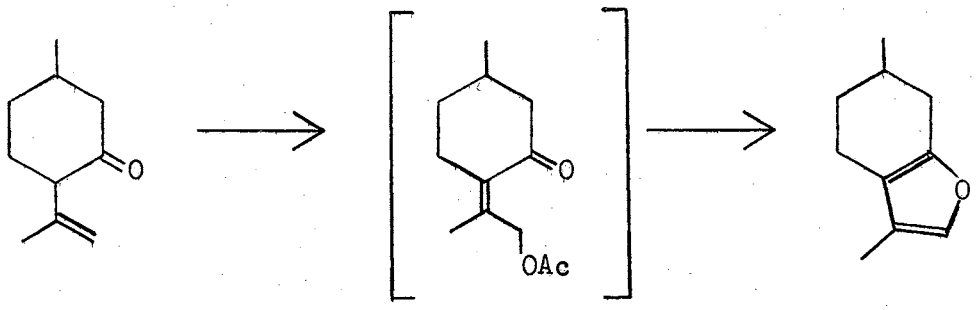
CIV



CV

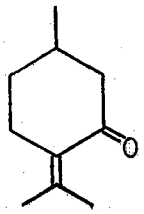
Pyrolysis Reactions

The reaction of mercuric acetate with isopulegone (XVI) which had been reported to give menthofuran (VIII) seemed to be a logical starting point (7). In the original work by Treibs (7), isopulegone was treated with mercuric acetate and the crude mixture was distilled to give the mixture of products containing menthofuran.

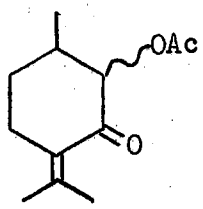


XVI XVII VIII

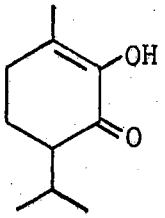
This reaction was repeated but the work-up was altered to prevent pyrolysis of the intermediate keto-ester. The work-up used was similar to that described by Reitsema (83) for the reaction of pulegone (II) with mercuric acetate. In the latter reaction, 2-acetoxypulegone (CVI) is the main product and Reitsema (83) found that in the presence of



II



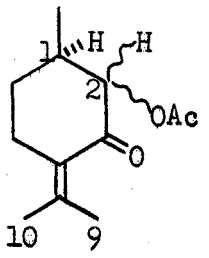
CVI



CVII

cis and trans

base, 2-acetoxypulegone was converted into diosphenol (CVII). Therefore, the work-up used in the isopulegone reaction involved adding the cooled reaction mixture to water, extracting the mixture with ether, and then washing the combined ether extracts with water until the acetic acid was removed. Drying and then distilling under high vacuum gave the product which was found to be identical with 2-acetoxypulegone obtained from pulegone by the procedure described by Reitsema (83). Identification was made by a comparison of the infrared and n.m.r. spectra and gas chromatograms. The gas chromatogram showed CVI to be a mixture of approximately equal amounts of two substances. An examination of the n.m.r. spectrum (Plate I) showed that XVII was not one of the substances and that the mixture consisted of the cis and trans isomers of 2-acetoxypulegone. The methyl protons of the isopropylidene group in both isomers appeared at δ 1.76 (C-10) and δ 1.84 (C-9). In both the cis and trans isomers the methyl protons of the isopropylidene group cis to the carbonyl group would be ex-



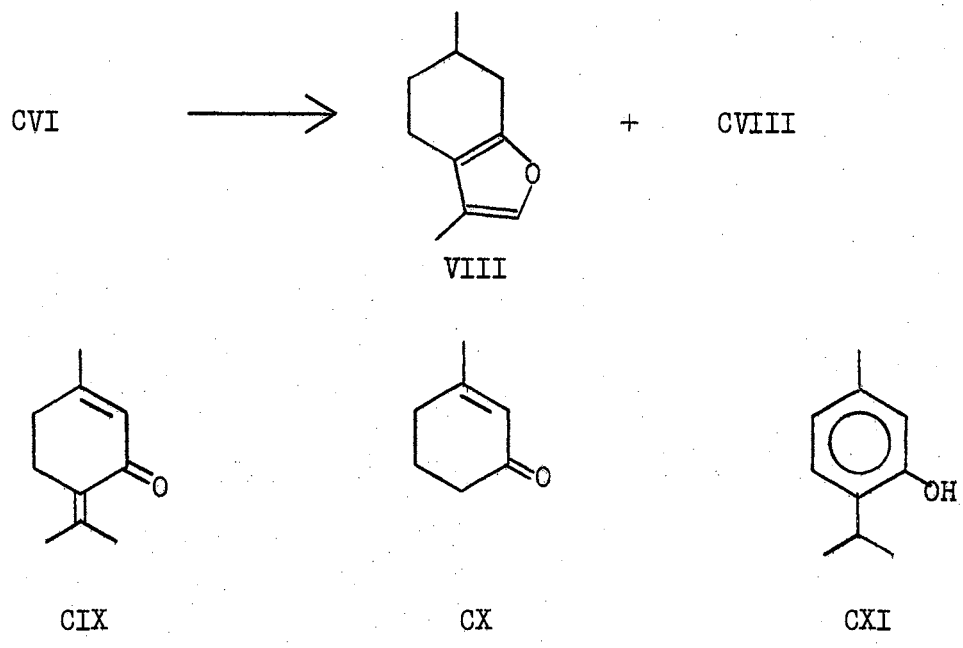
CVIa (cis, acetoxy group up)

CVIb (trans, acetoxy group down)

pected to show a paramagnetic shift compared with the methyl protons trans to the carbonyl group (84). The previously proposed intermediate XVII would be expected to show only one methyl group in this region of the n.m.r. spectrum. The protons of the C-1 methyl group in CVI appeared as a pair of doublets. The cis isomer (CVIa), in which the acetoxy group is cis to the C-1 methyl, showed a doublet centered at δ 0.96 (J = 7 c.p.s., 1.8 protons). The trans isomer (CVIb) showed the doublet centered at δ 1.05 (J = 5.5 c.p.s., 1.2 protons).

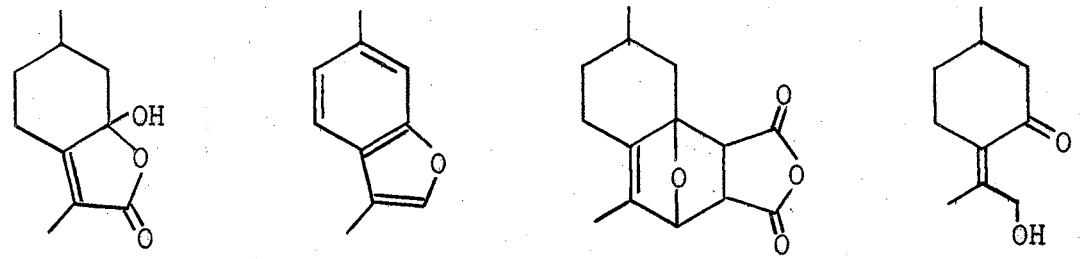
The C-2 proton in the cis isomer appeared as a doublet centered at δ 5.10 (J = 5.5 c.p.s., 0.6 protons) whereas in the trans isomer it appeared as a doublet centered at δ 4.64 (J = 10.5 c.p.s., 0.4 protons). The coupling constants of cis 1,2 protons are known to be smaller than those of the corresponding trans protons (84).

Pyrolysis of the mixture of cis- and trans-2-acetoxypulegone gave essentially optically pure menthofuran (VIII) in 43% yield and, in additon, a variable amount of another component CVIII was obtained which might have arisen from thermal cracking of piperitenone (CIX), the product of normal pyrolysis. The component CVIII was shown by



gas chromatography (v.p.c.) not to be 3-methyl-2-cyclohexenone (CX) or thymol (CXI).

The major pyrolysis product was identified as menthofuran by its optical rotation and a comparison of its infrared and n.m.r. spectra and gas chromatogram with those of authentic menthofuran prepared by a modified procedure of Treibs (4). Its identity was confirmed by a com-

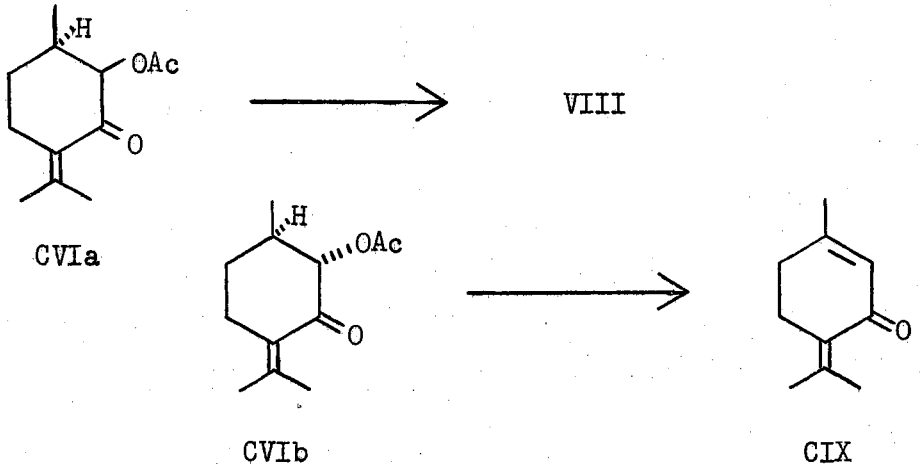


parison of the melting points of the autoxidation product CXII, the picrate of the benzofuran CXIII obtained by dehydrogenation with palladium on carbon, and the maleic anhydride adduct CXIV with the melting points of these derivatives reported in the literature (85,

86,87).

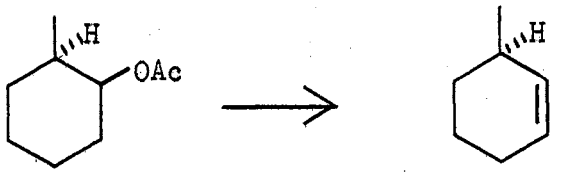
The lactol CXII, the autoxidation product of menthofuran, has long been suspected of being identical with a substance of the same melting point obtained from the air oxidation of pulegone (73,85). The identity of the two was shown by a comparison of the melting points, mixed melting points, and infrared spectra of the lactol obtained from air oxidation of menthofuran and from air oxidation of pulegone. As the air oxidation of pulegone progressed the specific rotation gradually changed from +27° to -4.12°, presumably due to the formation of the autoxidation product CXII which exhibits a negative rotation (85). Also, an intermediate such as 9-hydroxypulegone (CXV) has been suspected of being involved (85). Attempts to isolate such an alcohol from the reaction mixture were unsuccessful. Another product isolated was found to be β-methyladipic acid.

In view of the fact that the pyrolysis of cis- and trans-2-acetoxypulegone gave menthofuran and a product of unknown identity, it might be hypothesized that each of the isomers was pyrolyzing to



a different product. Thus, trans-2-acetoxypulegone (CVIb) might pyrolyze more easily than the cis (CVIa) and give a product of normal

pyrolysis, piperitenone (CIX). The reason for this stems from pyrolysis studies of acetates in which a "cis elimination" of acetic acid occurs to give an olefin, usually in yields of 75% or higher (88). For example cis-2-methylcyclohexyl acetate (CXVI) gives mainly 3-methylcyclohexene (CXVII) (88). Similarly the cis-2-acetoxypulegone (CVIa), in which the acetoxy group and hydrogen are trans, should be more difficult to pyrolyze in the normal manner and might be the isomer that leads to menthofuran. This would account for the apparent



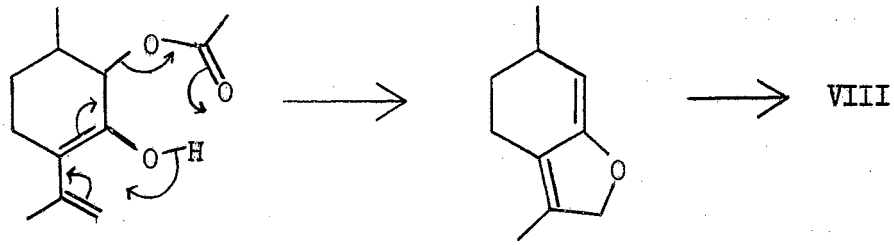
CXVI CXVII

low yield of menthofuran since if only half of the mixture of cis- and trans-2-acetoxypulegone were cis (60% indicated by n.m.r.), then the observed 43% yield would represent a yield of 86% based on CVIa.

The only way to unequivocally prove this hypothesis is to obtain a pure isomer of CVI. Attempts to separate the two isomers by column chromatography and by gas chromatography were unsuccessful. Also, an attempt to epimerize the mixture to a single isomer was not successful. If one isomer actually did pyrolyze more easily than the other, that is at a lower temperature, a separation might be effected in this way. By starting at lower temperatures, and pyrolyzing at increasingly higher temperatures, it was found that some menthofuran was formed at 315° but the unknown component CVIII was not detected until higher temperatures were reached. By analyzing the pyrolyzates by gas chromatography it

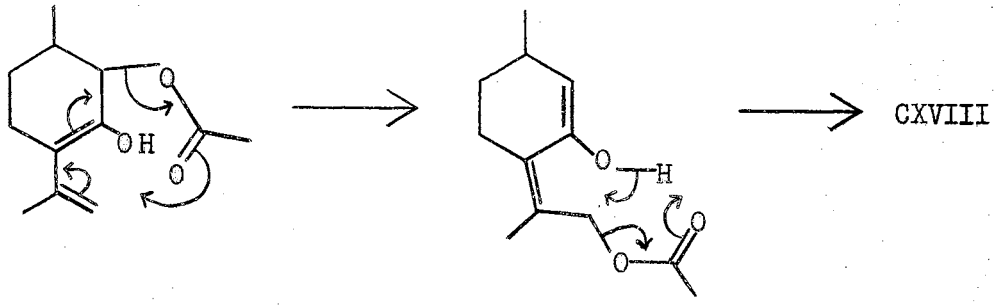
was also found that the ratio of unreacted isomers of 2-acetoxypulegone did not change, indicating that one isomer was not pyrolyzing in preference to the other. Also, it was found that CVIII was not formed upon pyrolyzing menthofuran at 450°, thereby indicating that CVIII was not a cracking product of menthofuran.

The pyrolysis of 2-acetoxypulegone to yield optically active menthofuran is unusual and cannot involve piperitenone (CIX) as an intermediate since this would yield racemic menthofuran. A mechanism



CXVIII

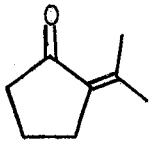
involving the intermediate CXVIII might be operative (89). Molecular models show that the distance between the carbonyl of the acetate and



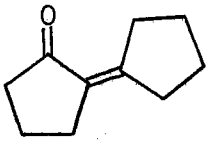
XVII

the C-9 hydrogens is small enough to allow interaction to occur (89). Another possible pathway to menthofuran might first involve a rearrangement to an intermediate such as 9-acetoxypulegone (XVII) which then might lose acetic acid as shown.

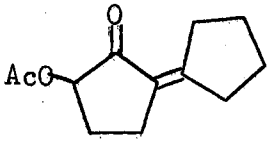
To test the generality of this unusual acetate pyrolysis, several compounds containing functional groups in an arrangement analogous to 2-acetoxypulegone were prepared. The base-catalyzed condensation of acetone with cyclopentanone gave 2-isopropylidenecyclopentanone (CXIX) and a smaller amount of the self-condensation product of cyclopentanone CXX as reported (90,91). Treatment of CXX with mercuric acetate gave a very small yield of impure acetate CXXI. The purity and quantity were so low that nothing definite could be concluded from its pyrolysis.



CXIX

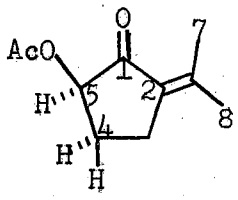


CXX



CXXI

However, the second compound obtained from the condensation reaction, CXIX, gave upon treatment with mercuric acetate the desired acetate



CXXII

CXXII in about 18% yield. Its structure was supported by its infrared and n.m.r. spectra. The infrared spectrum showed absorption at 1745 cm.$^{-1}$ (acetate carbonyl), 1712 cm.$^{-1}$ (α, β-unsaturated ketone in a five-membered ring), 1638 cm.$^{-1}$ (double bond), and 1235 cm.$^{-1}$ (carbon-oxygen-carbon frequency of the acetate ester). Its n.m.r. spectrum

showed the C-8 methyl protons of the isopropylidene group at δ 1.84 (3 protons), while those at C-7 appeared as a doublet centered at δ 2.18 (J = 1.1 c.p.s., 3 protons). The groups in a similar steroid system have been observed to exhibit similar chemical shifts as well as a similar coupling constant due to allylic coupling (92). The methyl of the acetate group appeared as a sharp singlet at δ 2.04 (3 protons). The proton at C-5 appeared as a quartet centered at δ 5.1 ($J_{5,4\text{-trans}}$ = 8 c.p.s., $J_{5,4\text{-cis}}$ = 12 c.p.s., 1 proton). The smaller coupling constant was assigned to the C_5, C_4-trans coupling on the basis of the probable dihedral angle between the two (84).

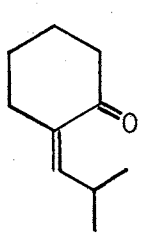
Pyrolysis of CXXII at 425° and then at 525° gave in each case a light yellow oil which showed only a trace of the characteristic furan absorption at 220 mμ while the infrared spectrum showed strong absorption due to a hydroxyl group plus bands characteristic of the starting material. It is interesting to note that Morel and Verkade (81) were also unsuccessful when attempting to prepare the δ-sultones of ketones CXIX and CXX which were to be pyrolyzed to the corresponding furans.

The reaction of mercuric acetate with mesityl oxide and α-ionone did not result in the formation of any usable amount of acetoxy ketones although starting material was consumed in each case. Other methods of introducing the acetoxy group on mesityl oxide were also found unsuccessful.

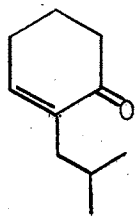
If an intermediate such as CXVIII were involved in the pyrolysis reaction leading to menthofuran, a suitably designed molecule might allow this type of intermediate to be trapped. For that purpose, <u>cis</u>- and <u>trans</u>-2-isobutylidenecyclohexanone (CXXIII) was prepared by

the reaction of isopropylmagnesium chloride with 2-hydroxymethylene-cyclohexanone, a reaction similar to that described by Dreiding and Nickel (93). The structure of CXXIII was supported by spectral analysis. The infrared spectrum showed the conjugated carbonyl group and the double bond.

