STUDIES IN THE SYNTHESIS OF DITERPENOID ALKALOIDS

By

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TABLE OF CONTENTS

LIST OF PLATES

CHAPTER I

HISTORICAL BACKGROUND AND INTRODUCTION

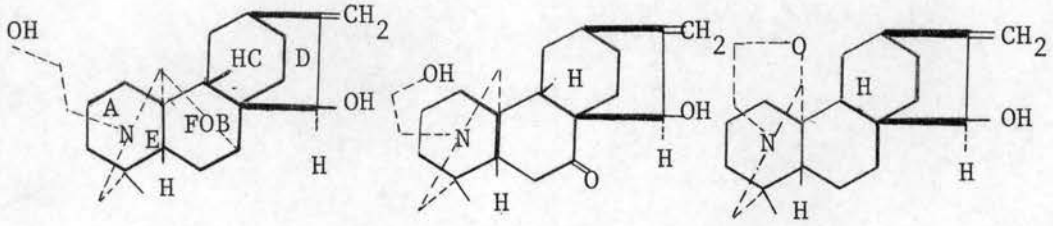
Isolation

The plants of Delphinium and Aconitium genera have intrigued and fascinated man for many years, not only because of their insecticidal properties or poisonous effect on cattle, but also because of their medicinal properties. The extract of the plant Aconitium heterophyllum has reportedly been used as a bitter tonic, expectorant, febrifuge, and in treatment of dyspepsia and dysentery in Indian folk medicine (8). It is perhaps the same kind of fascination which probably accounts for the interest of organic chemists in these plants. The alkaloids isolated from plants of both genera were named "Aconite alkaloids" by Jacobs (8).

The alkaloid ajaconine, I, (m.p. 167°, $[\alpha]_D^{EtOH}$ - 122, pK_a 11.8 in 80% methanol) was given its name by Keller and Volker (1) who found it among the bases extracted from Delphinium ajacis seeds. Hunter (2) confirmed its presence in the plant and was responsible for the preparation of its derivatives. Goodson (3) assigned it the correct empirical formula, $C_{22}H_{33}NO_3$, and showed it to be an unsaturated base, but was misled into suggesting the presence of an N-methyl group based on the products obtained from the Herzig-Meyer determination.

Pelletier (4) isolated the alkaloid atidine, II, (m.p. 182.5-183.5°, $[\alpha]_D^{29}$ - 47, pK_a 7.53) from the highly basic fraction of the

extract of Aconitium heterophyllum, and assigned it the empirical formula, $C_{22}H_{33}NO_3$. Pelletier suggested it to be a pentacyclic, tertiary base of the dihydroxy-atisine type, containing a carbonyl group in a six-membered ring. However, Pelletier's original suggestion of a carbonyl group at C-1 or C-3 (C-4 or C-2(5)) based on his conclusions from



I II III

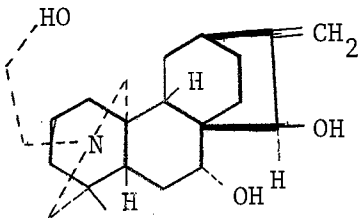
the basicities of atidine and its tetrahydro derivatives was later proved wrong (20).

Structure Elucidation of Ajaconine

The structure elucidation of ajaconine was made a little bit easier, though not simple in any way, by the structure elucidation of atisine, III (6-9).

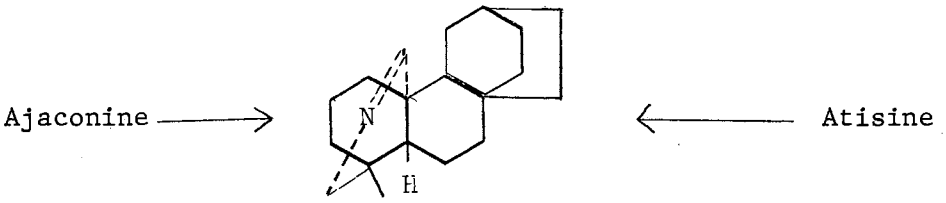
Ajaconine, I, gave an immonium salt and its reduction by sodium borohydride to dihydro base IV without the loss of oxygen, established the presence of a carbinolamine-ether system (10,11). The similarity of the D rings of ajaconine, I, and atisine, III, was also shown by the spectral data and by isomerization of the allylic alcohol to a ketone.

Thus the empirical formula, properties, and chemistry of ajaconine were strikingly similar to those of atisine, and the possibility was entertained that ajaconine was a monohydroxy atisine.



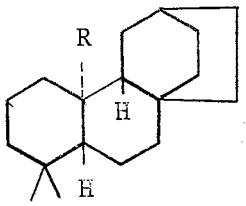
IV

Ajaconine, I, was shown to have the same carbocyclic skeleton as atisine, III, by its conversion to oxygen free azomethine V, previously obtained from atisine (12). The azomethine V has been further degraded



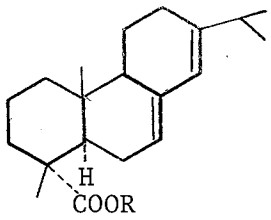
V

to VIa (13), which in turn has been converted into VIb (14). Carbocyclic structure VIb has been synthesized (14,34) from already totally synthesized (14,16) abietic acid, VIIa, and a mirror image relationship between the synthetic and degraded product has been shown to exist (14). This work puts the absolute stereochemistry of the carbocyclic skeleton of ajaconine on a firm basis.



VIa, R = CH_2OH or CHO or COOH

VIb, R = CH_3

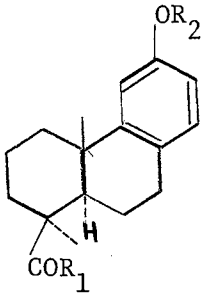


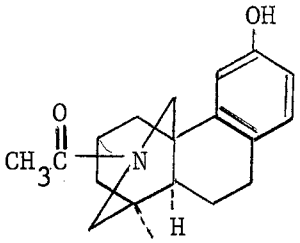
VIIa, R = H

VIIb, R = CH_3

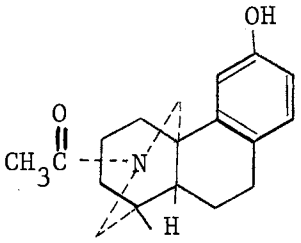
The proof of structure and absolute stereochemistry of ring E in

ajaconine was provided by the partial synthesis of N-acetyl phenol VIII from O-methylpodocarpic acid, IXa, (17). Synthetic VIII was shown to





VIII



X

IXa, R_1 = OH R_2 = CH_3

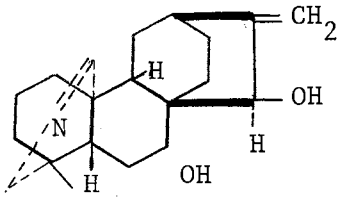
IXb, R_1 = OCH_3 R_2 = CH_3

IXc, R_1 = N_3 R_2 = CH_3

IXd, R_1 = OH R_2 = H

be the enantioner of X, which had been previously prepared from atisine (18). Since the same azomethine, V, was obtained from ajaconine, I, and atisine, III, (12) the above conclusions also apply to ajaconine.

Finally, Edwards et al. (19) after extensive investigations and a partial synthesis of ajaconine from azomethine, XI, obtained by degradation of ajaconine, I, established that the remaining oxygen atom was



XI

attached at C-7 and present as an ether bridge having a cis relationship to the nitrogen-containing bridge.

Structure Elucidation of Atidine, II

Earlier work of Pelletier (4) had indicated atidine, II, to be a pentacyclic, tertiary base of the dihydroatisine type containing a carbonyl group in a six-membered ring. By Wolff-Kishner reduction to dihydroatisine, XIV, Pelletier (21) confirmed his earlier conclusions. This work established the stereochemistry of the molecule. The position of the keto group at C-7 was established, when the triacetate XIIIb (21) (one of the products obtained after sodium borohydride reduction) was found to be identical with the triacetate (20) prepared by sodium borohydride reduction of ajaconine, I.

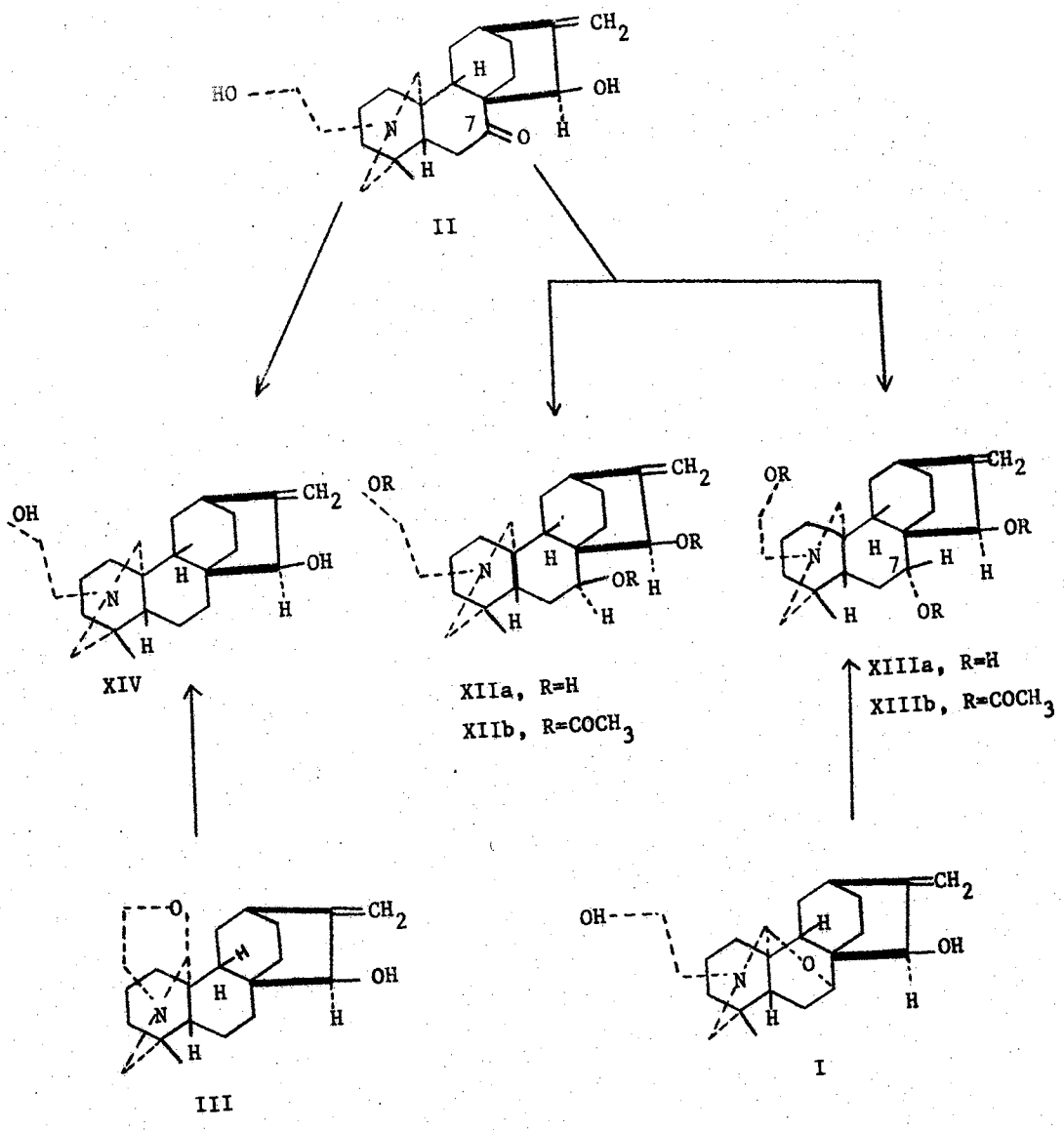
Studies in the Synthesis of Ajaconine, I, and Atidine, II

The final synthetic portrait in the majority of cases, is a blend of all the exploratory efforts of different research groups directed at solving the synthetic intricacies of small portions of the molecule in question. With this in mind one can understand why the studies in the synthesis of the complex diterpenoid alkaloids have been centered around two important objectives:

(A) Synthesis of the Tetracyclic amine system.

(B) Construction of the Bicyclo[2,2,2]octane system.

Syntheses of atisine, a less diabolical alkaloid compared to ajaconine, I, and atidine, II, have been achieved recently by four different groups (21-27). These synthetic efforts represent an immense and an important contribution, but with the exception of Wiesner's *et al.* (27) the other synthetic schemes lack the flexibility of being useful for the synthesis of other members of the aconite group, such as ajaconine and atidine.


HO
CH2
OH
N
7
O
H
II
XIV
XIIa, R=H
XIIb, R=COCH3
XIIIa, R=H
XIIIb, R=COCH3
III
I

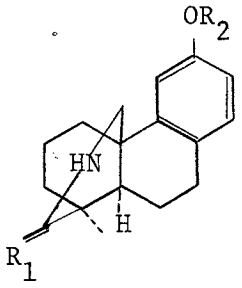
(A) Construction of the E and F Ring Systems

Two main approaches have been developed for the synthesis of the E and F ring systems.

(a) A photochemical insertion reaction utilizing a cis C-4 acyl azide group and the C-10 methyl group.

(b) The utilization of an already active C-10 group in ring A to give the nitrogen-containing E ring.

Edwards and ApSimon (17) developed the first approach, utilizing O-methylpodocarpic acid, IXa. Lactam XVa was obtained, when acyl azide

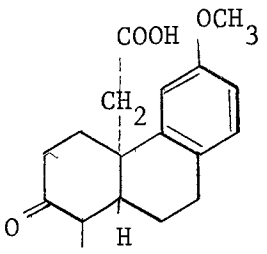


XVa, $R_1 = O$ $R_2 = CH_3$

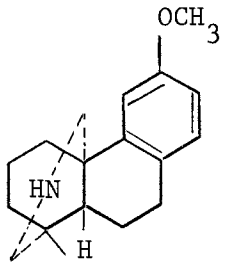
XVb, $R_1 = H_2$ $R_2 = H$

IXc was irradiated, and the lactam XVa by a two-step sequence was converted to XVb. This approach has been used in one of the total syntheses of atisine (22).

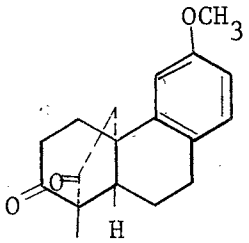
Wiesner, Valenta and associates (29), utilizing XVI, developed another approach, in which the C-10 methyl was functionalized. The key step in this synthetic scheme is the ingenious intramolecular acylation of XVI, giving XVIII, which was converted into XIX by preferential thioketalization and Raney-nickel treatment. Dialdehyde XX was prepared from XIX by a three-step sequence, involving pyrolysis of the benzoate, conversion of the resulting olefin to a diol with osmium tetroxide,



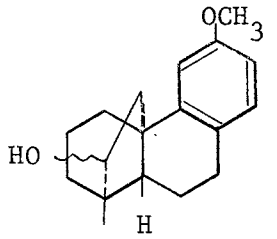
XVI



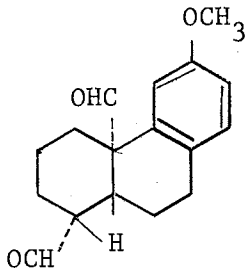
XVII



XVIII



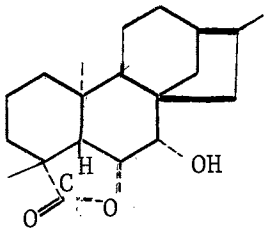
IXI



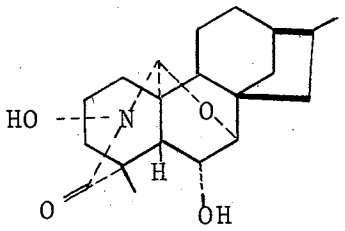
XX

followed by cleavage of the diol with lead tetraacetate. Finally hydrogenation of the oxime of dialdehyde XX gave XVII, whose identity with the degradation product of atisine, III, serves to substantiate the assigned structure XVII.

Barton (25) utilizing the rearrangement named after him, constructed the E and F ring system by the photolysis of the nitrite ester of XXI. However, the lactam obtained, XXII, was not converted into the carbinolamine ether system.

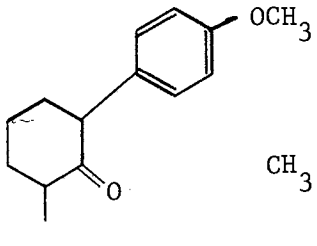


XXI

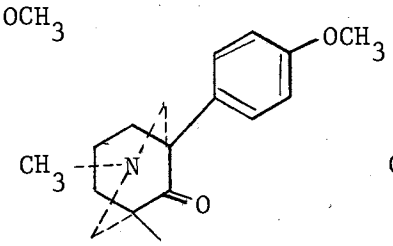


XXII

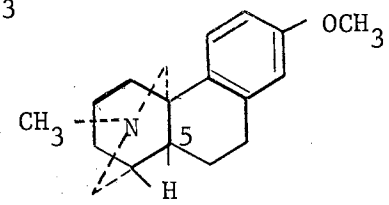
In a novel one-step approach to the construction of ring E, Iwai, and associates (26) effected a biscondensation in the Mannich reaction,



XXIII



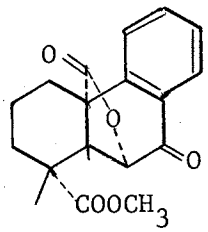
XXIV



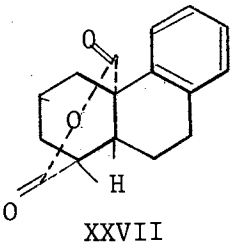
XXV

between XXIII, formaldehyde and methylamine to give XXIV. This approach, though elegant, suffers from the lack of stereospecificity at C-5 in XXV, which in turn was prepared from XXIV by a series of reactions.

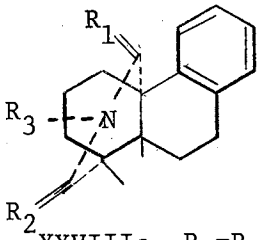
Another successful approach by Tahara and associates (23) involves the use of ketolactone XXVI, which was synthesized from abietic acid,



XXVI

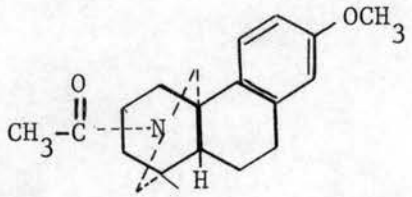


XXVII



XXVIIIa, $R_1=R_2=O$, $R_3=H$
XXVIIIb, $R_1=R_2=H$, $R_3=COCH_3$

VIIa. Ketolactone XXVI, by a three-step sequence, was converted into anhydride XXVII, which on heating with urea gave keto-imide XXVIIIa. Keto-imide XXVIIIa when reduced with lithium aluminum hydride, followed by acetylation gave XXVIIIb. Tahara et al. (23) have further converted XXVIIIb into XXIX, which in turn has already been transformed into atisine (21).



XXIX

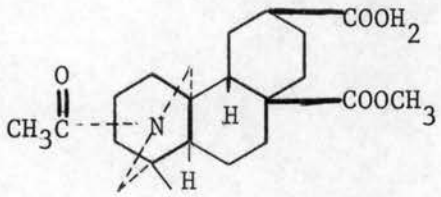
A large body of literature due to Barton et al. (25,27,28,29,30) and Wettstein et al., exists which could be utilized in considering methods for the construction of the ether bridge (F ring in ajaconine). These workers, utilizing a variety of reagents, e.g., lead tetraacetate, silver acetate, and mercuric oxide under thermal and photolytic conditions, have been able to construct the equivalent of the F ring system of ajaconine in steroid systems.

(B) Construction of the Bicyclo[2.2.2]octane C,D Ring System

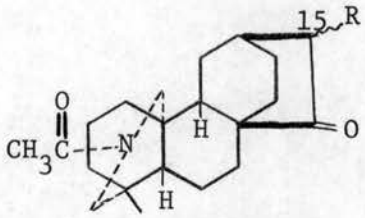
Four completely different approaches have been developed for the construction of the bicyclo[2.2.2]octane C,D ring system.

