STUDIES IN OXIDATIVE DECARBOXYLATION

By

OFELIA ANOCHE SERVANDO

Bachelor of Science

Silliman University

Dumaguete City, Philippines

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STUDIES IN OXIDATIVE DECARBOXYLATION

Thesis Approved:

Leon N. Zalkow
Thesis Adviser

A. A. Dermer

J. H. Boyer
Dean of the Graduate College

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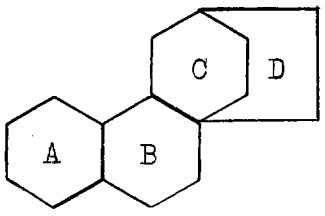
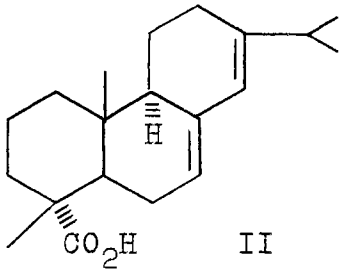
HISTORICAL AND INTRODUCTION

The synthesis of diterpenoid alkaloids which possess the bicyclo[2·2·2]octyl C, D ring system, I, has been the subject of investigation by many workers. Many synthetic pathways were used, one of which is through the Diels-Alder reaction between abietic acid, II, and various dienophiles (1, 2) such as maleic anhydride, III. The Diels-Alder adducts formed possess the carbon skeleton I, and may be transformed into the desired compounds by appropriate synthetic methods.

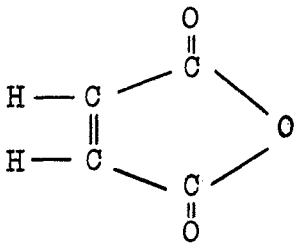
The most readily accessible Diels-Alder adduct of abietic acid is maleopimaric acid [the adduct with maleic anhydride] (1). Maleopimaric acid has been found to possess the stereochemistry depicted in IV (4-8). Maleopimaric acid and fumaropimaric acid, VI, [the adduct with fumaric acid, V] were used by Zalkow and Girotra (3, 7) as starting materials in the synthesis of compounds containing the carbon skeleton I.



I

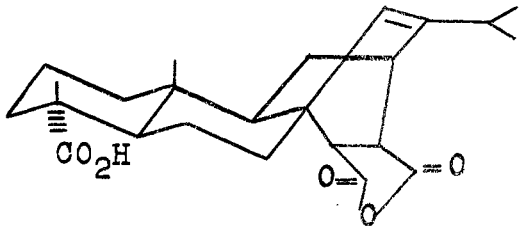


II



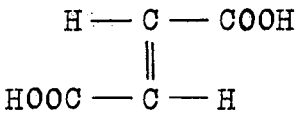
III

maleic anhydride



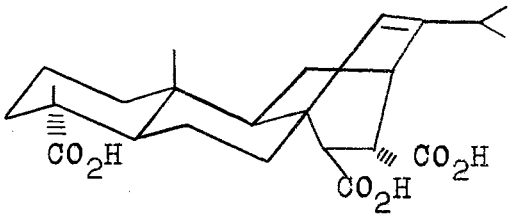
IV

maleopimaric acid



V

fumaric acid



VI

fumaropimaric acid

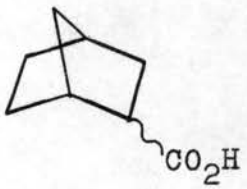
Compounds IV and VI, although having the desired carbon skeleton, I, contain such functional groups as the isopropyl and the D-ring carboxyl groups (or anhydride moiety) which are not present in the diterpenoid alkaloids to be synthesized. The use of compounds IV and VI in these synthetic studies therefore presents the problem of removing these functional groups.

An obvious method of removing the D-ring carboxyl groups or anhydride moiety from these Diels-Alder adducts is oxidative decarboxylation using tetravalent lead compounds. Detailed studies of oxidative decarboxylation using such oxidants have been reported only since 1952 when Doering and co-workers (9, 10) reported that 1,2-

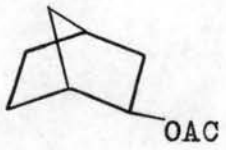
dicarboxylic acids yield olefins when treated with lead dioxide.

Doering's procedure was later applied by Beckman and Schaler (11) to decarboxylate anhydrides of dicarboxylic acids. In 1958 Grob (12, 13) reported an improved oxidative bisdecarboxylation procedure using lead tetraacetate in benzene or in acetonitrile in the presence of an organic base. Grovenstein (14) later modified Grob's procedure by using pyridine instead of benzene as a solvent for the lead tetraacetate oxidations.

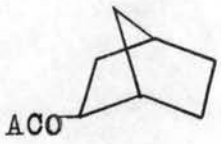
However, lead tetraacetate oxidations have furnished a variety of products, rather unforeseen in several instances, and mechanisms have been suggested that would lead to such products. For example, lead tetraacetate decarboxylation may result in products containing acetoxy groups, as was observed by Corey and Casanova (15), who obtained compounds VIII and IX by the lead tetraacetate oxidation of VII. The enantiomeric products VIII and IX were presumed to arise through a common carbonium ion intermediate.



VII



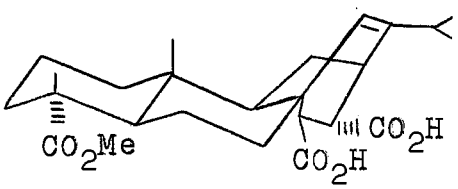
VIII



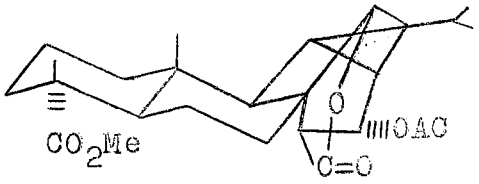
IX

Ayer and MacDonald (16) observed that decarboxylation with lead tetraacetate gave products resulting from ring rearrangement. Lead tetraacetate oxidation of X gave

lactone XI.