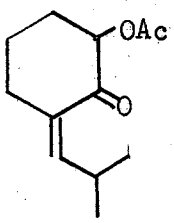
The n.m.r. spectrum showed CXXIII to be a mixture of isomers, one with the isopropyl group cis to the carbonyl group and the other trans. The vinylic proton signals of CXXIII appeared as a pair of triplets, one centered at δ 6.25 with a splitting of 2 c.p.s. and the other centered at δ 6.45 with a splitting of 2 c.p.s. The signals of the methyl protons of the isopropyl group appeared as a pair of doublets, one centered at δ 0.93 and the other centered at δ 1.05, each with a coupling constant of J = 6 c.p.s. Although the coupling constants of the vinylic proton signals are of the correct order of magnitude for allylic and homoallylic coupling, an unambiguous assignment would be difficult without having one of the isomers pure. Presumably, each set of vinylic and isopropyl proton signals would be assigned to a cis or trans isomer of CXXIII on the basis of the known deshielding of protons cis to a carbonyl group in such a system (84). Although the infrared and n.m.r. spectra are consistent with the



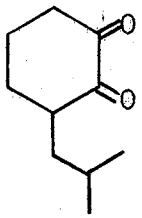
CXXIII



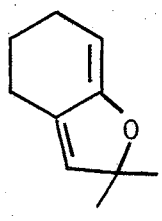
CXXIV



CXXV



CXXVI



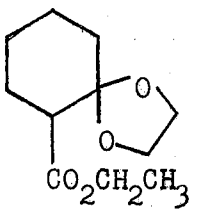
CXXVII

cis and trans

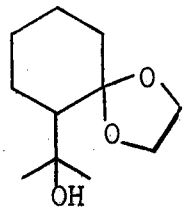
structure CXXIII, neither of these data allow a distinction to be made between CXXIII and its double-bond isomer CXXIV. However, the calculated ultraviolet absorption maximum for CXXIII is 242 mμ and the extinction coefficient should be below 10,000 while the corresponding constants for CXXIV are 237 mμ and above 10,000 (94). The observed values, λ_{max}^{EtOH} 244 mμ, ε 7330, clearly confirm structure CXXIII.

Treatment of CXXIII with mercuric acetate gave in low yield what was presumably the desired acetate CXXV as indicated by its infrared and n.m.r. spectra. However, it gave a positive ferric chloride test indicating the presence of some of the diosphenol CXXVI. The acetate fraction was shown by thin layer chromatography (t.l.c.) to be a mixture of five components. The small quantity precluded purification so the crude product was pyrolyzed directly. The ultraviolet spectrum of the pyrolyzate showed absorption only at the wavelength of the starting material, about 242 mμ. The expected diene CXXVII would have an absorption maximum at 234 mμ (94).

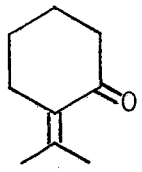
Finally, 2-isopropylidenecyclohexanone (CXXVIII) was prepared



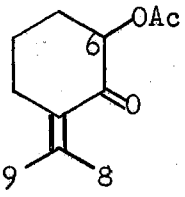
CXXIX



CXXX



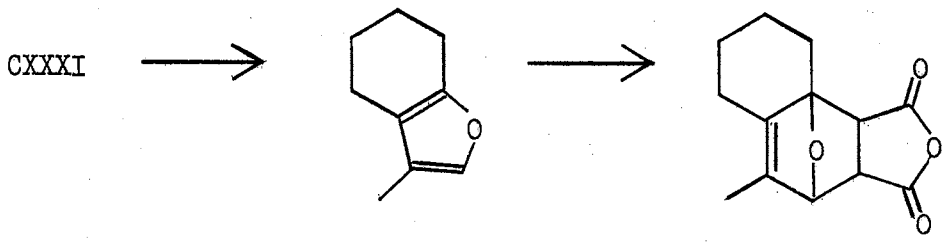
CXXVIII



CXXXI

according to a previously published procedure utilizing the reaction of methylmagnesium iodide with the ketal-ester CXXIX giving the ketal-alcohol CXXX (5). Removal of the ketone protecting group and then dehydration by distillation over iodine gave the known ketone CXXVIII

(5). Treatment with mercuric acetate gave the expected 6-acetoxy-2-isopropylidenecyclohexanone (CXXXI). Its structure was verified by its infrared and n.m.r. spectra and elemental analysis. The n.m.r. spectrum of CXXXI (Plate II) exhibited peaks at δ 1.85 (3 protons) assigned to the C-8 protons and δ 1.78 (3 protons) assigned to the C-9 protons, while the C-6 proton appeared as a quartet centered at δ 5.02 ($J_{6,5\text{-cis}}$ = 6.5 c.p.s., $J_{6,5\text{-trans}}$ = 11 c.p.s., 1 proton).

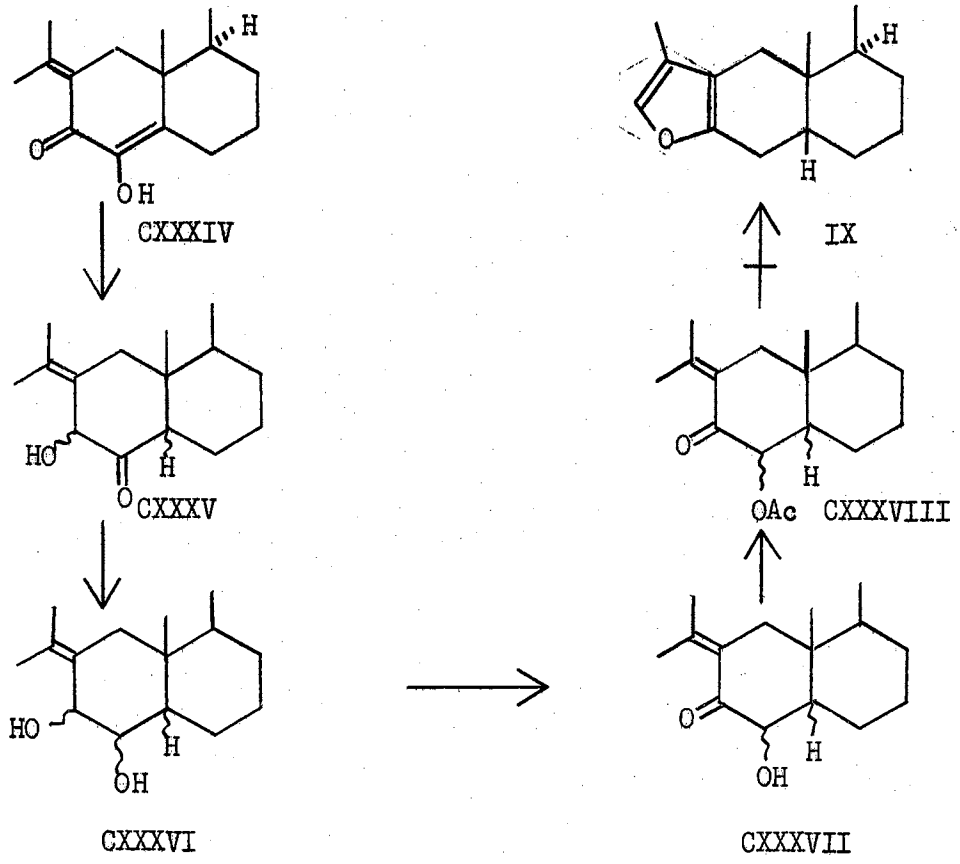


CXXXII CXXXIII

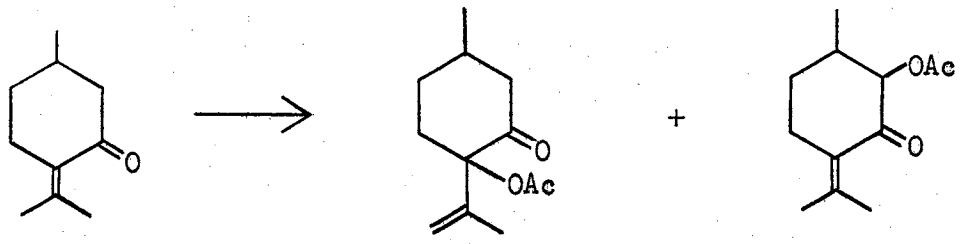
Pyrolysis of the acetate gave in low yield the expected 3-methyl-4,5,6,7-tetrahydrobenzofuran (CXXXII), which was identified by its infrared, n.m.r. and u.v. spectra which were very similar to those of menthofuran. The infrared spectra of menthofuran and the furan CXXXII had common absorption in the following regions: 735, 752, 1110, 1087, 1642, and 1565 $cm.^{-1}$. In the n.m.r. spectrum of the furan CXXXII, the aromatic proton appeared as a singlet at δ 6.88 and the methyl group appeared at δ 1.85. The structure was confirmed by the formation of a maleic anhydride adduct CXXXIII which gave the correct elemental analysis.

In order to try to extend the use of this unusual acetate pyrolysis, a conversion of hydroxyeremophilone (CXXXIV) to furanoeremophilane (IX) was considered. Two reductions of CXXXIV with lithium aluminum hydride presumably gave the ketol CXXXV and then

the diol CXXXVI. Oxidation with manganese dioxide gave an α,β-unsaturated ketone presumed to be CXXXVII which was acetylated to give the acetoxyketone CXXXVIII. The infrared and n.m.r. spectra are consistant with the structures given for the intermediates CXXXV through CXXXVIII. Although pyrolysis of CXXXVIII did not give the expected furan, the actual product obtained did not contain any carbonyl functions indicating that an unusual pyrolysis had occurred.



Lead tetraacetate is known to react with olefins and ketones to give allylic acetates and α-acetoxyketones (95,96). The reaction of lead tetraacetate with pulegone (II) in benzene gave in 46% yield 4-acetoxyisopulegone (CXXXIX) and only a trace of 2-acetoxypulegone (CVI).



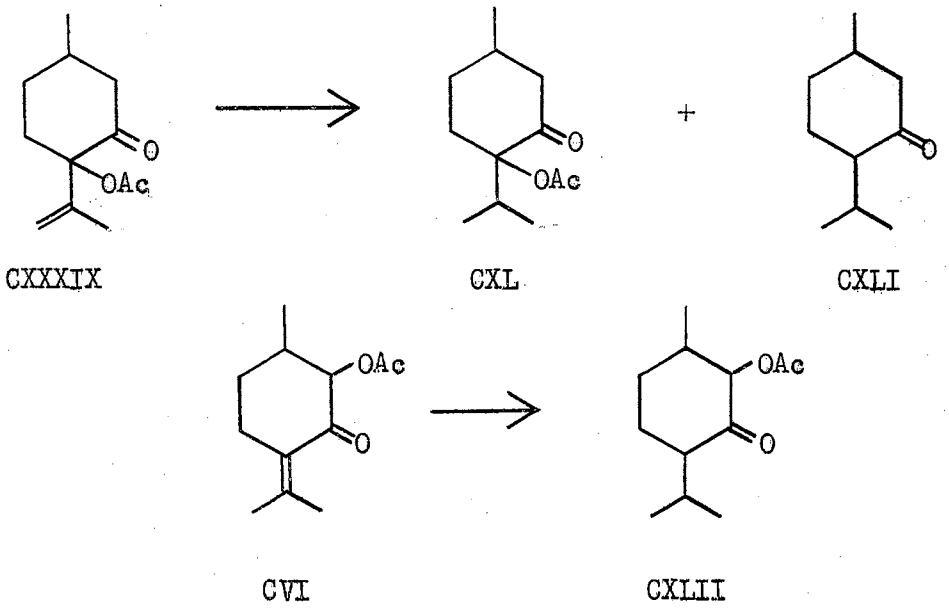
II CXXXIX CVI

Gas chromatography showed that the main acetate fraction was not CVI by a relatively large difference in retention times but did show CVI in trace amounts. The infrared spectrum of CXXXIX (Plate III) showed carbonyl bands at 1739 and 1710 cm.$^{-1}$ indicating that the α,β-unsaturated carbonyl was not present as in II and CVI. The n.m.r. spectrum of CXXXIX (Plate IV) clearly showed it to be a mixture of two isomers, cis and trans. The C-1 methyl signal appeared as a pair of doublets (J = 5.5 c.p.s.) of approximately equal intensity centered at δ 0.98 and 1.03. Also, there were two acetoxy methyl signals of equal intensity at δ 1.97 and 2.03 confirming the presence of two isomers. Although several different columns were tried, the mixture could not be resolved by v.p.c. The n.m.r. spectrum also showed a complicated multiplet in the region δ 4.95 - 5.20 integrating for two protons. Since the C-2 hydrogen of CVI had been found to appear at the same place as terminal methylene protons, an assignment of this multiplet could not be made at this point. The infrared spectrum of CXXXIX did not show an intense band at 890 cm.$^{-1}$, characteristic of a terminal methylene group, but only a rather weak one.

Hydrogenation of CXXXIX gave the dihydro derivative CXL and

menthone (CXLI). The formation of menthone indicated that no skeletal rearrangement had occurred in the conversion of II to CXXXIX. Analysis by v.p.c. showed CXL not to be identical to CXLII, the hydrogenation product of CVI.

The infrared spectrum of CXL showed carbonyl bands as before at 1740 and 1718 cm.$^{-1}$. The n.m.r. spectrum showed the absence of the



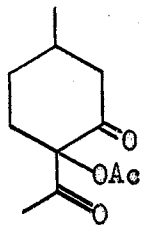
CXXXIX CXL CXLI

CVI CXLII

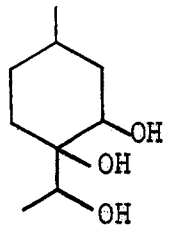
complicated multiplet at δ 4.95 - 5.20; thus this multiplet arose from olefinic protons and not from a proton attached to a carbon bearing an acetoxy group. The strong characteristic band in the infrared spectrum usually found for olefinic protons of the isopropenyl group at 890 cm.$^{-1}$ was absent in the spectrum of CXXXIX as previously mentioned but other cases are known in which this band is absent (97). This information suggested the structure CXXXIX (cis and trans) for the product of the reaction of lead tetraacetate with pulegone. The acetoxy group, being allylic and α to a carbonyl, would be expected to be susceptible to hydrogenoly-

sis and thus menthone was formed in the hydrogenation, even with rhodium on alumina catalyst which has been shown to be very mild with respect to hydrogenolysis (98).

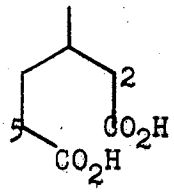
The structure of CXXXIX was proven as indicated below. Ozonolysis of CXXXIX gave formaldehyde and the diketone CXLIII. Formaldehyde was



CXLIII



CXLIV

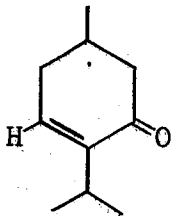


CXLV

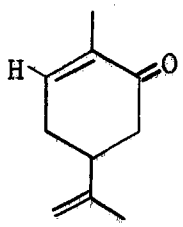
obtained in 33% yield as determined by its dimedone derivative. The diketone CXLIII gave a positive iodoform test and a negative ferric chloride test. The presence of the methyl ketone was confirmed by the n.m.r. spectrum. The diketone was then reduced with lithium aluminum hydride to give the triol CXLIV which was not directly isolated but was oxidized with potassium permanganate to give β-methyladipic acid (CXLV). This acid was identified by mixed melting point with an authentic sample prepared from pulegone (99). Both acids were converted into their dimethyl esters which gave identical infrared spectra and retention times in v.p.c. The isolation of this acid showed that the acetoxy group could not have been located at C-2 or C-5, two positions of pulegone that might be expected to be reactive toward lead tetraacetate.

Additional evidence that the acetoxy group was located at C-4 was provided by the pyrolysis of CXL which gave an α,β-unsaturated ketone CXLVI shown not to be pulegone (II) by comparison of the

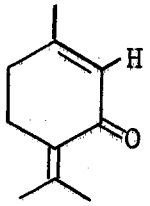
infrared and n.m.r. spectra and by v.p.c. The n.m.r. spectrum of CXLVI showed the vinylic proton at δ 6.61, as would be expected for a β-proton on an α,β-unsaturated ketone system and as found in carvone (CXLVII)



CXLVI



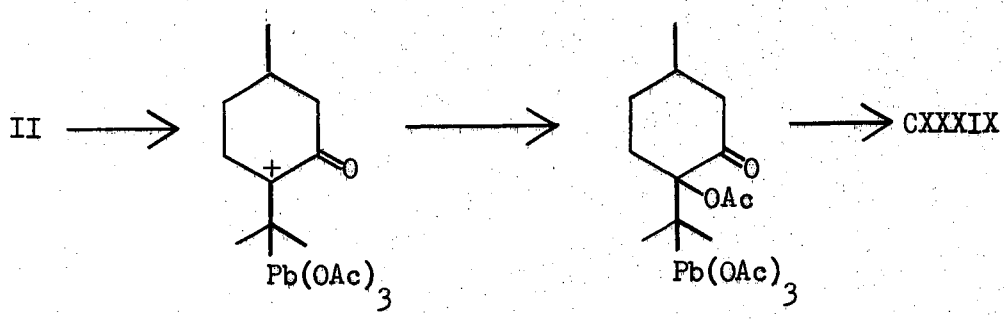
CXLVII



CIX

while in piperitenone (CIX) the α-proton of the α,β-unsaturated ketone system appeared at δ 5.87 (100).

The species $Pb^{+}(OAc)_3$ may be involved in the reaction of lead tetraacetate with olefins in benzene (101). In this case, any mechanism

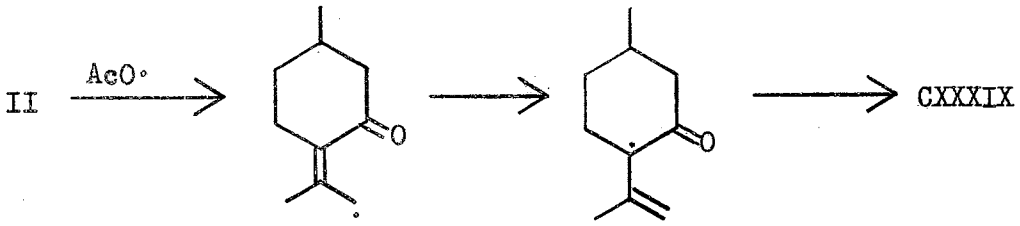


CXLVIII cis and trans

must involve an intermediate which would allow the formation of both cis and trans products. A mechanism involving the intermediate CXLVIII would meet this condition (102).

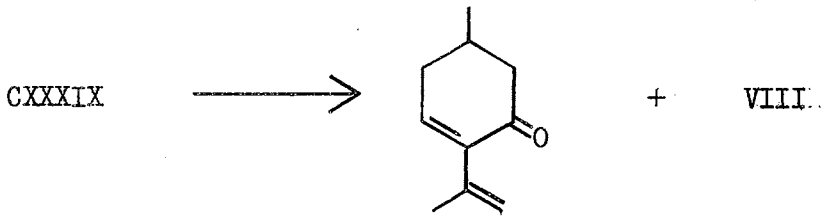
A free-radical mechanism may be involved in the reaction of lead tetraacetate with ketones in benzene solvent (96). If free-radicals are involved, the following mechanism involving the intermediate CXLIX, which would account for the two isomers produced , might be operative. The

detailed mechanism of this reaction has not been studied.