One of the methods, developed by Pelletier and Parthasarthy (31), evolves from monocarboxylic ester XXX, which was obtained in the degradation of atisine, III. The reaction sequence for the reconstruction

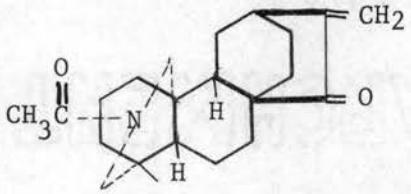
of the bicyclooctane system, involved one carbon homologation of the secondary carboxyl group via the Arndt-Eistert reaction, followed by ring closure of the cis oriented ester functions in a Dieckmann



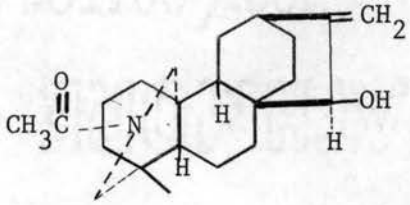
XXX



XXXIa, R=H
XXXIb, R=CH_3



XXXII

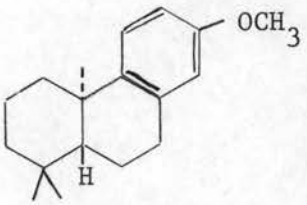


XXXIII

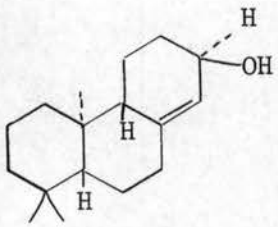
cyclization and finally, hydrolysis and decarboxylation to give XXXIa. Methylation of ketone XXXIa in the presence of sodium hydride in dimethyl sulfoxide gave XXXIb as a mixture of C-15 epimers. Bromination and dehydrobromination gave XXXII, which be reduction of the C-16 keto group gave a mixture of allylic alcohols from which the desired isomer XXXIII was separated.

Another successful approach in the synthesis of the C-D ring systems utilized by Ireland and coworkers (32) involved the use of allylic alcohol XXXV, which was obtained by lithium-ammonia reduction, followed by hydride reduction of racemic XXXIV. The reaction of XXXV with ethyl-vinyl ether and subsequent hydrolysis of the vinyl ether afforded XXXVI,

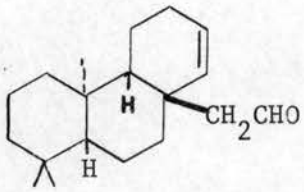
which was converted into XXXXVII. Photosensitized oxidation of XXXVII, followed by reduction of the allylic peroxides led to a separable mixture of two epimeric alcohols, XXXIXa and XXXIXb. No stereochemical assignments to the two epimers were made, but the presence of each in



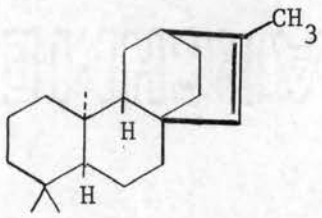
XXXIV



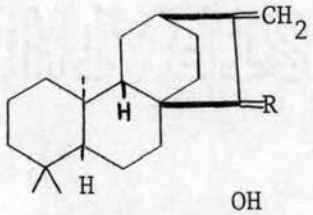
XXXV



XXXVI



XXXVII



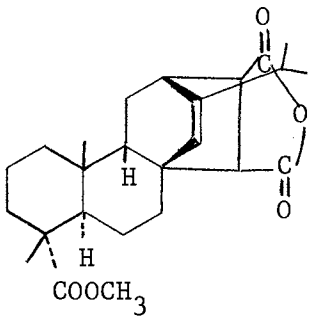
XXXIXa, R= OH
H

XXXIXb, R= OH
H

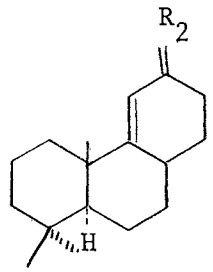
the reaction mixture assured the success of this method.

A completely different approach by Zalkow and Girotra (24,37,38) involved the use of abietic acid, VIIa, and podocarpic acid, IXd, both of which have been totally synthesized (15,16). Diacetate XLIb obtained from enone XLIa, which in turn was prepared (35) from methyl-O-methyl-podocarpate, was pyrolysed to a diene mixture. The Diels-Alder addition of maleic anhydride to the diene mixture gave adduct XLII (36), in addition to two other abnormal adducts (37). The adduct XLII by a sequence of four steps was converted into XLIIIb, thus providing a bicyclo[2.2.2]octane ring system, which could be utilized for the

introduction of the D ring substituents. The feasibility of this approach is further emphasized by earlier work (38) on maleopimaric acid XL, in which these workers successfully synthesized the isoprenoid cyclic skeleton XLIV, the racemic isomer of which has been converted into the C,D ring system of atisine by Ireland et al. (32). The

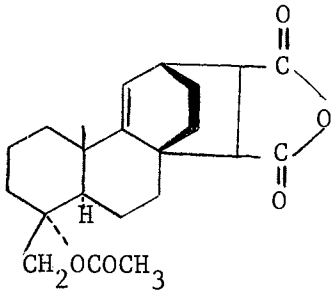


XL

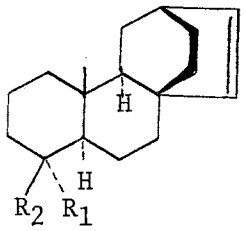


XLIa, R_1=OH, R_2=O

XLIb, R_1=R_2=$OCOCH_3$

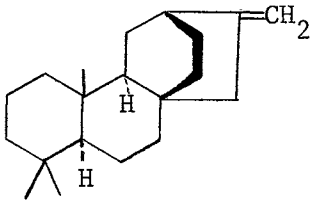


XLII



XLIIIa, R_1 = CH_2OH, R_2 = CH_3

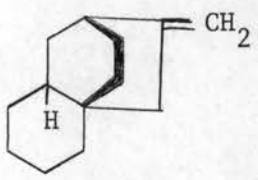
XLIIIb, R_1 = CH_3, R_2 = CH_2OH



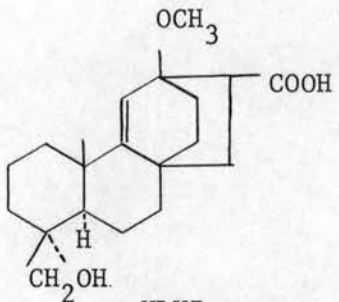
diterpene atisirene recently isolated by Sukh Dev et al. (40), from Erthroxylon monogynum has been found to be the enantiomer of XLIV, synthesized previously by Zalkow and Girotra (38).

Efforts to explore the utility of podocarpic acid, IXd, as a starting material for the construction of the C,D ring system of atisine

have also been recorded by Othman and Rogers (39). The feasibility of



XLV



XLVI

their approach was quite apparent when they were able to convert 6-methoxytetralin to XLV; however, when the same sequence of reactions was applied to podocarpic acid, these workers reported that an impractically poor yield of XLVI was obtained. Moreover, no mention was made as to whether the carboxyl group on the bridge was suitably located for the introduction of the exo-methylene and allylic alcohol group present in the aconite alkaloids.

Rationale to the Synthesis of Ajaconine and Atidine

The investigations, which are the subject of this dissertation, were undertaken as an overall aim, the development of a general approach to the synthesis of "aconite alkaloids," using podocarpic acid, IXd, as the starting material.

Podocarpic acid, IXd, besides being readily available, contains an aromatic C ring which could be utilized to construct not only the bicyclo[2.2.2]octane C,D ring system, but also to introduce the oxygen function at C-7. Since C-7 is the benzylic position in podocarpic acid, the most advantageous time to introduce the oxygen function would be while the C-ring was still aromatic, because it would be very

difficult, if not impossible, to introduce it in a saturated alicyclic system. In addition to possessing a trans A-B ring junction, podocarpic acid has a carboxyl group at C-4 cis to the angular methyl group at C-10, and this would certainly be another asset to the synthesis of the heterocyclic E ring, as demonstrated by the work of Apsimon and Edwards (17). This synthetic approach would lead to the enatiomer of the naturally occurring alkaloids, because the configuration of the A-B ring juncture in the starting acid is antipodal to the corresponding centers in ajaconine, I, and atidine, II.

Podocarpic acid, IXd, has been subjected to a series of reactions in order to synthesize intermediates useful in the synthesis of ajaconine, I, and atidine, II. This approach has provided tetracyclic intermediates, of unequivocal structure, potentially useful for the synthesis of "aconite alkaloids" having a bicyclo[2.2.2]octane C,D ring system.

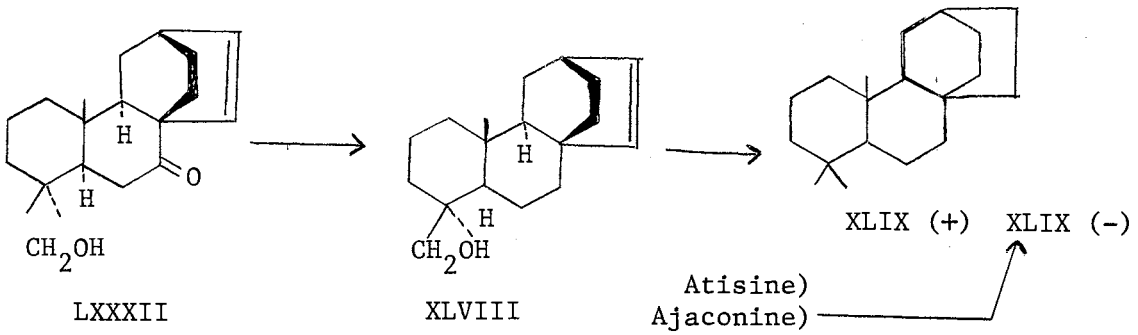
CHAPTER II

RESULTS AND DISCUSSION

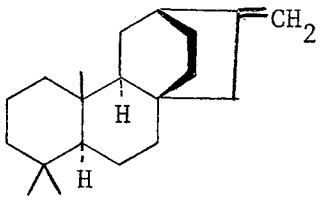
Synthesis of Intermediate LXXXII from Podocarpic Acid

The main objective of this study, as already described in Chapter I, was to secure a versatile intermediate from podocarpic acid, which could be used for the synthesis of all diterpenoid alkaloids having a bicyclo[2.2.2]octane ring system. Podocarpic acid was considered to be a very attractive starting material since it allowed construction of the nitrogen-containing ring E and provided a means of introducing an oxygen atom at C-7, both of which are required in the syntheses of ajaconine, I, and atidine, II.

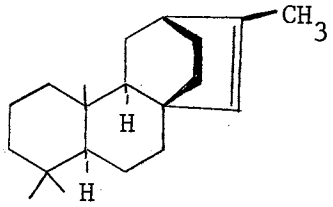
Tetracyclic intermediates LXXXII, prepared from podocarpic acid, has been converted into the previously synthesized (36) XLVIII, which in turn has been converted into (+) XLIX. The compound (-) XLIX,



prepared from atisine and ajaconine (13,14) has been shown to be enatiomeric with the synthetic product (+) XLIX, first synthesized from maleopimaric acid (14,34). The conversion of LXXXII to XLVIII constitutes a total synthesis of (+) atisirene, L, (38) and (±) isoatisirene, LI, (32) from podocarpic acid, since XLVIII has already been converted into these natural products.



L

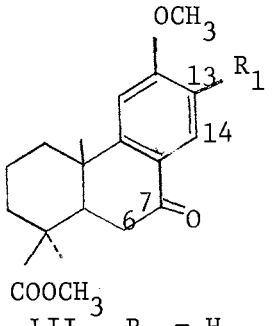


LI

Attempted Syntheses of LXXXII

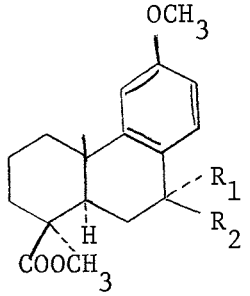
In any successful synthesis of atidine, II, and ajaconine, I, it is necessary to place an oxygen function at C-7 which could be utilized for the construction of the F ring. In this approach, based on podocarpic acid, the oxygen function was introduced at an early stage by oxidation of methyl O-methyl podocarpate to LII employing chromium trioxide in acetic acid. Having introduced the keto function at C-7, the next objective was the reduction of the aromatic ring via the Birch reduction without the loss of the oxygen function at C-7. A carbonyl function can often be protected during a Birch reduction by conversion to an acetal or an enol ether; after reduction of the benzene ring, the carbonyl group is recovered by treatment with acid. This approach, however, cannot be utilized with aryl ketones because acetals and enol ethers undergo hydrogenolysis. It was planned to overcome this difficulty by shifting the ketone function from C-7 to LII to C-6, thus providing a means for introducing the oxygen function at C-7 at a later

stage in the synthetic sequence.



LII, R_1 = H

LIII, R_1 = Br

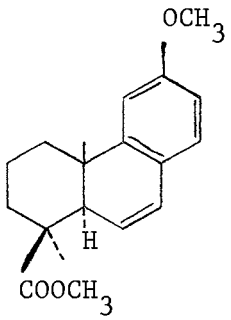


LIVa, R_1 = OH, R_2 = H

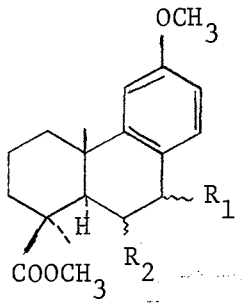
LIVb, R_1 = H, R_2 = OH

Attempted Conversion of LII to LVI

Compound LII was reduced with sodium borohydride to give a mixture of LIVa and LIVb, which when dehydrated with dilute hydrochloric acid gave LV. The presence of the double bond was established by the appearance of a sharp two-proton signal at δ6.31 in the n.m.r. spectrum, in addition, a three-proton multiplet, due to the phenyl group appeared at δ7.0-7.5. The appearance of the C-10 methyl group at δ0.8 (due to the shielding effect of the double bond) provided durther evidence for



LV



LVI, R_1 = H R_2 = O

LVII, R_1 = Br R_2 = OH

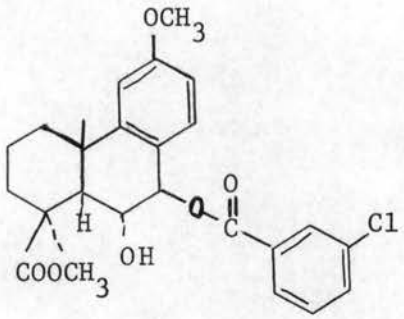
LVIII, R_1 = OH R_2 = Br

structure LV. Two approaches utilizing LV were employed to arrive at LVI.

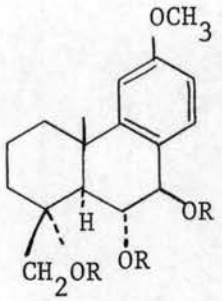
The first approach envisioned a three-step process: (i) preparation of a mixture of bromohydrins LVII and LVIII using N-bromosuccinimide under acidic conditions; (ii) very mild oxidation with chromium trioxide and acetic acid; (iii) debromination of the reaction products with zinc and acetic acid to give a separable mixture of LII and LVI. However, when LV was subjected to the above sequence of reactions, only LII and LIII were obtained. Compound LIII showed a positive Beilstein test. Comparison of the n.m.r. spectrum of LIII with that of LII supports the assigned structure. In the case of LII, the C-14 proton appears as a doublet (J = 8 cps.) centered at δ7.83, due to coupling with the C-13 proton, and the deshielding effect of the spatially close ketone function. In addition a two-proton (C-11,C-13) multiplet was centered at δ6.66. However, in the case of compound LIII only a one-proton singlet centered at δ6.9, and a one-proton singlet centered at δ8.25 appeared in the n.m.r. spectrum, thus indicating the absence of C-13 proton. Both compounds showed the presence of a conjugated keto group (5.98μ). The presence of the bromine atom on the aromatic ring was further indicated by the downfield shift of the signal for the methoxyl group (δ3.98) in LIII as compared to the methoxyl signal in LII (δ3.86).

The second approach envisioned the conversion of LV to the corresponding epoxide with m-chloroperbenzoic acid, followed by treatment with lithium aluminum hydride and then mild oxidation. The treatment of LV with m-chloroperbenzoic acid gave LIX. The n.m.r. spectrum of LIX showed the presence of seven phenyl protons (multiplet, δ6.61-8.08),

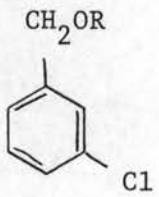
a six-proton signal (δ3.71) for the methoxyl and ester groups. The



LIX



LX, R = H
LXI, R = $COCH_3$



LXII, R = H
LXIII, R = $COCH_3$

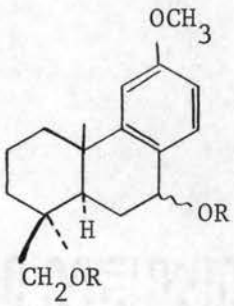
infrared spectrum showed two carbonyl bands at 4.78 and 5.85 μ. This evidence served as the basis for the tentative assignment of structure LIX. Compound LIX was reduced with lithium aluminum hydride to give a mixture of LX and LXII, which was acetylated with pyridine and acetic anhydride to give a separable mixture of LXI and LXIII. The n.m.r. spectrum of LXI showed signals at δ1.70 (3), 2.08 (3), and 2.18 (3) for three acetoxyl groups; 1.10 (3) and 1.33 (3) for two methyl groups; δ6.72-7.85 (multiplet) for three phenyl protons and δ3.81 (3) for the methoxyl group. Similarly, the n.m.r. spectrum of compound LXIII showed signals at δ1.91 (3) for the acetate function, a two-proton singlet at δ5.05, and a multiplet at δ7.13-7.33 (3).

Since the above mentioned approaches were unsuccessful, an attempt was made to add maleic anhydride directly to the aromatic system of LII, under photolytic conditions as previously reported in the case of benzene (41). However, on irradiation of a solution of LII and maleic anhydride no addition products were obtained; instead a crystalline product which analyzed for $C_{19}H_{23}O_3$ was obtained. The infrared spectrum of this material did not show any of the conjugated carbonyl

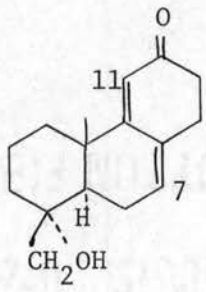
absorptions present in LII; the material was not further investigated.

Synthesis of LXXXII

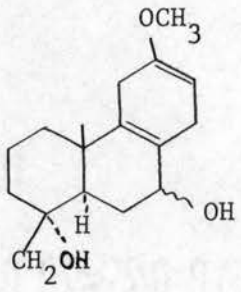
Compound LII was reduced with lithium aluminum hydride to give the dihydroxy compound LXV. The presence of the two hydroxyl groups in LXV



LV, R = H
LXVI, R = $COCH_3$



LXVII



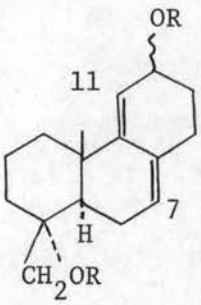
LXVIII

was shown by the preparation of the diacetyl derivative LXVI; the n.m.r. spectrum of which showed two acetoxy signals at δ1.98 and 2.03. Without purification, LXV was reduced using sodium, absolute alcohol and ammonia followed by acidic hydrolysis to give dienone LXVII. The n.m.r. spectrum of LXVII showed the C-11 and C-7 protons as two multiplets of one proton each, centered at δ5.88 and 6.1 respectively. The I.R. and U.V. spectra showed the presence of conjugated ketone and hydroxy functions (2.9, 6.04 μ; λ_{max}^{EtOH} 289 mμ, ε = 17,500). The formation of dienone LXVII from the Birch reduction intermediate LXVII may be visualized as arising by acid hydrolysis of the enolic ether followed by dehydration of the C-7 hydroxyl group to give the completely conjugated system.

