STUDIES IN THE SYNTHESIS OF ATISINE

By

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CHAPTER I

HISTORICAL AND INTRODUCTION

Isolation and Structure Elucidation

Plants belonging to various species of _Aconitum_ and _Delphinium_
genera have been the subject of many chemical investigations. These two
genera produce several series of closely related monobasic alkaloids.
The poisonous nature of some of their species, coupled with the complex
nature of their alkaloid content, has attracted the increasing attention
of organic chemists. It was Jacobs who coined the name "aconite alkaloids"
for bases of both genera.

Atisine, a member of the aconite alkaloids, has long been known to
be present in the roots of _Aconitum heterophyllum_, and was first des-
cribed and named by Broughton (1) in 1877. It was not until 1937 that
Lawson and Topps (2) assigned the correct molecular formula ($C_{22}H_{33}NO_2$)
to this varnish -- like base, though its numerous crystalline derivatives
were already known (3).

A systematic chemical investigation of this aconite alkaloid was
initiated by Jacobs and his collaborators at the Rockefeller Institute in
1936. These researches disclosed the relationship of functional groups
together with its diterpenoid nature, and provided deep insight into the
complex and interesting chemistry of atisine (4). The first structure to
be proposed, I, by Jacobs (4) was later corrected by Wiesner and his
group (5), who assigned structure II (no stereochemistry indicated at

1

that time) mainly on the striking parallelism between the chemistry of
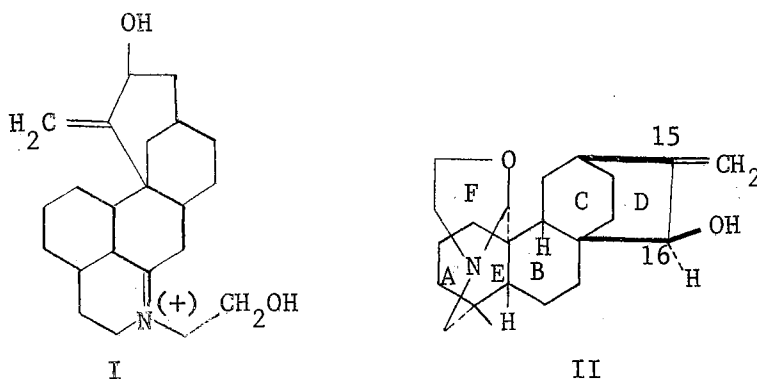
atisine and that of the closely related Garrya alkaloids (6, 7). The

degradative evidence accumulated over years in support of the structure

II and the work on related alkaloids have been reviewed in three articles

(8 - 10). Djerassi and co-worker (11) have established the absolute

configuration of atisine and it can now be fully represented by structure

II.

Synthetic Approaches to Atisine

Atisine has been of particular importance recently because it is less

complex than the other aconite alkaloids and was the first of the group

for which synthetic approaches were offered. The two total syntheses of

this alkaloid (12 - 16), reported very recently, can be considered as

the outcome of efforts of various research groups which were directed

toward solving the intricacies of smaller portions of this complex

molecule (17 - 26). The problem involves three distinct phases. One,

synthesis of the nitrogen-containing E ring, second, construction of the

C/D bicyclo[2.2.2]octane ring system with means of introducing the

desired substituents at C-15 and C-16, and finally, elaboration of the

oxazolidine F ring. Prior to the achievement of total syntheses, success

had been recorded in each of the phases described above. These develop-
ments will be surveyed before mention is made of the sequence of reactions
which led to the two total syntheses.

The construction of the carbocyclic system has not been a great
point of concern because work done in the steroid field had already led
to many methods for its synthesis (27). Construction of the nitrogen-
containing E ring, however, offered a new challenge. The means of build-
ing the C/D ring system also had to be provided within the molecule
chosen for the construction of the E ring. Most workers engaged in this
pursuit chose the stable anisole ring for the subsequent elaboration of
the bicyclooctane ring system.

Construction of the E Ring

One successful solution to the synthesis of the E ring, recorded by
Edwards and ApSimon (18), utilizes the cis-C-4-CO_2H and the C-10-CH_3 of
O-methylpodocarpic acid, III, for construction of the E ring. Photolysis

III, R = CO_2H; R⁻ = CH_3 V   VI
IV, R = CON_3; R⁻ = CH_3
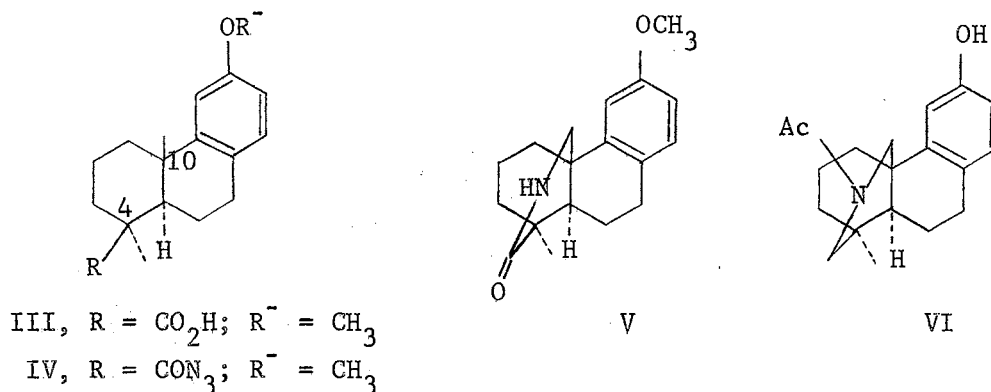
of O-methylpodocarpic acid azide, IV, was shown to yield the desired
lactam V. These authors have further shown that the phenol VI, derived
from V, bears an enantiomeric relationship to the corresponding compound

obtained in the degradation of atisine (28).

Wiesner, Valenta and associates (19) have described another approach to this problem. They have been able to bridge ring A with a nitrogen-containing ring by the introduction of a functional group at C-10 and then an intramolecular acylation of C-4. This stereospecific synthesis of the racemic amine VII begins with the alkylation of the tetralone VIII with ethyl bromoacetate using the enamine method and subsequent conversion of the keto ester IX to the tricyclic unsaturated keto acid X by means of the Robinson-Mannich reaction. Reduction of X with lithium in
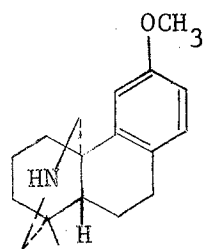
VII
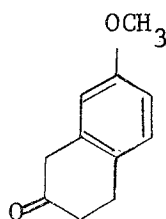
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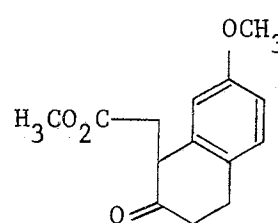
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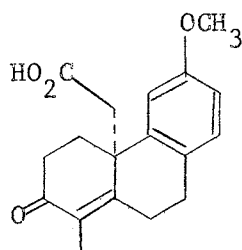
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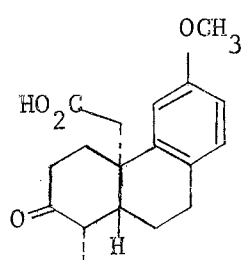
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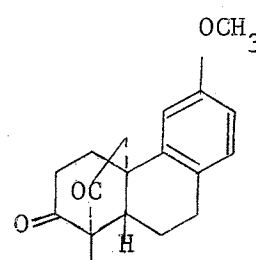
XII

ammonia yields the saturated keto acid XI with the desired <u>trans</u> A/B ring junction.

A prolonged treatment of XI with p-toluenesulfonic acid in boiling benzene resulted in the acylation at C-4 to yield the thermodynamically stable diketone XII. Selective thioketalization of the six-membered ring

ketone in XII followed by treatment with Raney nickel in ethanol provided

the alcohol XIII. The olefin XIV, obtained by pyrolysis of the benzoate
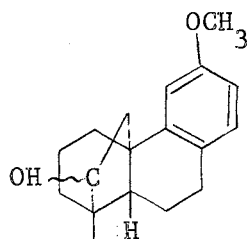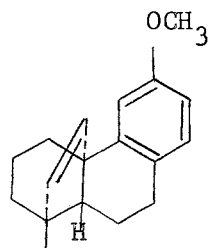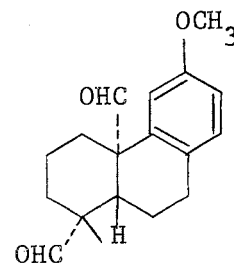
XIII   XIV   XV

of XIII, when treated with osmium tetroxide and then with lead tetra-

acetate furnished the dialdehyde XV. The final stage of the synthesis

was completed by the catalytic hydrogenation of the oxime derivative of

XV. The dl-amine VII was found to be identical in its infrared spectrum

with the optically active form prepared by lithium aluminum hydride-

reduction of the lactam V synthesized earlier by Edwards and ApSimon

(18).

A nonstereospecific but elegant approach recently described by Iwai,

Ogiso and Shimizu (20) offers yet another path for incorporation of the

nitrogen-containing ring E in a suitable carbocyclic system. These

authors realized the introduction of the E ring at an early stage of

synthesis by effecting a condensation of formaldehyde and methylamine

with the ketone XVI. The resulting ketone XVII was converted into the

α,β-unsaturated aldehyde XVIII by condensation with lithium ethoxyacetyl-

ide, partial reduction and then acid-catalyzed rearrangement. Catalytic

hydrogenation of XVIII, which followed a nonstereoselective path because
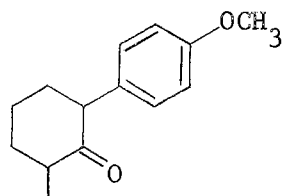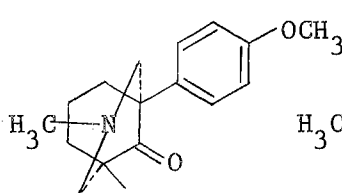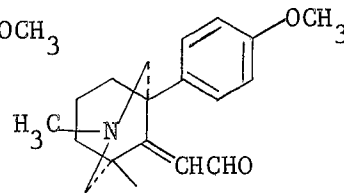
XVI   XVII   XVIII

of inherent limitations in the synthetic scheme, yielded the isomeric

aldehydes XIX and XX. The aldehydes were separately subjected to hydride-

reduction and their polyphosphonic acid-catalyzed cyclization yielded

$$\text{XIX, } R = \begin{cases} CH_2CHO \\ H \end{cases}$$

$$\text{XX, } R = \begin{cases} H \\ CH_2CHO \end{cases}$$
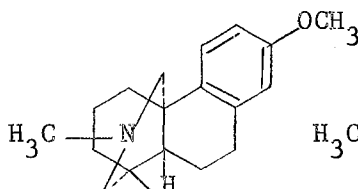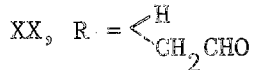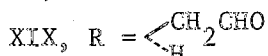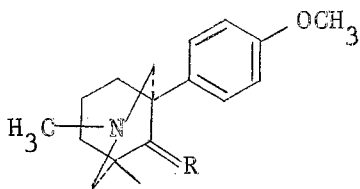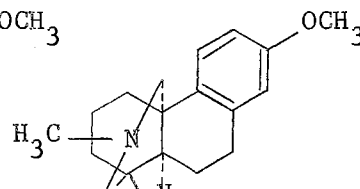
XXI   XXII

the tetracyclic amines XXI and XXII. Unfortunately, these workers did

not succeed in establishing which isomer was to be represented by XXI

and which by XXII.

Construction of the Bicyclo[2.2.2]octane C/D Ring System

Very recently much work has been directed toward construction of the

bicyclooctane ring system (21-24, 26). Different types of compounds

have been subjected to chemical manipulation in order to achieve this

end. Pelletier and Parthasarathy (21) used XXIII obtained earlier as a

degradation product of atisine (25, 29, 30); Ireland and Bell (22)

started with racemic XXIV; Ayer and co-workers (24) utilized abietic

acid, XXV, while Othman and Rogers (23) selected podocarpic acid, XXVI,

as a starting material. The synthetic investigations of Zalkow and

Girotra (26, 31-33) in this series which are the subject of this disser-

tation started with abietic acid and podocarpic acid.

XXIII   XXIV   XXV
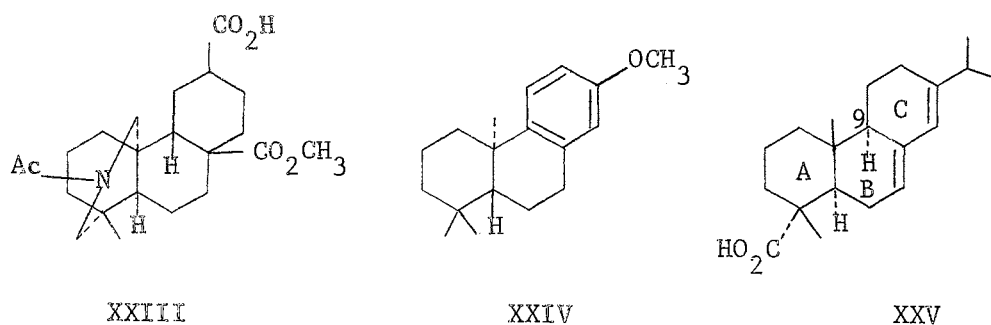
Pelletier and Parthasarathy (21) in a recent communication, have

described the conversion of XXIII to XXXIV; the latter compound had

already been reconverted to atisine (25, 34, 35). Diester XXVII obtained

by homologation of XXIII via the Arndt-Eistert procedure was converted

into a mixture of epimeric keto esters XXVIII by the Dieckmann cyclization

method. Hydrolysis of XXVIII followed by decarboxylation gave the

ketone XXIX which on alkylation with methyl iodide yielded a mixture of

epimeric ketones XXX containing the methyl group at the desired position.

Bromination of XXX followed by dehydrobromination afforded the enone

XXXI which on reduction afforded a mixture of allylic alcohols from

which the desired isomer XXXII could be separated from the by-product

XXXIII. Hydrolysis of XXXII yielded the amino alcohol XXXIV previously

XXVI XXVII XXVIII, R = CO₂CH₃
XXIX, R = H
XXX, R = CH₃

XXXI XXXII, R = Ac XXXIII
XXXIV, R = H
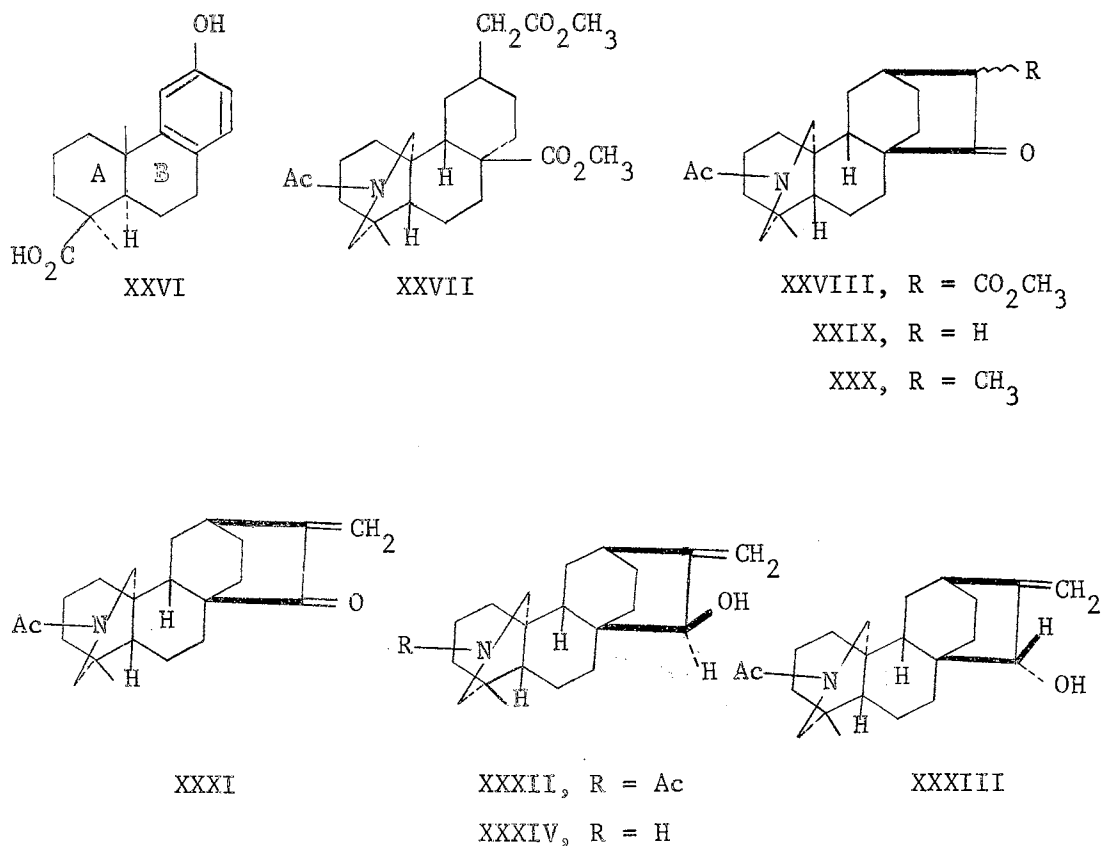
available from atisine and which, in turn, has already been reconverted

to the parent alkaloid (25, 34, 35). This work offered a synthesis of

atisine from the ester XXIII, which was previously obtained by the

degradation of atisine.

Ireland and Bell (22) followed a different approach in the synthesis

of the C/D ring system. This successful synthetic pursuit started with

the racemic tricyclic ether XXIV, which on Birch reduction followed by

hydrolysis yielded the ketone XXXV. Reduction of XXXV with sodium boro-

hydride afforded the allylic alcohol XXXVI, an important intermediate

which has been ingeniously utilized by these authors in the accomplishment

of several related syntheses (36, 37). Equilibration of XXXVI with ethyl

XXXV

XXXVI

XXXVII

XXXVIII

XXXIX

XL, R = O
XLI, R = CH$_2$
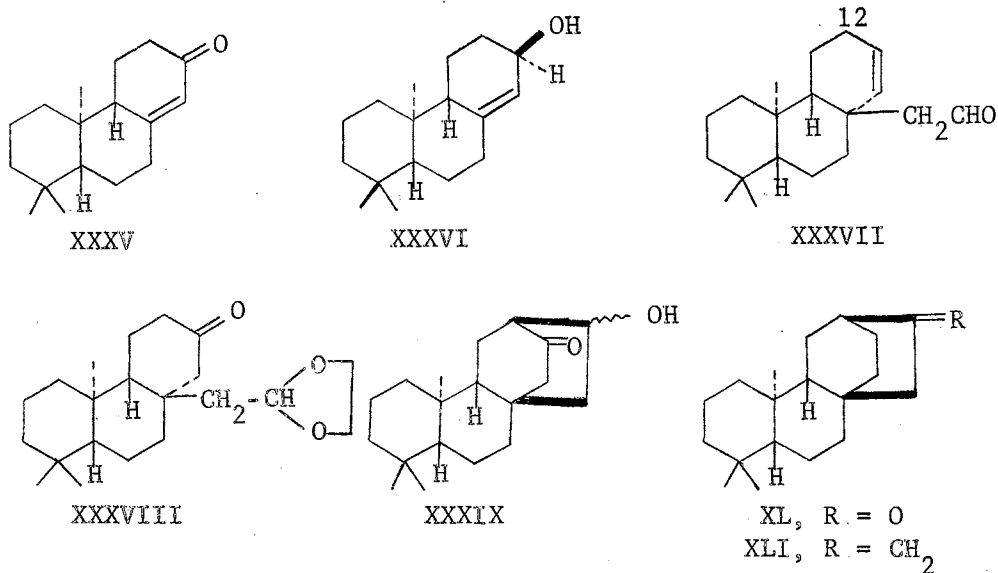
vinyl ether and subsequent pyrolysis of the resulting vinyl ether

afforded the aldehyde XXXVII. The desired activation of the C-12-

methylene was achieved by preparation of the acetal ketone XXXVIII via

hydroboration-oxidation of the ethylene acetal of XXXVII. Ring closure

was effected by acid-catalyzed aldol-type condensation; then Wolff-

Kishner reduction of the tetrahydropyranyl ether of the resulting alcohol

XXXIX, followed by acid-catalyzed cleavage of the ether moiety and

finally Jones oxidation, afforded the desired ketone XL.

Treatment of XL with methylenetriphenylphosphorane yielded the

exocyclic olefin XLI which was transformed into its endocyclic isomer

XLIII via allylic bromination with N-bromosuccinimide and then reduction

of the resulting primary allylic bromide XLII with lithium aluminum

hydride. Photosensitized oxidation of XLIII followed by reduction of

the resulting rearranged allylic hydroproxides led to introduction of

the hydroxyl group at C-16 and gave the separable mixture of allylic

alcohols XLIV and XLV. It was not possible, however, to determine

XLII   XLIII   XLIV, R = —OH / H

XLV, R = —H / OH
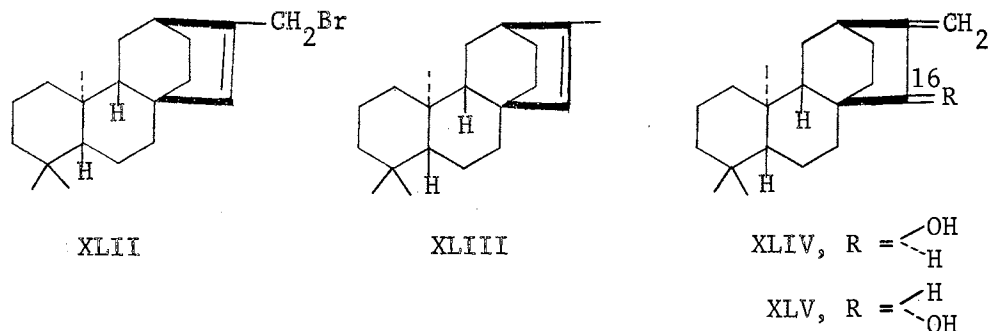
which isomer was to be represented by XLIV and which by XLV.

Investigations to explore the utility of podocarpic acid, XXVI, as a starting material for the synthesis of atisine have recently been recorded by Othman and Rogers (23). In order to test the applicability of their synthetic scheme they undertook experiments with compounds of the 2,4a-ethanodecahydronaphthalene series. The feasibility of their approach was quite apparent when they were able to effect the conversion of 6-methoxytetralin, XLVI, to XLVII. These workers have extended this approach to podocarpic acid and have been able to synthesize XLVIII, unfortunately in very poor yield. Moreover they do not mention whether

XLVI   XLVII   XLVIII
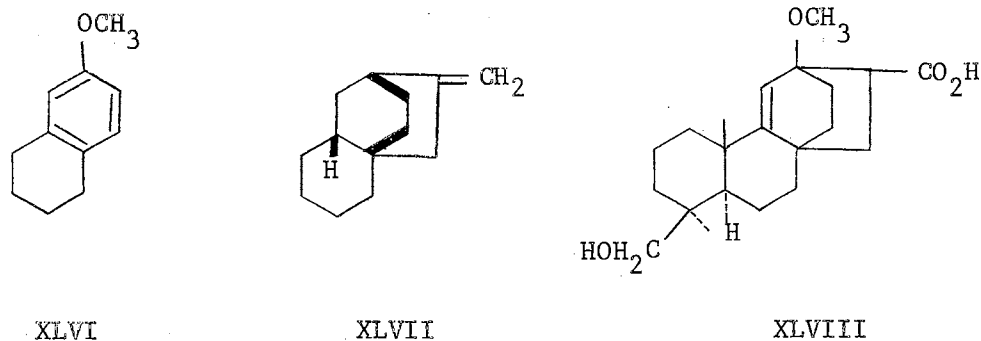
the carboxyl group in XLVIII is on the bridge suitable for ultimate

introduction of the methylene group and the hydroxyl group as present

in atisine.

Ayer and co-workers (24) following a path similar to that of Zalkow

and Girotra (26), have synthesized the tetracyclic hydrocarbon XLIX from

abietic acid. The construction of the C/D ring system was realized by

use of the Diels-Alder reaction between L and maleic anhydride. The
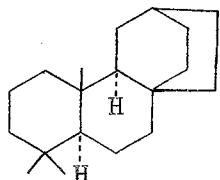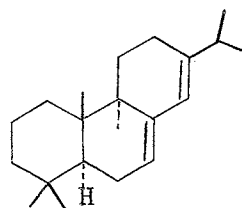
XLIX   L

synthesis of XLIX, besides being important from a synthetic point of

view, has provided more confirmatory evidence regarding the absolute

configuration of atisine, since XLIX is enantiomorphic with the same

hydrocarbon obtained from atisine (24).

Construction of the Oxazolidine F Ring

Construction of the oxazolidine F ring was first realized by Wiesner

and his co-workers (7) in the case of the related Garrya alkaloids.

Guided by these results, Pelletier and Jacobs (25) performed a similar

sequence of experiments in the atisine series. The amino alcohol XXXIV,

a degradation product of atisine, was shown to yield dihydroatisine LI,

by alkylation with ethylene chlorohydrin. Careful oxidation with osmium

tetroxide afforded a 60 - 70% yield of isoatisine, LII. The interconversion

of atisine and isoatisine (34, 35) coupled with the synthesis of the

LI   LII
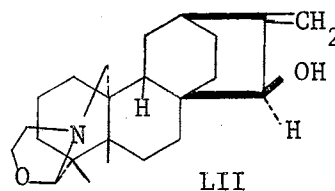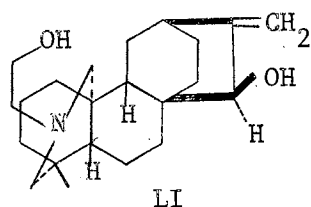
latter from the amine XXIV constitutes an important phase in the recently

described total syntheses (12-16).