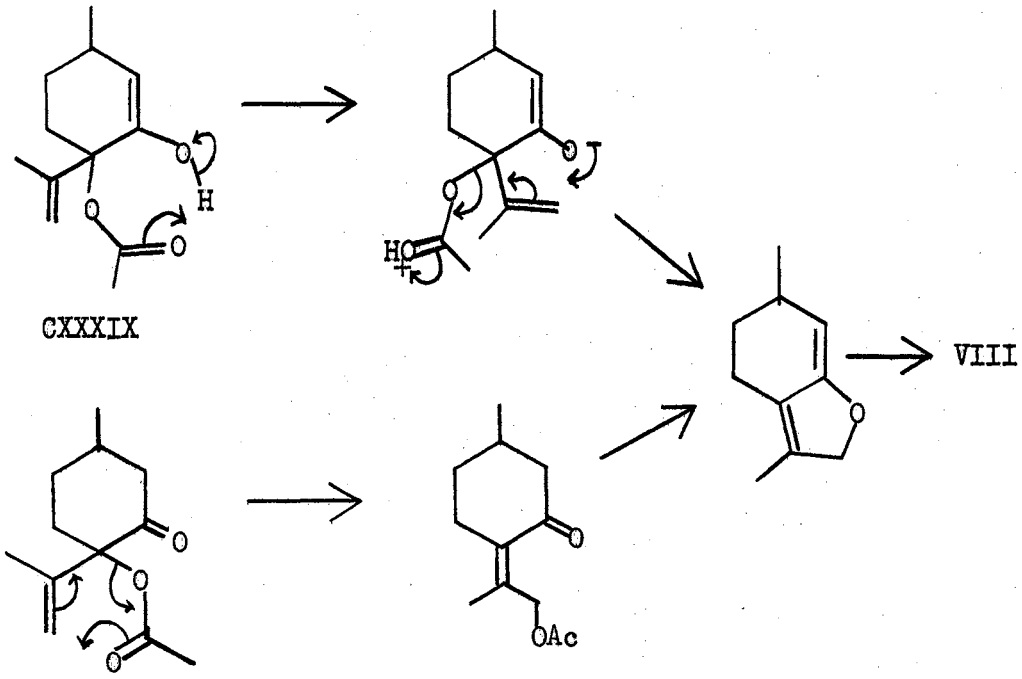
CXLIX

The pyrolysis of CXXXIX gave in 63% yield a mixture containing 56% of the expected diene CL and 44% menthofuran (VIII). Thus, pyrolysis of both 2-acetoxypulegone and 4-acetoxyisopulegone gave menthofuran. Menthofuran is apparently not produced from the diene CL since repyrolysis of the initially formed mixture of CL and VIII did not change the ratio of the two products. The formation of the



CL

diene CL apparently occurs by the usual pyrolysis mechanism. The mechanism shown below could account for the formation of menthofuran. It is conceivable that CXXXIX might undergo an allylic rearrangement to give 9-acetoxypulegone (XVII) which then would give menthofuran as suggested before (7).

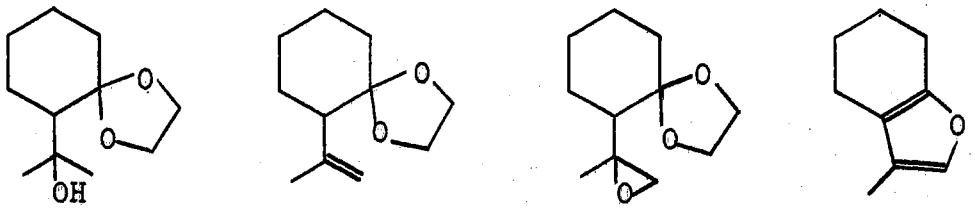


XVII

Other Reactions Leading to Furan Formation

As pointed out earlier, several reactions of certain masked 1,4-dicarbonyl compounds which resulted in furan formation have been reported (73,77). Also, as previously stated, perhaps the best way to introduce an isopropyl function adjacent to a ketone involves an intermediate such as the ketal-alcohol CXXX. This kind of a system is known to be capable of dehydration to the terminal olefin as in CLI (103). Formation of the epoxide CLII and then treatment with aqueous acid should result in removal of the ketone protecting group to give an intermediate ketone analogous to that in the isopulegone sequence (73). The corresponding furan CXXXII should then be formed directly from the ketal-epoxide CLII . To test this sequence the

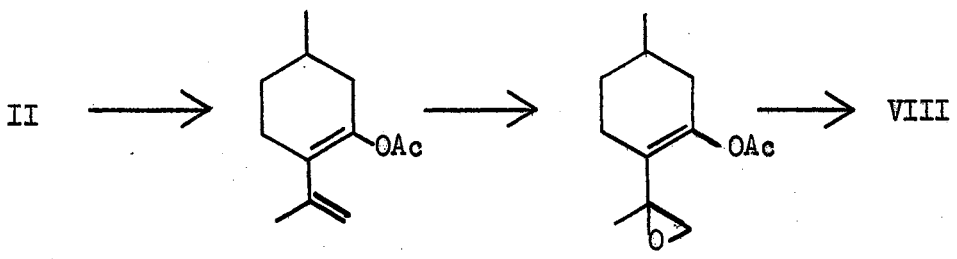
following reactions were performed. The known ketal-alcohol CXXX (5) was dehydrated with phosphorus oxychloride in pyridine to give the olefin CLI. The infrared spectrum of the olefin showed absorption maxima at 3085, 1641, and 892 cm.$^{-1}$. The n.m.r. spectrum showed the



CXXX CLI CLII CXXXII

vinylic protons as a singlet at δ 4.6, (2 protons) and the ketal-methylene hydrogens at δ 3.6 (4 protons) while the methyl group on the double bond gave a signal at δ 1.6 (3 protons). The structure was also supported by its elemental analysis. The olefin CLI was converted, by m-chloroperbenzoic acid, into the epoxide CLII which was not isolated as such but treated with aqueous sulfuric acid. Chromatography of the crude product gave the furan CXXXII in less than 10% yield. The infrared spectrum was identical to the infrared spectrum of CXXXII obtained by pyrolysis.

Another group which easily reverts to a ketone is the enol acetate group. Also, since the isopropylidene group is available through the sequence already mentioned as in the synthesis of pulegone (II) (5,6), its conversion into a furan system would be useful. The enol acetate could be useful only if it could be formed with rearrangement of the double bond to the terminal position. It was found that the double bond of pulegone (II) could be rearranged to the terminal position by preparing the enol acetate, 3-acetoxy-p-mentha-3,8-diene



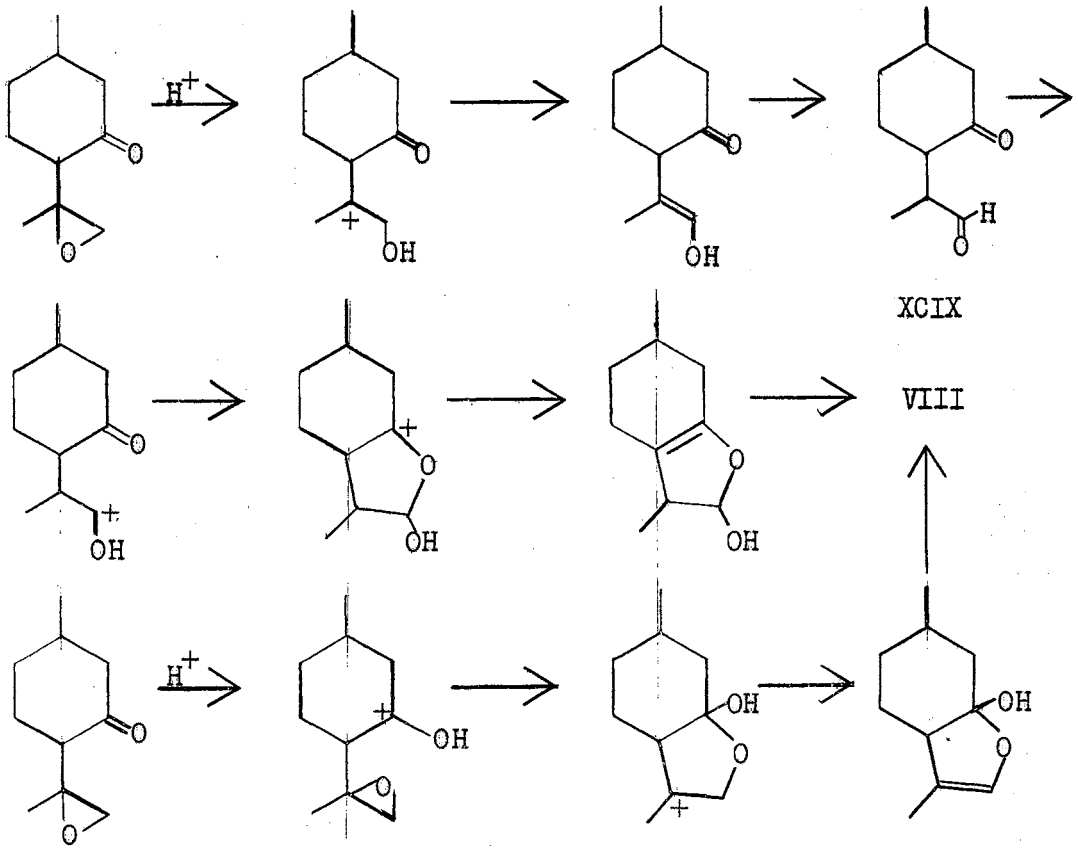
CLIII CLIV

(CLIII). The enol acetate was prepared by treating pulegone with acetic anhydride in carbon tetra chloride solvent in the presence of a catalytic amount of 70% perchloric acid. The structure CLIII was supported by the infrared spectrum showing absorption for the double bond at 3078, 1640, and 901 $cm.^{-1}$, the acetate carbonyl at 1755 $cm.^{-1}$, and the acetate carbon-oxygen-carbon linkage at 1220 $cm.^{-1}$. The n.m.r. spectrum showed absorption due to the terminal methylene, methyl on the double bond, secondary methyl, and acetate methyl. The enol acetate was converted to the epoxide by treatment with m-chloroperbenzoic acid. The infrared spectrum showed the loss of all three maxima due to the terminal double bond while the acetate carbonyl absorption remained at 1755 $cm.^{-1}$. The n.m.r. spectrum showed the acetate methyl, secondary methyl, methyl on the epoxide ring and two protons of the epoxide ring. Treatment of the epoxide with aqueous perchloric acid gave menthofuran which was identified by t.l.c. comparison with authentic menthofuran. On silica gel menthofuran was found to have R_f values of 0.64 (petroleum ether) and 0.77 (benzene).

The acid-catalyzed cyclization of 1,4-dicarbonyl compounds to furans has long been presumed to involve the intermediate formation of a mono- or dienol (104). It seems however, that to rationalize a

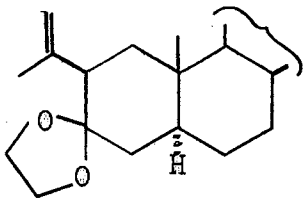
mechanism it is not necessary to postulate such enol intermediates for formation of furans from 1,4-dicarbonyl compounds. Neither is it necessary, for example, to postulate the 1,4-dicarbonyl compound XCIX as an intermediate in the formation of menthofuran from the epoxide CLIII.

Several similar mechanisms can be written and indeed several might be operative for the formation of a furan from a 1,4-dicarbonyl com-



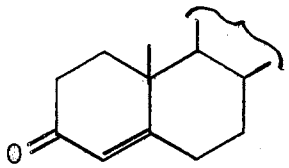
pound of any given form. Two such examples of mechanisms are given, the first involving the dicarbonyl compound XCIX.

The cholestane model CLV prepared according to Djerassi (103) was subjected to the same series of reactions as the olefin CLI but no furan was formed as determined by the ultraviolet absorption of the product.

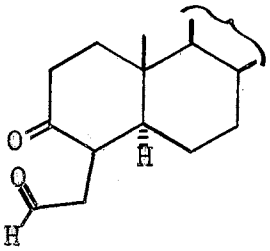


CLV

Another cholestane derivative, CLVI, was monoalkylated with allyl bromide by a procedure analogous to that described by Atwater (105). Reduction with sodium and alcohol and then reoxidation gave the saturated ketone. Ozonolysis followed by reductive work-up gave the intermediate keto-aldehyde CLVII which was not isolated but treated directly with boron trifluoride etherate for forty-eight hours. By following the reaction with t.l.c. the starting material was shown to disappear and two products appeared. Neither of the products proved to be a furan.



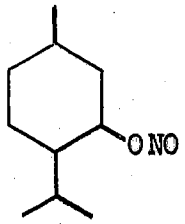
CLVI



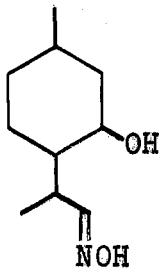
CLVII

Several reactions, brought about by the action of light, have been useful in introducing functional groups on relatively inert methyl groups (106). Therefore, the photolysis of menthyl nitrite (CLVIII) was investigated as another means of synthesizing menthofuran. The photolysis of menthyl nitrite (CLVIII) gave a low yield (less than 10%) of the oxime CLIX. Further oxidation gave a lactol, presumably CLX.

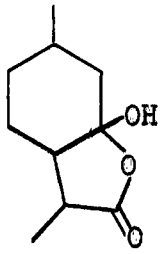
Other photolyses carried out on pulegone, isopulegone and other exam-



CLVIII



CLIX

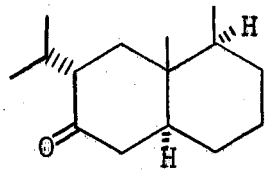


CLX

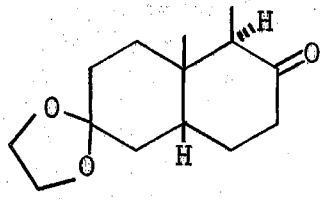
ples, did not lead to any identifiable products.

Efforts Concerned with the Synthesis of the Carbon Skeleton of Furanoterpenes

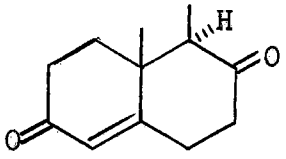
In the general approach considered for the total syntheses of the larger furanoterpenes, the first problem is the synthesis of the main skeleton of the molecule itself. In the case of compounds possessing the unusual non-isoprenoid eremophilane skeleton, several synthetic



CLXI



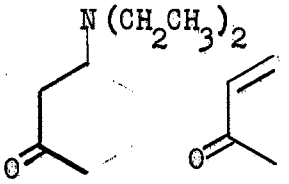
CLXII



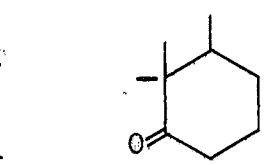
CLXIII

routes have been investigated and as a result the intermediates CLXI, CLXII, and CLXIII have been synthesized (107,108,109). Since each route is lengthy, the desirability of a shorter one is apparent. One potentially attractive such route to the basic decalone system was the Robinson ring closure of 2,3-dimethylcyclohexanone (CLXIV) with methyl vinyl ketone (CLXV). Since the intermediate carbanion CLXIVa might be expected to be attacked from the less hindered side, the product CLXVI

should have the desired stereochemistry at C-4 as shown.

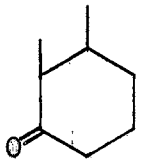


CLXVII

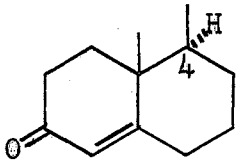


CLXV

CLXIVa

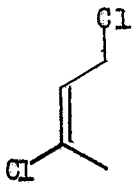


CLXIV

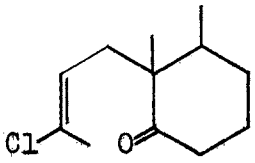


CLXVI

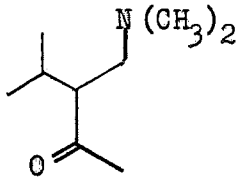
After many exploratory reactions involving the ketone CLXIV and the methiodide salt of 1-diethylamino-3-butanone (CLXVII) or methyl vinyl ketone itself, the best yield of product obtained was less than 15%. The product was also shown by n.m.r. to contain material of the



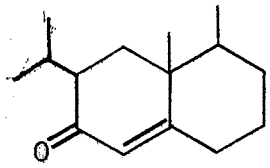
CLXVIII



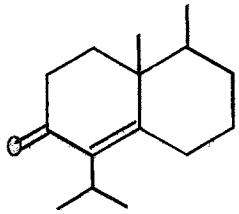
CLXIX



CLXX



CLXXI

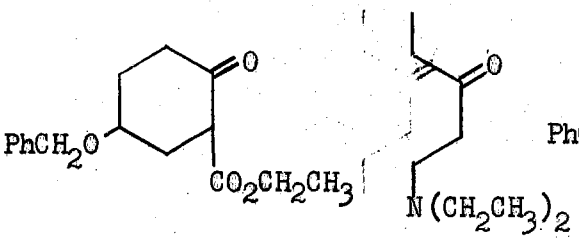


CLXXII

undesired stereochemistry at C-4. The condensation of the ketone CLXIV and 1,3-dichloro-2-butene (CLXVIII) to give the chloroketone CLXIX, and then cyclization by known methods gave a product identical to that obtained from the other condensations and in about the same

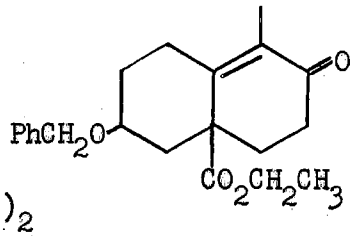
overall yield (110). The condensation of the methiodide salt of 1-dimethylamino-2-isopropyl-3-butanone (CLXX) with the ketone CLXIV while expected to give the decalone CLXXI was found to be unsuccessful. Alkylation of the ketone CLXVI with isopropyl iodide and potassium t-butoxide gave the ketone CLXXII instead of the desired ketone CLXXI.

An alternate approach which would be potentially valuable for the synthesis of members of the furanopetasin group involved the condensation of the keto-ester CLXXIII with the methiodide salt of 1-diethylamino-3-pentanone (CLXXIV) to give the decalone CLXXV. However, the



CLXXIII

CLXXIV

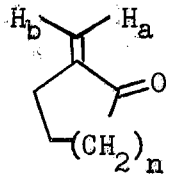


CLXXV

introduction of the bridgehead methyl by 1,4-addition of methylmagnesium iodide could not be effected. A similar approach by others also failed at the same step (108).

Some NMR Observations

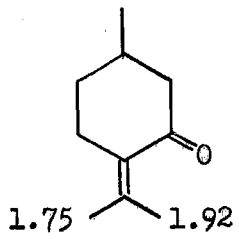
It is known that protons lying in the plane of a carbon-oxygen

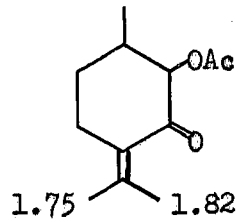


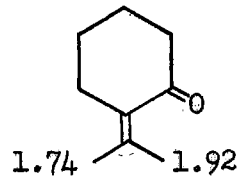
CLXXVI

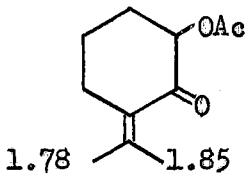
double bond are subjected to deshielding effects, and in their n.m.r. spectra the signals appear at a lower field (84). This is illustrated by Jackman (84) with several compounds of the general structure CLXXVI where the proton H_a is shifted down field with respect to H_b.

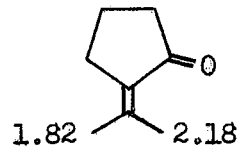
During the course of this investigation several compounds were encountered which also illustrate this effect. They are shown below with the assignments given in δ values relative to tetramethylsilane as an internal standard.