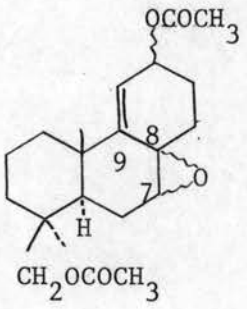
There was quite a major loss of methoxyl and hydroxyl function

(C-7) due to hydrogenolysis and it has been reported (42) that complete cleavage of the benzylic alcohol function occurs when there is no methoxyl group at the para position of the aromatic ring. Birch (43) has attempted to explain the lesser degree of cleavage in the para methoxyl containing case as being due to salt formation of the benzylic alcohol and reinforcement of the negative charge on oxygen by the p-methoxyl group.

On reduction with sodium borohydride followed by acetylation with pyridine and acetic anhydride, dienone LXVII gave LXIXb. The n.m.r. spectrum of LXIXb showed a two-proton multiplet (C-7,C-11) centered at δ5.51 and a signal for six acetoxy protons centered at δ2.0. The diacetate LXIXb was selectively epoxidized with m-chloroperbenzoic acid to give LXX. The n.m.r. spectrum of LXX showed that the upfield portion of the lowfield multiplet present in the spectrum of diacetate LXIXb, had almost disappeared in the formation of the epoxide and the remaining downfield portion at δ5.74 integrated for one proton. This suggested



LXIXa, R = H
LXIXb, R = $COCH_3$

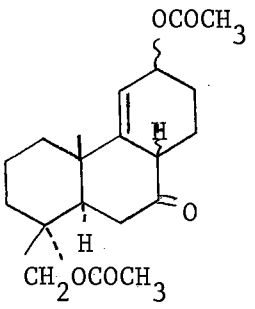


LXX

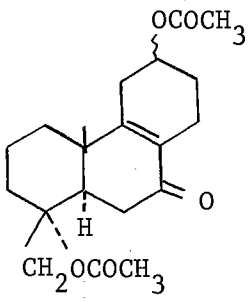
that the C-7, C-8 double bond was epoxidized, since the proton at C-11 would be expected to be deshielded by the acetoxy function (44). Epoxidation of the C-7, C-8 double bond was further supported by the

fact that the methyl signals in the n.m.r. spectrum were unaffected.

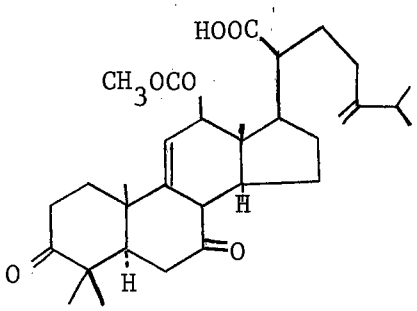
The epoxide LXX was isomerized to LXXI with boron trifluoride-etherate complex. The infrared spectrum of LXXI showed the presence of an unconjugated ketone (5.82 μ) and an acetate function (5.75 μ). This conclusion was further supported by isomerization of LXXI to LXXII by



LXXI

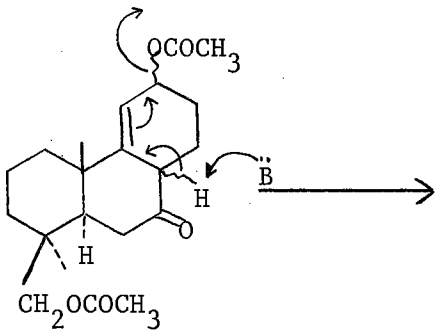


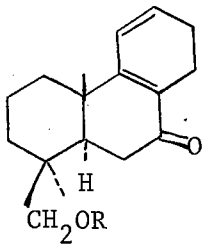
LXXII



LXXIV

refluxing the former in glacial acetic acid. The infrared spectrum of LXXII showed the presence of a conjugated ketone (6.0 μ). The keto-acetate LXXI when refluxed with 1% methanolic potassium hydroxide gave LXXIa. The same elimination was affected by chromatography of LXXI on alumina to give a purer and better yield of LXXIb. A similar elimination



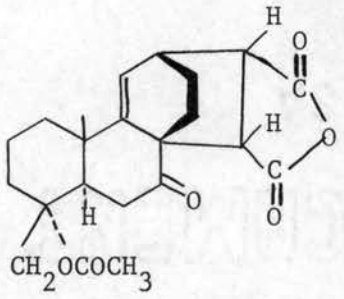


LXXIa, R = H

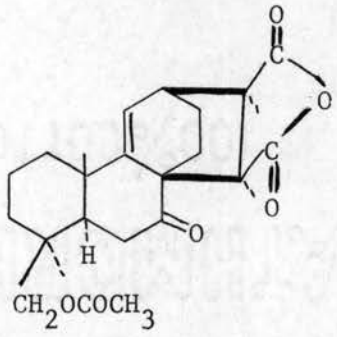
LXXIb, R = $COCH_3$

was observed (45) in the case of the triterpene polyprenic acid, LXXIV, which possesses essentially the same B,C ring system as present in keto acetate LXXI. Dienone LXXIb showed a maximum in the ultraviolet at 303 mμ (ε6,040) and its n.m.r. spectrum showed a two-proton signal centered at δ6.38 in addition to three signals at δ1.0, 1.05 and 2.01, each integrating for three protons.

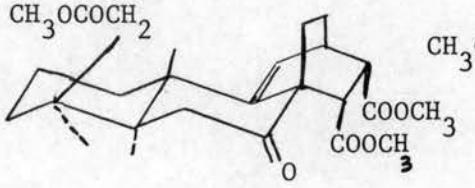
Dienone LXXIb when heated with maleic anhydride in refluxing toluene gave two adducts, LXXIV and LXXV. The following facts suggested the



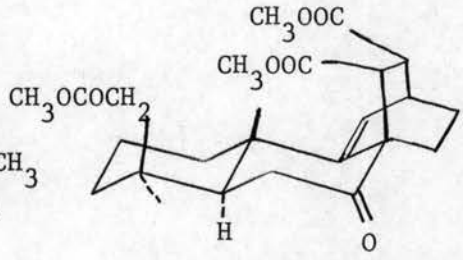
LXXIV



LXXV



LXXVI (Ester groups cis to each other)



LXXVI (Ester groups cis to each other)

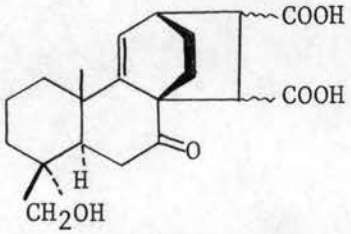
above structural assignments for adducts LXXIV and LXXV.

(i) The n.m.r. spectra of diesters LXXVI and LXXVII (obtained by the action of diazomethane on a methanolic solution of the anhydrides LXXIV

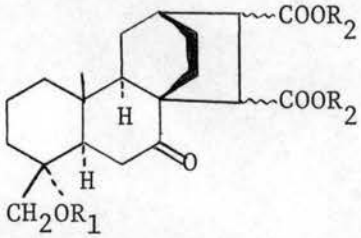
and LXXV, respectively) showed that diester LXXVI underwent no significant change in the position of its methyl groups (δ 1.02, 1.12) as compared to the parent anhydride LXXIV (Plate I) (δ 1.01, 1.18). However, the diester LXXVII showed deshielding of one methyl group (δ 1.0, 1.31) as compared to the methyl group signals in the parent anhydride LXXV (Plate II) (δ 1.02, 6 protons). Spectra data thus indicated that the C-10 methyl group in LXXVII was deshielded due to the close proximity of the ester groups. The C-10 and C-11 methyl groups in LXXVI would not be expected to show any significant change.

(ii) Adduct LXXIV reacted vigorously with diazomethane in methanolic ether, whereas the reaction with LXXV was much slower (as evidenced by rate of nitrogen evolution).

The diester LXXVI resisted all attempts at hydrogenation. Saponification of LXXVI gave hydroxy diacid LXXVIII which, in contrast to LXXVI, was hydrogenated to yield LXXXI, the hydrogen being absorbed from less hindered α-side. The ease of hydrogenation of LXXVIII may be



LXXVIII. (Carboxyl groups trans to each other)

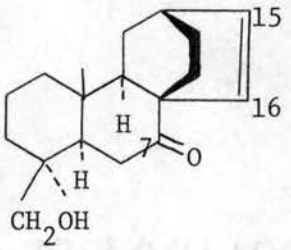


LXXIX, $R_1 = COCH_3$ $R_2 = H$

LXXX, $R_1 = COCH_3$ $R_2 = CH_3$

LXXXI, $R_1 = H$ $R_2 = H$

ascribed to the trans relationship of the carboxyl groups, the epimerization having occurred during saponification as observed in similar cases (37). Acetylation of LXXXI gave LXXIX which on decarboxylation and saponification gave keto alcohol LXXXII in addition to the starting material isolated as the diester LXXX. The n.m.r. spectrum of keto alcohol LXXXII (Plate III) showed two methyl singlets centered at δ0.97



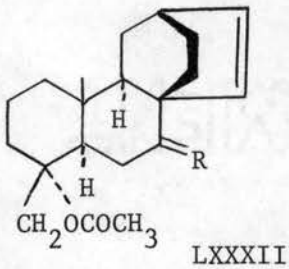
LXXXII

and 1.15 respectively, and two one-proton multiplets centered at δ6.28 and 6.76. The multiplet at δ6.76 has been assigned to the C-16 olefinic proton, the low field position being due to deshielding by the C-7 carbonyl group. Its infrared spectrum (Plate IV) showed absorption characteristic of a cis disubstituted double bond (3.27, 3.28, 14.3 μ) and a keto group (5.92 μ). The mass spectrum of the keto alcohol LXXXII (Plate VIII) (discussed on p. 31, 33) showed the parent peak at m/e 288 ($C_{19}H_{28}O_2$ = 288) and the base peak at m/e 257 (M^+ - 31). Further evidence for structure LXXXII and its precursors was obtained by conversion of LXXXII to XLVIII via Wolff-Kishner reduction. Compound XLVIII was found to be identical (I.R., nmr, and m.p.) with the same compound prepared previously from podocarpic acid (36).

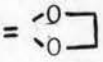
The compound LXXXII was acetylated to give LXXXIII which in turn was converted into its ketal derivative LXXXIV by the usual method. The n.m.r. spectrum of ketal LXXXIV showed a four-proton signal at

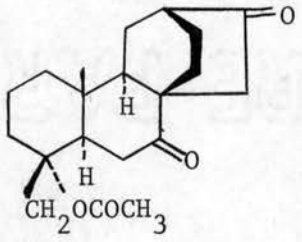
δ3.96 for the ketal methylene protons which overlapped the quartet due to the acetoxy methylene at C-4. The mass spectrum of the ketal LXXXIV, (Plate IXa) (discussed on p. 32, 34) showed the parent peak at m/e 374 ($C_{23}H_{34}O_4$ = 374) and the base peak at m/e 294 (M^+ - 80).

The ketal LXXXIV upon hydroboration followed by oxidation (with hydrogen peroxide-sodium hydroxide and then chromium trioxide-pyridine) gave LXXXV which contained traces of LXXXVI as detected by the mass spectrum (p. 35). Both isomers LXXXV (Plate XI) and LXXXVI (Plate XII) showed the parent peak at m/e 346 ($C_{21}H_{30}O_4$ = 346). However, the base

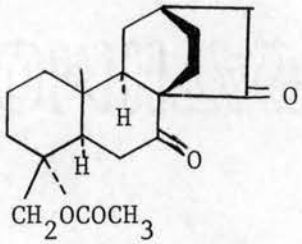


LXXXIII R=O

LXXXIV, R= 



LXXXV

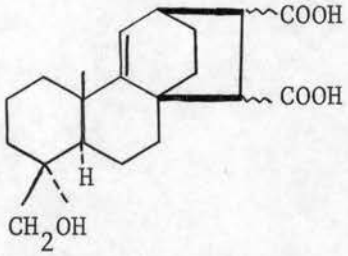


LXXXVI

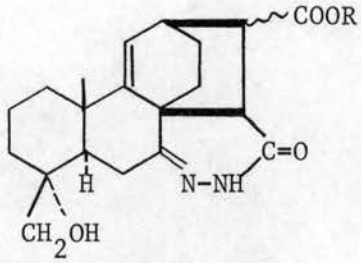
peak for LXXXV occurred at m/e 79 (M^+ - 267) while the base peak for LXXXVI came at m/e 122 (M^+ - 224). The structure LXXXV was assigned to the major component by analogy with the results of hydroboration on similar systems (38).

In an attempt to correlate LXXV with known LXXXIX (37) via Wolff-Kishner reduction, a compound containing an acid group (5.77 μ) and an amide linkage (5.99 μ) was obtained. The n.m.r. spectrum of its derived diester showed a three-proton signal centered at δ3.8. On the basis of the above spectral data and elemental analysis, structures LXXXVII and LXXXVIII have been tentatively suggested for the acid and its ester respectively. Since LXXV was not required in our synthetic scheme it

was not further investigated.

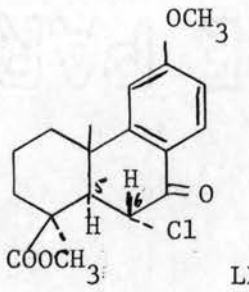


LXXXIX



LXXXVII, R = H
LXXXVIII, R = CH_3

During the aforementioned studies an attempt was made to open the aromatic ring of LII by ozonolysis followed by oxidative work-up of the reaction product with hydrogen peroxide and conc. hydrochloric acid. The aromatic ring, however, did not cleave, but a chlorinated compound,



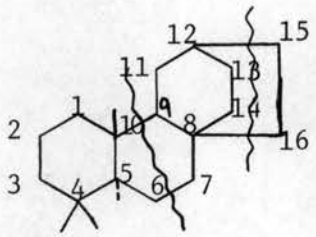
LXXXIX

LXXXIX (positive Beilstein test, λ_{max}^{KBr} 15.38 μ) was obtained. The n.m.r. spectrum of this compound showed signals at δ0.93, 1.51, 3.91 and 3.75 (three protons each) and two one-proton doublets (J = 8 cps.) at δ2.3 for C-5 and δ5.76 for C-6 proton. The coupling constant of 8 cps. indicated a trans relationship of the C-5 and C-6 protons. This trans relationship has also been suggested for the corresponding bromo derivatives on the basis of coupling constants (46).

The Mass Spectra of the Synthetic Intermediates (Plates VIII-XI) (LXXXII, LXXX, LXXXIV, LXXXV, LXXXVI)

In the case of tri and tetracyclic diterpenes, it is now apparent

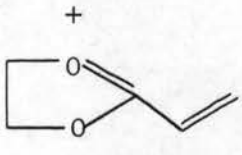
that the fragmentation of ring B (C6-7, C9-10 bond cleavage along with a loss of hydrogen atom) is of general importance, and if an ester group is present at C-4, this may be expelled with an additional hydrogen atom during the fragmentation (50). The retro Diels-Alder reaction has also



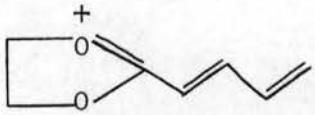
been utilized to explain the fragmentation and the location of double bonds in the resin acids (50).

Mass spectrometric studies of the compounds LXXX, LXXXII, LXXXIV, LXXXV, and LXXXVI which have similar tetracyclic skeleta, have not only helped to put the assigned structures on a firm basis but also has aided in the structural assignments of isomeric compounds.

Rationalizations based on accepted physical-organic concepts for the major fragments observed in the mass spectra of LXXX, LXXXII and LXXXIV are shown on pages 33, 34. The most common feature of these spectra (Plates VIII-XI) is the retro Diels-Alder reaction, which gives fragments of m/e 107 in the case of LXXXII, m/e 303 (M^+ - 145) in LXXX, and m/e 294 (M - 80) in LXXXIV, the latter by double retro Diels-Alder reactions resulting in the elimination of acetylene and butadiene. It is relevant to point out that spectral fragmentation of ketals is so pronounced as to over shadow the effect of other functional groups and a fragment of m/e 99 or m/e 125 (which ever is possible) is noticed in the mass spectra of compounds having ketal functions (50). This type of fragmentation is so favored that it is not interfered with by the



m/e 99

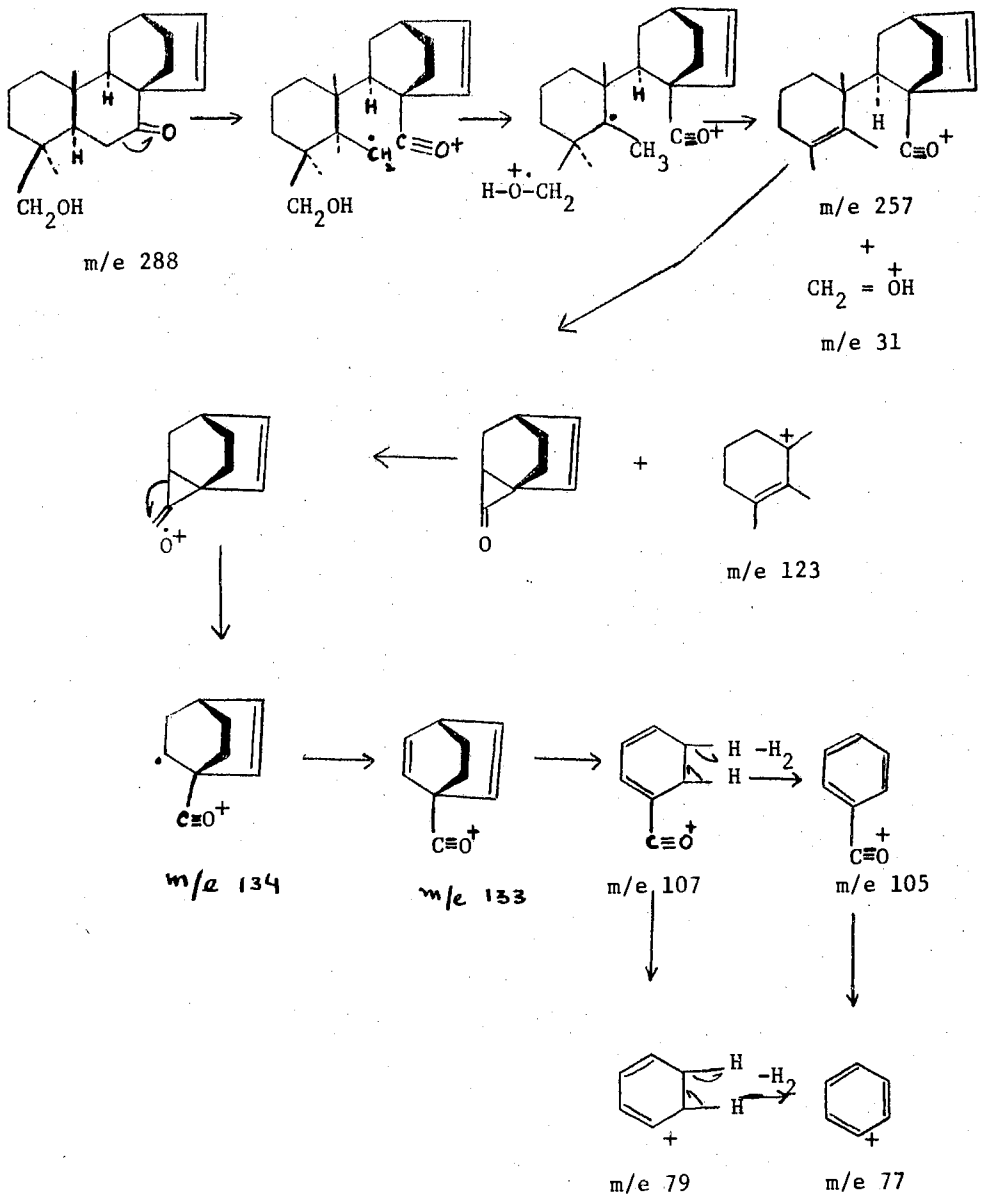


m/e 125

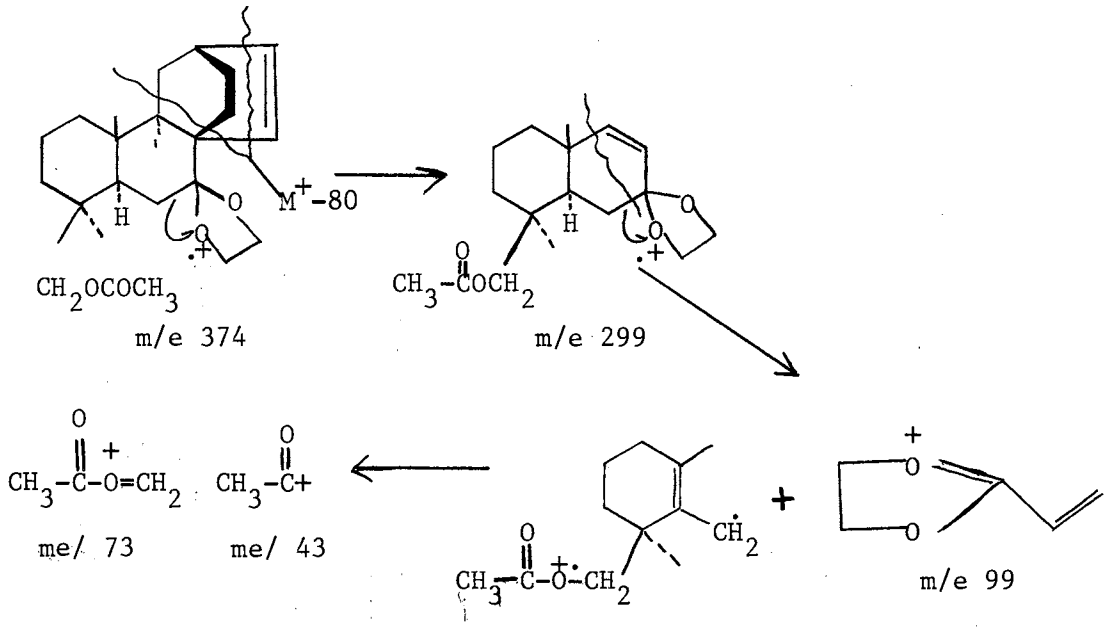
decomposition modes associated with certain other functional groups. In the case of LXXIV (Plate IX, p. 34) m/e 99 results after the double retro Diels-Alder resulting in the elimination of acetylene and butadiene to give fragment m/e 294 (M^+ - 80). Fragment m/e 294 (M^+ - 80) on further fragmentation (as shown on p. 34) can give m/e 49, m/e 43, and m/e 73. The elimination of fragments m/e 31, m/e 105, m/e 107, m/e 133, m/e 135, and m/e 123 (p. 33) in the case of LXXXII, (Plate III) lends further support to the presence of a bicyclo[2.2.2]octene system, the hydroxymethylene group at C-4 and the existence of a carbonyl function at C-7. These conclusions are further supported by the fragmentation (m/e 294, m/e 99, m/e 73, m/e 43) of the ketal LXXXIV, (Plate IX) which is derived from LXXXII (p. 34).

