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Iowa State University of Science and Technology
Ph.D., 1962
Chemistry, organic

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DERIVATIVES OF AROMATIC RESIN ACIDS

by

Richard William James Carney

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

1962

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DEDICATION

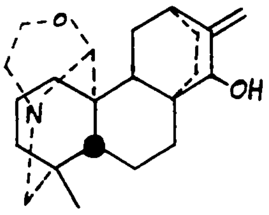
To Joyce, Lynda, Cathy
and
my parents

INTRODUCTION

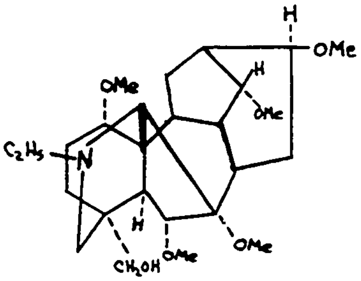
The purpose of the research here described is to initiate a study of the possible transformation of dehydroabietonitrile into a naturally occurring diterpenoid alkaloid, e.g. atisine, and to study the configuration and conformation of various derivatives of aromatic resin acids, especially of ring A-B *cis* derivatives.

HISTORICAL

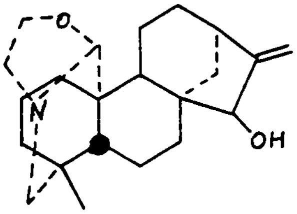
The diterpenoid alkaloid family can be divided into three groups of structurally related substances (1). The first two groups consist of alkaloids derived from the various species of Aconitum and Delphinium. One group is comprised of comparatively simple, non-oxygenated, nontoxic amino alcohols generally called the atisines. Atisine (I), from which the group derives its name, has been isolated from the roots of Aconitum heterophyllum (2,3,4). The second group called aconitines are much more toxic and are distinguished by many substituents (chiefly methoxy, hydroxy, and acyloxy groups). Lycoctonine (II), a member of this second group, has been extensively investigated in recent years (5,6,7,8,9). The third group consists of those diterpenoid alkaloids contained in the several species of



I



II

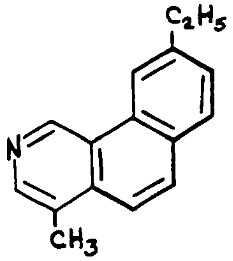


III

Garrya and are denoted by this name. Veatchine (III) derived from Garrya ventchii is isomeric with atisine. This similarity has aided in the clarification of the chemistry of these diterpenoid alkaloids.

A Degradation Product of Atisine

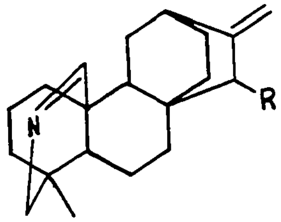
The dehydrogenation experiments by Lawson and Topps (10) and lately by Jacobs and Craig (11) yielded two products, a $C_{16}H_{15}N$ base IV and 1-methyl-6-ethylphenanthrene.



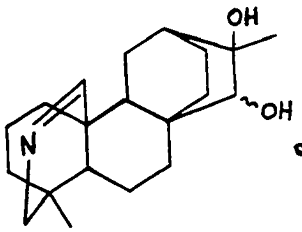
IV

These two compounds account for all but three carbon atoms of atisine and relate the heterocyclic ring of the alkaloid to the rest of its molecular framework. It was from this evidence as well as the similarities in the chemistry of atisine and of veatchine which led Wiesner (12) to propose structure I for atisine. However no rigorous proof had been presented for this structure until the studies of Edwards and coworkers (13,14,15).

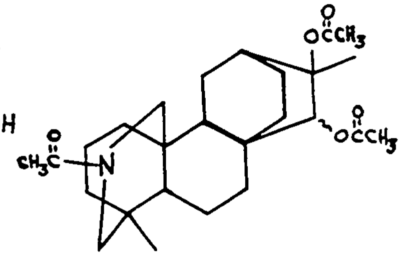
Dvornik and Edwards (13,14) have shown that when atisine hydrochloride is boiled with acetic anhydride an atisine diacetate hydrochloride is formed. Liberation of this hydrochloride and warming in non-polar solvents permits an unusual Hofmann degradation to occur yielding a C-20 azomethine acetate Va. Hydration of the exocyclic double bond of Vb gave the diol VI which on reduction and acetylation yielded VII. Partial hydrolysis and oxidation gave VIII which on treatment with trifluoroacetic acid followed by



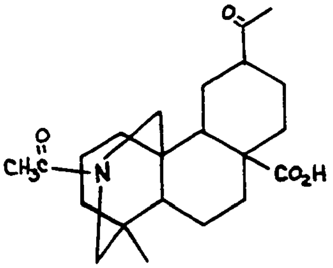
Va R = $OCOCH_3$
Vb R = OH



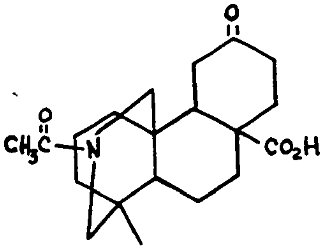
VI


$CH_3\overset{O}{C}$
N
$O\overset{O}{C}CH_3$
$O\overset{O}{C}CH_3$

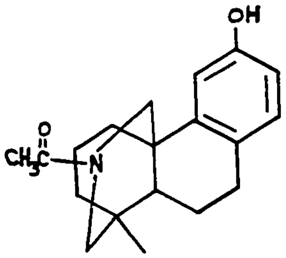
VII


$CH_3\overset{O}{C}$
N
O
CO_2H

VIII


$CH_3\overset{O}{C}$
N
O
CO_2H

IX


$CH_3\overset{O}{C}$
N
OH

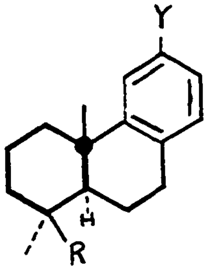
X

hydrolysis and dichromate oxidation yielded the keto acid IX. Dibromination of IX followed by dehydrohalogenation gave a crystalline phenol X.

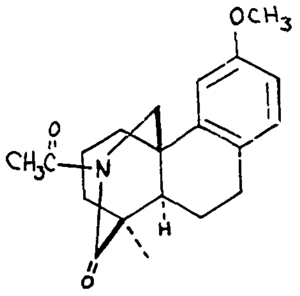
The optical rotation of the phenol X was found to be antipodal to that of podocarpic acid (15). The absolute configuration of atisine has recently been determined by Djerassi (16,17,18).

Partial Synthesis of a Degradation Product of Atisine

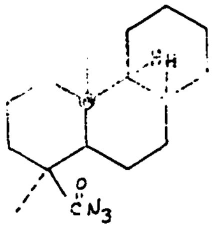
ApSimon and Edwards (19,20) reported the partial synthesis of the mirror image of the atisine degradation product X *via* a nitrene intermediate. The azide XIa of O-methyl-podocarpic acid (XIb) was prepared *via* the acid chloride and hydrazide. Photolysis of the azide XIa in hexane gave a 25% yield of a mixture of lactams. The δ-lactam predominated but a 5% yield of γ-lactam was also



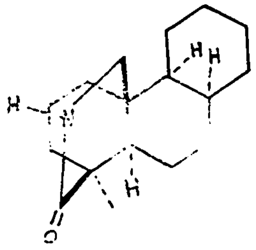
XIa R = CON_3 Y = OMe
XIb R = CO_2H Y = OMe
XIc R = CO_2Me Y = OH
XId R = CO_2H Y = OH
XIe R = CO_2Me Y = H
XIf R = CO_2H Y = H
XIg R = CH_2OH Y = H
XIh R = CH_2OH Y = OMe



XII



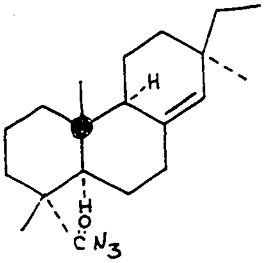
XIII



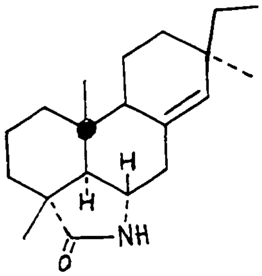
XIV

produced. Due to the absence of the high-field signal expected for the angular methyl group (C-10) in the p.m.r. spectrum structure XII was assigned to the δ-lactam.

The photolysis of XIII yielded 65% isocyanate (also obtained by refluxing the azide for one hour in hexane), 25% δ-lactam, and a trace of γ-lactam. The δ-lactam XIV was assigned on the basis of a p.m.r. spectrum. The signal for the angular methyl group (C-10) which appeared at 58 c.p.s. in the spectrum of the parent and 55 c.p.s. in that of the hydrazide was missing from the spectrum of the lactam (p.m.r. spectra of carbon tetrachloride solutions with tetramethylsilane as internal standard). When the azide XV from dihydropimaric acid was irradiated in hexane a 26% yield of the γ-lactam XVI resulted (20).



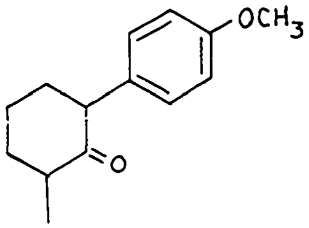
XV



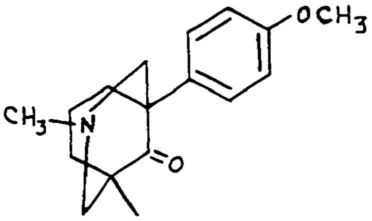
XVI

Iwai, Ogiso and Shimizu (21) have attempted the total synthesis of the skeleton of the atisine series of alkaloids by the following novel scheme.

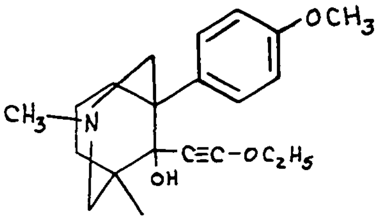
Formylation of 2-(p-methoxyphenyl) cyclohexanone with ethyl formate followed by hydrogenation gave the ketone XVII which with methylamine and formaldehyde gave the basic ketone XVIII. The ketone XVIII was reacted with ethoxyethyhyllithium to give XIX which was partially hydrogenated to give XX. Treatment of the ethoxyvinyl alcohol XX with phosphorus tribromide gave the α,β-unsaturated aldehyde XXI, which on catalytic reduction on palladium-charcoal gave two epimaric saturated aldehydes that could be separated by fractional crystallization. Reduction with lithium aluminum hydride afforded two epimeric alcohols which upon heating with polyphosphoric acid gave the epimeric phenanthrene derivatives XXII. Evidence for the relative



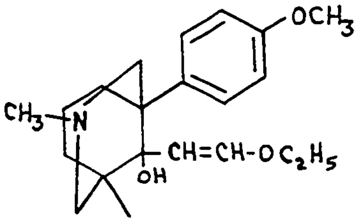
XVII



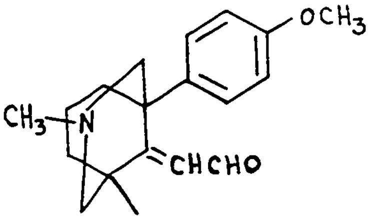
XVIII



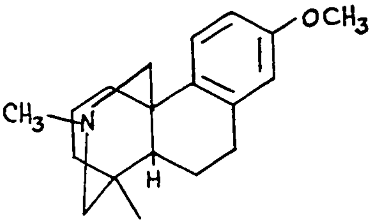
XIX



XX



XXI

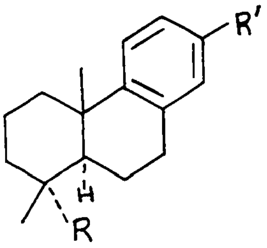


XXII

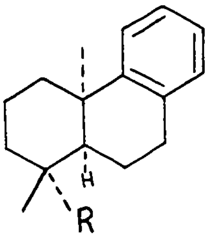
stereochemistry of C-5 was provided by the diagnostic test for A-B cis and trans ring juncture by Wenkert and Jackson (22).

Stereochemistry of A-B Ring Juncture

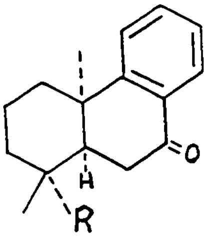
Wenkert and Jackson (22) found that dehydroabietonitrile (XXIIIa) was deisopropylated under the influence



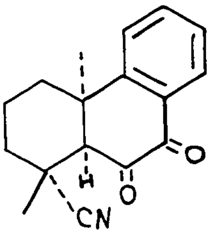
XXIIIa R = CN R' = i-Pro
XXIIIb R = CO_2Me R' = i-Pro
XXIIIc R = CO_2H R' = i-Pro
XXIIId R = CO_2Me R' = H
XXIIIe R = CN R' = H
XXIIIf R = CH_2OH R' = i-Pro



XXIVa R = CN
XXIVb R = CO_2Me
XXIVc R = CH_2NH_2
XXIVd R = CHO

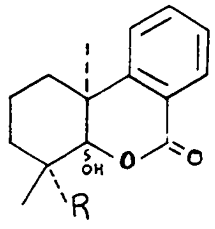


XXVa R = CN
XXVb R = CO_2Me

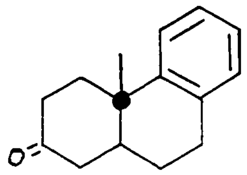


XXVI

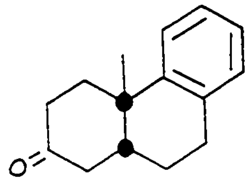
of aluminum chloride in benzene solution. The reaction led to a mixture whose major product proved to be XXIVa. Its oxidation by chromic acid yielded 26% ketone XXVa, 41% diketone XXVI, an acid, whose structure was shown later by Wenkert and Chamberlin (23) to be XXVIIa, and 22% starting material. When under identical oxidizing conditions none of the compounds XXIIIa, XXIIIb, XXIIIc, XXIIId, XXVIII, and XXIX gave α-diketone, it appeared that a new method for the determination of the stereochemistry of the A-B ring juncture in the 4,4-disubstituted hydrophenanthrenes had been uncovered and that the deisopropylation product possessed an A-B cis ring fusion.



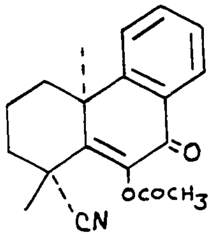
XXVIIa R = CN
XXVIIb R = CO_2Me



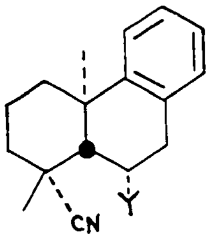
XXVIII



XXIX

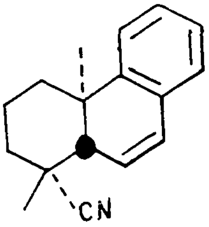


XXX

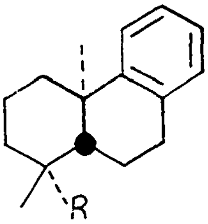


XXXla Y = $OCOCH_3$
XXXlb Y = OH
XXXlc Y = ONO

The A-B cis stereochemistry of the deisopropylation product was demonstrated in the following manner. The compound was converted into an enol acetate XXX which on catalytic hydrogenation gave a 6-acetoxy product XXXla. Mild pyrolysis produced a styrene XXXII which was hydrogenated to a dihydro derivative XXXIIIa isomeric with XXIIIe.



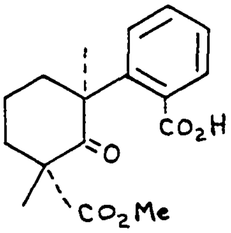
XXXII



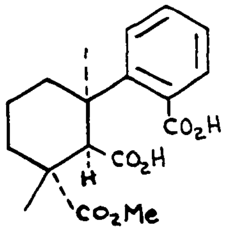
XXXIIIa R = CN
XXXIIIb R = CHO
XXXIIIc R = CH_2NH_2
XXXIIId R = CO_2H
XXXIIIe R = $CONHNH_2$

Study of the minor products of the deisopropylation of dehydroabietonitrile (XXIIIa) by Wenkert and Chamberlin (23) led to the isolation of XXIIIe, a stereoisomer of XXIVa. The minor product was exposed to chromic acid oxidation giving the 7-keto product, hence indicative of the presence of an A-B trans configuration.

Ohta and Ohmori (24,25) investigated the deisopropylation of dehydroabietic acid (XXIIIc) and showed that the reaction mixture consisted of two acids whose stereochemistry corresponded to the nitriles XXIVa and XXXIII. Subsequent chromic acid treatment of this mixture gave two ketones and one acid corresponding to those found by Wenkert and co-workers (22,23). Similar results were obtained when XXIVb was oxidized with chromic acid yielding XXVb, XXVIIb, and XXXIV.

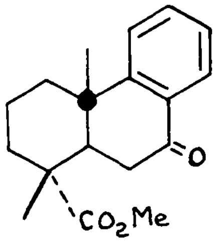


XXXIV

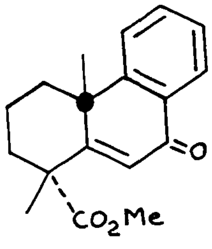


XXXV

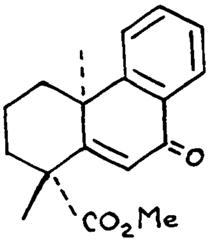
The structure of the oxidation product of methyl deisopyldehydroabietate (XXIIId), previously assumed (24,25) to be methyl 5-hydroxy-6,7-diketodeisopropyldehydroabietate (XXVIIb) was shown to be a 6,7-diketo compound by its oxidation to XXXV with alkaline hydrogen peroxide in the cold (26). Bromination of XXXVI and XXVb gave the 6-bromo



XXXVI

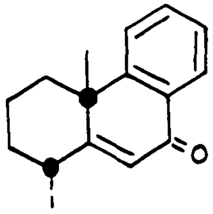


XXXVII

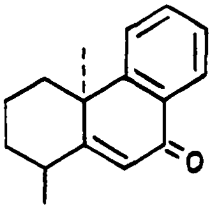


XXXVIII

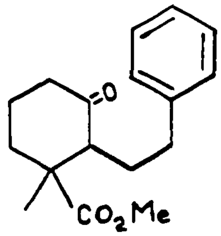
derivatives which were readily dehydrobrominated to give XXXVII and its isomer XXXVIII. During alkaline hydrolysis XXXVII and XXXVIII decarboxylated yielding XL and XLI.



XL



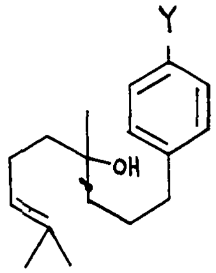
XLI



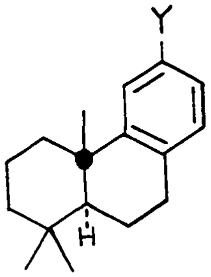
XLII

The stereochemical method of Wenkert and Jackson (22) has been used frequently (27,28,29,30,31,32). Ghatak and co-workers (27,28) were able to differentiate between two epimeric synthetic acids, dl-desoxypodocarpic acid and dl-cis-desoxypodocarpic acid by this method. Compound XLII obtained by hydrocyanic acid addition, hydrolysis, and esterification of the corresponding α-β unsaturated ketone was reacted with methyl magnesium iodide and dehydrated to give a complex mixture which was cyclized with polyphosphoric acid. Two crystalline acidic products were obtained and esterified. Upon oxidation with chromic acid the high-melting ester gave 50% methyl dl-7-ketodesoxypodocarpate thereby establishing the A-B trans juncture whereas the low melting ester gave a 27% yield of a yellow crystalline diketone ester. The diketo-ester was converted to the enol-acetate and catalytically hydrogenated to give the same high-melting ester thereby establishing the second isomer as *dl*-*cis*-desoxypodocarpic acid.

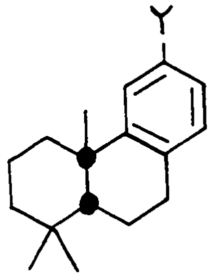
Fétizon and Delobelle (29,30,33,34) report that cyclization of XLIIIa gives XLIIIc and XLIVa as well as cyclizations of XLIIIb gives XLIIId and XLIVb. Oxidation of 64 g.



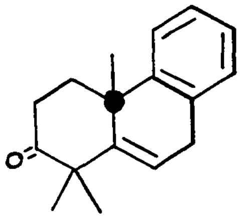
XLIIIa Y = OMe
XLIIIb Y = H



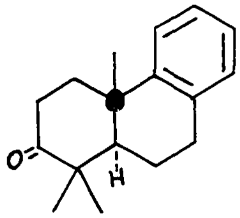
XLIIIc Y = OMe
XLIIId Y = H



XLIVa Y = OMe
XLIVb Y = H



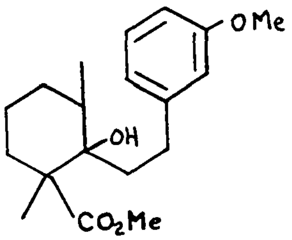
XLV



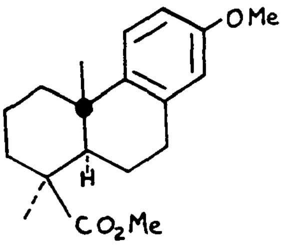
XLVI

of XLIIIc with chromic acid gave 65.5% monoketone and 6% diketone while 500 mg. of XLIIId gave 56.6% monoketone. Oxidation of XLIIIc gave 5.2% acidic material and 91% neutral material which was chromatographed on alumina resulting in 23.3% monoketone. Treatment of the d-isomer of XLIIIc with chromic acid gave 11% acidic material and 48.7% monoketone.

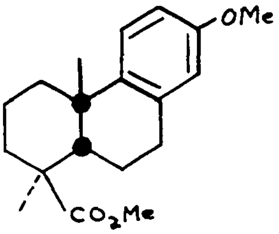
Oxidation of XLIVb yielded only 16% diketone. Catalytic reduction of XLV gave XLVI which on Huang-Minlon reduction gave XLIIId while Huang-Minlon reduction of XLV followed by catalytic reduction yielded XLIVb. Chromic acid oxidation of XLIVb obtained from this series of reductions yielded 44.7% diketone while oxidation of XLIIId yielded 47.8% monoketone.



XLVII

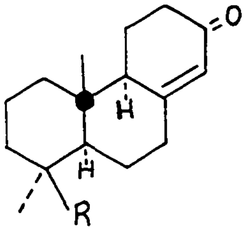


XLVIII

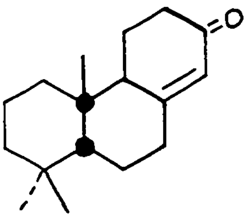


XLIX

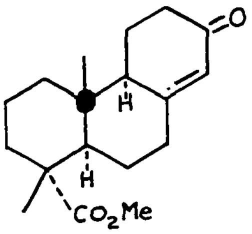
In the cyclization of XLVII with phosphoric oxide Barltrop and Day (31) found a mixture of two stereoisomeric tricyclic esters, XLVIII and XLIX which were separated by chromatography. Reduction of the aromatic ring of XLVIII with lithium-bronze afforded compounds La and Lb and on esterification gave Lc.



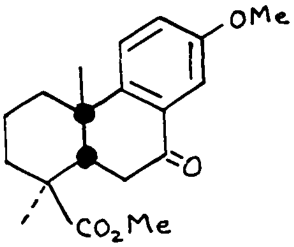
La R = CH_2OH
Lb R = CO_2H
Lc R = CO_2Me



LIa R = CH_2OH
LIb R = CO_2Me



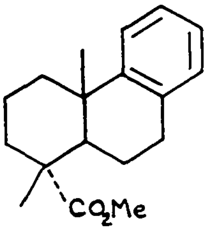
LII



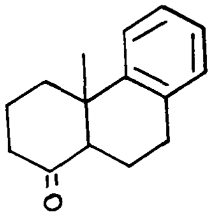
LIII

Similarly, reduction of ester XLIX by lithium-bronze gave a hydroxyketone LIa which on chromic acid oxidation and esterification yielded LIb. The synthetic keto-ester was not identical with the tricyclic keto-ester LII derived from neoabietic acid. Oxidation of XLIX with chromium trioxide gave 18% starting material, 10% acidic material, 11% LIII and the remainder was lost on an alumina column.

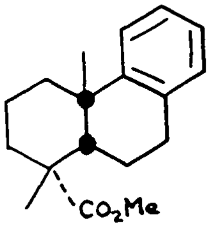
Saha, Ganguly and Dutta (32) applied the diagnostic test to ester LIV derived from condensation of ketone LV with ethyl cyanoacetate, addition of hydrocyanic acid, hydrolysis to the anhydride, formation of a half-ester,



LIV



LV

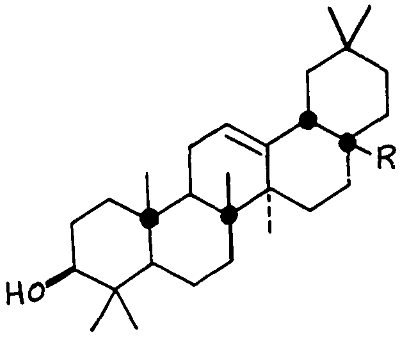


LVI

esterification to a diester, hydrolysis to a second half-ester, Hunsdiecker degradation of the resulting sodium salt and esterification. The ester obtained was subjected to the chromic acid oxidation and a 22% yield of a yellow diketo-ester, m.p. 185-187°, was obtained. No other products were reported. The configuration at C-4 was also assigned to the abietic acid series obtained by Ghatak (27). Therefore it was concluded that the above compound was cis-5-iso-deisopropyldehydroabietic acid.

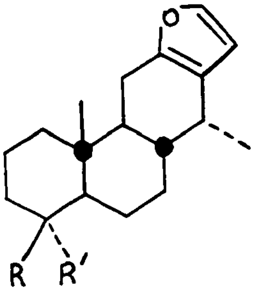
Stereochemistry at C-4

Wenkert and Jackson (35) proposed in 1958 a diagnostic tool, reductive hydrolysis, for differentiating axial from equatorial carboxyl groups in rigidly held ring systems. When methyl podocarpate (XIc) was exposed to lithium-liquid ammonia reduction, the product was mainly podocarpic acid (XId). Likewise methyl desoxypodocarpate (XIe), an axial ester, on reductive hydrolysis gave a 77% yield of the acid XIf and a 23% yield of alcohol XIg. Methyl oleanolate (LVIIa), a less sterically hindered axial ester yielded 68% oleanolic acid (LVIIb) and 28% erythrodiol (LVIIc). However, methyl dehydroabietate (XXIIIb), an equatorial ester, afforded 3% dehydroabietic acid (XXIIIc) and 62% dehydroabietol (XXIIIf).



LVIIa R = CO_2Me
LVIIb R = CO_2H
LVIIc R = CH_2OH

Wenkert and Beak (36) have recently described a new method for the determination of the stereochemistry at C-4 by converting the carboxy group to a primary alcohol and noting the differences of chemical shift of the hydroxymethyl group in the p.m.r. spectrum. The stereochemistry of the hydroxymethyl group was determined by observing that an axial group shows its quartet about 24 c.p.s. downfield from that of an equatorial group. The axial systems O-methylpodocarpol (XIh) and vouacapenol (LVIIIa) reveal their quartets at 221 c.p.s. (J = 11.3 c.p.s.) and 216 c.p.s. (J = 10.9 c.p.s.), respectively, while the equatorial compounds dehydroabietol (XXIIIf) and vinhaticol (LVIIIb) show four peaks centered at 197 c.p.s. (J = 10.4 c.p.s.) and 195 c.p.s. (J = 10.2 c.p.s.), respectively. On this basis hydroxytotarol with its AB quartet centered at 220 c.p.s. (J = 10.9 c.p.s.) was assigned an axial hydroxymethyl group. However, this method is limited to compounds possessing no



LVIIIa R = CH_2OH R' = Me
LVIIIb R = Me R' = CH_2OH
LVIIIc R = CO_2Me R' = Me
LVIIId R = Me R' = CO_2Me
LVIIIe R = Me R' = CHO
LVIIIf R = CHO R' = Me

other hydrogens which would yield signals in the hydroxymethyl region. In some cases inspection of the spectra of the carbinol acetates proved useful due to the appreciable downfield shift (37) of their methylene quartets as found in dehydroabietyl acetate, 230 c.p.s. (J = 10.5 c.p.s.) and O-methylpodocarpyl acetate, 250 c.p.s. (J = 11.3 c.p.s.).

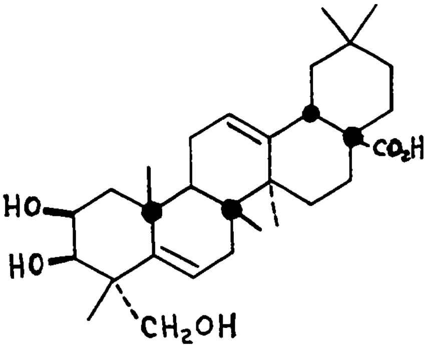
The absolute configuration of hydroxytotarol was also determined by Cambie and Mander (38) by comparing the hydroxymethyl C-O stretching vibration of hydroxytotarol (9.68μ) with those observed in compounds of the podocarpol series (9.66-9.68μ) which show a frequency shift from that in the abietol series (9.50μ).