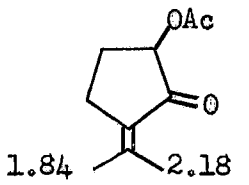












Summary

α,β-Unsaturated ketones such as pulegone (II) have been found to react with mercuric acetate in acetic acid to give α'-acetoxy-α,β-unsaturated ketones. Pyrolysis of these acetoxy ketones gives the

desired furan system. Since optically pure menthofuran (VIII) was obtained from the pyrolysis of CVI, the pyrolysis cannot proceed through an intermediate such as piperitenone (CIX) resulting from the "cis elimination" of acetic acid as in normal acetate pyrolysis. A mechanism for the formation of menthofuran from CVI has been suggested. The reaction was found to be limited to cases where the functional groups were part of a 6-membered ring as with CVI.

In contrast to mercuric acetate, lead tetraacetate in benzene was found to react with pulegone to give 4-acetoxyisopulegone (CXXXIX), a product of double-bond migration. Pyrolysis of the latter also gave the desired furan. Possible mechanisms for this novel pyrolysis were also discussed.

Several masked 1,4-dicarbonyl compounds could be cyclized to the furan but in lower yields.

Approaches to the synthesis of the non-isoprenoid eremophilane sesquiterpene skeleton were investigated.

CHAPTER III

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5 spectrometer; n.m.r. spectra were determined with the Varian A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal standard ($\delta = 0$). Gas chromatograms, unless otherwise indicated, were obtained with the Aerograph Hy-Fi gas chromatograph using a hydrogen flame detector and a column 1/8 in. x 5 ft. of 5% SE-30 on acid-washed Chromosorb W, with hydrogen and nitrogen flow rates of 30 ml./min. Thin layer chromatograms were run on silica gel and detection was with iodine vapor.

Reaction of Mercuric Acetate with Isopulegone (XVI).

(-)-Isopulegone was prepared from isopulegol acetate as follows: a solution of 15.5 g. of isopulegol acetate, 2.4 g. sodium, and 30 ml. of 95% ethanol was refluxed for 4 hrs. After cooling, the solution was adjusted to pH 6 with dilute sulfuric acid, and then extracted with ether. The ether extract, after washing with water and drying over anhydrous magnesium sulfate, gave on distillation 8.9 g. (73%) of isopulegol, b.p. 40-41° at 0.1 mm. Hg; ν_{max}^{film} 3450, 1643, 890 $cm.^{-1}$.

A solution of 8.6 g. of isopulegol in 50 ml. dry acetone was cooled in an ice bath and treated with Jones (111) reagent until the

brown color persisted. Water was added and the solution extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the extract was distilled to give 5.1 g. (60%) of isopulegone, b.p. 52-54° at 0.7 mm. Hg ; ν_{max}^{film} 1710, 1643, 891 cm.$^{-1}$; $[\alpha]_D^{25}$ + 4.33° (c 2.50 in ethanol). This optical rotation indicates the presence of 11% (+)-iso-isopulegone, $[\alpha]_D$ +144.4°, and 89% (-)-iso-pulegone, $[\alpha]_D$ -13.5° (112). The infrared spectrum and gas chromatogram of this product indicated the absence of any pulegone.

A mixture of 16.5 g. of isopulegone, 35 g. of mercuric acetate, and 50 ml. of glacial acetic acid was refluxed with stirring for 2 hrs. After cooling, the reaction mixture was poured into 400 ml. of water and the resulting mixture separated from the mercury and extracted 4 times with 50-ml. portions of ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. Fractional distillation of the residue gave (a) 4.65 g., b.p. 57-59° at 1 mm. Hg; (b) 1.2 g., b.p. 60-89° at 0.9 mm. Hg; and then (c) 2.67 g., b.p. 90-100° at 0.7 mm. Hg. Analysis by v.p.c. at 180° showed (a) to be a mixture of 80% pulegone and 20% isopulegone whose retention times were 1.25 and 0.95 min. respectively. Fraction (c) was an acetate whose infrared and n.m.r. spectra and gas chromatogram were found to be identical to those of 2-acetoxypulegone (CVI) obtained from the reaction of (+)-pulegone (II) with mercuric acetate according to Reitsema (83). 2-Acetoxypulegone (CVI) exhibited the following properties: b.p. 110-112° at 1.4 mm. Hg [reported (88) 102° at 4 mm. Hg]; $[\alpha]_D^{25}$ -14.46° (c 2.31 in ethanol) [reported (83) $[\alpha]_D^{25}$ -15.88]; λ_{max}^{EtOH} 252 mμ ε 6214 [reported (83) λ_{max}^{alc} 252 mμ, ε 6010]; ν_{max}^{film} 1738, 1690, 1615, 1232 cm.$^{-1}$; n.m.r. (Plate I) δ 0.96

(doublet, J = 5.5 c.p.s., 1.2 protons), 1.05 (doublet, J = 7 c.p.s., 1.8 protons), 1.76 (3), 1.84 (3), 2.07 (3), 4.64 (doublet, J = 10.5 c.p.s., 0.4 proton), and 5.10 (doublet, J = 5.5 c.p.s., 0.6 proton). Analysis by v.p.c. at 170° showed two components in approximately equal amounts with retention times of 5 and 5.3 min.

Pyrolysis of 2-Acetoxypulegone (CVI).

A solution of 4.85 g. of 2-acetoxypulegone in 25 ml. of benzene was slowly passed through a 1.5 cm. x 17 cm. pyrex column packed with 3/32 in. glass helices, at 450°; the solution was forced through the column under positive nitrogen pressure. V.p.c. analysis at 165° using a thermistor detector showed the pyrolyzate to contain two components in a ratio of 0.33 to 0.67 with retention times of 1.5 and 5.8 min. respectively. V.p.c. analysis of the pyrolyzate from another pyrolysis of CVI conducted under identical conditions as above showed CVIII to be less than 5% of the mixture of CVIII and VIII. The component in smaller amount, CVIII, was shown not to be thymol (CXI) or 3-methyl-2-cyclohexenone (CX) by v.p.c. comparison with authentic samples. The component of longer retention time and in larger amount was found to be menthofuran (VIII). Removal of the benzene at reduced pressure also resulted in the removal of CVIII and gas chromatographic analysis showed only the presence of menthofuran with minor impurities (less than 5%). The benzene eluent was found to contain 1.5 g. of menthofuran (43% yield) and no unchanged 2-acetoxypulegone. The pyrolysis of 5-ml. portions of a solution of 0.750 g. 2-acetoxypulegone in 15 ml. of benzene was conducted as above except that the temperature was varied. By v.p.c. analysis no menthofuran was detected at 210° and

both isomers of CVI were present in their original proportions. At 315° menthofuran was detected but no CVIII and no change in the isomer ratio of CVI was observed. At 348° both menthofuran and CVIII were present. Menthofuran was subjected to the same pyrolysis conditions as used for CVI and at a temperature of 460°. Analysis of the pyrolyzate by v.p.c. at 100° showed the absence of CVIII.

The menthofuran obtained from the pyrolysis of CVI had the following properties after distillation; λ_{max}^{EtOH} 220 mμ, ε 5852; $[\alpha]_D^{25}$ + 87.46° (c 1.87 in ethanol) (reported (87) $[\alpha]_D^{25}$ + 81° for natural menthofuran, and +92° for menthofuran prepared from pulegenol sulfonic ester according to Treibs (4)]; the infrared spectrum was identical in all respects with an authentic sample prepared by a modified procedure of Treibs (4); n.m.r. δ 1.07 (doublet, J = 5.5 c.p.s., 3 protons), 1.85 (doublet, J = 1 c.p.s., 3 protons), and 6.84 (1). The autoxidation product CXII (m.p. 186-187°) and maleic anhydride adduct CXIV (m.p. 132-133°) of the isolated menthofuran were identical in melting points to those previously reported (85,87).

The dehydrogenation of menthofuran was accomplished by heating 0.528 g. of menthofuran at 200° for 18 hrs. in the presence of 0.103 g. of 10% palladium on carbon in a nitrogen atmosphere. Chromatography on 60 g. of activity I acid-washed alumina and elution with petroleum ether (b.p. 60-90°) gave the product CXIII which was distilled to give 0.103 g. of a colorless oil showing one spot by t.l.c., R_f 0.714 (benzene); ν_{max}^{film} 806, 1042, 1091, 857 $cm.^{-1}$; n.m.r. δ 2.38 (3), 2.13 (doublet, J = 2 c.p.s., 3 protons) 6.8-7.4 (3); m.p. picrate, 76-77° [reported (86) 75-76°].

Preparation of Authentic Menthofuran (VIII).

Menthofuran was prepared by a procedure similar to that described by Treibs (4) except the work-up which was altered. A colorless mixture of sulfuric acid and acetic anhydride was prepared by slowly adding 100 g. of concentrated sulfuric acid at 0° to 200 g. of acetic anhydride at 0°. To this cold mixture was added, with stirring and over a period of 30 min., 100 g. of pulegone which had been cooled to 0°. The resulting dark brown solution was kept cold for 3 hrs., diluted with an equal volume of water, and stirred overnight. The precipitate was filtered and washed with water. Recrystallization from hot methanol gave 50 g. of the δ-sultone as white crystals, m.p. 83-86° [reported (4) 85°]; ν_{max}^{KBr} 3078, 1653, 1583, 1360, 1199, 774, 742 $cm.^{-1}$; n.m.r. δ 6.22 (1), 1.99 (doublet, J = 3 c.p.s., 3 protons), 1.08 (doublet, J = 6 c.p.s., 3 protons); λ_{max}^{EtOH} 273 mμ, ε 4640, 259 mμ, ε 3188, 253 mμ, ε 2000. Isolation of an additional 8.7 g. from the mother liquor brought the yield to 41%. According to the procedure of Treibs (4), a mixture of 42.8 g. of the δ-sultone and an equal weight of zinc oxide was heated in a distillation apparatus under a nitrogen atmosphere. The crude product which distilled was dried over anhydrous magnesium sulfate and redistilled to give 20 g. (66%) of menthofuran, b.p. 93-94° at 18-19 mm. Hg [reported (4) 80° at 18 mm. Hg].

Preparation of the Autoxidation Product CXII of Menthofuran.

Menthofuran was air oxidized by forcing dry air through 2 g. of menthofuran for 6 days. The resulting mixture was dissolved in ether

and extracted with 10% sodium hydroxide several times. The combined extracts were acidified with 10% hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. Recrystallization from acetone gave the product, m.p. 186-188° [reported (85) 188-189°].

Preparation of the Maleic Anhydride Adduct CXIV of Menthofuran.

To a solution prepared by dissolving 5 g. of maleic anhydride in 15 ml. benzene was added 1.66 g. of menthofuran. Heat was evolved and the whole mass solidified upon standing. Recrystallization from benzene gave the product, m.p. 128-130° (dec) [reported (87) 133°].

Air Oxidation of Pulegone (II).

Pulegone was subjected to air oxidation by forcing air through pulegone at the rate of 0.5 to 1 ml./sec. for 25 days at room temperature. Samples were taken every five days until a period of 25 days had elapsed whereupon a precipitate formed.

The infrared spectra of the samples showed an increasing absorption due to hydroxyl, a new carbonyl at 1725 $cm.^{-1}$, and a decrease in the absorption at 1680 $cm.^{-1}$ due to pulegone. The oxidation was also followed by optical rotation and ultraviolet absorption and these data are presented in Table I.

A portion of the resulting oxidation mixture from above was dissolved in ether and extracted with 10% sodium hydroxide several times. The combined basic extracts were acidified with 10% hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and

TABLE I

AIR OXIDATION OF PULEGONE (II).

Sample No.	Total Days	$[\alpha]_D^{25}$	λ_{max}^{EtOH}	ε
0	0	+27	252	4373
1	5	+ 7.8	252	3262
2	10	+ 6.21	252	2667
3	15	+ 3.1	250	2207
4	20	+ 0.36	248	1970
5	25	- 4.12	249	1901

the solvent removed. The resulting residue after recrystallization several times from methanol gave the product in low yield. The infrared spectrum was identical to that of the autoxidation product of menthofuran. The melting points of both products were 186-188° alone and on admixture. The change to a negative rotation was presumably due to the presence of the autoxidation product, $[\alpha]_D^{30}$ -61.6° (85).

A second portion of the oxidation reaction mixture was dissolved in ether and treated with excess diazomethane. The crude product (13.75 g.) was chromatographed on 500 g. of activity I acid-washed alumina. The first fractions, obtained by elution with benzene and chloroform, proved to be mainly pulegone. Elution with chloroform-methanol (5:1) gave a small fraction whose infrared spectrum and gas chromatogram were identical to those of dimethyl β-methyladipate. The preparation of this ester is described elsewhere in this chapter.

Further elution gave several large fractions exhibiting similar infrared spectra. These were combined and distilled giving a small quantity of distillate: ν_{max}^{film} 3465, 1730, 1658 cm.$^{-1}$, indicating a methyl ester was present. The distillate was dissolved in ether and extracted with 10% sodium hydroxide to remove any autoxidation product that might be present. The ether solution was then washed with water and dried. The infrared spectrum of the residue after removal of solvent was unchanged indicating that the molecule contained an ester, hydroxyl, and an α,β-unsaturated ketone and was therefore not the sought 9-hydroxypulegone (CXV).

A third portion of the 25-day oxidation reaction mixture was dissolved in ether, extracted with 10% sodium hydroxide, the ether solution washed with water, dried, and solvent removed to give a product whose infrared spectrum showed ν_{max}^{film} 3510, 1725, 1660 cm.$^{-1}$. The product was treated with acetic anhydride and pyridine overnight. The resulting reaction mixture was dissolved in ether, extracted with 10% hydrochloric acid, washed with water, and dried. The resulting residue after evaporation of solvent did not show signals in its n.m.r. spectrum due to protons attached to a carbon bearing a hydroxyl group indicating that the hydroxyketone CXV was not present.

Attempted Base Epimerization of 2-Acetoxypulegone (CVI).

A solution of 2-acetoxypulegone (0.2 g.) in 25 ml. of benzene was treated with sodium hydride (0.2 g.) with stirring for 7 hrs. at room temperature. The resulting mixture was slowly added to 100 ml. of dilute acetic acid, the solution extracted with ether, the combined ether extracts washed with water and dried, and after removal of

solvent, distilled. Infrared spectra of the starting mixture and the product were identical. The n.m.r. spectrum of the product shows the presence of two doublets at δ 5.10 and 4.64 assigned to the proton at C-2 and corresponding to the two isomers. V.p.c. analysis at 135° showed both isomers in about equal proportions as described for the initial mixture, with retention times of 5.25 and 5.8 min.

Reaction of Mercuric Acetate with 2-Isopropylidenecyclopentanone (CXIX) and Pyrolysis of CXXII.

The ketone CXIX was prepared by the base-catalyzed condensation of acetone with cyclopentanone (90,91). A mixture of 35 g. of the ketone CXIX, 85.5 g. of mercuric acetate, and 70 ml. of glacial acetic acid was refluxed with stirring for 1½ hrs. Work-up as with pulegone and then distillation gave an acetate fraction which was redistilled to give 6.84 g. (18% yield) of CXXII, b.p. 85-86° at 0.35 mm. Hg; ν_{max}^{film} 1745, 1712, 1638, 1235 $cm.^{-1}$; n.m.r. δ 1.84 (3), 2.18 (3), (doublet, J = 3 c.p.s., 3 protons), 2.04 (3), and 5.1 (quartet, $J_{5,4\text{-trans}}$ = 8 c.p.s., $J_{5,4\text{-cis}}$ = 12 c.p.s., 1 proton).

The pyrolysis of 2 g. of CXXII under conditions identical to those described for 2-acetoxypulegone (CVI) at 425° gave 0.15 g. of a yellow oil whose infrared and ultraviolet spectra were characteristic of the starting material. Pyrolysis at 525° gave, with much charring, a yellow oil whose infrared and ultraviolet spectra were less characteristic of the starting material but clearly not those expected of a furan.

Oxidation of α-Ionone with Mercuric Acetate.

A mixture of 55 g. of α-ionone (Givaudan-Delawanna), 85.5 g. of mercuric acetate, and 70 ml. of glacial acetic acid was refluxed for 2 hrs. The mixture turned black as usual. The mixture was added to 500 ml. of water and the resulting mixture extracted with ether and the combined extracts washed with water until the washings were free of acetic acid and color. The extracts were dried, the solvent removed, and the residue distilled giving only starting material and a residue.

Some Reactions of Mesityl Oxide.

A mixture of 37 g. of freshly distilled mesityl oxide, 85.5 g. of mercuric acetate, and 70 ml. of glacial acetic acid was refluxed for 2.5 hrs. The work-up was identical to that described above and gave on distillation only starting material and residue.

Following conditions established by Glazier (113) in the steroid field, a mixture of 10 g. of mesityl oxide, 23 g. of cupric bromide, and 50 ml. of tetrahydrofuran was refluxed for 2 hrs. The reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed. The resulting residue was shown by infrared analysis not to contain any unsaturated ketone.

Following the procedure of Ringold and Stork (114) with examples from the steroid field, a mixture of 10 g. of mesityl oxide, 23 g. of iodine, 5.7 g. of calcium oxide, and 100 ml. of 50% methanol-tetrahydrofuran was stirred for 2 hrs. at room temperature. The reaction mixture was diluted with water, extracted with ether, and the combined

ether extracts washed with water and dried. Most of the solvent was removed on a steam bath giving a light yellow solution. Further heating caused rapid decomposition to a black oil. The light yellow ethereal solution from another run was diluted with 75 ml. of 95% ethanol and 45 ml. of water, and then 15 g. of potassium acetate added. The resulting mixture was refluxed for 3 hrs., diluted with water, and extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed. Distillation of a small quantity gave the product expected to be α-acetoxymesityl oxide which rapidly decomposed on standing; ν_{max}^{film} 1755, 1705, 1638, 1240 cm.$^{-1}$. Since the infrared spectrum indicated the absence of a conjugated carbonyl or terminal double bond in the product, it was not investigated further.

Preparation of 2-Isobutylidenecyclohexanone (CXXIII).

Following a procedure of Dreiding and Nickel (93) for the preparation of 2-ethylidenecyclohexanone, a mixture of 20 g. of 2-hydroxymethylenecyclohexanone, prepared according to Ainsworth (115), in 200 ml. of dry ether was cooled to -10° and treated with isopropylmagnesium chloride prepared from 26 g. isopropyl chloride and 21 g. of magnesium turnings in 500 ml. of dry ether. The temperature was maintained below 0° during the addition which took 1 hr. The stirred mixture was kept at -10° for another hr., treated with 10% hydrochloric acid until the salts dissolved, and the mixture extracted with ether. The combined ether extracts were washed several times with 10% sodium hydroxide, and then with saturated sodium chloride, dried with anhydrous sodium sulfate, and the solvent removed. Distillation gave the desired product in approximately 30% yield, b.p. 51-52° at 0.15 mm. Hg;

[reported (116) 97-99° at 5 mm. Hg]; ν_{max}^{film} 1688, 1612 cm.$^{-1}$; λ_{max}^{EtOH} 244 mμ, ε 7630; n.m.r. δ 6.45 (triplet, splitting of 2 c.p.s., 0.5 protons), 6.24 (triplet, splitting of 2 c.p.s., 0.5 protons), 0.93 (J = 6 c.p.s., 3 protons), 1.05 (doublet, J = 6 c.p.s., 3 protons); η_D^{25} 1.4800 [reported (116) 1.4808].