The retro Diels-Alder reaction has been utilized in this laboratory for confirming structures XCI and XC to the two isomeric ketones (54). It is apparent that before the retro Diels-Alder reaction can take place in XCI and XC the corresponding radical ions a and b will be produced, and their ease of formation will depend on their relative stabilities; one would expect the tertiary radical ion b to be more stable than the secondary radical ion a. Both the mass spectra of the isomeric ketones show the existence of the fragment m/e 230 (M - 44, $C_2H_{11}O$) but in the spectrum of XC the m/e 230 (M - 44) fragment is the base peak (100%), while in the spectrum a XCI it represents only 12% of the base peak. These structural assignments are in agreement with

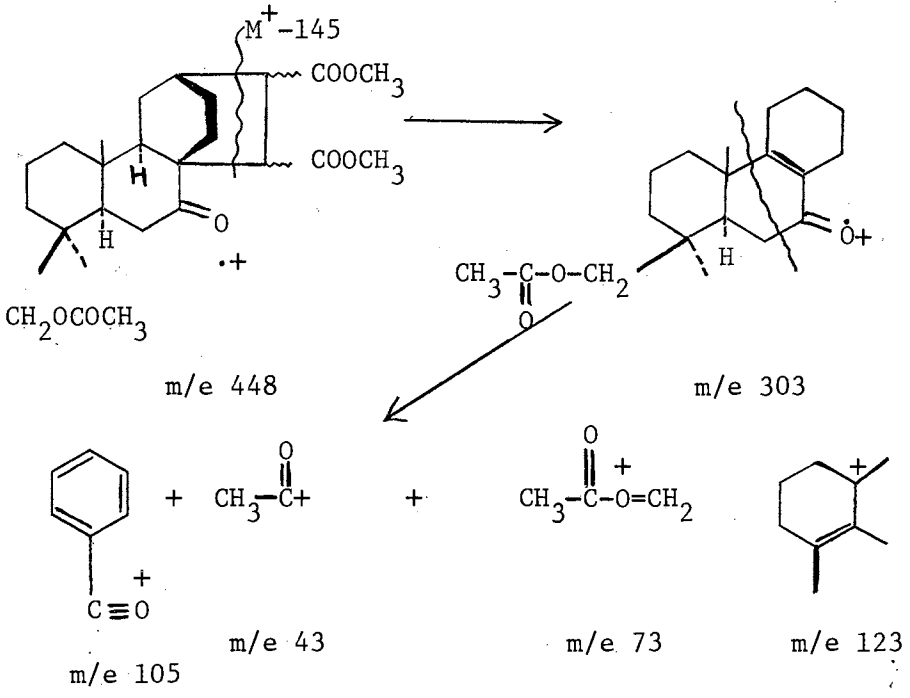
Fragmentation of Compound LXXXII

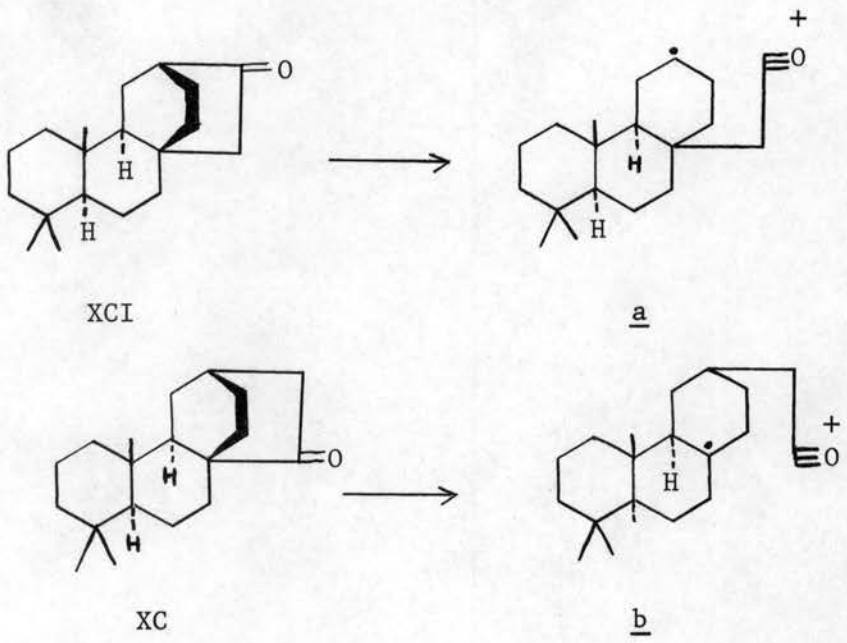


Fragmentation of Compound LXXXIV



Fragmentation of Compound LXXX





XCI a

XC b

the optical rotatory dispersion studies on these compounds (55). The final and conclusive structure proof of XCI and therefore of XC was obtained by correlation with an authentic sample of XCI (racemic) of unequivocal structure.

The above approach when applied to LXXXV, (Plate XI) and LXXXVI, (Plate XII) was not successful because of other pronounced modes of decomposition associated with the C-4 acetoxymethylene group and the C-7 carbonyl group. However, structure LXXXV was assigned to the major reaction product based on the results of hydroboration on similar systems (38). The base peak at m/e 122 can be reconciled by the C6-7, C9-10 bond cleavage and the elimination of acetic acid. The base peak of m/e 79 in LXXXV probably results from the C6-7, C9-10 bond cleavage followed by the secondary fragmentation of fragment m/e 107 and fragment m/e 105 as shown on page 33. The mass spectrum of LXXXV showed fragments at m/e 303 (M - 43) and the mass spectrum of LXXXVI showed a

fragment at m/e 301 (M - 45); in both cases not more than 6% of the base peak, so no conclusions could be drawn.

CHAPTER III

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana, and Alfred Bernhardt, Microanalytical Laboratories, Mulheim, West Germany. Infrared spectra were recorded using Beckman IR-5 and Perkin-Elmer 237B spectrophotometers. Nuclear magnetic resonance spectra were recorded with a Varian A-60 N.M.R. spectrometer, using tetramethylsilane as an internal standard (δ=0). Ultraviolet spectra were recorded with Beckman spectrophotometer, Model DK-1. Mass spectra were recorded using a LKB model 9000 chromatography-single focussing mass spectrometer in conjunction with gas-liquid chromatography. The ion source was of the electron bombardment type, employing a rhenium filament. A jet-type molecular separator, of Becker-Ryhage design, was used for sample (to carrier gas) enrichment. These spectra were obtained through the courtesy of Dr. John R. Dyer, Georgia Institute of Technology, Atlanta (Georgia) and Dr. C. C. Sweely, University of Pittsburgh, Pittsburgh (Pennsylvania).

Preparation of Methyl-O-Methyl 7-Ketopodocarpate L11.

Methyl O-methylpodocarpate, IXb, was prepared according to the method of Sherwood and Short (47) starting from podocarpic acid which in turn was isolated from rimu resin.

To a solution of 6.0 g. of methyl 0-methylpodocarpate in 60 ml. of aqueous acetic acid, 7.5 g. of chromium trioxide in 80 ml. of aqueous acetic acid (4:1) was added. The reaction mixture was allowed to stand for 18 hours at room temperature, after which it was diluted with a saturated brine solution. Solid material appeared when the sides of the flask were scratched. This material was collected by filtration and on recrystallization from methanol gave 4.5 g. of compound LII (71.2% yield) m.p. 122-124° (reported (48) 121-123°). λ_{max}^{KBr} 5.82, 5.98, 6.25 ; n.m.r. ($CDCl_3$): 1.26 (3), 1.07 (3), 3.86 (3), 3.68 (3), 6.66 (2, multiplet), 7.83 (1, doublet, J = 8 cps.)

Attempted Addition of Maleic Anhydride to Methyl 0-Methyl-7-Keto-podocarpate, LII.

A solution of 10 g. of maleic anhydride and 10.5 g. of compound LII in 350 ml. of tetrahydrofuran was irradiated with a 200-watt Hanovia u.v. lamp for 16 hours using a quartz filter. The temperature of the reaction solution was maintained below 20°.

The reaction mixture, after irradiation, was evaporated to dryness, and the residue dissolved in 200 ml. of benzene. The benzene solution was washed thoroughly with water until the washings did not show a black color with Congo red paper thus indicating the complete removal of maleic anhydride. The organic layer was dried over magnesium sulfate and evaporated to yield 7.4 g. of an oily material. This material in methanol was treated with ethereal diazomethane to esterify any anhydride which might be present as an adduct with compound LII. The crude oily material was chromatographed over 420 g. of Merck acid-washed alumina (activity I). Only one crystalline compound (1.75 g.), m.p. 168-170°,

was obtained. The oily residue was not further investigated. The crystalline compound did not undergo hydrogenation with 5% platinum on carbon or saponification with 30% sodium hydroxide and in both cases the compound was quantitatively recovered. λ_{max}^{KBr} 5.8, 6.23 μ; n.m.r. ($CDCl_3$): δ 1.52 (3), 1.04 (3), 3.66 (6), 6.33-6.73 (3, multiplet).

Anal. Calcd. for $C_{19}H_{23}O_3$: C, 76.32; H, 7.75

Found: C, 76.21; H, 7.81

Attempted Conversion of Methyl-O-Methyl-7-Oxopodocarpate to Methyl-O-Methyl-6-Oxopodocarpate

Preparation of Compound LV.

To a hot solution (on a steam bath) of 2 g. of compound LII in 100 ml. of an 80:20 mixture of methanol and water, a solution of 0.7 g. of sodium borohydride in 10 ml. of 80% methanol was added slowly with continuous stirring. After an hour, the solution was heated to 80° and then allowed to cool. The reaction mixture was treated with 2N hydrochloric acid and then extracted with ether. The ether extract was evaporated and the residue dissolved in 100 ml. of methanol. Enough concentrated hydrochloric acid was added to bring the solution to pH 2. This solution was allowed to stand overnight, when compound LV separated out as needles. On filtration, 1.7 g. of compound LV, m.p. 81-82°, was obtained. $\lambda_{max.}^{KBr}$ 5.82, 6.23 μ; n.m.r. (CCl_4): δ 0.8 (3), 1.23 (3), 3.61 (3), 3.71 (3), 6.31 (2), 7.0-7.5 (3, multiplet).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00

Found: C, 75.79; H, 8.12

Preparation of Bromohydrin LVIII.

N-Bromosuccinamide (1.9 g.) was added over a period of twenty minutes to a well stirred solution of 3 g. of LV in 100 ml. of tert. butanol and 20 ml. of 1N sulfuric acid. A yellow color appeared near the end of the addition. The solution was stirred for five hours at room temperature after which the mixture was diluted with water and extracted with ether. The ether extract was washed with a 5% sodium bicarbonate solution followed by a thorough washing with water. The ether extract was dried over magnesium sulfate and evaporated to yield 2.8 g. of crude LVIII.

λ_{max}^{film} 3.0, 5.8, 6.2 μ.

Oxidation and Debromination of Bromohydrin LVIII.

Bromohydrin LVIII (2.8 g.) was dissolved in 100 ml. of glacial acetic acid and to this solution, a solution of 0.64 g. of chromium trioxide in 10 ml. of 90% acetic acid was added. The resulting solution was stirred for 2 hours, diluted with water, and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to yield 2.5 g. of a viscous oil. To a solution of this oily material in 10 ml. of glacial acetic acid, 3 g. of zinc dust was added. The mixture was stirred for twenty minutes at 80^{o} after which the zinc dust was removed by filtration and washed with ether. The filtrate was diluted with water and extracted with ether. The combined ether extract was washed with 5% sodium bicarbonate solution, thoroughly washed with water, dried over magnesium sulfate and finally evaporated to yield 2.1 g. of an oily material. This material when chromatographed over Merck acid-washed alumina (50 g. activity I) gave two products, 1.1 g.

of LII in the benzene eluent, m.p. 119-120° (reported m.p. 121-123° (49)), and 0.81 g. of a conjugated ketonic product LIII in the 5% benzene-Skelly B eluent, m.p. 154-156°. λ_{max}^{KBr} 5.8, 5.98, 6.23 μ; n.m.r. ($CDCl_3$): δ 1.13 (3), 1.28 (3), 3.73 (3), 3.98 (3), 6.9 (2), 8.25 (1).

Epoxidation of Methyl-0-Methyl-Δ^6-podocarpate

A solution of 10.9 g. of m-chloroperbenzoic acid in 100 ml. of dry ether was added dropwise to a well stirred solution of 15 g. of LV in 100 ml. of dry ether. The solution was stirred for two hours at 25°, after which a solution of 5% sodium sulfite was added dropwise, until the solution did not show a positive starch-iodide test. The ether layer was washed with a cold 10% sodium bicarbonate solution and the washings were tested with concentrated hydrochloric acid until no precipitate of m-chloroperbenzoic acid was obtained. The ether layer was thoroughly washed with water, dried over magnesium sulfate and evaporated to yield 19.2 g. of LIX as a viscous oil.

λ_{max}^{film} 2.82, 5.78 (shoulder), 5.85 μ; n.m.r. (CCl_4): δ 3.71 (6), 6.61-8.08 (7).

Lithium Aluminum Hydride Reduction of LIX.

A solution of 19.2 g. of LIX in ether was added dropwise to a well stirred suspension of 2.2 g. of lithium aluminum hydride in dry ether. The reaction mixture was refluxed for twenty-four hours, after which it was decomposed carefully with wet ether followed by water. The aluminum hydroxide precipitate was removed by filtration and the filtrate extracted with ether. The ether extract was washed with water then dried over magnesium sulfate. On evaporation the ether extract

gave 16.4 g. of a mixture of LX and LXII, n.m.r. (CCl_4): δ 3.38 (2, quartet), 4.41 (2, singlet), 3.7 (3), 6.75-7.33 (7, multiplet with a strong signal at δ 7.1).

Preparation and Separation of Compounds LXI and LXIII.

The mixture of LX and LXII (1 g.) was dissolved in 10 ml. of pyridine, to which 5 ml. of acetic anhydride was added. The solution was allowed to stand overnight and the usual workup gave 0.92 g. of the acetylated product. The acetylated material, when chromatographed over 40 g. of Merck acid-washed alumina (activity I), gave 0.19 g. of LXIII and 0.46 g. of LXI. n.m.r. (LXI) (CCl_4): 1.1 (3), 1.33 (3), 1.7 (3), 2.08 (3), 2.18 (3), 3.81(3), 6.72-7.85 (3, multiplet); λ_{max}^{film} 5.75, 6.23 μ.

n.m.r. (LXIII) (CCl_4): δ 1.91 (3), 5.05 (2), 7.13-7.33 (3); λ_{max}^{film} 5.75, 6.23 μ.

Preparation of LXV and LXVI.

A solution of 30 g. of LII in 200 ml. of dry tetrahydrofuran was added dropwise to a well stirred suspension of 3 g. of lithium aluminum hydride in tetrahydrofuran, after which the reaction mixture was refluxed for 12 hours. The reaction mixture was cautiously decomposed with wet ether, followed by ice and water and extracted with ether. The ether extract was washed thoroughly with water, dried over magnesium sulfate and evaporated to yield 26.5 g. of LXV as a glassy solid, λ_{max}^{film} 3.0 μ.

The n.m.r. spectrum of the acetate of LXV, LXVI (acetylation using pyridine and acetic anhydride) showed the following signals:

n.m.r. (CCl_4) δ 1.98 (3), 2.03 (3), 1.25 (3), 3.71 (3).

Preparation of Dienone LXVII.

Sodium metal (16 g.) in small pieces was added to a well stirred solution of 23 g. of LXV in 200 ml. of absolute alcohol and 700 ml. of ammonia, in a three-liter, three-necked flask fitted with a dry ice condenser and a mechanical stirrer. The blue color obtained on addition of sodium metal disappeared after thirty minutes. The reaction mixture was decomposed slowly by the dropwise addition of water and the ammonia was removed at reduced pressure. The waxy material which separated out was extracted with ether and the ether extract thoroughly washed with water, dried over magnesium sulfate and evaporated to yield 21.4 g. of a glassy material.

The reduction product so obtained was dissolved in 100 ml. of methanol and to it a solution of 10 ml. of concentrated hydrochloric acid in 10 ml. of methanol was added. The solution was allowed to stand for eight hours at room temperature, then diluted with water and thoroughly extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated. The viscous mass obtained on evaporation was triturated with a little ether, whereupon it began to crystallize. Repetition of this process gave a total of 8.4 g. (42.1% based on LII) of LXVII, m.p. 131-134°. The analytical sample was obtained by recrystallization from carbon tetrachloride, m.p. 132-134°. λ_{max}^{KBr} 6.05, 2.9 μ; n.m.r. ($CDCl_3$): ε 1.0 (3), 1.05 (3), 3.75 (2, quartet), 5.88 (1), 6.1 (1); λ_{max}^{EtOH} 289 mμ. (ε = 17,500)

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.46; H, 9.23

Found: C, 78.67; H, 9.65

Preparation of LXIXa and LXIXb.

A solution of 0.8 g. of sodium borohydride in 10 ml. of water was added to a well stirred solution of 1.38 g. of LXVII in 20 ml. of ethanol and the solution allowed to stir overnight. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to yield 1.32 g. of LXIXa. λ_{max}^{film} 3.0 μ.