King, Godson and King (39) report a difference of the rate of hydrolysis of axial and equatorial esters. Hydrolysis in 0.5 N ethanolic potassium hydroxide of methyl podocarpate (XIc) for 2 hours gave no acid, of methyl vouacapenate (LVIIIc) for 4.5 hours gave 1.3% acid, of methyl abietate (XXIIIb) for 2.25 hours gave 40.9% acid and of methyl vinhaticoate (LVIIId) for 2.25 hours gave 64.6% (calculated from ester numbers).

Hydrolysis of the ester XLVIII and XLIX was very difficult but comparative experiments (31) showed that ester XLVIII contained an ester group apprecially more hindered than that of ester XLIX. When heated with a 30% solution of potassium hydroxide in slightly aqueous ethylene glycol at 150° for 5 hours, ester XLVIII and XLIX gave 35% and 87% yields, respectively, of the corresponding acids.

Sherwood and Short (40) found that methyl O-methylpodocarpate was very resistant to hydrolysis and was unaffected by boiling 0.5 N alcoholic potassium hydroxide. But with excess of concentrated aqueous alcoholic potassium hydroxide at 150° for 4 hours almost complete hydrolysis was obtained.

In the structure study of bassic acid T. J. King and J. P. Yardley (41) found that the p.m.r. spectrum of the aldehyde of methyl dehydroisopropylidenebassate showed a singlet peak at 538 c.p.s., an unusually low value for an aldehyde (normal ca. 579 c.p.s.). They also indicated that this low value has stereochemical implications because the chemical shift for the aldehyde proton of the fully substituted equatorial aldehyde vinhatical (LVIIIe) (42) and its axial epimer vouacapenal (LVIIIf) (39) are 554 c.p.s. and 586 c.p.s., respectively.



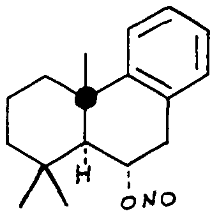
LIX

DISCUSSION

As a part of a series of reactions which were to transform dehydroabietonitrile (XXIIIa) into atisine (I), a naturally occurring diterpenoid alkaloid, a two-phase program was initiated. The key step to both schemes was that of irratiating an acid azide and a nitrite in order to form the E ring of the natural product.

The method of Wenkert and Jackson (22) was used to prepare desoxypodocarponitrile enantiomer (XXXIIIa), its oxidation product, 6,7-diketodesoxypodocarponitrile enantiomer (XXVI), and the latter's enol acetate XXX. Wenkert and Tahara (43) found that when large excess of palladium-on-carbon was used to reduce the enol acetate XXX a proportion of products different from that observed previously was obtained (22). Upon hydrogenation using a large excess of catalyst a yield of 54% desoxypodocarponitrile enantiomer (XXXIIIa) and 12% 6-acetoxydesoxypodocarponitrile enantiomer (XXXI) was obtained. Lithium aluminum hydride reduction of desoxypodocarponitrile (XXXIIIa) using only three-fourths of a mole of hydride and refluxing for one hour in tetrahydrofuran, followed by hydrolysis with 10% hydrochloric acid, yielded 90.5% desoxypodocarpal enantiomer (XXXIIIb) and 8.5% desoxypodocarpyl amine enantiomer (XXXIIIc). Oxidation of the aldehyde with alkaline hydrogen peroxide yielded only 20% acid XXXIIId, but upon potassium permanganate oxidation a 94% yield resulted. Desoxypodocarpic acid hydrazide enantiomer (XXXIIIe) was prepared by the formation of the corresponding acid chloride and treatment with 95% hydrazine hydrate dissolved in ethanol. The crystalline hydrazide could be purified easily by crystallization or sublimation. The photolysis was carried out on the azide, formed by nitrous acid treatment of the hydrazide in acetic acid followed by extraction into hexane, in the dried hexane solution by exposure to a Hanovia high pressure mercury arc lamp for one hour. The residue obtained after evaporation could be chromatographed on alumina to yield three compounds. One product gave an infrared absorption spectrum band at 4.40μ characteristic of isocyanates. Absorption at 5.94μ in the spectrum of the second compound indicated it to be a γ-lactam. The third compound gave a band at 6.05μ characteristic of a δ-lactam. While other pressing work did not permit complete characterization of these products, the results were compatible with those of ApSimon and Edwards (44,45) in their work on podocarpic acid (XId) (see Historical section).

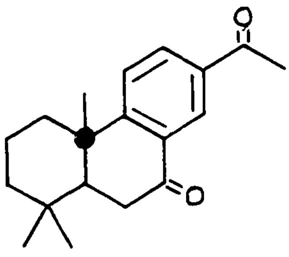
Another approach to the problem of ring-E formation lay in the possible use of the Barton reaction (46). Alkaline hydrolysis of 6-α-acetoxydesoxypodocarponitrile enantiomer (XXXIa) in ethanol gave good yields of 6-α-hydroxydesoxypodocarponitrile enantiomer (XXXIb). This hydroxy-nitrile could be nitrosated with nitrosyl chloride in pyridine to give the crystalline 6-α-nitrite XXXIc. Photolysis of this compound in dry benzene using a pyrex filter sleeve at 20° for a period of one hour gave a residue, after evaporation, which was refluxed with acetic anhydride. Chromatography of the products on acidic (pH 4-5) alumina, activity I, yielded 6-α-acetoxypodocarponitrile enantiomer (XXXIa). No other products were identified. Results obtained by Wenkert and Bredenberg (47) upon photolysis of LX indicate that the photolysis does follow the



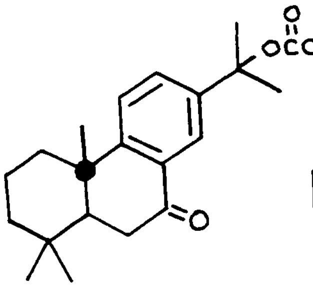
LX

alkoxy radical rearrangement mechanism the Barton reaction (46) to some extent giving a low yield of desired hydroxy aldoxime. The low yields of the Barton reaction in these two cases may be attributable to the presence of the neighboring benzylic methylene group. However, despite the extensive study of the Barton reaction by Kabasahalian and co-workers (48,49,50,51,52) no example of hydrogen migration between vicinal carbon atoms exists at this time.

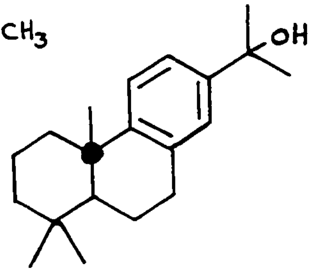
In connection with another study it became necessary to transform dehydroabietonitrile into variously substituted C-13 derivatives of deisopropyldehydroabietane. This was accomplished by lithium aluminum hydride reduction of dehydroabietonitrile (XXIIIa) to the imine followed by hydrolysis to the aldehyde which gave upon Huang-Minlon (53) reduction dehydroabietane. Chromic acid oxidation (54) gave two products, 7-keto-13-acetyldeisopropyldehydroabietane (LXI) and 7-keto-5-acetoxydehydroabietane (LXII). Huang-Minlon reduction of LXII yielded LXIII. While attempted dehydration of LXIII with phosphorous pentoxide in hexane (55) was poor, the use of phosphorous oxychloride in pyridine which gave up to 40% yield of olefin. Following the



LXI

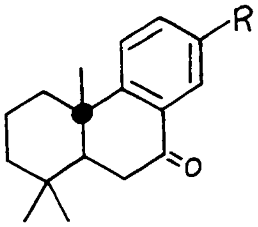


LXII

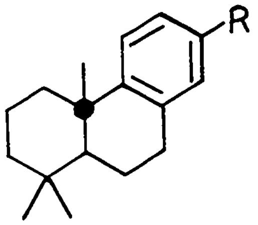


LXIII

method of Ohta (56), I was treated with iodine in anhydrous pyridine and thereupon hydrolyzed with alkali. The resulting acid LXIVa was esterified to LXIVb. Huang-Minlon reduction of the keto-acid LXIVa gave LXVa, which on esterification yielded LXVb. Treatment of LXVb with excess methylmagnesium iodide (57) gave LXIII which was identical in all respects with the compound formed from Huang-Minlon reduction of LXII.



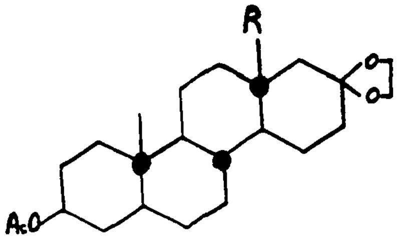
LXIVa R = CO_2H
LXIVb R = CO_2Me



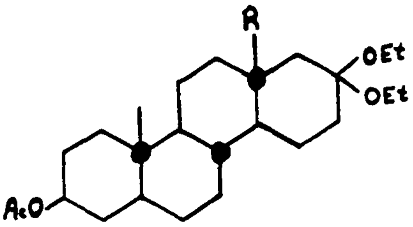
LXVa R = CO_2H
LXVb R = CO_2Me

The conversion of nitriles to aldehydes is a synthetic route of considerable importance (58). Brown et al. (59) have been able to convert nitriles to aldehydes by a variety of different lithium alumino-hydrides. Lithium aluminum hydride reduction of steroidal cyano-derivatives has been reported by Nagata (60).

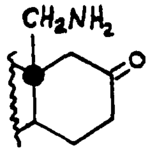
Reduction of LXVIa with excess lithium aluminum hydride has been reported to give only the aldehyde LXVIb. However,



LXVIa R = CN
LXVIb R = CHO



LXVIIa R = CN
LXVIIb R = CHO
LXVIIc R = CH_2NH_2



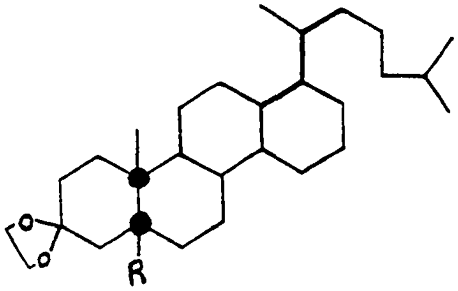
LXVIII

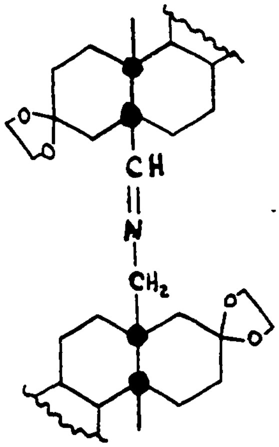
with the corresponding diethylketal LXVIIa both the aldehyde LXVIIb and amine LXVIIc were produced. The difference of results was attributed to a difference in the stability of the presumed intermediate imino-aluminum-ketal complexes in the two cases.

Reduction of LXIXa in tetrahydrofuran at 0° for 30 minutes and 25° for 3 hours using 0.56 moles of lithium aluminum hydride gave, after exposure to 2N sodium hydroxide for 5 minutes, aldehyde LXIXb, amine LXIXc, and the "dimeric" imino LXX.

Table I. Percentage of Products from Lithium Aluminum Hydride Reductions of Diterpenoid Nitriles

	XXXIIIa	XXIVa	XXIIIa
aldehyde	90.5	45.6	43.2
amine	8.5	47.8	52.2



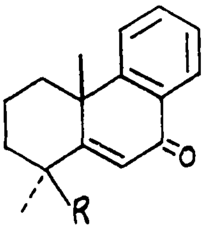


LXIXa R = CN
LXIXb R = CHO
LXIXc R = CH_2NH_2

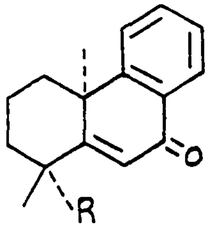
LXX

Reduction of desoxypodocarponitrile enantiomer XXX (XXXIIIa) with 0.74 moles of lithium aluminum hydride in tetrahydrofuran gives 90.5% of the aldehyde XXXIIIb and only 8.5% amine XXXIIIc, whereas almost equal amounts of aldehyde and amine are produced in the case of XXIVa and XXIIIa (see Table I). However, when XXIVa is reduced with lithium aluminum hydride in ether followed by mild hydrolysis only a "dimeric" imine was obtained which could be hydrolysed under more stringent conditions to the amine XXIVc and aldehyde XXIVd (110).

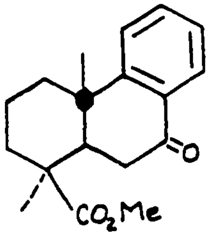
In connection with another study we needed to prepare both LXXIa and LXXIb. Podocarpic acid was desoxygenated and then oxidized by chromic acid (22) to methyl 7-keto-desoxypodocarpate (LXXIII). Selenium dioxide oxidation of this material gave almost quantitative yield of the enone ester LXXIb. Hydrolysis of LXXIb with ethanolic potassium hydroxide (25) resulted in poor yields. However, on treatment with anhydrous lithium iodide in refluxing collidine (61) a quantitative yield of the decarboxylated compound LXXIa was obtained.



LXXIa R = H
LXXIb R = CO_2Me

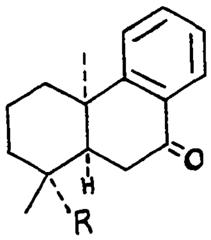


LXXIIa R = H
LXXIIb R = CO_2Me
LXXIIc R = CN



LXXIII

Compound LXXIIa was prepared by first preparing LXXIIIa by aluminum chloride treatment of dehydroabietonitrile (22) followed by chromic acid oxidation (22,24). Preparation

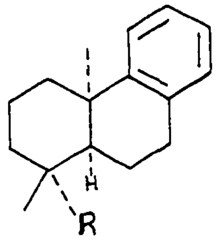


LXXIIIa R = CN
LXXIIIb R = CO_2Me

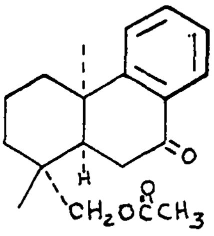
of LXXIIc by selenium dioxide oxidation of LXXIIIa gave only about 40% of the desired enone nitrile LXXIIc along with 25% 6,7-diketone. Since hydrolysis and decarboxylation of LXXIIc could not be accomplished, a more desirable pathway was followed.

Methyl 7-keto-5-isodesoxypodocarpate enantiomer (LXXIIIb) could be obtained by hydrolysis, esterification and chromic acid oxidation (24) of 5-isodesoxypodocarponitrile enantiomer (XXIVa). Upon treatment of LXXIIIb with excess selenium dioxide in both refluxing acetic acid or refluxing nitrobenzene over a 16-hour period failed to give any α-β unsaturated keto ester LXXIIb. Therefore, LXXIIIb was brominated and dehydrobrominated to yield LXXIIb (25). Treatment of LXXIIb as before with anhydrous lithium iodide in refluxing collidine yielded the desired decarboxylated material LXXIIa.

For another study, to be discussed presently, it was necessary to prepare several other derivatives of the A-B cis-podocarpic acid enantiomer system. Lithium aluminum hydride reduction of LXXIVa yielded both LXXIVb and LXXIVc. Huang-Minlon reduction of LXXIVb gave LXXIVd in 75% yield. Reduction of LXXIVf with lithium aluminum hydride in tetrahydrofuran gave crystalline LXXIVe which on acetylation gave LXXIVg. Chromic acid oxidation of LXXIVg in acetic anhydride (25) yielded LXXV.

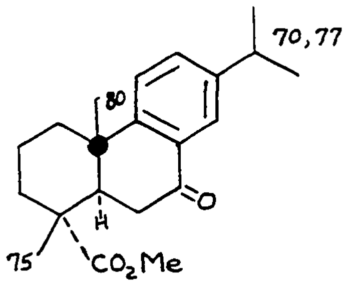


LXXIVa R = CN
LXXIVb R = CHO
LXXIVc R = CH_2NH_2
LXXIVd R = CH_3
LXXIVe R = CH_2OH
LXXIVf R = CO_2Me
LXXIVg R = CH_2OCOCH_3

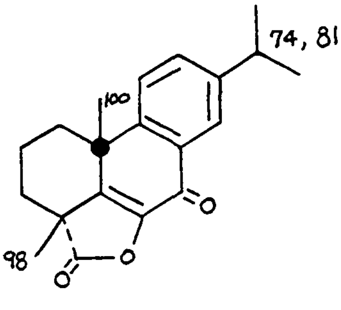

O
H
$CH_2O\overset{O}{C}CH_3$

LXXV

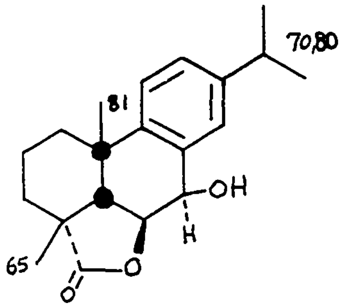
In an earlier study (62) an unusual α-oxidation was reported. Upon exposure of methyl 7-ketodehydroabietate (LXXVI) to t-butyl hydroperoxide in the presence of a trace of sulfuric acid in acetic acid for 55 hours at 50-55° a keto-lactone LXXVII had been formed identical with the keto-lactone formed by selenium dioxide oxidation of methyl


70,77
80
O
H
75
CO_2Me

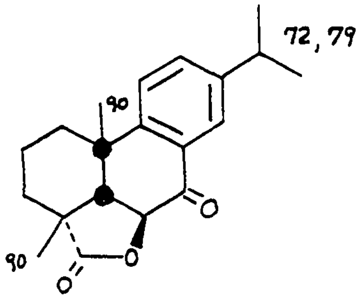
LXXVI


74, 81
100
O
98
O
O

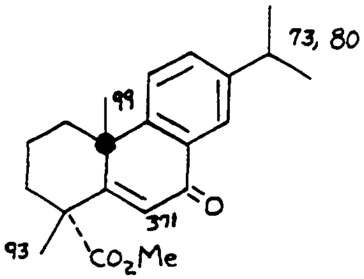
LXXVII


70,80
81
OH
H
65
O
O

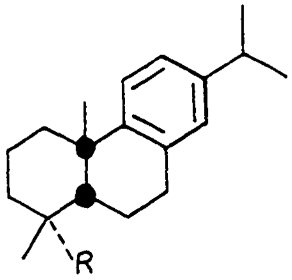
LXXVIII



LXXIX



LXXX



LXXXIa R = CO_2H
LXXXIb R = CO_2Me
LXXXIc R = CH_2OH

7-ketodehydroabietate (63). Sodium borohydride reduction had led to a hydroxylactone LXXIX, whose oxidation with chromic acid had yielded a keto-lactone LXXX different from LXXVII but easily convertible into the latter by selenium dioxide oxidation.

Methyl 7-ketodehydroabietate (LXXVI) had been brominated and the 6-bromo compound exposed to solvolysis. Collidine treatment of the latter, in a manner in which a 6-bromo-7-ketopodocarpic acid derivative has been reported to have been converted into C-6 lactone (64), had yielded only the elimination product LXXX. However, dimethyl sulfoxide treatment (65) of the 6-bromo compound had yielded the enol-lactone LXXVII.

Although the structure of the enol-lactone LXXVII was well established the stereochemistry at C-5 and C-6 of

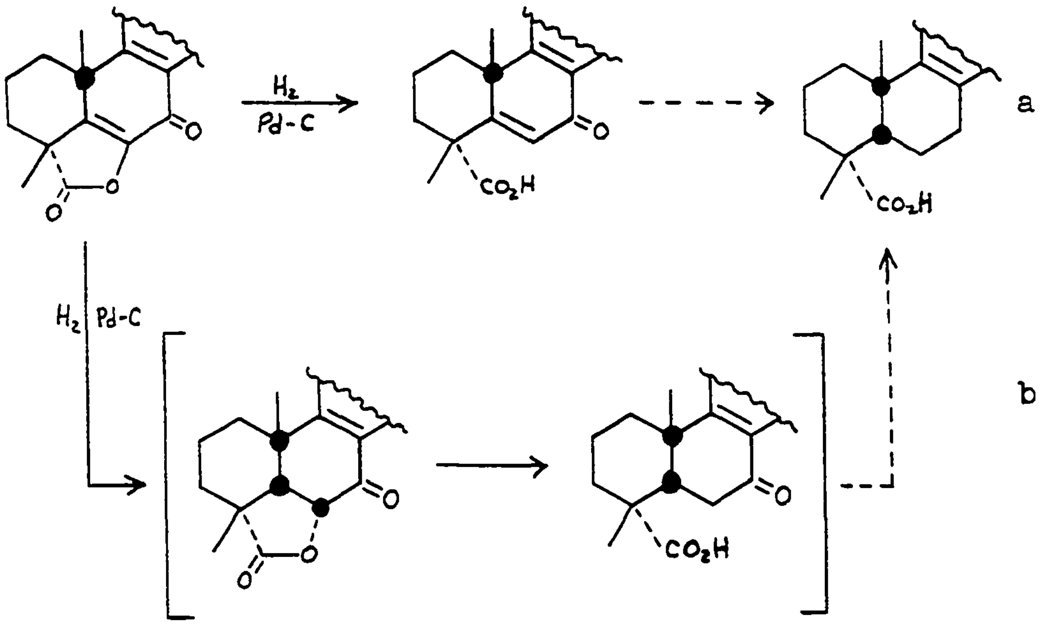
LXXVIII and LXXIX had not been determined. Upon Clemmenson reduction (66) of LXXIX a crystalline acid LXXXIa, m.p. 121-124°, was obtained. Esterification yielded the ester LXXXIb, m.p. 98-100°. The acid was 5-isoabietic acid, a structure assignment confirmed later by a p.m.r. study of a large group of diterpenic acid derivatives.

When a private communication from Mahapatra and Dodson (67) indicated that a dl-deisopropyl analogue of LXXVII had been converted to dl-5-isodeisopropyldehydroabietic acid on catalytic hydrogenation, the same reduction of LXXVII, previously claimed to have led to dehydroabietic acid (XXIIIc) itself (62), was reinvestigated. This time the reaction led to 5-isodehydroabietic acid (LXXXIa), identical in all respects with the product of the Clemmensen reduction of LXXIX. In view of this new turn of events it became desirable to determine the C-6 stereochemistry of LXXIX, and to reconsider the possible mechanism of the hydrogenation of the enol-keto-lactone LXXVII.

The p.m.r. spectrum of LXXIX was taken and found to possess a pair of doublets corresponding to the C-5 and C-6 hydrogens. The C-6 doublet was centered at 341 c.p.s. (J = 13 c.p.s.) while that of C-5 at 304 c.p.s. (J = 13 c.p.s.) (relative to an internal tetramethylsilane standard) The C-4 and C-10 methyl peaks coalesced at 90 c.p.s. while the doublet of the isopropyl methyl groups was centered at 75.5 c.p.s. (J = 7 c.p.s.).

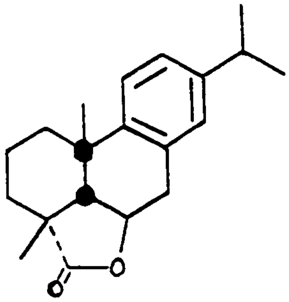
Inspection of models of the two possible C-6 epimers of LXXIX revealed them both to be rigid and quite inflexible. The dihedral angle made by C-5, C-6 and their single hydrogen atoms proved to be close to 0° in the _cis_ case and close to 180° in the _trans_ case. On the basis of the correlations of spin-spin coupling constants with dihedral angles by Karplus (68) and later Johnson (69), the J value in the former isomer would be expected to be less than 10 c.p.s., while that of the latter can approach 16 c.p.s. The observed coupling constant of 13 c.p.s. suggests a C-5-β , C-6-α _trans_ configuration for the ketolactone LXXIX. Since there is little likelihood that C-6 isomerization had occurred during the oxidation of LXXVIII to LXXIX, the hydroxylactone LXXVIII probably has a similar C-5, C-6 stereochemical arrangement. Unfortunately a p.m.r. spectral check on this point was not possible because of the overlap of another proton signal from either the hydroxyl group or the C-7 hydrogen in the region (293-312 c.p.s.) of the C-6 hydrogen signal.

The hydrogenation of the enol-keto-lactone LXXVII is open to two formal mechanistic interpretations. One, path a, involves hydrogenolysis at C-6 followed by β -side



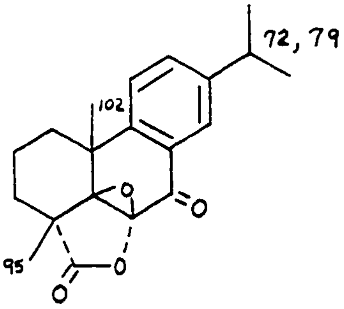
hydrogenation. This pathway is open to objections. The reduction of the enone ester LXXX gave only the A-B trans compound, methyl dehydroabietate (XXIIIb). However the effect of the difference of a C-4 carboxyl vs. its ester on the course of hydrogenation is not known. All analogous cases of octalones have given only trans decalins on hydrogenation.

Path b involves hydrogenation of the $\Delta^{5,6}$ double bond from the β side followed by hydrogenolysis at C-6 and normal reduction thereafter. As a possible test of this route, keto-lactone LXXIX was hydrogenated. While the product was not fully characterized, it proved to be neutral and its infrared spectrum (carbonyl band at 5.65μ) showed it to be a γ-lactone, presumably LXXXII. Although this experimental would appear to speak against path b as the route of hydrogenation of LXXVII, the test lactone LXXIX is a C-6 epimer of the hypothetical hydrogenation intermediate—a fact which may be important enough to change the course of reduction.

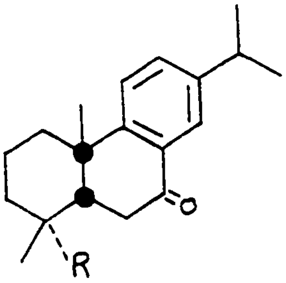


LXXXII

All reactions of the enol-keto-lactone LXXVII involving the introduction of asymmetry into C-5 appear to occur from the β side. The hydrogenation (path b) may be one case, while other examples included the following. When during the preparation of more lactone LXXVII the temperature was allowed to increase after a period of time at 50-55°, a new product accompanied the desired lactone. Its infrared spectrum (Nujol), C = 0 5.55 (s), 5.89 (s)μ; C = C 6.20 (s)μ; ultraviolet spectrum (95% ethanol); λmax. 212, 260, 312 mμ, and elemental analysis showed it to be a 5,6-epoxylactone LXXXIII. Of the two possible configurations only the stereochemistry as depicted in LXXXIII seems sterically reasonable.



LXXXIII



LXXXIVa R = CO_2H
LXXXIVb R = CO_2Me

The reduction of LXXVII with zinc and acetic acid gave 5-iso-7-ketodehydroabietic acid (LXXXIVa) which on esterification yielded methyl 5-iso-7-ketodehydroabietate (LXXXIVb) identical with that obtained from chromic acid oxidation of methyl 5-isodehydroabietate (LXXXIb). This would indicate that chemical reduction as well as possibly hydrogenation occurs from the β side.

The p.m.r. spectrum of LXXVII exhibits a multiplet at 490 c.p.s. due to the C-14 hydrogen, a doublet centered at 452 c.p.s. (J = 0.8 c.p.s. due to the C-11 and C-12 hydrogens), seven peaks of the expected septet for the isopropyl methine hydrogen centered at 182 c.p.s. (J = 7 c.p.s.), a 100 c.p.s. C-10 methyl peak, a 98 c.p.s. C-4 methyl peak (or vice versa) and a doublet centered at 77.5 c.p.s. (J = 7 c.p.s.) of the isopropyl methyl groups.

The paramagnetic shift of the C-4 and C-10 methyl groups as compared to lactone LXXIX is due to the fact that the methyl groups are within the deshielding region of the C-5, C-6 double bond. It is noteworthy that the enone ester LXXX has one of its methyl groups (99 and 93 c.p.s.) more shielded than the rigid system LXXVII.

It is also interesting to note that the epoxy-keto-lactone LXXXIII has its methyl groups (95 and 102 c.p.s.) less shielded than its desoxy counterpart, LXXIX (90 and 90 c.p.s.).

The C-14 hydrogen in LXXXIII shows a doublet centered at 473 c.p.s. (J = 2 c.p.s.), the C-11 and C-12 hydrogens show a multiplet centered at 445 c.p.s., while the doublet for the isopropyl methyl groups is at 75.5 c.p.s. (J = 7 c.p.s.).

The C-10 and C-4 methyl peaks of LXXVIII appear at 81 c.p.s. and 65 c.p.s., respectively, while the doublet of the isopropyl methyl groups shows up at 73.5 c.p.s. (J = 7 c.p.s.).

The chromic acid oxidation (22) of methyl 5-isodehydroabietate (LXXXIb) gives predominately monoketone. Chromatography of the crude product led to 93% of methyl 5-iso-7-ketodehydroabietate, some material, presumably diketone, stuck to the column and a trace of acidic material was obtained. When methyl 5-isodehydroabietate (LXXXIb) is reduced with lithium aluminum hydride to the alcohol LXXXIc, acetylated with acetic anhydride and then oxidized with chromic acid a 55:45 ratio of diketone to monoketone was obtained.