Reaction of CXXIII with Mercuric Acetate and Pyrolysis of the Acetate CXXV.

A mixture of 31.5 g. of CXXIII, 63 g. of mercuric acetate, and 52 ml. of glacial acetic acid was stirred and refluxed for 3 hrs. During this time the mixture turned an intense blue and deposited elemental mercury. Work-up as with pulegone and distillation gave 16.5 g. of starting material and about 1 g. of a crude acetate fraction showing five components by t.l.c. in benzene, R_f 0.071, 0.27, 0.39, 0.46, and 0.58, with the starting material exhibiting R_f 0.27. The crude acetate fraction gave b.p. 80° at 0.1 mm. Hg; ν_{max}^{film} 1725, 1685, 1615, 1234 cm.$^{-1}$; n.m.r. spectrum was complicated but showed some signals due to acetate methyls. The mixture gave a positive ferric chloride test. The material could not be purified by further small-scale fractional distillation.

Pyrolysis of the acetate fraction under conditions identical to those above and at a temperature of 510° followed by a similar work-up and then distillation gave a yellow oil which showed by infrared and ultraviolet analysis no evidence of diene formation.

Reaction of 2-Isopropylidenecyclohexanone (CXXVIII) with Mercuric Acetate.

A mixture of 8 g. of the ketone CXXVIII, prepared according to the procedure of Mukherji and co-workers (5), 18 g. of mercuric acetate, and 20 ml. of glacial acetic acid was refluxed for 20 min. By this time elemental mercury had deposited and the mixture was allowed to cool and then worked up as usual. Distillation gave 1.8 g. of starting material and 1 g. of acetate CXXXI, b.p. 90-100° (bath temperature) at 0.5 mm. Hg; ν_{max}^{film} 1750, 1699, 1626, 1240 cm.$^{-1}$; n.m.r. (Plate II) δ 1.85 (3), 1.78 (3), 5.02 (quartet, $J_{6,5\text{-cis}} = 6.5$ c.p.s., $J_{6,5\text{-trans}} = 11$ c.p.s., 1 proton). V.p.c. analysis at 180° showed a single peak, retention time 1.25 min.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.25; H, 8.24.

Pyrolysis of 6-Acetoxy-2-isopropylidenecyclohexanone (CXXXI).

A solution of 0.755 g. of the acetate CXXXI in 15 ml. of benzene was pyrolyzed at 450° under the same conditions as before. Analysis of the pyrolzate by v.p.c. at 150° showed a single peak, retention time 0.5 min. The benzene solution was washed with 10% sodium bicarbonate, water, and then dried over anhydrous magnesium sulfate. Distillation, after removal of solvent, gave 0.140 g. (27%) of 3-methyl-4,5,6,7-tetrahydrobenzofuran (CXXXII) as a colorless oil, b.p. 120° (bath temperature) at 30 mm. Hg; ν_{max}^{film} 1650, 1572, 1100, 896, 732 cm.$^{-1}$; λ_{max}^{EtOH} 223 mμ, ϵ 4818; n.m.r. spectrum δ 1.85 (3) 6.88 (1).

The maleic anhydride adduct CXXXIII was prepared by adding the furan to a saturated benzene solution of maleic anhydride and allowing to stand. Recrystallization from benzene gave m.p. 140-144° (dec.).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.03. Found: C, 66.72;

H, 6.10.

Reductions of Hydroxyeremophilone (CXXXIV).

To a solution of 1.0009 g. of hydroxyeremophilone in 75 ml. of dry ether was added 0.5 g. of lithium aluminum hydride. The mixture was refluxed for 3 hrs.; the excess hydride was destroyed by successively adding wet ether and then a saturated solution of ammonium chloride. The mixture was then extracted with ether, the combined extracts dried over anhydrous magnesium sulfate, and the solvent removed giving crude ketol CXXXV, ν_{max}^{film} 3440, 1712, 1680 (weak), cm.$^{-1}$. The crude material gave a slight coloration with ferric chloride indicating some had rearranged to a diosphenol. Since distillation resulted in further rearrangement to the diosphenol as evidenced by its infrared spectrum, a further reduction was performed without purification. The second reduction was performed exactly as above to give 0.866 g. (86%) of the crude diol CXXXVI, ν_{max}^{film} 3410, 1712 (weak) cm.$^{-1}$; n.m.r. spectrum showed δ 1.8 due to methyls on a double bond. The weak carbonyl absorption was presumably due to the ketone resulting from the reduction of the contaminating diosphenol.

Oxidation of the Diol CXXXVI.

The crude diol from above was dissolved in 100 ml. of petroleum ether (b.p. 60-90°) and treated with 10 g. of manganese dioxide prepared according to Attenburrow and co-workers (117). After stirring for 6 hrs. the mixture was filtered, the solid washed with acetone, and the solvent removed giving 0.565 g. (65%) of the ketol CXXXVII, ν_{max}^{film} 3430, 1712, 1660 cm.$^{-1}$.

Acetylation of the Ketol CXXXVII.

The crude ketol from above was treated with 10 ml. of acetic anhydride and 10 ml. of pyridine with stirring for 22 hrs. at room temperature. The mixture was diluted with ether, washed with water several times, dried over anhydrous magnesium sulfate and the solvent removed giving 0.420 g. of the crude acetate CXXXVIII, ν_{max}^{film} 3440 (weak), 1728, 1660, 1242 cm.$^{-1}$; n.m.r. spectrum showed methyl signals at δ 1.7-1.8 indicating the presence of an isopropylidene group.

Pyrolysis of the Acetate CXXXVIII.

The crude acetate from above was dissolved in 10 ml. of spectrograde cyclohexane and pyrolyzed at 400° under the same conditions used for the other pyrolyses. The crude pyrolyzate was reduced in volume on a rotary evaporator and the residue chromatographed on 10 g. of activity I acid-washed alumina. Elution with cyclohexane gave an oil, λ_{max}^{EtOH} 240-245; ν_{max}^{film} 2940, 1450, 1380 (weak), 755 (weak), 743 (weak) cm.$^{-1}$; n.m.r. δ 1.3 and 0.95. It may be concluded from these data that no furan was formed. The pyrolysis is of interest since the product lacked carbonyl absorption in the infrared indicating that an unusual acetate pyrolysis occurred.

Preparation of cis- and trans-4-Acetoxyisopulegone (CXXXIX).

A solution prepared by adding 15.2 g. of pulegone and 55 g. of lead tetraacetate to 150 ml. of dry benzene was refluxed until it gave a negative starch-iodide test (approximately 2 hrs.). After cooling, the benzene solution was washed with water until the wash water was neutral to litmus paper and the benzene layer was then dried over

magnesium sulfate and concentrated with a rotary evaporator. Fractional distillation of the residue gave (a) 6.6 g., b.p. 25-75° at 0.5 mm. Hg; then (b) 5.41 g., b.p. 75-90° at 0.5 mm. Hg. Gas chromatography of (b) showed only about 5% of CVI, the remainder being CXXXIX. The retention times of CVI and CXXXIX were 3 and 2 min. respectively at 180°. Under the conditions used in the v.p.c., an authentic sample of CVI gave a double peak centered at 3 min., whereas CXXXIX gave a single sharp peak at 2 min. Several other v.p.c. columns also failed to resolve CXXXIX into its two components. However, the n.m.r. spectrum of CXXXIX (Plate IV) showed that it was an approximately equal mixture of cis and trans isomers by the appearance of two acetoxy signals of almost equal intensity at δ 1.97 and 2.03 and by the appearance of a pair of doublets for the C-1 methyl group. Redistillation of fraction (b) gave the analytical sample of CXXXIX, b.p. 87° at 0.5 mm. Hg; ν_{max}^{film} 3095, 1745, 1700, 1648, 1239, and 895 (very weak and broad) cm.$^{-1}$ (Plate III).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.34; H, 8.86.

CXXXIX (0.5 g.) was added to a solution prepared by dissolving 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate in 10 ml. of water and ethanol was added until the turbid solution became clear. The solution was heated on the steam bath for 3 min., then cooled overnight. The solid precipitate was recrystallized from ethanol-water and gave m.p. 205-208° (dec.). The elemental analysis indicated that, in forming the semicarbazone, CXXXIX had lost the elements of acetic acid.

Anal. Calcd. for $C_{11}H_{17}N_3O$; C, 63.74; H, 8.27. Found: C, 63.37; H, 8.20.

Hydrogenation of CXXXIX and CVI.

CXXXIX (1 g.) in 30 ml. of absolute ethanol was hydrogenated in the presence of 0.1 g. of 10% palladium on charcoal at atmospheric pressure and room temperature until hydrogen uptake appeared to cease. The catalyst was removed by filtration and the solvent was removed with a rotary evaporator. Distillation gave a lower-boiling fraction (bath temperature of 50-70° at 0.5 mm. Hg) which was shown to be mostly menthone (CXLI) by v.p.c., and a higher-boiling fraction (bath temperature of 80-95° at 0.5 mm. Hg) which was rich in CXL. The analytical sample of CXL was obtained by preparative v.p.c. using an Aerograph Autoprep with a column $\frac{1}{4}$ in. x 10 ft. of 10% silicone rubber on Chromosorb P at 150° with a flow rate of 88 ml./min.; ν_{max}^{film} 1748, 1724, and 1240 $cm.^{-1}$. Hydrogenation with 5% rhodium on alumina gave similar results.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 68.13; H, 9.47.

CVI was hydrogenated in a similar manner to give CXLII. V.p.c. comparisons of CXL and CXLII using a $\frac{1}{4}$ in. x 10 ft. Craig polyester succinate column at 130° with a thermal detector and a helium flow rate of 62 ml./min. showed that individually and on admixture CXL and CXLII had retention times of 12.3 and 14 min., respectively.

An authentic sample of l-menthone was prepared by Jones (111) oxidation of l-menthol and it was identical by infrared and v.p.c. with CXLI isolated as described above.

Preparation of Authentic l-Menthone (CXLI).

A mixture of 39.1 g. of l-menthol (Mallinckrodt) in 100 ml. of

acetone was cooled to 15° and treated with an excess (80 ml.) of the Jones (111) reagent. The mixture was stirred vigorously during the addition which lasted 7 hrs. The mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and distillation after removal of solvent gave 32 g. (83%) of menthone, b.p. 129-130° at 72 mm. Hg [reported (118) b.p. 81° at 10 mm. Hg]; ν_{max}^{film} 1710 cm.$^{-1}$; showing one spot by t.l.c., R_f 0.35 (benzene).

Pyrolysis of CXL.

A solution containing 0.2 g. of CXL in 10 ml. of benzene was forced through a 1.5 cm. x 17 cm. Vycor column packed with 3/32 in. glass helices and heated to a temperature of 300° under nitrogen pressure (77 ml./min.). The crude pyrolyzate was washed with 10% sodium bicarbonate, then water, and finally dried over anhydrous magnesium sulfate. Removal of the benzene with a rotary evaporator and distillation of the residue gave an impure product consisting mainly of an α,β-unsaturated ketone (ν_{max}^{film} 1675 cm.$^{-1}$), presumably CXLVI, which when compared by v.p.c. at 100°, (H_2 and N_2 flow rates of 20 ml./min.) with pulegone (II) and menthone (CXLI) alone and on admixture gave the following retention times: 3.5 (CXLI), 3.8 (CXLVI), and 4.7 min. (II). The n.m.r. spectrum of CXLVI showed an olefinic proton at δ 6.61; carvone is reported to show its analogous vinylic proton β to the carbonyl group at δ 6.75, whereas piperitone shows its vinylic proton α to the carbonyl group at δ 5.87.

Ozonolysis of CXXXIX and Conversion of CXXXIX to β-Methyladipic Acid CXLV.

A stream of oxygen containing 3% ozone was passed through a solution prepared by dissolving 1.14 g. of CXXXIX in 15 ml. of methylene chloride at -70° until the characteristic blue color persisted. The solution was then stirred with 0.2 g. of zinc dust and 15 ml. of water at room temperature for 3 hrs. After filtration, the organic layer was washed with water several times, a saturated methanolic solution of dimedone was added to the combined aqueous wash solution, and the resulting aqueous solution was heated for 30 sec. After cooling, the formaldehyde-dimedone derivative precipitated (0.532 g.) and gave m.p. 191-192° alone and on admixture with an authentic sample.

The organic layer was dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. The residue was distilled to give 0.65 g. of diketone CXLIII, b.p. 90-100° (bath temperature) at 0.1 mm. Hg; ν_{max}^{film} 1750, 1740, 1720, and 1240 cm.$^{-1}$; n.m.r. δ 1.02 (doublet, J = 6 c.p.s., 3 protons) and 2.12 (6). CXLIII gave a negative test with methanolic ferric chloride and gave iodoform (m.p. 120°) with sodium hypoiodite.

An ether solution of CXLIII (0.35 g.) was added to an ether solution of lithium aluminum hydride (0.5 g.) and the resulting mixture was stirred at room temperature for 2 hrs. After the usual work-up, the ether layer was concentrated to yield 0.2 g. of triol CXLIV (ν_{max}^{film} 3400 cm.$^{-1}$), which was directly oxidized. A solution prepared by adding 0.14 g. of CXLIV and 0.51 g. of potassium permanganate to 20 ml. of water and 5 ml. of dioxane was stirred overnight at room

temperature. After the manganese dioxide was removed by filtration, the solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and, upon the addition of petroleum ether (b.p. 30-60°), β-methyladipic acid (CXLV) precipitated. After recrystallization from ether-petroleum ether, CXLV gave m.p. 85-88° alone and on admixture with an authentic sample of β-methyladipic acid obtained by the oxidation of pulegone according to Semmler (99).

Both CXLV and the authentic sample of β-methyladipic acid were converted into their dimethyl esters with ethereal diazomethane and the v.p.c. (1/8 in. x 6 ft. column of 10% silicone rubber on Chromosorb W with hydrogen and nitrogen flow rates of 20 ml./min.) at 135° gave identical retention times (3.6 min.) alone and on admixture. The infrared spectra of the two ester samples were superimposable.

Pyrolysis of CXXXIX.

A solution of 0.2 g. of CXXXIX in 10 ml. of benzene was pyrolyzed, as described above in the pyrolysis of CXL, to give pyrolyzate fraction A. A small sample of pyrolyzate A was stored under nitrogen; the remainder was repyrolyzed under the same conditions to give pyrolyzate B. V.p.c. analysis showed that pyrolyzates A and B were identical. V.p.c. analysis using a 1/4 in. x 10 ft. column of 10% SE-30 on Chromosorb W at 145° and a helium flow rate of 50 ml./min. with a thermal detector showed the pyrolyzate to contain 44% menthofuran (VIII), retention time 8.0 min., identified by comparison with an authentic sample, and 56% of another component, presumably CL, retention time 9.5 min. Under these conditions the starting material CXXXIX showed a retention time

of 30.5 min.

Distillation of the pyrolyzate gave a 63% yield of product which was a mixture of menthofuran (VIII) and CL. The infrared spectrum of the mixture clearly showed the presence of menthofuran by its characteristic bands at 1570, 1108, 764, and 732 cm.$^{-1}$; in addition, the bands at 3080, 1660, 1640, and 888 cm.$^{-1}$ could be assigned to CL. The n.m.r. spectrum of the mixture likewise showed the presence of menthofuran by its characteristic signals at δ 1.07 (doublet, J = 5.5 c.p.s.) and δ 6.84. The signals at δ 1.05 (doublet, J = 4 c.p.s.) and δ 5.07 (doublet, J = 13 c.p.s.), and a multiplet in region δ 6.7-7.0 could be assigned to CL.

Dehydration of the Ketal-Alcohol CXXX.

A mixture of 5 g. of the ketal-alcohol CXXX, 50 ml. of anhydrous pyridine, and 20 ml. of phosphorus oxychloride was allowed to stand overnight. The resulting mixture was added slowly to 500 ml. of ice and water. The mixture was extracted with ether, the combined ether extracts washed with water until neutral, dried over anhydrous magnesium sulfate, and the solvent removed. Distillation gave 2.77 g. (61%) of the olefin-ketal CLI, b.p. 70° (bath temperature) at 0.4 mm. Hg; ν_{max}^{film} 3088, 1642, 890, 1180-1040 cm.$^{-1}$; n.m.r. δ 4.92 (2), 3.95 (4), and 1.92 (3).

Anal. Calcd. for $C_{11}H_{18}O_2$; C, 72.49; H, 9.95. Found: C, 72.55; H, 10.07.

Formation of 3-Methyl-4,5,6,7-tetrahydrobenzofuran (CXXXII).

A mixture of 4.07 g. of CLI, 4.8 g. of m-chloroperbenzoic acid,

and 75 ml. of dry ether was stirred at room temperature until all of the peracid had been consumed (4 hrs.). Then 10 ml. of water, 10 ml. of methanol, and 0.5 ml. of concentrated sulfuric acid were added and the resulting mixture refluxed for 5 hrs. under a nitrogen atmosphere. After cooling, the mixture was diluted with ether, washed with saturated sodium bicarbonate, water, then dried over anhydrous magnesium sulfate and the solvent removed. Chromatography on 65 g. of activity I acid-washed alumina by elution with petroleum ether (b.p. 60-90°) gave a fraction which when distilled gave the desired furan in less than 10% yield, b.p. 120° (bath) at 30 mm. Hg. The infrared spectrum was identical to that of the furan prepared by pyrolysis.

Formation of 3-Acetoxy-p-mentha-3,8-diene (CLIII) and Its Conversion to Menthofuran (VIII).

A mixture of 15.2 g. of pulegone (II), 500 ml. of CCl_4, 100 ml. of acetic anhydride, and 1 ml. of 70% perchloric acid was stirred at room temperature for 1 hr., extracted with water, dried and distilled to give the enol acetate CLIII in 70% yield; b.p. 70° (bath) at 0.5 mm. Hg; ν_{max}^{film} 3065, 1758, 1640, 1220, 902 $cm.^{-1}$; n.m.r. δ 4.8 (2), 2.0 (3), 1.8 (3), and 1.03 (doublet, $J = 5$ c.p.s., 3 protons).

A mixture of 2 g. of CLIII, 2 g. of m-chloroperbenzoic acid, and 50 ml. of dry ether was stirred overnight. The resulting ether solution was washed with 10% sodium bisulfite solution until a negative starch iodide test was observed, then washed with 10% sodium bicarbonate solution, water, and then dried over anhydrous magnesium sulfate. Removal of solvent gave the crude epoxide CLIV, ν_{max}^{film} 1753, 1220 $cm.^{-1}$,

n.m.r. δ 2.6, 2.06, 1.28, and 1.0 (doublet, J = 5 c.p.s.). Since distillation resulted in material whose infrared spectrum was significantly different from the crude material, the epoxide was not purified but used directly in the next step. Treatment of the crude epoxide with aqueous methanol and sulfuric acid on a steam bath for 10 minutes gave the characteristic blue color associated with the oxidation of menthofuran. Water was added to the mixture which was then extracted with ether and the combined extracts washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. The presence of menthofuran was determined by t.l.c. comparison of the crude products with authentic menthofuran which exhibited on silica gel an R_f 0.64 in petroleum ether (b.p. 60-90°) or 0.77 in benzene.