The diol LXIXa upon acetylation with pyridine and acetic anhydride, followed by the usual work-up gave 1.6 g. of LXIXb as a viscous mass which could not be crystallized. λ_{max}^{film} 5.75 μ; n.m.r. (CCl_4): δ 0.95 (3), 1.05 (3), 2.0 (6), 4.15 (2, quarter), 5.51 (2, multiplet).

Selective Epoxidation of Diacetate LXIXb.

Meta-chloroperbenzoic acid (9.7 g.) in 50 ml. of dry ether was added dropwise to a well stirred cold solution of 17.5 g. of diacetate LXIXb in 80 ml. of dry ether. The solution was stirred for one hour at ice bath temperature and then stirred overnight at room temperature. At this stage, the reaction mixture did not show very much excess peracid with starch iodide paper; however, a few ml. of 10% sodium sulfite solution were added to insure that no trace of peracid was left. The reaction mixture was washed with 4% sodium bicarbonate solution, and the washings were tested with hydrochloric acid, until no precipitate or milkiness appeared, due to liberation of meta-chloroperbenzoic acid. The organic layer was washed four times with water, dried over magnesium sulfate and evaporated to yield 17.1 g. of LXX as a viscous mass. This material was not purified or crystallized to avoid opening of the epoxide and was used as such in the next reaction.

λ_{max}^{film} 5.75 μ; n.m.r. (CCl_4): δ 1.0 (3), 1.05 (3), 1.75 (3), 1.78 (3), 5.74 (1, multiplet).

Isomerization of LXX to Keto Acetate LXXI.

A solution of 0.5 ml. of boron trifluoride-etherate complex in 2 ml. of dry benzene was added to a well stirred solution of 4.0 g. of LXX in 100 ml. of dry benzene at 10°. A yellow color appeared when the boron trifluoride solution was added. The solution was stirred for 4 1/2 minutes, decomposed with water and extracted thoroughly with ether. The ether extract was washed thoroughly with water, dried over magnesium sulfate and evaporated to yield 3.62 g. of LXXI as a viscous yellow gum. λ_{max}^{film} 5.72, 5.8, 6.0 μ (weak).

Isomerization of LXXI to LXXII.

The unconjugated keto acetate LXXI (1.0 g.) in 10 ml. of glacial acetic acid was heated on a steam bath for 2 1/2 hours after which it was diluted with water and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to yield 0.87 g. of crude LXXII as viscous oil. λ_{max}^{film} 5.75, 6.0 μ.

Preparation of Dienone LXXIa.

Keto acetate LXXI (0.6 g.) was dissolved in 25 ml. of 1% methanolic potassium hydroxide solution and heated on a steam bath for thirty minutes. The reaction mixture, after cooling, was diluted with water and the organic material extracted into ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to give 0.35 g. of LXXIa as viscous oil. λ_{max}^{EtOH} 308 mμ. λ_{max}^{film} 2.9, 6.0 μ.

Preparation of Dienone LXXIb.

A solution of 16.87 g. of LXXI in 15 ml. of benzene was absorbed on an alumina column (300 g., activity II Merck acid washed (column made with petroleum ether) and the column was not eluted for two hours. The column was then eluted with benzene. The combined benzene fractions gave 12.65 g. of dienone LXXIb as viscous yellow gum. $\lambda_{max}^{Dioxane}$ 308mμ. (ϵ = 6,040); λ_{max}^{film} 5.75, 6.02 μ; n.m.r. (CCl_4): δ 1.0 (3), 1.15 (3), 2.01 (3), 4.16 (2, quartet), 6.38 (2).

Elution of the column with ether gave another 1.52 g. of a very crude fraction which contained some LXXIb.

Diels-Alder Addition of Maleic Anhydride to Dienone LXXIb.

A solution of 12 g. of dienone LXXIb, 11.76 g. of maleic anhydride and a trace of trichloroacetic acid in 15 ml. of xylene was refluxed for two hours. After twenty minutes, the color of the solution changed from yellow to brown. The reaction mixture was cooled, and 50 ml. of ether was added to it, which resulted in the precipitation of a crystalline material, 5.81 g., m.p. 198-251°. This material on fractional crystallization from chloroform containing a few ml. of ether gave 2.15 g. of LXXV, m.p. 270-272° and 2.8 g. of LXXIV, m.p. 200-203° was obtained from the mother liquor.

The filtrate left after removal of the crude crystalline product (m.p. 198-251°), was washed thoroughly with water until the washings did not show a black color with Congo red paper, indicating thereby the complete removal of excess maleic anhydride. The organic layer was dried over magnesium sulfate and evaporated to a volume of about 50 ml. This solution was chilled in the freezer when another 2.69 g. of crude

LXXIV, m.p. 196-201°, was obtained. This material on recrystallization from chloroform-ether mixture gave 2.49 g. of pure LXXIV, m.p. 200-203°. The Diels-Alder addition reaction thus provided two adducts, 5.29 g. of LXXIV, m.p. 200-203° and 2.15 g. of LXXV, m.p. 270-272°.

Adduct LXXV, m.p. 270-272°.

λ_{max}^{KBr} (Plate VI) 5.40, 5.62, 5.8, 5.85 μ; n.m.r. (Plate II) ($CDCl_3$): δ 1.02 (6), 2.08 (3), 6.1 (1, doublet, J = 7 cps)

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 69.06; H, 7.06

Found: C, 68.62; H, 6.85

Adduct LXXIV, m.p. 200-203°.

λ_{max}^{KBr} (Plate V) 5.45, 5.65, 5.8, 5.85 μ(shoulder); n.m.r. (Plate I) ($CDCl_3$): δ 1.01 (3), 1.18 (3), 2.05 (3), 6.1 (1, doublet, J = 7 cps).

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 69.06; H, 7.06

Found: C, 68.65; H, 7.03

Esterification of Adducts LXXIV and LXXV.

Methanolic ether solutions containing 100 mg. each of LXXIV and LXXV were taken separately and esterified with ethereal diazomethane. The action of diazomethane was much faster in the case of adduct LXXIV as compared to LXXV, as evidenced by the rate of evolution of nitrogen. Adduct LXXIV gave diester LXXVI (90 mg.), m.p. 161-163°, after recrystallization from methanol, whereas diester LXXVII from adduct LXXV could not be crystallized.

Diester LXXVI, m.p. 161-163°.

n.m.r. ($CDCl_3$): δ1.02 (3), 1.12 (3), 2.06 (3), 3.51 (3), 3.58 (3), 5.93 (1, doublet, J = 7 cps.); λ_{max}^{KBr} 5.71, 5.75, 5.8, 5.87μ.

Diester LXXVI n.m.r. ($CDCl_3$): δ 1.0 (3), 1.31 (3), 2.1 (3), 3.53 (3), 3.53 (3), 3.6 (3), 5.83 (1, doublet, J = 7 cps.).

Attempts to hydrogenate diester LXXVi with 5% platinum on carbon in ethyl acetate and glacial acetic acid were unsuccessful.

Preparation of LXXVIII.

A suspension of 2 g. of diester LXXVI in a mixture of 100 ml. of 10% sodium hydroxide and 40 ml. of methanol was refluxed under nitrogen on a steam bath for 4 hours. The clear solution, after cooling, was diluted with water, dried over magnesium sulfate and evaporated to yield 1.94 g. of a glassy material, which on recrystallization from ether and n-hexane gave 1.6 g. of LXXVIII, m.p. 245-247°.

λ_{max}^{KBr} 2.9 (broad), 5.8 μ (broad); n.m.r. (CD_3COCD_3): δ 0.9 (3), 1.1 (2, quarter), 5.1 (disappears with addition of D_2O), 6.15 (1, doublet, J = 7 cps.)

Hydrogenation of LXXVIII.

Compound LXVIII (2.2 g.) was hydrogenated in the presence of 0.5 g. of 5% platinum on carbon in 40 ml. of acetic acid at room temperature. Hydrogen absorption was very slow. Removal of the catalyst by filtration, followed by removal of acetic acid under vacuum gave 2.32 g. of a solid product, which on recrystallization from ether and n-heptane gave 2.1 g. of LXXXI, m.p. 248-250°. λ_{max}^{Nujol} 5.88, 5.72 μ.

Anal. Calcd. for $C_{21}H_{30}O_6$ 1/2 mol. CH_3COOH.

Found: C, 65,41; H, 8.68

Calcd. C, 65.08; H, 7.94

Preparation of LXXX, LXXXII, and LXXXIII.

Diacid LXXXI (2.32 g.) was dissolved in 5 ml. of pyridine and 3 ml. of acetic anhydride and the mixture was allowed to stand overnight. The reaction mixture was worked up in the usual manner to give 2.41 g. of LXXIX. This material was utilized for the decarboxylation reaction without purification.

Diacid LXXIX (1.5 g.) was dissolved in 30 ml. of anhydrous pyridine at 80°. The system was flushed with nitrogen and a constant flow of nitrogen was maintained. Lead tetraacetate (1.05 g.) was added which resulted in the vigorous evolution of carbon dioxide. When the evolution of carbon dioxide had ceased, another 1.5 g. of lead tetraacetate was added. The reaction mixture was refluxed for one hour, after which, pyridine was distilled and the solid material left was thoroughly extracted with boiling ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to yield 0.69 g. of a brownish gum which did not crystallize.

The decarboxylated material so obtained was dissolved in 50 ml. of methanol, to which 20 ml. of 7% sodium hydroxide solution was added. The solution was refluxed for one hour under nitrogen, cooled, diluted with water and extracted with ether. The water layer (alkaline solution) was saved and the ether extract was dried over magnesium sulfate. The ether extract on evaporation gave a semisolid, which on crystallization from ether and petroleum ether (b.p. 40-60°) gave 0.196 g. (10.45%) of LXXXII, m.p. 149-150°.

λ_{max}^{KBr} (Plate IV) 2.83, 3.28, 3.27, 5.92, 14.3 μ; n.m.r. (Plate III) ($CDCl_3$): δ 0.97 (3), 1.15 (3), 6.28 (1, multiplet), 6.78 (1, multiplet).

The mass spectrum (Plate VIII) gave the parent peak at m/e 288 (37.3%, actual mol. wt. 288) and base peak at m/e 257 (M^+-31).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12, H, 9.79

Found: C, 79.08; H, 9.75

The alkaline water solution left after removal of LXXXII (from four experiments, 1.0 g. of LXXIX used in each experiment) was acidified with 6N hydrochloric acid. The solution was extracted with ether, the ether extract washed with water, dried over magnesium sulfate and evaporated to give 2.2 g. of a viscous material. This material on esterification with ethereal diazomethane followed by acetylation with pyridine and acetic anhydride by the usual procedure gave 2.3 g. of a semisolid material, which on crystallization from methanol gave 1.6 g. (37.5%, based on LXXXI) of LXXX, m.p. 171-173°.

λ_{max}^{Nujol} 5.78, 5.92 μ; n.m.r. ($CDCl_3$): δ 0.91 (3), 1.08 (3), 2.05 (3), 3.65 (3), 3.76 (3).

The mass spectrum (Plate X) gave the parent peak at m/e 448 (22.2%, Actual mol. wt. 448) and base peak at m/e 303 (M^+-145).

Gas liquid chromatography (on 2% SE-30, 6' x 1/8" column at 280°) of the material left after the removal of LXXX and LXXXII showed it to be a mixture of four components with retention times of 1.5 min., 2.1 min. (major component), 1.6 min., and LXXXII with retention time of 2.45 min.

Wolff-Kishner Reduction of LXXXII.

A solution prepared from potassium hydroxide (0.7 g.), 7 ml. of diethylene glycol, 1.5 ml. of 95% hydrazine and 0.097 g. of LXXXII was refluxed under nitrogen for four hours, after which water was distilled

out. Another 0.5 ml. of hydrazine was added and the solution refluxed overnight under nitrogen. The reaction mixture was cooled, distilled with water, and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to yield 89 mg. of XLVIII, m.p. 148-150° after recrystallization from methanol (reported m.p. 151-152° (36)). λ_{max}^{KBr} 3.0, 14.45 μ; n.m.r. ($CDCl_3$ - CS_2 mixture): δ0.9 (3), 0.905 (3), 3.56 (2, quarter), 6.0 (2, multiplet).

Conversion of LXXXII to LXXXIV.

Compound LXXXII (0.28 g.) on acetylation with pyridine and acetic anhydride by the usual method gave 0.3 g. of LXXXIII, m.p. 136-140°, λ_{max}^{Nujol} 5.85, 5.92 μ., which was used as such for the preparation of LXXXIV.

Compound LXXXIII (0.3 g.), 10 ml. of dry benzene, 2 ml. of ethylene glycol and a trace of p-toluenesulphonic acid monohydrate was heated at reflux in a flask provided with a Dean-Stark separator for a period of twenty hours. The reaction mixture, after cooling, was added to 100 ml. of 5% sodium bicarbonate solution and the solution was thoroughly extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to yield 0.26 g. of a semisolid. This was recrystallized from petroleum ether (b.p. 40-60°) giving 0.21 g. of LXXXIV, m.p. 110-111°. λ_{max}^{KBr} 3.27, 3.28, 5.72, 14.3 μ; n.m.r. ($CDCl_3$): δ 0.91 (3), 1.0 (3), 1.98 (3), 6.12 (2 multiplet), 3.96 (6, multiplet). The mass spectrum (Plate IX) gave the parent peak at m/e 374 (55.38%, actual mol. wt. 374) and the base peak at m/e 294 (M^+-80).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 73.96; H, 9.50

Found: C, 74.14; H, 9.25

Hydroboration of the LXXXIV. Preparation of LXXXV.

Diborane produced by the dropwise addition of a solution of 1 g. of sodium borohydride in dry diglyme to 2 ml. of boron trifluoride-etherate complex in dry ether, was swept with nitrogen into a reaction vessel containing 0.5 g. of LXXXIV in 40 ml. of dry tetrahydrofuran at 8-10°. The reaction mixture after the addition of diborane was stirred for two hours and then decomposed by dropwise addition of a solution of 5 ml. of 30% hydrogen peroxide and 5 ml. of 1N sodium hydroxide until there was no effervescence. The solution was diluted with water extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to yield 0.68 g. of a non-crystalline product. λ_{max}^{KBr} 2.9, 5.8 μ.

A solution of 0.68 g. of the hydroborated product in 10 ml. of dry pyridine was added to a mixture of 0.8 g. of chromium trioxide in 12 ml. of pyridine, which in turn was cooled in an ice bath. The reaction mixture was stirred for two hours, after which it was poured into ice water. The aqueous solution was extracted with ether, the extract was washed respectively with 5% hydrochloric acid and water. The organic layer was dried over magnesium sulfate and the removal of the solvent gave 0.51 g. of non-crystalline ketonic product, λ_{max}^{film} 5.8, 5.9 μ. Gas liquid chromatography of the material on 2% SE-30 at 280° (6 ft. column, 1/8 inch diameter, flow rate 80 ml./min) showed it to be a mixture of five components with retention times of 0.6, 0.8, 0.95, 1.15, and 1.5 min.

This ketonic material on chromatography over alumina (25 g., activity II, Merck acid-washed) and elution with chloroform gave 89 mg. of crude LXXXV, which on crystallization from methanol gave 52 mg. of LXXXV, m.p. 171-173°, which contained a trace of LXXXVI as seen in the

mass spectrum. λ_{max}^{KBr} 5.8, 5.85, 5.9 μ; n.m.r. ($CDCl_3$): δ 0.98 (3), 121 (3), 4.06 (2, quartet).

The mass spectrum (Plate XI) showed the parent peak at m/e 346 (14%, actual mol. wt. 346) and base peak at m/e 79 (M^+-267). The other isomer (LXXXVI) showed the parent peak at m/e 346 (20%, actual mol. wt. 346) and the base peak at m/e 122 (M^+-229) (Plate XII). No other chromatographic fraction could be crystallized.

Wolff-Kishner Reduction of LXXV.

A solution of 0.84 g. of LXXV, 2.8 g. of potassium hydroxide and 3 ml. of 80 or 90% hydrazine in 20 ml. of diethylene glycol was refluxed under nitrogen for four hours, after which about 2 ml. of solution was distilled out and refluxing was then continued overnight under nitrogen. The reaction mixture was decomposed with 6N hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and on evaporation gave 0.72 g. of a crude product, which on crystallization from methanol gave 0.52 g. of LXXXVII, m.p. 260-261°. λ_{max}^{KBr} 5.76, 5.94 μ.

Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 67.80; H, 7.59

Found: C, 68.02; H, 7.64

The n.m.r. spectrum of LXXXVIII, in trifluoroacetic anhydride showed the following signals: δ 1.13 (6), 3.8 (3), 6.05 (1).

Preparation of LXXXIX.

Ozone was passed through a solution of 5 g. of LII in 20 ml. of methylene chloride and 10 ml. of methanol. The reaction mixture was treated with 5 ml. of 20% hydrogen peroxide and 1 ml. of concentrated

hydrochloric acid and was allowed to stir overnight. The reaction mixture was heated on a steam bath for one hour, diluted with water and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to give 4.6 g. of yellow oily product. The product thus obtained was crystallized from methanol-water to give a colorless cyrstalline product, LXXIX, m.p. 123-124°. λ_{max}^{KBr} 5.82, 5.95, 15.38 μ; n.m.r. ($CDCl_3$): δ 0.93 (3), 1.51 (3), 3.75 (3), 3.91 (3), 5.76 (1, doublet, J = 8 cps.), 7.9 (1, doublet, J = 8.0 cps.) and δ 2.3 (1, doublet, J = 8.0)

Anal. Calcd. for $C_{19}H_{23}O_9Cl_1$: C, 65.23; H, 6.62

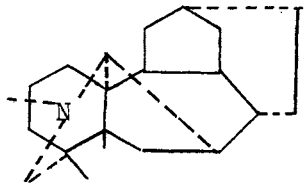
Found: C, 65.44; H, 6.56

CHAPTER IV

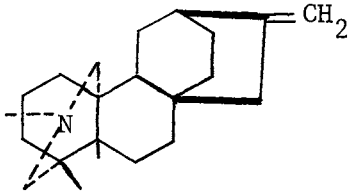
DITERPENOID CONTENT OF *DELPHINIUM AJACIS* SEEDS

Introduction

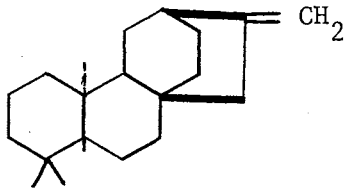
The seeds of *Delphinium ajacis* have been the subject of investigation by various groups (6,19,56,57) the world over. In addition to fatty acids (57), novel diterpenoid alkaloids (6,19) having substituted skeleta XCII and XCIII have been isolated. Rigorous structure proofs



XCII



XCIII

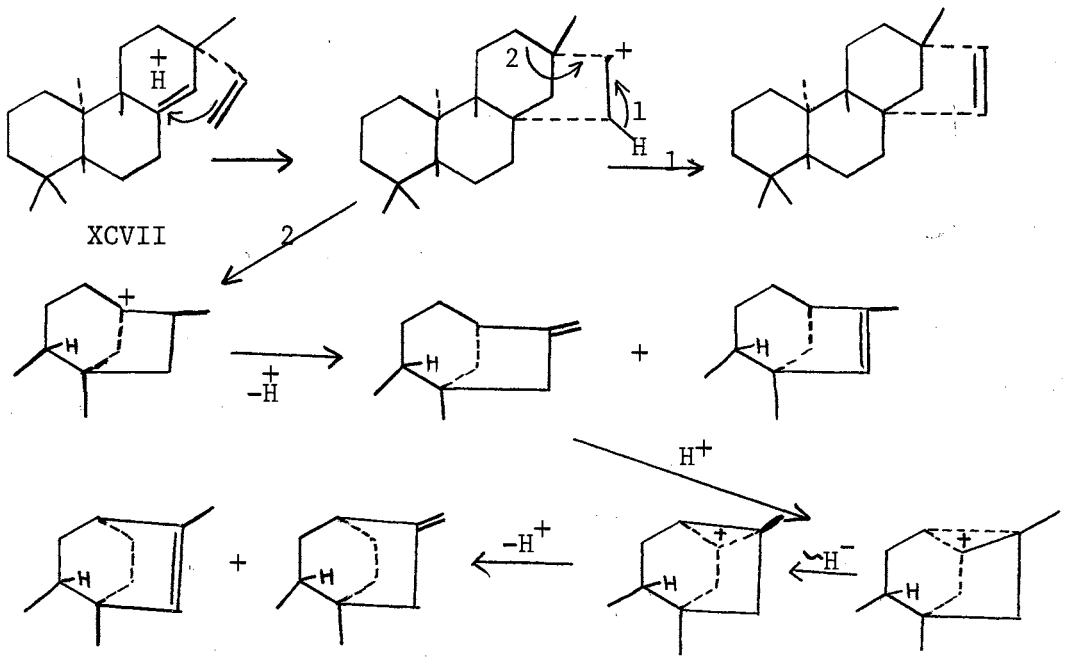


XCIV

have been provided for these diterpenoid alkaloids (6,19).