X



XI

Kochi (17) has recently presented evidence that the oxidative decarboxylation of organic acids with lead tetra-acetate proceeds via a free radical chain process, and lead triacetate is implicated as an intermediate. The following sequence was proposed for the oxidation of an organic acid, RCOOH:

$$Pb(O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3)_4 + RCOOH \longrightarrow Pb(O\text{-}\overset{O}{\overset{\|}{C}}\text{-}R)_4 + 4CH_3COOH$$

Initiation:

$$Pb(O_2CR)_4 \longrightarrow Pb(O_2CR)_3 + R\cdot + CO_2$$

Propagation

$$Pb(O_2CR)_3 \longrightarrow Pb(O_2CR)_2 + R\cdot + CO_2$$

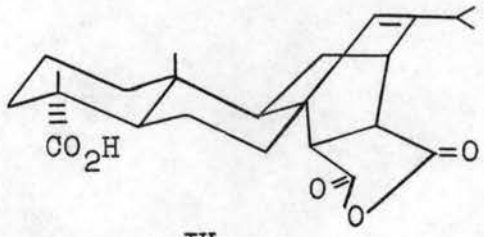
$$R\cdot + Pb(O_2CR)_4 \longrightarrow Pb(O_2CR)_2 + R^+ \text{ (esters, alkenes, etc)}$$

Termination

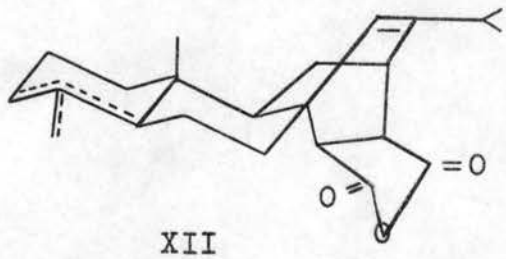
$$R\cdot + Pb(O_2CR)_3 \longrightarrow Pb(O_2CR)_2 + R^+ \text{ (esters, alkenes, etc)}$$

Kochi postulates that the spectrum of products obtainable with diverse acids is attributable to variation of the efficiencies of the initiation and propagation steps with the structure of the acid.

Maleopimaric acid, IV, was oxidatively decarboxylated with lead tetraacetate in pyridine to give the mixture of dienes, XII (18). Fumaropimaric acid, VI, under the same

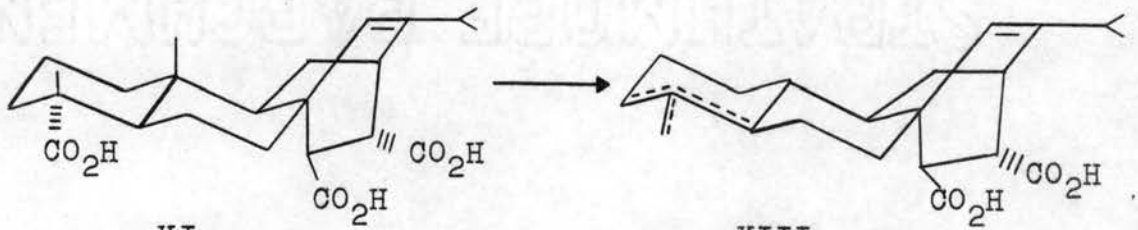


IV

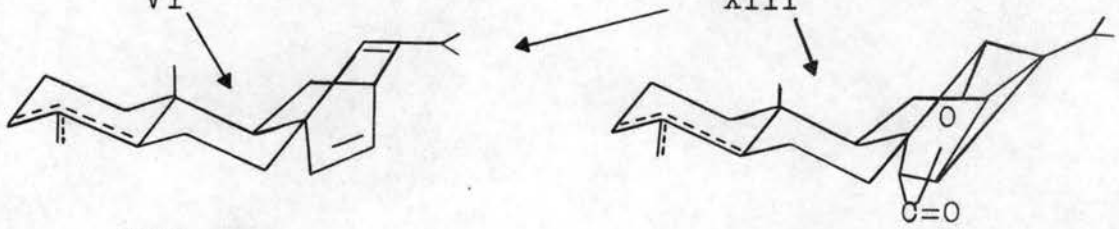


XII

conditions gave olefins XIII and XIV. Olefin XIII on further treatment with lead tetraacetate gave cyclopropyl lactone XV in addition to XIV (19). The aforementioned



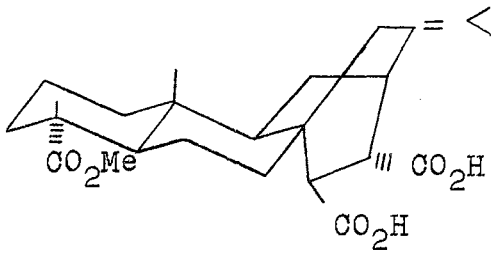
VI XIII



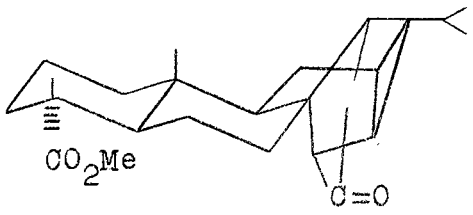
XIV XV

products were presumed to arise through a carbonium ion intermediate.

Methyl fumaropimarate, X, on treatment with lead tetraacetate gave XVI as the major product (18). The formation of XVI was rationalized as a concerted process

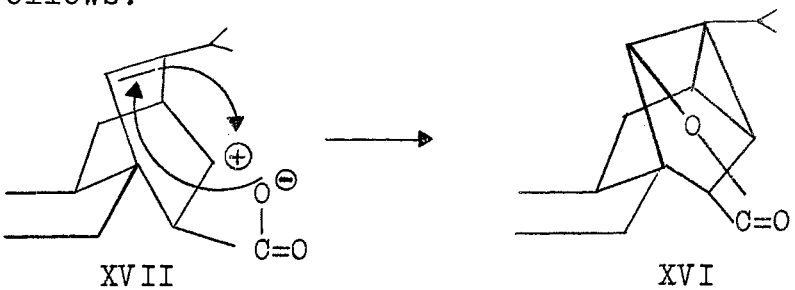


X



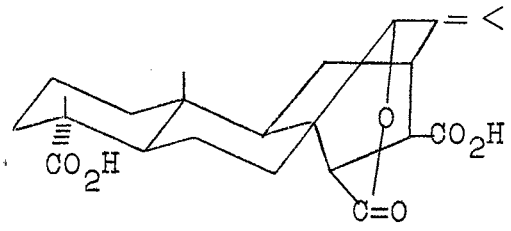
XVI

as follows:

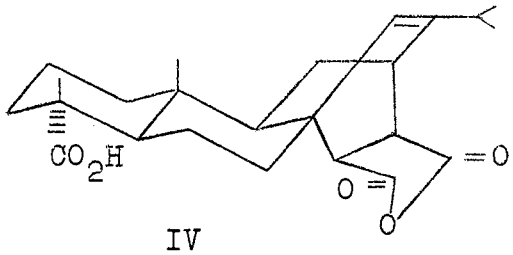


XVII XVI

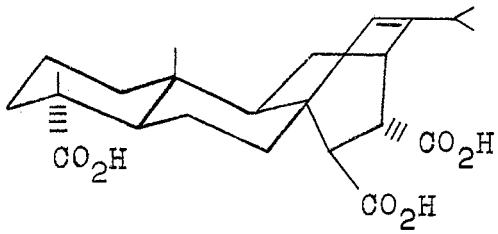
Compound XVIII, possessing a structure very close to maleopimaric acid, IV, and fumaropimaric acid, VI, was previously synthesized in this laboratory (19).