Total Syntheses

Nagata and his associates (12) have very recently described the

first synthesis of atisine in the racemic form. These authors have

utilized the tricyclic conjugated ketone LIII, available from 6-methoxy-

1-tetralone, LIV, in four steps by the Stork method (38). This molecule

possesses all the features necessary for the introduction of the nitrogen-

containing E ring as well as the construction of C/D ring system. The

LIII   LIV   LV, R = O

LVI, R = CHO / H

LVII, R = CH₃ / CHO

LVIII   LIX   LX, R = CN

LXI, R = COCH₃
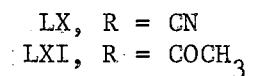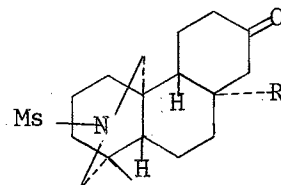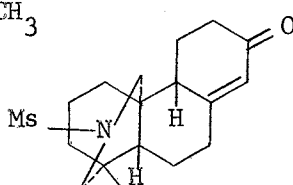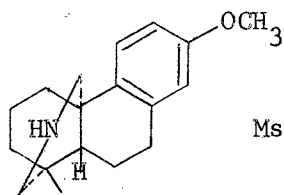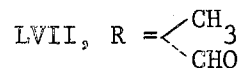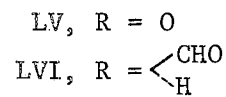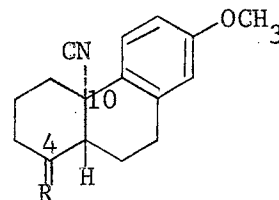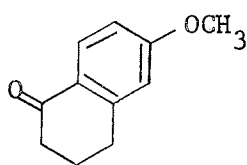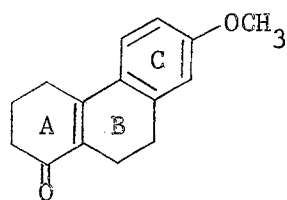
bridging of the A ring by the nitrogen-containing E ring, which was first

to draw the attention of these workers, was achieved through the intro-

duction of suitable substituents at C-10 and C-4 and intramolecular

condensation between these groups. The two necessary substituents were

introduced as follows. Hydrocyanation of LIII with hydrogen cyanide

and diethylaluminum chloride followed by epimerization through crystalli-

zation in the presence of hydrochloric acid afforded a good yield of LV

with the desired trans fused A/B ring system. Treatment of the cyano

ketone LV with p-tolyloxymethylenetriphenylphosphorane followed by acid

hydrolysis gave LVI. Stereoselective methylation of LVI afforded LVII

with the C-4-methyl group trans to the C-10-cyano group; the latter

compound on alkaline hydrolysis, ethylation and finally reduction with

lithium aluminum hydride provided the cyclic secondary amine LVIII.

The construction of the E ring having been completed, attention was

turned toward the construction of the bicyclooctane C/D ring system.

The free base LVIII was converted into the conjugated ketone LIX via a

modified Birch reduction, then mesylation and finally acid treatment.

If the E ring is ignored, this ketone possesses all the features of the

ketone XXXV used earlier by Ireland and Bell (22) in the construction of

the C/D ring system. Comparison of the two synthetic routes used to

attain the same goal suggests the variety of ways one can follow to

realize the same objective. The approach of the Japanese workers,

though lengthy, represents a novel and well planned sequence of reactions.

The problem of functionalizing the cyclohexenone ring so as to construct

the C/D ring system was achieved by hydrocyanation of LIX. The resulting

cyano ketone LX, which possesses the desired trans B/C ring junction, on

ketalization, treatment with methyllithium and acid hydrolysis afforded

the diketone LXI. Cyclization of LXI by dilute alkali followed by

acetylation and stereoselective reduction with sodium borohydride provided

the alcohol LXII. The hydroxyl group in LXII was transformed into a

LXII   LXIII   LXIV, $R_1 = \overset{O-\!\!\rule{0pt}{1.2ex}}{\underset{O-\!\!\rule{0pt}{1.2ex}}{\big\langle}}$

$R_2 = H$

LXV, $R_1 = O$

$R_2 = Ms$

LXVI, $R_1 = Ms$ LXIX   LXX, $R = \overset{OH}{\underset{H}{\big\langle}}$

$R_2 = O$

LXVII, $R_1 = Ms$ LXXI, $R = \overset{H}{\underset{OH}{\big\langle}}$

$R_2 = CH_2$

LXVIII, $R_1 = Ac$

$R_2 = CH_2$
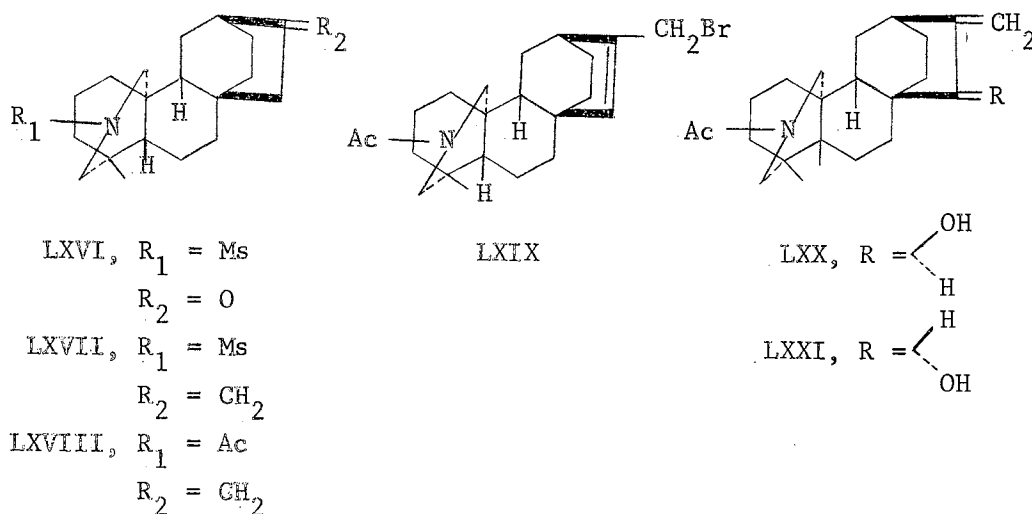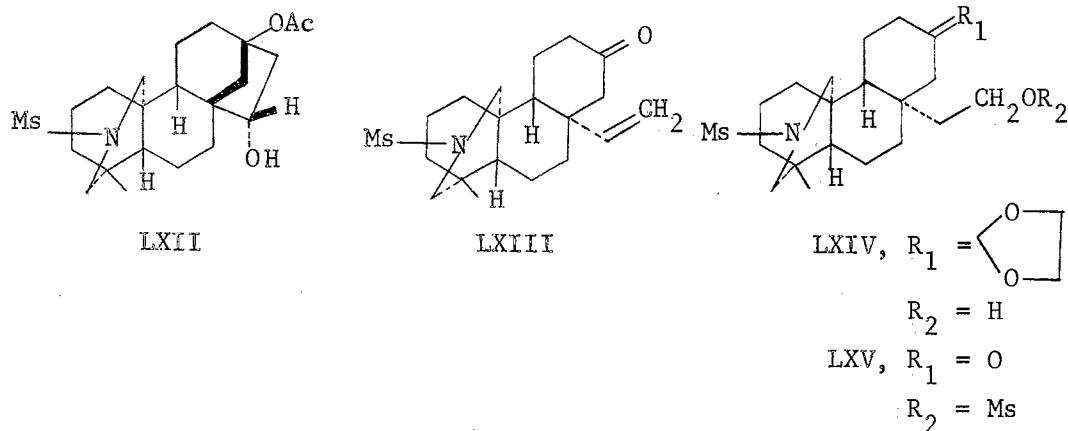
mesyl group in order to effect a facile alkaline degradation of the

bicyclo[3.2.1]octane ring system. The vinyl ketone LXIII thus obtained

was ketalized, hydroborated and then oxidized to the hydroxy ketal

LXIV which after deketalization and mesylation yielded LXV. Cyclization

of LXV with potassium tert-butoxide afforded the desired pentacyclic

ketone LXVI thus completing the synthesis of the carbon skeleton of the

alkaloid.

Introduction of the desired allylic alcohol system was effected as

follows. The exocyclic olefin LXVII obtained via the Wittig reaction of the ketone LXVI with methylenetriphenylphosphorane on Birch reduction and subsequent acetylation yielded the N-acetyl compound LXVIII. Bromination of the olefin LXVIII with N-bromosuccinimide afforded mainly the rearranged allylic bromide LXIX. Epoxidation of LXIX followed by treatment with zinc and ethanol gave a separable mixture of allylic alcohols LXX and LXXI. Both were found to be identical with the naturally derived materials by the complete identity of infrared spectra. Since the transformation of LXX to atisine in the natural series had already been performed, this work amounted to a stereospecific total synthesis of dl-atisine (25, 34, 35).

Masamune (13-16) has followed an altogether different approach to achieve the total synthesis of atisine. The first phase was the conversion of the tetrahydronaphthalene carboxylic acid LXXII into the racemic ketone LXXIII possessing the bicyclo[3.2.1]octane system (13). The second stage comprised the synthesis of garryine, LXXIV, one of the Garrya alkaloids, from LXXIII (15). The last phase involved the degradation of veatchine, LXXV, into the dimethyl ester LXXVI (16). Since the interconversion of garryine, LXXIV, and veatchine, LXXV, (39), and the synthesis of atisine from LXXVI had already been accomplished, this work represents a total synthesis of atisine (21, 25, 34, 35).

LXXII   LXXIII   LXXIV

LXXV   LXXVI
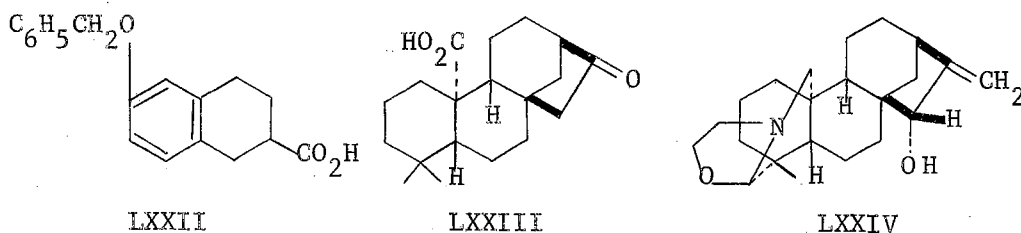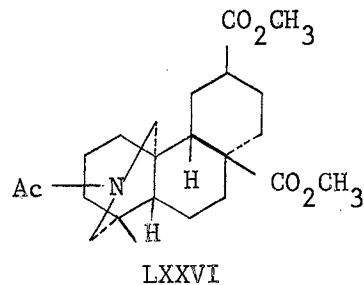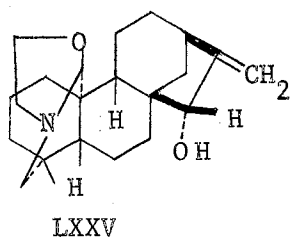
Transformation of veatchine, LXXV, into LXXVI and XXIII was initiated

by the conversion of the former to the already known azomethine LXXVII

(11) and then to the amide LXXVIII. Oxidation of LXXVIII with sodium

metaperiodate and potassium permangnate gave the diacid LXXIX, the

dimethyl ester of which was epimerized to the trans isomer LXXX by treat-

ment with sodium methoxide. Selective saponification of LXXX afforded

the monoester carboxylic acid LXXXI. The problem of the synthesis of

LXXVI now resolved to the removal of the carbomethoxy group from C-13

LXXVII   LXXVIII   LXXIX

LXXX, R = OCH_3

LXXXI, R = OH

LXXXII, R = CH_3

LXXXIII, R_1 = H, OH

R_2 = H

LXXXIV, R_1 = O

R_2 = H

LXXXV, R_1 = O

R_2 = CO_2CH_3
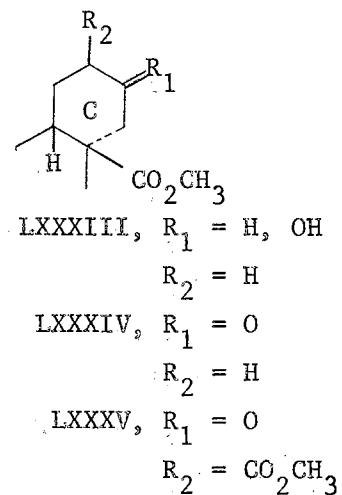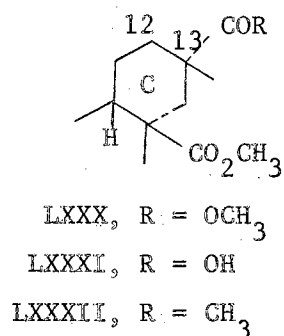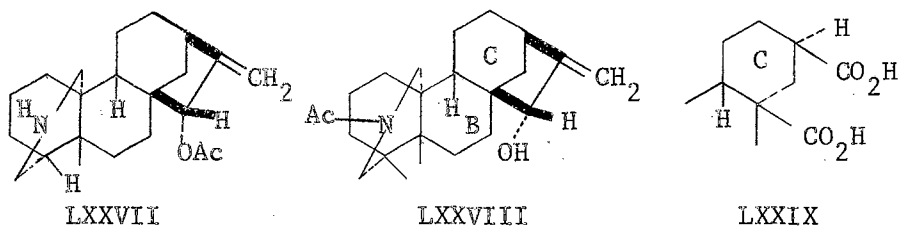
and its subsequent introduction at C-12 which was accomplished as follows. Treatment of LXXXI with oxalyl chloride followed by dimethylcadmium provided the methyl ketone LXXXII which on oxidation by the Baeyer-Villiger procedure and then mild alkaline hydrolysis afforded the hydroxy compound LXXXIII. Oxidation of LXXXIII with chromic acid gave the ketone LXXXIV which on treatment with dimethyl carbonate and sodium methoxide afforded the β-keto ester LXXXV. An unsaturated dimethyl ester was obtained via sodium borohydride-reduction of LXXXV and then acid-catalyzed dehydration of the resulting epimeric alcohols, which on hydrogenation and treatment with sodium methoxide provided LXXVI. The dimethyl ester LXXVI and monomethyl ester carboxylic acid XXIV derived by alkaline hydrolysis of LXXVI were found to be identical with those from atisine in all respects, thus completing the synthesis of atisine.

Rational to the Synthesis of Atisine from Podocarpic Acid

In view of the recent and increasing interest in the synthesis of atisine as evident from the summary given above, our investigations in this field, which are the subject of this dissertation, hardly require any further justification. The diterpenoid acids, abietic acid, XXV, and podocarpic acid, XXVI, were selected as starting materials. Each of these acids offers certain advantages over the other, but they have many structural features in common. Besides their ready availability, the presence of the tricyclic carbon skeleton with a trans fused A/B ring system was one of their common attractive features. Also ring C of both the acids, because of its unsaturated character, appeared to be an asset which could be utilized to construct the bicyclooctane ring system. It seems relevant to point out here that any synthetic approach

based on the utilization of these diterpenoid acids would lead to the
mirror image of the naturally occurring isomer since the absolute con-
figurations of the A/B ring junctures in these acids and that of C-9 in
abietic acid are antipodal to those of the corresponding centers in
atisine (11).

Abietic acid is by far the most common resin acid and can be pre-
pared from rosin by the action of heat or of acids (40). Like levopimaric
acid, LXXXVI, it reacts with maleic anhydride, though at high temperature,
to give an adduct, maleopimaric acid, which has been assigned the
stereochemistry shown in LXXXVII. This assignment was based mainly on

LXXXVI   LXXXVII   LXXXVIIIa C-15 β-CO$_2$CH$_3$
                                             LXXXVIIIb C-15 α-CO$_2$CH$_3$
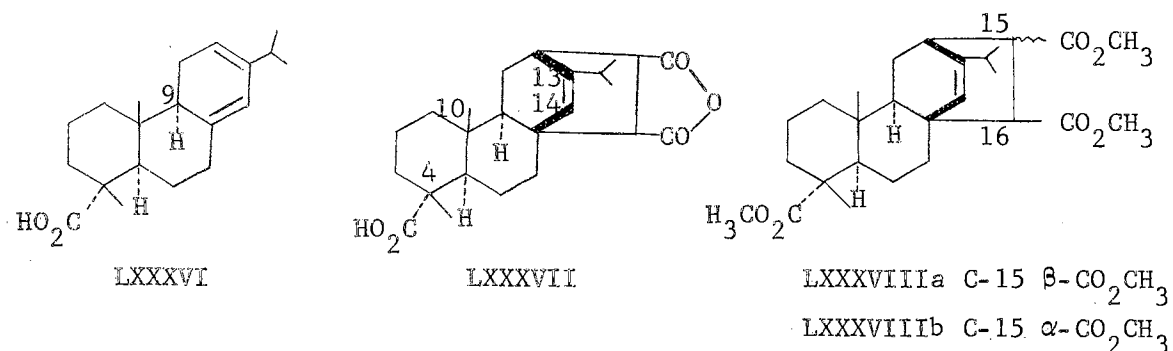
studies of molecular models coupled with the observation that a single
isomer is obtained in the reaction (41). At that time the configuration
at C-9 in levopimaric acid had not been definitely established, and
in fact, Klyne (42), using the method of molecular rotation difference,
had assigned it the β-configuration. Recent chemical and rotatory
dispersion evidence has established the α-orientation at C-9 (43, 44).
Nuclear magnetic resonance and chemical studies of maleopimaric acid
and related compounds have clearly established that maleopimaric acid
does, indeed, correspond to LXXXVII (45-57). The appearance of the C-10
methyl group at an unusually high field in the n.m.r. spectrum of this
compound shows that the double bond at 13,14-position exhibits a

long-range shielding effect. This fact requires the α-configuration at C-9 in maleopimaric acid to allow the C-10 methyl group and the double bond to be spatially close to each other for the observed shielding to occur.

Maleopimaric acid possesses a bicyclo[2.2.2]octane C/D ring system and offers all the necessary features for elaboration of the C/D ring system of atisine. Removal of the isopropyl group, a step toward the intended goal, was considered to be feasible in view of the earlier studies of Ruzicka and Kaufmann (48) which showed that the isopropyl group rather than the double bond is attacked during the action of ozone on the trimethyl ester of maleopimaric acid, LXXXVIIIa.

Another feature of importance in LXXXVII is the bridge carrying the anhydride moiety, which is stereochemically situated in such a way that it offers, after the transformation of anhydride to a suitable group, a means for the subsequent elaboration of the allylic alcohol system as present in atisine itself. It is apparent that maleopimaric acid, unfortunately, does not offer an obvious way for the incorporation of the nitrogen-containing E ring. The α-carboxyl group at C-4, which is situated trans to the methyl at C-10, does not offer an access to this objective. On the other hand, podocarpic acid possesses a β-carboxyl group at C-4 and was considered to be an important starting material from this point of view. Recent observations of Edwards and ApSimon (18), which were recorded during the progress of our work, have clearly emphasized the importance of the carboxyl group of podocarpic acid in this respect. However, the fact that no derivative of podocarpic acid possessing the desired bicyclo[2.2.2]octane C/D ring system was then known necessitated the modification of its C ring in such a way

as to construct the C/D ring system. It was also necessary to know

unambiguously the structure of such an intermediate before further

synthetic investigations were continued. In this respect, maleopimaric

acid appeared to be indispensable because it offered an access to com-

pounds useful for determining the structure of those derived from

podocarpic acid.

Maleopimaric acid has been successfully subjected to a series of

reactions in order to elaborate the bicyclo[2.2.2]octane C-D ring

system (26, 31, 32). These studies, besides being fruitful in the

realization of the above objective, made available compounds of

unequivocal structures for the purpose of comparison with those derived

from podocarpic acid and thereby allowed unambiguous structure elucida-

tion of the tetracyclic intermediates derived from podocarpic acid (33).

CHAPTER II

RESULTS AND DISCUSSION

Construction of the Bicyclo[2.2.2]octane Ring System in Abietic Acid Series

The purpose of the present studies as already described in Chapter I

was to explore a route to the synthesis of the bicyclo[2.2.2]octane ring

system of atisine using abietic acid, XXV, and podocarpic acid, XXVI, as

starting materials. Also, the latter starting material was considered

to be invaluable for extension of the synthetic scheme into construction

of the nitrogen-containing E ring of atisine.

The choice of abietic acid as a starting material was natural

because maleopimaric acid, the Diels-Alder adduct of abietic acid and

maleic anhydride of unambiguous structure LXXXVII, is readily available.

Also, the experiments in this series were expected to make available the

tetracyclic compounds of known structures which were foreseen to play

an important part in the success of studies in the podocarpic acid series.

In view of this, investigations were first conducted in the abietic

acid and then in the podocarpic acid series.

The synthesis of the tetracyclic hydrocarbon XLIX from maleopimaric

acid was planned as a first phase because it possessed the complete carbon

skeleton of atisine and was considered to be important in structure

elucidation of tetracyclic compounds in the podocarpic acid series. Also,

comparison of XLIX with the hydrocarbon derived from atisine would give

more confirmatory evidence regarding the absolute configuration of

21

atisine, in support of which only indirect evidence was available at the time this work was started. The second phase of these investigations was the complete elaboration of the C/D ring system of atisine. This work resulted in the synthesis of the exocyclic olefin LXXXIX. The further conversion of the racemic form of LXXXIX to XLIV was recently reported by Ireland and Bell (22) and amounted to a total synthesis of

LXXXIX
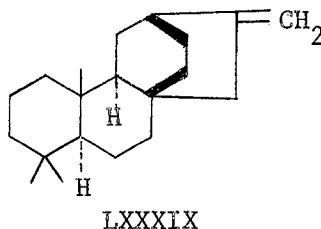
the C/D ring system from abietic acid since the latter compound has already been synthesized (49-51).

Action of Ozone on LXXXVIIIa and Synthesis of XLIX

The conversion of LXXXVII into XLIX involved three phases: One, removal of the isopropyl group of ring C; second, removal of the anhydride moiety of ring D; and finally, conversion of the C-4 carboxyl to methyl.

Ruzicka and Kaufmann (48) came across an unusual reaction during their studies directed toward the structure elucidation of abietic acid. They found that the isopropyl group rather than the double bond of ring C was attacked during the action of ozone on the trimethyl ester of maleopimaric acid LXXXVIIIa. They were able to isolate the α,β-unsaturated ketone XCa and the diene XCI. An examination of a molecular model of LXXXVIIIa clearly indicates that both faces of the double bond are hindered, thus suggesting an explanation for the abnormal ozonolysis

XCa, C-15 CO$_2$CH$_3$ β

XCb, C-15 CO$_2$CH$_3$ α

XCI
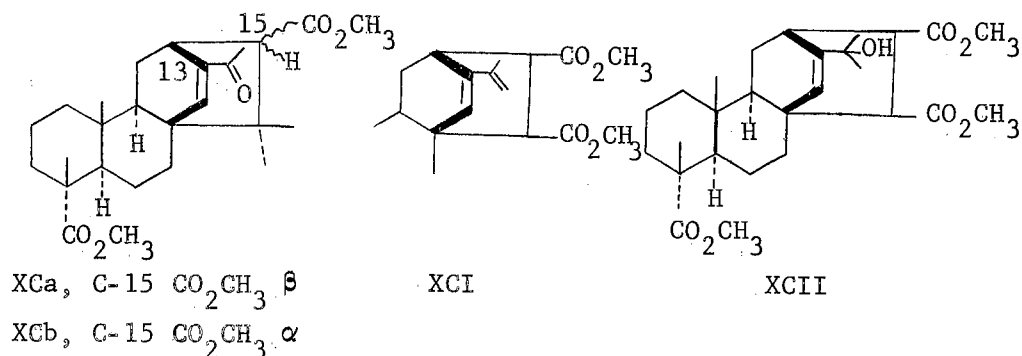
XCII

observed by Ruzicka and Kaufmann. They suggested the following scheme to explain the reaction. The formation of XCa was visualized as taking
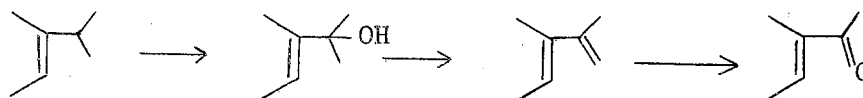
place by hydroxylation of LXXXVIIIa followed by dehydration of the resulting alcohol XCII to the diene XCI, and finally attack of ozone on the less hindered double bond of XCI. However, the hydroxy compound XCII, the proposed intermediate, was not isolated.

The abnormal ozonolysis of LXXXVIIIa leading to XCa suggested a means of functionalizing and subsequent removal of the isopropyl group. In order to prepare XCa as an intermediate for the synthesis of XLIX, and to shed more light on the course of this unusual reaction, the trimethyl ester LXXXVIIIa was subjected to the action of ozone.

Following the previous procedure a solution of LXXXVIIIa in acetic acid was exposed to a steady stream of oxygen-containing ozone for

forty-eight hours at room temperature. The crude product was separated into acidic ($\approx$20%) and neutral ($\approx$80%) fractions. The neutral fraction was further separated into nonketonic ($\approx$25%) and ketonic ($\approx$75%) fractions using Girard's T reagent. Hydrolysis of the Girard derivative gave the previously reported ketone XCa, together with a second ketone XCIIIa ($C_{24}H_{34}O_7$). Nuclear magnetic resonance spectroscopy proved to be particularly useful in arriving at the structure of XCIIIa. Ayer, McDonald and Sothers (46) have made a detailed study of the n.m.r. spectra of derivatives of maleopimaric acid. These workers observed that in compounds such as LXXXVIII and XCa (Plate I), double bond at C-13, C-14 has a long-range shielding effect on protons of the methyl group at C-10. These protons appear at $\approx$ δ0.50 in compounds such as LXXXVIII and XCa, whereas the protons of the methyl group at C-4 appear at approximately δ1.10. Removal of the C-13, C-14 double bond results in a shift of the C-10 methyl protons to $\approx$ δ1.0.

The signal at highest field in the n.m.r. spectra of XCIIIa (Plate II) appeared at δ0.83, and the vinylic proton present in the
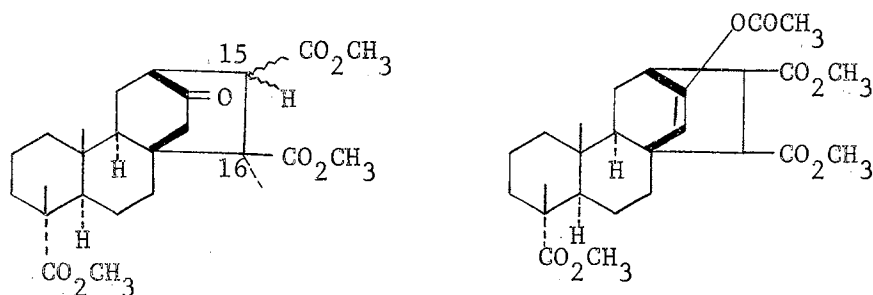
XCIIIa, C-15 β-carbomethoxy   XCIV

XCIIIb, C-15 α-carbomethoxy

spectra of LXXXVIIIa (δ5.31) and XCa (δ6.90) was absent. Both LXXXVIIIa

and XCa gave a positive test for a double bond with tetranitromethane,

but XCIIIa did not. The n.m.r. spectrum of XCIIIa also indicated the

absence of an isopropyl group, and of a methyl group attached to a car-

bonyl group (as present in XCa at δ2.36). On the basis of these facts

together with the elemental analysis and infrared spectrum, it appeared

likely that this ketone possessed structure XCIIIa. Since the double

bond in LXXXVIIIa was so hindered as to be unaffected by ozone, it

seemed possible that the Baeyer-Villiger reaction on XCa would likewise

proceed without attack on the double bond and would lead, therefore, to

ester XCIV. Hydrolysis of ester XCIV should give XCIIIa. This was

found to be the case. Treatment of XCa with peroxytrifluoroacetic acid

afforded a 61% yield of XCIV. The n.m.r. spectrum of XCIV showed the

C-14 vinyl proton at δ5.34, upfield from the C-14 proton in XCIIIa,

since in the latter compound the double bond is conjugated. The methyl

protons of the acetoxy group in XCIV appeared at δ2.18 and the C-10

methyl protons at δ0.75. Acid-catalyzed hydrolysis of XCIV at room

temperature gave XCIIIa identical in all respects with that isolated

from the ozonolysis reaction mixture.