Wenkert (52) has postulated that the biogenetic precursors of the tetracyclic diterpenes and diterpenoid alkaloids are pimaradiene of the type XCVII (only relative stereochemistry indicated) which could cyclize to give different diterpenoid compounds. These diterpenoid compounds especially atisirene, XCIV, could be the precursors of the alkaloids isolated from *Delphinium ajacis*. However, it might be pointed out that no tetracarboxyclic diterpenes have ever been isolated from the same plant along with the corresponding diterpenoid alkaloids.

Our main objective in the study of the Delphinium seeds was an



attempt to isolate diterpenes, which could be correlated with the diterpenoid alkaloids and other diterpenes which might appear as the by-products in the above biosynthetic sequence. We have been successful in isolating a mixture of compounds as their acetates (named components A, B, C, D) from which component B has been separated in pure form. Evidence for the existence of the tetracarbocyclic diterpenoid structure in components A, B, C. D is presented.

Experimental

Melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237-B spectrophotometer and n.m.r. spectra were recorded with a Varian A-60 spectrometer, using tetramethylsilane as an internal reference ($\delta = 0$). The gas-liquid

chromatographic studies were done employing the F and M Biomedical gas chromatograph model 400. The chloroform extract of Delphinium ajacis seeds which were previously extracted with 5% acetic acid and petroleum ether (39% of weight of the seeds) was used in the studies and will be referred to as delphinium oil. Silica gel, 0.05-0.2 mm (E. Merck AG. Darmstadt, Germany) and neutral aluminum oxide (M. Woelm, Eschwege, Germany) were used for chromatographic separations. Mass spectra were recorded using a LKB model 9000 chromatography-single focussing mass spectrometer in conjunction with gas-liquid chromatography. The ion source was of the electron bombardment type, employing a rhenium filament. A jet-type molecular separator, of Becker-Ryhage design, was used for sample (to carrier gas) enrichment. These spectra were obtained through the courtesy of Dr. John R. Dyer, Georgia Institute of Technology, Atlanta (Georgia) and Dr. C. C. Sweely, University of Pittsburgh, Pittsburgh (Pennsylvania).

Preparation of 5% Silver Nitrate-Coated Silica Gel

To a solution of 10 g. of silver nitrate in 120 ml. of water, 200 g. of silica gel was added with constant shaking to form a slurry. On evaporation of water from the homogeneous slurry, dry, slightly pink silica gel was obtained. This material was dried overnight at 120° and then used for chromatography.

Saponification of Delphinium Oil

A solution of 120 g. of sodium hydroxide in 350 ml. of water was added slowly to a well stirred emulsion of 600 g. of delphinium oil in one liter of water. The temperature of the reaction rose to 70° after

the complete addition of sodium hydroxide solution. The reaction mixture was stirred for one hour, after which it was heated on a steam bath for eight hours. During this period, the temperature of the solution did not rise above 80°. The saponified mixture was diluted with water (three liters) and thoroughly extracted with ether. The ether extract after washing with water, drying over magnesium sulfate, and evaporation gave 5.2 g. of a semisolid material. This material on crystallization from ethyl acetate-methanol gave 4.3 g. of a solid product, m.p. 124-134° λ_{max}^{KBr} 2.93, 6.13 and 12.5 μ; n.m.r. ($CDCl_3$) showed strongly methyl signals at δ0.7, 1.01, 1.26, 1.7 and two signals in the olefinic region at δ 4.7 and 5.4. The gas-liquid chromatograph of the material indicated it to be a mixture of six components, their retention times being 1.0 min., 1.2, 1.33, 1.5, 1.7, and 1.9 on 2% SE-30 at 290° (6 ft. column, 1/8 inch diameter and flow rate 80 ml./min.).

The basic layer after extraction with ether was neutralized with 1:1 hydrochloric acid and the precipitated material was extracted with ether. The ether extract was washed thoroughly with water and dried over magnesium sulfate. On evaporation, the ether extract gave 445.5 g. of an oily material, λ_{max}^{film} 5.87, 13.88 μ.

Purification of the Neutral Component

The crude neutral mixture (obtained above) was acetylated with acetic anhydride and pyridine and after the usual work-up gave 4.1 g. of a semi-solid. This material could not be purified by fractional crystallization. Chromatography of the acetylated material on 200 g. of neutral alumina gave 1.1 g. of a hydrocarbon fraction (pet. ether to

15% benzene-pet. ether fraction) and 2.7 g. of a solid, m.p. 110-128° (15% benzene-pet. ether and more polar solvents) λ_{max}^{KBr} 5.8, 13.3, and 13.8 μ.

Chromatography of Acetate Mixture on 5% Silver Nitrate-Coated Silica Gel

Chromatography of 2.7 g. of the acetate mixture (obtained in the last experiment) on 200 g. of 5% silver nitrate-coated silica gel gave 2.14 g. of the same mixture (40% benzene-n-hexane to 60% benzene-n-hexane) which on crystallization from ethyl acetate and methanol mixture gave 1.9 g. of a solid mixture. The gas-liquid chromatograph of the mixture showed it to be a mixture of four components (A, B, C, D) with retention times 6.55 min., 8.88, 9.9, and 11.30 on 2% SE-30 at 230°. The mass spectra of components A, B, C, and D showed the parent peaks at m/e 394 (1%), m/e 379 (60%), m/e 396 (61.3%), m/e 398 (55.5%), and base peaks at m/e 43, m/e 43, m/e 55, and m/e 43, respectively. In addition to this mixture, component B, 0.206 g. (eluted by 70% benzene-n-hexane to 100% benzene) with minute traces of other components was obtained. This component B was rechromatographed on 50 g. of 5% silver nitrate-coated silica gel when 0.176 g. of component pure B was obtained, λ_{max}^{Nujol} 3.27, 5.8, 6.13, 12.5, and 13.88 μ; n.m.r. ($CDCl_3$): δ 0.68 (3), 1.01 (6), 1.63 (3), 1.95 (3), 4.68 (2), and 5.4 (1). The mass spectrum of this compound showed the parent peak at m/e 379 (88.7%) and the base peak at m/e 41.

Saponification of Component B

A solution of 0.5 g. of sodium hydroxide in 10 ml. of water was added to 0.1 g. of component B already dissolved in 10 ml. of methanol.

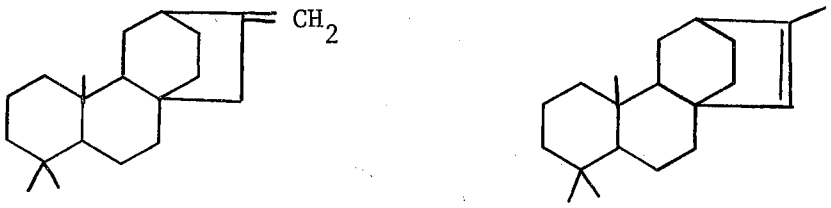
The solution was refluxed on a steam bath for one hour, after which it was cooled, diluted with water, and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate. The ether extract on evaporation gave a solid product, which when recrystallized from ethyl acetate-methanol gave 70 mg. of a product, m.p. 137-138.5°. λ_{max}^{Nujol} 2.95, 6.13, 12.5, and 13.88 μ.

Anal. Calc'd for $C_{20}H_{32}O$: C, 83.40; H, 11.20

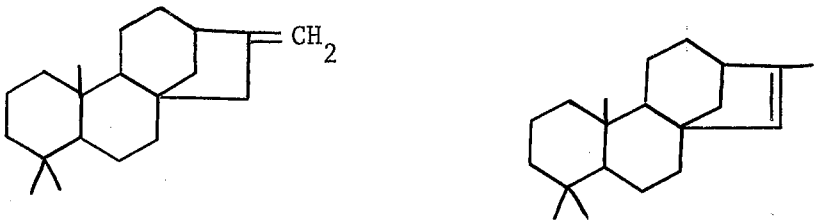
Found: C, 83.56; H, 11.65

Results and Discussion

Delphinium oil was saponified to give a neutral fraction, which when acetylated and chromatographed on 5% silica gel gave a mixture of four components (A, B, C, D) and some of the pure component B. The n.m.r. spectrum of component B, showed, in addition to methyl signals at δ 0.68 (3), 1.01 (6), 1.63(3), the presence of one acetate function (δ1.95) and olefinic signals at δ 4.68 (two protons) and δ 5.4 (one proton). Due to the existence of a methyl signal at δ 1.63 (methyl on a double bond) and two separate olefinic signals at δ 4.48 and 5.4, it is presumed that component B is a mixture of two substituted isomeric systems such as XCV or XCVI (position of acetate not indicated) which could not be separated.



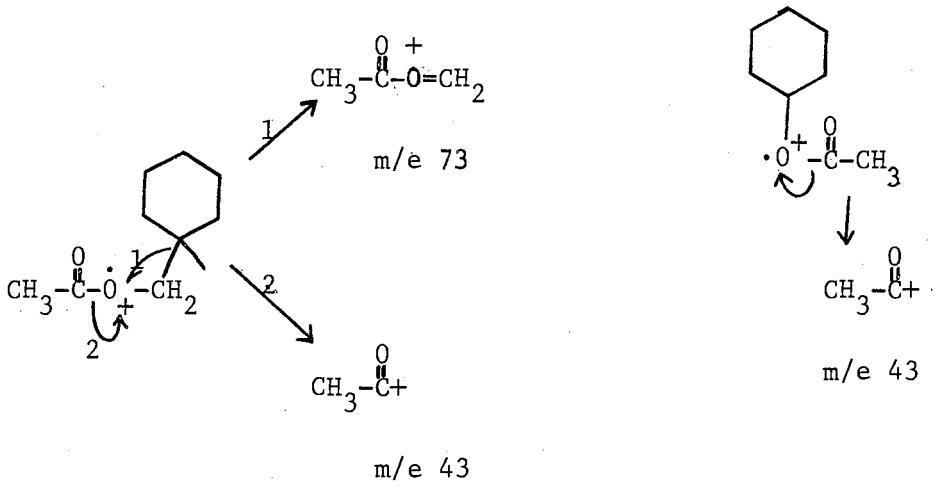
System XCV



System XCVI

The infrared spectrum of component B showed the presence of an exo methylene group (6.13, 12.5 μ) and an acetate function (5.8 μ). Component B on saponification gave a material, which did not show any carbonyl function in its infrared spectrum and its elemental analysis was consistent with the required analysis for a monohydroxy derivative of the compounds indicated under system XCV or XCVI. The mass spectrum of component B gave the parent peak at m/e 379 (88.7%) and the base peak at m/e 41. At this stage we cannot explain the high mol. wt. 379 rather than the expected value of 330 observed by mass spectrometry. Further work on this is being done which is beyond the scope of this dissertation.

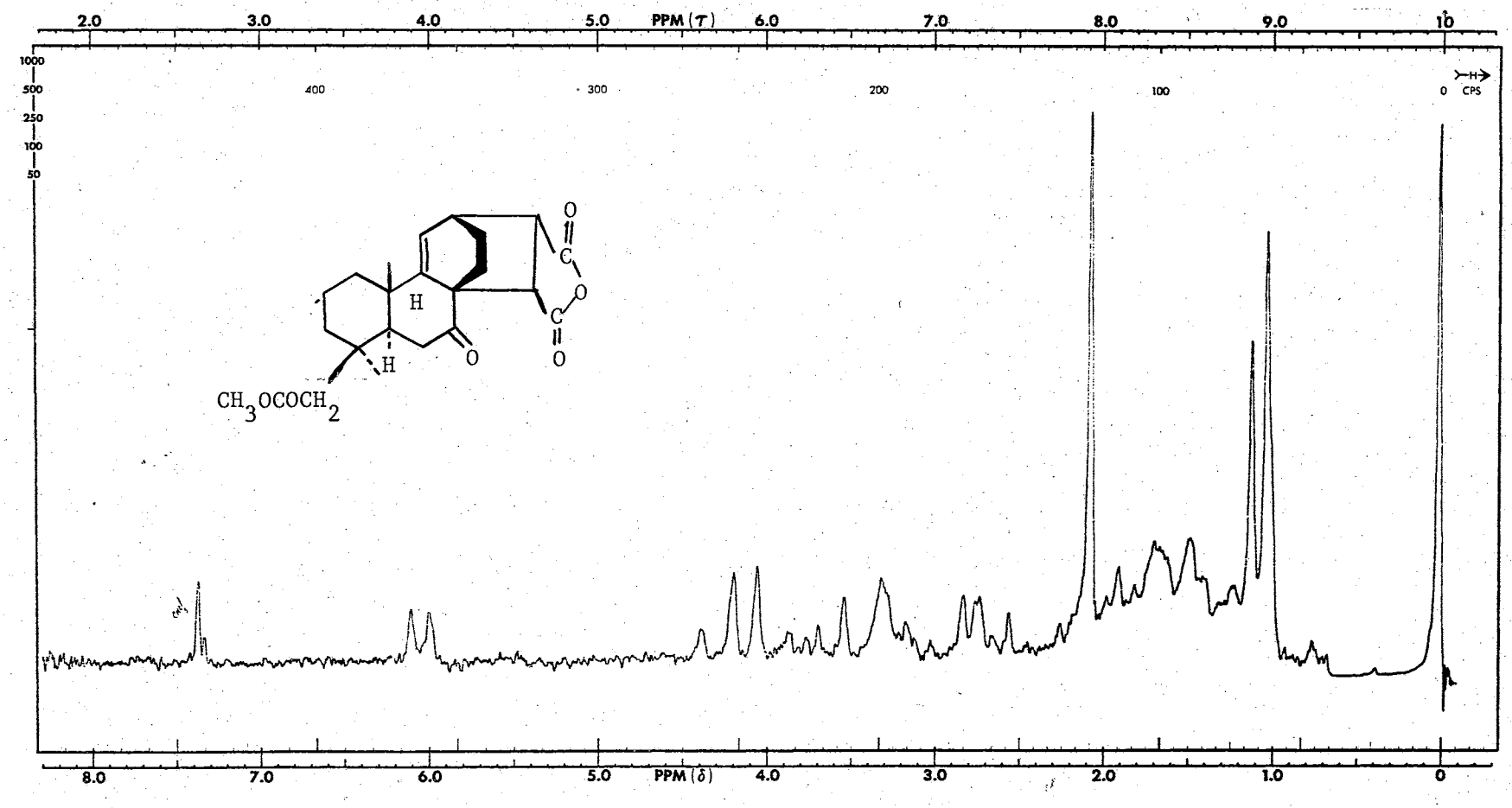
The mass spectra (Plates XIII-XVI) of components A, B, C, and D showed the parent peaks at m/e 394 (1%), m/e 379 (60%), m/e 396 (61.3%), m/e 398 (55.5%), and base peaks at m/e 43, m/e 43, m/e 55 and m/e 43, respectively. The common base peak (m/e 43) with the exception of component C, which does show m/e 43 to an extent of 65% is due to the elimination of the $CH_3-\overset{O}{\overset{\|}{C}}+$ fragment, also noted in all the synthetic intermediates (p. 31-34). However, in the case of the synthetic intermediates (p. 31-34) the acetate group is primary in its nature and fragment m/e 73 always accompanied m/e 43, which is what would be expected, but in the components A, B, C, D the absence of m/e 73 probably



indicates the secondary nature of the acetate group.

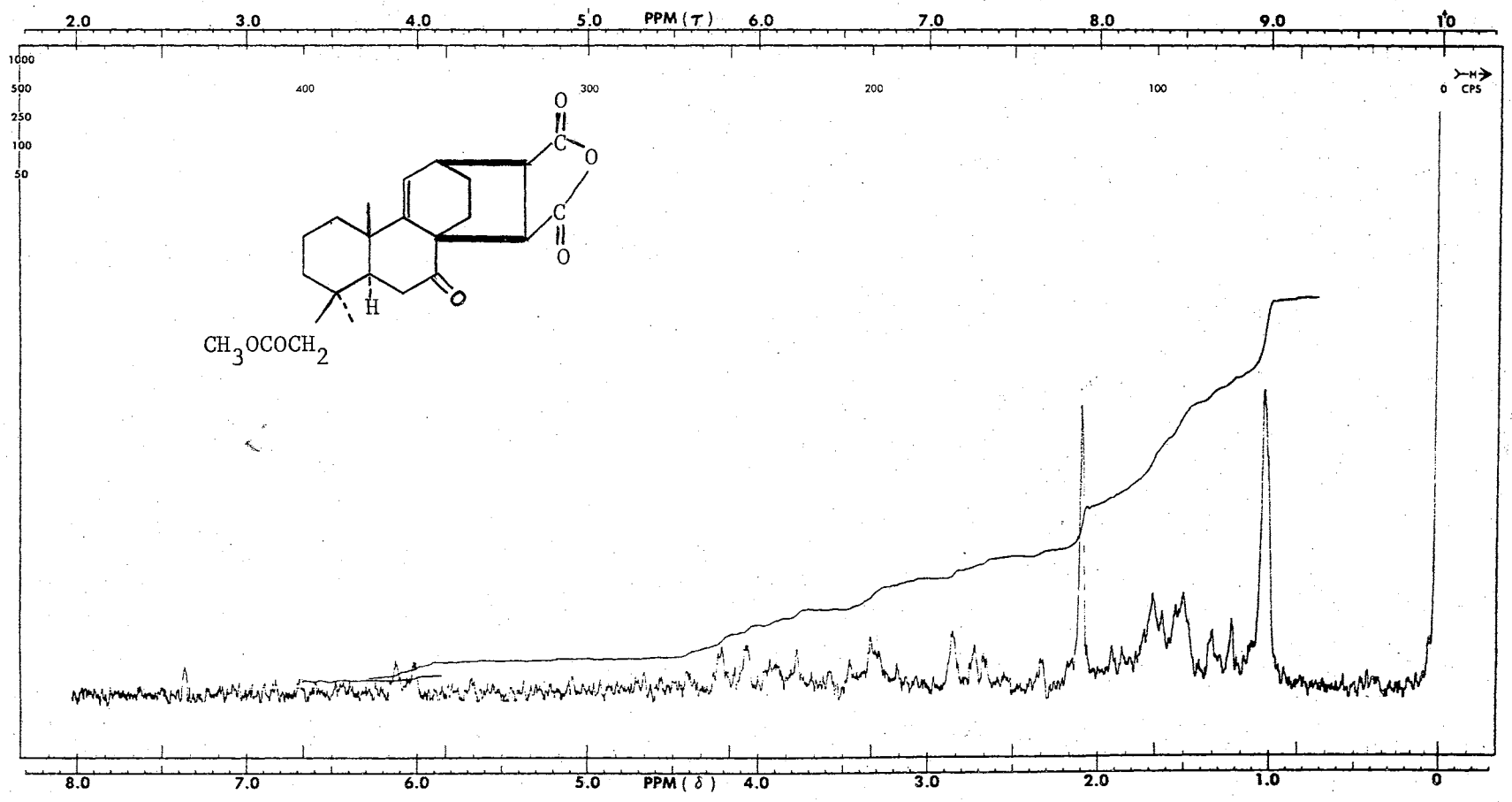
Another common feature of the mass spectra of these compounds is the loss of M-14 to 17 from the parent peak followed by a loss of M-27 to 29, depending upon whether one or three mass units are lost along with acetylene. Such a retro Diels-Alder reaction is also noticeable in the synthetic intermediates (p. 31-34) although it is more pronounced, probably due to the presence of a keto group at C-7. The existence of other fragments, m/e 107, m/e 105, m/e 81, m/e 145, and m/e 147 which are present in the mass spectrum of phyllocladene (49) (almost the same intensity) would indicate the existence of the parent tetracyclic diterpenoid skeleton. The occurrence of the retro Diels-Alder reaction resulting in the loss of acetylene along with one to three mass units (27 to 29) after the loss of the methyl group from the parent peak would indicate the existence of the bicyclo[2.2.2]octane system in the parent molecule.