In reviewing the previous work (see Historical section) one finds that the correlation in results and hence the use of the diagnostic test first proposed by Wenkert and Jackson (22) are difficult. It appears that the work of Ghatak *et al*. (27,28) and Fétizon *et al*. (29) fit the original diagnostic test, but yields of similar *cis* as well as *trans* compounds vary as much as 30%. In the case of Barltrop and Day (31) a *cis* material has been assigned on the basis of obtaining an "appreciable amount of acidic material". Dutta *et al*. (32) report the oxidation of methyl *dl*-5-isodeisopropyldehydroabietate with chromic acid and obtain a low yield (22%) of diketone.

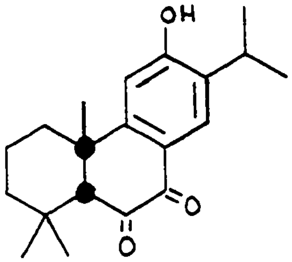
It appears from these observations that the variation of results in the chromic acid oxidation are due to the differences in reaction conditions.

Various chemical means have been cited (see Historical section) for the determination of the stereochemistry of the A-B ring juncture as well as the stereochemistry at C-4 of diterpenic compounds. Recent advances in the correlation of stereochemistry and nuclear magnetic resonance spectra for diterpenoid substances (36,70,71,72,73,74) have also occurred.

It was first noted by Beak (75) that in comparing the proton magnetic resonance spectra of O-methylpodocarpol and cis desoxypodocarpol, the C-4 methyl shifted from 63 c.p.s. to 19 c.p.s., while that of the C-10 methyl remained constant at 71 c.p.s. This has led us to examine the proton magnetic resonance spectra of both ring A-B cis as well as ring A-B trans derivatives of aromatic resin acids in the hope of obtaining an overall correlation of configuration and conformation of these substances.

The initial correlations between the chemical shifts of methyl groups and structure were made in the steroid field (76,77,78,79,80) and extrapolated to the diterpenes (70,71). It was noted that the assignment of the highest field methyl group absorption in xanthoperol (LXXXV) to the C-10 methyl (70) disregarded the magnetic moment of the adjacent benzene ring (81).

On the basis of the work of Chien (82), Beak (75) and that to be presented herein indicates that a paramagnetic



LXXXV

shift of approximately 21 c.p.s. would be expected for a c-10-methyl group relative to a system wherein ring C is hydroaromatic. Therefore the reassignment of peaks in the xanthoperol spectrum was made so that the highest field absorption be assigned to one of the C-4 methyl groups (75).

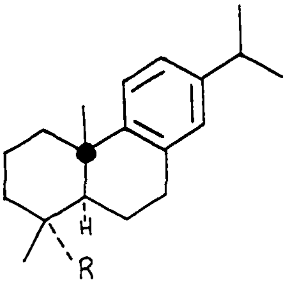
The chemical shifts of four series of aromatic diterpenes are listed in Table II and III. On the basis of these models correlations applicable to rigid six-membered carbocyclic rings can be made.

If one considers dehydroabietic acid (see Table I, structure LXXXVIa) the assignment of the C-4 and C-10 methyl groups at 73 c.p.s. and 77 c.p.s., respectively, can be made. The C-11, C-12 and C-14 aromatic complex appears between 417 and 431 c.p.s. while the five peaks of the expected septet for the isopropyl methine hydrogen is centered at 173 c.p.s. (J = 7 c.p.s.). A doublet, centered at 73.5 c.p.s. (J = 7 c.p.s.), is characteristic of the isopropyl methyl groups and is found to remain constant and independent of the nature of the C-4 substituents and the C-5 stereochemistry.

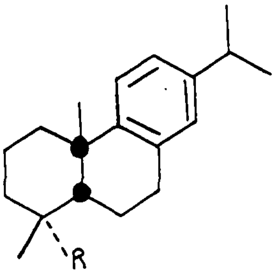
Since dehydroabietic acid possesses the trans A-B ring juncture the conformation can be depicted as XC where R is equal to CO_2H. Since the carboxyl is equatorial no effect would be expected at C-10 due to the conical region associated with the carbonyl (37). Upon examination of the C-10 methyl peak when varying R from acid to ester, aldehyde, nitrile, aminomethyl, hydroxymethyl, acetoxymethyl and methyl, one finds a range of 7 c.p.s. from 70 to 77 c.p.s.

Since the R group is attached to a carbon holding one methyl and two methylene groups, one might expect that a good model for the determination of the methyl position would be the neopenyl system (see Table III).

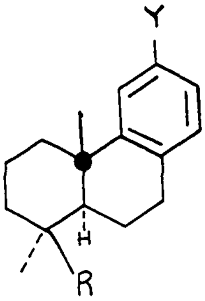
Determination of the p.m.r. spectra of these neopenyl models revealed (see Table III) the methyl peaks to occur within ± 1 c.p.s. of those of the dehydroabietic acid derivatives LXXXVIa-h. This further substantiates the previous assignments of C-4 and C-10 methyl groups.



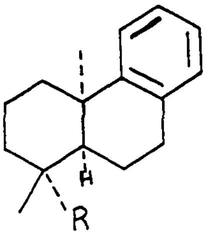
LXXXVI



LXXXVII



LXXXVIII



LXXXIX

Table II. Chemical Shifts of C-4 and C-10 Methyl Groups in c.p.s.

	a		b			c			d		
R =	CO_2H		CO_2Me			CHO			CN		Y
	C-4	C-10	C-4	C-10	ester	C-4	C-10	CHO	C-4	C-10	
LXXXVI	72	77	73	77	221	70	74	557	84	70	
LXXXVII	89	90	83	83	204				76	73	
LXXXVIII	80	67	77	63	221	67	64	595	86	83	H
	80	62	77	63							OMe
	81	68	77	61							OH
LXXXIX	79	67	73	64	222	73	51	574	95	76	

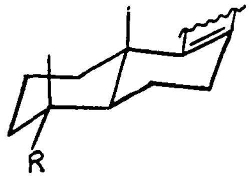
	e		f		g			h		
R =	CH_2NH_2		CH_2OH		CH_2OAc			CH_3		Y
	C-4	C-10	C-4	C-10	C-4	C-10	C-4	C-4	C-10	
LXXXVI	53	73	52	73	57	73	57	57	71	
LXXXVII			62	72	60	73				
LXXXVIII	60	72	63	71			57	57	71	H
			62	70	63	72	57	57	71	OMe
			63	71						OH
LXXXIX	20	71	19	71	24	72	19	54	69	

Table III. Chemical Shifts of Methylene Quartets in c.p.s.

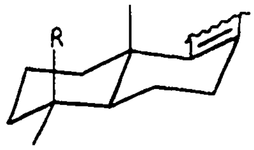
	CH_2NH_2	CH_2OH	CH_2OAc	OAc
LXXXVI	150 (J=4)	199 (J=11)	223 (J=11)	122
LXXXVII		179 (J=11)	202 (J=11)	115
LXXXVIII		222 (J=11)	250 (J=11)	123
LXXXIX	152 (J=13)	200 (J=11)	233 (J=11)	125

Table IV. Chemical Shifts of Neopental Derivations

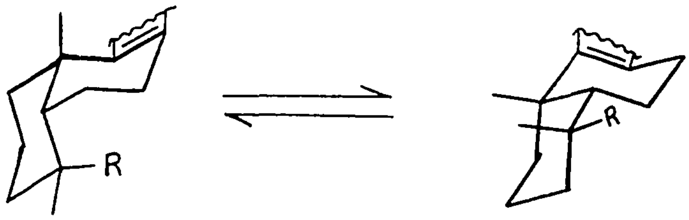
	CO_2H	CO_2Me		CHO	CN	CH_2NH_2		CH_2NH_2	
	Me	Me	OMe	Me	Me	Me	CH_2	Me	CH_2
Me_3CR	74	72	221	69	83	53	145(s)	53	198(s)



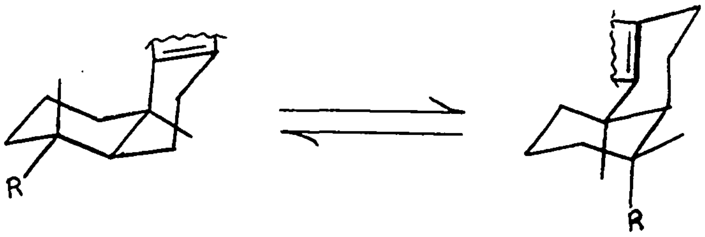
XC



XCI



XCIIa XCIIb



XCIIIa XCIIIb

Further data may be obtained from the p.m.r. spectra, as shown in the tables II and III such as the position of the equatorial carbomethoxy group at 221 c.p.s., the aldehyde hydrogen singlet at 557 c.p.s., the quartet of the aminomethylene centered at 150 c.p.s. (J = 4 c.p.s.), the quartet of the hydroxymethylene centered at 199 c.p.s. (J = 11 c.p.s.), the quartet of the acetoxymethylene centered at 233 c.p.s. (J = 11 c.p.s.) as well as the acetate methyl which gives a singlet at 122 c.p.s.

It has been noted (37) that acyloxy and hydroxy substituents produce large shifts in adjacent hydrogens while that of the corresponding nitrogen analogue causes much smaller paramagnetic shifts. This indeed is observed in the above methylene cases.

It would be expected that the aminomethyl, hydroxymethyl, acetoxymethyl and methyl groups would have very little deshielding effect on the geminal methyl group. Such is the case, the methyl peak appearing at approximately 54 c.p.s.

Therefore, one observes a methyl group on the same carbon as a hydroxymethyl, aminomethyl, acetoxymethyl or methyl to undergo a paramagnetic shift of approximately 18 ± 2 c.p.s. when the hydroxymethyl group is transformed into a carbomethoxy, carboxy, or aldehyde function. An even greater paramagnetic effect is observed in the case of the nitrile geminal methyl which is shifted 30 c.p.s. downfield. These apparent shifts are due to the deshielding effect of the freely rotating carbonyl on the one hand and the inherent deshielding of the nitrile.

If one now looks at the 5-isodehydroabietic acid series represented by LXXXVII, one's attention is drawn to the diamagnetic shift of 17 c.p.s. of the carbomethoxy group. Also a diamagnetic shift of 20 c.p.s. is noted in the quartet of the hydroxymethyl, a 31 c.p.s. shift in the quartet of the acetoxymethyl, as well as a 7 c.p.s. shift in the acetate's methyl peak.

In the examination of the two conformational structures, XCIIa and XCIIb, one notes that in XCIIa the axial functional group R overlaps with the π-electrons of the aromatic ring while in XCIIb the equatorial R is far removed from the ring.

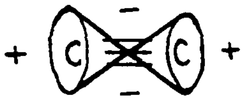
Therefore, one would expect that if the functional group is associated with the region of positive shielding above or below the plane of the aromatic ring a diamagnetic shift should be observed. It is then possible to designate XCIIa as the conformation of LXXXVIIb, LXXXVIIf and LXXVIIg. Analoguously LXXXVIIa and LXXXVIId possess the XCIIa conformation.

In the podocarpic acid series LXXXVIII one must consider the 1,3 diaxial interactions of the substituent R and the angular methyl group (see XCI). If one assumes the abietic acid series (LXXXVI) to be the standard, the 1,3 diaxial interaction can now be calculated to be a diamagnetic shift of approximately 10 c.p.s. in those cases where the R substituents are carboxyl, carbomethoxy or aldehyde groups. This diamagnetic shift can be assumed to be due to the carbonyl oriented in such a way so as to place the C-10 methyl in the conical region associated with positive shielding above or below the plane of the carbon-oxygen double bond. The diamagnetic shift of the 1,3 diaxial nitrile and C-10 methyl seems to follow this pattern, however, a greater shift is observed. In the tetrahedral substituents (LXXXVIIIe-h) there is no 1,3 diaxial field interaction and one would expect no shift in the angular methyl group. The latter indeed is observed not to vary more than ± 1 c.p.s. from the standard dehydroabietic acid series. One might expect some variation in the chemical shift of the C-4 methyl group in the axial and equatorial cases. However, no uniform shifts occur, but all peaks are within 7 c.p.s. of each other. In the podocarpic acid series there seems to be no effect on the angular methyl group by C-12 aromatic substituents such as hydroxy or methoxyl groups.

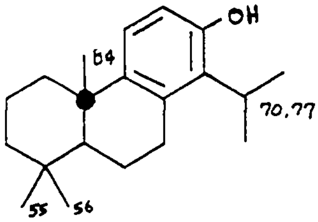
If one now turns to the fourth series, the *cis* podocarpic acid enantiomer series (LXXXIXa-h) the diamagnetic shift of the C-4 methyl in the tetrahedrally substituted derivatives is noted (LXXXIXc-h). This observation is the same as that in the *cis* abietic acid series LXXXVII where an axial substituent overlapped with the magnetic field of the aromatic ring causing a diamagnetic shift of the hydrogen signal. In the case at hand, when one looks at the two conformations possible (XCIIIa-b), the C-4 methyl group can be axial and overlapping with the aromatic ring or equatorial without any overlapping. The data indicates that conformation XCIIIa is favored when the substituent at C-4 is tetrahedral.

In those cases where the substituent R is linear or trigonal the C-4 and C-10 methyl group peaks appear to be anomalous. A clue of the conformation of these compounds can be gained from the chemical shift of the aldehyde hydrogen atom. Dehydroabietal (LXXXVIc) exhibits its equatorial aldehyde hydrogen at 557 c.p.s. as a singlet while the axial aldehyde hydrogen of podocarpal (LXXXVIIIc) appears as a doublet at 595 c.p.s. ($J = 1$ c.p.s.). King, Godson and King (39) have observed p.m.r. signals of axial aldehyde hydrogens at 486 c.p.s. and of equatorial hydrogens at 554 c.p.s. among non-aromatic diterpenoids. Meyer (83) has observed that axial aldehydes have their hydrogen signals as doublets. The aldehyde hydrogen of cis podocarpal enantiomer appeared as a doublet at 574 c.p.s. (J - 1 c.p.s.), hence midway between the axial or equatorial cases. However the fact that the methyl signals (51 and 73 c.p.s.) of the A-B cis aldehyde fit neither conformations, XCIIIa or XCIIIb, implies that ring A is distorted from its normal chain conformation. This trend toward a boat form must be different in the aldehyde than in the acid (67 and 79 c.p.s.), ester (64 and 73 c.p.s.) and nitrile (76 and 95 c.p.s.) of similar configuration. Presumably the size of the C-4 substituent has a strong effect on the ring A conformation of these compounds. It is interesting to note that the effect of the magnetic current around a nitrile group on neighboring hydrogen atoms is similar to that discussed by Jackman (37) regarding the long-range shielding affect of the carbon-carbon triple bond XCIV.

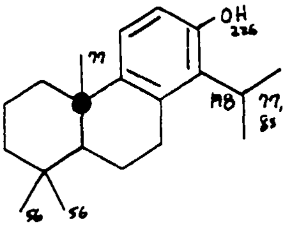
As indicated above, no variation in the chemical shift of the isopropyl doublet in the dehydroabietic systems nor any in the C-10 methyl signals of variously ar-substituted podocarpic acid derivatives LXXXVIIIa-h was observed. However, the p.m.r. spectra of C-13 hydroxylated compounds revealed a paramagnetic shift of the C-10 methyl signals (Compare XCV, XCVI and XCVII).



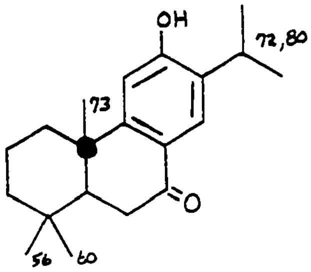
XCIV


OH
84
70,77
55
56

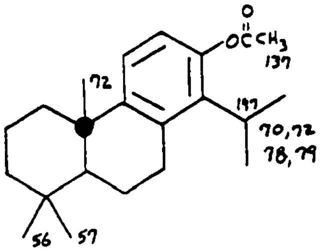
XCV


OH
226
77
148
77,
85
56
56

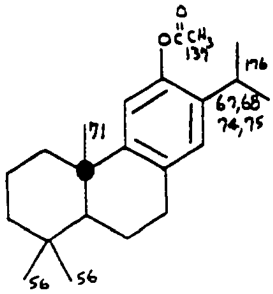
XCVI


OH
72,80
73
O
56
60

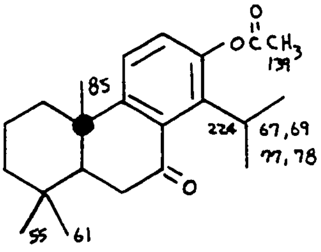
XCVII


O
OCCH3
137
72
197
70,72
78,79
56
57

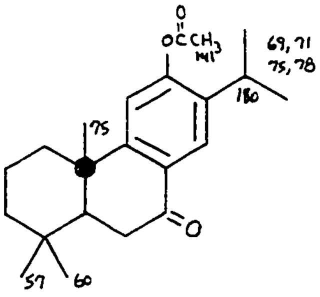
XCVIII


O
OCCH3
137
176
71
67,68
74,75
56
56

XCIX


O
OCCH3
139
85
224
67,69
77,78
O
55
61

C


O
OCCH3
141
69,71
75,78
180
75
O
57
60

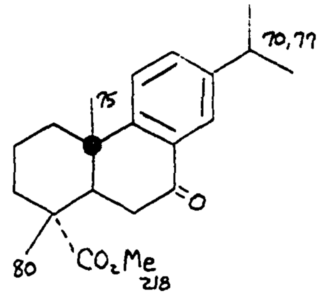
CI

In every compound (XCVIII, XCIX, C and CI) possessing an acetoxy group ortho to the isopropyl function two pairs of doublets are observed for the isopropyl methyl groups. Most likely this splitting is a consequence of the restriction of rotation of the isopropyl group by the acetoxy function.

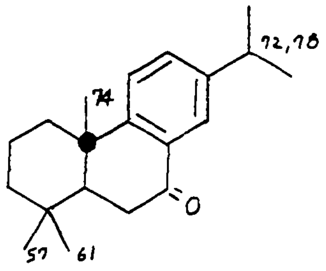
In order to pursue the conformation of the four series further it became desirable to observe the p.m.r. spectra of C-7 oxygenated aromatic diterpenoids. Insight could also be obtained by the determination of their optical rotatory dispersion (see Figure 18, 19, 20).

While the introduction of a planar carbonyl group at C-7 (as in CII, CIII, CIV, CV, CVI, and CVII) has no effect on the C-10 methyl group, it causes a downfield drift of up to 9 c.p.s. in the chemical shift of the axial C-4 methyl function. As the 7-oxygenated podocarpic acid systems (CVIII, CIX, CX, CXI) indicate, the equatorial C-4 methyl group remains unaffected. The effect of the C-7 carbonyl group on the axial C-4 methyl function probably is a consequence of the change of the electronic environment of the axial β-hydrogen at C-6 with which the methyl group is interacting in an unfavorable 1,3-diaxial fashion.

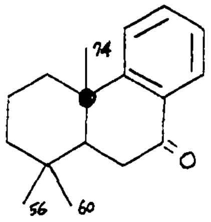
Upon comparing the 7-keto derivatives CXII and CXIII in the 5-isodehydroabietic acid series with the parent


70,77
75
O
80
CO₂Me
218

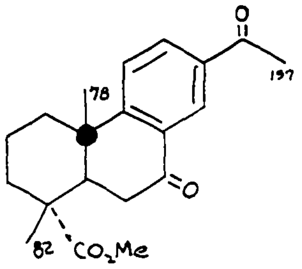
CII


72,78
74
O
57
61

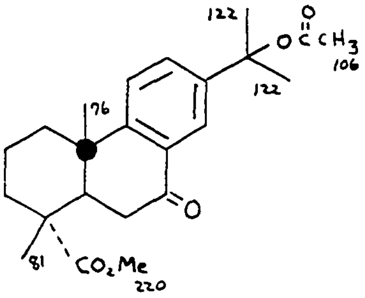
CIII



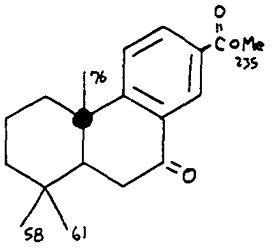
CIV


O
197
78
O
82
CO₂Me

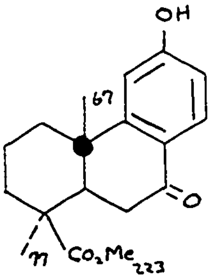
CV


122
O
OCCH₃
106
122
76
O
81
CO₂Me
220

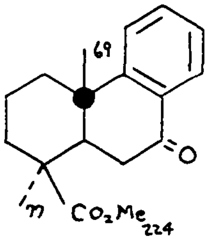
CVI


O
COMe
235
76
O
58
61

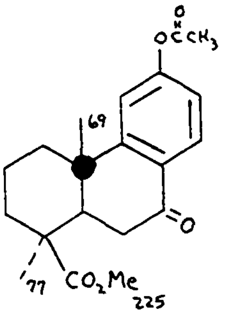
CVII


OH
67
O
77
CO₂Me
223

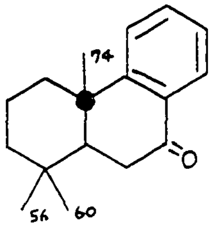
CVIII


69
O
77
CO₂Me
224

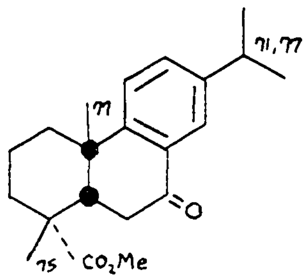
CIX


O
OCCH₃
69
O
77
CO₂Me
225

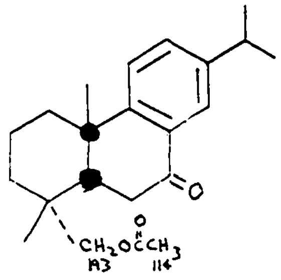
CX



CXI

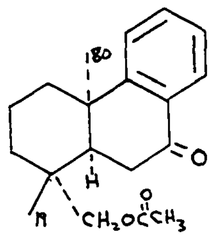

71,77
77
75
CO2Me
O

CXII

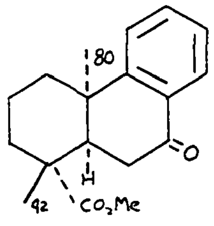

O
CH2OCCH3
113
114
O

CXIII

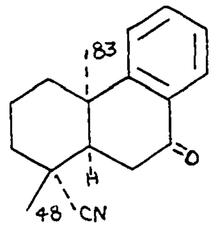
5-isononoxygenated derivatives (LXXXVIIb and LXXXVIIc) one notes no appreciable shift in the C-4 and C-10 methyl groups and only a small shift in the doublet of the isopropyl methyl groups. However, the large diamagnetic shift of 26 c.p.s. of the methyl group of the ester in CXII and of 9 c.p.s. of the methylene quartet of the acetoxymethyl group in CXIII speak in favor of conformation XCIIa for these substances wherein the C-4 axial substituents overlap the aromatic ring and hence are shielded by it.


180
H
O
11
CH2OCCH3
O

CXIV


80
H
92
CO2Me
O

CXV



CXVI

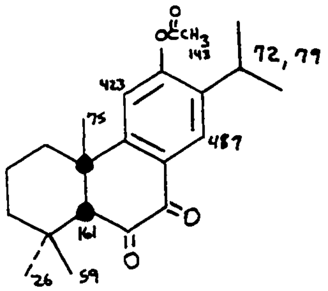
It appears by comparing CXIV with its nonoxygenated parent LXXXIXg that it also possesses conformation XCIIIa, although the C-4 methyl group in CXIV is more shielded by 5 c.p.s. than that in LXXXIXg. Compounds CXV and CXVI are similarly related to their 7-unoxygenated precursors.

The optical rotatory dispersion curves of the 7-keto compounds reveal that all A-B _trans_ substances (see Figure 18) have a similar positive multiple Cotton effect differing only slightly in intensities. The differences in substitutions at the assymetric center at C-4 probably are responsible for the change in the observed intensities. Comparison of the optical rotatory dispersion curves of various _cis_ and _trans_ 7-keto derivatives, (see Figure 19) show them to be very similar. It appears that the configuration at C-10 controls the sign of the optical rotatory dispersion curve, because one will note that, when the C-10 methyl group is β , a positive multiple Cotton curve is obtained, whereas a α C-10 methyl group reveals itself as a negative multiple Cotton curve.

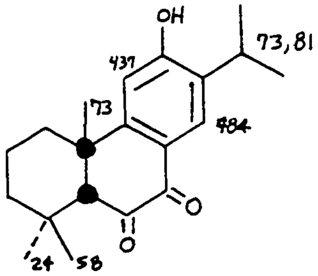
It also is interesting to compare the ring B diketone derivatives of aromatic diterpenoids and again try to assert their conformations. The acetoxymethyl quartet appears at 198 c.p.s. (J = 12 c.p.s.), an upfield shift of 4 c.p.s. from the parent non-oxygenated derivative but 5 c.p.s.

downfield as compared to the 7-keto derivative. Therefore it appears that a slight deshielding occurs in the dicarbonyl derivative as compared to the monoketone. The C-5 hydrogen appears as a singlet at 164 c.p.s. The C-5 hydrogen of CXVII and CXVIII appears as a singlet as in CXIX at 160 ± 1 c.p.s., while their C-4 methyl function is st strongly shielded by the aromatic ring and/or the C-6 and C-7 carboxyl groups. In CXX both the C-4 methyl group and the C-5 hydrogen are deshielded by ca. 30 c.p.s. Then all four diketones possess a conformation similar to XCIIa.

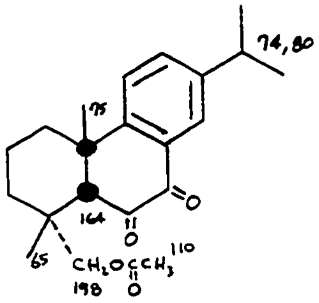
This view is confirmed by the optical rotatory dispersion curves (see Figure 20) of these dicarbonyl systems. Once again a multiple Cotton curve is observed in which the configuration at C-10 methyl group controls the sign of the curve. The variations in the region between 450 and 500 mμ appear to be due to the differences in the substituents at the asymetric center at C-4.



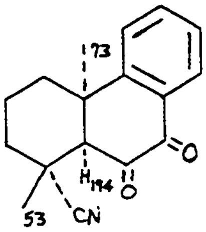
CXVII



CXVIII


74,80
75
164
65
CH₂OCCH₃
110
198
O
O
O

CXIX


73
H
194
O
O
53
CN

CXX

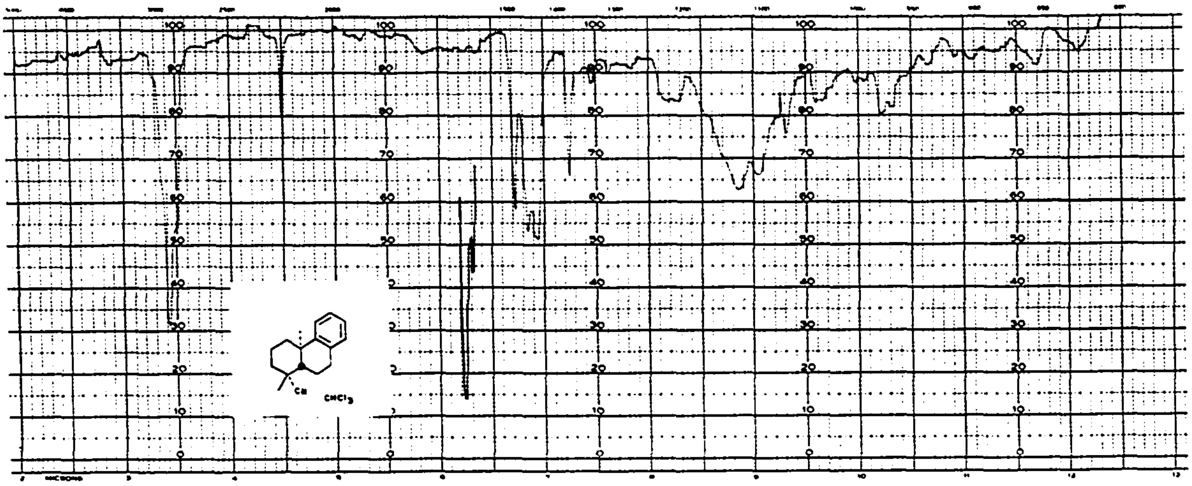
SPECTRA

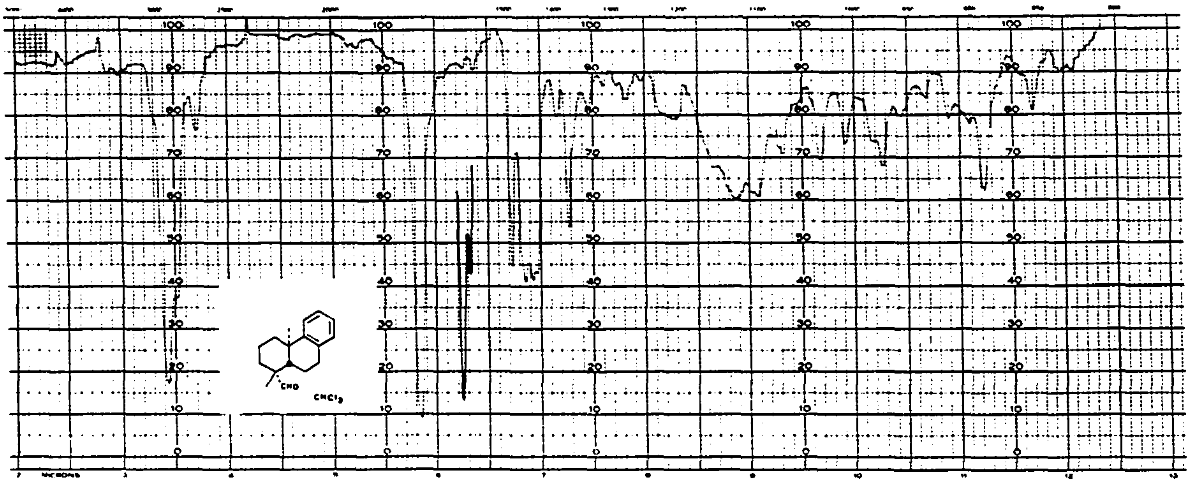
The optical rotatory dispersion curves were taken in dioxane solution. Concentrations for these measurements are expressed in grams/100 ml.