XVIII

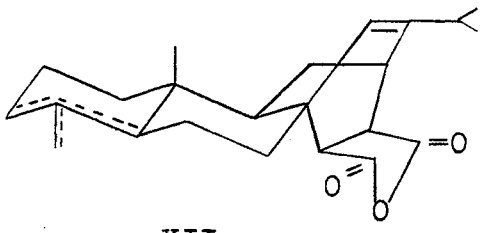


IV

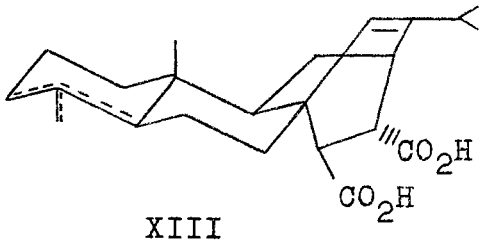


VI

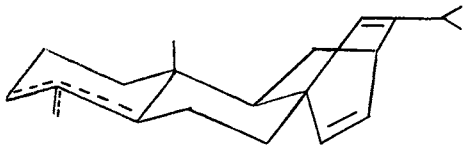
It might be recalled that the lead tetraacetate oxidation products of IV and VI gave an appreciable percentage of a complicated mixture of dienes XII, XIII, XIV and XV (18).



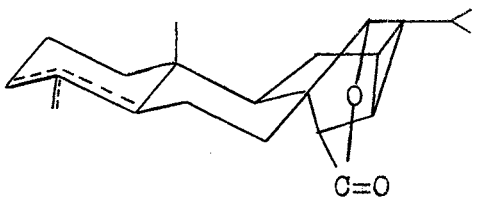
XII



XIII

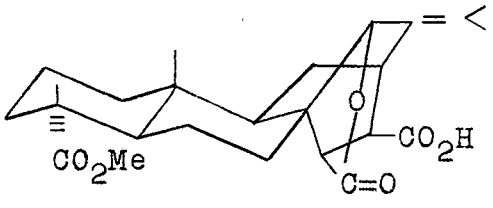


XIV

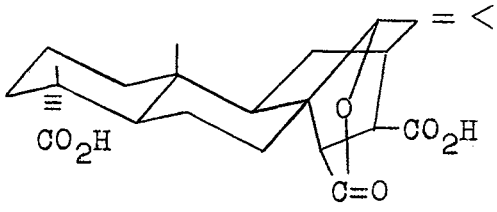


XV

Such mixtures of dienes could be avoided by transforming the C_4 carboxyl group of the compound to be oxidized into a carbomethoxy group. Therefore compound XX instead of XVIII was chosen for study. Compound XX, which contains a C_4 carbomethoxy group and a C_{15} carboxyl group, has not been previously prepared.

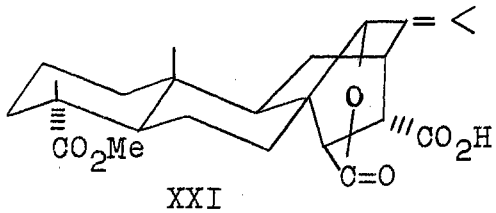


XX



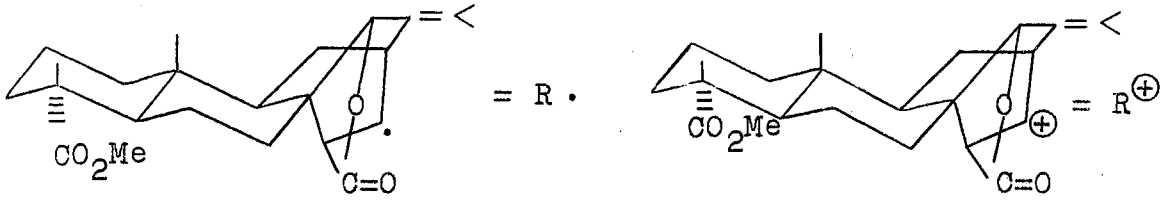
XVIII

It is interesting to speculate on the nature of the lead tetraacetate oxidation products of compound XX as well as those of its C_{15} epimer XXI. Following Kochi's (17)



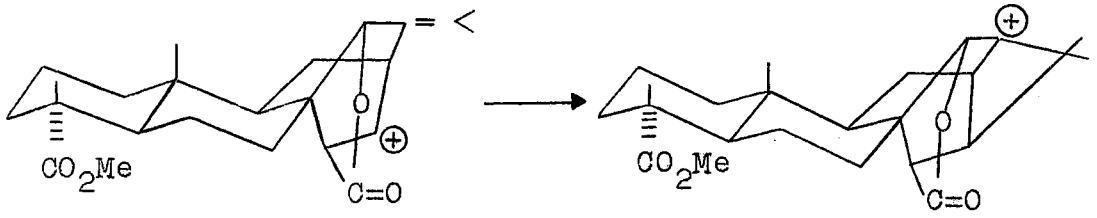
XXI

mechanism for the lead tetraacetate oxidation of organic acids, a number of oxidation products may be theoretically predicted from the oxidation of compounds XX and XXI. Both of these would give rise to the same free radical XXII, which in turn would generate the carbonium ion XXIII in the propagation step.