PLATE I



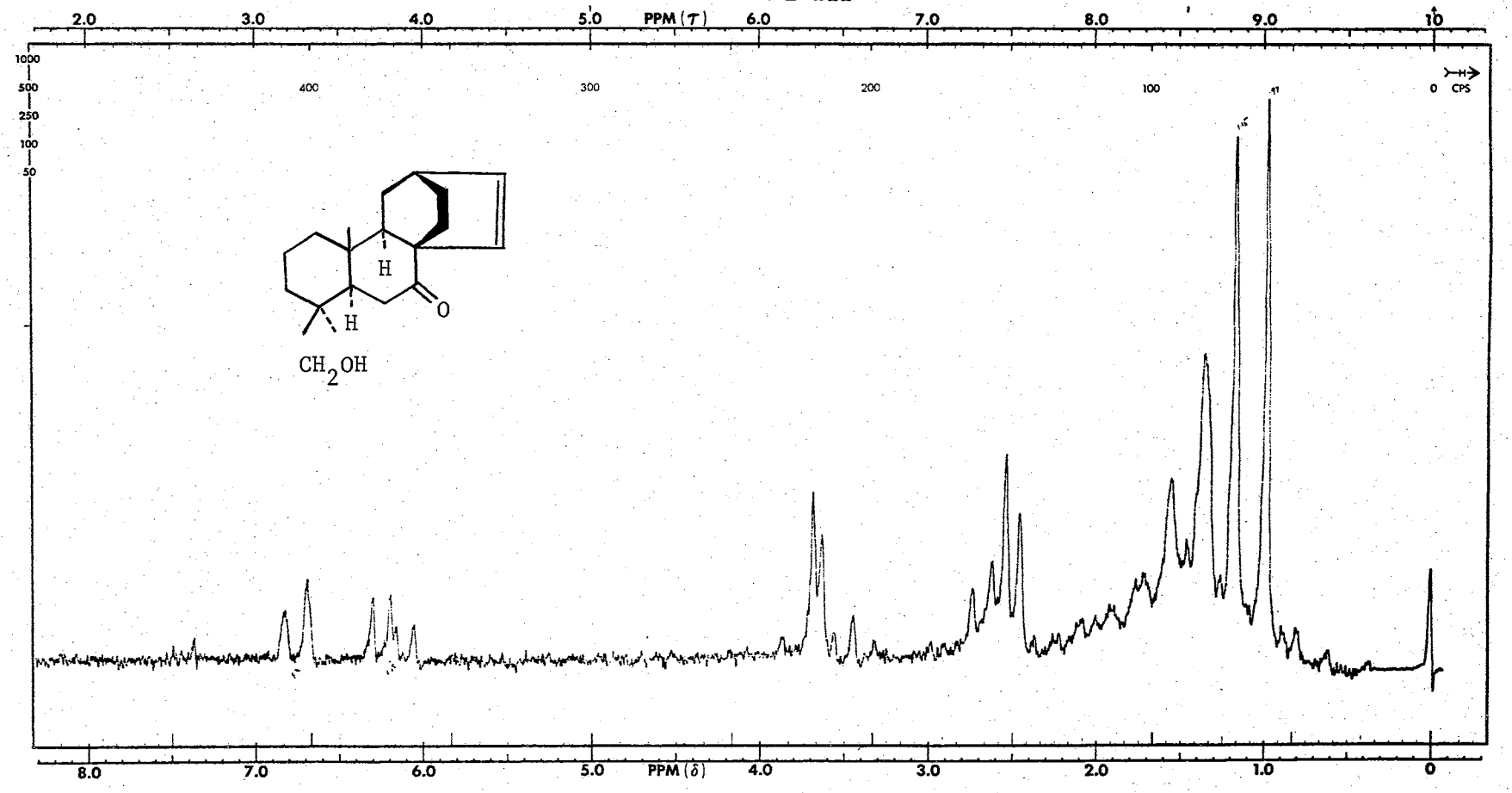
N.M.R. Spectrum of LXXIV.

PLATE II



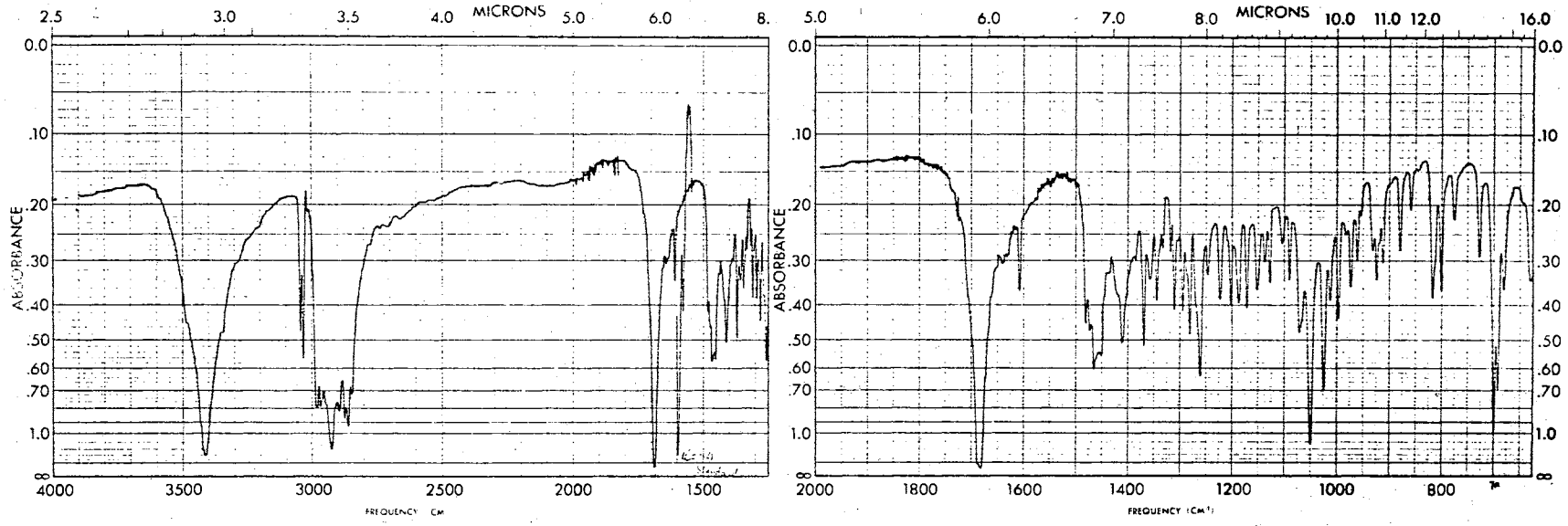
N.M.R. SPECTRUM OF LXXV.

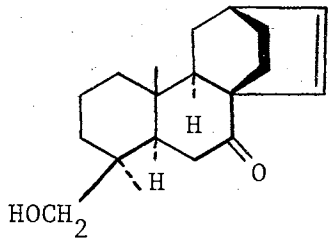
PLATE III



N.M.R. Spectrum of LXXXII.

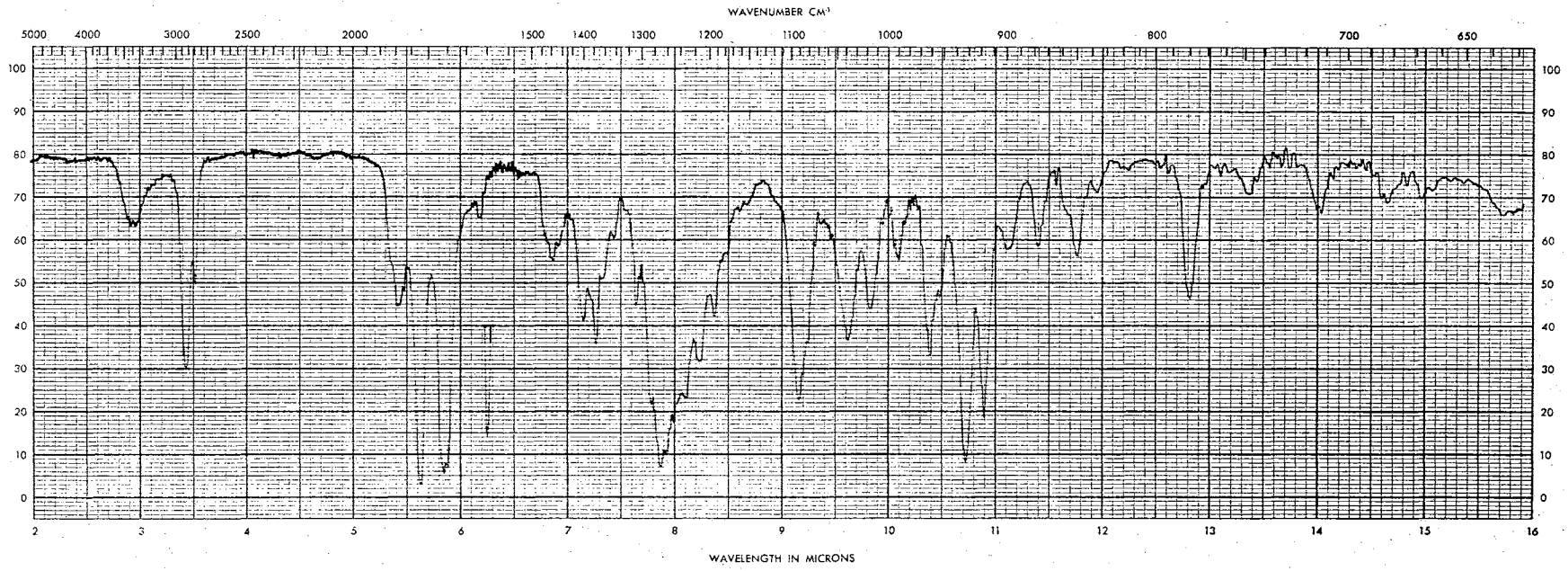
PLATE IV

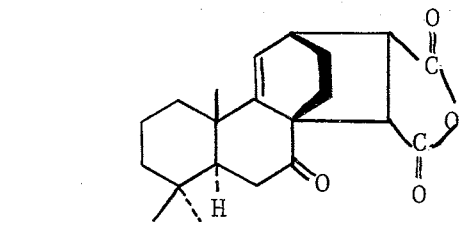




Infrared Spectrum of LXXXII.

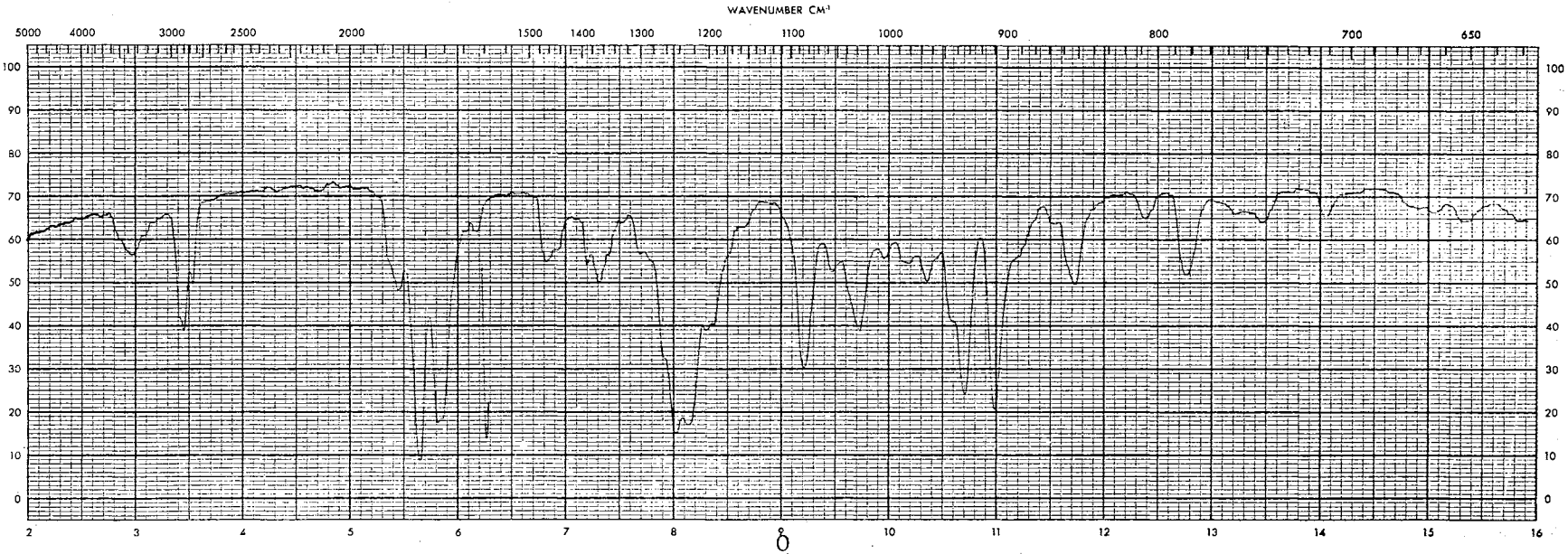
PLATE V





Infrared Spectrum of LXXIV.

PLATE VI



Infrared Spectrum of LXXV

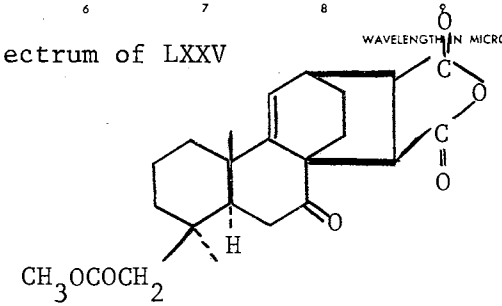
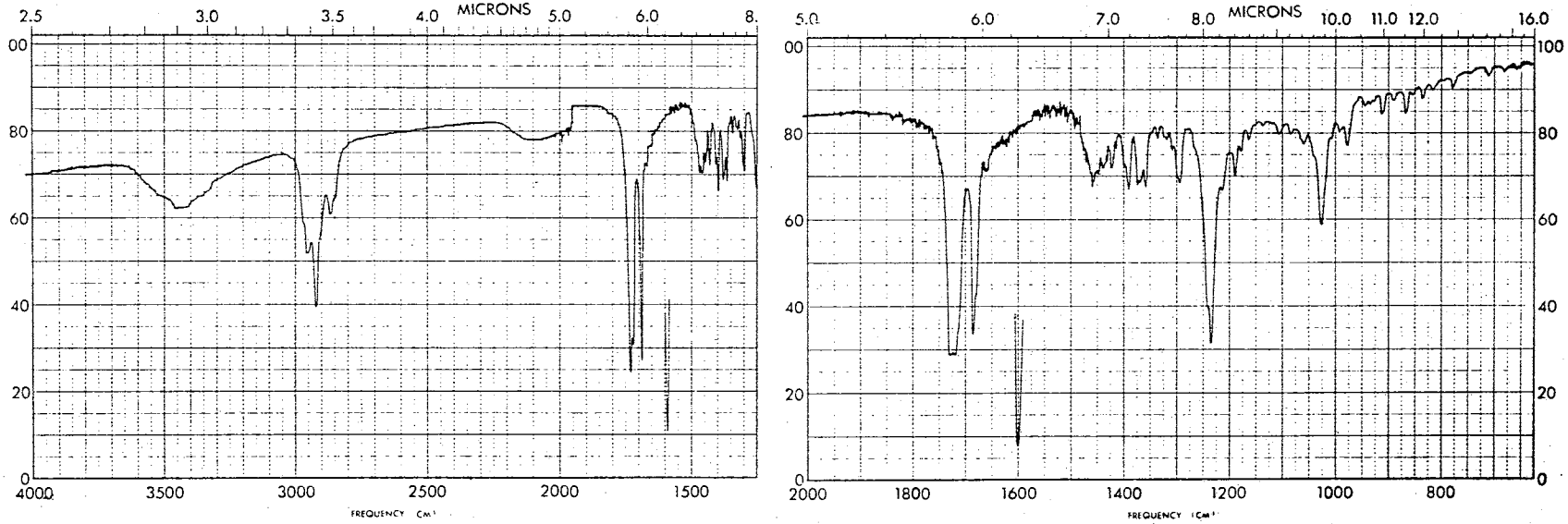