The nuclear magnetic resonance spectra were obtained from dilute deuterochloroform solutions using a Varian Model A-60 Spectrometer. Resonance positions were determined by pre-calibrated charts relative to tetramethylsilane as internal standard. Peak positions were expressed in c.p.s. (cycles per second).

All infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer unless denoted by the term "Infracord". The latter refers to those spectra taken on a Perkin-Elmer model "Infracord" infrared spectrophotometer.

Figure 1. Infrared Spectra


CN
CHCl3
MICRONS
100
90
80
70
60
50
40
30
20
10
0


CHO
CHCl3
MICRONS
100
90
80
70
60
50
40
30
20
10
0

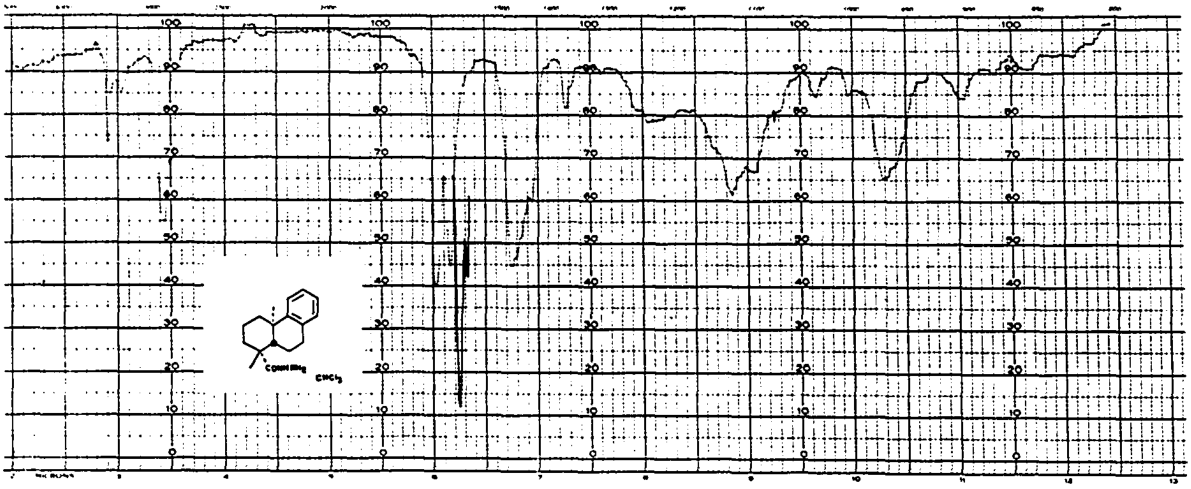
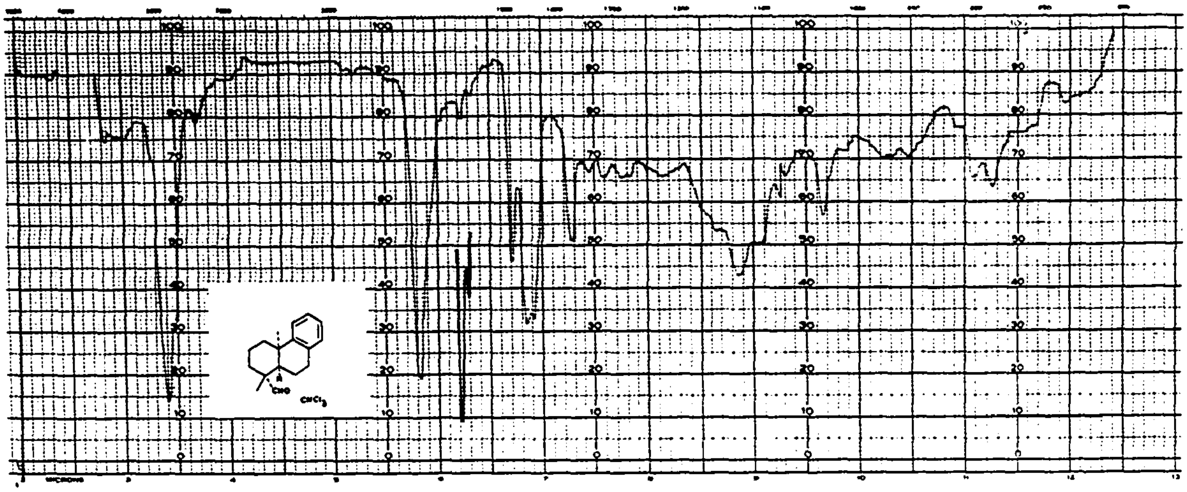
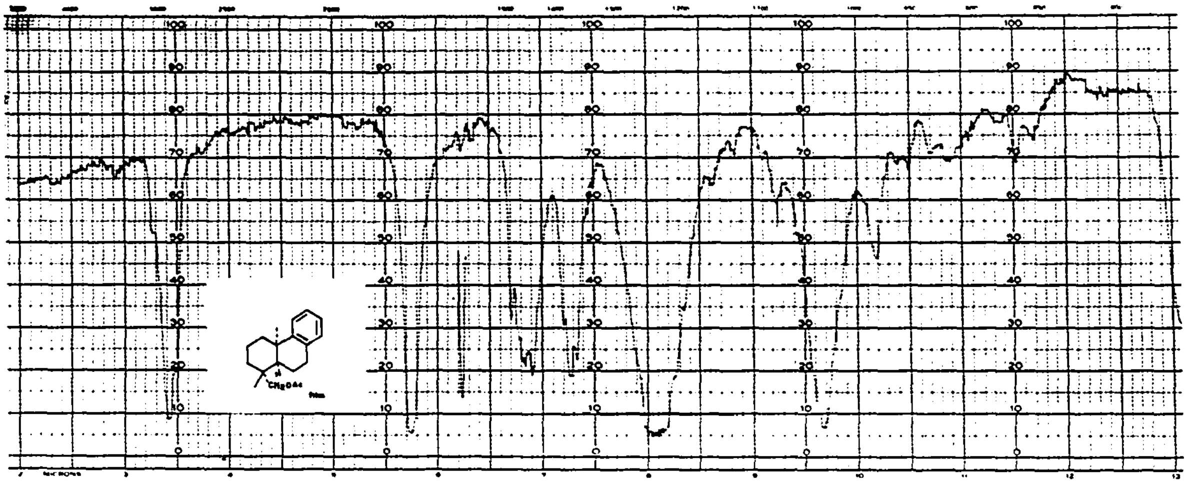

CONHMe2
CHCl3
MICRONS
100
90
80
70
60
50
40
30
20
10
0

Figure 2. Infrared Spectra


H
CHO
CHCl$_3$
MICRONS


H
CH$_2$OAc
film
MICRONS

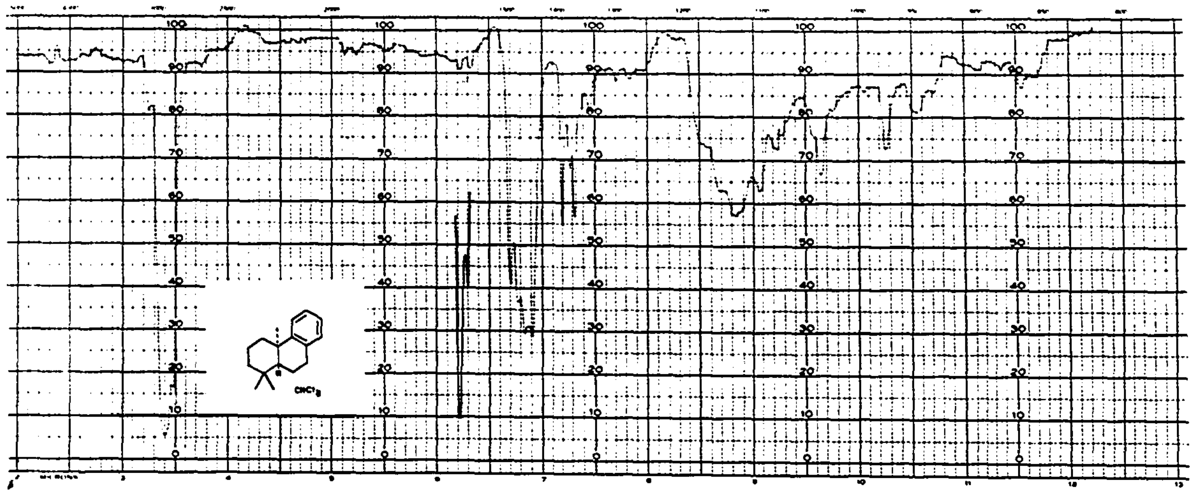
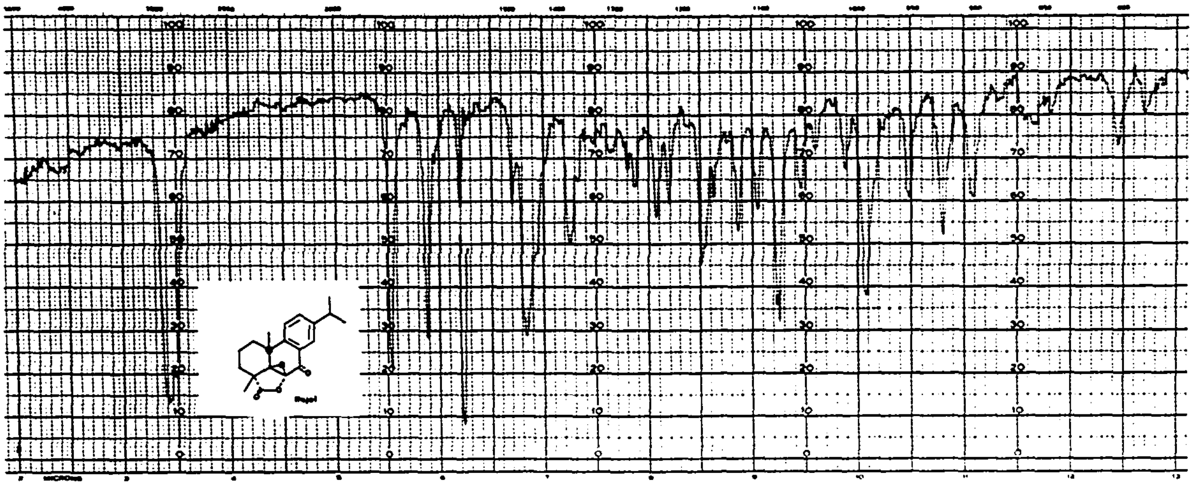
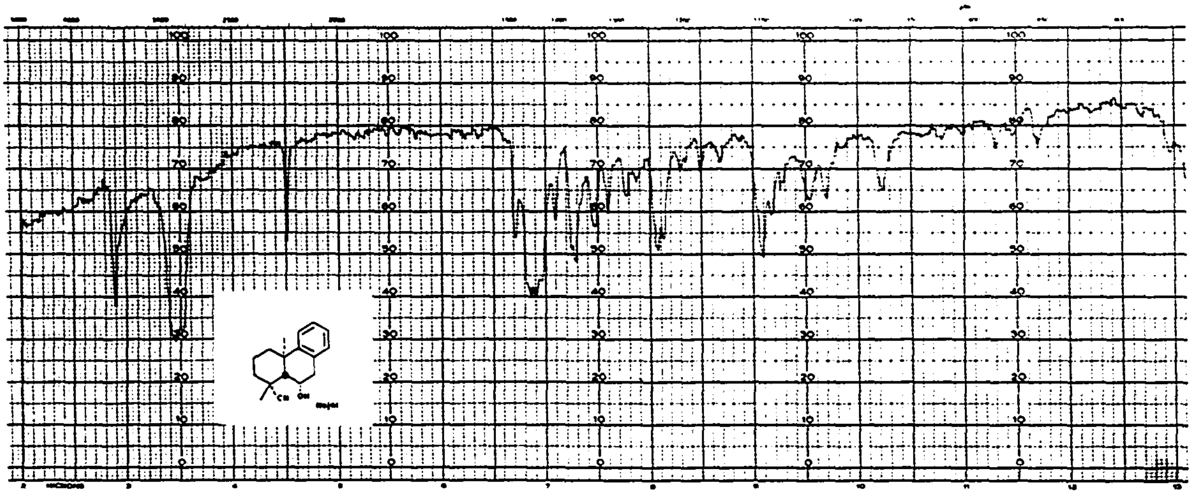

H
CHCl$_3$
MICRONS

Figure 3. Infrared Spectra


100
90
80
70
60
50
40
30
20
10
0
Nujol


100
90
80
70
60
50
40
30
20
10
0
CN
OH
Nujol

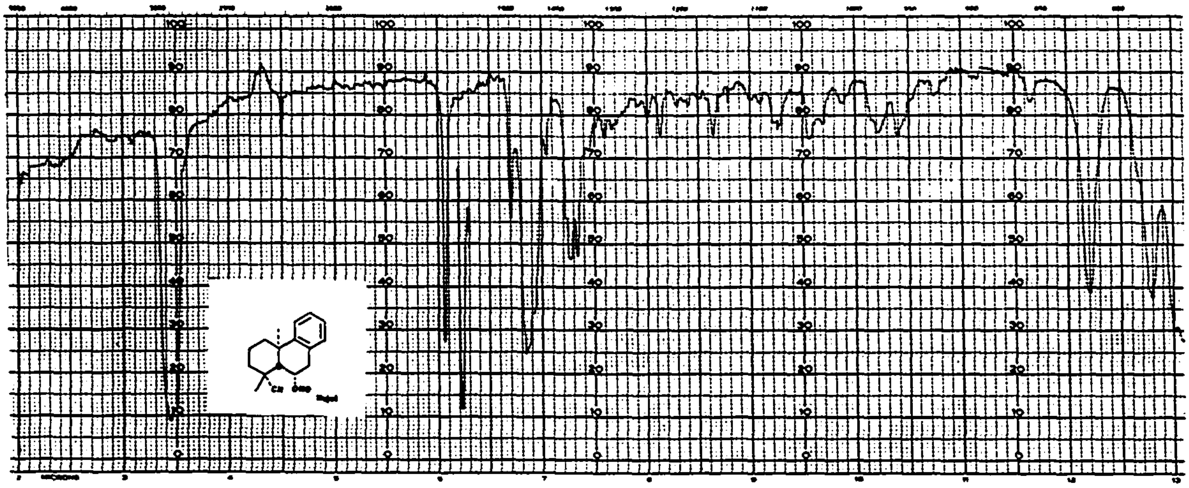
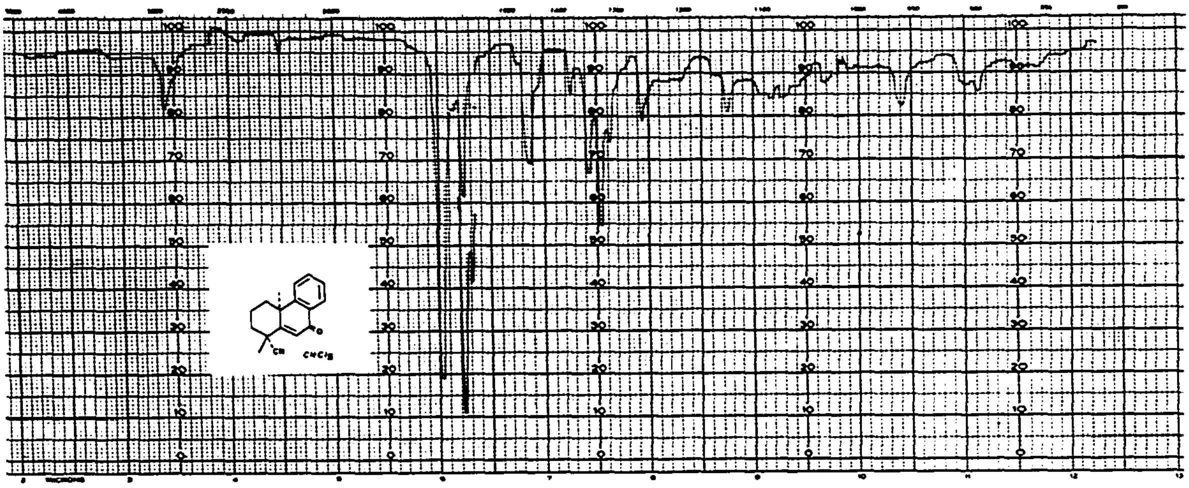
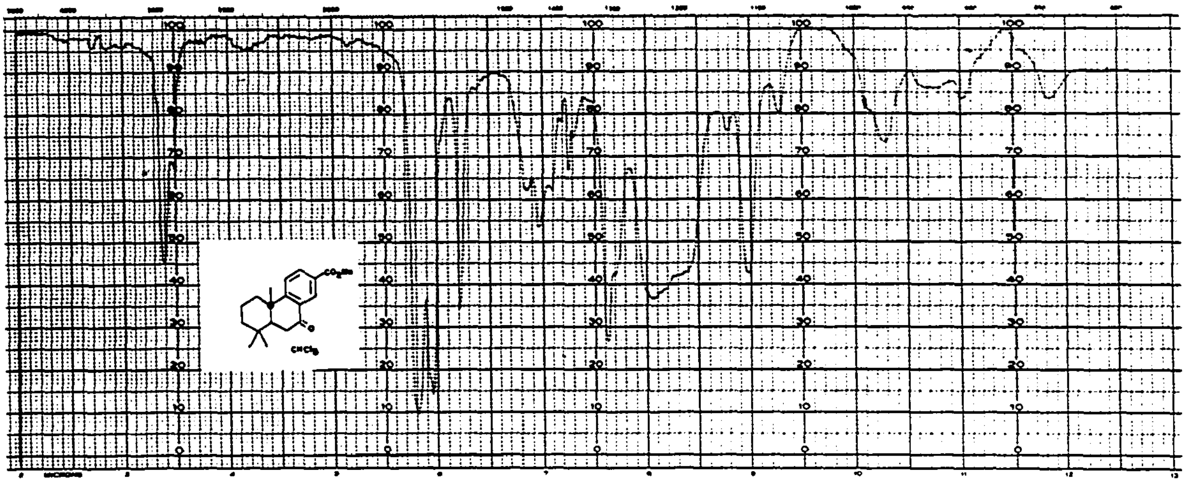

100
90
80
70
60
50
40
30
20
10
0
CN
OMs
Nujol

Figure 4. Infrared Spectra


CN
CHCl3
100
90
80
70
60
50
40
30
20
10
0
MICRONS


CO2Me
CHCl3
100
90
80
70
60
50
40
30
20
10
0
MICRONS

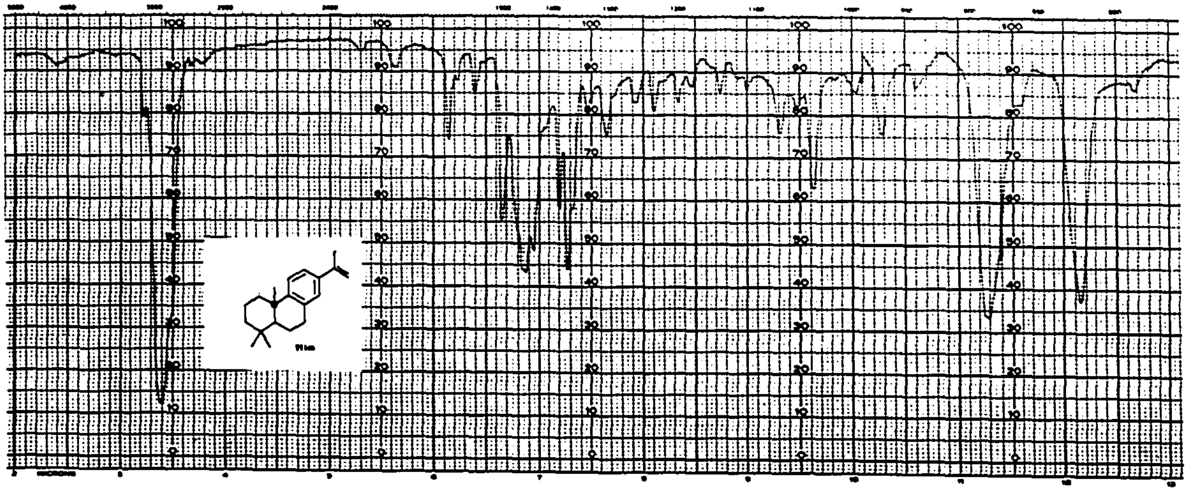
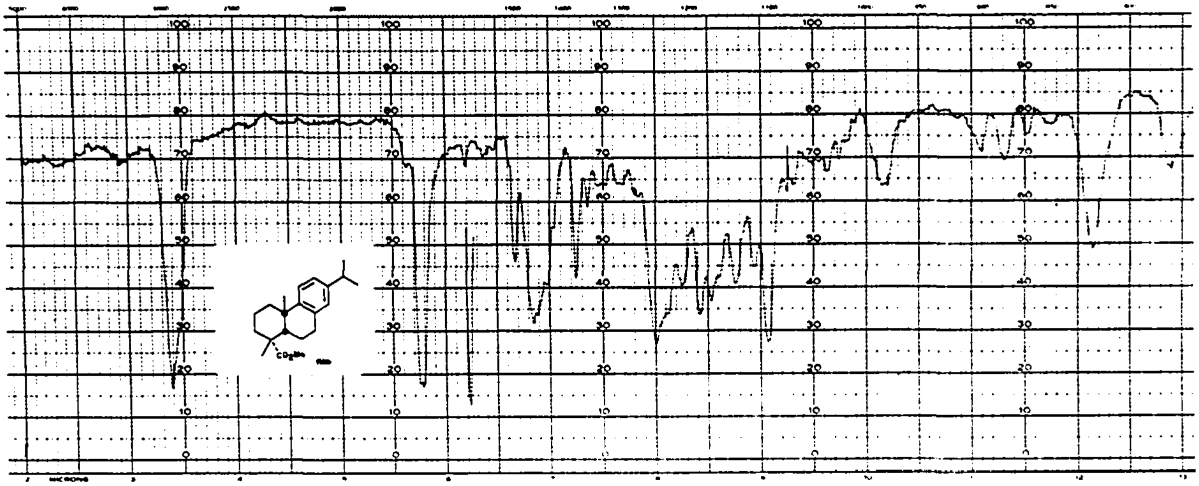
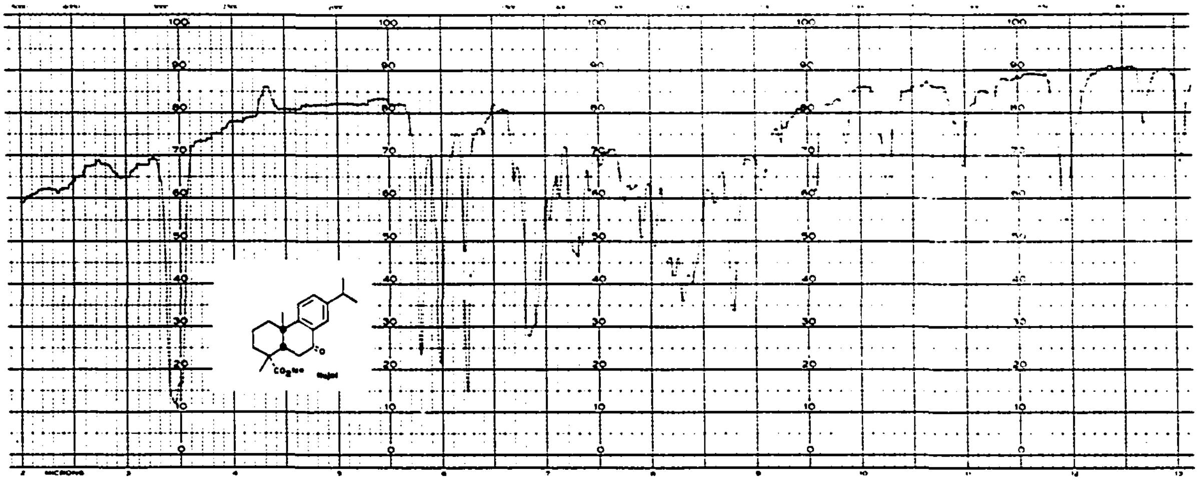

film
100
90
80
70
60
50
40
30
20
10
0
MICRONS

Figure 5. Infrared Spectra


100
90
80
70
60
50
40
30
20
10
0
MICRONS
2
3
4
5
6
7
8
9
10
11
12
13
CO2Me


100
90
80
70
60
50
40
30
20
10
0
MICRONS
2
3
4
5
6
7
8
9
10
11
12
13
O
CO2Me

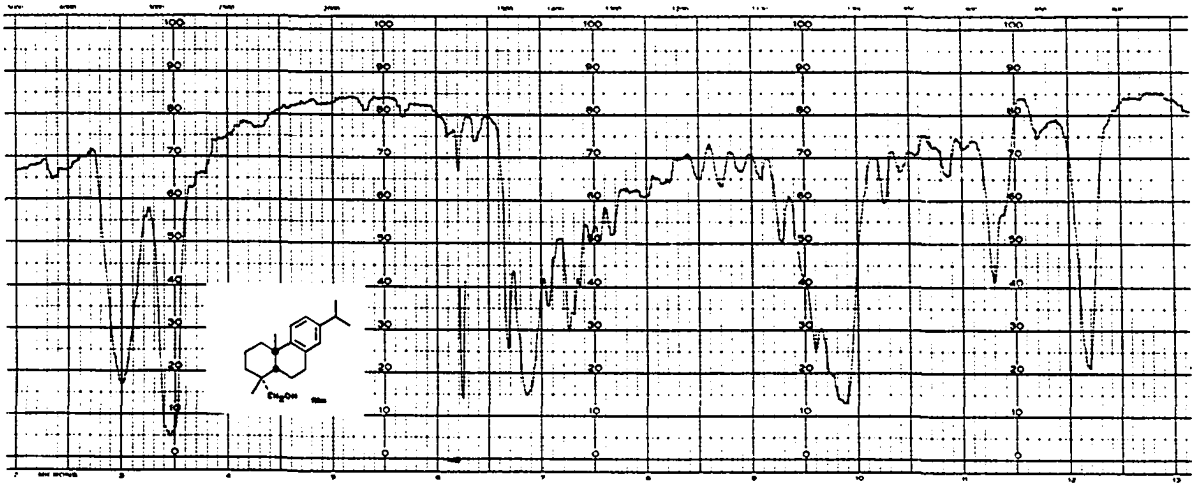
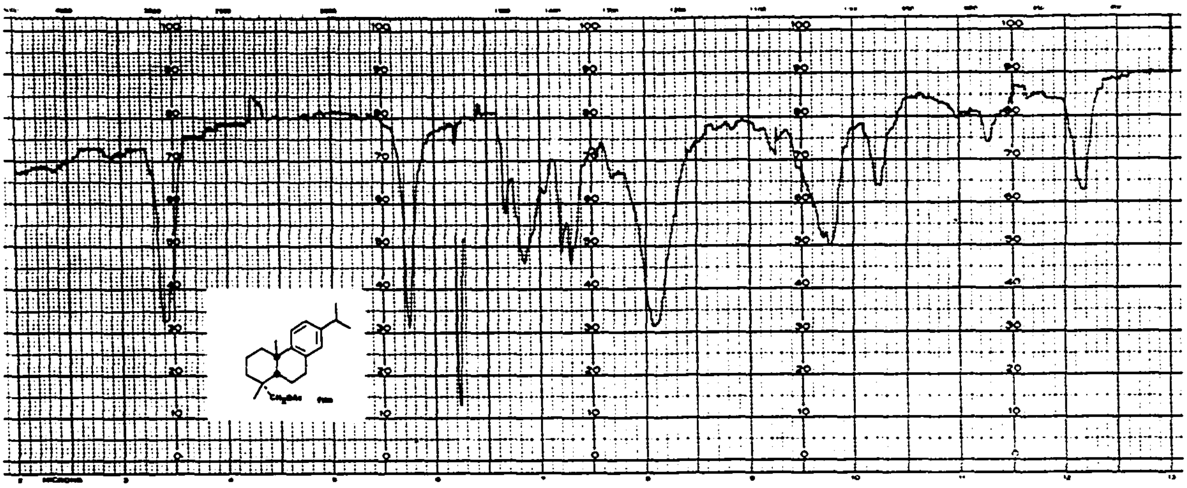
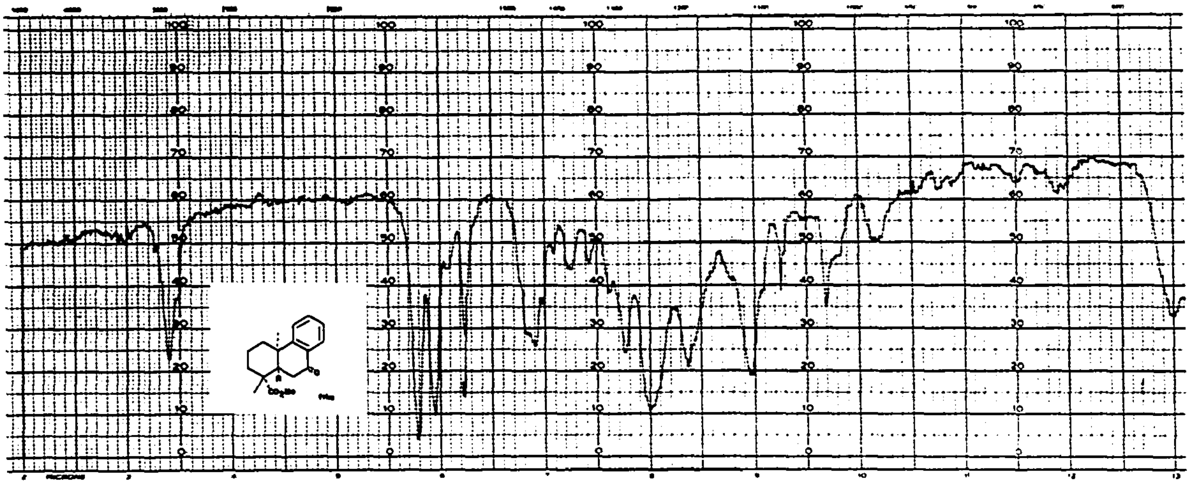