Attempted Cyclization of CLV.

The cholestane derivative CLV (0.05 g.), prepared according to Djerassi and co-workers (103), was dissolved in ether and treated with 0.10 g. of m-chloroperbenzoic acid at room temperature overnight. The solution was diluted with 10 ml. of 95% ethanol and treated with 5 drops of concentrated sulfuric acid overnight. The mixture washed with water and dried over anhydrous magnesium sulfate. Removal of solvent gave the material which did not exhibit absorption in the 200 mμ region characteristic of furans.

Attempted Cyclization of 4-α-(2-Oxoethyl)-cholestan-3-one (CLVII).

Following the procedure by Atwater (105), the alkylation was conducted as follows: to a solution of potassium t-butoxide prepared by dissolving 0.152 g. of potassium in 6 ml. of anhydrous

t-butyl alcohol was added a hot solution of 1 g. of Δ^4-cholesten-3-one in 15 ml. of hot t-butyl alcohol. To this refluxing solution was added with stirring 0.315 g. of allyl bromide in 30 ml. of t-butyl alcohol over a period of 2 hrs. After addition was complete the mixture was refluxed for 30 min. After cooling, it was diluted with ether, washed with dilute acetic acid, saturated sodium bicarbonate solution, then water, and finally dried. Removal of solvent and chromatography on 50 g. of silica gel with benzene-petroleum ether (b.p. 60-90°) (3:7) gave the monoalkylated product in approximately 45% yield, showing one spot by t.l.c., R_f 0.28 (benzene); ν_{max}^{film} 3078, 1640, 904, 1668, 1605 $cm.^{-1}$.

The ketone from above (2.08 g.) was dissolved in absolute ethanol and treated with 20 g. of sodium in small pieces over a period of 5 hrs. The resulting mixture was diluted with ether, washed successively with dilute acetic acid, saturated sodium bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. Removal of solvent gave the crude alcohol which was oxidized by the Jones (111) procedure to give 0.300 g. of the saturated ketone, which showed one spot by t.l.c., R_f 0.44 [ethyl acetate-benzene (4:96)] and was recrystallized from absolute ethanol; m.p. 104-104°; ν_{max}^{KBr} 1700, 912 $cm.^{-1}$.

The above ketone (0.200 g.) in 30 ml. of methylene chloride was treated with excess ozone at -70°. The resulting blue solution was allowed to warm to room temperature, treated with 10 ml. of water and 0.2 g. of zinc dust. The mixture was then stirred 3 hrs., filtered, diluted with ether, washed with water, and dried over anhydrous magnesium sulfate. The keto-aldehyde which showed one spot by t.l.c., R_f 0.56 [ethyl acetate-benzene (4:96)] was not isolated but treated with 10 drops of boron trifluoride-etherate at room temperature. After

48 hrs., t.l.c. showed the absence of any starting material and the presence of two products, R_f 0.76 and R_f 0.25, with the latter being in greater quantity. Chromatography in 20 g. of alumina gave by elution with petroleum ether (b.p. 60-90°) a small amount of the component of R_f 0.76; λ_{max}^{EtOH} 251 mμ; $\nu_{max}^{HCCl_3}$ 1710 cm.$^{-1}$. Further elution with chloroform gave approximately 0.1 g. of the component of R_f 0.25; $\nu_{max}^{HCCl_3}$ 1715 cm.$^{-1}$. These data indicate that neither of the two products was a furan.

Attempted Alkylations of Some Cholestan-3-one Derivatives.

The pyrrolidine enamine of cholestan-3-one was prepared according to a reported procedure (119). A mixture of 1 g. of cholestanone, 0.81 g. of freshly distilled pyrrolidine, and 15 ml. of toluene was refluxed for 3 hrs. After that time the excess pyrrolidine and toluene were removed under vacuum.

The crude enamine from above, 0.5 g. of isopropyl iodide, and 10 ml. of toluene were refluxed 3 hrs. Then 10 ml. of water was added, and the refluxing continued for another hr. The mixture was diluted with ether, the ether layer washed with water, dried, and the solvent removed. The resulting crystalline material exhibited a melting point identical to that of cholestan-3-one. Two other reactions using up to an 8-molar excess of isopropyl iodide gave the same results.

The pyrrolidine enamine from 1 g. of cholestanone was dissolved in 20 ml. of benzene and 0.33 g. of freshly distilled allyl bromide was added. After refluxing for 16 hrs. 10 ml. of water was added and refluxing continued for another hr. The reaction mixture was diluted with ether, the ether layer washed with water, dried, and the solvent

removed under vacuum. The resulting crystalline material proved to be cholestanone as determined by melting point and infrared spectrum. Attempts by others to introduce groups into the 2 position of cholestanone via the enamine have also not been successful (120).

A mixture of 1 g. of 2-methoxalylcholestan-3-one, prepared according to Nelson and Schut (120), 2 g. of freshly distilled allyl bromide, 0.5 g. of potassium carbonate, and 20 ml. of acetone was refluxed for 16 hrs. The reaction mixture was dissolved in ether, the ether washed with water, dried, and the solvent removed. The infrared spectrum of the crude reaction mixture indicated that the alkylation did not take place.

A mixture of 0.1 g. of cholestanone, 25 ml. of benzene, and 0.1 g. of sodium hydride was refluxed for 2.5 hrs., 15 ml. of acetone was added and the mixture allowed to stand overnight. The reaction mixture was taken up in ether, washed with water, dried, and the solvent removed to give starting material as determined by its melting point and infrared spectrum.

The enol acetate of cholestanone was prepared according to a published procedure (121). Treatment of 0.15 g. of the enol acetate with 0.170 g. of m-chloroperbenzoic acid in 20 ml. of chloroform overnight did not give the expected epoxide. A similar treatment for a longer period also failed to give the epoxide.

The α-epoxide of Δ^2-cholestene was then prepared according to Plattner and Furst (122). To an ether solution of isopropylmagnesium iodide, prepared from 0.20 g. of isopropyl iodide and excess magnesium turnings, was added 0.15 g. of the epoxide in 20 ml. of ether. The resulting reaction mixture was refluxed for 4 hrs. the excess Grignard

reagent destroyed with wet ether, and then water, and 10% hydrochloric acid added. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed, giving the crude product, ν_{max}^{film} 3310 cm.$^{-1}$. The crude material was dissolved in acetone and treated with 10 drops of Jones (111) reagent. The resulting mixture was diluted with ether, washed with water several times, and dried over anhydrous magnesium sulfate. Removal of the solvent gave the ketone ν_{max}^{film} 1710 cm.$^{-1}$; m.p. 164-167°. The melting point indicated that the product was not the expected 2-α- or 2-β-isopropylcholestanone since both ketones are known and exhibit melting points lower than 164° (103). The β-epoxide is also known to give an abnormal Grignard reaction (123).

In an effort to utilize the Feist-Bernary (104) synthesis, a solution of 0.090 g. of 2-α-bromocholestan-3-one, prepared according to the procedure of Fieser and Dominguez (124), in aqueous pyridine was treated with a slight excess of ethyl acetoacetate for 2 days at room temperature. The mixture was then diluted with ether, washed with water, dried, and the solvent removed. The starting material, identified by its melting point, was recovered.

A reaction employing similar amounts of the two reactants dissolved in a pyridine-ether mixture also gave starting material.

A small amount of ethyl acetoacetate was dissolved in ether and treated with excess sodium hydride. After the evolution of hydrogen had ceased, an equimolar amount of 2-α-bromocholestanone was added and the mixture refluxed 3 hrs. The excess base was destroyed by the addition of cold water, the solution was saturated with salt, diluted with ether, and the ether layer washed with water, and then dried.

Removal of solvent under reduced pressure gave the crude product. Its infrared and n.m.r. spectra show no indication of absorption due to the expected furan. Use of benzene as a solvent instead of ether gave similar results.

In an attempt to utilize an alkylation described in a note by Stork (125), a solution of 1 g. of Δ^4-cholestan-3-one in 100 ml. of freshly distilled liquid ammonia was treated with 0.036 g. of lithium metal. The initial blue color of the lithium quickly disappeared as it was added, and finally a deep blue color remained upon the addition of the last piece of lithium. This was a ratio of 1 mole of ketone to 2 equivalents of lithium. Then 0.350 g. of (1 mole equivalent) of freshly distilled allyl bromide was added dropwise. Upon the addition of the first drop the blue color disappeared, the rest was added, and the mixture was allowed to reflux 1 hr. The ammonia was then allowed to evaporate, ether added, then water, and then 2 g. of ammonium chloride. The ether layer was washed with water, dried, and the solvent removed. The n.m.r. spectrum of the resulting material indicated it to be starting material.

Some Attempted Photolyses.

A solution of 6.1 g. of pulegone in 200 ml. of reagent-grade benzene was photolyzed using a pyrex filter and a Hanovia 200-watt mercury lamp. The solution was mixed by a stream of oxygen-free dry nitrogen through it. The entire photolysis cell was cooled so that the temperature did not rise above 50° at any time. Two-milliliter samples were taken every 30 min. so the experiment could be followed by gas chromatography and n.m.r. After 3 hrs. no change was detected by v.p.c. and

n.m.r. analysis. Another photolysis of pulegone using a Corex filter gave the same results.

A solution of 5 g. of pulegone in 350 ml. of absolute ethanol was photolyzed for 48 hrs. at 70° using a quartz filter. No change was detected by v.p.c.

A solution of 7 g. of isopulegone in 350 ml. of methanol was photolyzed through quartz for 7 hrs. The infrared spectrum of the crude reaction product showed no change had occurred.

The photolysis of 5 g. of bidiphenyleneethylene, prepared according to Fuson and Porter (126), in benzene for 14 hrs. using a quartz filter produced no identifiable product.

Although none of the above photolyses resulted in transformations, anthracene was readily dimerized by the light produced by the same lamp used above.

The Preparation of Menthyl Nitrite (CLVIII).

Nitrosyl chloride, prepared according to Morton and Wilcox (127), was distilled into a solution of 10 g. of menthol in 125 ml. of anhydrous pyridine until a red color persisted. Water was added and the mixture extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, water, and then dried. Removal of the solvent gave the crude nitrite, ν_{max}^{film} 1610, 1640, 1650 cm.$^{-1}$.

The Photolysis of Menthyl Nitrite (CLVIII).

The crude nitrite ester from above was dissolved in 300 ml. of benzene and photolyzed at 25° with a 200-watt Hanovia mercury lamp using a pyrex filter. After 1 hr. and 40 min. the reaction was com-

plete as determined by the disappearance of the characteristic absorption in the infrared spectrum. After removal of solvent, 1.5 g. of the crude reaction mixture was chromatographed on 55 g. of 60-100 mesh Florisil. Elution with benzene and chloroform gave mainly menthol and ketonic products amounting to 1.37 g. of material. Finally, elution with methanol-chloroform (4:96) gave 0.110 g. of material whose infrared spectrum (ν_{max}^{film} 3230 broad, 1600 cm.$^{-1}$) indicated it to be an oxime, presumably CLIX.

The crude oxime from above was dissolved in 5 ml. of anhydrous pyridine and added to the chromium oxide-pyridine complex prepared according to Sarett and co-workers (128) by dissolving 0.5 g. of chromium oxide in 10 ml. of pyridine. The mixture was allowed to stand overnight, diluted with water and extracted with ether. The combined ether extracts were washed with water several times, and dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.10 g. of a crude lactol, presumably CLX, as product, ν_{max}^{film} 3380, 1785 cm.$^{-1}$.

Hydrogenation of 2,3-Dimethylphenol.

This reduction was performed similarly to that already described (129). A solution of 100 g. of 2,3-dimethylphenol (Aldrich) in 200 ml. of absolute ethanol was introduced into a one-liter high pressure hydrogenation reaction vessel. Then, 18 ml. of settled Raney nickel (W-2) was added and the reaction vessel assembled. After flushing with nitrogen and then hydrogen, the hydrogen pressure was increased to 1750 p.s.i. After the temperature was raised to 175° the pressure dropped steadily for approximately 30 min. After cooling, the contents of the reaction vessel were filtered, dissolved in ether, washed with

water and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 97.6 g. (93%) of 2,3-dimethylcyclohexanol, b.p. 47-48° at 0.2 mm. Hg [reported (129) b.p. 77-79° at 12 mm. Hg].

Oxidation of 2,3-Dimethylcyclohexanol.

A solution of 97.6 g. of the alcohol in 400 ml. of reagent acetone was cooled to 10° while 200 ml. of Jones (111) reagent was added with vigorous stirring. The progress of the reaction was followed by infrared analysis. When complete, water was added, the resulting mixture extracted with ether, and the combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 82.5 g. (85%) of 2,3-dimethylcyclohexanone (CLXIV), b.p. 35° at 1.2 mm. Hg [reported (130) b.p. 63° at 15 mm. Hg]. Although the semicarbazone of this material was found to be not homogeneous, that derivative prepared from ketone which had been epimerized with base gave m.p. 203-304° [reported (130) m.p. 201-202 (dec.)].

Condensation of Ketone CLXIV with Methyl Vinyl Ketone CLXV.

The following procedure was found to give the best results in effecting the condensation and is similar to that described by Djerassi and co-workers (110). To a solution of 75 g. of CLXIV in 305 ml. anhydrous ether was added 9.15 g. of sodium in small pieces. After the initial reaction had subsided, the mixture was refluxed with stirring until all the sodium had dissolved. It was then cooled in an ice bath and a solution of 113 g. of the methiodide salt of 1-diethylamino-3-butanone (CLXVII), prepared according to Wilds, Nowak, and McCaleb (131),

in 200 ml. of dry pyridine was added during 1 min. After cooling for an hr., the mixture was refluxed for 2 hrs., cooled, 1 l. of water added and extracted with ether, the combined extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate solution and water, then dried over anhydrous magnesium sulfate, the solvent removed, and the residue distilled. A total of 34 g. of starting material was collected along with about 17 g. of a higher-boiling fraction. Redistillation of the higher boiling fraction gave 4 g. of starting material and 6.9 g. of product CLXVI, b. p. 84-86° at .02 mm. Hg; ν_{max}^{film} 1670, 1615 $cm.^{-1}$. About 0.300 g. was chromatographed on 10 g. of activity I acid-washed alumina. Elution with benzene-petroleum ether (b.p. 60-90°) (6:4) gave the ketone CXLVI free of the saturated ketone, b.p. 93-98° (bath temperature) at 0.2 mm. Hg; n.m.r. spectrum showed the secondary methyl as two doublets, one centered at δ 0.92 (J = 5.5 c.p.s.) and the other centered at δ 0.96 (J = 5.5 c.p.s.), the bridgehead methyl at δ 1.1, and the olefinic proton at δ 5.62. Based on consumed starting material, 6.9 g. represents a 13.2% yield.

Alkylation of CLXVI.

According to an analogous procedure described by Johnson (132), a mixture of 0.5 g. of ketone CLXVI, 1 g. of potassium t-butoxide and 10 ml. of t-butyl alcohol was cooled in a nitrogen atmosphere. Then 6.9 g. of isopropyl iodide was added and the mixture brought to room temperature and then refluxed for 2 hrs. The cooled mixture was diluted with water, extracted with ether and the combined ether extracts washed with water and dried over anhydrous magnesium sulfate. Removal of solvent and distillation gave 0.34 g. of the product, ν_{max}^{film} 1658, 1588, 1710

cm.$^{-1}$; n.m.r. spectrum showed a complicated absorption in the region δ 0.8 to 1.3 and a lack of signals due to olefinic protons.

Condensation of 2,3-Dimethylcyclohexanone (CLXIV) with 1,3-Dichloro-2-butene (CLXVIII) and Cyclization of CLXIX.

Following the condensation and cyclization procedure described by Djerassi and co-workers (110), a suspension of 0.46 g. of sodium t-amylate in 20 ml. of benzene was added to a cold solution of 3 g. of the ketone CLXIV and 1.8 g. of freshly distilled 1,3-dichloro-2-butene (K&K) in 25 ml. of anhydrous benzene. After coming to room temperature the mixture was heated at reflux for 3 hrs., then cooled, and diluted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. Distillation gave in 28% yield the chloroketone CLXIX, b.p. 90-120° (bath temperature) at 0.2 mm. Hg; ν_{max}^{film} 1715, 1660 cm.$^{-1}$; the n.m.r. spectrum showed two doublets due to the secondary methyl, one centered at δ 0.96 (J = 6 c.p.s., 1.5 protons) and the second centered at δ 1.03 (J = 7 c.p.s., 1.5 protons), δ 0.98 (3), 2.08 (3), and the vinylic proton as a quartet centered at δ 5.52 (J_{a_1x} = 6 c.p.s., J_{a_2x} = 14 c.p.s., 1 proton).

A 1 g. sample of the chloroketone CLXIX from above was cooled in an ice bath and 3 ml. of concentrated sulfuric acid was slowly added with mixing. The resulting dark red mixture was allowed to stand 24 hrs., then poured into water and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. Distillation gave in 30% yield the desired ketone whose infrared spectrum was essentially identical to that of the previously prepared ketone CLXVI.

Preparation of 1-Dimethylamino-2-isopropyl-3-butanone (CLXX) and Its Condensation with 2,3-Dimethylcyclohexanone (CLXIV).

This preparation was accomplished using a procedure analogous to that described for the preparation of 1-diethylamino-3-butanone (131). A mixture of 100 g. of 4-methyl-2-pentanone (Eastman), 20 g. of dimethylamine hydrochloride, 9 g. of paraformaldehyde, 75 ml. of methanol, and 5 drops of concentrated hydrochloric acid was refluxed for 12 hrs. The mixture was then cooled, neutralized with a solution of 8.5 g. of potassium hydroxide in 40 ml. of water, and extracted 5 times with 150-ml. portions of ether. The combined ether extracts were washed with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After removal of the solvent, distillation gave the product in 60% yield, b.p. 54-57° at 2.0 mm. Hg; ν_{max}^{film} 1712 cm.$^{-1}$; n.m.r. δ 0.9 (doublet, J = 6 c.p.s., 6 protons), 2.18 (6), 2.48 (3). The picrate (from methanol) exhibited a melting point of 101-102°. The preparation of this aminoketone from the starting materials used here has been reported but no derivatives were given (133).

As before, the condensation was carried out by dissolving 0.92 g. of sodium in a solution of 8 g. of 2,3-dimethylcyclohexanone (CLXIV) in 50 ml. of ether. To this cooled solution was added a solution of the methiodide salt prepared by dissolving the salt from 6.3 g. of 1-dimethylamino-2-isopropyl-3-butanone (CLXX) and 5.7 g. of methyl iodide in 20 ml. of anhydrous pyridine. After keeping cool for 1 hr. the mixture was refluxed for 2 hrs., then 100 ml. of water was added and the resulting mixture extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, then water, and dried. Removal of the solvent

and distillation gave an estimated 1.1 g. of product, b.p. 130° (bath temperature) at 0.1 mm. Hg; ν_{max}^{film} 1710 (strong), 1658 (weak); n.m.r. spectrum showed weak signals due to olefinic protons. The crude material was chromatographed on 15 g. of activity I acid-washed alumina. Elution with petroleum ether (b.p. 60-90°) gave a small amount of unsaturated ketone, ν_{max}^{film} 1658, 1615 cm.$^{-1}$; n.m.r. spectrum showed only a weak signal due to a vinylic proton. The infrared spectrum was not identical to that of the known ketone obtained from hydroxyeremophilone (134).