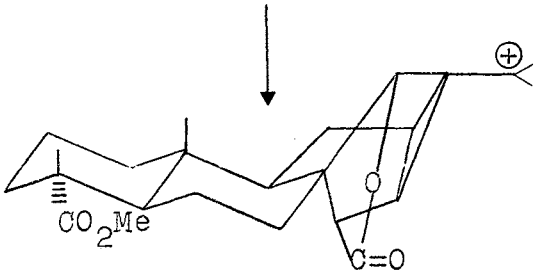


XXII XXIII

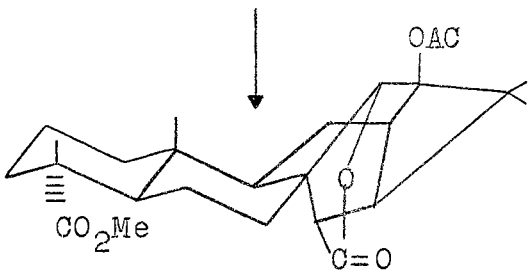
The carbonium ion XXIII may be stabilized in any of the following ways to give a variety of hypothetical products:



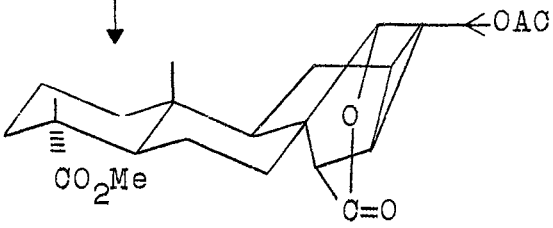
XXIII XXIV



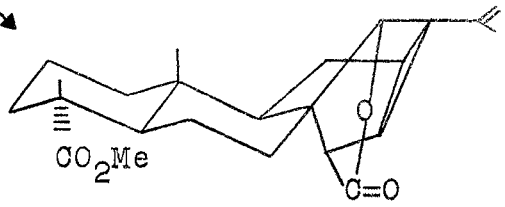
XXVI



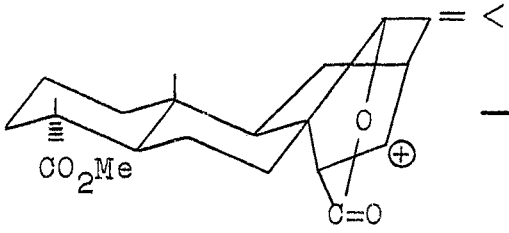
XXV



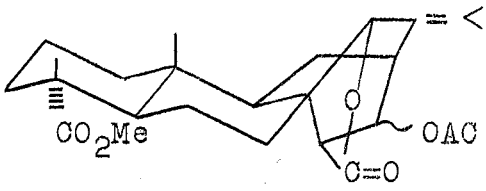
XXVIII



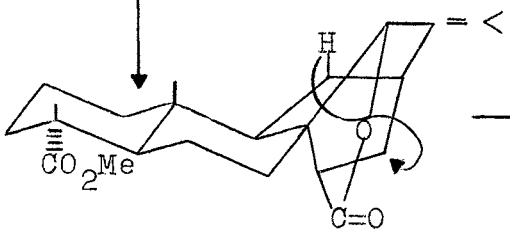
XXVII



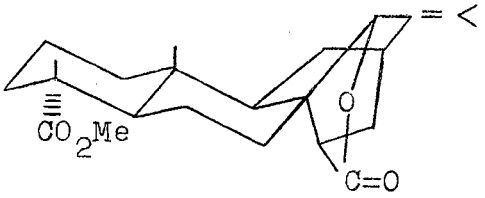
XVIII



XXIX

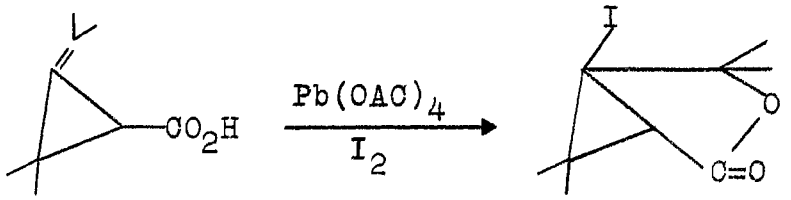


XXX



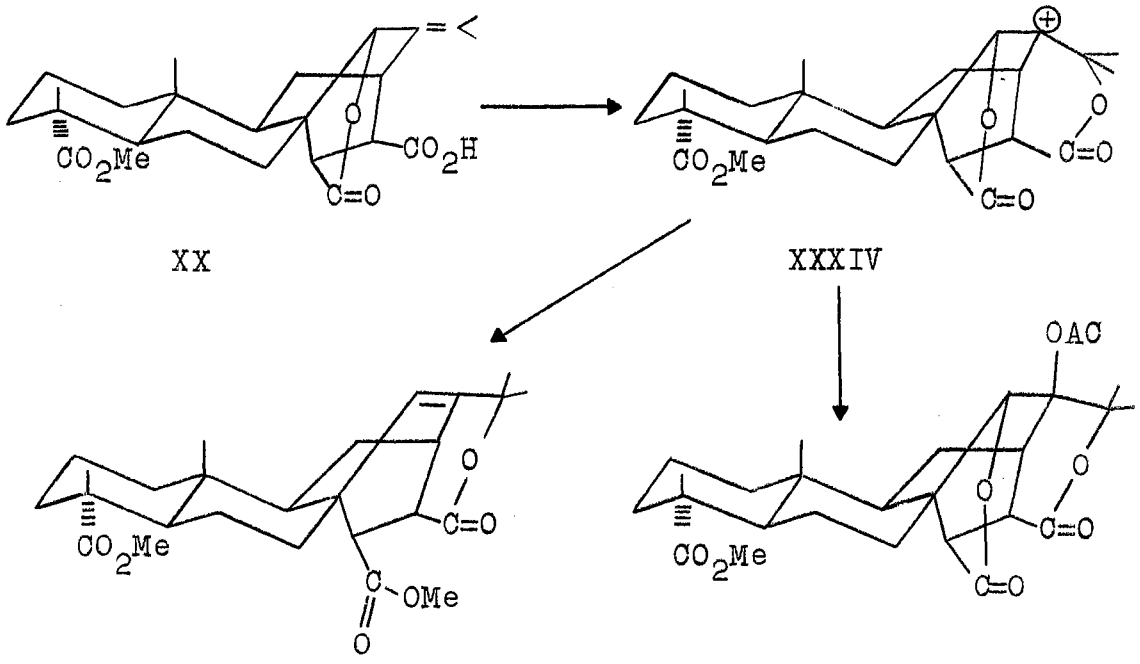
XXXI

Another oxidation product of compound XX is suggested by the decarboxylation of XXXII to give XXXIII (20).