100
90
80
70
60
50
40
30
20
10
0
MICRONS
2
3
4
5
6
7
8
9
10
11
12
13
CH2OH

Figure 6. Infrared Spectra


MICRONS
CO2Me


MICRONS
H
O
CO2Me

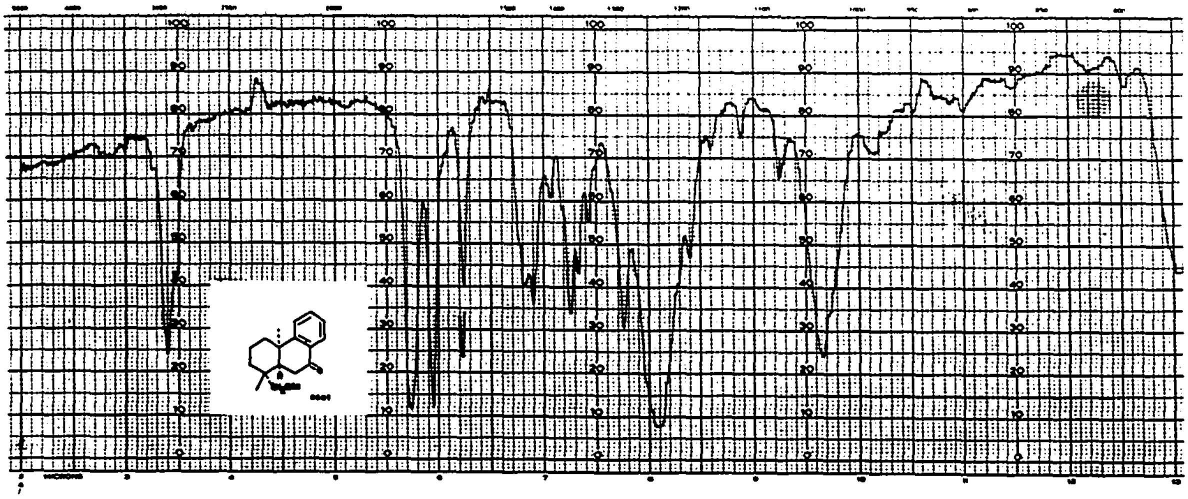

MICRONS
H
O
CO2Me

Figure 7. Proton Magnetic Resonance Spectra

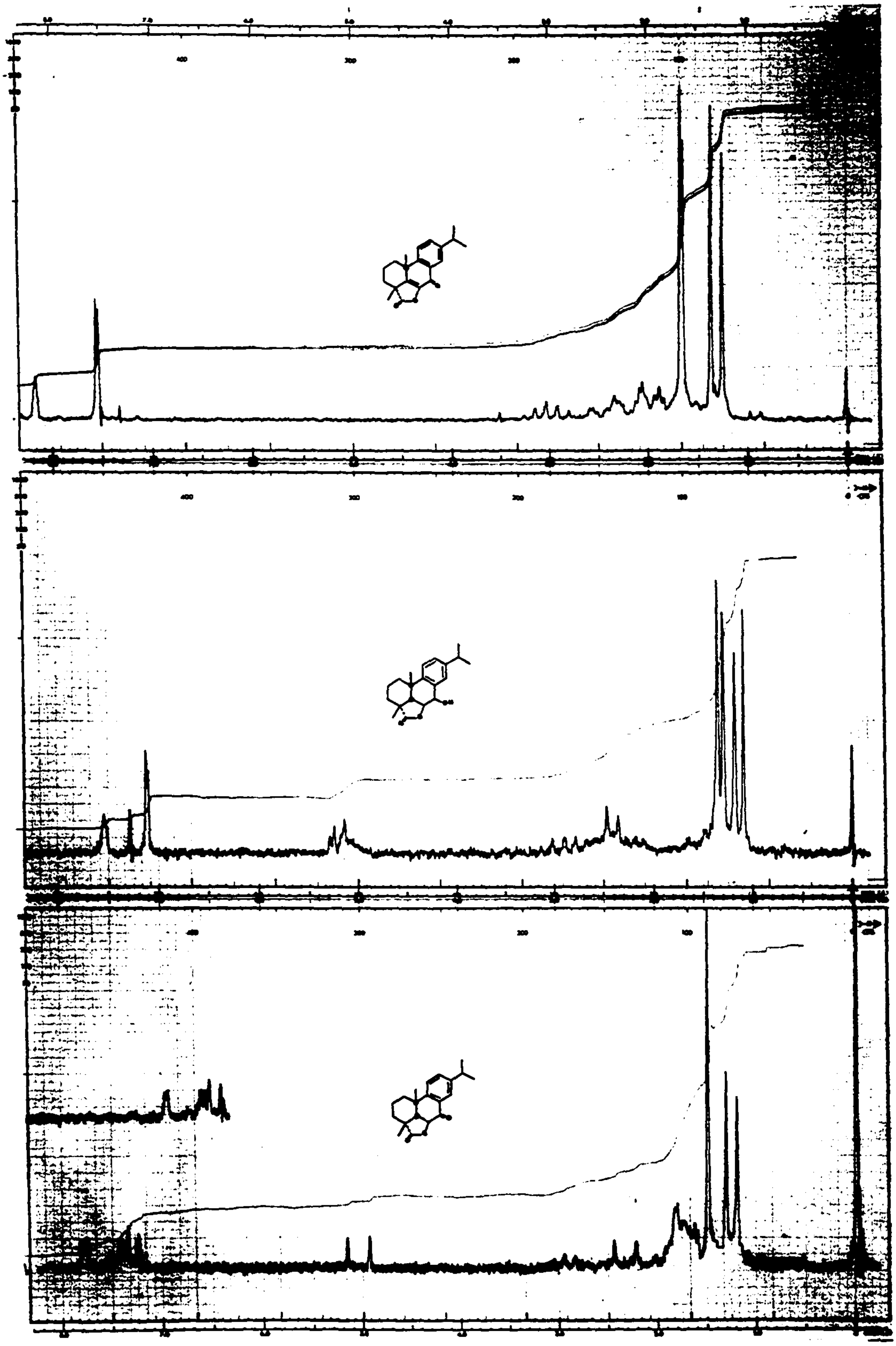
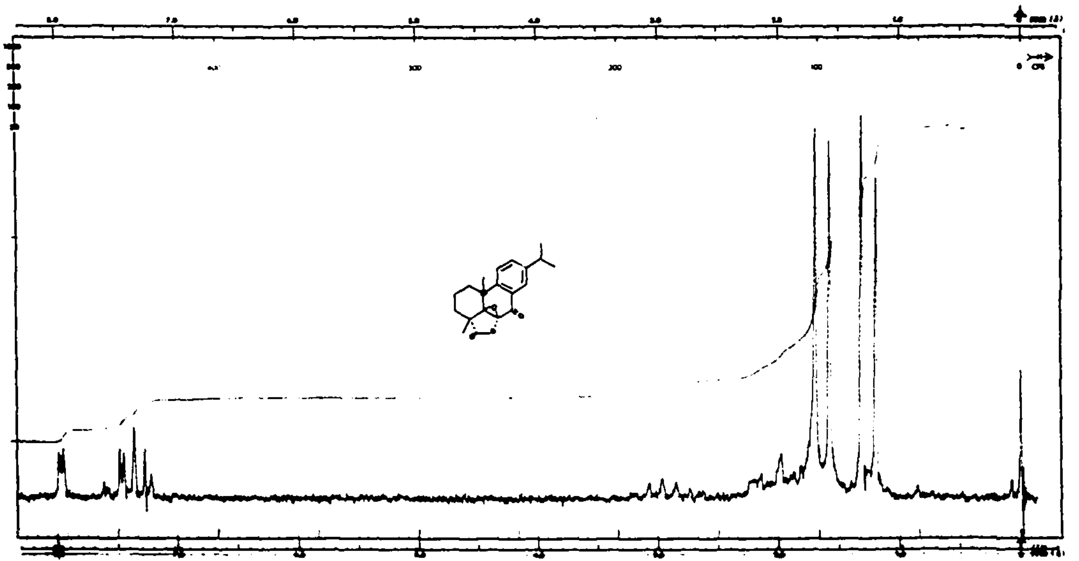
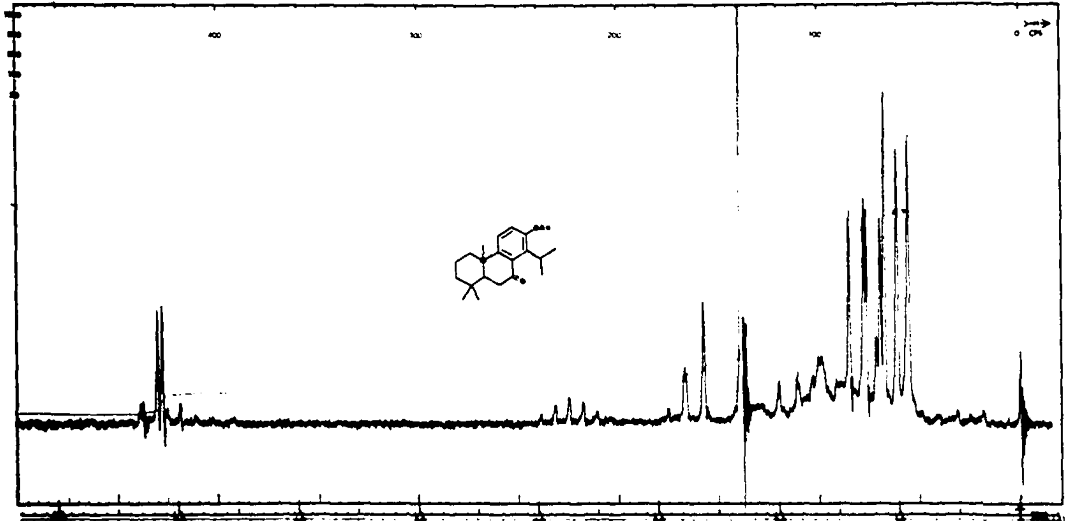


Figure 8. Proton Magnetic Resonance Spectra


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)
300
200
100
0 CPS


400
300
200
100
0 CPS

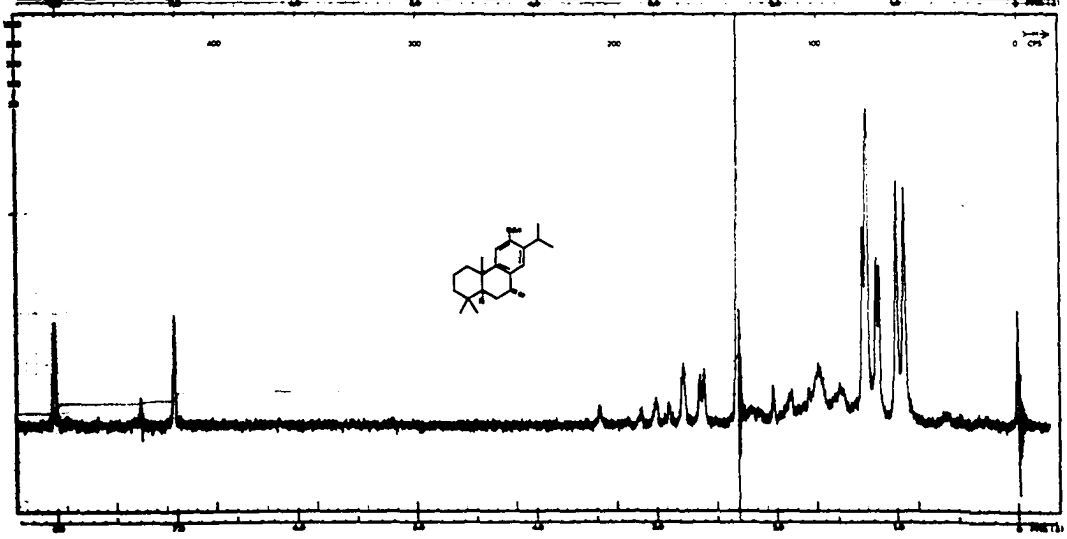
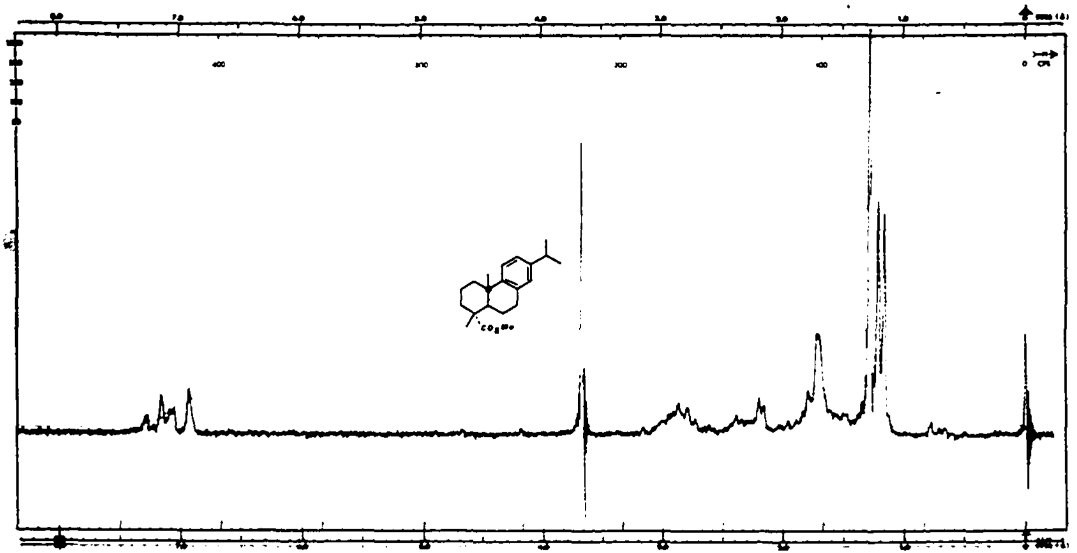
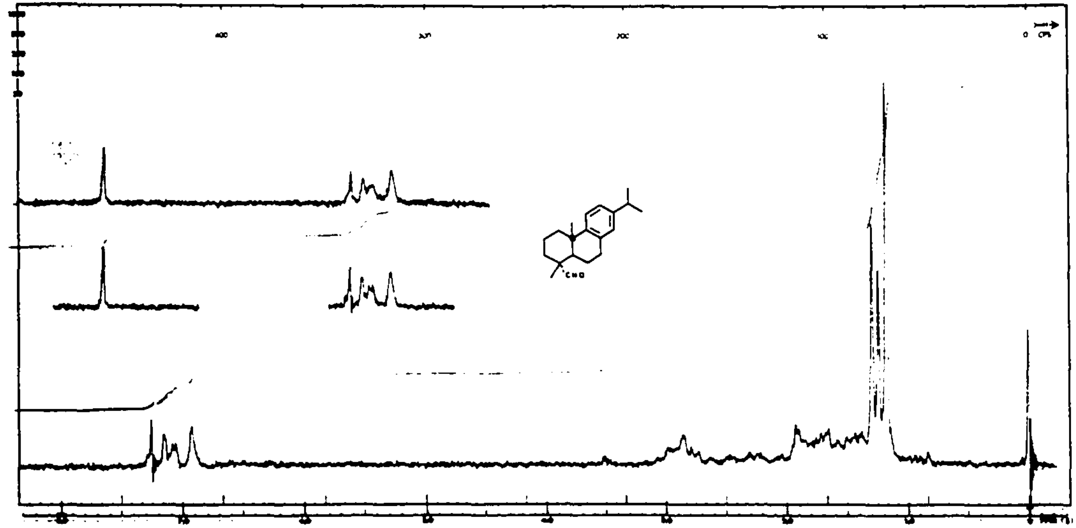

400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)

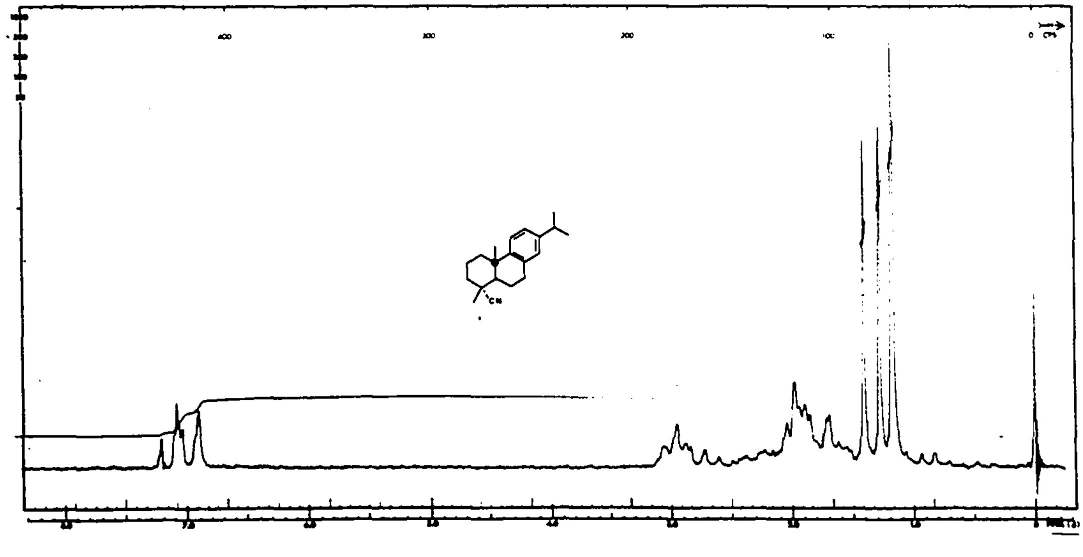
Figure 9. Proton Magnetic Resonance Spectra



8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 ppm (δ)
400
300
200
100
0 CPS
CO2Me



400
300
200
100
0 CPS
CHO



400
300
200
100
0 CPS
CH3
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 ppm (δ)

Figure 10. Proton Magnetic Resonance Spectra

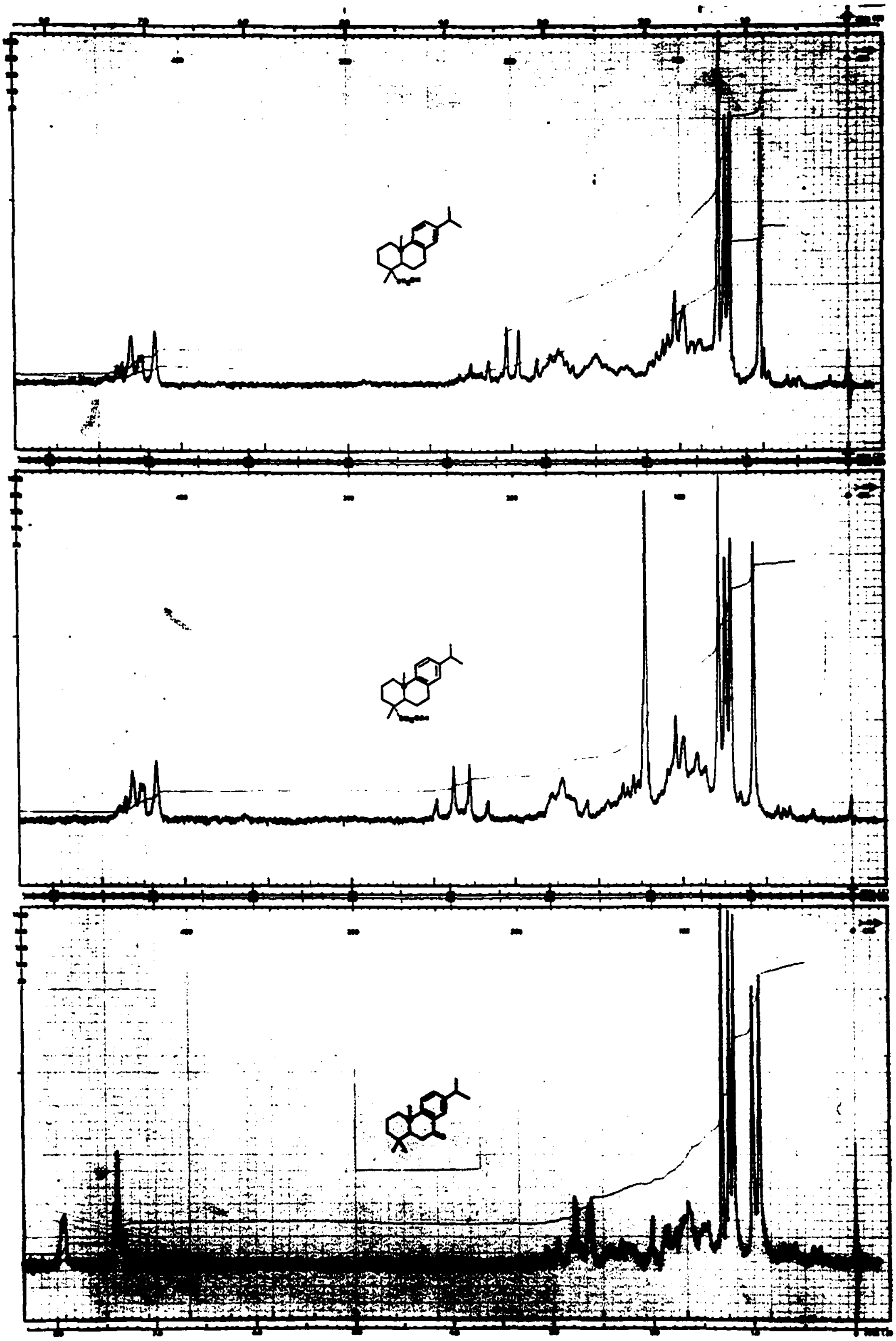
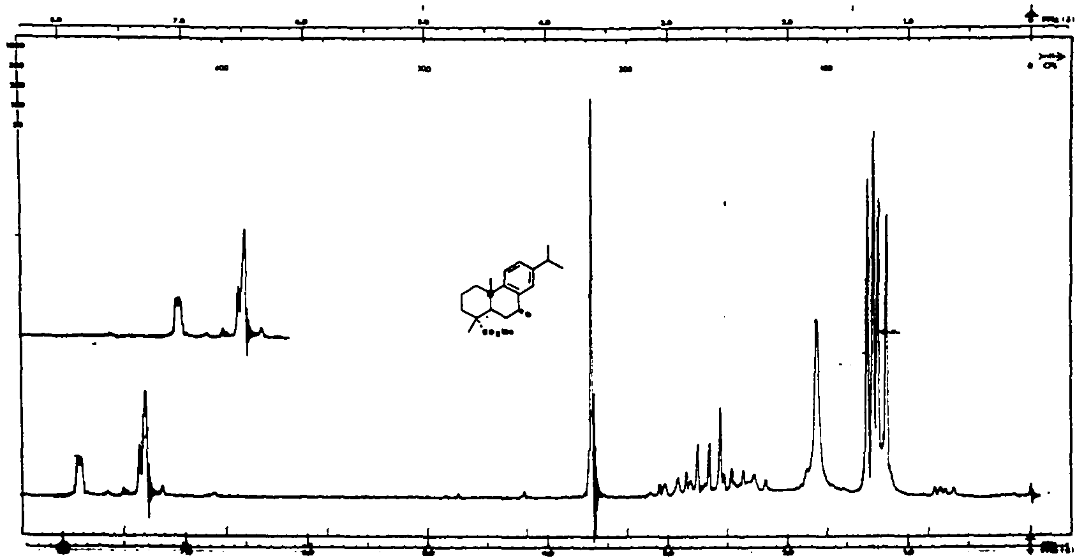
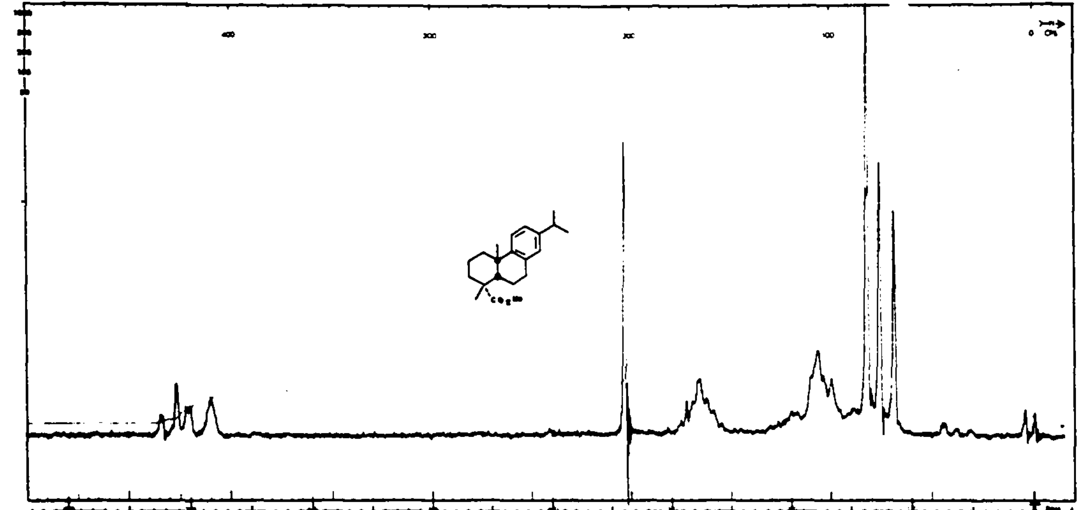


Figure 11. Proton Magnetic Resonance Spectra


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)
400
300
200
100
0 CPS
CO₂Me