A second compound, XCV, was isolated in low yield from the Baeyer-

Villiger reaction mixture. This substance was found not to be the

tetramethyl ester resulting from the insertion of an oxygen atom on the

methyl side of ketone XCa; the latter ester, XCVIIIa, was available for

comparison. The infrared and n.m.r. spectra of XCV showed it to be an

alcohol and to contain three carbomethoxy groups. Since the C-10 methyl

protons appeared at δ0.67 in the n.m.r., the C-13, C-14 double bond

was apparently still present. However, no vinylic protons were evident

and an unexplained 3-proton signal was present at $\delta 3.05$. No satisfactory

structure for XCV has yet been offered.

When LXXXVIIIa, XCa, and XCIIIa were refluxed in alkaline solution

then the resulting acids re-esterified with diazomethane, the respective

isomeric compounds LXXXVIIIb, XCb, and XCIIIb were obtained. The tri-

methyl ester LXXXVIIIb was identical with that obtained from the Diels-

Alder reaction between methyl abietate and fumaric acid followed by

esterification with diazomethane (52). The more stable _trans_ isomers

were assigned structures in which the C-15 carboxyl group is down (α),

since Ayer and co-workers (46) reported the conversion of LXXXVIIIb

to a γ lactone XCVI with the oxygen atom attached at C-15 and because

of recent work from this laboratory (52). Both XCVI and the C-15

epimer of XCVI have been prepared by Zalkow and co-workers (45, 52).
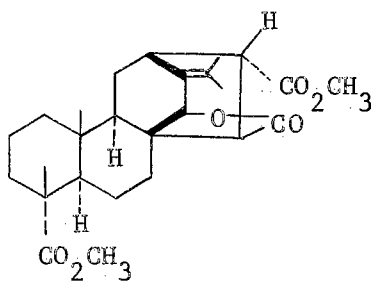
XCVI
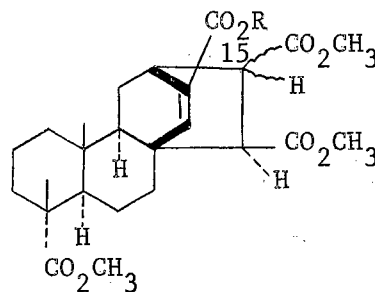
XCVII,   C-15 α-carbomethoxy, R = H

XCVIIa, C-15 α-carbomethoxy, R = CH$_3$

XCVIII, C-15 β-carbomethoxy, R = H

XCVIIIa, C-15 β-carbomethoxy, R = CH$_3$

The acids XCVII and XCVIII were isolated from the acidic fraction

of the ozonolysis product; after esterification with diazomethane, they

were separated by chromatography on alumina. The first material to be

eluted from the column, XCVIIa, could also be prepared from XCVIIIa by

alkaline isomerization followed by re-esterification. The haloform

reaction of XCa, followed by esterification with diazomethane, gave

XCVIIa identical in all respects with that isolated from the ozonolysis

experiment. The n.m.r. spectra of XCVIIa and XCVIIIa were completely

consistent with the suggested structures.

After chromatography on alumina, the nonketonic portion of the

neutral fraction obtained from the ozonolysis of LXXXVIIIa yielded

three previously unreported compounds, XCII (m.p. 194-196°), XCIX

(m.p. 264-265°), and C (m.p. 220-221°). In addition, the ultraviolet

spectrum of the noncrystalline part of this fraction indicated the

presence of approximately 15% of the previously reported diene XCI.

Compound XCII, when treated with phosphorus oxychloride in pyridine,

gave a substance which had the same ultraviolet spectrum as XCI. The

infrared and n.m.r. spectra of XCII and its conversion to a diene with

the ultraviolet chromophore of XCI supported the structure XCII. The

presence of a hydroxyl group was shown by the band at 3472 cm.$^{-1}$ in

the infrared, and by the n.m.r. ($\delta 5.0$ which disappeared on the addition

on deuterium oxide). Three carbomethoxy groups were established by

three sharp signals (three protons each) at $\delta 3.58$, 3.60, 3.67 in the

n.m.r., and by a band at 1727 cm.$^{-1}$ in the infrared. The double bond

at C-13, C-14 was apparent from the position of the C-10 methyl protons

at $\delta 0.62$ and by the C-14 vinyl proton at $\delta 5.70$. The double bond also

gave a weak peak at 1638 cm.$^{-1}$ in the infrared. The two methyl groups

flanking the carbon containing the hydroxyl group had n.m.r. signals

at $\delta 1.22$ and $\delta 1.28$, downfield from where the isopropyl methyl

protons appeared in LXXXVIII ($\delta 1.08$). The isolation of XCII provided

strong support for Ruzicka's proposed oxidation scheme (48).

Compound XCIX ($C_{26}H_{38}O_7$), obtained in very low yield, exhibited a
hydroxyl group (3401 cm.$^{-1}$) and three carbonyl bands (1739, 1718, and
1691 cm.$^{-1}$) in its infrared spectrum. The band at highest wavelength
was assigned to a δ-lactone and the other two to the A- and D-ring ester
groups. Since XCIX had no signals in its n.m.r. spectrum at field
higher than δ1.0, and gave a negative test with tetranitromethane, the
absence of a double bond was concluded. On the basis of this evidence
structures XCIXa and XCIXb were suggested for this compound. Another
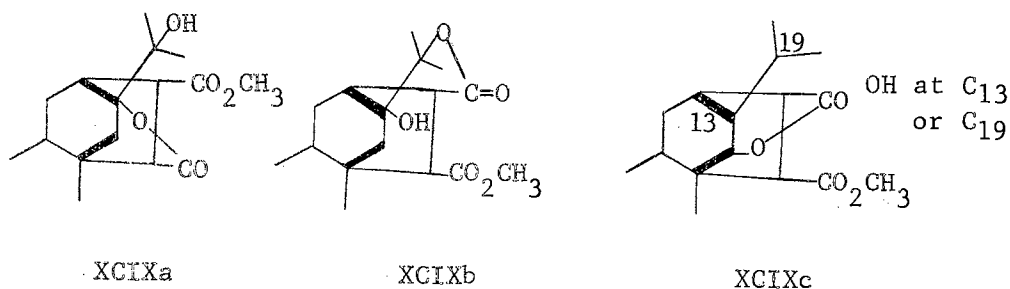
structure containing a δ-lactone, XCIXc, was not considered a likely
possibility because of the absence of a signal in the n.m.r. spectrum
corresponding to the C-14 proton (45, 46).

The third crystalline compound isolated from the nonketone fraction
was assigned structure C. Compound C exhibited a hydroxyl band (3448
cm.$^{-1}$) and a band due to a γ-lactone (1786 cm.$^{-1}$) in the infrared.
The n.m.r. spectrum showed that the compound contained two carbomethoxy
groups and no C-13, C-14 double bond (tetranitromethane test was nega-
tive). Methyl protons of the isopropyl group were moved downfield
(δ1.35 and 1.47) showing that an oxygen atom was attached at C-19.
The C-14 proton appeared at δ4.35. If the lactone had been attached
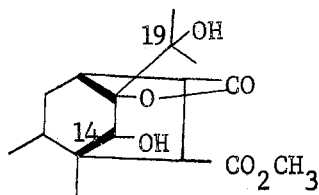
C

at C-14, then this latter proton would have been expected to give a

signal at ≈ δ5.00.

It is not possible to offer a detailed mechanism for the unusual

ozonolysis observed in this case. However, it does appear likely that

Ruzicka's original suggestion of a stepwise oxidation of the isopropyl

group is valid. A scheme of oxidation as shown can be visualized.
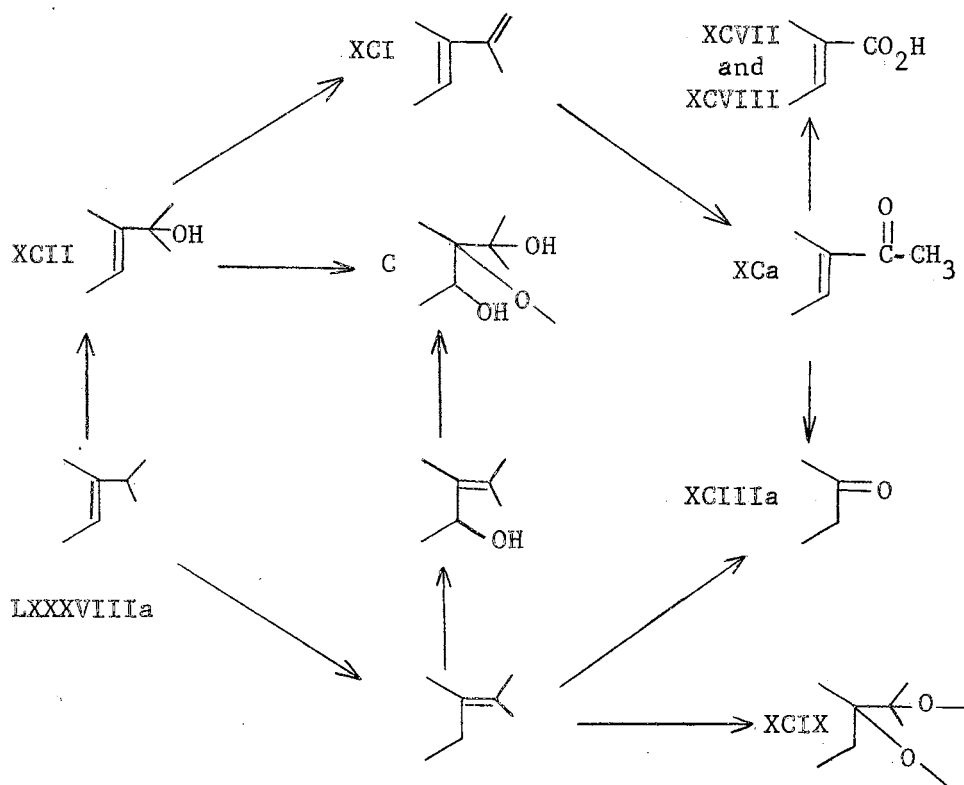
Peracetic acid, formed by the prolonged action of ozone on the acetic acid solvent, may be the active oxidizing agent. If this were the case, then XCIIIa might arise from XCa via a Baeyer-Villiger reaction followed by hydrolysis in the work-up. However, XCVII and XCVIII must not arise from XCa by the action of peracetic acid, since in that case the methyl esters and not the free acids should have been isolated. Ketone XCIIIa may arise by a double bond migration to give an isopropylidine group, followed by cleavage of the double bond. Lactones XCIX and C also may arise from the same intermediate by hydroxylation followed by lactonization.

Baeyer-Villiger oxidation of XCa followed by mild acid hydrolysis, as mentioned earlier, afforded the ketone XCIIIa. The synthesis of XCIIIa accomplished the first phase, namely, the removal of the isopropyl group, involved in the conversion of LXXXVII into XLIX. The remaining transformations were effected as follows.

Trimethyl ester XCIIIa was partially hydrolyzed to the diacid ester CI. The most obvious method of removing 1,2-dicarboxyl groups is that of oxidative bisdecarboxylation. However, this method has been known to be quite unreliable (53-55). A recent modification of the oxidative bisdecarboxylation procedure (56, 57) which utilizes lead tetraacetate in pyridine was found to convert CI to the unsaturated keto ester CII in good yield. The n.m.r. spectrum of CII showed the protons of the C-10 methyl group at $\delta 0.93$, no noticeable shielding effect being exerted by the carbonyl group. In contrast, the C-10 methyl protons in LXXXVII and XCa appeared at $\delta 0.59$ and 0.50, a much larger shielding effect resulting from the C-13, C-14 double bond.

XCIIIa ⟶   [structure]   ⟶   [structure]

CI   CII

(+) XLIX ⟵   [structure]   ⟵   [structure]

CV, R = CO₂CH₃   CIII, R = CH₃
CVI, R = CH₂OH   CIV, R = H
CVII, R = CHO

II ⟶   [structure]   ⟶   (-) XLIX

CVIII
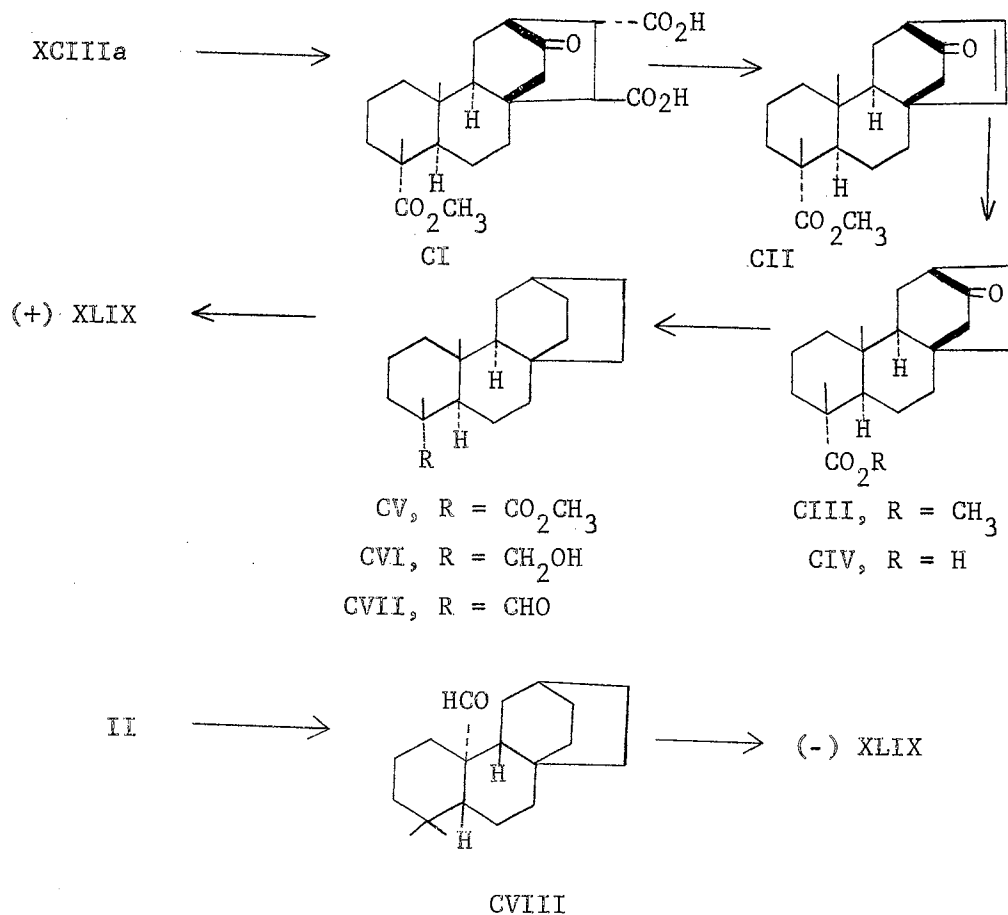
Thus the n.m.r. spectrum of CII provided additional support for the assignment of the double bond at C-15, C-16. The two vinyl protons at C-15 and C-16 appeared as three peaks centered at $\delta6.1$, while the protons of the C-4 methyl group appeared at $\delta1.12$ and the protons of the carbomethoxy group at $\delta3.62$.

The further conversion of CII to XLIX was accomplished as follows. The double bond of CII was reduced smoothly using palladium-on-charcoal catalyst to give CIII. Under identical conditions the double bond of LXXXVII was unaffected. The C-10 methyl protons of the saturated ketone CIII appeared slightly upfield ($\delta0.82$) from the corresponding protons in CII, while the C-4 methyl protons in CIII ($\delta1.10$) were in almost the identical position to corresponding protons in CII. The carbonyl showed

an absorption band at exactly the same wavelength (1724 cm.$^{-1}$) in both

CII and CIII. Compound CIII was saponified to give the keto acid CIV

in order to prevent reaction of the ester grouping with hydrazine during

the Wolff-Kishner reaction (56). The carbonyl band of the keto acid

CIV was removed smoothly by the Huang-Minlon procedure (58) to give an

acid which was converted directly into the ester CV with diazomethane.

The n.m.r. spectrum of CV showed the C-10 methyl protons at δ0.95,

while C-4 methyl protons appeared at δ1.10. Reduction of CV with

lithium aluminum hydride gave the alcohol CVI, which showed two sharp,

three-proton singlets at δ0.73 and δ0.97, and a pair of doublets (J =

10 c.p.s.) at δ2.98 and δ3.36 corresponding to the two protons attached

to the carbon bearing the hydroxyl group; the hydroxyl proton appeared

at δ2.18 and this signal disappeared on the addition of deuterium

oxide. Oxidation of alcohol CVI with chromic anhydride and pyridine

(59) gave aldehyde CVII which was characterized by infrared only

(v_{max}^{KBr} 2680, 1724 cm.$^{-1}$) because of its rapid oxidation. Huang-Minlon

reduction of CVII gave hydrocarbon XLIX (87%) as white needles, m.p.

86-87°, $[\alpha]$D + 38.7°. The n.m.r. spectrum (Plate III) of XLIX showed

three sharp, three-proton singlets at δ0.82, 0.85, and 0.93 correspond-

ing to the two methyl groups at C-4 and the one at C-10, respectively.

Ayer, McDonald and Iverach (24) likewise synthesized (+) XLIX

by a related sequence of reaction and, in addition, found that it

was, as predicted, enantiomeric with the product obtained by Wolff-

Kishner reduction of CVIII, which had been previously obtained from

atisine by ApSimon, Edwards, and Howe (60).

Synthesis of LXXXIX

The unsaturated keto ester CII, an intermediate obtained in the preparation of XLIX, was selected for the synthesis of LXXXIX. Olefin LXXXIX possesses the entire diterpenoid skeleton of atisine in its correct relative configuration.

Reducation of keto ester CII with lithium aluminum hydride gave a mixture of alcohols (CIXa and b) which was oxidized directly to give the keto aldehyde CX. Huang-Minlon reduction of CX gave crystalline alkene CXI. The n.m.r. spectrum (Plate IV) of CXI showed the three methyl-group protons at C-4 and C-10 as sharp singlets at $\delta 0.82$, $\delta 0.87$ and $\delta 0.96$. No shielding effect of the C-15, C-16 double bond on the protons of the C-10 methyl group was noticed. The vinylic protons in CXI appeared as three sharp lines at $\delta 5.92$, $\delta 5.95$ and $\delta 6.02$. The double bond in CXI was hydrated by the Brown procedure (61) to yield a mixture of alcohols CXII (a, b) and CXIII (a, b) which was treated with chromic anhydride in pyridine. Chromatography of the oxidation product on alumina gave two ketones, A (m.p. 145-146°, ν_{max}^{KBr} 1730 cm.$^{-1}$) and B (m.p. 146-148°, ν_{max}^{KBr} 1721 cm.$^{-1}$) in a ratio of approximately 4:1, the less abundant isomer B being eluted first. That no skeletal rearrangement had occurred in these transformations was shown by the facile conversion of both ketones A and B to the hydrocarbon (+) XLIX by the Huang-Minlon procedure. The n.m.r. spectra of ketones A and B were very similar except that in A the methylene protons adjacent to the carbonyl group gave a signal at $\delta 1.82$ whereas in ketone B these protons appeared at $\delta 2.17$. Ketone A gave a positive Cotton effect in its optical rotatory dispersion curve whereas ketone B showed a negative

Cotton effect. Although the above information did not allow an unambiguous decision to be made as to the structures of isomers A and B, the ratio of products obtained in the hydroboration reaction and subsequent oxidation and the order of elution in chromatography indicated that A possessed the less hindered carbonyl group, i.e. structure CXIV; therefore, B presumably had structure CXV. In order to obtain more information which would be useful in distinguishing A and B the isomeric ketone CXVI, of unequivocal structure, was prepared for comparison purposes.

Keto ester CII was converted to the cyclic ketal CXVII by the usual procedure. The n.m.r. spectrum of CXVII showed the protons of carbomethoxy group at $\delta 3.58$ and those of ketal group at $\delta 3.77$ as a singlet. The vinylic protons were present at $\delta 5.85 - 5.94$. Lithium aluminum hydride reduction of CXVII provided the alcohol CXVIII which was converted to the aldehyde CXIX by oxidation with chromic anhydride and pyridine. Compound CXIX was then reduced to CXX by the Huang-Minlon procedure. Hydrolysis of the latter compound gave keto alkene CXXI, previously prepared by Ayer and co-workers (24) by a different procedure. Huang-Minlon reduction of CXXI gave the previously described alkene CXI, while catalytic reduction of CXXI gave the saturated ketone CXVI, which gave as previously shown (24), a positive Cotton effect in its optical rotatory dispersion curve. Unfortunately, it is not possible to use the Octant Rule for predicting configuration in these cases since the C/D ring systems possess boat confirmations (62). Using an empirical approach, it can be seen that ketone CXIV possesses a mirror-image relationship to ketone CXVI with regard to the C/D ring system and on this basis the unknown ketone with a negative Cotton

CII →

CXVII, R = CO$_2$CH$_3$
CXVIII, R = CH$_2$OH
CXIX, R = CHO
CXX, R = CH$_3$

CXXI

CXVI

CIXa, R = $<^{OH}_{H}$

CIXb, R = $<^{H}_{OH}$

CX

CXI

CXXII

CXIIa, R=$<^{OH}_{H}$

CXIIb, R=$<^{H}_{OH}$

CXIIIa, R = $<^{OH}_{H}$

CXIIIb, R = $<^{H}_{OH}$

CXV

→ XLIX ←

CXIV

→ LXXXIX
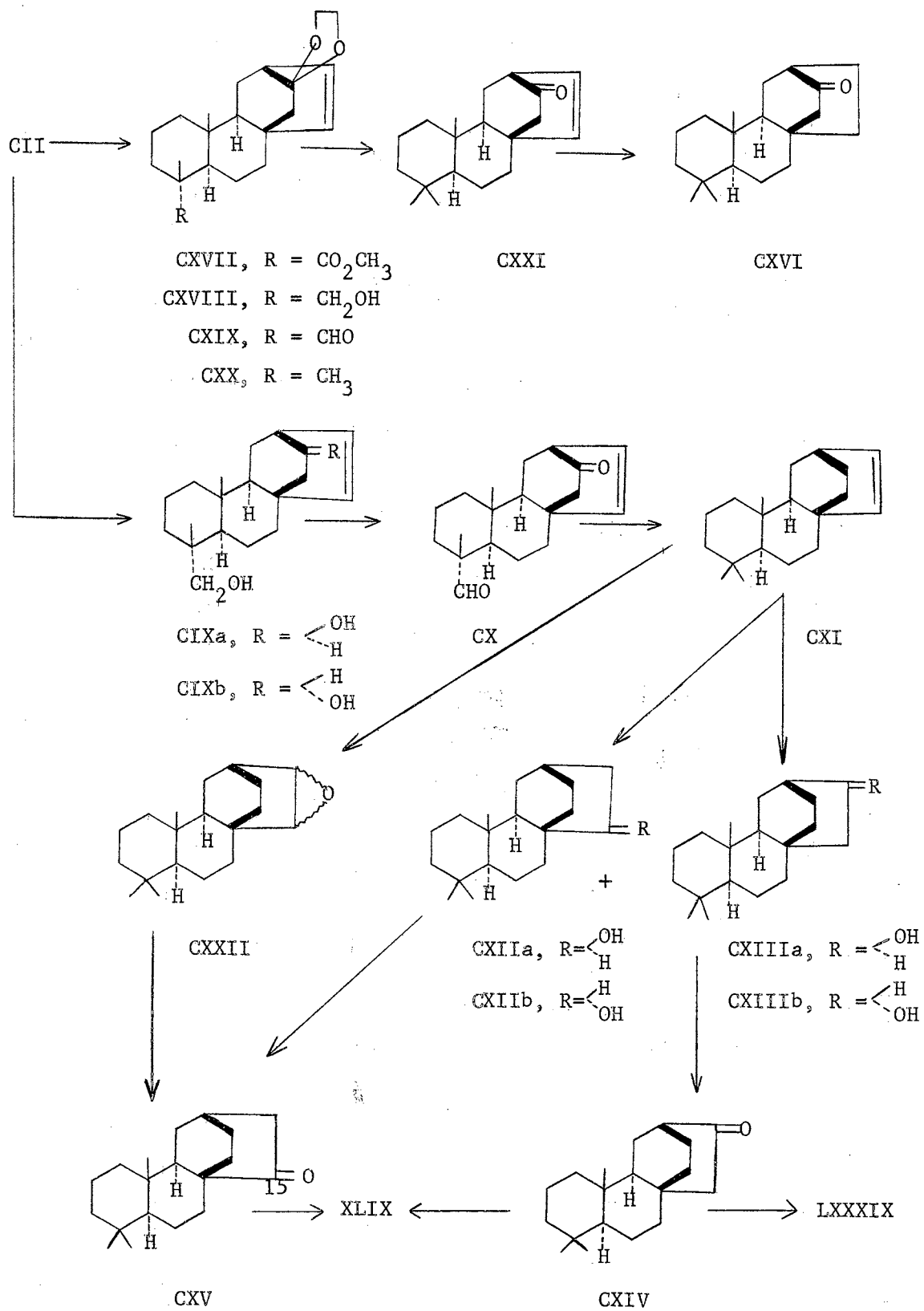
effect (B) might be assigned structure CXIV. However, this turned out
to be incorrect. During the course of this investigation Bell and
Ireland (22) published their synthesis of racemic ketone CXIV by a path
which placed carbonyl unequivocally at C-15. Comparison of the infrared
and nuclear magnetic resonance spectra of racemic CXIV, kindly supplied
by Dr. Ireland, with spectra of our ketone A showed that the two were
identical, and hence ketones A and B possessed structures CXIV and CXV
respectively. Ketone (+) CXIV was then converted to alkene LXXXIX
by use of the Wittig reagent (63), thus completing the synthesis of
the enantiomeric diterpenoid carbon skeleton of atisine. Bell and
Ireland (22) likewise have reported the conversion of racemic CXIV to
racemic LXXXIX and succeeded in introducing a hydroxyl group at C-16
of LXXXIX.

Alkene CXI was readily converted into epoxide CXXII. However,
when CXXII was treated with methylmagnesium iodide the expected intro-
duction of a methyl at C-15 and/or C-16 did not occur. The product of
the Grignard reaction gave, on oxidation with chromic anhydride in
pyridine, the previously obtained ketone CXV. The unexpected preparation
of the C-16 alcohol on treatment of epoxide CXXII with methylmagnesium
iodide occurred either by direct reduction of the epoxide or by
rearrangement of the epoxide to a C-16 ketone followed by reduction of
the latter under the reaction conditions.