XXXII XXXIII

Compound XX could by analogy react to give XXXIV which would ultimately give XXXV or XXXVI.



XX XXXIV

XXXV XXXVI

This research is concerned with the synthesis of XX, the reaction of XX with lead tetraacetate, and the isolation of a product formed by this reaction.

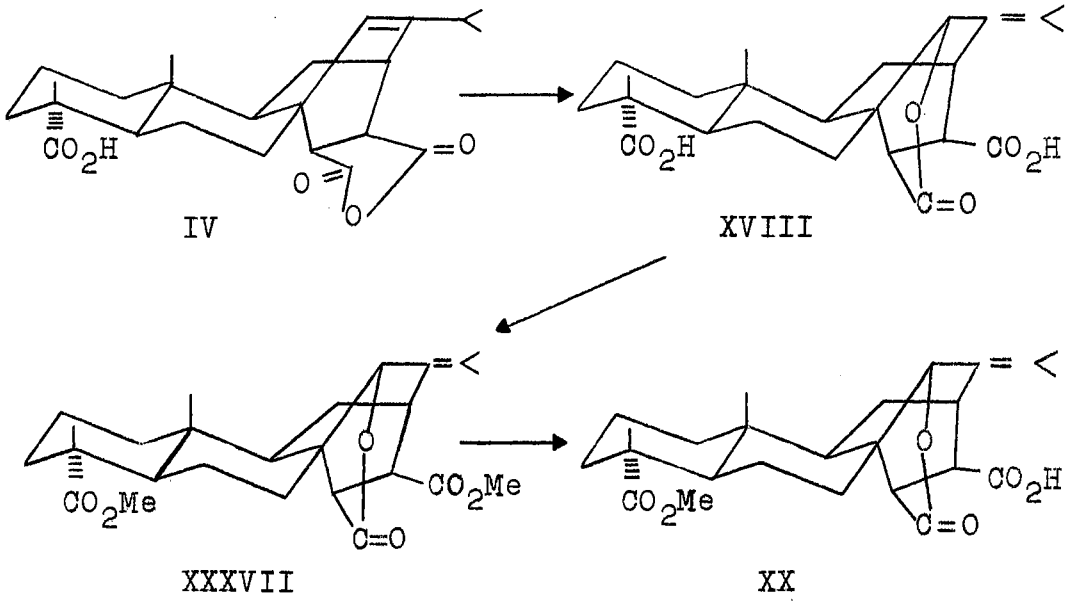
DISCUSSION AND RESULTS

A. Synthesis of Compound XX

Since compound XX has not previously been described, the first part of this research is concerned with its synthesis. Two synthetic pathways were tried but only one gave the desired compound in a readily isolable form.

1. Method I

The synthesis of compound XX has been accomplished by the following route:



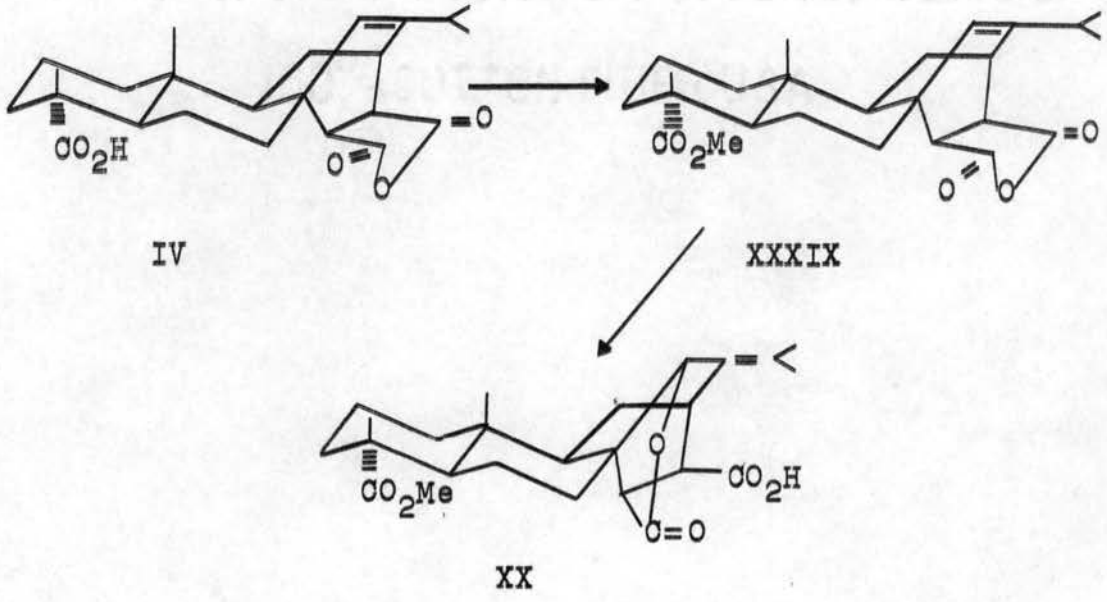
Alkaline permanganate oxidation of maleopimaric acid IV resulted in compound XVIII in 90% yield (19). Treatment of XVIII with ethereal diazomethane gave the dimethyl ester XXXVII.

Saponification of the dimethyl ester XXXVII was difficult without concomitant epimerization of the C_{15} carboxyl group or saponification of the C_4 carbomethoxy group. Selective saponification of the C_{15} carbomethoxy group of XXXVII was first attempted with methanolic sodium hydroxide solution. The NMR spectrum of the reaction product showed no carbomethoxy protons indicating that both the C_4 and C_{15} carbomethoxy groups had been saponified. It was therefore decided to try a milder reagent for saponification and a 10% aqueous potassium carbonate solution was chosen. Saponification with this reagent for 15 hours and acidification of the reaction product with cold 5% hydrochloric acid resulted in a precipitate, the IR spectrum of which showed acid absorption at 3000 - 3300 cm^{-1} and ester absorption at 1250 cm^{-1}. This material could not be purified by recrystallization from methanol, methanol-water, or benzene-petroleum ether mixtures. Three products were isolated by chromatography of the crude saponification mixture. The first product isolated by column chromatography was shown to be the diester XXXVII by comparison of its physical properties with those of an authentic sample (m.p., IR, NMR). The second product obtained from the column crystallized upon removal of the solvent and addition of petroleum ether and was assigned structure XX on the basis of the following evidence. Its infrared spectrum showed acid absorption at 3000 - 3300 cm^{-1} and ester absorption at 1250 cm^{-1}; its NMR spectrum showed 3 protons due to a carbo-

methoxy group. The third compound isolated from the column was shown to be the dicarboxylic acid XVIII by comparison of its physical properties with those of an authentic sample.