Preparation of cis- and trans-1,4-Cyclohexanediol (Quinitol).

This reduction was accomplished under conditions essentially identical to those described in the literature (135). The reaction vessel was charged with approximately 400 ml. of a saturated solution of hydroquinone (Eastman) in absolute ethanol and 10 ml. of settled Raney nickel catalyst (W-2). After flushing the assembled reaction vessel with nitrogen and then hydrogen, the hydrogen pressure was increased to approximately 1500 p.s.i. The temperature was increased to 150° and the reaction was completed within an hr. After cooling, the catalyst was allowed to settle and the suspended catalyst removed by filtration. At this point more hydroquinone could be reduced utilizing the same catalyst several times. The solvent was removed from the reaction mixture and the quinitol recrystallized from acetone.

Preparation of 4-Benzyloxycyclohexanol.

According to the procedure of Prins (136), 4-benzyloxycyclohexanol was prepared as follows: during 15 min. 11.5 g. of sodium was

added to a boiling solution of 58 g. of quinitol in 400 ml. of absolute dioxane and the resulting mixture refluxed for 5 hrs. and then cooled to room temperature. A solution of 59 g. of benzyl bromide in 60 ml. of dioxane was added within 10 min., and the mixture refluxed for 18 hrs. After cooling 50 ml. of methanol was added and the solution diluted with 350 ml. of acetone. The precipitate was removed by filtration and the solvent removed from the filtrate under reduced pressure. The residue was dissolved in ether, washed with water, and dried. Removal of the solvent and distillation gave 35 g. of the monobenzyl ether, b.p. 118-120° at 0.1 mm. Hg [reported (136) b.p. 101-103° at 0.02 mm. Hg]; ν_{max}^{film} 3380, 1100-1060, 735, 697 $cm.^{-1}$.

Oxidation of 4-Benzyloxycyclohexanol.

A mixture of 43.7 g. of 4-benzyloxycyclohexanol in 200 ml. of reagent acetone was cooled to 10° and treated with a slight excess of Jones (111) reagent. The mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed. Distillation of the residue gave 38.9 g. (90%) of the ketone, b.p. 114-115° at 0.15 mm. Hg [reported (136) b.p. 118-120° at 0.14 mm. Hg]; ν_{max}^{film} 1710, 1110-1060 $cm.^{-1}$; n.m.r. δ 7.32 (5), 4.53 (2), 3.7 (1 proton). Other oxidations resulting in slightly lower yields have been reported (136,137).

Condensation of 4-Benzyloxycyclohexanone with Diethyl Oxalate and Decarbonylation of the Glyoxylate.

The following procedures are analogous to those described by Snyder, Brooks, and Shapiro (138) for the condensation of cyclo-

hexanone with diethyl oxalate and decarbonylation of the resulting glyoxylate. A mixture of 30 g. of the ketone and 21.5 g. of diethyl oxalate at 5° was added to a cold solution of sodium ethoxide prepared by dissolving 3.4 g. of sodium in 60 ml. of absolute ethanol. The resulting brown mixture was stirred for 1 hr. in an ice bath and stirred 6 hrs. at 25°. When it was neutralized by adding a mixture of 4 ml. of concentrated sulfuric acid in 32 g. of ice and then diluted with water, the product separated as a red oil. The aqueous layer was extracted with ether, the extracts combined with oil, and washed with water. The solution was dried by azeotroping with benzene and then the remaining solvent removed. A portion of the resulting crude glyoxylate was distilled to give b.p. 185° (bath temperature) at 0.1 mm. Hg; n.m.r. spectrum showed δ 7.3 (5), 4.5 (2), 3.7 (multiplet, splitting of 5 c.p.s., 1 proton), 4.28 (quartet, J = 7 c.p.s., 2 protons), and 1.3 (triplet, J = 7 c.p.s., 3 protons).

The crude glyoxylate from above was decarbonylated in the presence of a small amount of powdered soft glass and a trace of iron filings at 170° for 5 hrs. Distillation gave 16.73 g. (45% from 4-benzyloxycyclohexanone) of ethyl 2-oxo-5-benzyloxycyclohexane-carboxylate (CLXXIII), b.p. 165-170° at 0.5 mm. Hg; ν_{max}^{film} 1740, 1720, 1652, 1230, 1100, 736, 698 $cm.^{-1}$; n.m.r. δ 7.3 (5), 4.52 (2), 3.68 (multiplet, 1 proton), 4.19 (quartet, J = 7 c.p.s., 2 protons), and 1.25 (triplet, J = 7 c.p.s., 3 protons). The material gave a positive ferric chloride test.

Condensation of the Ketoester CLXXIII with the Methiodide Salt of 1-Diethylamino-3-pentanone (CLXXIV).

To a cold, stirred solution of 2.76 g. of the keto-ester in 10 ml. of absolute ethanol was added a solution of sodium ethoxide prepared by dissolving 1.13 g. of sodium in 25 ml. of absolute ethanol. The methiodide salt, prepared by the reaction of 1.45 g. of 1-diethylamino-3-pentanone CLXXIV and 1.5 g. of methyl iodide, in 6 ml. of absolute ethanol was then added dropwise. The mixture was stirred in an ice bath for 1.5 hrs. and then refluxed for 3.5 hrs. The cooled mixture was diluted with water, extracted with ether, and the combined ether extracts washed with water, 10% hydrochloric acid, and then water. The ether solution was then dried over anhydrous magnesium sulfate and the solvent removed giving 2.7 g. (78%) of crude product CLXXV, ν_{max}^{film} 1725, 1668, 1615, 1228, 1105, 733, 696 $cm.^{-1}$; n.m.r. δ 7.25 (5), 4.45 (multiplet, 2 protons), 3.5-4.2 (multiplet, 3 protons), 1.72 (3), and 1.1 (triplet, J = 0.98 c.p.s., 3 protons).

Attempted 1,4-Addition of Methylmagnesium Iodide to the Ketone CLXXV.

A procedure completely analogous to that described by Birch and Robinson (139) was used to bring about the 1,4-addition of methylmagnesium iodide to the α,β-unsaturated ketone CLXXV in the presence of cuprous bromide. However, a product could not be isolated that corresponded to the desired substance.

Plate I

Nuclear Magnetic Resonance Spectrum of 2-Acetoxypulegone (CVI)

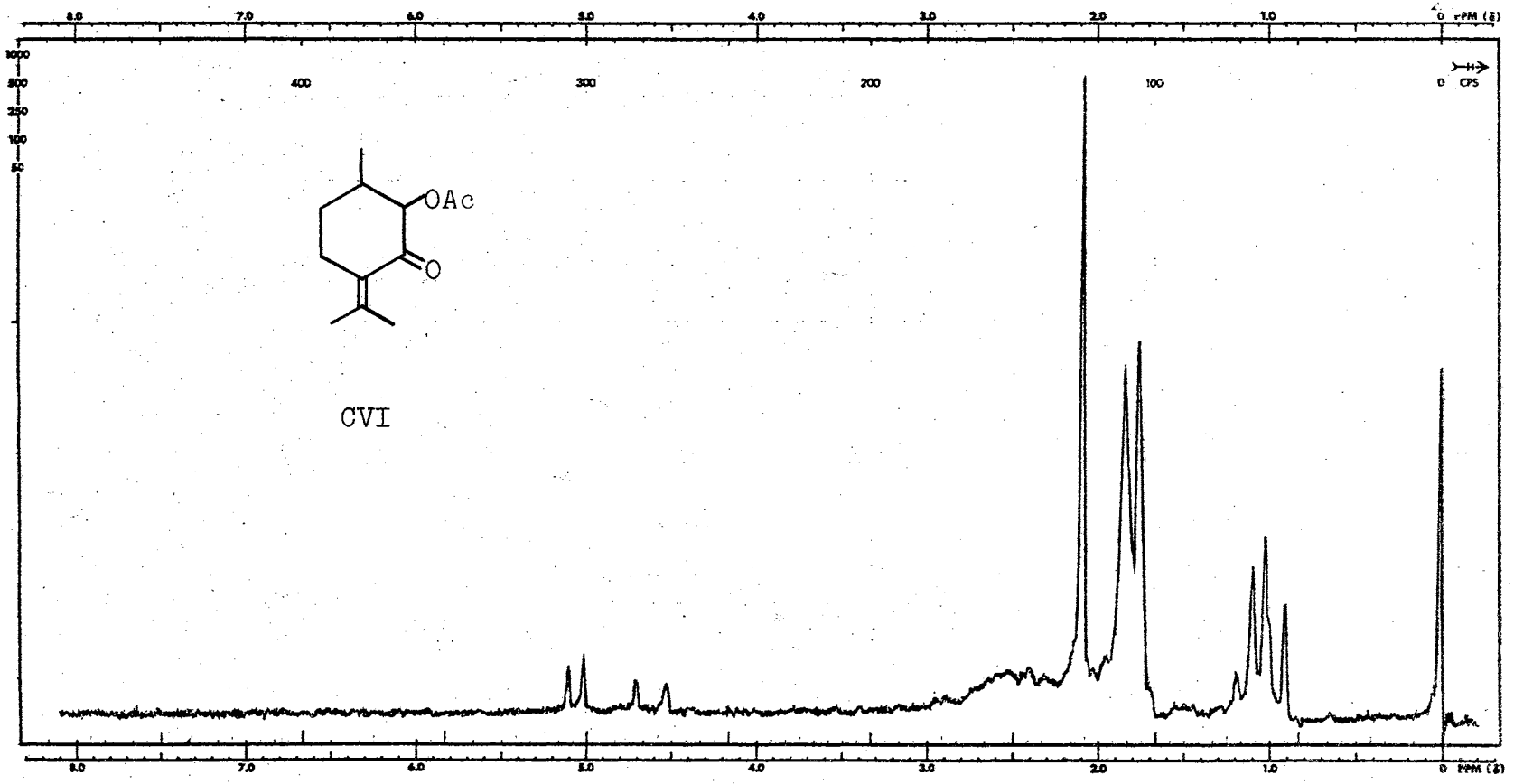


Plate II

Nuclear Magnetic Resonance Spectrum of 6-Acetoxy-2-isopropylidenecyclohexanone (CXXXIX)

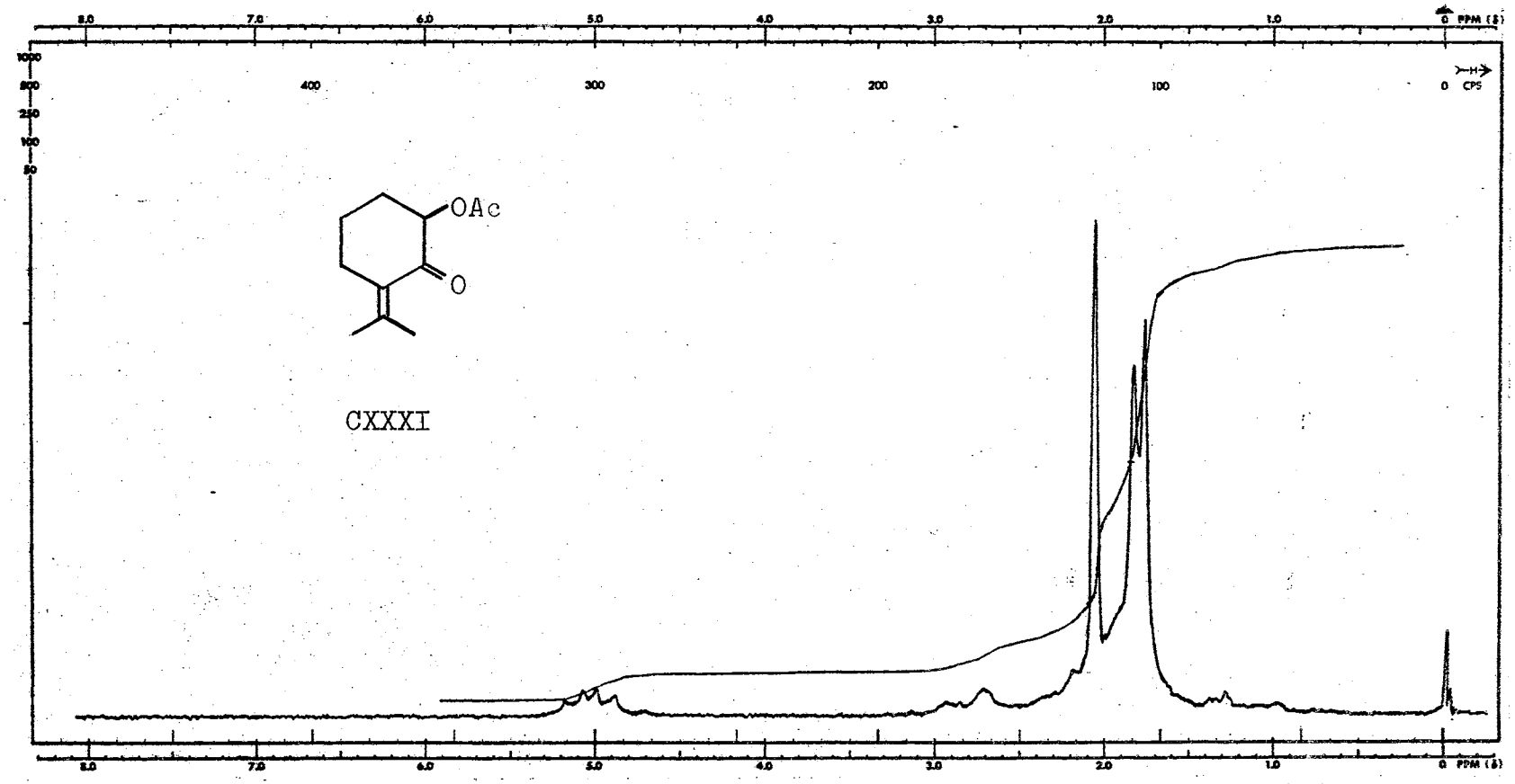
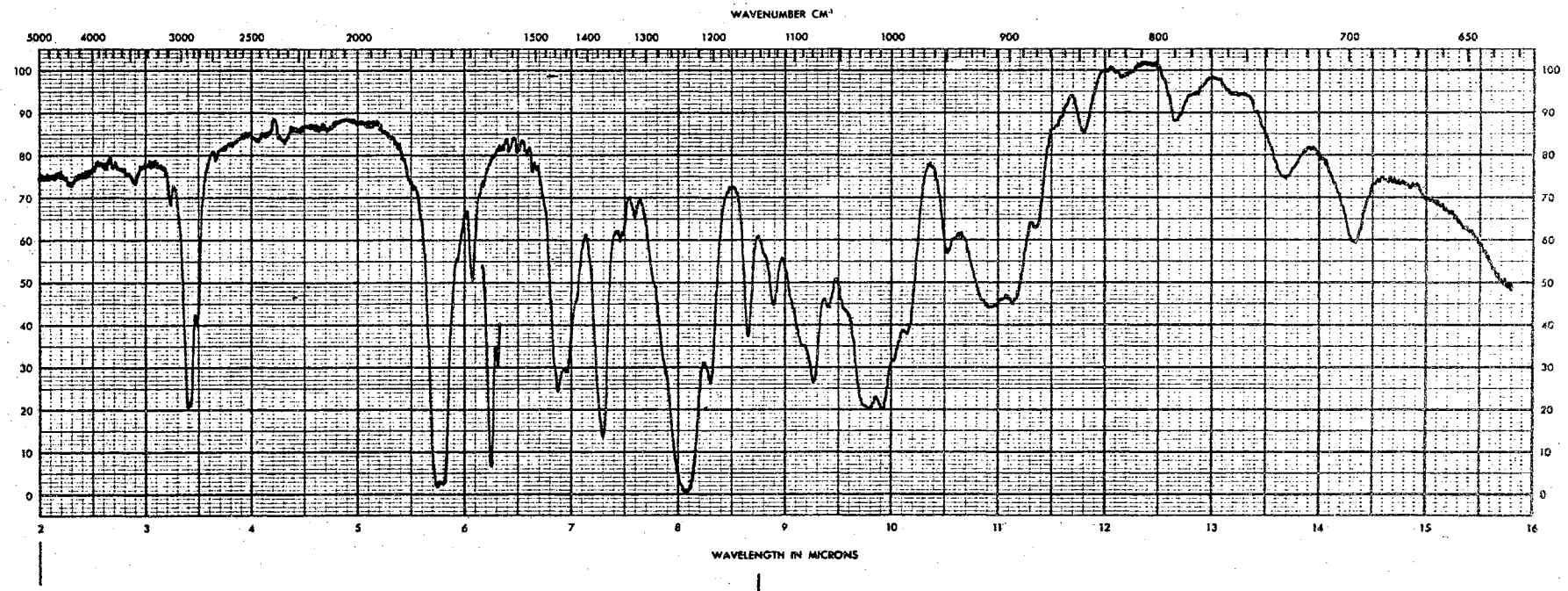
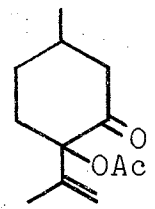


Plate III

Infrared Spectrum of 4-Acetoxyisopulegone (CXXXIX)