An Approach to the Synthesis of Atisine from Podocarpic Acid

The rationale for selecting podocarpic acid, XXVI, as a starting
point for the synthesis of atisine was as follows: (a) it had been
totally synthesized (64) and possessed the required trans A/B ring

fusion, (b) it possessed a carboxyl group at C-4 <u>cis</u> to the bridgehead
methyl group at C-10, which had already been used to construct the
nitrogen-containing E ring by Edwards and ApSimon (18), and (c) the
aromatic C ring of podocarpic acid had been reduced earlier (65) to
give an α,β-unsaturated ketone CXXIII which we visualized could be
converted into a diene useful for construction of the C/D ring system
by the Diels-Alder reaction. Of course, any synthesis beginning with
podocarpic acid would lead, if successful, to the enantiomer of natural
atisine. The major uncertainty in this synthetic approach involved
the nature of the C-ring diene produced. To be useful, this diene
must be either $\Delta^{8,11}$ or $\Delta^{8(14),12}$. Since the various dienoic resin acids
were known to give a single Diels-Alder adduct of the desired type (40),
the path undertaken appeared to offer promise. It should also be noted
that ultimately an α-hydrogen atom would have to be introduced at C-9
and a means of introducing the D-ring methylene and hydroxyl groups
would be required. It was anticipated that all of these requirements
would be met by a $\Delta^{8,11}$ diene or by a $\Delta^{8(14),12}$ diene possessing a
C-9 α-hydrogen atom. In either case a dienophile, such as maleic
anhydride, would be expected to enter from the less-hindered α-side
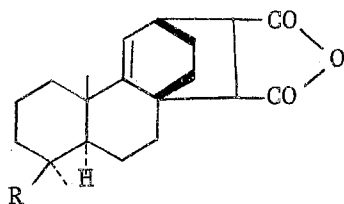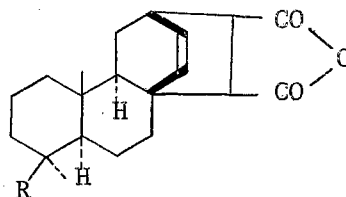
CXXIVa   CXXIVb

to give CXXIVa or CXXIVb. Again, hydrogenation of CXXIVa would be expected to proceed from the less-hindered α-side to give the desired C-9 α-hydrogen. Both CXXIVa and CXXIVb would possess anhydride groupings on the necessary bridge for introduction of the D-ring methylene and hydroxyl groups of atisine. Oxidative decarboxylation of the anhydride moiety, after hydrogenation of the double bond, as previously described (26, 32) for CI obtained from abietic acid, would give the D-ring olefin and the further conversion of such an olefin to the D-ring of atisine with its C-15 methylene group and C-16 hydroxyl group of required stereochemistry has been described by Ireland and Bell (22). In actual fact, the desired diene was obtained but it gave an unexpected Diels-Alder adduct.

The α,β-unsaturated ketone CXXIII, previously described by Bible and Burtner (65), was prepared from podocarpic acid, XXVI, via treatment of XXVI with dimethyl sulfate, lithium aluminum hydride reduction of the resulting methyl O-methylpodocarpate, CXXV, to O-methylpodocarpinol, CXXVI, and finally reduction of CXXVI by the modified Birch procedure. CXXIII was reduced with sodium borohydride and the resulting diol acetylated to give the diacetate CXXVII as a viscous oil which was pyrolyzed in a dynamic system at $\approx 300^{\circ}$. The resulting mixture of dienes, CXXVIII and CXXIX, was treated with maleic anhydride in refluxing xylene and gave two crystalline adducts CXXX and CXXXI in approximately 30% and 12% yield respectively. The diene CXXIX apparently arises by allylic rearrangement of the α,β-unsaturated acetate CXXVII followed by elimination of acetic acid in a normal fashion (66).

OCH$_3$

O

OAc

XXVI ⟶

R

HOCH$_2$

AcOCH$_2$

CXXV, R = CO$_2$CH$_3$

CXXIII

CXXVII

CXXVI, R = CH$_2$OH

AcOCH$_2$ CXXVIII

11 12 13
9 8 14

AcOCH$_2$ CXXIX

O—CO
OC
H
10 8
AcOCH$_2$ H
CXXX

CO
O
CO
10
AcOCH$_2$ H
CXXXI
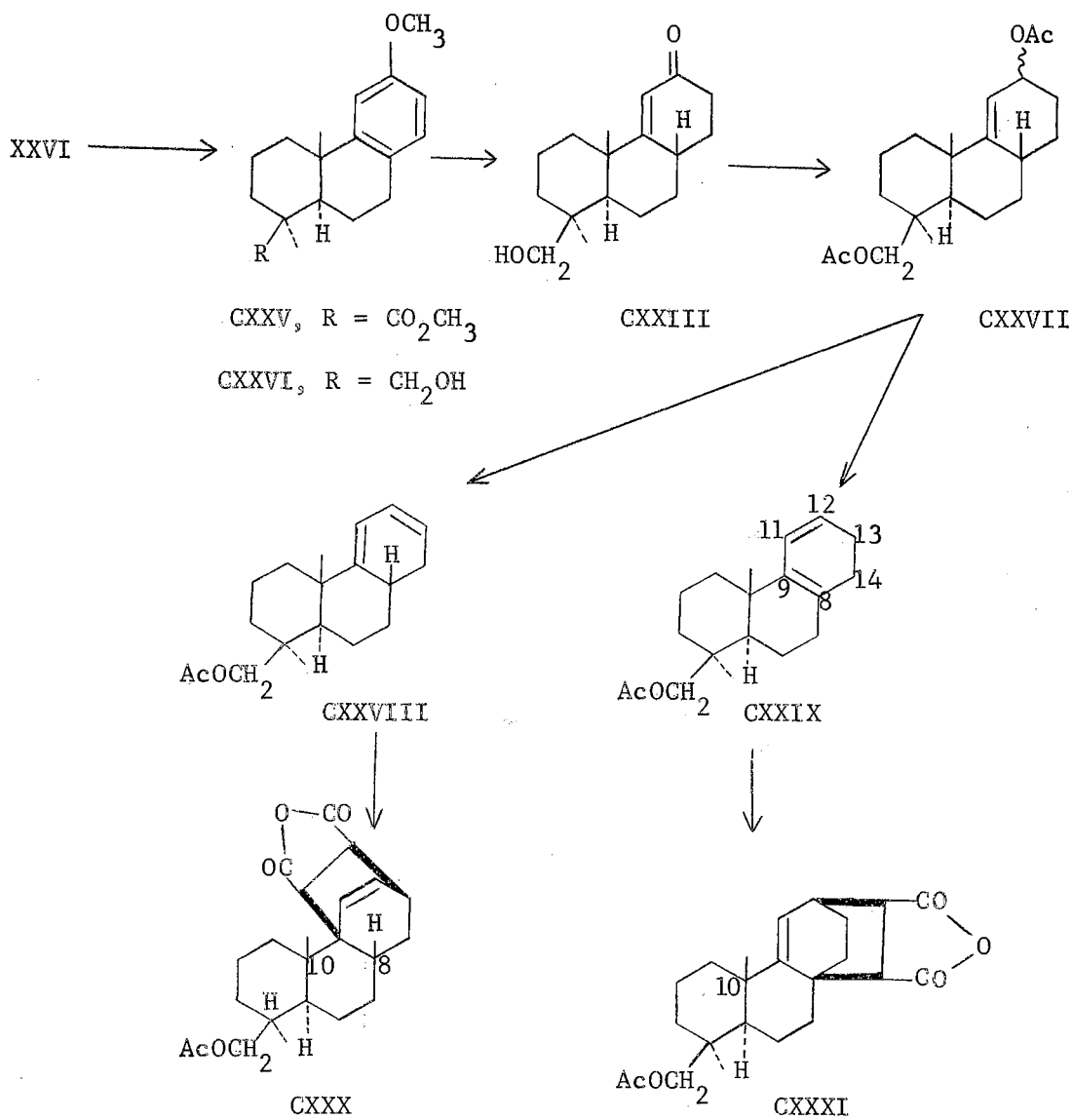
Anhydride CXXXI, which crystallized first, showed a single vinylic proton in its n.m.r. spectrum (Plate V), and the C-10 methyl group showed no shielding by the D-ring double bond (26, 46, 47). Methanolic diazomethane converted CXXXI into the dimethyl ester CXXXII which resisted all attempts at hydrogenation. Saponification of CXXXII gave the hydroxy diacid CXXXIII which was acetylated to give CXXXIV. The carboxyl groups in CXXXIII and CXXXIV are presumed to be trans,

epimerization occurring during saponification as observed in similar cases (31). Treatment of CXXXIV with lead tetraacetate in an attempt to effect oxidative bisdecarboxylation failed to yield the desired product containing a bicyclo[2.2.2]octane C/D ring system. The product obtained after saponification has been assigned structure CXXXV on the basis of its infrared, ultraviolet and n.m.r. spectra and apparently arises in a reverse Diels-Alder reaction of the intermediate bicyclo-[2.2.2]octadiene, the driving force for the retro Diels-Alder reaction being the stability of the aromatic ring produced.

The hydroxy diacid CXXXIII, in contrast to CXXXII, was readily hydrogenated to yield CXXXVI, hydrogen being absorbed from the less hindered α-side. Acetylation gave CXXXVII which was smoothly decarboxylated to give, after hydrolysis, the alcohol CXXXVIII. The n.m.r. spectrum (Plate VI) of CXXXVIII showed the C-10 methyl group to be highly shielded ($\delta 0.53$) by the spatially close C-13 double bond; in addition, the spectrum clearly showed the presence of two vinylic protons. That structure CXXXVIII was indeed correct and hence structure CXXXI also, was demonstrated by the further conversion of CXXXVIII to hydrocarbon XLIX, previously prepared from maleopimaric acid, LXXXVII, (26), by catalytic hydrogenation to CXXXIX, oxidation of CXXXIX to the aldehyde CXL and finally Wolff-Kishner reduction of CXL. The stereochemistry at C-9 in maleopimaric acid is well established (45-47) and the hydrogen at C-9 in CXXXVI - CXLII is therefore known to be α.

Alcohol CXXXVIII was converted into alkene CXLII by chromic anhydride oxidation to give CXLI followed by Wolff-Kishner reduction. That the double bond in CXLII and therefore in CXXXVIII was located at C-13 and not at C-15 was clearly shown by comparison of CXLII with CXI,
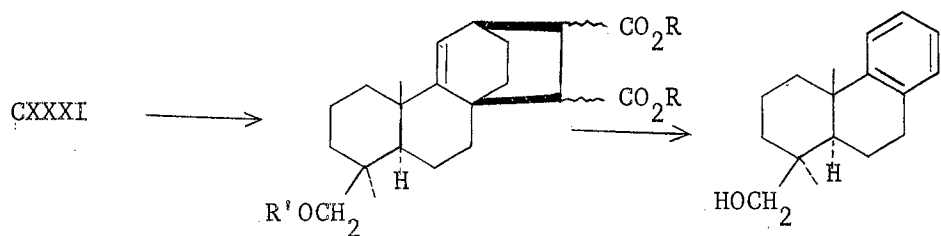
CXXXI $\longrightarrow$

CXXXII, R' = COCH$_3$, R = CH$_3$
carbomethoxy groups _cis_

CXXXIII, R' = H; R = H
carboxyl groups _trans_

CXXXIV, R' = COCH$_3$, R = H
carboxyl groups _trans_
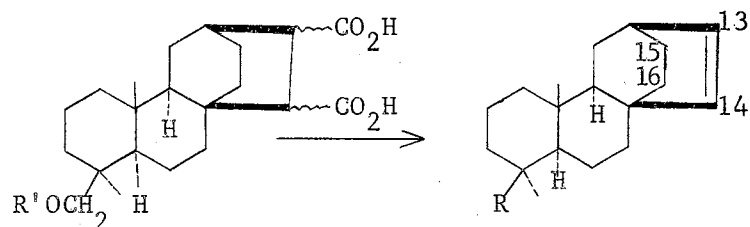
CXXXV

CXXXVI, R' = H

CXXXVII, R' = COCH$_3$

CXXXVIII, R = CH$_2$OH

CXLI, R = CHO

CXLII, R = CH$_3$
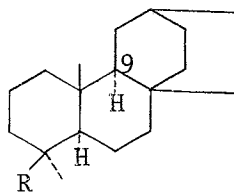
CXXXIX, R = CH$_2$OH

CXL, R = CHO

XLIX, R = CH$_3$

the latter being available from maleopimaric acid (32). In the n.m.r.
spectrum of CXLII the C-10 methyl signal appeared at δ0.57, whereas in
CXI it appeared at δ0.82, thus indicating that in CXLII the double bond
was close enough to shield the C-10 methyl group. This unfortunate
situation made it difficult to introduce the C-15 methylene and C-16
hydroxyl groups of atisine into CXXXVIII. Alkene CXI has been used as
an intermediate for the further introduction of these groups (22, 32)
but, again unfortunately, CXI is derived from a precursor possessing
an α-C-4 carboxyl group, which prevents ready introduction of the
nitrogen-containing E ring of atisine.

Thus, we are faced with the situation of being able to synthesize
the carbon skeleton of atisine from both podocarpic and from abietic
acid but each pathway has a built-in deficiency. It is surprising
that CXXXI was produced in the first place, since it must arise from
diene precursor CXXIX by attack of the dienophile, maleic anhydride,
from the more-hindered top (β) side. This preference for attack from
the β-side must arise by some sort of directing influence of the
β-C-4 acetoxy group, since in the case of the resin acids only the
product arising from attack on the α-side is obtained (40).

Structure CXXX is tentatively suggested for the second crystalline
Diels-Alder adduct obtained from the mixture of C-ring dienes and
maleic anhydride as mentioned earlier. The n.m.r. spectrum (Plate VII)
of CXXX showed two vinylic protons (δ6.30) and of particular interest
was the appearance of one methyl singlet (C-10) at the unusually low
field of δ1.4; the other methyl singlet C-4 appeared in the usual place
(δ0.97). Hydrogenation of CXXX gave CXLIII, the n.m.r. spectrum of
which still showed a methyl signal at low field (δ1.26) indicating that

the observed deshielding could not have arisen entirely from the double bond. Treatment of CXXX with methanolic diazomethane gave dimethyl ester CXLIV which was readily hydrogenated to give CXLV. When CXLV was refluxed with 5% sodium hydroxide the half-acid ester CXLVI was obtained, which on reacetylation gave CXLVII, and on further treatment with ethereal diazomethane CXLVIII was obtained. The latter diester was shown to be isomeric with CXLV by thin-layer chromatography and by n.m.r. In CXLVI, CXLVII and CXLVIII the two D-ring carboxyl groups can, therefore, be assumed to be in the more stable trans arrangement, but since the C-10 methyl groups in CXLV, CXLVI, CXLVII and CXLVIII appear in essentially the same position in the respective n.m.r. spectra it can be assumed that it is the C-16 and not the C-15 carboxyl group that is epimerized in the conversion of CXLV to CXLVI. If the C-15 carboxyl group had been epimerized, a change would have been expected in the C-10 methyl group, which would have been reflected in the n.m.r. because of the relative closeness of this carboxyl group to the C-10 methyl group. It also follows, from an examination of molecular models, that the C-15 carbomethoxy is more hindered than the C-16 one and hence would be more resistant to saponification.

Vigorous alkaline saponification of CXLV gave the diacid CXLIX which after acetylation to give CL was oxidatively decarboxylated and, then hydrolyzed to give the alkene CLI. The n.m.r. (Plate VIII) spectrum of CLI showed two sharp singlets at high field ($\delta 0.87$ and 0.90), indicating no shielding or deshielding of the C-10 methyl group by the double bond, and in addition, two vinylic protons were present. Alkene CLI was converted into the saturated hydrocarbon CLIV by catalytic hydrogenation to CLII, then oxidation to CLIII with chromic anhydride in

CXXX ⟶ CXLIV

CXLV, R = R″ = CH₃
C-16 β CO₂CH₃
R′ = COCH₃

CXLVI, R = CH₃, R″ = H
C-16 α CO₂H
R′ = H

CXLVII, R = CH₃, R″ = H
C-16 α CO₂H
R′ = COCH₃

CXLVIII, R = R″ = CH₃
C-16 α CO₂CH₃
R′ = COCH₃

CXLIX, R = R″ = R′ = H
C-16 α CO₂H

CL, R = R″ = H
C-16 α CO₂H
R′ = COCH₃

CXLIII

CLVII, R′ = COCH₃
R = R″ = H

CLVIII, R = R′ = R″ = H

CLIX, R′ = H
R = R″ = CH₃

CLX, R′ = R″ = H
R = CH₃

CLI, Δ¹⁵, R = CH₂OH

CLII, R = CH₂OH

CLIII, R = CHO

CLIV, R = CH₃

CLVI, Δ¹⁵, R = CH₂OAc

CLV
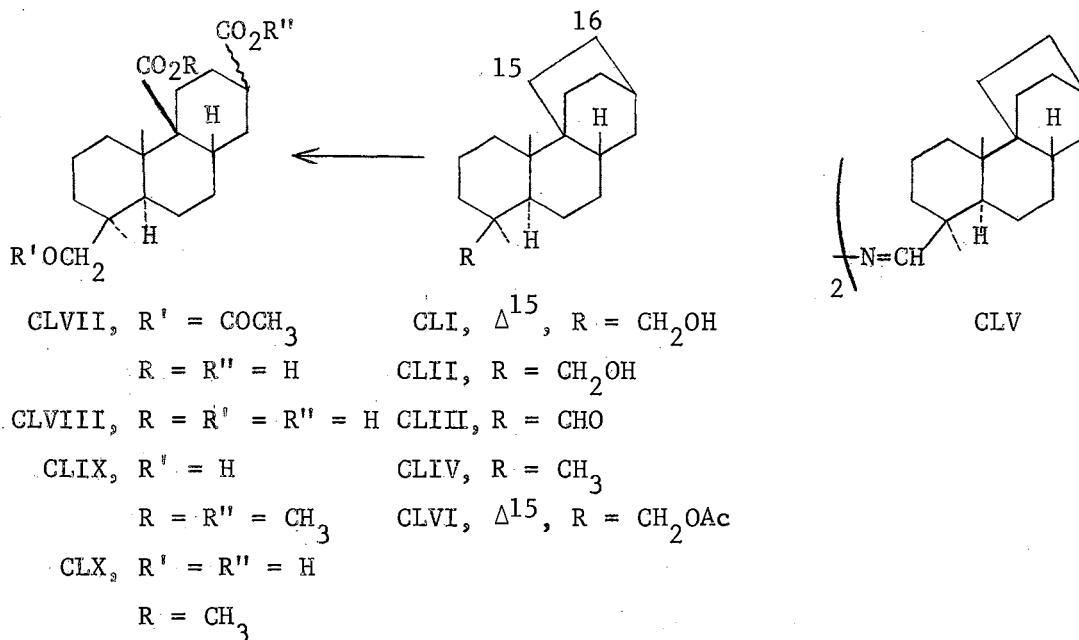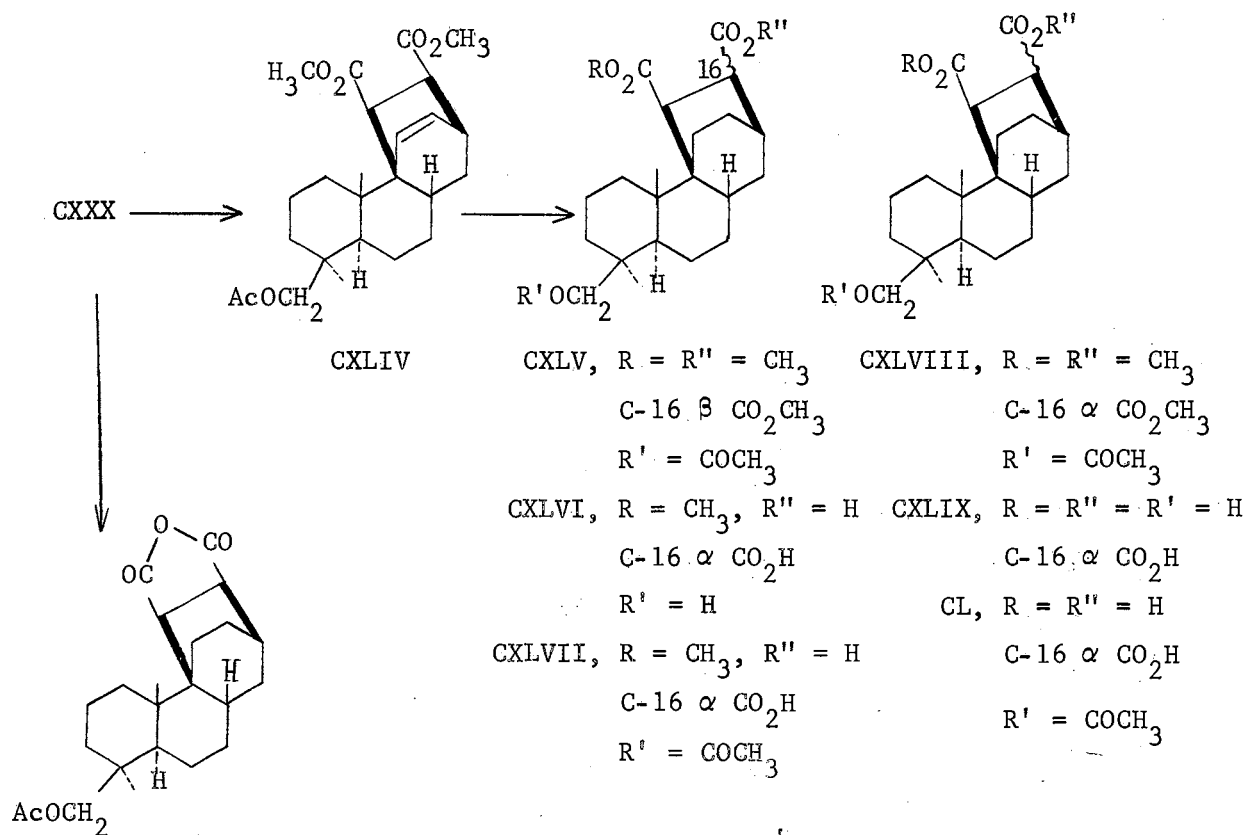
pyridine and finally Wolff-Kishner reduction. In the n.m.r. spectrum

of CLIV the three methyl groups at C-4 and C-10 appeared as sharp

singlets at δ0.85 (6 protons) and δ0.89 (3 protons). Hydrocarbon CLIV

was found to be different from the previously prepared hydrocarbon

XLIX in melting point and infrared and n.m.r. spectra. In addition to

CLIV, a second product isolated in the Wolff-Kishner reduction of CLIII

was found to be the dimeric product CLV.

That the carbon skeleton of CXXX, and hence all of its derivatives,

CXLIII - CLVI, is probably correct follows not only from the nature of

the acetate CXXVII which was pyrolyzed, but because of the following

observations. Anhydride CXXX was shown by n.m.r. to contain two vinylic

protons. In addition to CXXX only structures CLXI and CLXII are consist-

ent with this observation. If CLXI had been the correct structure for

CXXX then CLI would possess structure CLXIII; but CLI, after acetylation

to give CLVI, was ozonized to give diacid CLVII which gave on hydrolysis

followed by esterification the diester CLIX. Diester CLIX on alkaline

hydrolysis gave only the half-acid ester CLX. This is consistent with

CLXI   CLXII   CLXIII   CLXIV
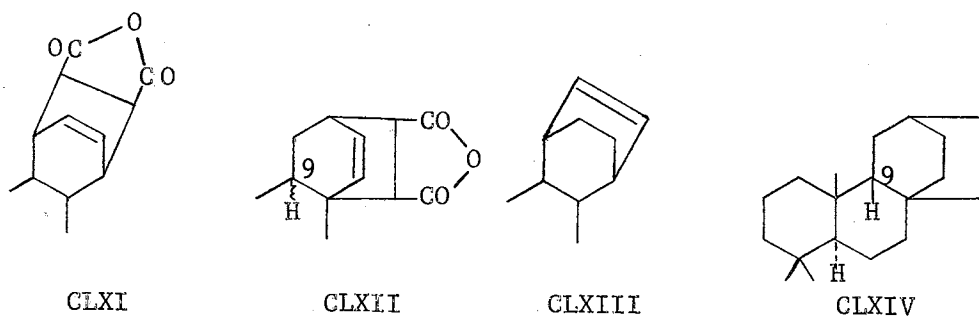
structures CXXX and CLXII, each of which would give rise to one tertiary

carboxyl group in the above sequence of reactions, but not consistent

with structure CLXI, which would be expected to give rise to two

unhindered secondary carboxyl groups. If structure CLXII had been

correct for CXXX, then hydrocarbon CLIV would have had structure XLIX
or it would be represented by CLXIV, the C-9 epimer of XLIX. But, as
mentioned above, CLIV was found not identical with XLIX and if CLXIV
had been correct then CLXII would have possessed a β-hydrogen at C-9.
An examination of Dreiding models clearly indicates that in such a case
the observed deshielding of the C-10 methyl group by the carbonyl group
could not occur.

The hydrogen at C-8 in CXXX is assigned the β-configuration because
it is known to have this configuration in CXXIII (65) from which CXXX
was prepared, and because an examination of Dreiding models reveals
that had this hydrogen been α, the deshielding of the C-10 methyl group
by an anhydride carbonyl group would not have occurred. In addition, if
the C-8 hydrogen were α the double bond in CLI would have deshielded
the C-10 methyl group, but this was not observed. The n.m.r. observa-
tions also indicate that the anhydride moiety in CXXX is anti to the
double bond -- an exception to the much used Alder rule (67). It is
interesting to note that this Diels-Alder adduct also arises by attack
of the dienophile from the more-hindered β (top) side of the diene.

After determining the structures of Diels-Alder adducts CXXX
and CXXXI and noticing that both of these were "abnormal" adducts an
examination of the mother liquor left after the separation of crystal-
line CXXX and CXXXI was undertaken. These studies led to the
isolation of a third adduct, but its structure elucidation is beyond
the scope of this thesis.

CHAPTER III

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab., Inc., Indianapolis, Indiana. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard ($\delta = 0$). Ultraviolet spectra were obtained with the Beckman recording spectrophotometer Model DK1. Thin-layer chromatograms were run on 25μ thick silica gel-coated glass plates using benzene-ethyl acetate (5:1) as the mobile phase and detection was by iodine vapors.

Ozonolysis of Trimethyl Ester of Maleopimaric Acid, LXXXVIIIa.

The trimethyl ester LXXXVIIIa was prepared as previously described (40) and ozonized as follows. A rapid stream of ozone (approximately 3%) was passed through a solution of 29.8 g. of LXXXVIIIa, in 225 ml. of glacial acetic acid for forty-eight hours at room temperature. After the addition of 15 ml. of water, the solution was stirred for a short time and then taken to dryness on a steam bath using the water aspirator. The glassy yellow solid thus obtained was then separated into acidic and neutral fractions; it was dissolved in ether and the resulting solution was repeatedly extracted with 5% ice-cold sodium hydroxide

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solution until the alkaline extract was colorless. The ether layer, after drying over anhydrous sodium sulfate, was evaporated to give 22.7 g. of the yellow neutral fraction.

The aqueous sodium hydroxide extracts were combined, made acidic with dilute hydrochloric acid and extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the combined extracts were concentrated to yield 4.52 g. of glassy acidic fraction.

The Ketonic Fraction. Isolation of Ketones XCa and XCIIIa.