2. Method II

The desired compound XX could conceivably be prepared directly from methyl maleopimarate, XXXVIII, by alkaline permanganate oxidation. This would eliminate selective saponification of the dimethyl ester XXXVII obtained from the permanganate oxidation of maleopimaric acid IV and subsequent esterification. The following alternative route was therefore suggested for the synthesis of the desired compound XX.



IV XXXIX XX

An ethereal solution of maleopimaric acid IV was esterified with excess ethereal diazomethane to give the mono-methyl

ester XXXIX.

In order to prepare the desired compound XX from XXXIX, a modification had to be made in the permanganate oxidation of maleopimaric acid IV described in method I. Methyl maleopimarate XXXIX will not dissolve in sodium hydroxide solution at room temperature, whereas maleopimaric acid IV will do so readily. Therefore methyl maleopimarate XXXIX was first refluxed on a steam bath with sodium hydroxide solution until the resulting suspension became homogeneous. To determine whether methyl maleopimarate would undergo ring opening of the anhydride moiety under the above conditions without undergoing saponification of the C_4 carbomethoxy group or epimerization of the C_{15} or C_{16} carboxyl groups, a portion of the sodium hydroxide-methyl maleopimarate solution was acidified with cold 5% hydrochloric acid. The resulting precipitate which was recrystallized from ether was identical in melting point and in infrared spectrum to that of methyl maleopimarate XXXIX.

The remaining solution of sodium hydroxide-methyl maleopimarate was therefore oxidized with potassium permanganate under the previously described conditions (20). The oxidation product was worked up as usual to obtain a solid, the infrared and NMR spectra of which showed acid, ester and isopropylidene groups. All attempts to crystallize compound XX from the crude oxidation product failed. Thin layer chromatography showed only one spot. The crude acid was esterified with diazomethane, and the ester thus

obtained was chromatographed on a glass plate coated with a thin layer of silica gel. It showed 3 spots, proving the presence of at least three components. As it is quite improbable to obtain 3 products by the simple procedure of esterification of an acid, this fact at least indicates that the crude acid was a mixture of more than one component.

Finally, since the desired compound XX could not be crystallized from the crude permanganate oxidation product of methyl maleopimarate XXXIX and thin layer chromatography did not indicate the purity of the products obtained, it appeared to be more expedient to obtain compound XX by means of the procedure previously outlined in method I. In method I, the dimethyl ester XXXVII is readily crystallized from the crude permanganate oxidation product and thin layer chromatography can be used to separate the products obtained on saponification.

B. Lead Tetraacetate Oxidation of XX

Compound XX was prepared according to method I. Lead tetraacetate oxidation of XX was carried out under a nitrogen atmosphere using a measured excess of lead tetraacetate (5 moles of lead tetraacetate per mole of compound XX). Pyridine, twice distilled from potassium hydroxide, was used as the solvent and the temperature was maintained below 70° C.

The crude oxidation product was treated in the usual manner. The yellow partially crystalline solid which

crystallized from the ether extract was chromatographed over activity III alumina. The first product isolated came off in 1:12 ether-benzene eluent. This compound when crystallized from ether-petroleum ether, then from ether alone, had m.p. 248°. The analytical sample (m.p. 263-265°) was crystallized twice from ethyl acetate-skelly solve F. Thin layer chromatography showed 1 spot (R_f = 0.47). The infrared spectrum showed absorption due to lactone (1715 cm^{-1}) and ester (1775 cm^{-1}) groups. The NMR spectrum gave signals due to carbomethoxy (τ = 6.31), acetoxyl (τ = 8.175) and isopropylidene (τ = 8.26) groups. It is postulated that the compound is an acetate but further work has not been done to determine the position of attachment of the acetoxyl group.

The other products obtained from the chromatographic column have not been further investigated.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Incorporated, Indianapolis, Indiana. Infrared spectra were recorded with a Beckman IR-5 spectrometer and n.m.r. spectra were recorded with a Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ=0). Thin-layer chromatograms (TLC) were run on 35-μ-thick Silica Gel G-coated glass plates using 5:1 benzene-methyl acetate as the mobile phase unless otherwise indicated; iodine vapors were used for detection.

Maleopimaric Acid IV

Maleopimaric acid IV is commercially available from Distillation Products Industries, Eastman Kodak Company. The maleopimaric acid used in these experiments was crystallized several times from acetic acid and dried at 100 - 130° and 1 mm. and had the following properties: m.p. 229 - 230°; ν_{max}^{KBr} 1845, 1779, 1710 cm^{-1}.

Permanganate Oxidation of Maleopimaric Acid, IV. Preparation of Lactone XVIII

Lactone XVIII was prepared from maleopimaric acid, IV, as previously described (8).

Esterification of XVIII. Preparation of XXXVII

The dimethyl ester XXXVII was prepared from the lactone, XVIII, as previously described (8).

Saponification of XXXVII With Potassium Carbonate

Dimethyl ester XXXVII (9.0 g.) in 200 cc. of an aqueous 10% potassium carbonate solution was heated on a steam bath until the suspension became homogeneous. The solution was cooled, filtered, and the filtrate acidified with cold 5% hydrochloric acid. The resulting precipitate, 8.0 g., was collected by filtration and dried under vacuum at room temperature. γ_{max}^{KBr} 1250, 3000 - 3300 cm^{-1}. TLC showed this product to be a mixture of 3 compounds. This crude saponification mixture (18 g.) was chromatographed on 450 g. of BDH Silica-Gel slurried in benzene. The ether-benzene (2:1) eluent gave 13 g. of XX which crystallized from 3:1 ether-petroleum ether. m.p. 228 - 230°, γ_{max}^{mull} 1250, 3000 cm^{-1}, n.m.r. τ 6.31.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96

Found : C, 69.74; H, 7.89

The benzene eluent gave 1.9 g. of the starting material XXXVII as shown by comparison of its m.p. and IR and n.m.r. spectra with those of an authentic sample.

Ether-benzene eluent (4:1) gave 2.1 g. of a compound with spectral properties and m.p. corresponding to those of the diacid XVIII.