400
300
200
100
0 CPS
CO₂Me

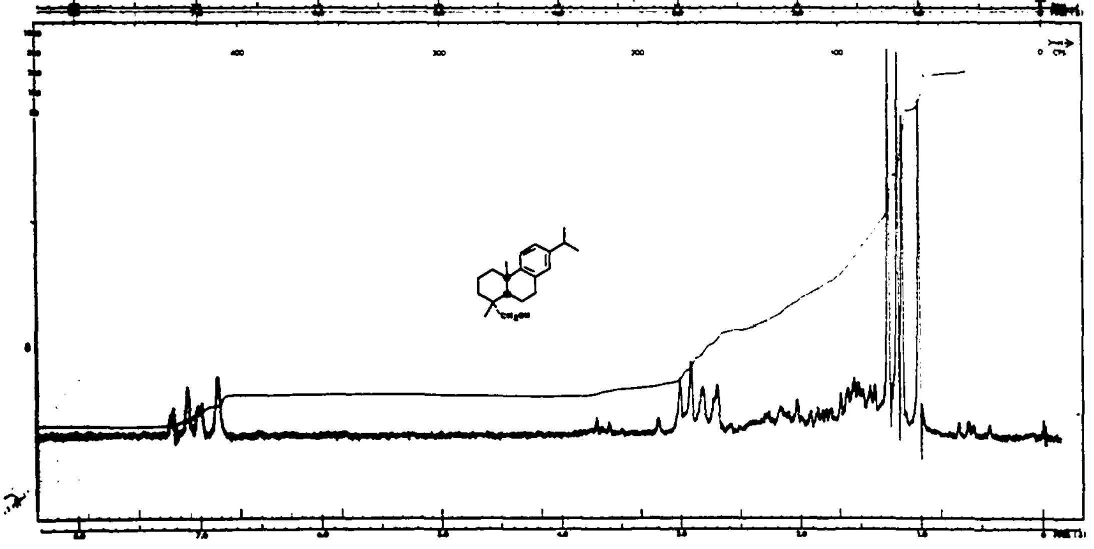
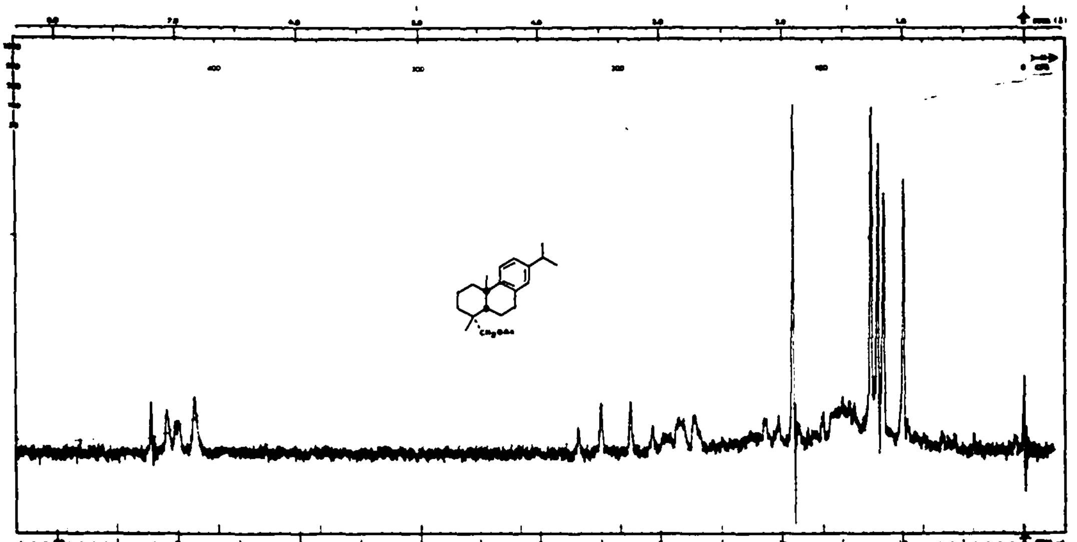
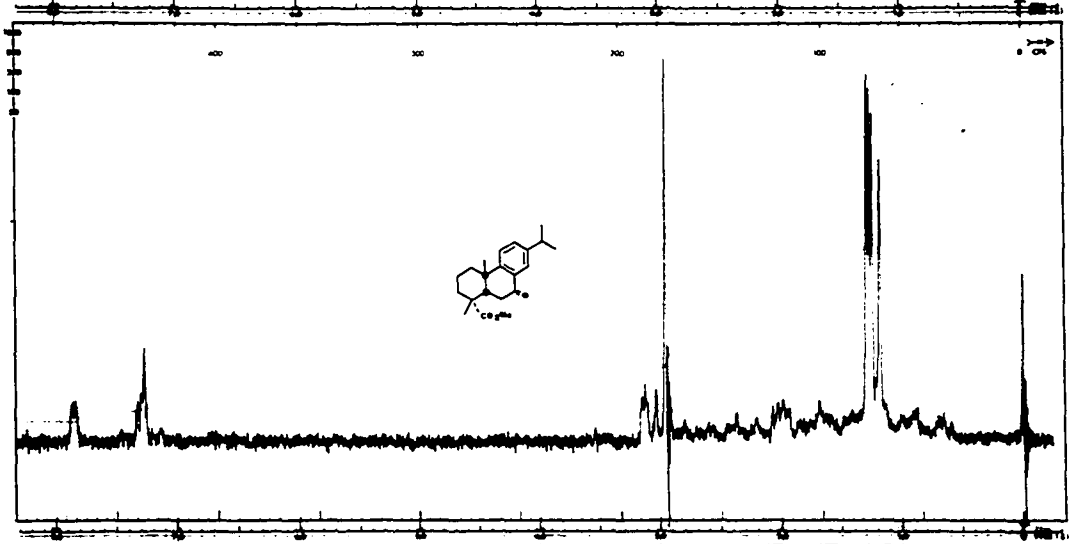

400
300
200
100
0 CPS
CH₂OH
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)

Figure 12. Proton Magnetic Resonance Spectra


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)
400
300
200
100
0
CPS
CH2OAc


400
300
200
100
0
CPS
CO2Me
O

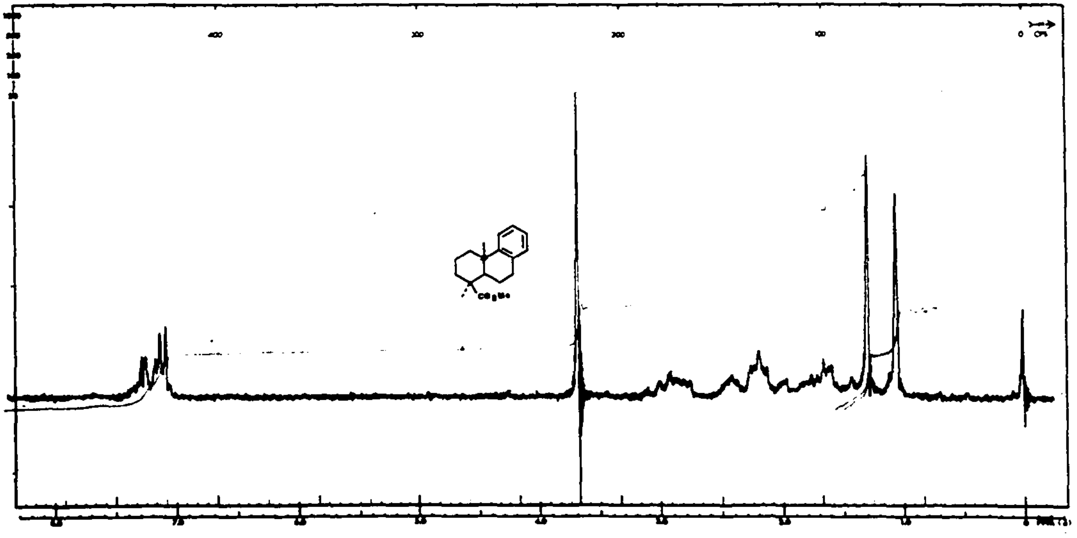
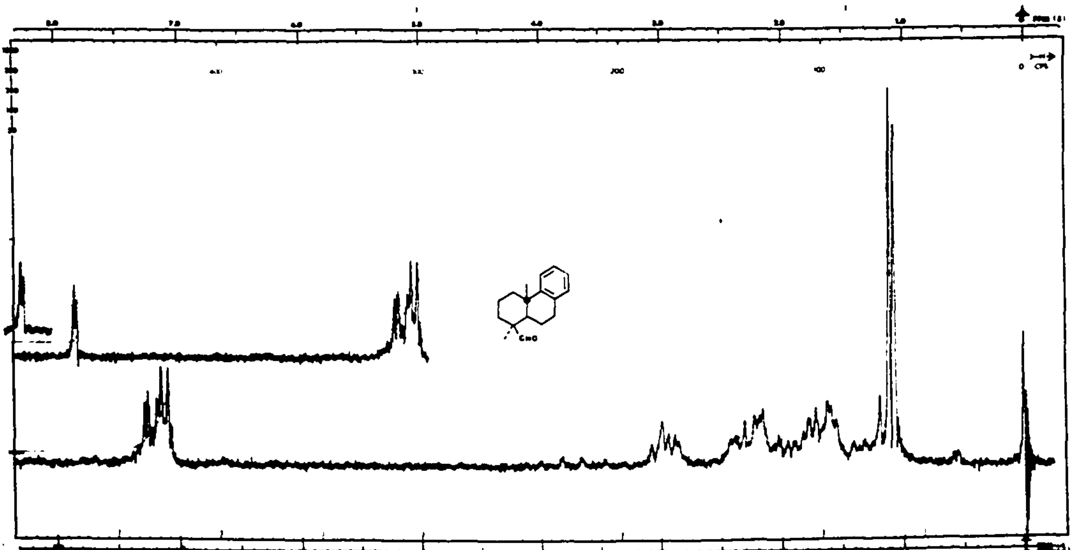
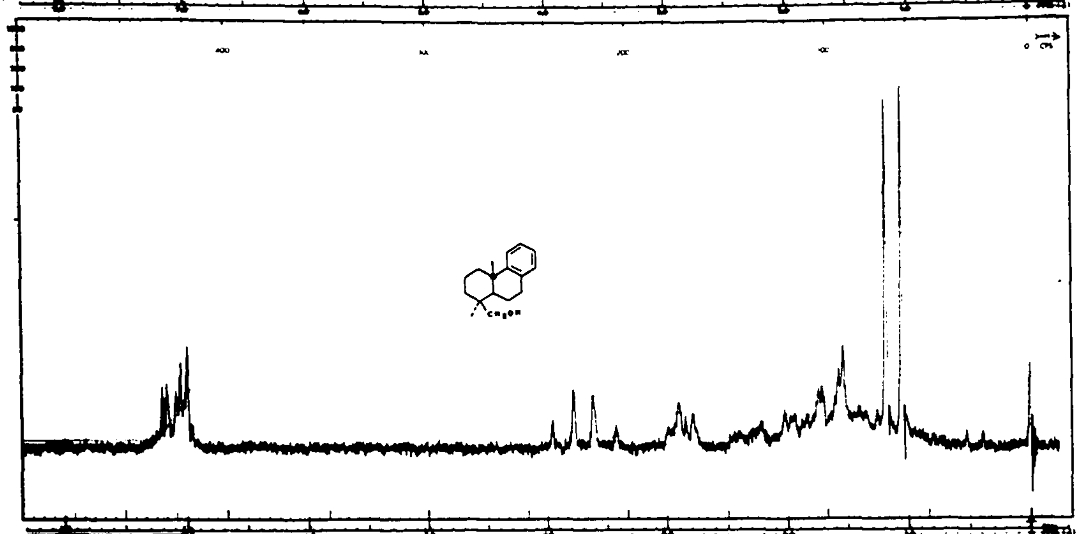

400
300
200
100
0
CPS
CO2Me
PPM (δ)

Figure 13. Proton Magnetic Resonance Spectra


CHO
400
300
200
100
0 CPS


CH2OH
400
300
200
100
0 CPS

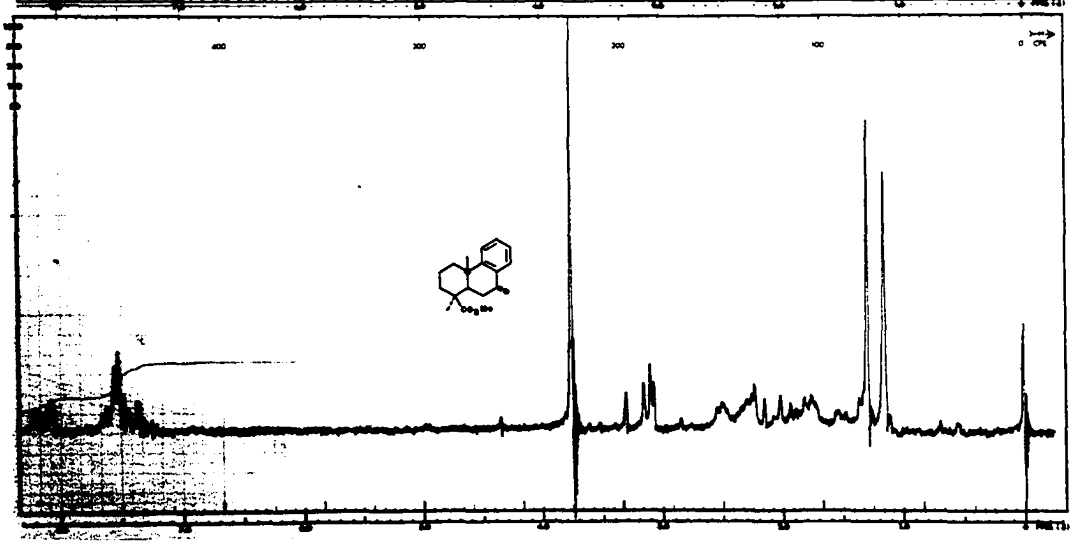
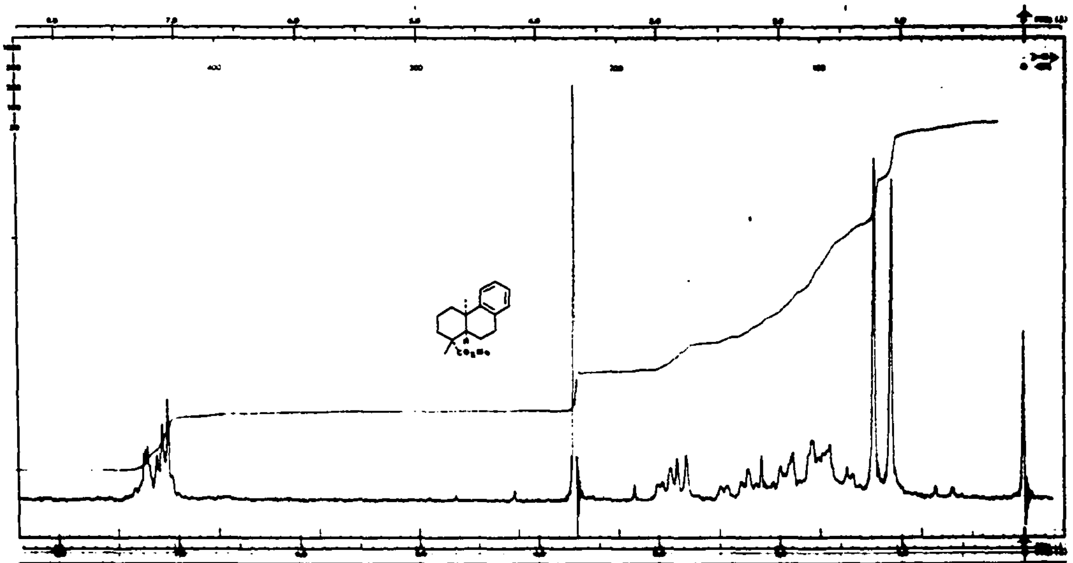
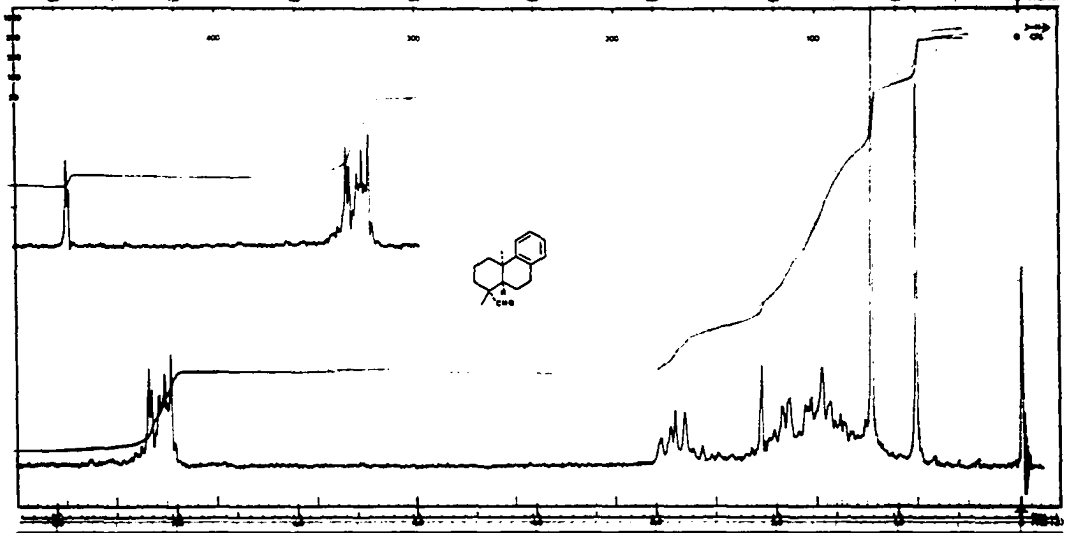

CO2Me
400
300
200
100
0 CPS

Figure 14. Proton Magnetic Resonance Spectra





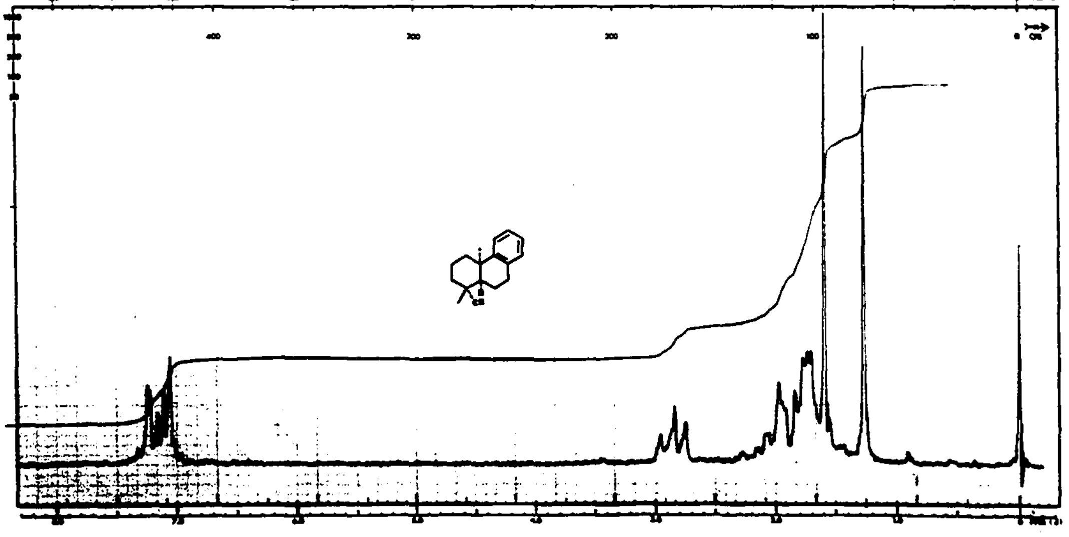
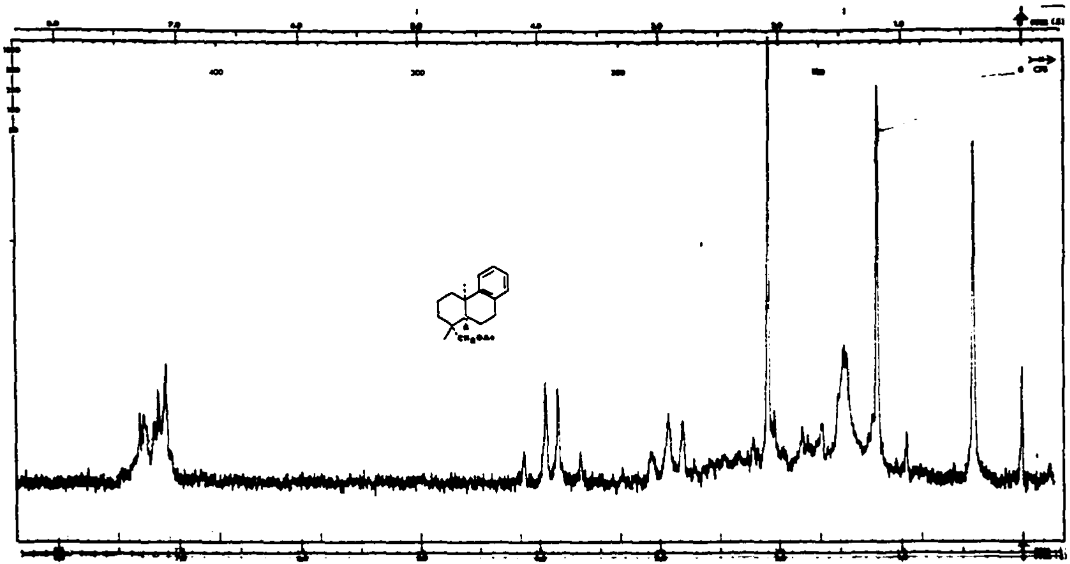
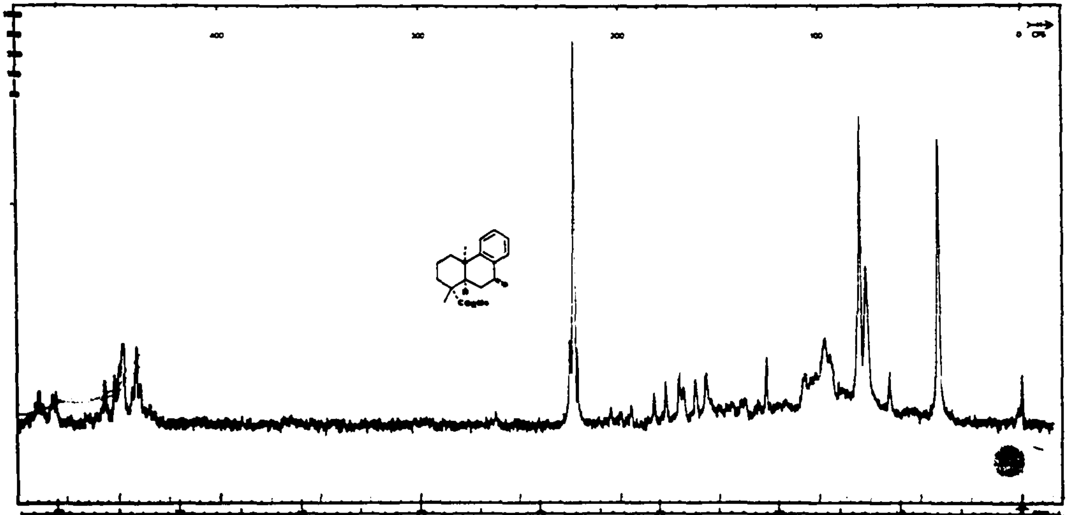


Figure 15. Proton Magnetic Resonance Spectra


CH2OAc
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)


CO2Me
400
300
200
100
0 CPS

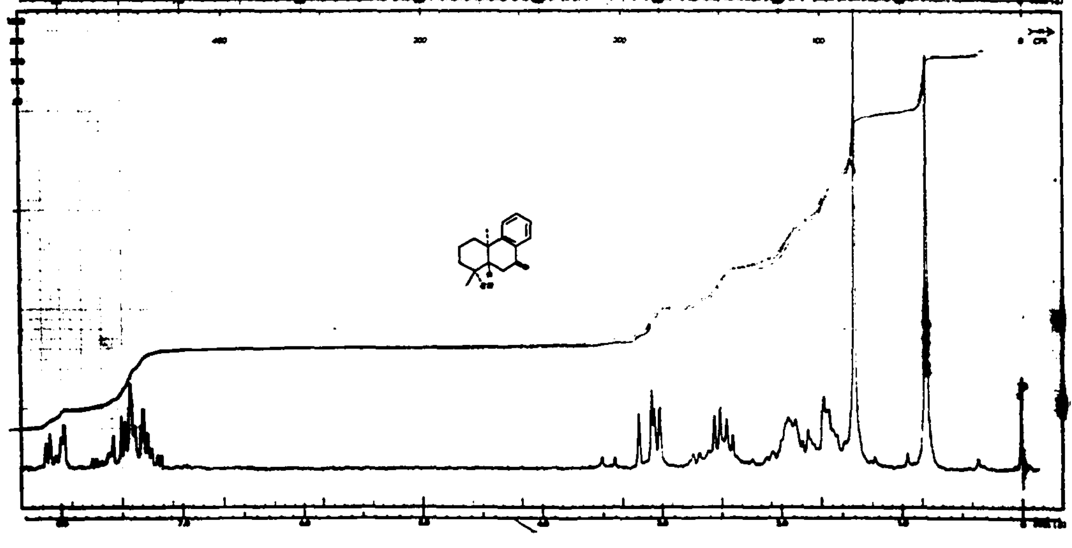

OH
400
300
200
100
0 CPS
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)