A solution of 6.75 g. of the above neutral fraction in 70 ml. of anhydrous methanol containing 2 ml. of glacial acetic acid and 2.7 g. of Girard's T reagent was refluxed for 4 hours. The cooled reaction mixture was then poured into a solution of 2.8 g. of sodium bicarbonate in 280 ml. of water, and this solution was extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate and concentrated to give 1.87 g. of the nonketonic fraction as a viscous gum. The separation of this fraction is described in the section on the nonketonic fraction.

The aqueous layer, which contained the ketones, was made acidic by adding 10 ml. of 6 N hydrochloric acid. After standing for one hour, ketone XCa crystallized and was collected by filtration, washed with water, and dried to give m.p. 161-163° (3.5 g.). Two recrystallizations from methanol gave m.p. 168-169° [reported (48) 168-169°]; v_{max}^{KBr} 1724, 1661 and 1610 cm.$^{-1}$; n.m.r. (Plate I) $\delta 0.50$ (3), 1.13 (3), 2.36 (3) and 6.90 (1).

The filtrate remaining after the removal of ketone XCa, on standing open to the atmosphere for 2 weeks became turbid and then was extracted

with ether. After washing with water and drying over anhydrous magnesium sulfate, evaporation of the ether gave 1.1 g. of ketone XCIIIa. Recrystallization from methanol gave 0.8 g., m.p. 193-194°; negative tetranitromethane test; ν_{max}^{KBr} 1745, 1740 and 1725 cm.$^{-1}$; n.m.r. (Plate II) $\delta 0.83$ (3), 1.12 (3). This compound exhibited a strongly negative Cotton effect in methanol solution (C, 0.0565) which was unchanged on the addition of a small amount of hydrochlorid acid: $[\alpha]_{589m\mu}$ -46°, $[\alpha]_{302}$ -1071°, $[\alpha]_{267}$ +302°, $[\alpha]_{250}$ -250°.

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.33; H, 7.88.

Found: C, 66.57; H, 7.95.

Ketone XCIIIa could also be isolated by further acidification of the aqueous filtrate remaining after the removal of ketone XCa.

Alkaline Isomerization of XCa. Preparation of XCb.

A solution prepared by dissolving 0.34 g. of XCa in 10 ml. of methanol and 25 ml. of 2 N sodium hydroxide was refluxed for 10 hours. After cooling, it was diluted with water, acidified with dilute hydrochloric acid and extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the ether extract was concentrated to give the crystalline trans acid; after crystallization from aqueous acetic acid it had m.p. 287-289°; ν_{max}^{KBr} 3703-2127, 1709, 1661 and 1626 cm.$^{-1}$.

Treatment of the crystalline trans acid with an ethereal diazomethane gave XCb as a viscous gum which could not be crystallized; n.m.r. (CCl$_4$) $\delta 0.50$ (3), 1.08 (3), 2.25 (3) and 6.88 (1).

Conversion of XCa into XCIIIa.

A solution of peroxytrifluoroacetic acid was prepared by the drop-wise addition of 3 ml. of trifluoroacetic anhydride to a suspension of 0.5 ml. of 90% hydrogen peroxide in 10 ml. of methylene chloride (68). This solution was added over a period of 15 minutes to a stirred suspension of 6.86 g. of dry, finely powdered disodium hydrogen phosphate in a solution of 5.5 g. of ketone XCa in 30 ml. of methylene chloride. After addition was complete, the solution was heated under reflux for one hour. The inorganic salts were removed by filtration and washed with methylene chloride. The combined methylene chloride layers were washed with 10% sodium carbonate, dried over anhydrous magnesium sulfate, and the solution finally concentrated to give 5.4 g. of crude products.

Two recrystallizations from a mixture of methanol-dioxane gave 3.5 g. (61%) of XCIV, m.p. 208-210°. The analytical sample of XCIV obtained by recrystallization from methanol gave m.p. 210-212°; v_{max}^{KBr} 1757, 1750, 1727, 1669 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.75 (3), 1.13 (3), 2.18 (3), 5.34 (doublet, 1 proton).

Anal. Calcd. for C$_{26}$H$_{36}$O$_8$: C, 65.52; H, 7.61.

Found: C, 65.41; H, 7.72.

Concentration of the mother liquor from which XCIV was obtained gave a viscous gum which upon the addition of methanol gave 0.55 g. of XCV. The analytical sample was obtained by recrystallization from methanol-acetone and had m.p. 268-271°; v_{max}^{KBr} 3425, 1725 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.67 (3), 1.12 (3), 3.05 (3) and 4.10 (doublet which disappears on addition of D$_2$O).

Anal. Calcd. for C$_{24}$H$_{34}$O$_8$: C, 63.98; H, 7.61.

Found: C, 64.04; H, 7.55.

A solution containing 3.37 g. of XCIV, 175 ml. of dioxane, 175 ml. of methanol and 100 ml. of 6 N hydrochloric acid was allowed to stand at room temperature for 10 hours. Addition of 1200 ml. of water yielded 2.95 g. of ketone XCIIIa, m.p. 191-193°. Recrystallization from methanol gave ketone XCIIIa of identical melting and mixed melting point, infrared and n.m.r. spectra, with XCIIIa obtained by treatment of LXXXVIIIa with ozone.

Alkaline Isomerization of XCIIIa. Preparation of XCIIIb.

A solution prepared by the addition of 0.5 g. of XCIIIa to 10 ml. of methanol, to which was added 15 ml. of 2 N sodium hydroxide, was refluxed for 3 hours. After cooling, it was diluted with 100 ml. of water and acidified with dilute hydrochloric acid, then extracted with ether. After washing with water and drying over anhydrous sodium sulfate, the ether extract was concentrated to yield an amorphous solid which was treated directly with an excess of an ethereal solution of diazomethane. The crude product was crystallized from methanol to give 0.41 g. of ketone XCIIIb; m.p. 148-149°; ν_{max}^{KBr} 1730 cm.$^{-1}$; n.m.r. (CDCl$_3$) $\delta 0.80$ (3), 1.13 (3).

<u>Anal</u>. Calcd. for C$_{24}$H$_{34}$O$_7$: C, 66.33; H, 7.88.

Found: C, 66.56; H, 8.03.

The Acidic Fraction. Isolation of Tetraesters XCVIIa and XCVIIIa.

The glassy acidic fraction (4.52 g.) obtained as described earlier was treated with an excess of ethereal solution of diazomethane. After the usual workup, the crude ester mixture (4.7 g.) was chromatographed directly on 200 g. of neutral activated alumina. Crystallization of the

glassy fraction, eluted with ether-benzene (1:9), gave 160 mg. of XCVIIa, m.p. 155-156° [reported (48) 152-153°]; ν_{max}^{KBr} 1724, 1709 and 1634 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.50 (3), 1.10 (3), 3.57 (3), 3.64 (3), 3.70 (3), 3.74 (3) and 6.93 (1). The remainder of the noncrystalline material eluted from the column was rechromatographed on neutral alumina. Elution with ether-benzene and crystallization from benzene-hexane gave an additional 60 mg. of pure XCVIIa and 340 mg. of pure XCVIIIa. Recrystallization from n-hexane-benzene gave m.p. 177-178°; ν_{max}^{KBr} 1754, 1712 and 1628 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.53 (3), 1.11 (3), 3.49 (3), 3.52 (3), 3.64 (3), 3.75 (3) and 6.92 (1).

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.52; H, 7.61.

Found: C, 65.93; H, 7.68.

The rest of the material eluted in the chromatography could not be crystallized. Infrared spectra of the noncrystalline fractions indicated the presence of hydroxyl containing compounds and γ-lactones.

Preparation of XCVIIa from XCVIIIa by Alkaline Isomerization.

A solution prepared by mixing 40 mg. of XCVIIIa, 5 ml. of methanol and 10 ml. of 2 N sodium hydroxide was refluxed for 8 hours. The cold reaction mixture was diluted with 50 ml. of water, acidified with dilute hydrochloric acid and extracted with ether. The ether layer, after drying over anhydrous sodium sulfate, was concentrated to give a white solid, which was directly esterified with a solution of diazomethane in ether. Evaporation of ether and crystallization of the residue from n-hexane-ether gave 34 mg. of XCVIIa, m.p. 155-156°, identical in all respects with that obtained as already described.

Preparation of XCVIIa from XCa by the Haloform Reaction.

Using the procedure reported by Ruzicka and Kaufmann (48) ketone

XCa was oxidized with sodium hypobromite. The crude acid product was

esterified directly with diazomethane to yield XCVIIa, m.p. 155-156°,

mixed m.p. 155-156°, [reported (48) m.p. 152-153], identical in all

respects with XCVIIa isolated as described above.

Alkaline Isomerization of LXXXVIIIa. Preparation of LXXXVIIIb.

A solution prepared by dissolving 0.30 g. of LXXXVIIIa in 10 ml.

of methanol and 25 ml. of 2 N sodium hydroxide, was refluxed for 10

hours, then cooled, diluted with 150 ml. of water, acidified with dilute

hydrochloric acid, and extracted with ether. The ether extract was

washed with water, dried over anhydrous sodium sulfate and concentrated

to give the crystalline acid. Recrystallization from aqueous acetic

acid gave m.p. 252-253°, with previous melting at 190-210° followed by

resolidification. This substance was identical in mixed melting point

and infrared spectrum with the product obtained from the Diels-Alder

reaction of abietic acid and fumaric acid (69).

Treatment of the acid with ethereal diazomethane gave LXXXVIIIb

as a viscous gum which could not be crystallized. The n.m.r. spectra

of LXXXVIIIa and LXXXVIIIb were almost identical, the C-10 methyl

protons appearing at δ0.60, and the C-14 vinylic proton at δ5.34.

The Nonketonic Fraction

The fraction (1.87 g.) remaining after removal of the ketones

with Girard's T reagent was chromatographed on neutral activated alumina

(100 g.). Elution with 25% ether - 75% benzene gave 1.26 g. of a viscous

gum from which was obtained, on crystallization with benzene-n-heptane,

40 mg. of compound C. Further elution with ether gave 0.34 g. of a

viscous gum which could be partially crystallized from aqueous methanol

to give 70 mg. of compound XCII. Rechromatography of the noncrystalline

material (1.08 g.) on 60 g. of neutral activated alumina gave as crystal-

line material 35 mg. of ketone XCIIIa (which apparently escaped reaction

with Girard's T reagent), 10 mg. of a new crystalline compound XCIX and

a further 50 mg. of C; these were all eluted with 25% ether - 75% benzene.

The remainder of the material could not be crystallized but is ultraviolet

spectrum (λ_{max}^{EtOH} 240 mμ, ϵ 2392) indicated the presence of 15% of the

previously reported diene XCI (λ_{max} 240 mμ, ϵ 17,780).

Compound C

This substance, obtained as described above, after crystallization

from benzene-n-heptane and drying at 140° and 1 mm. pressure for 10

hours had m.p. 220-221° and gave a negative tetranitromethane test;

ν_{max}^{KBr} 3448, 1786 and 1712 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ1.10, 1.17, 1.35, 1.47,

3.65, 3.70, 4.35 and 7.36.

Anal. Calcd. for C$_{26}$H$_{38}$O$_8$·0·5H$_2$O: C, 64.05; H, 8.06.

Found: C, 63.82, 64,12;

H, 7.82, 7.99.

Maleopimaric acid and related substances have been shown to tenacious-

ly hold solvents of crystallization and to form hydrates (69).

Compound XCII.

Recrystallization from methanol and drying for 12 hours at 140° and

1 mm. pressure gave m.p. 194-196°, and a positive tetranitromethane test;
v_{max}^{KBr} 3472, 1727, 1638 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.62, 1.15, 1.22, 1.33,
3.58, 3.70, 3.67, 5.0 (disappears with D$_2$O), 5.70 (doublet, 11 c.p.s.).

<u>Anal</u>. Calcd. for C$_{27}$H$_{40}$O$_7$·H$_2$O: C, 65.56; H, 8.55.

Found: C, 65.83; H, 8.33.

Reaction of XCII With Phosphorous Oxychloride.

A solution prepared by dissolving 0.132 g. of XCII in 5 ml. of
pyridine and 1 ml. of phosphorous oxychloride was heated on the steam
bath for 4 hours, then allowed to stand at room temperature for 12 hours.
The reaction mixture was diluted with water and then extracted with ether.
The ether extract was washed with dilute hydrochloric acid, then with
water, and finally dried over anhydrous sodium sulfate. Removal of the
solvent yielded 0.070 g. of a glassy product which resisted attempts
at crystallization. The infrared spectrum of this material showed no
O-H absorption and gave λ_{max}^{EtOH} 240 mμ (log ϵ 3.84). Reported (40) for
diene XCI, λ_{max} 240 mμ (log ϵ 4.25).

Compound XCIX.

Compound XCIX, eluted from alumina with 15% ether - 85% benzene,
had m.p. 264-265° after recrystallization from benzene-<u>n</u>-hexane and
drying for 10 hours at 60° and 1 mm., and gave a negative test with tetra-
nitromethane; v_{max}^{KBr} 3401, 1739, 1718 and 1691 cm.$^{-1}$; n.m.r., due to small
size of sample available, a strong spectrum could not be obtained, but
there were no signals at field higher than δ1.0.

<u>Anal</u>. Calcd. for C$_{26}$H$_{38}$O$_7$: C, 67.50; H, 8.28.

Found: C, 67.43; H, 8.01.

Preparation of CII.

A mixture of ketone XCIIIa (11.1 g.), methanol (55 ml.), sodium

hydroxide (2.1 g.) and water (66 ml.) was refluxed for 45 minutes.

After cooling, the reaction mixture was diluted with water (250 ml.),

acidified with 6 N hydrochloric acid and finally extracted with ether.

The ether extract was washed with water, dried over magnesium sulfate

and evaporated to give 10.9 g. of glassy solid which solidified on the

addition of ethyl acetate. The solid CI had m.p. 260-268° after recrystal-

lization from ethyl acetate-acetone; v_{max}^{KBr} 3279 (broad), 1730-1695 (broad)

cm.$^{-1}$; n.m.r. (CF_3CO_2H) $\delta 0.95$ (3), 1.22 (3) and 3.89 (3).

The noncrystalline residue was converted to the previously described

trimethyl ester XCIIIb with ethereal diazomethane; this latter ester

could be partially saponified as described above to give CI.

The diacid ester CI (8.1 g.) was dissolved in 150 ml. of pyridine

maintained at 70°, and 8.8 g. of lead tetraacetate was added to the

stirred solution under an atmosphere of nitrogen. After 10 minutes, when

the initial reaction had subsided, an additional 4.4 g. of lead tetra-

acetate was added, and the reaction mixture allowed the reflux for 1.5

hours. The pyridine was removed on the steam bath with a water aspirator,

and the dark brown residue was acidified with 6 N hydrochloric acid and

extracted with ether. The ether extract was washed with water, dried

over anhydrous magnesium sulfate, and evaporated to give 6.3 g. of a

brown solid. This solid was chromatographed on 100 g. of neutral alumina.

Elution with 750 ml. of benzene and 200 ml. of benzene-ether (9:1) gave

3.46 g. of CII, m.p. 166-168°. Analytical sample, prepared by recrystal-

lization from methanol, had m.p. 168-169°; positive tetranitromethane

test; ν_{max}^{KBr} 1724, 1616 and 1248 cm.$^{-1}$; n.m.r. (CCl$_4$) $\delta 0.93$ (3), 1.12 (3), 3.62 (3) and 6.06 - 6.13 (2).

<div align="center">

Anal. Calcd. for C$_{20}$H$_{28}$O$_3$: C, 75.91; H, 8.92.

Found: C, 75.90; H, 8.92.

</div>

Hydrogenation of CII. Preparation of CIII.

The unsaturated ketone CII (3.46 g.) was hydrogenated with 0.37 g. of 10% palladium-on-charcoal catalyst in 130 ml. of ethyl acetate at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 45 minutes. Filtration of the catalyst followed by evaporation of the ethyl acetate gave a quantitative yield of CIII, m.p. 128-130°. The analytical sample, prepared by recrystallization from hexane, had m.p. 129-130°, and gave a negative tetranitromethane test; ν_{max}^{KBr} 1724, 1248 cm.$^{-1}$; n.m.r. (CCl$_4$) $\delta 0.82$ (3), 1.10 (3) and 3.60 (3).

<div align="center">

Anal. Calcd. for C$_{20}$H$_{30}$O$_3$: C, 75.43; H, 9.49.

Found: C, 75.36; H, 9.94.

</div>

Preparation of CV.

A suspension of 3.5 g. of the saturated keto ester CIII, in a mixture of 100 ml. of 5% sodium hydroxide and 100 ml. of methanol was refluxed for 10 hours. The clear, cooled solution was diluted with 500 ml. of water and extracted with ether to remove unreacted CIII. The remaining aqueous alkaline solution was made acidic with 6 N hydrochloric acid and then extracted with ether. After washing with water and drying over anhydrous magnesium sulfate, the ether was evaporated to give 2.68 g. of keto acid CIV, m.p. 238-240°.

Keto acid CIV (2.63 g.) was added to a solution of 5 g. of potassium

hydroxide in 30 ml. of diethylene glycol and 5 ml. of 95% hydrazine. The

reaction solution was refluxed for 4 hours, after which the temperature

of the mixture was raised to 240° by distilling out water and hydrazine.

Hydrazine (5 ml.) was again added to the residue and refluxing was con-

tinued for an additional 12 hours. After the addition of 250 ml. of

water, the reaction mixture was made acidic with 6 N hydrochloric acid

and extracted with ether. After washing with water and drying over

anhydrous magnesium sulfate, the ether extract was evaporated to give a

solid which was directly treated with an excess of an ethereal solution

of diazomethane. Removal of the solvent gave crude CV, which on recrys-

tallization from methanol gave 2.5 g. (95%) of pure CV, m.p. 97-98°;

v_{max}^{KBr} 1724, 1253 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.95 (3), 1.10 (3) and 3.59 (3).

Anal. Calcd. for C$_{20}$H$_{32}$O$_2$: C, 78.89; H, 10.59.

Found: C, 78.54; H, 10.28.

Preparation of CVI.

Ester CV (2.18 g.) in 75 ml. of anhydrous ether was added dropwise to

a well stirred suspension of 600 mg. of lithium aluminum hydride in

100 ml. of anhydrous ether. After refluxing the reaction mixture for

3 hours, the excess hydride was decomposed by the addition of ethyl

acetate and then water. The solution was acidified with 6 N hydrochloric

acid and extracted with ether. The ether layer, after washing with water

and drying over anhydrous magnesium sulfate, was evaporated to give 1.9 g.

of residue which on crystallization from methanol gave 1.8 g. (91%) of

CVI (m.p. 129-310°). The analytical sample was obtained by further

recrystallization from n-hexane, m.p. 129-130°; v_{max}^{KBr} 3311, 1038 cm.$^{-1}$;

n.m.r. (CCl_4) $\delta 0.73$ (3), 0.93 (3), 2.18 (1 proton, disappear on the addition of D_2O), 2.98 (doublet, 1 proton) 3.36 (doublet, 1 proton).

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66.

Found: C, 82.93; H, 11.57.

Preparation of XLIX.

A solution of 0.79 g. of CVI in 10 ml. of anhydrous pyridine was added to a stirred mixture of 1 g. of chromic anhydride in 10 ml. of pyridine, and the entire mixture was then stirred at room temperature for 2 hours. After pouring into ice-water the solution was extracted with ether; the ether extract was successively washed with 5% hydrochloric acid and 5% sodium hydroxide, and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation and 0.7 g. of crude product was obtained. Crystallization from methanol gave the air-sensitive aldehyde CVII, m.p. 85-92°; ν_{max}^{KBr} 2680, 1724 cm.$^{-1}$. The alde-hyde was reduced to XLIX without further purification.

Potassium hydroxide (1.5 g.) was heated with 1.5 ml. of 95% hydrazine and 10 ml. of diethylene glycol until it dissolved. The aldehyde CVII (400 mg.) was added to this solution and the reaction mixture was refluxed for 3 hours. Some of the product sublimed into the condenser during this period. Excess hydrazine and water were distilled out of the solution until the temperature of the residue reached 240°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine (1.5 ml.) was again added to the residue and refluxing continued for 12 additional hours. The reaction mixture, distillate, and ether washings were combined, added to water (150 ml.), and the entire mixture was extracted with ether. The ether

extract was thoroughly washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave 350 mg. of hydrocarbon XLIX, m.p. 75-79°. The analytical sample was obtained by two crystallizations from acetone and had m.p. 86-87°; $[\alpha]_D$ + 38.7° (c 0.036 in CCl_4); ν_{max}^{KBr} (Plate IX) 2941, 1460, 1370 cm.$^{-1}$; n.m.r. (Plate III, CCl_4) 0.82 (3), 0.85 (3), 0.93(3).

<u>Anal</u>. Calcd. for $C_{19}H_{32}$: C, 87.61; H, 12.38.

Found: C, 87.96; H, 12.41.

Preparation of CIX.

A solution of CII (0.5 g.) in 50 ml. of anhydrous ether was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.16 g.) in 25 ml. of anhydrous ether. After the initial reaction was over, the mixture was refluxed for 3 hours. The excess hydride was decomposed by the successive addition of ethyl acetate and water, and the alkaline solution was made acidic with cold 6 N hydrochloric acid. The acidic solution was extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate and finally evaporated to yield 0.45 g. (m.p. 160-210°) of a mixture of CIXa and b; ν_{max}^{KBr} 3356, 1626, 1066, 1053, 1042, 719 and 696 cm.$^{-1}$. This mixture was used in the next transformation without further purification.

Preparation of CX.

A solution of 0.44 g. of CIX (a, b) in 15 ml. of anhydrous pyridine was added to a mixture of 1.2 g. of chromic anhydride in 10 ml. of pyridine. After stirring for 2 hours at room temperature, the mixture was poured into ice-water and extracted with ether. The ether extract

was successively washed with 5% cold hydrochloric acid and 5% cold sodium hydroxide, and then dried over anhydrous sodium sulfate. Removal of the solvent gave 0.42 g. of the crude air-sensitive keto aldehyde CX (m.p. 112-118°); v_{max}^{KBr} 2695, 1727, 1618, 708 and 680 cm.$^{-1}$; which was used as such in the following reaction.

Preparation of CXI from CX.

Potassium hydroxide (5 g.) was heated with 5 ml. of 95% hydrazine and 45 ml. of diethylene glycol until it dissolved. The keto aldehyde CX (2.69 g.) was added to this solution and the reaction mixture heated under reflux for 4 hours. Excess hydrazine and water were distilled out of the solution until the bath temperature reached 240°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine (5 ml.) was added to the residue, and the refluxing continued for additional 12 hours. The reaction mixture, distillate and ether washings were combined, added to water (250 ml.) and the entire mixture extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of ether yielded 2.3 g. of the crude unsaturated hydrocarbon CXI which on elution with petroleum-ether (60-80°) through 20 g. of neutral alumina yielded 2.04 g. of white crystalline solid (m.p. 82-83°). The analytical sample obtained by recrystallization from methanol had m.p. 84-85°; v_{max}^{KBr} (Plate X) 1616, 708 and 699 cm.$^{-1}$; n.m.r. (Plate IV) δ0.82 (3), 0.87 (3), 0.96 (3) and 5.9 - 6.02 (2).

Anal. Calcd. for $C_{19}H_{30}$: C, 88.29; H, 11.70.

Found: C, 88.16; H, 11.84.

Preparation of CXVII.

A mixture of CII (3.81 g.), 20 ml. of anhydrous benzene, 2 ml. of freshly distilled ethylene glycol and 0.03 g. of p-toluenesulfonic acid monohydrate was heated at reflux in a flask provided with a Dean-Stark separator for 20 hours. The cooled mixture was poured into 5% sodium carbonate solution and the organic layer washed with water. Drying over anhydrous magnesium sulfate and evaporation of the solvent yielded 4.30 g. of viscous oil which crystallized on the addition of petroleum-ether (30-60°). Recrystallization from n-heptane yielded 4.14 g. (95.3%) of CXVII; m.p. 95-97°. The analytical sample, obtained by recrystallization from the same solvent, had m.p. 98-99°; v_{max}^{KBr} 1724, 1623, 1250, 1109, 1093 and 689 cm.$^{-1}$; n.m.r. (CCl$_4$) δ1.03 (3), 1.10 (3), 3.58 (3), 3.77 (4), 5.85 - 5.94 (2).

<u>Anal</u>. Calcd. for C$_{22}$H$_{32}$O$_4$: C, 73.59; H, 8.94.

Found: C, 73.88; H, 8.88.

Preparation of CXVIII.

A solution of 3.8 g. of CXVII in 40 ml. of anhydrous ether was added dropwise to a well-stirred suspension of 0.28 g. of lithium aluminum hydride in 25 ml. of anhydrous ether and the reaction mixture was refluxed for 5 hours. The excess hydride was decomposed by the successive addition of ethyl acetate and water. After treatment with an excess of 20% aqueous ammonium chloride solution, the ether layer was separated and the aqueous layer extracted with more ether. The combined ether layers were washed with water, then dried over anhydrous magnesium sulfate. Removal of the solvent yielded 3.49 g. of crude CXVIII

which upon crystallization from ether-petroleum-ether gave 3.25 g. (92.8%) of CXVIII; m.p. 103-105°. The analytical sample was obtained by recrystallization from the same solvent and had m.p. 106-107°; ν_{max}^{KBr} 3460, 1621, 1093 and 698 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.73 (3), 1.05 (3), 3.78 (4) and 5.85 - 5.94 (2).

<u>Anal</u>. Calcd. for C$_{21}$H$_{32}$O$_3$: C, 75.86; H, 9.70.

Found: C, 75.85; H, 9.72.

Preparation of CXIX.

A solution of 2.91 g. of CXVIII in 15 ml. of anhydrous pyridine was added to a mixture of 4 g. of chromic anhydride and 30 ml. of anhydrous pyridine. After stirring at room temperature for 2 hours, the mixture was poured into ice-water and extracted with ether using Super Cel to break the emulsion. The organic layer was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated to yield 2.84 g. of crude CXIX which was subjected to the following reaction without further purification; ν_{max}^{KBr} 2681, 1724, 1626, 1093 and 701 cm.$^{-1}$.

Preparation of CXX.

A mixture of 2.76 g. of CXIX, 40 ml. of diethylene glycol, 6 ml. of 95% hydrazine and 5 g. of potassium hydroxide was gently heated to dissolve the potassium hydroxide and then refluxed for 4 hours. Excess hydrazine and water were distilled out of the solution at a bath temperature of 240°; 6 ml. of 95% hydrazine was again added and the reaction mixture refluxed for an additional 16 hours. The cold mixture was diluted with 250 ml. of water and extracted with ether. The organic layer was washed with water, and on drying over anhydrous magnesium

sulfate followed by evaporation of the solvent, it yielded 2.38 g. of partially crystalline material which on crystallization from methanol yielded 1.4 g. of pure CXX; m.p. 90-90.5°; v_{max}^{KBr} 1626, 1096 and 689 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.83 (3), 0.85 (3), 1.00 (3), 3.76 (4), 5.85 - 5.94 (2).