Preparation of Methyl Maleopimarate XXXIX

An ethereal solution of 20 g. of maleopimaric acid IV was esterified with excess ethereal diazomethane. Removal of ether and crystallization from methanol-water gave after drying at room temperature, compound XXXIX, m.p. 216 - 217°, γ_{max}^{mull} 1840, 1770, 1730 cm^{-1}.

Anal. Calcd. for $C_{24}H_{35}O_5$: C, 72.43; H, 8.27

Found : C, 72.56; H, 8.08

Permanganate Oxidation of XXXIX. Attempted Isolation of XX

To 10 g. of methyl maleopimarate XXXIX was added 200 cc. of a 10% aqueous sodium hydroxide solution and the resulting suspension was heated on a steam bath until the solution became homogeneous. A portion was acidifed with cold 5% hydrochloric acid solution. The resulting precipitate was filtered out and the collected solid dried and recrystallized from ether, m.p. 216 - 217°. The IR spectrum of this material was identical to that of methyl maleopimarate XXXIX.

The remaining solution of sodium hydroxide-methyl maleopimarate was oxidized with potassium permanganate under the previously used conditions (20). Some of the methyl maleopimarate began to precipitate from the solution upon cooling prior to the addition of the permanganate solution. The oxidation product was worked up as usual to obtain 8.2 g. of solid. All attempts to crystallize XX from this product failed.

Lead Tetraacetate Oxidation of XX

Compound XX (2.6 g.) dissolved in 40 cc. of pyridine twice distilled from potassium hydroxide was stirred under a nitrogen atmosphere at room temperature. Dry lead tetraacetate (3 g.) was added and the temperature slowly raised to 65° whereupon a vigorous evolution of gas was observed. When the reaction subsided, another 3 g. of lead tetraacetate was added. The addition of lead tetraacetate was continued until 15 g. had been added. The reaction mixture was cooled and the pyridine distilled off in a steam bath under vacuum. The residue was extracted with 200 cc. of ether in 50-cc. portions until the last ether extract was colorless. The residue was further treated with 200 cc. of 5% hydrochloric acid, filtered and the filtrate again extracted with 200 cc. of ether. The second ether extracts were combined with the first. The combined ether extract was concentrated to 50 cc. and washed twice with 50-cc. portions of 5% hydrochloric acid, then with 100 cc. of 5% sodium hydroxide. The ether layer was dried with magnesium sulfate, filtered and the ether removed by steam distillation to give 0.78 g. of crude product which was yellow and crystalline. This crude product was chromatographed on 45 g. of alumina (activity III) packed in benzene. An ether-benzene (1:12) eluent gave 0.50 g. of compound which crystallized from 1:3 ether-petroleum ether and then had m.p. 248 - 249°. TLC showed one major spot (R_f 0.30). Recrystallization from ethyl acetate-petroleum ether raised the m.p. to 263 - 265°. TLC showed one spot (R_f 0.47)

ν_{max}^{KBr} 1775, 1715, 1240 cm^{-1}. The n.m.r. spectrum gave signals at δ 0.8, 1.17, 1.74, 1.825, 2.8, 3.61, 5.5 and a broad peak centered at 5.212.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 70.25; H, 8.16

Found : C, 70.46; H, 7.93

SUMMARY

The dimethyl ester corresponding to the γ-lactone of 14-hydroxy-maleopimaric acid was prepared following a previously described procedure. Half saponification of the dimethyl ester was accomplished with aqueous potassium carbonate solution. The previously unprepared 4-carbomethoxy-14-hydroxymaleopimaric acid-γ-lactone (XX) was isolated by column chromatography as the major product. The selective saponification of the dimethyl ester was also attempted with sodium hydroxide solution but only resulted in a completely saponified compound.

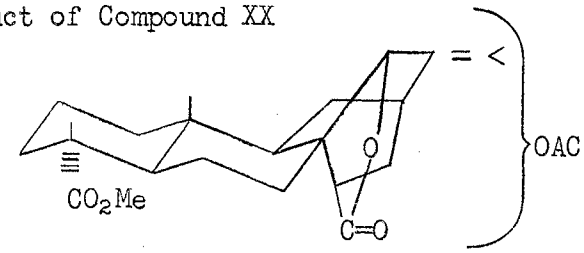
An alternative method of preparing XX was tried which eliminated the selective saponification of the dimethyl ester. An ethereal solution of maleopimaric acid was esterified with excess ethereal diazomethane to give the mono-methyl ester which was oxidized with alkaline potassium permanganate as described in the literature. A mixture of products was obtained which could neither be crystallized nor separated by thin-layer chromatography. Therefore, this alternative method was not used to prepare XX.

Compound XX was treated with lead tetraacetate. The mixture of products obtained was separated by column chromatography. The major product isolated from the

chromatographic column was identified as an acetate but the position of attachment of the acetate group to the rest of the molecule has not been determined.