PLATE VII



Infrared Spectrum of LXXXV

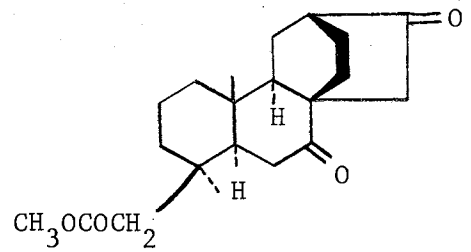


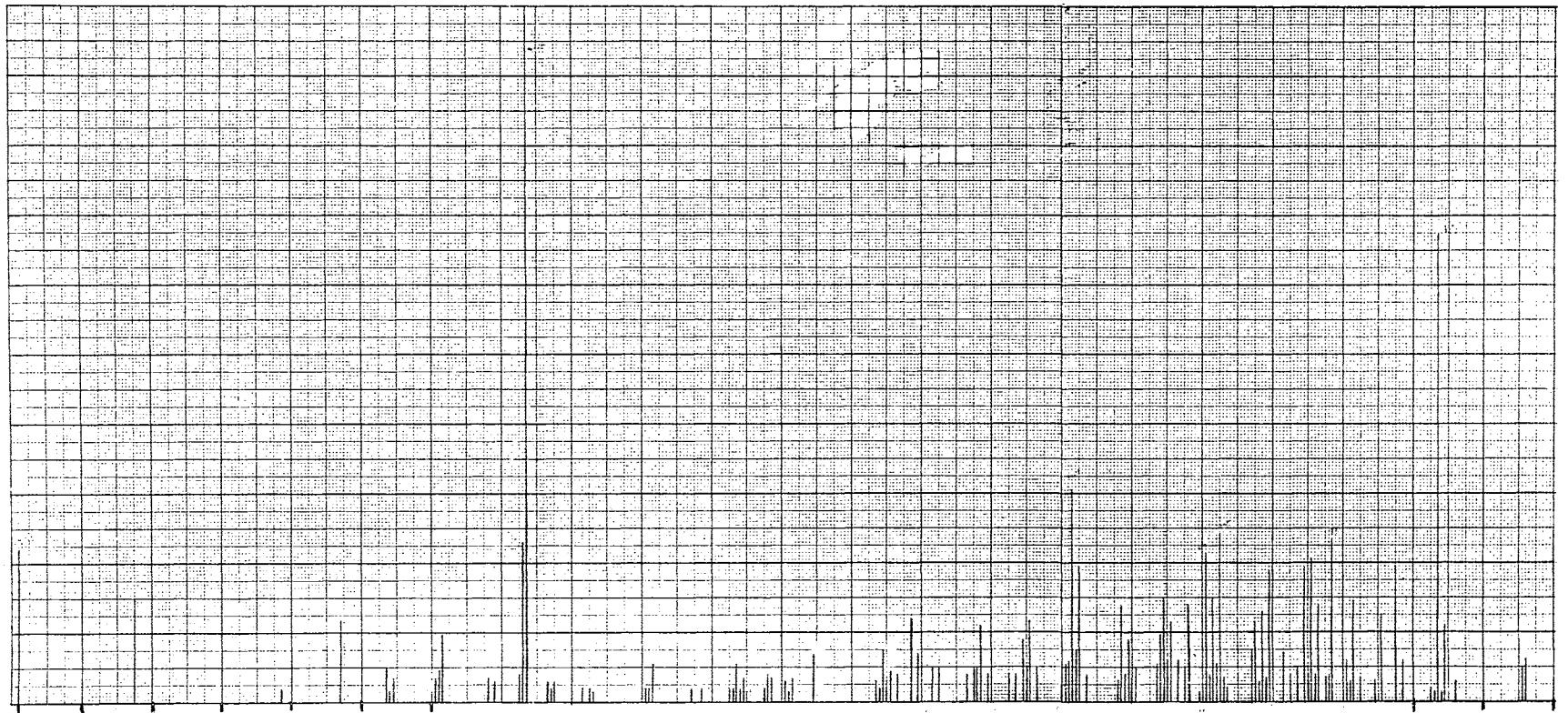
PLATE VIII

Mass Spectrum of LXXXII

PLATE IX

Mass Spectrum of LXXXIV

PLATE X



Mass Number

Mass Spectrum of LXXX

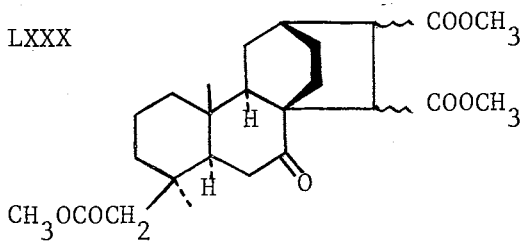
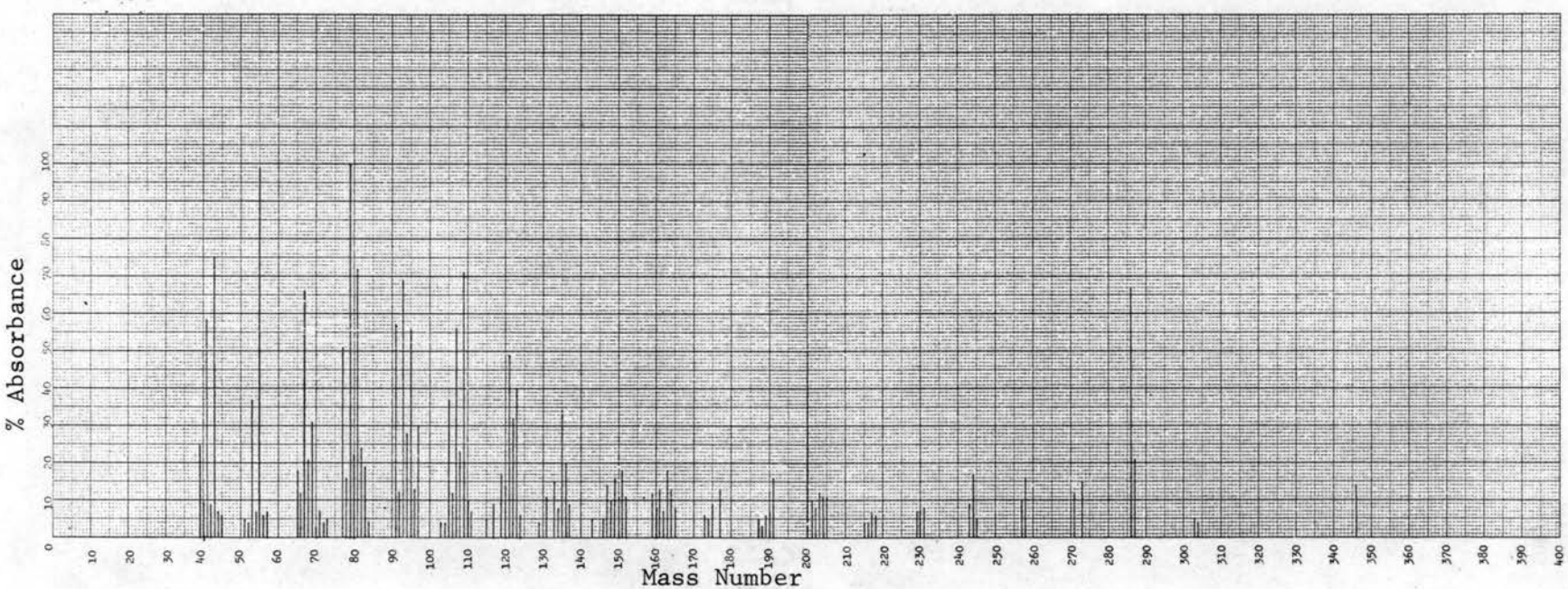


PLATE XI



Mass Spectrum of LXXXV

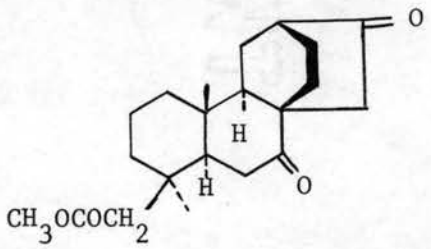
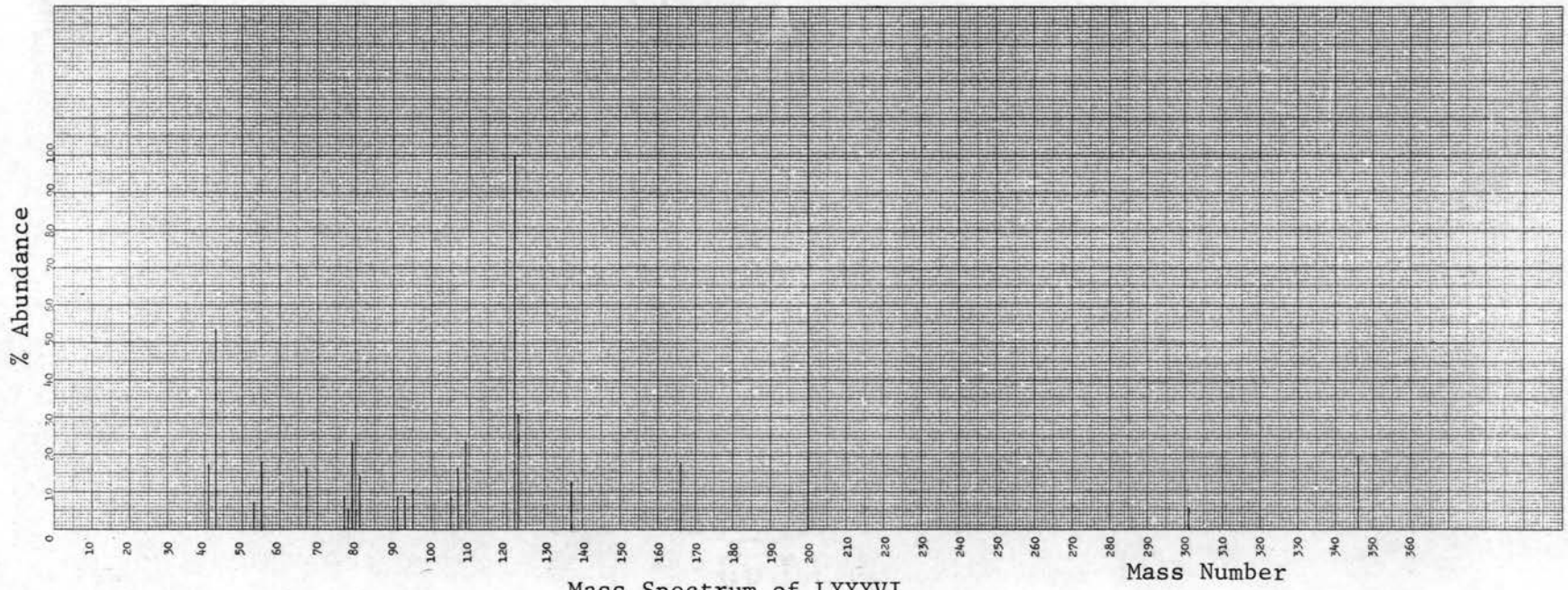


PLATE XII



Mass Spectrum of LXXXVI

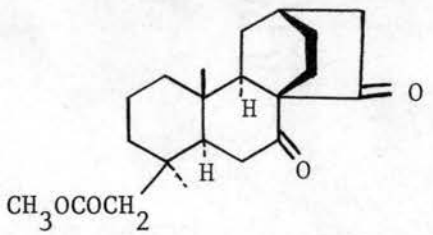
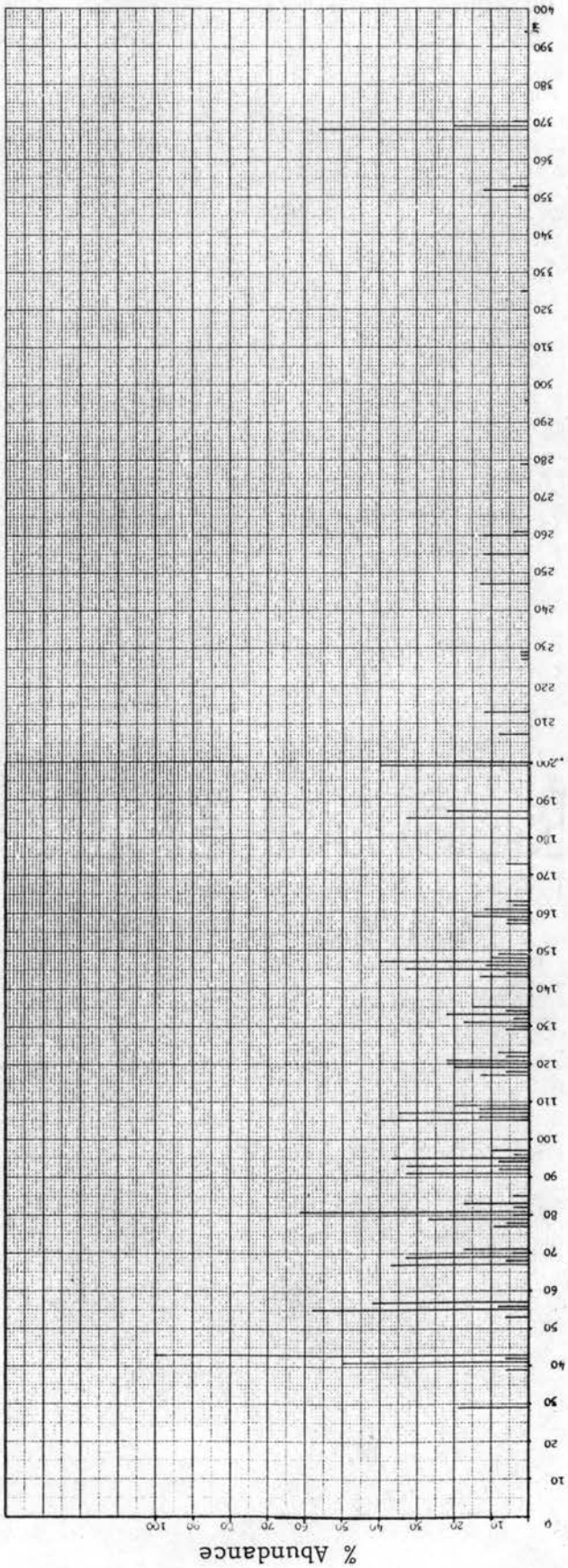
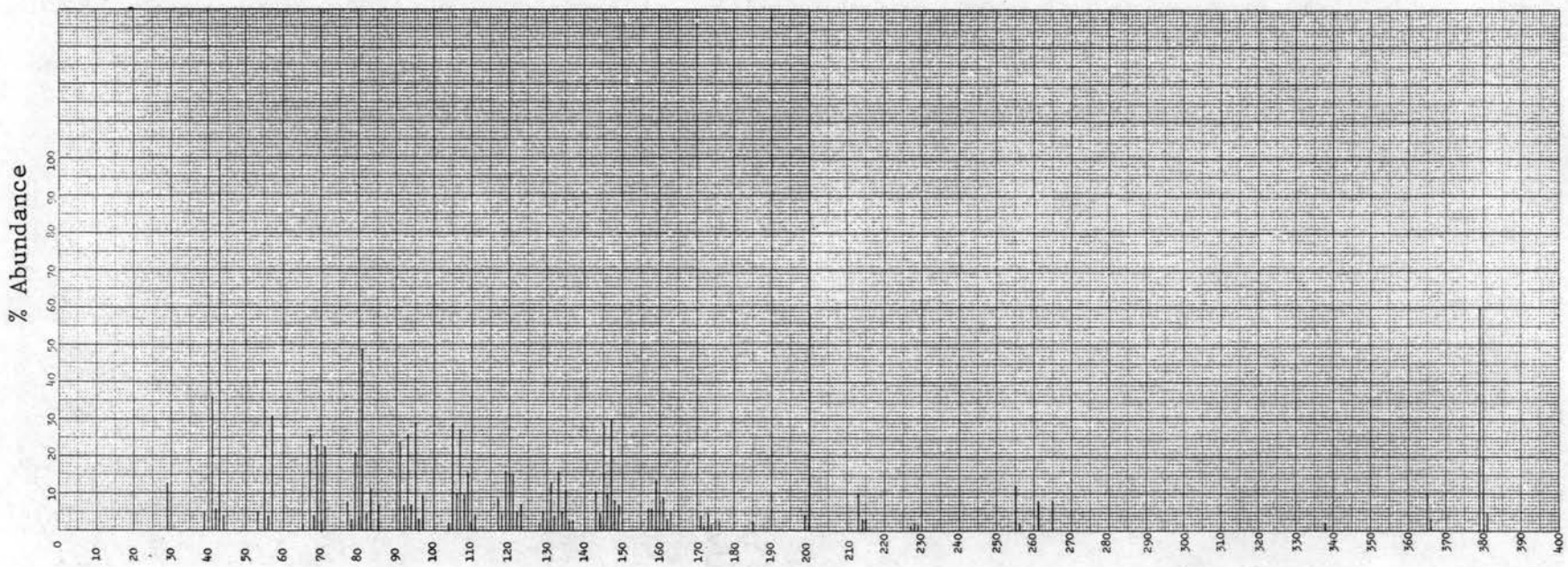


PLATE XIII



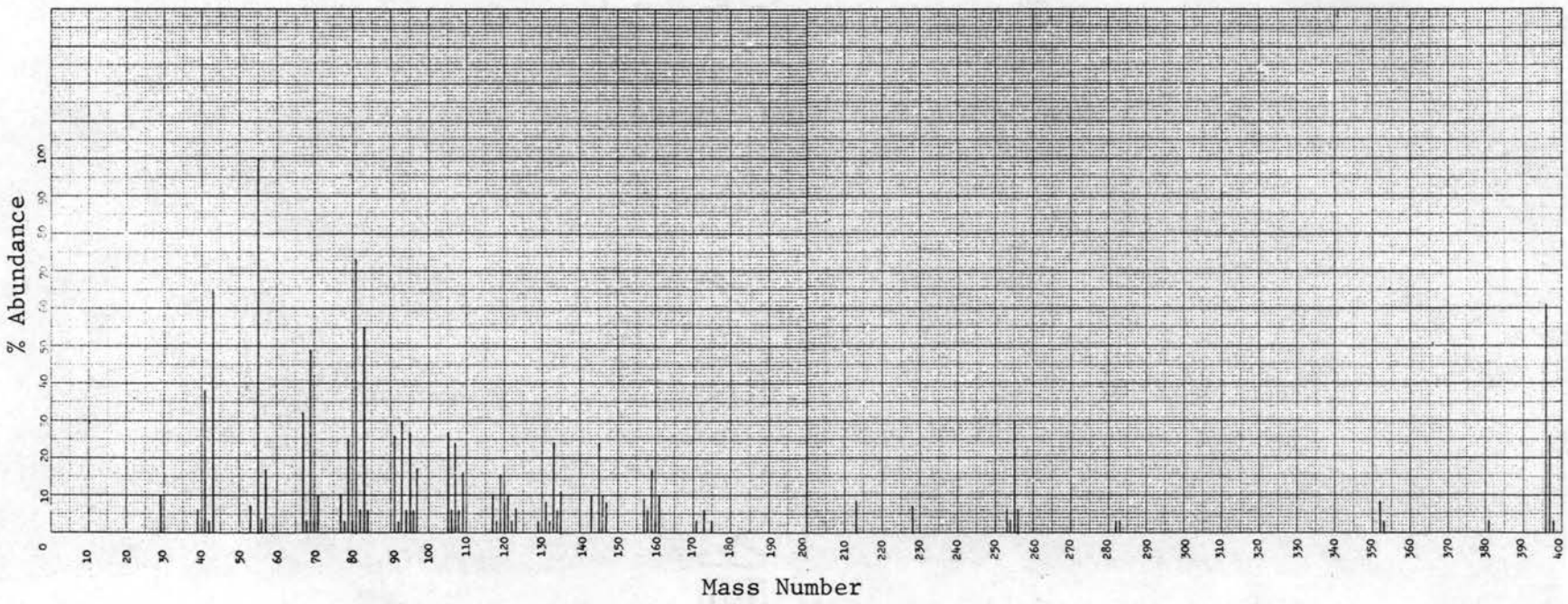
Mass Spectrum of Component A

PLATE XIV



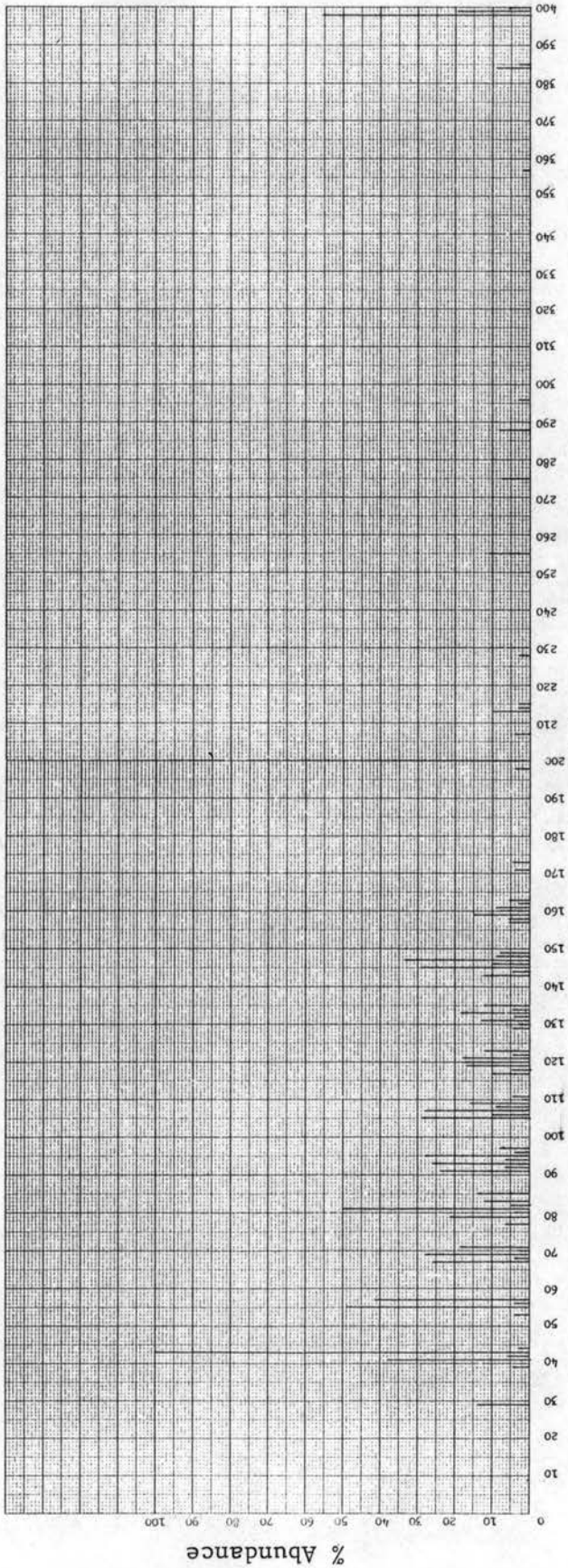
Mass Spectrum of Component B

Plate XV



Mass Spectrum of Component C

PLATE XVI



Mass Spectrum of Component D

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