<u>Anal</u>. Calcd. for C$_{21}$H$_{32}$O$_2$: C, 79.69; H, 10.19.

Found: C, 79.60; H, 10.54.

Preparation of CXXI.

Concentrated hydrochloric acid (5 drops) was added to a solution of 1.2 g. of CXX in 15 ml. of methanol, 25 ml. of dioxane and 5 ml. of water. The solution was stirred at room temperature for one hour and then diluted with water (150 ml.). The aqueous layer was extracted with ether and the extract successively washed with 5% sodium carbonate and water. Drying of the extract over anhydrous magnesium sulfate and evaporation of the solvent yielded 1.05 g. of a crystalline material which upon recrystallization from methanol gave 0.96 g. (93%) of pure CXXI, m.p. 119-120°; [reported (24) m.p. 123-124°]; v_{max}^{KBr} 1721 and 706 cm.$^{-1}$; n.m.r. (CCl$_4$) δ 0.83 (3), 0.93 (6), δ6.04 - 6.10 (2).

<u>Anal</u>. Calcd. for C$_{19}$H$_{26}$O: C, 83.76; H, 10.36.

Found: C, 83.71; H, 10.47.

Preparation of CXI from CXXI.

A mixture of 10 ml. of diethylene glycol, 2 ml. of 95% hydrazine and 2 g. of potassium hydroxide was heated under reflux until the potassium hydroxide dissolved. To the cooled mixture, 0.8 g. of the keto olefin CXXI was added and the solution was refluxed for 28 hours. Water (250 ml.) was added to the cooled reaction mixture and the solid that

precipitated was extracted into ether. The ether extract was washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a crystalline material which on recrystallization from methanol gave 0.6 g. (79%) of an olefin identical in all respects with CXI, previously obtained as described above.

Preparation of CXVI.

A solution of 0.062 g. of CXXI in 10 ml. of ethyl acetate was hydrogenated in the presence of 0.010 g. of 10% palladium-on-charcoal catalyst. The theoretical amount of hydrogen was absorbed within 10 minutes. The solid product CXVI, obtained after the removal of the catalyst and evaporation of the solvent, was crystallized from methanol, (0.55 g.); m.p. 125-126° [reported (24) m.p. 126-127°]; ν_{max}^{KBr} 1721 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.80 (6), 0.87 (3). Optical rotatory dispersion run in methanol (C 0.055): $[\alpha]_{589 \ m\mu} + 40^{\circ}$, $[\alpha]_{310} + 649^{\circ}$, $[\alpha]_{295} + 231^{\circ}$.

Preparation of CXXII.

Nine milliliters of an ethereal solution of monoperphthallic acid (4 m. moles) was added to a solution of 0.92 g. ($\approx$3.5 m. moles) of CXI in 7 ml. of ether and the mixture was allowed to stand for 48 hours at room temperature. After that interval, 25 ml. of ether was added to the reaction mixture and excess peracid was destroyed by washing the ether layer with an aqueous solution of potassium iodide. The organic layer was then respectively washed sodium thiosulfate, sodium carbonate solution and water. The ether layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.96 g. of the crude epoxide CXXII; ν_{max}^{KBr} 870 cm.$^{-1}$. Crystallization from acetone gave 0.42 g.

of epoxide which melted over a broad range (70-112°); n.m.r. (CCl$_4$) δ0.80 (3), 0.87 (3), 0.95 (3), 2.55 (doublet, J = 5 c.p.s.), 3.02 (triplet, J = 5 c.p.s.).

Conversion of CXXII to CXV.

CXXII (0.52 g.) in 15 ml. of anhydrous ether was added dropwise to an ethereal solution of methylmagnesium iodide (prepared by action of 0.15 ml. of methyl iodide in 5 ml. of dry ether on 0.05 g. of magnesium suspended in 2 ml. of anhydrous ether). The reaction mixture was refluxed for 42 hours, after an initial stirring at room temperature for 2 hours. The complex was hydrolyzed by means of 20% aqueous ammonium chloride solution. The clear ether layer was combined with ether extracts of the aqueous layer and washed with water. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.54 g. of semicrystalline alcoholic product; ν_{max}^{Nujol} 3356 and 1044 cm.$^{-1}$. This product was oxidized without further purification.

A solution containing 0.52 g. of the above alcohol in 7 ml. of dry pyridine was added to a mixture of 0.7 g. of chromic anhydride and 6 ml. of dry pyridine, and the reaction mixture was stirred for 8 hours at room temperature. The mixture was then poured into ice-water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 0.49 g. of partially crystalline solid (ν_{max}^{film} 1724 cm.$^{-1}$) which was suspended in 60 ml. of methanol and 15 ml. of 15% aqueous sodium hydroxide solution and the resulting mixture was heated at reflux for 8 hours. The cold mixture was diluted with 150 ml. of water and

extracted with ether. The organic layer was dried over anhydrous
magnesium sulfate and evaporation of the solvent yielded 0.34 g. of
yellow semicrystalline solid which was chromatographed over 40 g. of
neutral alumina. Elution with 50 ml. of benzene-ether (8.5:1.5) gave
0.114 g. of a ketone (m.p. 144-146°) which after crystallization from
methanol had m.p. 146-148°. This ketone was found to be identical in
all respects with CXV prepared as described below.

Preparation of CXII and CXIII.

To a well-stirred suspension of 0.21 g. of sodium borohydride in
20 ml. of anhydrous tetrahydrofuran containing 2.2 g. of CXI, there was
added 1 g. of boron trifluoride-etherate in 8 ml. of anhydrous tetra-
hydrofuran over a period of one hour at room temperature. After stir-
ring for 2 additional hours at room temperature the reaction mixture
was heated under reflux for one hour. To the cold mixture 4 ml. of
3 N sodium hydroxide followed by 4 ml. of 30% hydrogen peroxide was
added slowly. After 1.5 hours 50 ml. of ether was added to the reac-
tion mixture, the organic layer was separated, and washed with water.
The ether layer was dried over anhydrous magnesium sulfate and evapora-
tion of the solvent yielded 2.38 g. of a mixture of alcohols CXII and
CXIII; ν_{max}^{KBr} 3356, 1064 and 1050 cm.$^{-1}$.

Preparation of CXIV and CXV.

A solution of 2.37 g. of the above alcohol mixture in 30 ml. of
anhydrous pyridine was added to a mixture of 3 g. of chromic anhydride
and 30 ml. of anhydrous pyridine. The reaction mixture was stirred for
14 hours at room temperature after which it was poured into ice-water.

The aqueous solution was extracted with ether, the extract was washed respectively with 5% cold hydrochloric acid and 5% cold sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and removal of the solvent yielded 2.27 g. of crude ketonic product. Chromatography of the mixture of ketones on alumina and elution with petroleum-ether-benzene gave first 0.44 g. of pure CXV [m.p. 146-148°; ν_{max}^{KBr} 1724 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.85 (3), 0.88 (3), 1.07 (3), 2.17], then 0.422 g. of a mixture of CXIV and CXV and finally 1.12 g. of pure CXIV [m.p. 145-146°; ν_{max}^{KBr} 1730 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.85 (3), 0.88 (3), 1.02 (3), 1.82].

Ketone CXV: optical rotatory dispersion curve in methanol (C = 0.051): $[\alpha]_{589\ m\mu}$ + 19.6°, $[\alpha]_{342}$ 0°, $[\alpha]_{310}$ - 1242°, $[\alpha]_{300}$ - 776°.

Anal. Calcd. for C$_{19}$H$_{30}$O: C, 83.15; H, 11.01.

Found: C, 83.18; H, 11.20.

Ketone CXIV: optical rotatory dispersion curve in methanol (C = 0.051): $[\alpha]_{589\ m\mu}$ + 183.2°, $[\alpha]_{308}$ + 1145°, $[\alpha]_{290}$ + 760°.

Anal. Calcd. for C$_{19}$H$_{30}$O: C, 83.15; H, 11.01.

Found: C, 82.48; H, 11.16.

Both ketones CXIV and CXV on Huang-Minlon reduction gave hydrocarbon XLIX.

Preparation of LXXXIX.

Methyltriphenylphosphonium bromide, 0.6 g., [prepared from methyl bromide and triphenylphosphine (63)], was added to an ethereal solution of n-butyl lithium (obtained by addition of 0.21 g. of n-butyl bromide in 5 ml. of anhydrous ether to 0.021 g. of lithium in 5 ml. of ether) under an oxygen-free nitrogen atmosphere. The mixture was stirred for

2 hours. A solution of 0.25 g. of XCIV in 30 ml. of anhydrous ether was added to the mixture and stirring continued for 4 additional hours. Ether was distilled as anhydrous tetrahydrofuran was added, until most of the ether had been displaced (70). The reaction mixture was refluxed for 6 hours, then allowed to stand at room temperature overnight. The mixture was diluted with 100 ml. of water and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporation of the solvent yielded a gummy mass. Elution of this mixture through neutral alumina (30 g.) with 60 ml. of petroleum-ether (60-80°) followed by two crystallizations from methanol yielded 0.220 g. (88.7%) of the olefin LXXXIX, (m.p. 57-58°). The analytical sample was obtained by recrystallization from the same solvent and had m.p. 60-61° [reported (22) for the racemic compound, m.p. 54-55.5°]; v_{max}^{KBr} (Plate XI) 2681, 1653, 885 and 873 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.80 (3), 0.83 (3), 0.93 (3), 4.44 (doublet J = 2 c.p.s. one proton), 4.60 (broad, one proton).

Anal. Calcd. For C$_{20}$H$_{32}$: C, 88.16; H, 11.83.

Found: C, 88.16; H, 11.73.

Synthesis of Ketone CXXIII.

o-Methylpodocarpinol, CXXVI, was synthesized according to the method of Zeiss and co-workers (71), starting from podocarpic acid, XXVI, which in turn was isolated from rimu resin (72).

The α,β-unsaturated ketone CXXIII was prepared by the reduction of o-methylpodocarpinol with lithium and tert-butyl alcohol in a mixture of tetrahydrofuran and liquid ammonia (65).

Preparation of Diacetate CXXVII.

A solution of 20.3 g. of the ketone CXXIII in 650 ml. of ethanol was heated to reflux and treated with a solution of 12.6 g. of sodium borohydride in 150 ml. of 80% ethanol. The stirred mixture was refluxed for 2 hours, cooled and cautiously acidified with 6 N hydrochloric acid. Dilution with 1800 ml. of water gave an oily material which was extracted into ether. The organic layer was washed successively with water, dilute sodium hydroxide and water, and then dried over anhydrous magnesium sulfate. Removal of the solvent yielded the glassy diol, 20.1 g., ν_{max}^{KBr} 3390, 1647 and 1031 cm.$^{-1}$.

Acetic anhydride, 30 ml., was added to a solution of 21 g. of the crude diol in 120 ml. of anhydrous pyridine and the mixture was stirred at room temperature for 20 hours. After the addition of 200 ml. of water, the reaction mixture was washed successively with water, cold 5% hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate and evaporated to yield 27.5 g. of the viscous oily diacetate CXXVII; ν_{max}^{film} 1745, 1701, 1645 and 1105 cm.$^{-1}$.

Pyrolysis of Diacetate CXXVII. Preparation of Dienes CXXVIII and CXXIX.

A solution of 1.52 g. of CXXVII in 20 ml. of anhydrous benzene was pyrolyzed by dropwise addition into a column packed with glass helices maintained at 300-310°, under a steady stream of nitrogen. The addition took approximately 30 minutes and the compound was allowed to stay in the hot column for an additional 30 minutes. The cooled column was washed with benzene and the washings washed with cold 5% sodium carbonate solution and water respectively. The organic layer was dried over

anhydrous magnesium sulfate and evaporated to yield 1.26 g. of the oily

mixture of dienes CXXVIII and CXXIX; λ_{max}^{EtOH} 265 mμ (3380) and 276 (ϵ =

2800).

Preparation of Diels-Alder Adducts CXXX and CXXXI.

A solution of 28.14 g. of the diene mixture and 15 g. of maleic

anhydride in 80 ml. of xylene was refluxed for 6 hours in an atmosphere

of nitrogen. After addition of 100 ml. of ether, the cold yellow

solution was repeatedly extracted with water to remove the unreacted

maleic anhydride. During this process solid CXXXI, 2.73 g., m.p. 245-

250°, appeared in the organic phase and was collected by filtration.

Recrystallization from benzene gave the analytical sample of CXXXI,

m.p. 251-252°; ν_{max}^{KBr} 1845, 1779, 1730 and 1250 cm.$^{-1}$; n.m.r. (Plate V)

δ0.91 (3), 0.99 (3), 2.02 (3), 4.08 (doublet, 1 proton), 4.27 (doublet,

1 proton) and 5.81 (doublet, 1 proton).

<u>Anal.</u> Calcd. for $C_{20}H_{30}O_5$: C, 71.47; H, 7.82.

Found: C, 71.41; H, 7.75.

The filtrate was dried over anhydrous magnesium sulfate and removal

of a major portion of the solvent yielded a viscous liquid which could

be crystallized after the addition of a small amount of ether. After

several hours standing at 5°, crystalline CXXX was collected and dried,

7.16 g., m.p. 180-194°. The filtrate after removal of the solvent yielded

21.3 g. of a gummy mass, ν_{max}^{film} 1845, 1783, 1730 and 1235 cm.$^{-1}$.

Repeated crystallization of a small sample of CXXX from heptane-

benzene afforded the analytical sample, m.p. 213-5-214.5^o; ν_{max}^{KBr} 1845,

1779, 1730 and 1263 cm.$^{-1}$; n.m.r. (Plate VII) δ0.97 (3), 1.40 (3),

2.01 (3), 3.87 (doublet, 1 proton), 4.28 (doublet, 1 proton) and 6.30

(doubelt, 2 protons).

<u>Anal</u>. Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82.

Found: C, 71.18; H, 7.61.

Since the fractional crystallization method proved to be a lengthy and laborious process for the isolation of CXXX, it was found more convenient to isolate it in the form of its dimethyl ester. A suspension of 7 g. of crude CXXX, m.p. 180-194°, in 50 ml. of ether and 50 ml. of methanol was treated with an excess of ethereal diazomethane. Evaporation of the solvent and recrystallization twice from methanol yielded 5.1 g. of dimethyl ester CXLIV, m.p. 169-170°; ν_{max}^{KBr} 3049, 1748, 1727, 1645, 1242, 1227 and 710 cm.$^{-1}$; n.m.r. $(CDCl_3)$ $\delta 0.96$ (3), 1.21 (3), 2.05 (3), 3.53 (3), 3.55 (3), 3.88 (doublet, 1 proton), 4.36 (doublet, 1 proton) and 6.44 (multiplet, 2 protons).

<u>Anal</u>. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39.

Found: C, 69.38; H, 8.48.

<u>Preparation of Dimethyl Ester CXXXII</u>.

An excess of ethereal diazomethane was added to a suspension of 0.19 g. of CXXXI in 15 ml. of methanol and 15 ml. of ether. After standing overnight the reaction mixture, after eavporation of the solvent, yielded 2.1 g. of gummy dimethyl ester CXXXII which could be crystallized from dilute acetic acid only after long standing, m.p. 73-76°; ν_{max}^{KBr} 1748, 1639 and 1232 cm.$^{-1}$; n.m.r. (CCl_4) $\delta 0.86$ (3), 1.00 (3), 1.99 (3), 3.50 (3), 3.53 (3), 4.08 (doublet, 1 proton), 4.30 (doublet, 1 proton) and 6.08 (doublet, 1 proton).

A number of attempts to hydrogenate CXXXII at atmospheric pressure were unsuccessful.

Hydrolysis of CXXXII. Preparation of CXXXIII.

A suspension of 2.98 g. of CXXXII in a mixture of 25 ml. of 20%

sodium hydroxide and 25 ml. of methanol was refluxed for 8 hours. The

clear reaction mixture was diluted with 150 ml. of water, made acidic

with 6 N hydrochloric acid and then extracted with ether. The organic

layer was washed with water, then dried over anhydrous magnesium sulfate.

Evaporation of the solvent yielded 2.41 g. of crystalline CXXXIII which

after crystallization from ethyl acetate-methanol gave m.p. 251-253°;

2.2 g. The analytical sample was obtained by further recrystallization

from ethyl acetate-methanol and gave m.p. 253-255°; ν_{max}^{KBr} 3448, 1706 and

1020 cm.$^{-1}$; n.m.r. (CD_3CO_2D) δ0.92 (3), 1.00 (3), 3.61 (doublet, 1

proton), 3.97 (doublet, 1 proton) and 6.08 (doublet, 1 proton).

$\quad\quad\quad\quad$ Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34.

$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad$ Found: C, 69.29; H, 8.45.

Conversion of CXXXIII to CXXXV.

Acetylation of 0.93 g. of the hydroxy diacid CXXXIII with 2 ml.

of acetic anhydride in 5 ml. of anhydrous pyridine for 10 hours at

room temperature followed by the usual work up yielded 1.0 g. of the

crude amorphous acetate CXXXIV which was subjected to the action of

lead tetraacetate without further purification.

Acetate CXXXIV, 1.0 g., was dissolved in 25 ml. of anhydrous pyri-

dine at 70° and 1.1 g. of lead tetraacetate was added to the stirred

solution under an atmosphere of nitrogen. After 10 minutes, an additional

1.5 g. of lead tetraacetate was added and the reaction mixture allowed

to reflux for 1.5 hours. The pyridine was removed over a steam bath

with a water aspirator and the dark brown residue was extracted with
ether. The ether extract was washed with water, dried over anhydrous
magnesium sulfate and evaporated to give 0.66 g. of a brown gum.

A mixture of 0.66 g. of the above described material, 25 ml. of
15% sodium hydroxide and 25 ml. of methanol was heated at reflux for
3 hours. The cooled reaction mixture was diluted with 100 ml. of
water and extracted with ether. The organic layer was washed with water,
dried over anhydrous magnesium sulfate and evaporated to yield 0.17 g.
of a brown gum which was chromatographed over 9 g. of acid-washed
alumina (activity III). Elution with 40 ml. of benzene gave 0.087 g.
of crude gummy CXXXV which was identified only by its spectral properties,
ν_{max}^{film} 3401, 3049, 1036, 760 and 722 cm.$^{-1}$; λ_{max}^{EtOH} 272 mμ (ϵ = 436),
262 mμ (ϵ = 477), 257 mμ (ϵ = 469), 251 mμ (ϵ = 452) and 209 mμ (ϵ =
4770) and n.m.r. (CCl$_4$) δ6.91 - 7.33.

Preparation of CXXXVII.

Hydroxy diacid CXXXIII, 1.96 g., was hydrogenated with 0.40 g.
of 5% platinum-on-charcoal catalyst in 50 ml. of acetic acid at room
temperature. Removal of the catalyst by filtration followed by dilu-
tion of the filtrate with water and collection of the crystalline solid
gave 1.95 g. of CXXXVI contaminated with its acetate formed from the
glacial acetic acid solvent during hydrogenation.

A mixture of the above solid, 1.95 g., and 50 ml. of 5% sodium
hydroxide was heated on a steam bath for 2.5 hours. The cooled reac-
tion mixture was diluted with 150 ml. of water and made acidic by the
addition of 6 N hydrochloric acid. The crystalline product, 1.9 g.,
was collected on a filter, washed with water, and gave on drying m.p.

289-292°. Recrystallization from ethyl acetate-petroleum-ether (60-80°) raised the m.p. of CXXXVI to 291-294°; ν_{max}^{KBr} 3356, 1701 and 1111 cm.$^{-1}$; n.m.r. (CD$_3$CO$_2$D) δ0.72 (3), 0.94 (3).

A solution of 1.66 g. of CXXXVI and 2 ml. of acetic anhydride in 10 ml. of anhydrous pyridine was stirred at room temperature for 10 hours. After the addition of 50 ml. of ether, the reaction mixture was respectively washed with water, cold 5% hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate and evapora- ted to give 1.94 g. of a glassy mixture of CXXXVII and the mixed anhy- dride obtained by the interaction of CXXXVII and acetic anhydride. The hydrolysis of the mixed anhydride moiety was effected by refluxing 1.94 g. of the above mentioned mixture in a solution of 15 ml. of water and 30 ml. of dioxane for 7 hours. The cooled reaction mixture after dilution with 100 ml. of water gave 1.8 g. (97.3%) of crystalline CXXXVII, m.p. 216-220°. The analytical sample was obtained by crystal- lization from ethyl acetate-petroleum-ether (60-80°) and gave m.p. 218-220°; ν_{max}^{KBr} 3448, 3247, 1739, 1701 and 1242 cm.$^{-1}$.

<u>Anal</u>. Calcd. For C$_{23}$H$_{34}$O$_6$: C, 67.95; H, 8.43.

Found: C, 68.06; H, 8.86.

Preparation of CXXXVIII.

Diacid CXXXVII, 0.76 g., was dissolved in 30 ml. of anhydrous pyridine maintained at 70° and 0.8 g. of lead tetraacetate was added to the stirred solution under an atmosphere of nitrogen. After 10 minutes an additional 0.8 g. of lead tetraacetate was added and the reaction mixture was refluxed for 1.5 hours. The pyridine was removed on the steam bath with a water aspirator and the dark brown residue

was extracted into ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 0.56 g. of a gummy dark brown substance.

A solution of 0.56 g. of the above material in 20 ml. of 10% sodium hydroxide and 50 ml. of methanol was refluxed for 2 hours. The cooled reaction mixture was diluted with 100 ml. of water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.27 g. of a semi-solid which was chromatographed over 24 g. of acid-washed alumina (activity III). Elution with 100 ml. of benzene gave 0.116 g. (22.6%) of alkene CXXXVIII, m.p. 131-133°. The analytical sample was obtained by recrystallization from methanol and gave m.p. 133-135°; ν_{max}^{KBr} 3390, 3040, 1639, 1029, 722 and 700 cm.$^{-1}$; n.m.r. (Plate VI) δ0.53 (3), 0.91 (3), 2.47 (multiplet, 1 proton), 3.31 (doublet, 1 proton), 3.66 (doublet, 1 proton), 5.81 (quartet, 1 proton) and 6.03 (quartet, 1 proton).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.01.

Found: C, 82.16; H, 11.10.

Preparation of CXXXIX.

Hydrogenation of CXXXVIII, 0.13 g., in 10 ml. of ethyl acetate with 0.025 g. of 5% platinum-on-charcoal catalyst at atmospheric pressure followed by removal of the catalyst by filtration and evaporation of the filtrate yielded a quantitative amount of the saturated alcohol CXXXIX, m.p. 143-145°. The analytical sample, obtained by recrystallization from methanol, had m.p. 146-147°; ν_{max}^{KBr} 3390 and 1031 cm.$^{-1}$; n.m.r. (CDCl$_3$-CS$_2$) δ0.91 (3), 0.93 (3), 3.43 (doublet, 1 proton) and 3.76 (doublet, 1 proton).

<u>Anal</u>. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66.

Found: C, 82.22; H, 11.57.

Conversion of CXXXIX into XLIX.

Alcohol CXXXIX, 0.10 g. in 2.5 ml. of anhydrous pyridine was added to a mixture of 0.15 g. of chromic anhydride and 2.5 ml. of anhydrous pyridine. After stirring for 1.5 hours, the mixture was poured into ice-water and extracted with ether. The ether extract was washed with cold 5% hydrochloric acid and then with water. The organic layer was dried over anhydrous magnesium sulfate and evaporation yielded 0.090 g. of crude aldehyde CXL which was subjected to the following reaction without further purification.

A mixture of 0.085 g. of CXL, 5 ml. of diethylene glycol and 1 ml. of 95% hydrazine was heated at 110-120° for 1.5 hours. Potassium hydroxide, 1 g., was added to the cooled reaction mixture and the mixture was then refluxed for 6 hours. Excess hydrazine and water were distilled out until the temperature of the residue reached 220°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine, 0.5 ml. was again added to the residue and refluxing continued for an additional 8 hours. The reaction mixture, distillate and ether washing were combined, added to 20 ml. of water, and the entire mixture was extracted with ether. The ether extract was thoroughly washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.07 g. of an oil which was chromatographed over acid-washed alumina (activity III). Elution with 20 ml. of petroleum-ether (60-80°) yielded 0.040 g. of XLIX which on repeated recrystallization from methanol yielded 0.015 g., m.p. 86-87°, identical in every

respect with the tetracyclic hydrocarbon synthesized from maleopimaric acid.

Preparation of CXLII.

A solution of 0.075 g. of CXXXVIII in 1.5 ml. of anhydrous pyridine was added to a mixture of 0.090 g. of chromic anhydride and 1 ml. of anhydrous pyridine. After stirring at room temperature for one hour, the mixture was poured into ice-water and extracted with ether. The extract was washed with 5% hydrochloric acid then water and finally dried over anhydrous magnesium sulfate. Evaporation of ether yielded 0.065 g. of crude CXLI which was used in the following reaction without further purification.

A mixture of 0.065 g. of crude CXLI and 0.4 ml. of 95% hydrazine in 4 ml. of diethylene glycol was heated at 110-120° for 2 hours. After cooling, potassium hydroxide, 0.4 g., was added and the mixture refluxed for 10 hours. The turbid solution was poured into 20 ml. of water and extracted with ether. The ether extract was dried over an-hydrous magnesium sulfate, evaporated and the residue chromatographed over 5 g. of acid-washed alumina (activity III). Elution with 20 ml. of petroleum-ether (60-80°) yielded 0.030 g. of a solid which after repeated recrystallization from methanol yielded 0.010 g. of pure olefin CXLII, m.p. 71-73°; ν_{max}^{KBr} (Plate XII) 3040, 1639, 724 and 700 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.57 (3), 0.80 (3), 0.87 (3), 3.85 (multiplet, 1 proton) and 5.72 - 6.2 (multiplet, 2 proton).

Preparation of CXLIII.

The adduct CXXX, 0.15 g., was hydrogenated in 15 ml. of acetic

acid in the presence of 0.030 g. of 5% platinum-on-charcoal catalyst at room temperature. The uptake of hydrogen was over within 25 minutes. The filtrate, obtained after the removal of the catalyst, was diluted with 100 ml. of water and collection of the solid on a filter afforded a quantitative yield of CXLIII, m.p. 251-252$^{\text{o}}$. The analytical sample, obtained by recrystallization from benzene, had the same melting point; $\nu_{\text{max}}^{\text{KBr}}$ 1845, 1779, 1730 and 1258 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.97 (3), 1.26 (3), 2.05 (3), 3.94 (doublet, 1 proton), 4.33 (doublet, 1 proton).

<u>Anal</u>. Calcd. for C$_{23}$H$_{32}$O$_5$: C, 71.10; H, 8.30.

Found: C, 71.41; H, 8.31.

Preparation of CXLV.