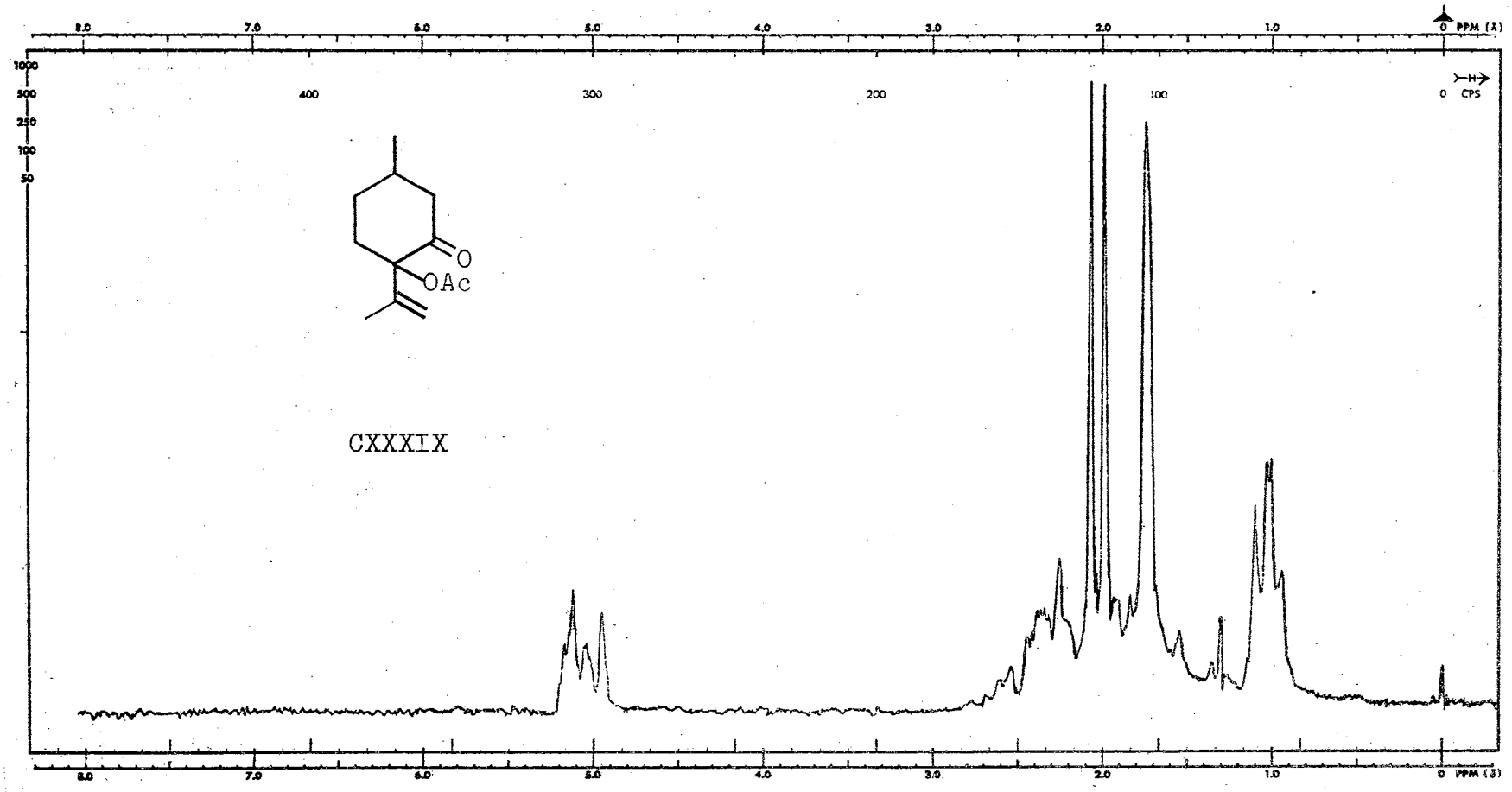




CXXXIX

Plate IV

Nuclear Magnetic Resonance Spectrum of 4-Acetoxyisopulegone (CXXXIX)



BIBLIOGRAPHY

1. Ruzicka, L., Proc. Chem. Soc. (London), 341 (1959).

2. Dean, F. M., "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963, p. 1-28.

3. Ueda, T., Nippon Kagaku Zasshi, 83, 341 (1962); Chem. Abstr., 59, 3857a (1963).

4. Treibs, W., Ber., 70B, 85 (1937).

5. Mukherji, S. M., Gandhi, R. P., and Vig, O. P., J. Indian Chem. Soc., 33, 853 (1956).

6. Black, C., Buchanan, G. L., and Jarvie, A. W., J. Chem. Soc., 2971 (1956).

7. Treibs, W., Lucius, G., Kogler, H., and Breslauer, H., Ann., 581, 59 (1953).

8. Ueda, T. and Fujita, Y., Chem. & Ind. (London), 1618 (1962).

9. Kotake, M., Kawasaki, I., Okamoto, T., Matsutani, S., Kusumoto, S., and Kaneko, T., Bull. Chem. Soc. Japan, 35, 1335 (1962).

10. Bohlmann, F., Winterfeldt, E., Studt, P., Laurent, H., Boroschewski, G., and Kleine, K., Ber., 94, 3151 (1961).

11. Arata, Y., Hazama, N., and Kojima, Y., Yakugaku Zasshi, 82, 326 (1962); Chem. Abstr., 58, 503g (1963).

12. Arata, Y., Nakanishi, T., and Asaoka, Y., Chem. Pharm. Bull. (Tokyo), 10, 675 (1962); Chem. Abstr., 59, 3972h (1963).

13. Valenta, Z. and Khaleque, A., Tetrahedron Letters, No. 12, 1 (1959).

14. Bohlmann, F., Winterfeldt, E., Laurent, H., and Ude, W., Tetrahedron, 19, 195 (1963).

15. Kawasaki, I., Matsutani, S., and Kaneko, T., Bull. Chem. Soc. Japan, 36, 623 (1963).

16. Arata, Y., Ohashi, T., Okumura, Z., Wada, Y., and Ishikawa, M., Yakugaku Zasshi, 83, 79 (1963); Chem. Abstr., 59, 3972c (1963).

17. Quilico, A., Grunanger, P., and Piozzi, F., Tetrahedron, 1, 186

(1957).

18. Ogawa, M. and Hirose, Y., Nippon Kagaku Zasshi, 83, 747 (1962); Chem. Abstr., 59, 1565b (1963).

19. Sakai, T., Nishimura, K., and Hirose, Y., Tetrahedron Letters, 1171 (1963).

20. Sorm, F., Ramanuk, M., Herout, V., Naves, Y. R., Tullen, P., Bates, R. B., and Sigel, C. W., Coll. Czech. Chem. Commun., 29, 1048 (1964).

21. Wolff, R. E., Ma, J. C. N., and Lukas, G., Compt. Rend., 257, 1784 (1963).

22. Lukas, G., Ma, J. C. N., McCloskey, J. A., and Wolff, R. E., Tetrahedron, 20, 1789 (1964).

23. Novotny, L., Herout, V., and Sorm, F., Tetrahedron Letters, 697 (1961).

24. Novotny, L., Jizba, J., Herout, V., and Sorm, F., Coll. Czech. Chem. Commun., 27, 1393 (1962).

25. Novotny, L., Herout, V., and Sorm, F., Coll. Czech. Chem. Commun., 27, 1400 (1962).

26. Hochmannova, J., Novotny, L., and Herout, V., Coll. Czech. Chem. Commun., 27, 1870 (1962).

27. Novotny, L., Jizba, J., Herout, V., Sorm, F., Zalkow, L. H., Hu, S., and Djerassi, C., Tetrahedron, 19, 1101 (1963).

28. Suchy, M., Herout, V., and Sorm, F., Coll. Czech. Chem. Commun., 29, 1922 (1964).

29. Mellor, J. M. and Munavalli, S., Quart. Rev. (London), 18, 270 (1964).

30. Djerassi, C., Williams, D. H., and Budzikiewiez, H., "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. II, Holden-Day, Inc., San Francisco, 1964, p. 151.

31. Cf. ref. 30, p. 167, ref. 10 of reference 30.

32. Kondo, H. and Sanada, T., J. Pharm. Soc. Japan, No. 526 1047 (1925); Chem. Abstr., 20, 2678 (1926).

33. Takeda, K., Minoto, H., and Horibe, I., Tetrahedron, 17, 2307 (1963).

34. Yoshioka, I., Takahashi, S., Hikino, H., and Sasaki, Y., Yakugaku Zasshi, 80, 1564 (1960); Chem. Abstr. 55, 9456h (1961).

35. Hikino, H. and Hikino, Y., Chem. Pharm. Bull. (Tokyo), 10, 641 (1962).

36. Hikino, H., Hikino, Y., and Yosioka, I., Chem. Pharm. Bull. (Tokyo), 12, 755 (1962).

37. Takeda, K. and Ikuta, M., Tetrahedron Letters, 277 (1964).

38. Erfan Ali, M. and Qudrat-i-Khuda, M., Chem. & Ind. (London), 463 (1960).

39. Canonica, L., Jommi, G., Manitto, P., and Pelizzoni, F., Tetrahedron Letters, 2079 (1963).

40. Erfan Ali, M. and Qudrat-i-Khuda, M., Sci. Res., 1, 135 (1964); Chem. Abstr., 61, 10718g (1964).

41. Finnegan, R. A., J. Org. Chem., 26, 3057 (1961).

42. Scott, A. I., Sim, G. A., Ferguson, G., Young, D. W., and McCapra, F., J. Am. Chem. Soc., 84, 3197 (1962).

43. Wettstein, A., Spillmann, M., and Miescher, K., Helv. Chim. Acta, 28, 1004 (1945).

44. Kaufmann, H. P. and Sen Gupta, A. K., Ber., 96, 2489 (1963).

45. Gopinath, K. W., Govindachari, T. R., Parthasarathy, P. C., and Viswanathan, N., Helv. Chim. Acta., 44, 1040 (1961).

46. Haeuser, J., Lombard, R., Lederer, F., and Ourisson, G., Tetrahedron, 12, 205 (1961).

47. Birtwistle, J. S., Case, D. E., Dutta, P. C., Halsall, T. G., Mathews, G., Sabel, H. D., and Thaller, V., Proc. Chem. Soc. (London), 329 (1962).

48. Castine, W. H., Wheeler, D. M. S., and Wheeler, M., Chem. & Ind. (London), 1832 (1961).

49. Burn, D. and Rigby, W., J. Chem. Soc., 2964 (1957).

50. Sumimoto, M., Tetrahedron, 19, 643 (1963).

51. Kaneko, C., Tsuchiya, T., and Ishikawa, M., Chem. Pharm. Bull. (Tokyo), 11, 271 (1963); Chem. Abstr., 59, 3967c (1963).

52. Kaneko, C., Tsuchiya, T., and Ishikawa, M., Chem. Pharm. Bull. (Tokyo), 11, 1346 (1963); Chem. Abstr., 60, 5563e (1964).

53. Overton, K. H., Weir, N. G., and Wylie, A., Proc. Chem. Soc. (London), 211 (1961).

54. Klyne, W., Chem. & Ind. (London), 1198 (1954).

55. Barton, D. H. R., Overton, K. H., and Wylie, A., J. Chem. Soc., 4809 (1962).

56. Barton, D. H. R., Balasubramanian, S. K., and Jackman, L. M., J. Chem. Soc., 4816 (1962).

57. King, F. E., Godson, D. H., and King, T. J., J. Chem. Soc., 1117 (1955).

58. Chapman, G. T., Jaques, B., Mathieson, D. W., and Arya, V. P., J. Chem. Soc., 4010 (1963).

59. Achmatowicz, O. and Wrobel, J. T., Tetrahedron Letters, 129 (1964).

60. Achmatowicz, O., Banaszek, H., Spiteller, G., and Wrobel, J. T., Tetrahedron Letters, 927 (1964).

61. Akisanya, A., Bevan, C. W. L., Halsall, T. G., Powell, J. W., and Taylor, D. A. H., J. Chem. Soc., 3705 (1961).

62. Sutherland, S. A., Sim, G. A., and Robertson, J. M., Proc. Chem. Soc. (London), 222 (1962).

63. Bevan, C. W. L., Rees, A. H., and Taylor, D. A. H., J. Chem. Soc., 983 (1963).

64. Bevan, C. W. L., Halsall, T. G., Nwaji, M. N., and Taylor, D. A. H., J. Chem. Soc., 768 (1962).

65. Arigoni, D., Barton, D. H. R., Corey, E. J., Jeger, O., Caglioti, L., Sukh Dev, Ferrini, P. G., Glazier, E. R., Melera, A., Pradhan, S. K., Schaffner, K., Sternhell, S., Templeton, J. F., and Tobinaga, S., Experientia, 16, 41 (1960).

66. Kubota, T., Matsuura, T., Tokoroyama, T., Kamikawa, T., and Matsumoto, T., Tetrahedron Letters, 325 (1961).

67. Kamikawa, T., Nippon Kagaku Zasshi, 83, 625 (1962); Chem. Abstr., 59, 534c (1963).

68. Narayanan, C. R., Pachapurkar, R. V., Pradhan, S. K., Shah, V. R., and Narasimhan, N. S., Chem. & Ind. (London), 322 (1964).

69. Narayanan, C. R., Pachapurkar, R. V., Pradhan, S. K., Shah, V. R., and Narasimhan, N. S., Chem. & Ind. (London), 324 (1964).

70. Connolly, J. D., Henderson, R., McCrindle, R., Overton, K. H., and Bhacca, N. S., Tetrahedron Letters, 2593 (1964).

71. McPhail, A. T. and Sim, G. A., Tetrahedron Letters, 2599 (1964).

72. Ollis, W. D., Ward, A. D., and Zelnik, R., Tetrahedron Letters,

2607 (1964).

73. Fritel, H. and Fetizon, M., J. Org. Chem., 23, 481 (1958).

74. Julia, S. and Moutonnier, C., Bull. Soc. Chim. France, 979 (1964).

75. Orr, J. C., Franco, M. L., Cross, A. D., and Sondheimer, F., Steroids, 3, 1 (1964); Chem. Abstr., 60, 12079g (1964).

76. Burness, D. M., J. Org. Chem., 21, 102 (1956).

77. Burness, D. M., Org. Syntheses, 39, 46 (1959).

78. Stetter, H. and Lauterback, R., Ber., 93, 603 (1960).

79. Wienhaus, H. and Dewein, H., Ber., 91, 256 (1958).

80. Morel, Th. and Verkade, P. E., Rec. Trav. Chim., 67, 539 (1948).

81. Morel, Th. and Verkade, P. E., Rec. Trav. Chim., 68, 619 (1949).

82. Morel, Th. and Verkade, P. E., Rec. Trav. Chim., 70, 35 (1951).

83. Reitsema, H. R., J. Am. Chem. Soc., 79, 4465 (1957).

84. Jackman, L. M., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, N. Y., 1959.

85. Woodward, R. B. and Eastman, R. H., J. Am. Chem. Soc., 72, 399 (1950).

86. Hansch, C., Scott, C., and Keller, H., Ind. & Eng. Chem., 42, 2114 (1950).

87. Bedoukian, P. Z., J. Am. Chem. Soc., 70, 621 (1948).

88. DePuy, C. H. and King, R. W., Chem. Rev., 60, 431 (1960).

89. Zalkow, L. H., Ellis, J. W., and Brennan, M. R., J. Org. Chem., 28, 1705 (1963).

90. Vavon, G. and Apchie, A., Bull. Soc. Chim. France, 43, 667 (1928).

91. Cornubert, R. and Borrel, C., Bull. Soc. Chim. France, 47, 958 (1930).

92. Bhacca, N. S. and Williams, D. H., "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964.

93. Dreiding, A. S. and Nickel, S. N., J. Am. Chem. Soc., 76, 3965 (1954).

94. Fieser, L. F. and Fieser, M., "Steroids", Reinhold, New York, 1959,

p. 15.

95. Criegee, R., Angew. Chem., 70, 173 (1958).

96. Cavill, G. W. K. and Solomon, D. H., J. Chem. Soc., 4426 (1955).

97. Zalkow, L. H. and Burke, N., Chem. & Ind. (London), 292 (1963).

98. Stocker, J. H., J. Org. Chem., 27, 2288 (1962).

99. Semmler, W., Ber., 25, 3513 (1892).

100. Bhacca, N. S., Johnson, L. F., and Shoolery, J. N., "High Resolution NMR Spectra Catalog", Varian Associates, Palo Alto, Calif., 1962.

101. Whitham, G. H., J. Chem. Soc., 2232 (1961).

102. Zalkow, L. H. and Ellis, J. W., J. Org. Chem., 29, 2626 (1964).

103. Djerassi, C., Hart, P. A., and Beard, C., J. Am. Chem. Soc., 86, 85 (1964).

104. Badger, G. M., "The Chemistry of Heterocyclic Compounds", Academic Press, New York, 1961.

105. Atwater, N. W., J. Am. Chem. Soc., 79, 5315 (1957).

106. Apsimon, J. W. and Edwards, O. E., Can. J. Chem., 40, 896 (1963).

107. Zalkow, L. H., Markley, F. X., and Djerassi, C., J. Am. Chem. Soc., 82, 6354 (1960).

108. Ireland, R. E., Church, R. F., and Shridhar, D. R., J. Org. Chem., 27, 707 (1962).

109. Djerassi, C. and Herbst, D., J. Am. Chem. Soc., 82, 4337 (1960).

110. Djerassi, C., Burakevich, J., Chamberlin, J. W., Elad, D., Toda, T., and Stork, G., J. Am. Chem. Soc., 86, 465 (1964).

111. Bowers, A., Halsall, T. G., Jones, E. R. H., and Lemin, A. J., J. Chem. Soc., 2548 (1953).

112. Ohloff, G., Osiecki, J., and Djerassi, C., Ber., 95, 1400 (1962).

113. Glazier, E. R., J. Org. Chem., 27, 4397 (1962).

114. Ringold, H. J. and Stork, G., J. Am. Chem. Soc., 80, 250 (1958).

115. Ainsworth, C., Org. Syntheses, 39, 27 (1959).

116. Tilichenko, M. N., Barbulescu, E., and Barbulescu, N., Rev. Chim. (Bucharest), 12, 631 (1961); Chem. Abstr., 57, 11042e (1962).

117. Attenburrow, J., Cameron, A. F. B., Chapman, J. H., Evans, R. M., Hems, B. A., Jansen, A. B. A., and Walker, T., J. Chem. Soc., 1094 (1952).

118. Guenther, E., "The Essential Oils", Vol. 2, p. 392, D. Van Nostrand Co., Inc., New York, 1949.

119. Heyl, F. W. and Herr, M. E., J. Am. Chem. Soc., 75, 1918 (1953).

120. Nelson, N. A. and Schut, R. N., J. Am. Chem. Soc., 80, 6630 (1958).

121. Dauben, W. G., Micheli, R. A., and Eastham, J. F., J. Am. Chem. Soc., 74, 3852 (1952).

122. Furst, A., and Plattner, P. A., Helv. Chim. Acta, 32, 275 (1949).

123. Rao, P. N. and Uroda, J. C., Tetrahedron Letters, 1117 (1964).

124. Fieser, L. F. and Dominguez, X. A., J. Am. Chem. Soc., 75, 1704 (1953).

125. Stork, G., Rosen, P., and Goldman, N. L., J. Am. Chem. Soc., 83, 2965 (1961).

126. Fuson, R. C. and Porter, H. D., J. Am. Chem. Soc., 70, 895 (1948).

127. Morton, J. R. and Wilcox, H. W., Inorg. Syntheses, 3, 48 (1953).

128. Poos, G. I., Arth, G. E., Beyler, R. E., and Sarett, L. H., J. Am. Chem. Soc., 75, 422 (1953).

129. Farmer, E. H. and Sutton, D. A., J. Chem. Soc., 10 (1946).

130. Nazarov, I. N., Ananchenko, S. N., and Torgov, I. V., Zhur. Obshehei Khim., 26, 819 (1956); Chem. Abstr., 50, 13845a (1956).

131. Wilds, A. L., Nowak, R. M., and McCaleb, K. E., Org. Syntheses, 37, 18 (1957).

132. Johnson, W. S., J. Am. Chem. Soc., 65, 1317 (1943).

133. Beilstein, III, 4, 897.

134. Zalkow, L. H. and Shaligram, A. M., unpublished results.

135. Olberg, R. C., Pines, H., and Ipatieff, V. N., J. Am. Chem. Soc., 66, 1096 (1944).

136. Prins, D. A., Helv. Chim. Acta, 40, 1621 (1957).

137. Gunar, V. I., Zav'yalov, S. I., and Krotov, A. I., Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk, 535 (1960); Chem. Abstr.,

54, 22405h (1960).

138. Snyder, H. R., Brooks, L. A., and Shapiro, S. H., Org. Syntheses, Coll. Vol. 2, 531 (1943).

139. Birch, A. J. and Robinson, R., J. Chem. Soc., 501 (1943).

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