Figure 16. Proton Magnetic Resonance Spectra

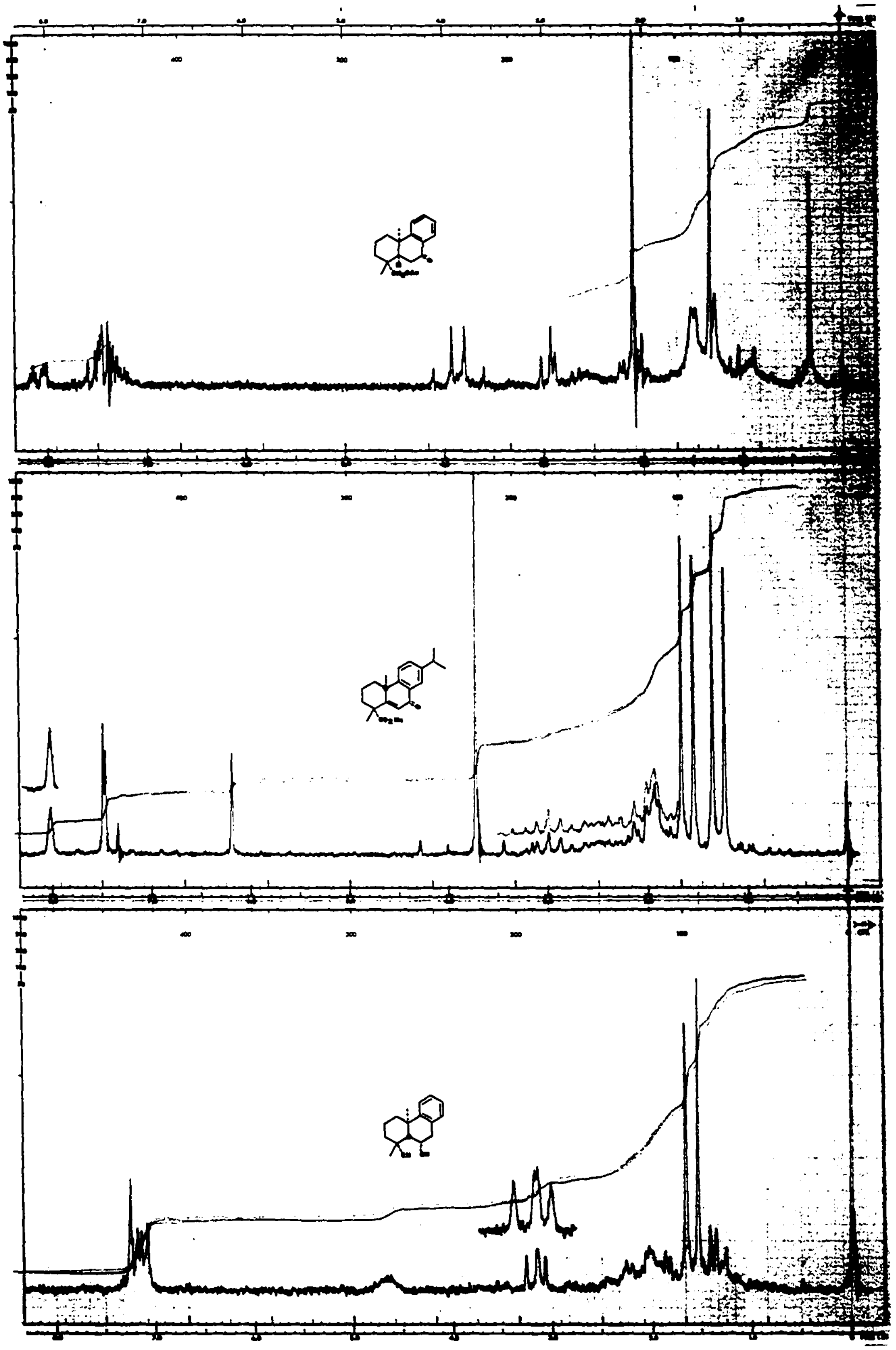


Figure 17. Proton Magnetic Resonance Spectra

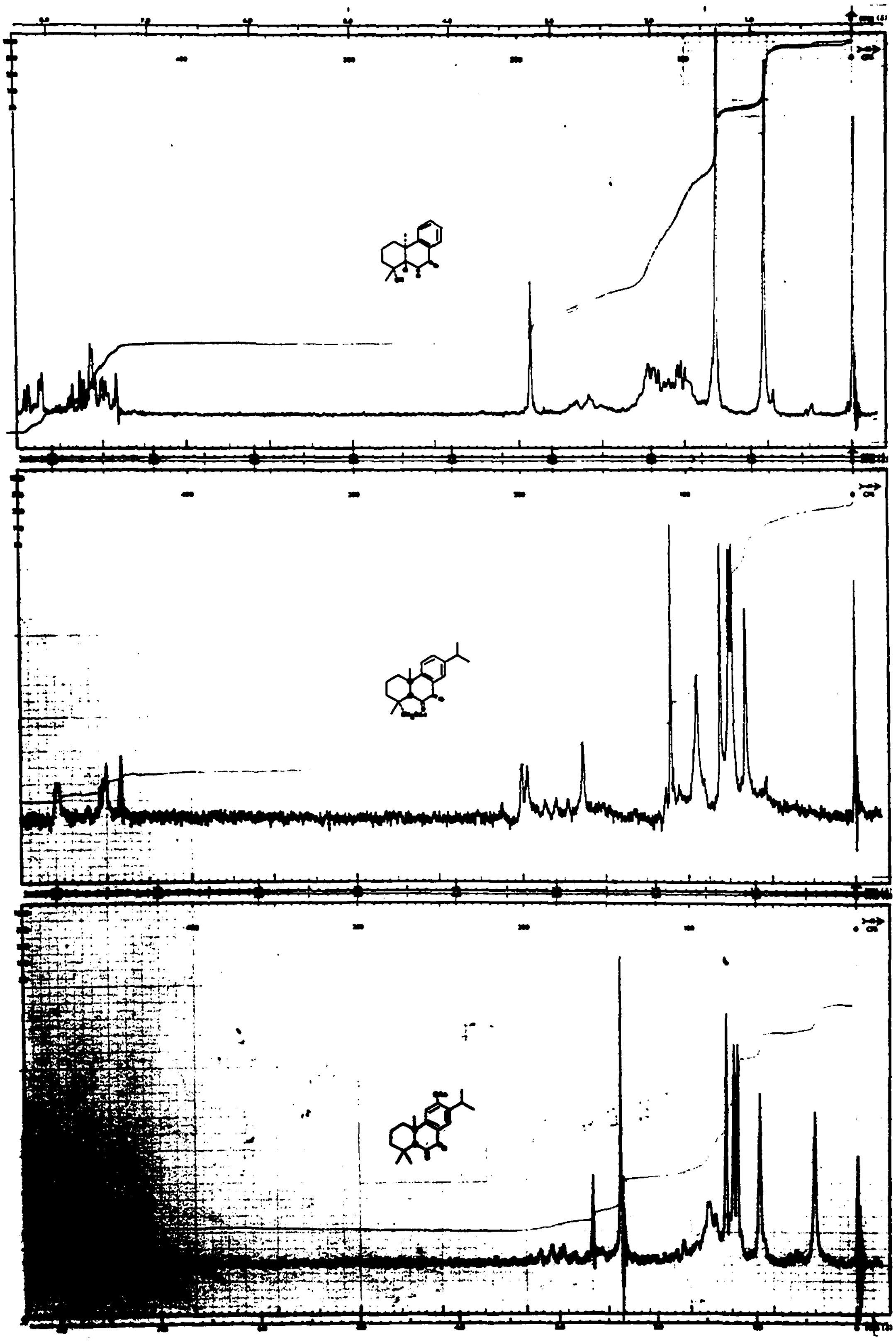


Figure 18. Optical Rotary Dispersion Curves

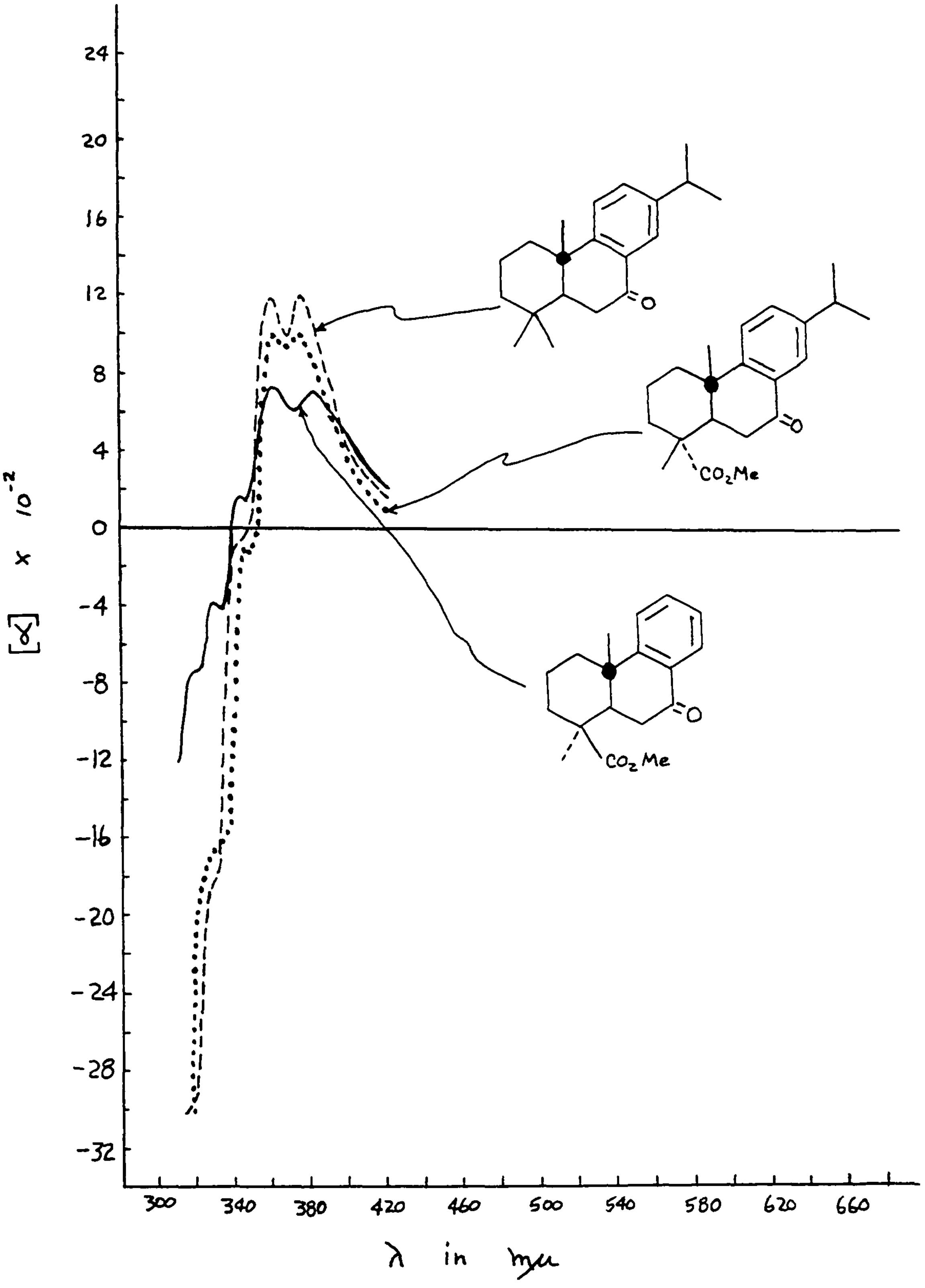

24
20
16
12
8
4
0
-4
-8
-12
-16
-20
-24
-28
-32
[α] x 10^-2
300
340
380
420
460
500
540
580
620
660
λ in mμ
CO₂Me
CO₂Me

Figure 19. Optical Rotary Dispersion Curves

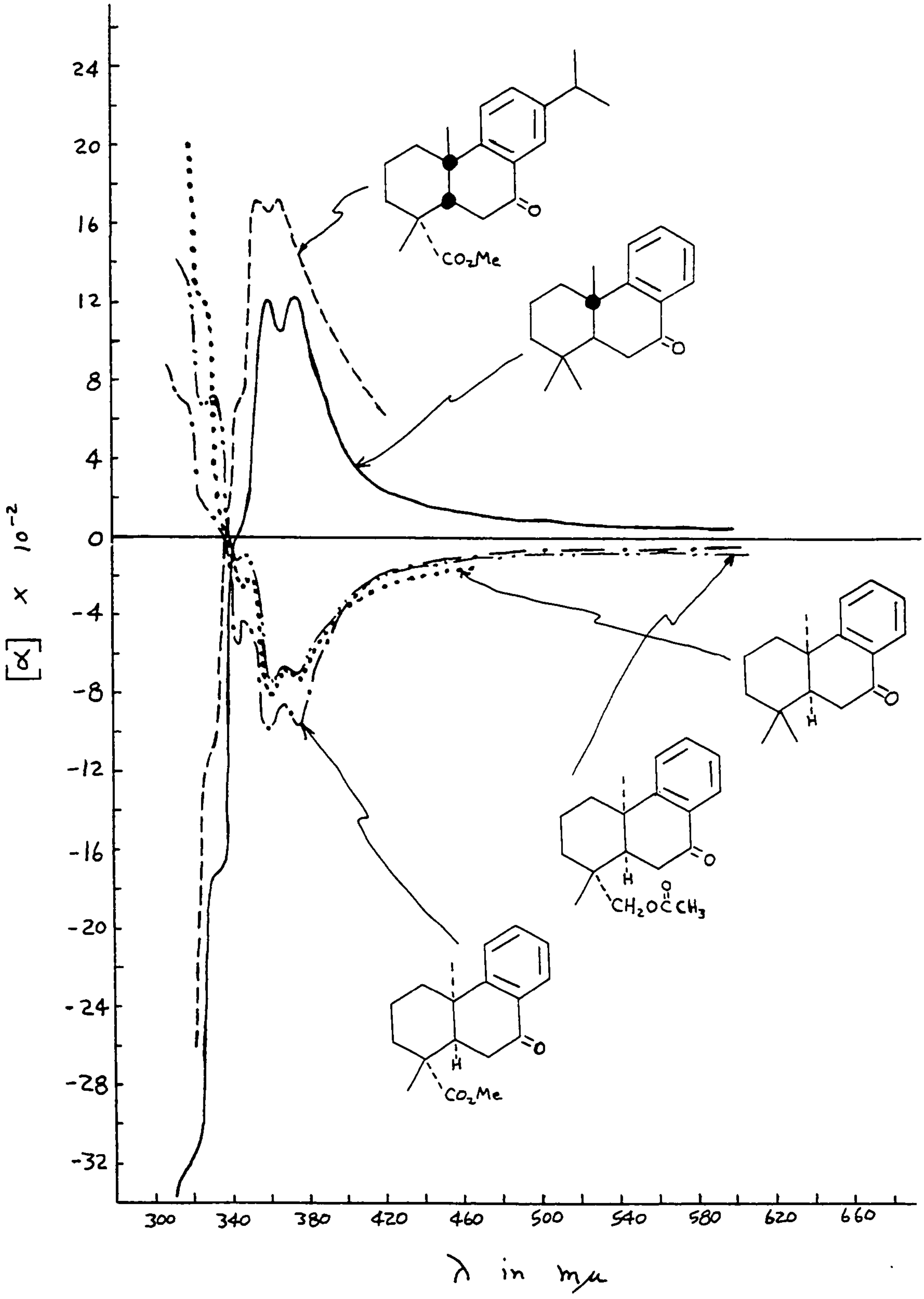
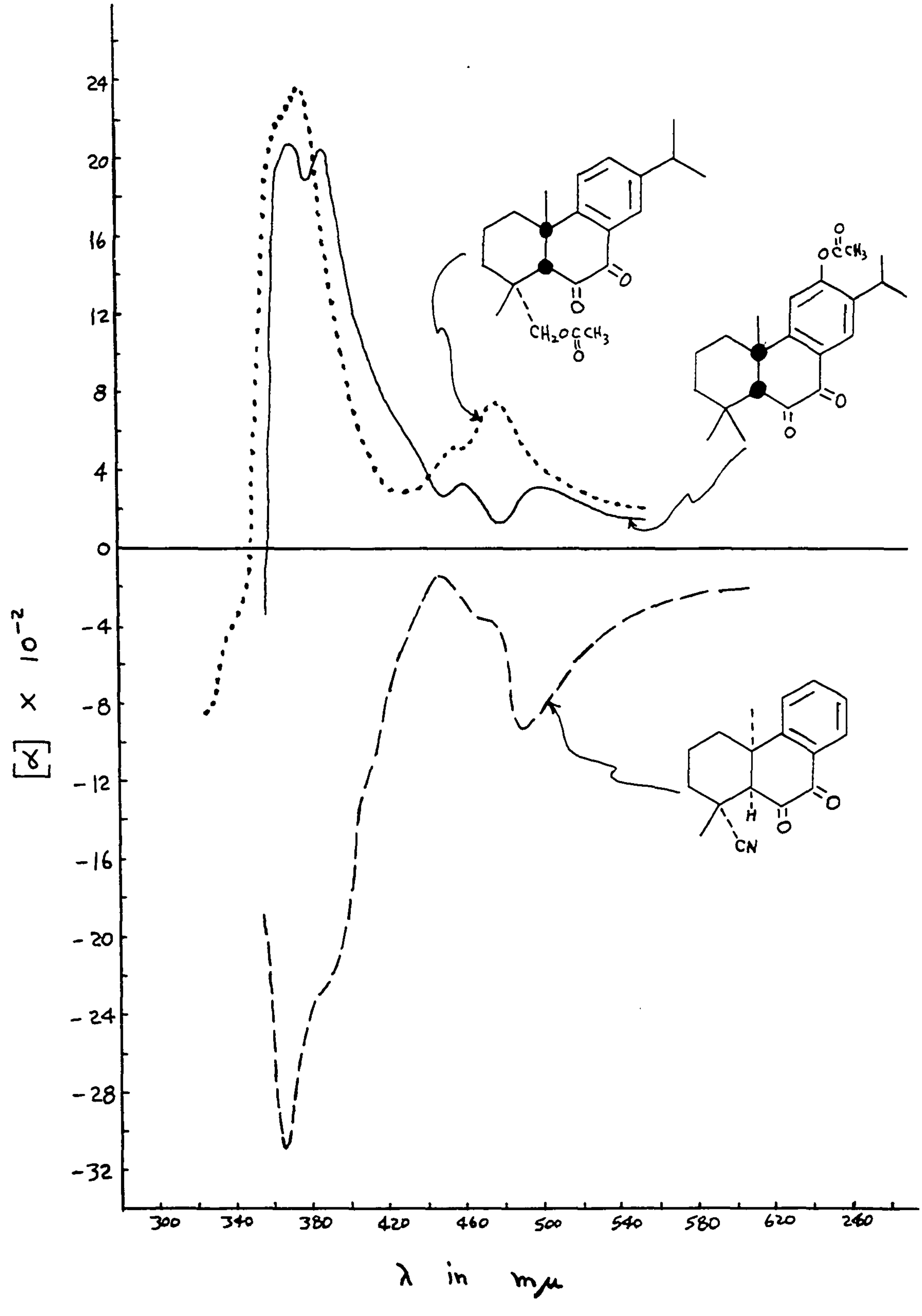

24
20
16
12
8
4
0
-4
-8
-12
-16
-20
-24
-28
-32
[α] × 10^{-2}
300
340
380
420
460
500
540
580
620
660
λ in mμ
CO$_2$Me
CH$_2$OCCH$_3$
H
O

Figure 20. Optical Rotary Dispersion Curves


24
20
16
12
8
4
0
-4
-8
-12
-16
-20
-24
-28
-32
[γ] × 10⁻²
300
340
380
420
460
500
540
580
620
260
λ in mμ
CH₂OCCH₃
O
OCCH₃
CN
H

EXPERIMENTAL

All melting and boiling points are uncorrected. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana, and Alfred Bernhardt, Mikroanalytisches Laboratorium, Mulheim (Ruhr), Germany. Optical rotations were measured in chloroform or ethanol solutions on an O. C. Rudolph polarimeter. The ultraviolet spectrum were run in 95% ethanol using a Carey model 14 recording spectrophotometer.

Chromatography was carried out with the use of three absorbents: Giulini Alumina obtained from Gerb. Giulini Gmbh., Ludwigshafen, Rhein, Germany; silica and a 50-50 mixture of Silica Gel G and Celite.

Thin-layer chromatography was carried out using Silica Gel G obtained from Research Specialties Company, 200 South Garrard Blvd., Richmond, California.

5-Isodesoxypodocarponitrile Enantiomer (XXIVa)

5-Isodesoxypodocarponitrile enantiomer, m.p. 107-108°, was prepared by the method of Wenkert and Jackson (22).

Proton magnetic resonance spectrum. See Figure 14.

Infrared spectrum. See Figure 14.

Optical rotation. See Figure 14.

Oxidation of 5-Isodesoxypodocarponitrile Enantiomer (XXIVa)

The procedure of Wenkert and Jackson (22) was followed to obtain 6,7-diketo-5-isodesoxypodocarponitrile enantiomer (XXVI) and 7-keto-5-isodesoxypodocarponitrile enantiomer (XXVa).

Infrared spectrum. See Figure 6 for 7-keto-5-isodesoxypodocarponitrile enantiomer.

Proton magnetic resonance spectrum. See Figure 17 and Figure 15, respectively.

Reduction of 5-Isodesoxypodocarponitrile Enantiomer (XXIVa)

A mixture of 600 mg. of 5-isodesoxypodocarponitrile enantiomer and 6.5 mg. fresh lithium aluminum hydride was refluxed in 40 ml. dry tetrahydrofuran for one hour. Excess lithium aluminum hydride was decomposed with water and the solvent removed under reduced pressure. There was added 30 ml. of 10% aqueous hydrochloric acid and the mixture refluxed for 4 hours. It was cooled and extracted with ether. The extract was dried over anhydrous magnesium sulfate and evaporated, yielding 277 mg. of crude, non-crystalline aldehyde (LXXIVb) which distilled at 85°/0.7 mm. Hg.

Analysis. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.40. Found: C, 83.68; H, 9.40.

Infrared spectrum. See Figure 2.

Optical rotation. $[\alpha]_D^{22}$ = +1.81 (c = 1.60, EtOH).

Proton magnetic resonance spectrum. See Figure 14.

Its 2,4-dinitrophenylhydrazon was crystallized from ethanol to give fine needles, m.p. 203-204°.

Analysis. Calcd. for $C_{23}H_{26}N_4O_4$: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.56; H, 6.19; N, 13.13.

The acidic solution was basified and extracted with ether. The ether solution was dried over magnesium sulfate and evaporated, yielding 291 mg. of crude amine. Crystallization from ether yielded the pure amine (XXIVc) m.p. 80-81°.

Analysis. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76. Found: C, 81.88; H, 10.52; N, 5.63.

Optical Rotation. $[\alpha]_D^{22}$ = +3.38 (c = 1.33, EtOH).

Infrared spectrum. λ max. 2.90(m) and 6.20(m) microns. (Infracord).

5-Isodesoxypodocarpane (LXXIVd)

A solution of 216 mg. of 5-isodesoxypodocarpal enantiomer and 3 ml. of hydrazine in 5 ml. anhydrous diethyleneglycol was heated at 140° for 1 hour. After cooling for 15 min. 2 g. of potassium hydroxide pellets were added. The condenser was removed (in hood) until the temperature had risen to 200° whereupon the solution was refluxed for

4 hours. Water was added to the cooled mixture and extracted with ether. The ether extract was washed with aqueous 10% hydrochloric acid, water, and dried over magnesium sulfate. Upon evaporation 153 mg. of crude 5-isodesoxypodocarpane was obtained b.p. 70°/0.7 mm. Hg. Upon distillation a crystalline product was obtained, m.p. 47-50°. [Lit. (25) b.p. 150-160°/4 mm. Hg, m.p. 53-54°]

Analysis. Calcd. for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.48; H, 10.61.

Infrared spectrum. See Figure 2.

5-Isodesoxypodocarpic Acid Enantiomer

A mixture of 18 g. of 5-isodesoxypodocarponitrile (LXXIVa), 30 g. of sodium hydroxide and 250 ml. of diethylene glycol was heated at 170° for 5 days. After the addition of 10 ml. of water the solution was heated at 190° for an additional 3 days. The cooled reaction solution was poured into water and extracted with ether. The extract was dried (magnesium sulfate) and evaporated to yield 1.47 g. of 5-isodesoxypodocarpamide. The aqueous phase then was acidified with 6 N hydrochloric acid and again extracted with ether. The extract was dried (magnesium sulfate) and evaporated to yield 16.53 g. of 5-isodesoxypodocarpic acid enantiomer, m.p. 159-160 (22).

Methyl 5-Isodesoxypodocarpate Enantiomer (LXXIVf)

An ether solution of diazomethane (made from 52 ml. of 50% potassium hydroxide, 20 g. N-nitrosomethylurea in ether) was added to an ether-methanol solution of 18.0 g. of the above acid. Two hours later the excess diazomethane was decomposed with acetic acid and the solvent removed under reduced pressure. Crystallization of the solid residue from methanol yielded 16.7 g. of ester, m.p. 87-89°. [Lit. (22) m.p. 90-90.5°]

Proton magnetic resonance spectrum. See Figure 14.

5-Isodesoxypodocarpol Enantiomer (LXXIVe)

A mixture of 200 mg. methyl 5-isodesoxypodocarpate enantiomer and 200 mg. lithium aluminum hydride was stirred overnight in 20 ml. dry tetrahydrofuran. Wet magnesium sulfate was added to decompose the excess hydride. Filtration and evaporation of the filtrate yielded 110 mg. of crude crystalline alcohol m.p. 55-60°. Sublimation gave pure 5-isodesoxypodocarpol enantiomer, m.p. 67-69°.

Analysis. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.52; H, 10.15.

Optical rotation. $[\alpha]_D^{22}$ = +5.55 (c = 0.99, EtOH).

5-Isodesoxypodocarpol Acetate Enantiomer (LXXIVL)

A mixture of 300 mg. 5-isodesoxypodocarpol enantiomer, 50 mg. anhydrous sodium acetate, and 20 ml. acetic anhydride was refluxed for 5 hours. Methanol was added and the solvent removed under reduced pressure. Water was added and the solution extracted with ether. The ether extract was washed with saturated sodium bicarbonate and with water, dried, and the solvent removed. A yield of 298 mg. of 5-isodesoxypodocarpol acetate was obtained which upon microdistillation gave a clear oil, b.p. ~140°/0.75 mm. Hg.

Analysis. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.54; H, 9.37.

Infrared spectrum. See Figure 2.

Optical rotation. $[\alpha]_D^{23} = -26.9$ (c = 1.04, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 15.

Methyl 7-Ketodesoxypodocarpate Enantiomer (LXXVI)

Methyl 7-ketodesoxypodocarpate enantiomer was prepared by the method of Ohta and Ohmori (24).

Methyl 6-Bromo-7-ketodesoxypodocarpate Enantiomer

The method of Ohta and Ohmori (25) was followed to prepare methyl 6-bromo-7-ketodesoxypodocarpate enantiomer.

Methyl $\Delta^{5,6}$-7-Ketodesoxypodocarpate Enantiomer (LXXIIb)

The method of Ohta and Ohmori (25) was followed in preparing methyl $\Delta^{5,6}$-7-ketodesoxypodocarpate enantiomer.

$\Delta^{5,6}$-7-Ketodesoxypodocarponitrile Enantiomer (LXXIIc)

A solution of 400 mg. of $\Delta^{5,6}$-7-ketodesoxypodocarponitrile enantiomer and 1.50 g. selenium dioxide, in 35 ml. acetic acid and 5 ml. water was refluxed for 1.5 hours. The precipitated selenium was filtered through a filter aid and the solvent removed. Water was added and the solution extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated to yield a yellow oil. Addition of hexane and benzene yielded 97 mg. of crystalline diketone identical with an authentic sample. Chromatography of the mother liquor on Giulini alumina, activity III, and elution with hexane-ether (9:1) gave 150 mg. of crystalline ene-one. Recrystallization from benzene-hexane and sublimation gave pure ^{5,6}-7-ketodesoxypodocarponitrile enantiomer, m.p. 213-214°.

Analysis. Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.20; H, 6.90; N, 5.5.

Infrared spectrum. See Figure 4.

Optical rotation. $[\alpha]_D^{23} = -112.9$ (c = 1.24, $CHCl_3$)

A solution of 1 g. of methyl $\Delta^{5,6}$-7-ketodesoxypodocarpate enantiomer and 3 g. of anhydrous lithium iodide was refluxed under nitrogen in 50 ml. dry collidine (distilled from calcium hydride) for 8 hours. Aqueous hydrochloric acid was added and extracted with ether. Ether extract was washed with 10% aqueous hydrochloric acid to remove collidine. After drying over magnesium sulfate and evaporation a yield of 300 mg. of crystalline solid was obtained. Sublimation afforded pure ketone LXXIIc, m.p. 119-120°. [Lit. (39) m.p. 120-121°]

5-Iso-7-ketodesoxypodocarpol Acetate Enantiomer (LXXV)

To a solution of 218 mg. of 5 iso-desoxypodocarpol acetate dissolved in 10 ml. acetic anhydride was added 100 mg. of chromium trioxide over a period of 3 hours. After stirring at room temperature for 16 hours, methanol was added and solvent removed under reduced pressure. Water was added and extracted with ether. The ether extract was washed with saturated sodium bicarbonate, water, dried, and solvent removed, yielding 243 mg. of crude product. Micro-distillation yielded the pure 5 iso-7-ketodesoxypodocarpol acetate enantiomer, b.p. ~160/0.75 mm. Hg.

Analysis. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.08; H, 8.13.

Infrared spectrum. See Figure 6.

Optical rotation. $[\alpha]_D^{23} = -45.8$ (c = 1.32, $CHCl_3$).

Optical rotatory dispersion curve. See Figure 19.

Proton magnetic resonance spectrum. See Figure 16.

Methyl $\Delta^{5,6}$-7-Ketodehydroabietate (LXXIb)

The previously described method by Wenkert, Carney, and Kaneko (62) was used to prepare methyl $\Delta^{5,6}$-7-keto-dehydroabietate.

Proton magnetic resonance spectrum. See Figure 16.

Dehydroabietal (LXXXVIc) and Dehydroabietyl Amine (LXXXVIe)

A mixture of 600 mg. of dehydroabietonitrile and 65 mg. fresh lithium aluminum hydride was refluxed in 12 ml. of dry tetrahydrofuran for one hour. The excess hydride was decomposed with water and the solvent removed under reduced pressure. To the residue was added 30 ml. of 10% aqueous hydrochloric acid and the mixture refluxed for 1 hour. It then was cooled and extracted with ether. The extract was dried over anhydrous magnesium sulfate and evaporated yielding 262 mg. of dehydroabietal, m.p. 90-91°. [Lit. (84) semicarbazone m.p. 217-219°]

Proton magnetic resonance spectrum. See Figure 9.

The acid solution was basified and extracted with ether. The ether solution was dried over magnesium sulfate and evaporated, yielding 317 mg. of amine (LXXXVIe) b.p. ~130°/2.5 mm. Hg. [Lit. (85) b.p. ca. 250°/12 mm. Hg, m.p. 41.0°]

Hydrogenation of Methyl $\Delta^{5,6}$-7-Ketodehydroabietate (LXXX)

A mixture of 100 mg. of methyl $\Delta^{5,6}$-7-ketodehydroabietate, 200 mg. of 10% palladium-on-charcoal, 3 drops of concentrated sulfuric acid and 15 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. Thereafter the palladium-on-charcoal was removed by filtration over a bed of celite. After evaporation under reduced pressure water was added and the mixture extracted with ether. The combined ether extract was dried over anhydrous magnesium sulfate and the solvent magnesium sulfate and the solvent removed. The resulting oil weighed 65 mg.

Thin-layer chromatography on silica, using 5% ethyl acetate — 95% chloroform to develop, was used to compare the reduced compound and methyl dehydroabietate. A single spot with identical R_f value resulted. Proton magnetic resonance analysis of both indicated that they were the same.

Proton magnetic resonance spectrum. See Figure 9.

Dehydroabietane (LXXXVIh)

The method of Wenkert and Beak (86) was used to prepare dehydroabietane.

Oxidation of Dehydroabietane

To a solution of 10 g. of dehydroabietane dissolved in 100 ml. acetic acid and 80 ml. acetic anhydride was added 15 g. of chromium trioxide over a 7-hour period. The temperature was kept between 20-25° by using an ice bath. The reaction mixture was left stirring at room temperature overnight. The mixture was poured into 320 g. of ice and 8 g. sodium acetate and stirred for 2 hours. The crude gum collected on the sides of the beaker. The solution was decanted and extracted with ether and the extract combined with the etheral solution of the gum. The combined ether extract was washed with water until the water layer was neutral. The extract was dried over magnesium sulfate and evaporated. The residue was chromatographed on alumina. Elution with hexane gave 6.7 g. of non-crystalline keto-acetate (LXII).

Further elution with 1:9 benzene-hexane gave 2.4 g. of the diketone which crystallized on standing. Crystallization of the solid from methanol gave 7-keto-13-acetyldeisopropyldehydroabietane (LXI), m.p. 143-145°.

Analysis. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.22; H, 8.16.

Optical rotation. $[\alpha]_D^{25}$ = +31.8 (c = 1.33, $CHCl_3$)(86).

16-Hydroxydehydroabietane (LXIII)

To a solution of 4.0 g. keto-acetate LXII in 100 ml. diethylene glycol was added 50 ml. anhydrous hydrazine. The solution was heated at 100° for 1.5 hours, cooled slightly before adding 30 g. of potassium hydroxide pellets. The condenser was removed and the temperature was raised to 190-200° and refluxed for 4 hours. Foaming was controlled by lowering the temperature. After the mixture had cooled, water was added and the mixture extracted with ether several times. The combined ether extract was washed with water, dilute hydrochloric acid, and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 3.2 g. of material which crystallized from hexane. Recrystallization from hexane afforded 16-hydroxydehydroabietane, m.p. 99-100°.

Analysis. Calcd. for $C_{20}H_{30}O$; C, 83.86; H, 10.56. Found: C, 83.69; H, 10.47.

Optical rotation. $[\alpha]_D^{27}$ = +52.5 (c = 1.70, $CHCl_3$) (86).

$\Delta^{16,17}$-Dehydroabietene

To a solution of 1.6 g. alcohol LXIII dissolved in 15 ml. dry pyridine was added 2 ml. of phosphorous oxychloride. The solution was stirred at room temperature overnight, after which water was cautiously added. The solution was made acidic with dilute hydrochloric acid and extracted with ether several times. The combined ether extract was washed with water and with saturated sodium chloride, and dried over magnesium sulfate. Evaporation yielded 3.2 g. of 7-keto-13-carboxydeisopropyldehydroabietane (LXIVa). Crystallization from methanol followed by sublimation gave a pure material m.p. 222-223°.