A solution of 0.19 g. of CXLIV in 20 ml. of acetic acid was stirred under an atmosphere of hydrogen with 0.050 g. of 5% platinum-on-charcoal catalyst at room temperature. After one hour, when the uptake of hydrogen had ceased, the catalyst was filtered off and the filtrate diluted with water. The crystalline product was collected on a filter and washed with water. A quantitative yield of pure diester CXLV, m.p. 169-170$^{\text{o}}$, was obtained on drying under vacuum. Recrystallization from methanol did not change the melting point; $\nu_{\text{max}}^{\text{KBr}}$ 1754, 1248 and 1238 cm.$^{-1}$; n.m.r. (CDCl$_3$) δ0.94 (3), 1.13 (3), 2.08 (3), 3.62 (6), 3.88 (doublet, 1 proton) and 4.35 (doublet, 1 proton).

<u>Anal</u>. Calcd. for C$_{25}$H$_{38}$O$_6$: C, 69.09; H, 8.81.

Found: C, 69.01; H, 8.60.

Preparation of CXLVI.

A suspension of 0.10 g. of CXLV in 5 ml. of methanol and 10 ml.

of 10% sodium hydroxide was refluxed for 6.5 hours. The cooled alkaline solution was made acidic with 6 N hydrochloric acid. The crystalline product was collected on a filter and washed with water. Dry CXLVI, obtained in quantitative yield, gave m.p. 209-211°. The analytical sample, recrystallized from aqueous methanol, showed m.p. 211-212°; ν_{max}^{KBr} 3460, 1727, 1695, 1242 and 1026 cm.$^{-1}$; n.m.r. (CD_3CO_2D) $\delta 0.96$ (3), 1.16 (3) and 3.66 (3).

<u>Anal</u>. Calcd. for $C_{22}H_{34}O_5 \cdot H_2O$: C, 66.80; H, 9.17.

Found: C, 66.55; H, 9.28.

Preparation of CXLVIII.

Acetylation of CXLVI with acetic anhydride and pyridine at room temperature provided acetate CXLVII which showed m.p. 155-156° after recrystallization from hexane-ethyl acetate; ν_{max}^{KBr} 3460, 3247, 1748, 1730, 1701 and 1241 cm.$^{-1}$; n.m.r. (CCl_4) $\delta 0.92$ (3), 1.17 (3), 1.98 (3) and 3.63 (3).

<u>Anal</u>. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.62.

Found: C, 68.85; H, 8.78.

Treatment of CXLVII with ethereal diazomethane gave CXLVIII as a viscous gum which could not be crystallized; ν_{max}^{film} 1748, 1730 and 1220 cm.$^{-1}$; n.m.r. (CCl_4) $\delta 0.91$ (3), 1.16 (3), 1.98 (3), 3.64 (3) and 3.68 (3). Thin-layer chromatography showed CXLVIII $(R_f$ 0.62) to be different from CXLV $(R_f$ 0.57).

Preparation of CXLIX.

A suspension of 3.5 g. of CXLV in 50 ml. of 25% aqueous methanolic sodium hydroxide was refluxed for 30 hours. The cold reaction mixture

was diluted with 100 ml. of water and made acidic with 6 N hydrochloric acid. The solid precipitate was taken up in ethyl acetate, the organic layer washed with water then dried over anhydrous magnesium sulfate and finally evaporated to yield 2.89 g. of crystalline CXLIX which after crystallization twice from a mixture of ethanol and ethyl acetate gave m.p. 270-277°, 2.5 g. After two further crystallizations from the same solvent it showed m.p. 296-300° (dec.); ν_{max}^{KBr} 3401, 3195, 1715 and 1020 cm.$^{-1}$.

Preparation of CL.

Acetylation of 2.33 g. of CXLIX with acetic anhydride in pyridine at room temperature gave 1.8 g. of the acetate CL, m.p. 273-277° (dec.) after recrystallization twice from ethyl acetate-hexane; ν_{max}^{KBr} 3448, 1751, 1695 and 1220 cm.$^{-1}$.

Preparation of CLI.

The acetoxy diacid CL, 0.53 g., was dissolved in 30 ml. of anhydrous pyridine, maintained at 70°, and 0.7 g. of lead tetraacetate was added to the stirred solution under an atmosphere of nitrogen. After 10 minutes an additional 1 g. of lead tetraacetate was added and the reaction mixture allowed to reflux for 1.5 hours. The pyridine was removed on the steam bath with a water aspirator and the dark brown residue was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 0.42 g. of a brown solid.

A suspension of 0.42 g. of the above solid in a mixture of 50 ml. of 5% sodium hydroxide and 25 ml. of methanol was refluxed for 2.5 hours. The cold solution was diluted with 100 ml. of water and extracted

with ether. The ether extract was dried over anhydrous magnesium
sulfate and evaporated to yield 0.32 g. of a yellow solid which was
chromatographed on 24 g. of acid-washed alumina (activity III). Elution
with 75 ml. of benzene afforded 0.22 g. (61.6%) of CLI, m.p. 120-121°;
v_{max}^{KBr} 3333, 3049, 1618, 1034 and 701 cm.$^{-1}$; n.m.r. (Plate VIII) δ 0.83
(3), 0.95 (3), 2.28 (multiplet, 1 proton), 2.87 (1), 3.24 (doublet,
1 proton), 3.65 (doublet, 1 proton) and 6.14 (doublet, 2 protons).

<u>Anal</u>. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02.

Found: C, 83.57; H, 11.07.

Preparation of CLII.

The unsaturated alcohol CLI, 0.200 g., was hydrogenated with 0.040
g. of 10% palladium-on-charcoal catalyst in 15 ml. of ethanol at room
temperature. After 2 hours, the catalyst was filtered off and dilution
of the filtrate with water followed by filtration and drying yielded
a quantitative amount of alcohol CLII, m.p. 141-142°. The analytical
sample, obtained by crystallization from methanol, showed m.p. 142-143°;
v_{max}^{KBr} 3333, 1036 cm.$^{-1}$; n.m.r. (CDCl$_3$-CS$_2$) δ0.85 (3), 0.93 (3), 3.38
(doublet, 1 proton) and 3.82 (doublet, 1 proton).

<u>Anal</u>. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66.

Found: C, 82.98; H, 11.59.

Preparation of CLIV.

A solution of 0.40 g. of CLII in 8 ml. of anhydrous pyridine was
added to a mixture of 0.50 g. of chromic anhydride in 5 ml. of anhydrous
pyridine and the entire mixture was then stirred for 1 hour. After
pouring into ice-water, the solution was extracted with ether, the

ether extract washed successively with 5% hydrochloric acid and water, and then dried over anhydrous magnesium sulfate. The solvent was removed by evaporation and 0.35 g. of the crude aldehyde CLIII was obtained, v_{max}^{film} 2577 and 1724 cm.$^{-1}$.

A mixture of 0.35 g. of CLIII, 1.5 ml. of 95% hydrazine and 10 ml. of diethylene glycol was heated at 110-120° for 2 hours. After cooling, 1.5 g. of potassium hydroxide was added and the mixture refluxed for 12 hours. The solution was poured into 50 ml. of ice-water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 0.31 g. of an oily product which was chromatographed on 6 g. of acid-washed alumina (activity III). Elution with 100 ml. of petroleum-ether (60-80°) yielded 0.24 g. of an oily substance which on addition of a mixture of methanol and ether deposited 0.045 g. of the azine CLV, m.p. 240-242°. The analytical sample was obtained by recrystallization from ethyl acetate and gave m.p. 249-253°; v_{max}^{KBr} 1639 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.72 (6), 1.03 (6) and 7.75 (2).

Anal. Calcd. for C$_{38}$H$_{60}$N$_2$: C, 83.75; H, 11.09.

Found: C, 83.72; H, 10.97.

After removal of CLV, the filtrate was evaporated to give a residue which on distillation (100-105° at 1 mm.) yielded 0.160 g. (42.5%) of oily CLIV, v_{max}^{film} 2915, 1387, 1370 cm.$^{-1}$; n.m.r. (CCl$_4$) δ0.85 (6) and 0.89 (3). Crystallization of a small sample from methanol-ether yielded crystalline hydrocarbon CLIV; m.p. 47-48°.

Anal. Calcd. for C$_{19}$H$_{32}$: C, 87.61; H, 12.38.

Found: C, 87.31; H, 12.31.

Preparation of CLVI and its Reaction with Ozone.

A solution of 0.135 g. of the unsaturated alcohol CLI in 2 ml. of anhydrous pyridine was acetylated with 0.5 ml. of acetic anhydride as described above. The crude acetate CLVI, 0.144 g., showed m.p. 89-91°; v_{max}^{KBr} 3067, 1745, 1650, 1235 and 703 cm.$^{-1}$; and was subjected to the action of ozone without further purification.

Ozone was passed at -70° through a 0.14 g. sample of CLVI dissolved in 20 ml. of methylene chloride until the solution turned deep blue. One ml. of hydrogen peroxide (30%) was then added to the solution and the entire mixture was stirred at room temperature for 6 hours. The excess peroxide was decomposed with a small amount of 10% palladium-on-charcoal catalyst. The catalyst was removed by filtration and the filtrate was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 0.16 g. of crude fluffy CLVII which was subjected to hydrolysis without further purification.

Preparation of CLIX and its Partial Hydrolysis.

A solution of 0.16 g. of crude CLVII in 25 ml. of 10% sodium hydroxide and 10 ml. of methanol was refluxed for 1.75 hours. The cooled solution was diluted with 50 ml. of water and extracted with ether. The alkaline layer was made acidic with dilute hydrochloric acid and extracted with ether. The latter ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield 0.084 g. of the crude hydroxy diacid CLVIII; m.p. 215-230°.

A solution of 0.084 g. of CLVIII in 10 ml. of ether was treated with an excess of ethereal diazomethane. After 2 hours, evaporation of

the solvent yielded 0.087 g. of the amorphous hydroxy dimethyl ester CLIX; n.m.r. (CCl_4) $\delta 3.68$, 3.58 and 3.62.

A solution of 0.087 g. of crude CLIX in 5 ml. of 5% sodium hydroxide and 5 ml. of methanol was refluxed for 1 hour. The cold reaction mixture was made acidic with 6 N hydrochloric acid and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield 0.079 g. of amorphous CLX; n.m.r. $(CDCl_3)$ $\delta 0.91$ (3), 0.98 (3), 3.69 (3) and 6.55 (broad, 2 protons, disappear on the addition of D_2O).
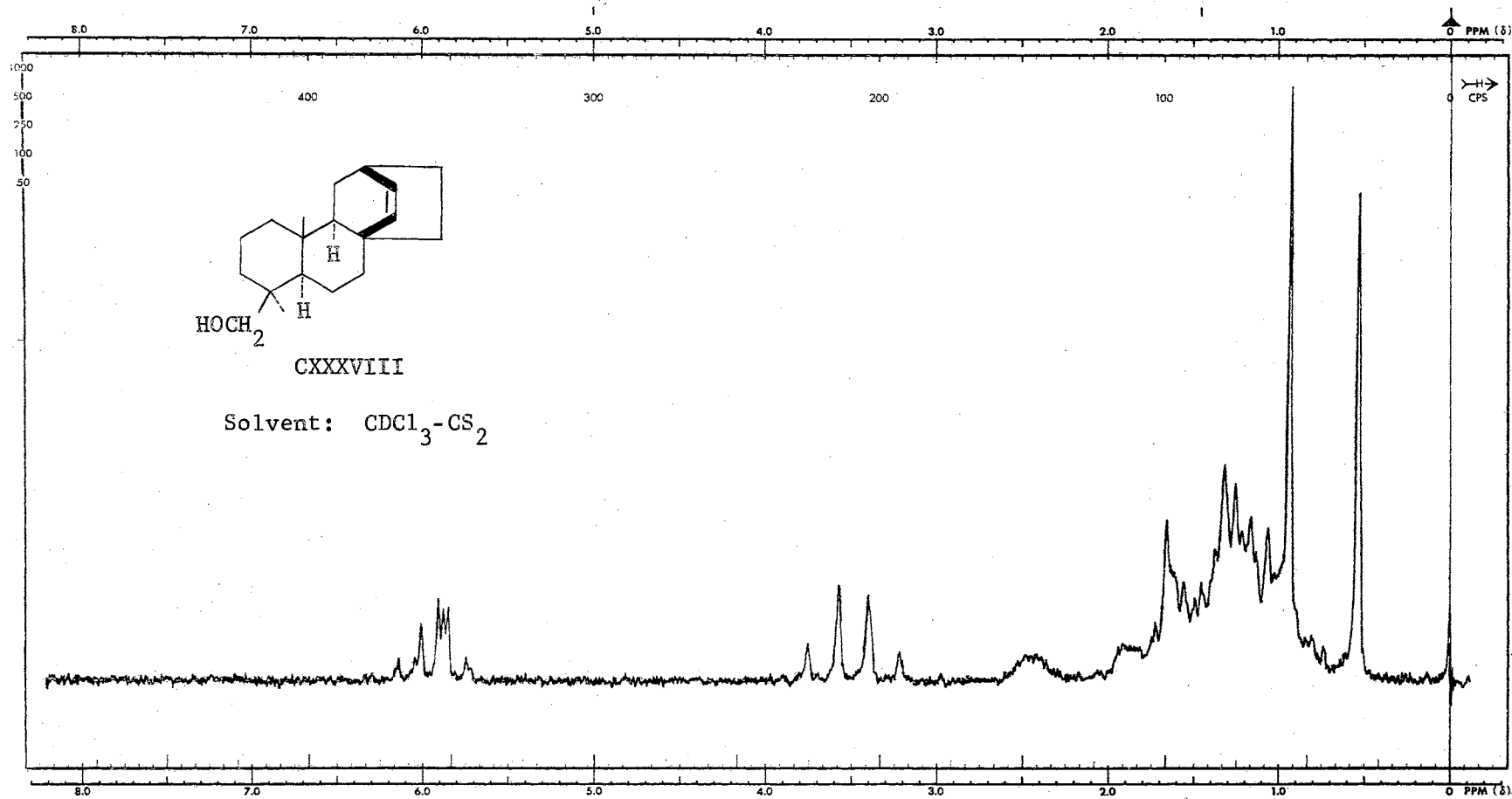
Plate I

Nuclear Magnetic Resonance Spectrum of XCa.
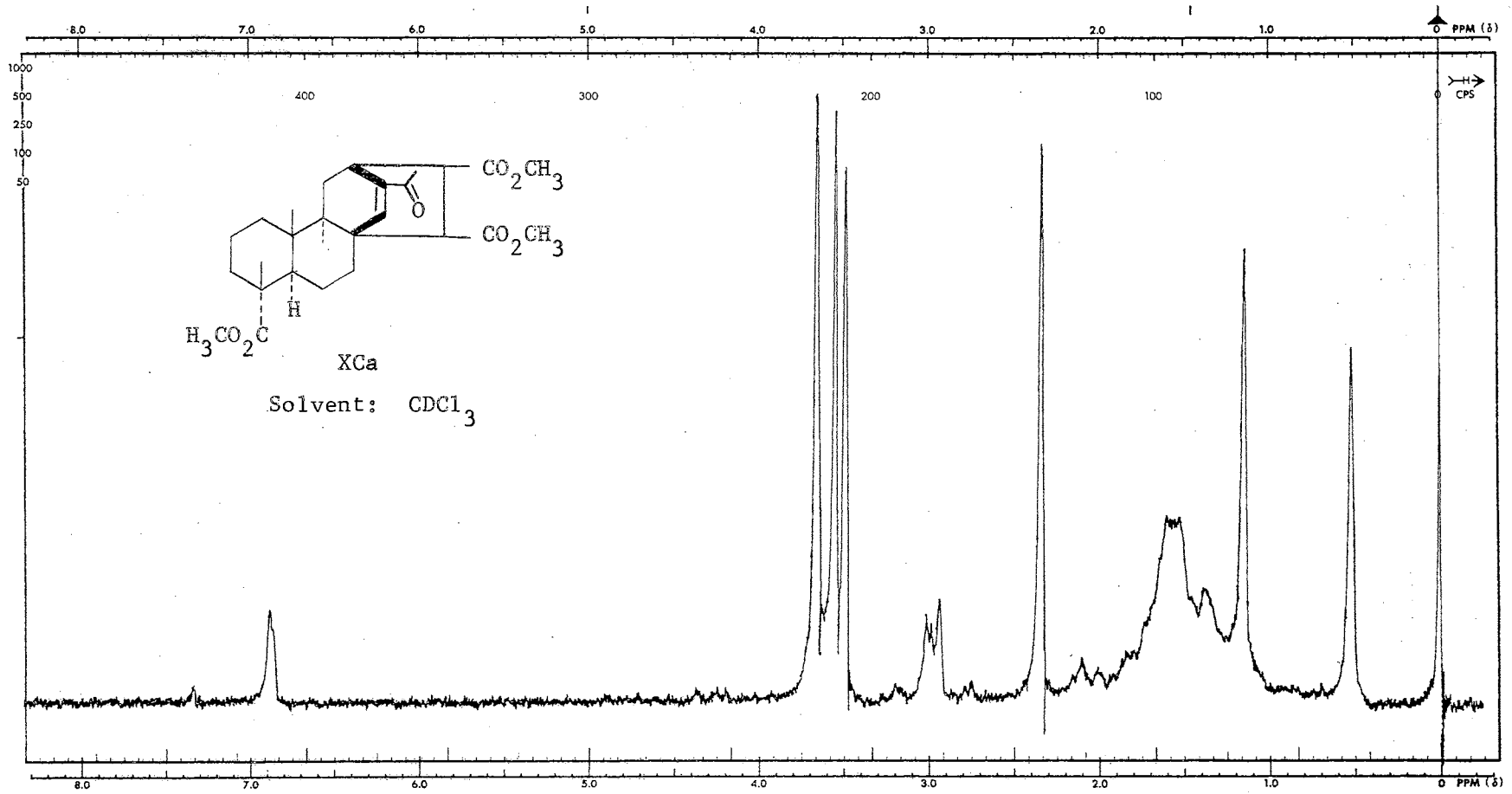
Plate II

Nuclear Magnetic Resonance Spectrum of XCIIIa

XCIIIa

Solvent: CDCl$_3$

CO$_2$CH$_3$

CO$_2$CH$_3$

H$_3$CO$_2$C

H
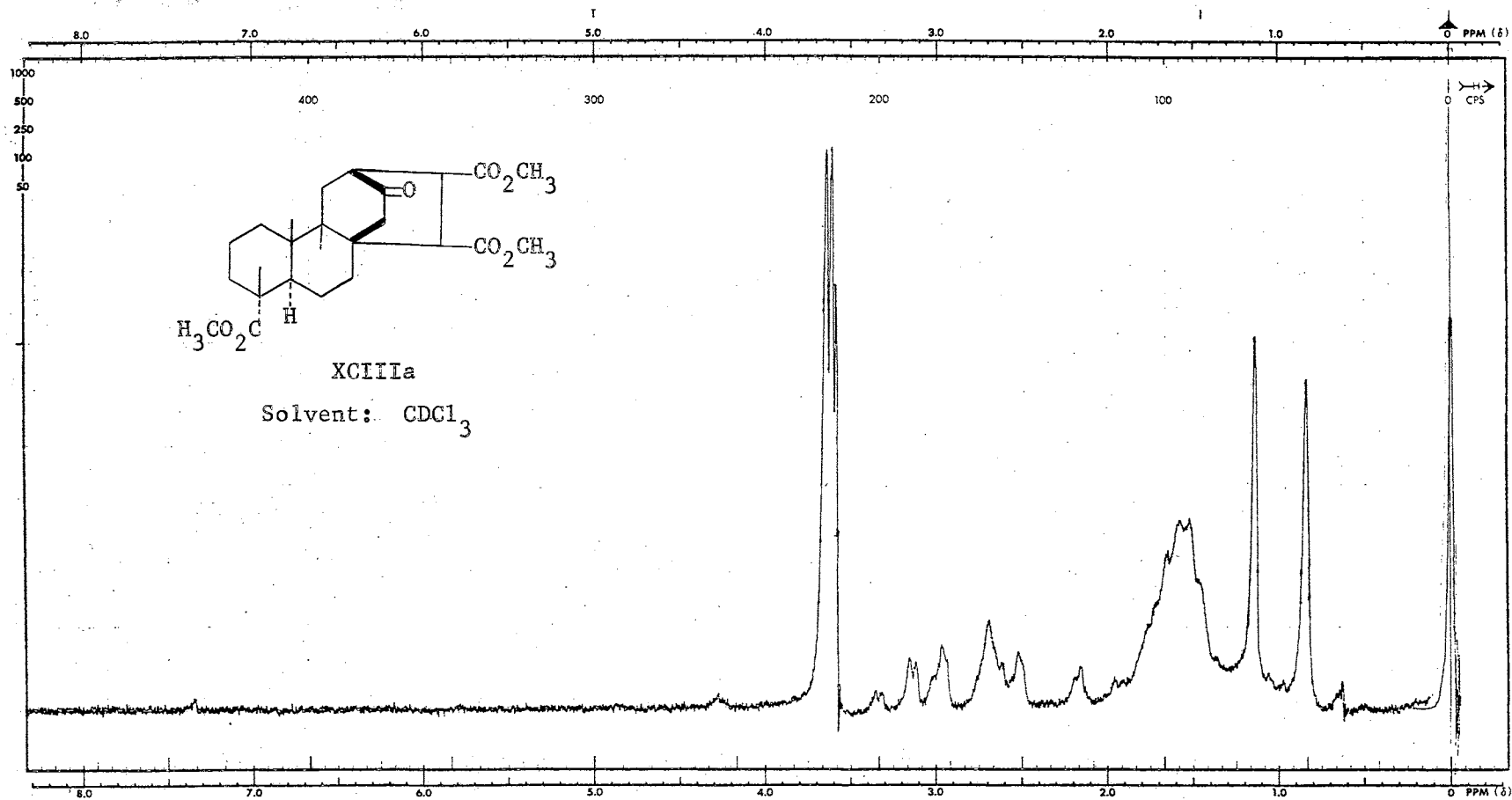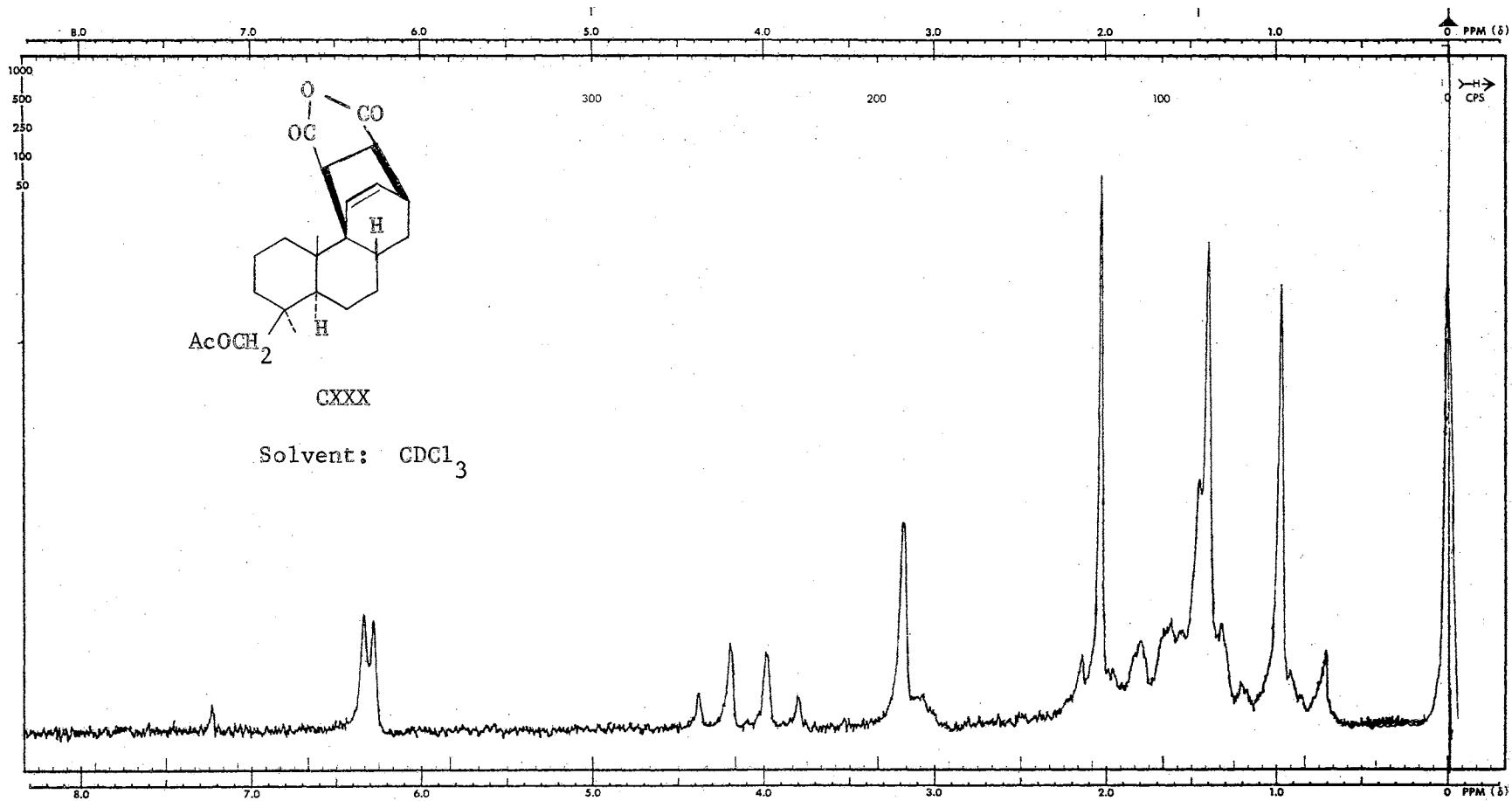
Plate III