Plate I

Infrared Spectrum of the Lead Tetraacetate Oxidation Product of Compound XX



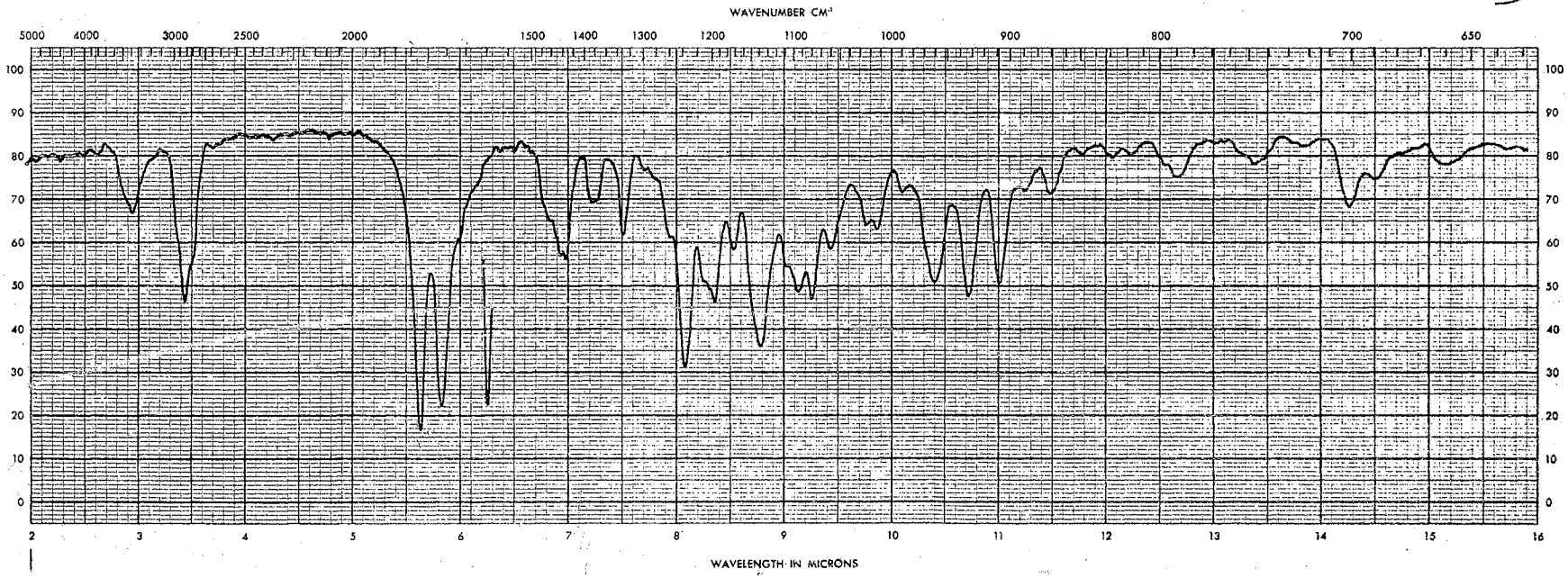
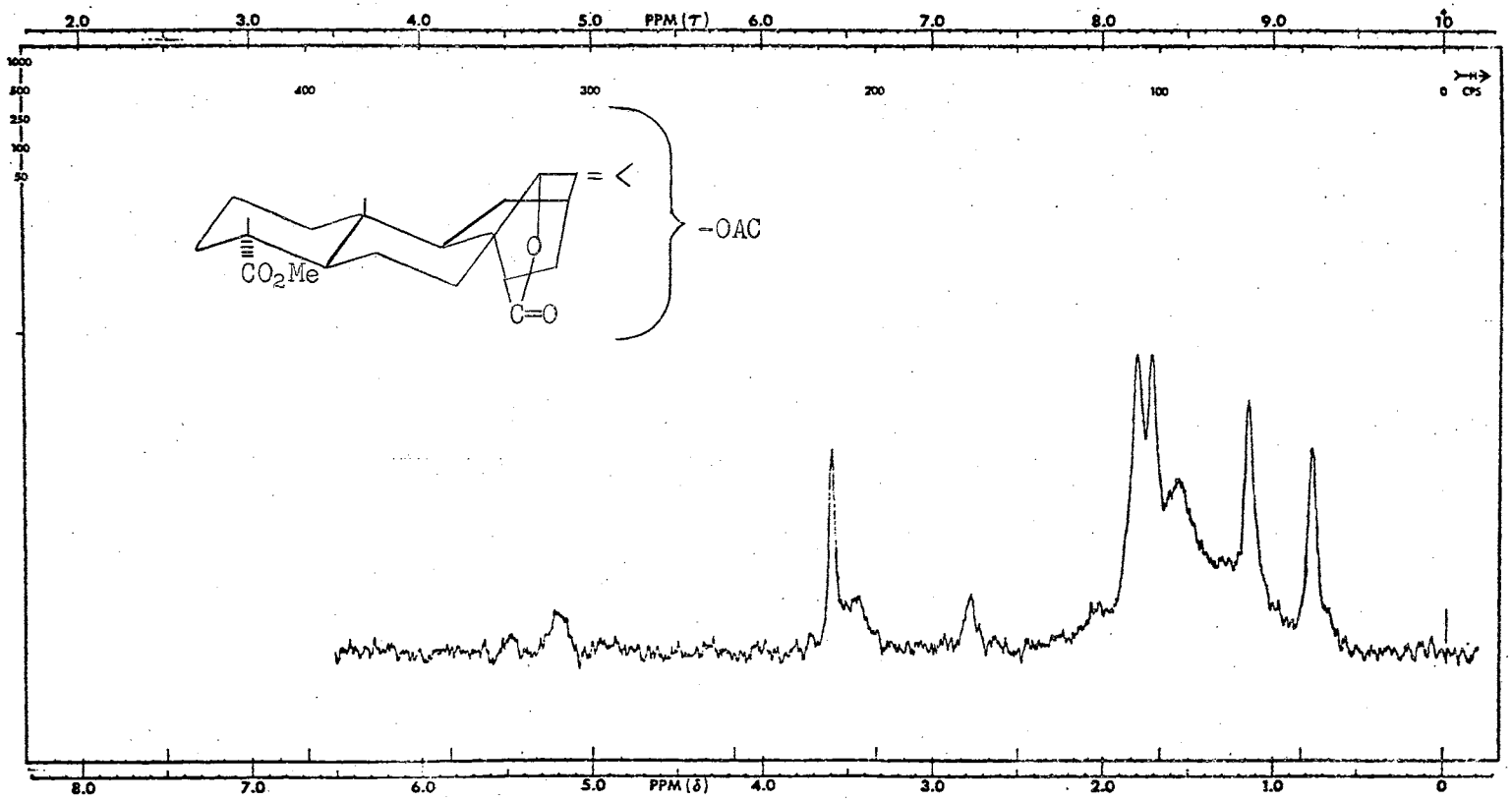


Plate II

Nuclear Magnetic Resonance Spectrum of the Lead Tetraacetate Oxidation Product of Compound XX



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VITA

Ofelia Anoche Servando

Candidate for the Degree of

Master of Science

Thesis: STUDIES IN OXIDATIVE DECARBOXYLATION

Major Field: Chemistry

Biographical:

Personal Data: Born in Bacolod City, Philippines, January 19, 1940 to Leopoldo L. and Magdalina Anoche. Married Edgar R. Servando, December 22, 1961. One child, Edgar Servando, Jr., born September 25, 1962.

Education: Graduated from Negros Occidental High School, Bacolod City, Philippines in 1955. Received the Bachelor of Science degree from Silliman University, Dumaguete City, Philippines with a major in Chemistry in 1959; completed the requirements for the Master of Science degree in May, 1966.

Professional Experience: Graduate teaching assistant, January, 1963 to August, 1965. Staff assistant, September, 1965 to May, 1966. All at Oklahoma State University.