Nuclear Magnetic Resonance Spectrum of XLIX

XLIX

Solvent: CCl_4
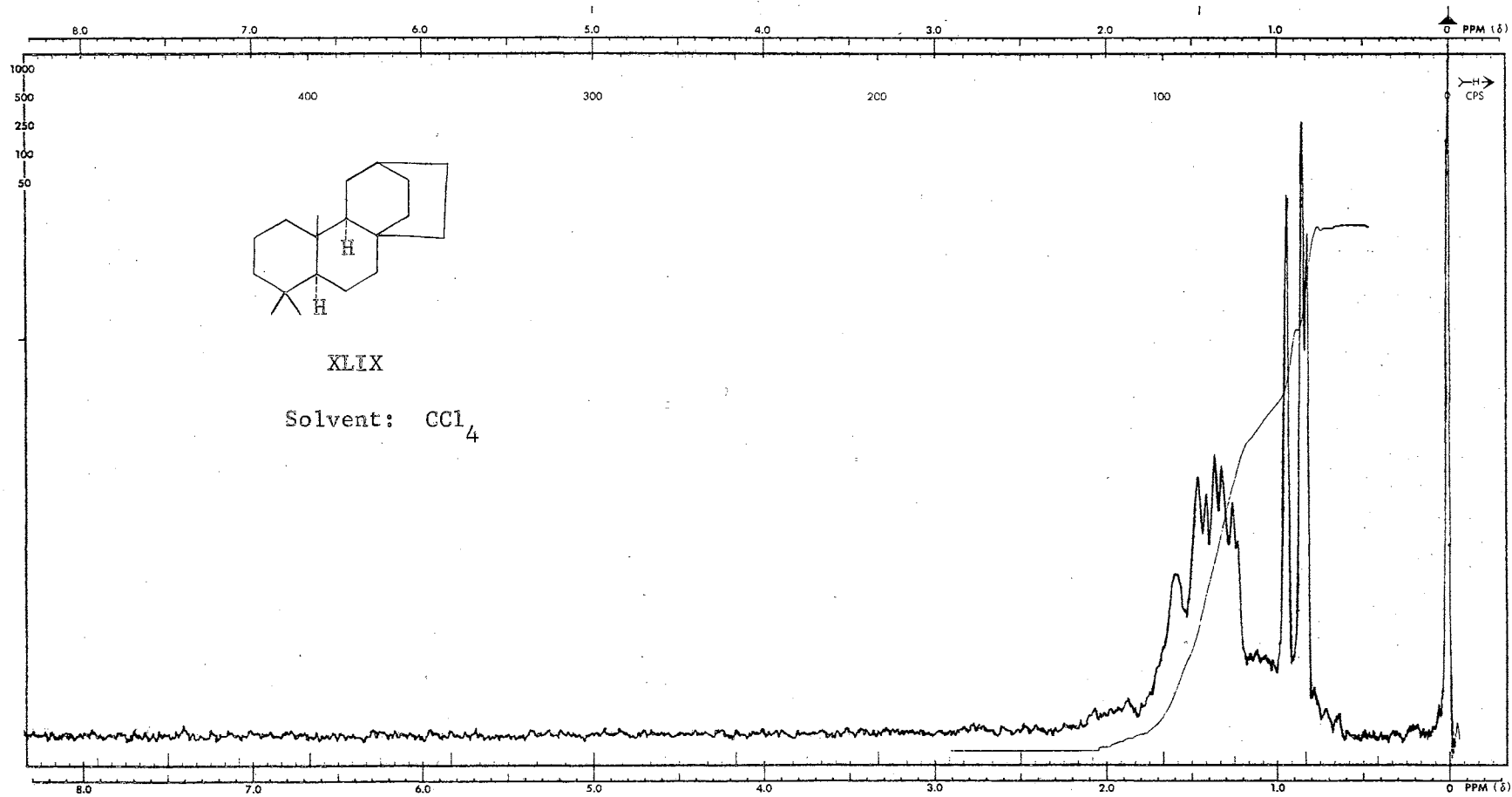
Plate IV

Nuclear Magnetic Resonance Spectrum of CXI
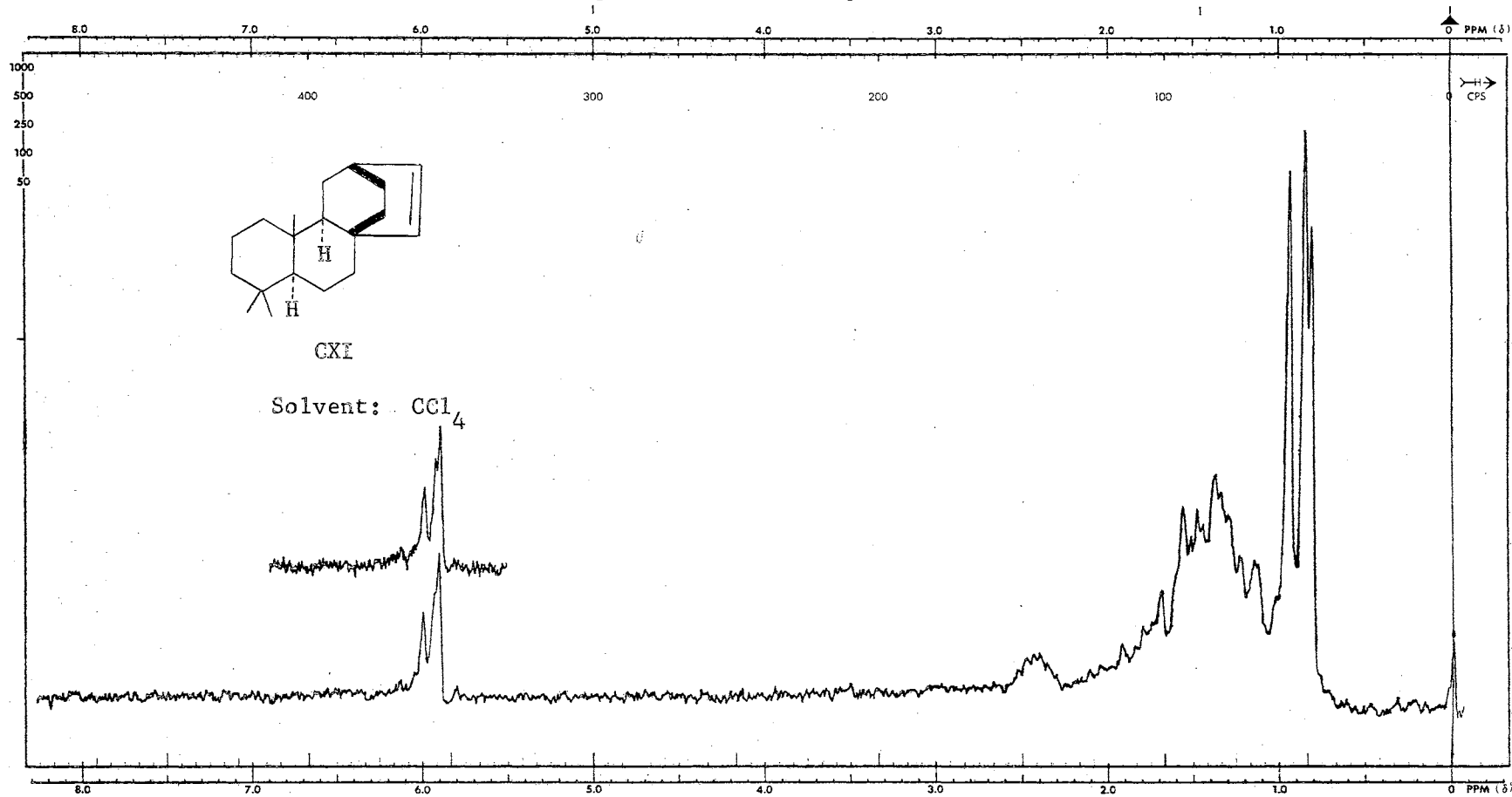
Plate V

Nuclear Magnetic Resonance Spectrum of CXXXI

CXXXI

Solvent: CDCl$_3$
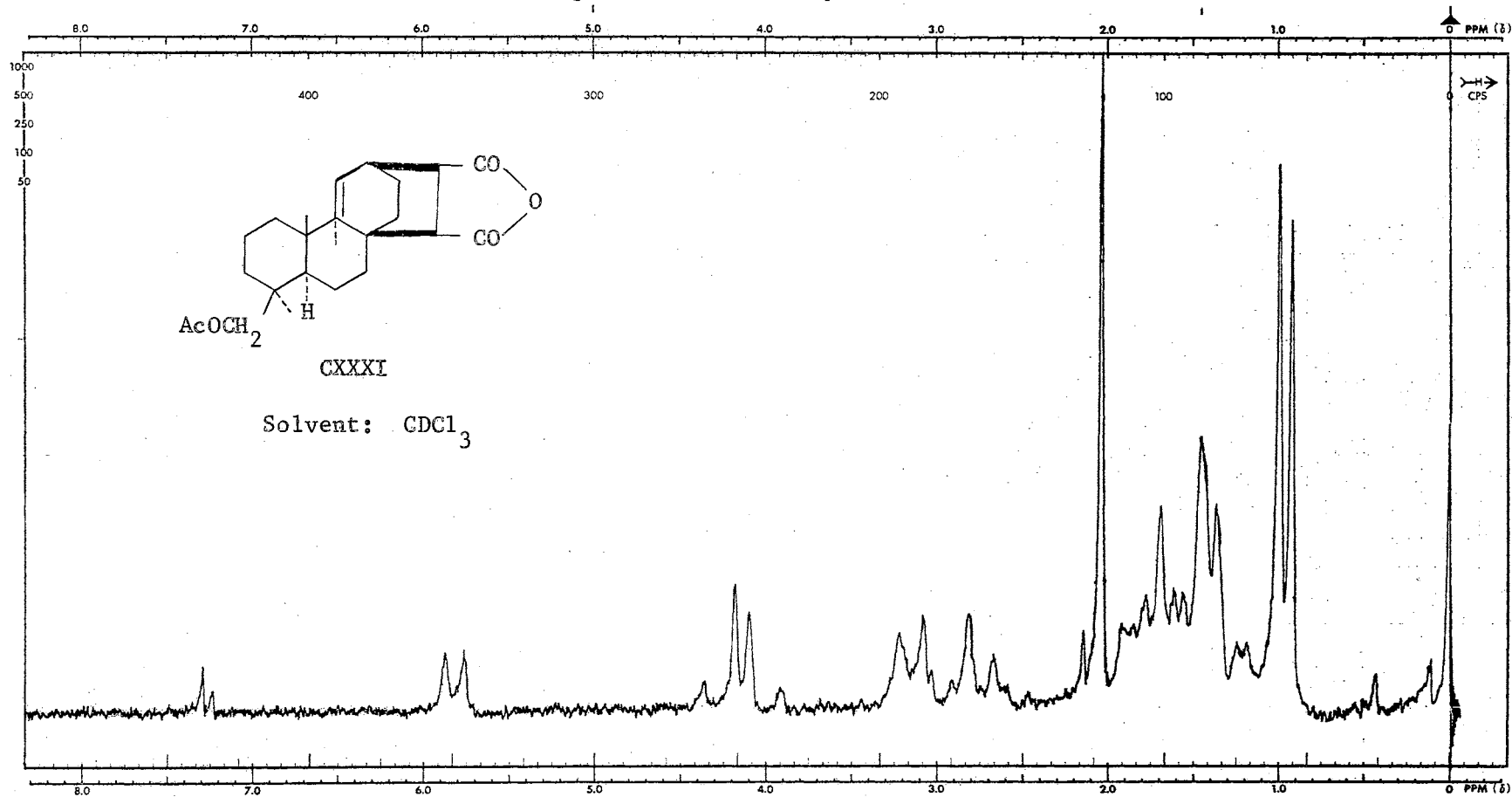
Plate VI

Nuclear Magnetic Resonance Spectrum of CXXXVIII

CXXXVIII

Solvent: $CDCl_3$-CS_2

Plate VII

Nuclear Magnetic Resonance Spectrum of CXXX

CXXX

Solvent: CDCl$_3$

Plate VIII

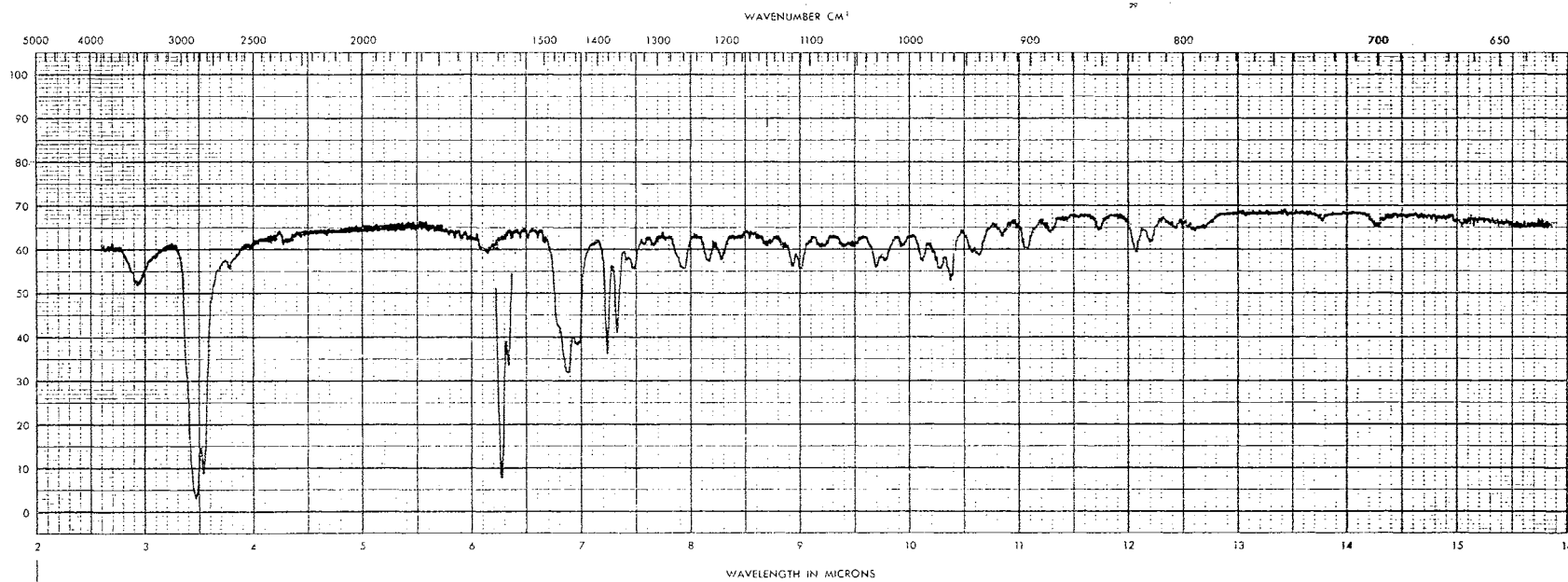Nuclear Magnetic Resonance Spectrum of CLI
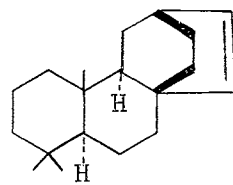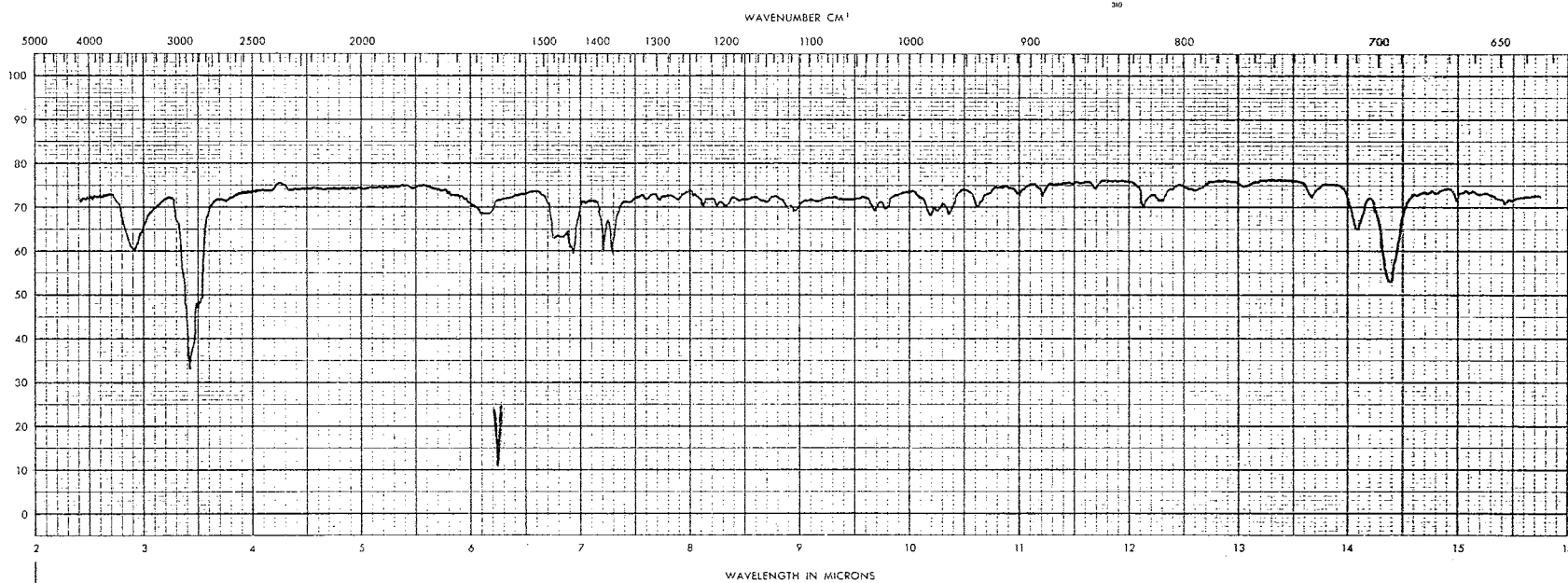

CLI

Solvent: CS_2
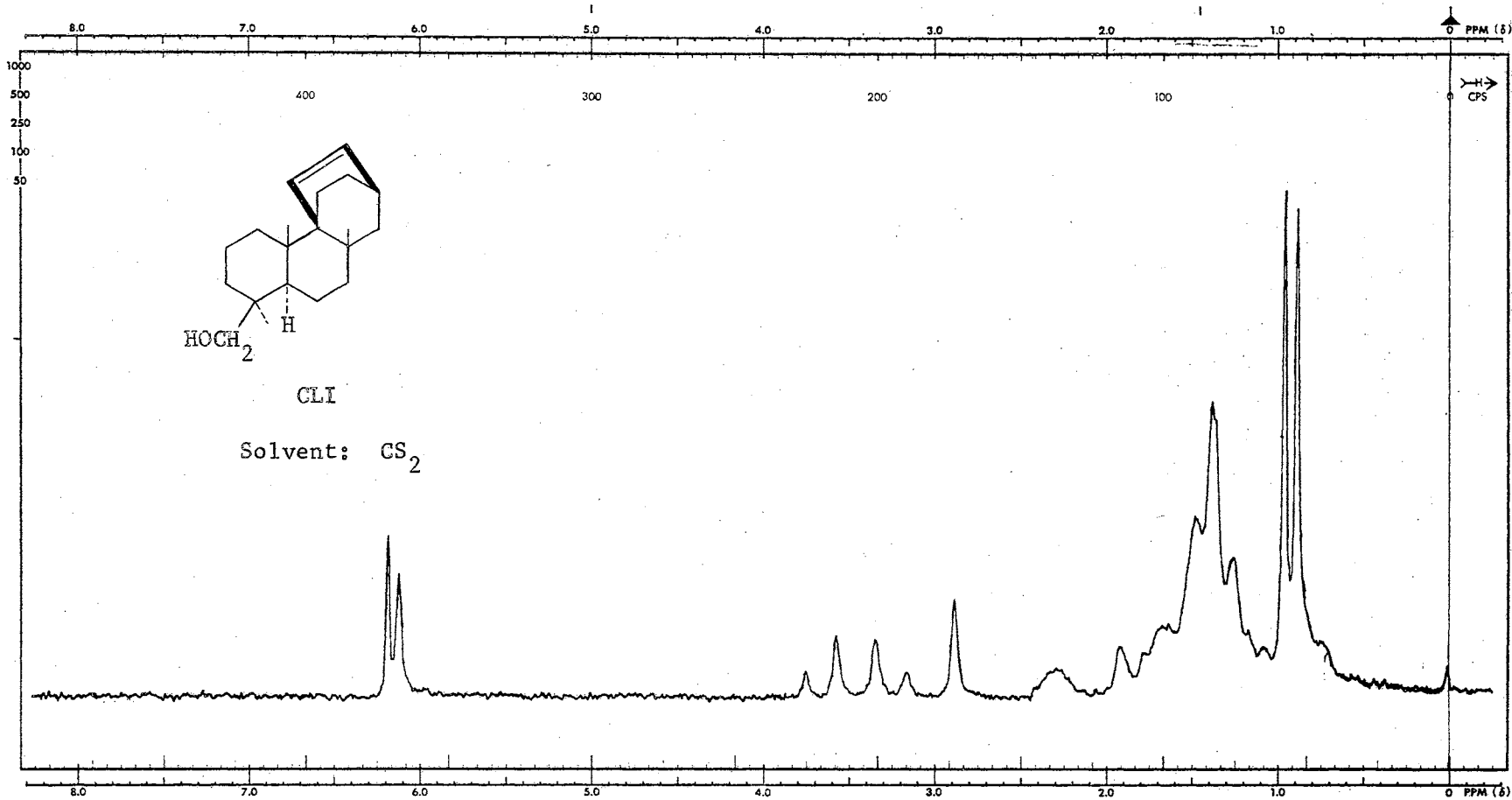
Plate IX

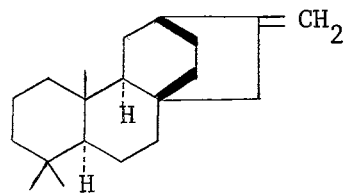## Infrared Spectrum of XLIX, KBr Pellet
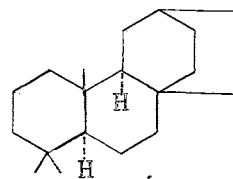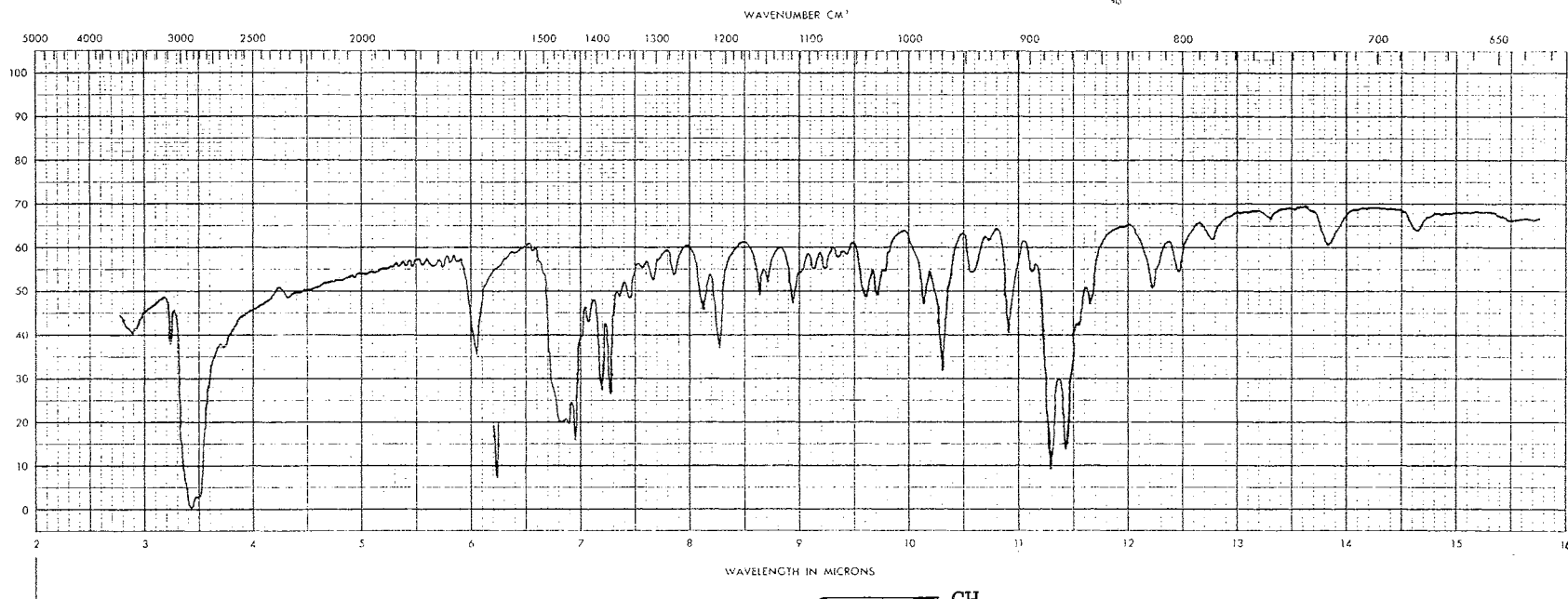

XLIX

Plate X

Infrared Spectrum of CXI, KBr Pellet
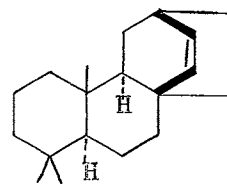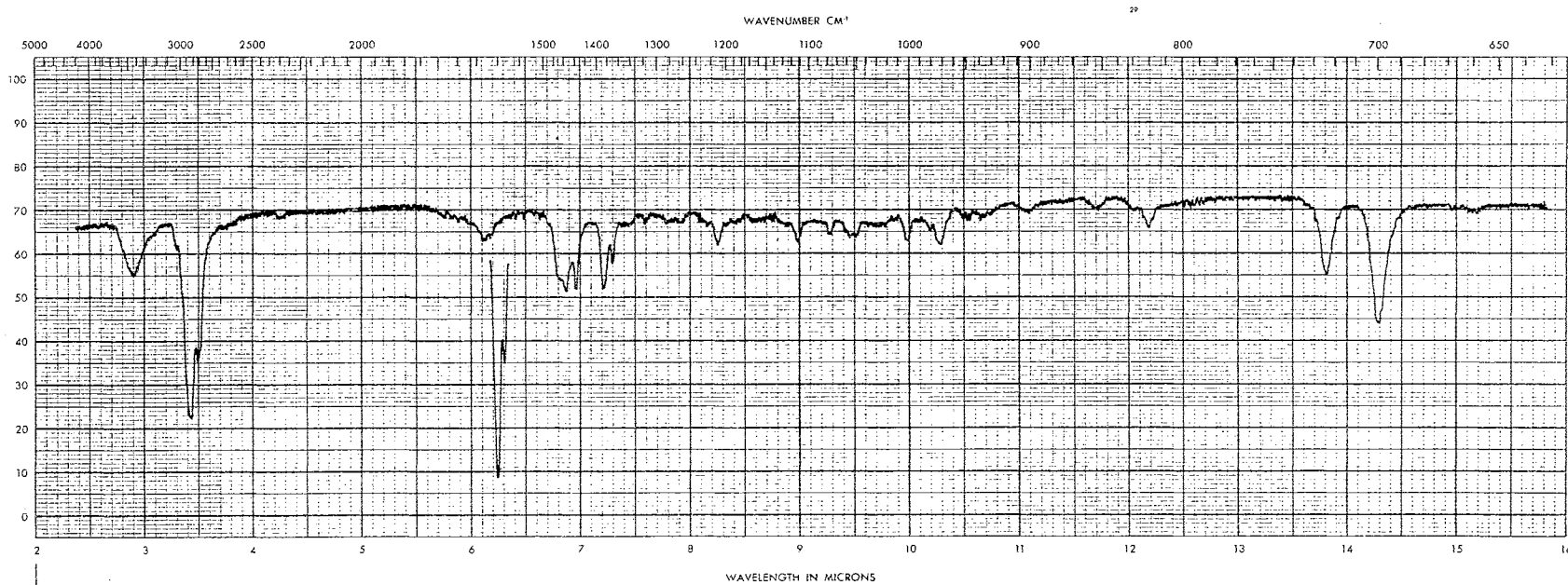

CXI

Plate XI

Infrared Spectrum of LXXXIX, KBr Pellet

LXXXIX

Plate XII

Infrared Spectrum of CXLII, KBr Pellet

CXLII

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