Analysis. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.39; H, 7.48.

Optical rotation. $[\alpha]_D^{23}$ = +41.0 (c = 0.21, $CHCl_3$).

An ether solution of diazomethane (from 200 mg. N-nitrosomethylurea and 3 ml. 50% potassium hydroxide in ether) was added to a solution of 100 mg. of 7-keto-13-carboxydeisopropyldehydroabietane in 10 ml. ether. After 15 min. the solution was evaporated under reduced pressure leaving 100 mg. of solid residue. Crystallization from methanol afforded pure 7-keto-13-carbomethoxydeisopropyldehydroabietane m.p. 105-107°.

Analysis. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.77; H, 8.08.

Infrared spectrum. See Figure 4.

Optical rotation. $[\alpha]_D^{23}$ = +10.7 (c = 1.08, $CHCl_3$).

13-Carbomethoxydeisopropyldehydroabietane (LXVb)

To a solution of 300 mg. of keto-acid LXIVa in 20 ml. of diethylene glycol was added 3.5 ml. of anhydrous hydrazine. The solution was heated at 100° for 1 hour and cooled slightly before the addition of 3.0 g. of potassium hydroxide pellets. The condenser was removed and the temperature raised to 190-200° and the mixture heated for 5½ hours. Aqueous hydrochloric acid was added to the cooled mixture and it was extracted with ether several times. The combines extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded the 7-desoxy acid LXVa. Sublimation gave a crystalline solid which softened at 113-115° and melted at 215-218°.

Analysis. Calcd. for $C_{19}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.98; H, 8.83.

Infrared spectrum. λ max. 5.82(s) microns (Infracord).

Optical rotation. $[\alpha]_D^{23}$ = +25.9 (c = 0.39, $CHCl_3$).

An ether solution of diazomethane was added to a solution of 100 mg. of the acid LXVa in 10 ml. ether. After

30 minutes the solution was evaporated under reduced pressure leaving a crystalline solid. Sublimation afforded an analytically pure residue LXVb m.p. 110-111°.

Analysis. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.40; H, 9.29.

Optical rotation. $[\alpha]_D^{23}$ = +56.4 (c = 1.35, $CHCl_3$).

16-Hydroxydehydroabietane (LXIII)

A flask containing 85 mg. (10 times excess) of magnesium was dried by heating with a free flame and keeping the contents under nitrogen. Upon cooling, dry tetrahydrofuran and 0.1 ml. methyl iodide was added. Bubbles began to form at once, whereupon more tetrahydrofuran and 0.4 ml. methyl iodide was added. The mixture was heated until most of the magnesium had dissolved. The ester LXVb (25 mg.) dissolved in tetrahydrofuran was added to the mixture and the latter refluxed for four hours. Aqueous ammonium chloride was added whereupon the solution was extracted with ether. After the ether was dried over anhydrous magnesium sulfate the solvent was removed under reduced pressure. Crystallization from hexane afforded 16-hydroxy-dehydroabietane (LXIII) m.p. 99-100°. Mixed melting point with authentic sample was undepressed.

Reduction of Keto-enolacetate Nitrile (XXX)

A mixture of 2.36 g. of keto-enolacetate nitrile XXX dissolved in 120 ml. ethyl acetate, 1.2 ml. concentrated sulfuric acid and 1.6 g. 10% palladium-charcoal was placed in a Parr hydrogenator under 10 pounds hydrogen and shaken for 8 hours. The catalyst was removed by filtration and the solvent removed. Water was added and the mixture extracted with ether. The extract was washed with saturated sodium bicarbonate and with water and dried over magnesium sulfate. A residue of 1.82 g. resulted. Chromatography of 3.2 g. of this residue on alumina, activity III, yielded 2.05 g. of desoxypodocarponitrile enantiomer (XXXIIIa) m.p. 87-88° (22) upon elution with hexane.

Infrared spectrum. See Figure 1.

Elution with 10-30% ether-hexane yielded 455 mg. of 6 α-acetoxydesoxypodocarponitrile enantiomer (XXXIa), m.p. 117-118° (22).

Lithium Aluminum Hydride Reduction of Nitrile XXXIIIa

A mixture of 600 mg. of desoxypodocarponitrile enantiomer (XXXIIIa) and 65 mg. lithium aluminum hydride was refluxed for one hour in 40 ml. anhydrous tetrahydrofuran. Water was added, the solvent removed under reduced pressure and 30 ml. of 10% hydrochloric acid added. The mixture was refluxed for 4 hours, cooled and extracted with ether. The extract was washed with water and dried (magnesium sulfate). Solvent removal yielded 549 mg. of crude aldehyde. Crystallization from methanol gave pure desoxypodocarpal enantiomer (XXXIIIb), m.p. 91-94°. The remaining aqueous solution was made basic and extracted with ether. The extract was dried (magnesium sulfate) and evaporated, yielding 52 mg. of crude amine. Distillation under reduced pressure gave pure desoxypodocarpyl amine enantiomer (XXXIIIc), b.p. ~95°/0.7 mm. Hg.

Analysis. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76. Found: C, 83.63; H, 10,54; N, 6.04.

Optical rotation. $[\alpha]_D^{22}$ = -7.78 (c = 2.99, EtOH).

Oxidation of Desoxypodocarpal Enantiomer (XXXIIIb)

Method I. A solution of 325 mg. potassium permanganate in 15 ml. of water was added over a 5-hour period with stirring to 500 mg. of desoxypodocarpal enantiomer dissolved in 50 ml. acetone. Sodium sulfite was added to destroy the excess permanganate. Aqueous hydrochloric acid was added and the solution extracted with ether. The extract was washed with 10% sodium hydroxide, whereupon the aqueous solution was acidified and extracted with ether. The extract was dried (sodium sulfate) and evaporated under reduced pressure. Crystallization of the residue yielded 501 mg. of acid. Recrystallization from methanol-water gave the pure desoxypodocarpic acid enantiomer (XXXIIId), m.p. 194-195°.

Method II. A solution of 32 mg. of aldehyde XXXIIIb, 2 ml. of 95% ethanol, 1 ml. 10% sodium hydroxide, and 0.5 ml. 30% hydrogen peroxide was combined and let stand for 25 hours. Extraction with ether yielded 11 mg. of desoxypodocarpic acid enantiomer (XXXIIId). Refluxing the above solution for 30 minutes gave overoxidation products indicated by absorption at 5.93μ (7-ketone) in the infrared.

Desoxypodocarpic Hydrazide Enantiomer (XXXIIIe)

A solution of 50 mg. of desoxypodocarpic acid enantiomer (XXXIIId), 2 drops of dry pyridine and 1 ml. of thionyl chloride was left standing at room temperature for 2 hours. The solution was evaporated under reduced pressure. The residue was dissolved in 10 ml. ether and 0.3 ml. 95% hydrazine hydrate in 1 ml. absolute ethanol at 0° was added. The mixture was shaken and after 5 minutes was poured into water and extracted with ether. The extract was dried (anhydrous magnesium sulfate) and evaporated under reduced pressure yielding 52 mg. of desoxypodocarpic hydrazide enantiomer, m.p. 162-168°. Recrystallization from ethyl acetate and sublimation yielded a pure sample m.p. 169-170°.

Analysis. Calcd. for $C_{17}H_{24}ON_2$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.77; H, 8.68; N, 10.26.

Infrared spectrum. See Figure 1.

Optical rotation. $[\alpha]_D^{22}$ = -127.8 (c = 0.80, EtOH).

Photolysis of Desoxypodocarpic Acid Azide Enantiomer

To 290 mg. of the hydrazide XXXIIIe dissolved in 10 ml. of acetic acid after cooling was added a saturated solution of 125 mg. of sodium nitrite in water and the mixture shaken for a few minutes. It was diluted with water and extracted with N-hexane. The extract was washed with ice water, with 5% sodium bicarbonate, again with water and then dried (sodium sulfate). The infrared spectrum of the hexane solution indicated absorption at 4.7μ (isocyanate) and 5.9μ (acid azide).

The hexane solution of the azide was irradiated using a water-cooled Pyrex vessel, a water-cooled Quartz immersion well and a 500 watt Hanovia high pressure mercury arc lamp. After an exposure of 1 hour the disappearance of the azide bands in the infrared spectrum was observed. The reaction mixture was evaporated and chromatographed on Giulini alumina, activity IV, in hexane. Elution with hexane gave 82 mg. of isocyanate as an oil, infrared spectrum 4.40μ. Hexane-benzene elution yielded 62 mg. of γ-lactam (infrared band at 5.98μ) as an oil. Ether-benzene elution gave 20 mg. of oily δ-lactam, (infrared band at 6.05μ).

6-α-Hydroxydesoxypodocarponitrile Enantiomer (XXXIb)

To a solution of 1.00 g. 6-acetoxydesoxypodocarponitrile enantiomer (XXXIa) dissolved in 100 ml. of ethanol was added 50 ml. of 10% sodium hydroxide. After stirring at room temperature under nitrogen for 19 hours the ethanol was removed under reduced pressure. Water was added and the solution extracted with ether. The ether extracted washed with water, dried (magnesium sulfate), and solvent removed, yielding 843 mg. of crude crystalline product. Recrystallization from ethyl acetate-chloroform gave the pure 6-hydroxydesoxypodocarponitrile enantiomer, m.p. 204-205°.

Analysis. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.15; H, 8.44; N, 5.36.

Infrared spectrum. See Figure 3.

Optical rotation. $[\alpha]_D^{23}$ = -32.1 (c = 1.11, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 16.

6-α-Hydroxydesoxypodocarponitrile Nitrite Enantiomer (XXXIc)

Nitrosyl chloride gas was bubbled through a stirring solution of 100 mg. of 6-hydroxypodocarponitrile enantiomer (XXXIb) dissolved in 15 ml. dry pyridine and cooled to between -20° and -30°. When the solution appeared to have a persistent reddish-brown color, water was added and the crystalline precipitate filtered and washed with water to give 108 mg. of crude product. Recrystallization from methylene chloride-hexane gave the pure nitrite XXXIc, m.p. 189-191°.

Analysis. Calcd. for $C_{17}H_{20}O_2N_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.09; H, 7.34; N, 10.03.

Infrared spectrum. See Figure 3.

Optical rotation. $[\alpha]_D^{23}$ = -26.6 (c = 1.07, $CHCl_3$).

Photolysis of 6-α-Hydroxydesoxypodocarponitrile Nitrite Enantiomer (XXXIc)

The apparatus consisted of a water-cooled Pyrex vessel, a water-cooled Quartz immersion well and a 500 watt Hanovia high pressure mercury arc lamp with a pyrex filter sleeve. A solution of 350 mg. of 6-α-hydroxydesoxypodocarponitrile nitrite enantiomer in 150 ml. of dry benzene was irradiated at about 20° for 1 hour with mixing at 10 minute intervals.

After standing overnight the solvent was removed. The residue was dissolved in 10 ml. acetic anhydride to which was added 100 mg. sodium acetate and refluxed for 1 hour. Chromatography on Guilini alumina, activity I (pH 4-5), and elution with 5% ether-hexane gave 120 mg. of 6-α-acetoxydesoxypodocarponitrile enantiomer (XXXIa) No other products could be identified.

Methyl Desoxypodocarpate (XIe)

Methyl desoxypodocarpate was prepared by the procedure of Wenkert and Jackson (28).

Proton magnetic resonance spectrum. See Figure 12.

Methyl 7-Ketodesoxypodocarpate (XXXVI)

The procedure of Wenkert and Jackson (22) was used in preparing methyl 7-ketodesoxypodocarpate.

Optical rotatory dispersion curve. See Figure 18.

Proton magnetic resonance spectrum. See Figure 13.

Methyl $\Delta^{5,6}$-7-Ketodesoxypodocarpate (LXXIb)

A mixture of 2.8 g. of methyl 7-ketodesoxypodocarpate and 5 g. of freshly sublimed selenium dioxide in 80 ml. acetic acid and water (enough for dissolution) was refluxed for 6 hours. The mixture was filtered and the solvent removed under reduced pressure. Water was added, the mixture extracted with ether and the extract dried over magnesium sulfate and evaporated. Crystallization from methanol gave 2.8 g. of crude product. Recrystallization gave pure methyl $\Delta^{5,6}$-7-ketodesoxypodocarpate, m.p. 105-106 [Lit. (25) m.p. 105-106°].

Analysis. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.76; H, 7.21.

Optical rotation. $[\alpha]_D^{23}$ = +164.9 (c = 0.69 $CHCl_3$).
$[\alpha]_D^{22}$ = +149.18 (c = 0.85 EtOH).

Hydrolysis of Methyl $\Delta^{5,6}$-7-Ketodesoxypodocarpate (LXXIb)

To 60 ml. collidine (distilled from calcium hydride) was added 2 g. of ene-one ester LXXIb and 5 g. lithium iodide (freshly dried by heating under vacuum until all water was removed). This mixture was refluxed under nitrogen for 10.5 hours. The solution cooled and upon the addition of water, extracted with ether. The extract was washed with 10% hydrochloric acid and with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, yielding 1.59 g. of crystalline product. Sublimation afforded a pure analytical sample of ketone LXXIa, m.p. 119-120°. [Lit. (25) m.p. 120-121°]

Analysis. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.19; H, 8.43.

Optical rotation. $[\alpha]_D^{23}$ = +54.7 (c = 0.51, $CHCl_3$).
$[\alpha]_D^{22}$ = +99.9 (c = 0.72, EtOH).

A mixture of 30 ml. of 12% potassium hydroxide-ethanol solution and 530 mg. of ene-one ester LXXIb was refluxed for 2 hours. The solvent was evaporated under reduced pressure and water was added. The mixture was extracted with ether and the extract dried over anhydrous magnesium sulfate. Evaporation of the solution under reduced pressure yielded 430 mg. of crude product.

Chromatography on silica yielded only a small amount of the decarboxylated product LXXIa.

5(6)-Dehydro-6-hydroxy-7-ketodehydroabietic Lactone (LXXVII)

5(6)-Dehydro-6-hydroxy-7-ketodehydroabietic lactone was prepared according to the procedures of Wenkert, Carney and Kaneko (62).

Proton magnetic resonance spectrum. See Figure 7.

6-Hydroxy-7-hydroxydehydroabietic Lactone (LXXVIII)

The procedures of Wenkert, Carney and Kaneko (62) were followed in preparing 6-hydroxy-7-hydroxydehydroabietic lactone.

Proton magnetic resonance spectrum. See Figure 7.

6-Hydroxy-7-ketodehydroabietic Lactone (LXXIX)

The procedures of Wenkert, Carney and Kaneko (62) were followed in preparing 6-hydroxy-7-ketodehydroabietic lactone.

Proton magnetic resonance spectrum. See Figure 7.

Methyl 5-Isodehydroabietate (LXXXIb)

To a solution of 28 mg. of 6-hydroxy-7-ketodehydroabietic lactone (LXXIX) dissolved in 2 ml. acetic acid was added zinc amalgam (made by shaking 3 g. zinc metal, 20 mesh, 0.3 g. mercuric chloride, 0.24 ml. concentrated hydrochloric acid, and 4 ml. water for 5 min.) and 6 ml. of 6 N hydrochloric acid. This mixture was refluxed 50 hours. The mixture was cooled, decanted and extracted with ether. The extract was washed with 5% aqueous sodium hydroxide. The aqueous extract was acidified with hydrochloric acid and extracted with ether. The organic extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure, yielding 16 mg. of 5-isodehydroabietic acid (LXXXIa). Crystallization from aqueous methanol gave pure acid, m.p. 121-124°.

Analysis. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.01; H, 9.18.

Optical rotation. $[\alpha]_D^{23}$ = -106 (c = 0.57, $CHCl_3$)

An etheral solution of 120 mg. of 5-isodehydroabietic acid was treated with an ether solution of excess diazomethane for 3 hours. The solution was evaporated under reduced pressure yielding methyl 5-isodehydroabietate LXXXIb. Sublimation yielded the pure ester, m.p. 98-100°.

Analysis. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.99; H, 9.48.

Infrared spectrum. See Figure 5.

Optical rotation. $[\alpha]_D^{23}$ = -58.5 (c = 1.25, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 11.

Hydrogenation of 6-Hydroxy-7-ketodehydroabietic Lactone (LXXIX)

A mixture of 17 mg. of 6-hydroxy-7-ketodehydroabietic lactone, 50 mg. of 10% palladium-charcoal and 2 drops of concentrated sulfuric acid in 15 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. When the uptake of hydrogen ceased, the catalyst was filtered using Celite as a filter-aid and the solvent removed under reduced pressure. Water was added and the mixture extracted with ether. The extract was washed with 5% sodium hydroxide, water and dried (magnesium sulfate). Evaporation of the ether yielded 16 mg. of a lactone. Infrared 5.65μ (γ-lactone). Acidification of the aqueous extract, extraction with ether, drying of the ether solution (magnesium sulfate) and evaporation yielded no acidic material.

Reduction of 5(6)-Dehydro-6-hydroxy-7-ketodehydroabietic Lactone (LXXVII)

A mixture of 260 mg. of 5(6)-dehydro-6-hydroxy-7-ketodehydroabietic lactone (LXXVII), 400 mg. of 10% palladium-charcoal and 5 drops of concentrated sulfuric acid in 20 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. After a four-mole uptake of hydrogen, the reaction ceased, the catalyst was filtered, and the solvent removed under reduced pressure. Water was added and the mixture extracted with ether. The extract was dried (anhydrous magnesium sulfate) and evaporated. Crystallization from aqueous methanol gave 5-iso-dehydroabietic acid LXXXIa, m.p. 121-124°, infrared spectrum and p.m.r. spectrum identical with that obtained by zinc-hydrochloric acid reduction of 6-hydroxy-7-ketodehydroabietic lactone.

Oxidation of Methyl 5-Isodehydroabietate (LXXXIb)

To a solution of 200 mg. methyl 5-isodehydroabietate dissolved in 2.5 ml. acetic acid, was added 250 mg. chromium trioxide dissolved in 4 ml. acetic acid and 1 ml. water. After stirring at room temperature for 15 hours saturated sodium chloride was added and the mixture extracted with chloroform. The extract was washed with 5% aqueous sodium hydroxide and water, dried (anhydrous magnesium sulfate) and evaporated under reduced pressure, yielding 209 mg. of neutral material.

Chromatography of 50 mg. of neutral material on alumina, activity III, and elution with 10% benzene-hexane gave 45 mg. of keto-ester LXXXIV, m.p. 98-100°, after two sublimations.

Analysis. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.41; H, 8.71.

Infrared spectrum. See Figure 5.

Optical rotation. $[\alpha]_D^{23}$ = +9.9 (c = 1.22, $CHCl_3$).

Optical rotatory dispersion curve. See Figure 19.

Proton magnetic resonance spectrum. See Figure 12.

Addification of the aqueous solution and extraction with chloroform yielded 9 mg. of acidic material.

Reduction of Methyl 5-Isodehydroabietate (LXXXI)

To a solution of 100 mg. of methyl 5-isodehydroabietate dissolved in 25 ml. of dry tetrahydrofurone was added 200 mg. of lithium aluminum hydride and the mixture refluxed overnight. After wet sodium sulfate was used to decompose the excess lithium aluminum hydride, the mixture was filtered and the solvent removed under reduced pressure. The oily residue was distilled, b.p. ~110/0.25 mm. Hg. Upon standing the 5-isodehydroabietol (LXXXIc) crystallized, m.p. 61-62°.

Analysis. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.92; h, 10.59.

Infrared spectrum. See Figure 5.

Optical rotation. $[\alpha]_D^{23.5} = -9.7$ (c = 0.94, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 11.

5-Isodehydroabietol Acetate

A mixture of 29 mg. of 5-isodehydroabietol (LXXXI), 5 mg. of anhydrous sodium acetate, and 4 ml. of acetic anhydride was refluxed for 2 hours. Methanol was added and the solvent removed under reduced pressure. Water was added and the solution extracted with ether. The ether extract was washed with saturated sodium bicarbonate and with water, dried (magnesium sulfate), and the solvent removed. A yield of 34 mg. of 5-isodehydroabietol acetate was obtained which upon micro-distillation gave a clear oil, b.p. ~90°/0.25 mm. Hg.

Analysis. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.87. Found: C, 80.44; H, 10.01.

Infrared spectrum. See Figure 6.

Optical rotation. $[\alpha]_D^{23.5} = +3.3$ (c = 0.96, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 12.

Reduction of 5(6)-Dehydro-6-hydroxy-7-ketodehydroabietic Lactone (LXXVII)

A solution of 45 mg. lactone LXXVII dissolved in 10 ml. acetic acid to which 50 mg. zinc dust had been added, was refluxed for a total of 6 hours. After each 30-minute period of refluxing an additional 25 mg. of zinc dust were added. The acetic acid was removed under reduced pressure,water was added and the mixture extracted with ether. The extract was dried and the solvent removed. Since the infrared spectrum of the crude product indicated that the reduction was not complete, the residue was dissolved in 5 ml. acetic acid, 300 mg. of zinc dust were added, the mixture refluxed for 5.5 hours and the reaction worked up as before. The ether solution was extracted with 5% sodium hydroxide, the aqueous solution acidified and extracted with ether. The organic extract was dried (magnesium sulfate) and the solvent removed under reduced pressure, yielding 20 mg. of impure material. Chromatography on a column of 50% Silica Gel G and 50% Celite and elution with chloroform yielded nonidentifiable impurities. Upon eluting with 5% acetic acid in chloroform a crystalline acidic material was obtained and on sublimation gave 5-iso-7-ketodehydroabietic acid (LXXXIVa), m.p. 174-180°.

Analysis. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.35; H, 8.10.

An etheral solution of 5-iso-7-ketodehydroabietic acid (LXXXIVa) was treated with an etheral solution of excess diazomethane. After evaporation under reduced pressure the resulting methyl ester was compared with the known ester by thin-layer chromatographic technique, using 5% chloroform-95% ethyl acetate as the eluting solvent. Identical spots were obtained.

Isolation of 5(6)-epoxy-6-hydroxy-7-ketodehydroabietic Lactone (LXXXIII)

When the normal procedures for formation of 5(6)-dehydro-6-hydroxy-7-ketodehydroabietic lactone (LXXVII) was altered so that the temperature was raised from 55° after several hours to 100° a mixture crystallized on the usual work up. Chromatography of 500 mg. of this mixture on 25 g. Silica Gel G mixed with 25 g. Celite afforded a reasonable separation. Eluting with 25% chloroform in benzene gave 48 mg. of 5(6)-epoxy-6-hydroxy-7-ketodehydroabietic lactone. Recrystallization from ethanol or methanol gave a pure sample, m.p. 241-242°.

Analysis. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; O, 19.61. Found: C, 73.35; H, 6.91; O, 19.68.

Infrared spectrum. See Figure 3.

Optical rotation. $[\alpha]_D^{23.5} = -105.8$ (c = 0.7, $CHCl_3$).

Proton magnetic resonance spectrum. See Figure 8.

Ultraviolet spectrum. λmax. 212, 260, 312 millimicrons. λmin. 232, 288 millimicrons.

The second portion eluted off the columns was a 67 mg. mixture of two lactones. Continued elution with the same solvent gave a total of 359 mg. of 5(6)-dehydro-6-hydroxy-7-ketodehydroabietic lactone (LXXVII).

5-Isodehydroabietonitrile

5-Isodehydroabietic acid (LXXXIa), 400 mg., was refluxed with 10 ml. of thionyl chloride for 2 hours. After vacuum removal of the excess thionyl chloride the residue was dissolved in dry tetrahydrofuran and added to a lithium amide suspension, prepared by the addition of 700 mg. of lithium and a few crystals of ferric nitrate to 200 ml. of liquid ammonia. The mixture was stirred for 2 hours and left standing until the ammonia had evaporated. The residue was decomposed with 10% hydrochloric acid and extracted with ether. Evaporation yielded 260 mg. of nitrile-amide mixture. This was combined with 10 ml. of thionyl chloride and refluxed 8 hours. After the excess reagent was removed under reduced pressure water was added and the solution extracted with ether. Evaporation of the solvent gave 236 mg. of brown oil. Chromatography on alumina activity III gave 120 mg. of almost clear oil, b.p. ~145°/0.75 mm. Hg.

5-Iso-6,7-diketodehydroabietol Acetate (CXIII)

To a solution of 200 mg. of 5-isodehydroabietol acetate, dissolved in 2.5 ml. of acetic acid, was added 250 mg. of chromium trioxide, dissolved in 1 ml. water and 4 ml. acetic acid. After stirring at room temperature for 16 hours, saturated sodium chloride was added and the mixture extracted with ether. The ether extract was washed with 5% sodium hydroxide and with water, dried, and the solvent removed to yield 209 mg. of neutral material. Trituration with hexane followed by crystallization from hexane gave the yellow crystalline 5-iso-6,7-diketodehydroabietol acetate, m.p. 102-108°.

Analysis. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.93; H, 8.03.

Infrared spectrum. See Figure 17.

Optical rotation. $[\alpha]_D^{22}$ = +115.4 (c = 0.91, $CHCl_3$)

Optical rotatory dispersion curve. See Figure 20.

The basic extract was acidified and extracted with ether. The ether extract was washed with water, dried and evaporated yielding 13 mg. of acidic material.

Hydrolysis of C-4 Esters XXIIIb, LXXVI, XIe and LXXIII

General Procedure. A solution of 80 mg. ester, 0.6 ml. of 10% potassium hydroxide, and 4 ml. ethylene glycol was refluxed (bath temperature 195-200°) for 4 hours. The solution was cooled, diluted with water acidified with 6 N hydrochloric acid, and extracted with ether. The ether extract was washed with water, 5% sodium hydroxide, and dried (magnesium sulfate). The aqueous extract was acidified, extracted with ether and dried (magnesium sulfate).

Methyl Dehydroabietate (XXIIIb)

From 80 mg. of methyl dehydroabietate was obtained 40.5 mg. of ester and 39.2 mg. of acid.

Methyl 7-Ketodehydroabietate (LXXVI)

From 80 mg. of methyl 7-ketodehydroabietate was obtained 1 mg. of ester and 72.5 mg. of acid.

Methyl Desoxypodocarpate (XIe)

From 80 mg. of methyl desoxypodocarpate was obtained 76.2 mg. of ester and 3.5 mg. of acid.

Methyl 7-Ketodesoxypodocarpate (LXXIII)

From 80 mg. of methyl 7-ketodesoxypodocarpate was obtained 57.5 mg. of ester and 17.3 mg. of acid, m.p. 185-195°.

Analysis. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.25; H, 7.59.

SUMMARY

The conversion of dehydroabietonitrile to desoxypodocarpic acid azide enantiomer and 6-α-hydroxydesoxypodocarponitrile enantiomer nitrite has been achieved and the intermediates characterized. The conversion of these compounds by photolysis to a degradation product of atisine, a diterpenoid alkaloid has been only partially successful.

The degradation of the C-13 isopropyl group of dehydroabietane to carboxyl derivatives as well as its conversion to $\Delta^{15,16}$ dehydroabietene has been achieved.

5(6)-Dehydro-6-hydroxy-7-ketodehydroabietic lactone has been converted to 5-isodehydroabietic acid. Methyl 5-isodehydroabietate has been oxidized to the C-7 monoketone and 6,7-diketone. Lithium aluminum hydride reduction of methyl 5-isodehydroabietate yielded the alcohol which was acetylated and oxidized with chromic acid to the 6,7-diketone. The 5-isodehydroabietonitrile was prepared from the acid.

Zinc-acetic acid reduction of 5(6)-dehydro-6-hydroxy-7-ketodehydroabietic lactone yielded 5-iso-7-ketodehydroabietic acid, while Clemmenson reduction of 6-hydroxy-7-ketodehydroabietic lactone gave 5-isodehydroabietic acid.

Huang-Minlon reduction of _cis_-podocarpal enantiomer gave _cis_-podocarpane. Lithium aluminum hydride reduction

of methyl cis-podocarpate yielded the alcohol which was acetylated and oxidized to the 7-keto derivative.

An efficient method for the hydrolytic decarboxylation of methyl $\Delta^{5,6}$-7 ketopodocarpate enantiomer and methyl $\Delta^{5,6}$-7 ketodehydroabietate is described.

The rate of hydrolysis of methyl dehydroabietate and methyl podocarpate and their 7-keto derivatives has been compared. The hydrogenation of methyl $\Delta^{5,6}$-7 ketodehydroabietate to methyl dehydroabietate is described.

Various A-B cis and trans derivatives as well as ring-B oxygenated derivatives of aromatic diterpenes have been prepared and their conformations determined by means of nuclear magnetic resonance and optical rotatory dispersion methods.

The stereochemical relationship of the C-5 and C-6 hydrogens of 6-hydroxy-7-ketodehydroabietic lactone has been established.

LITERATURE CITED

1. Karel Wiesner and Zdenek Valenta, *Progress in the Chemistry of Organic National Products*, Vol. XVI, Springer-Verlag, Vienna, 1958.

2. A. Wright, Report on the Aconite Alkaloids, Yearbook of Pharmacy, 1879.

3. H. A. D. Jowett, Contributions to our Knowledge of the Aconite Alkaloids, Part XIII, On Atisine, the Alkaloid of Aconitum heterophyllum, *J. Chem. Soc. (London)*, *69*, 1518 (1896).

4. A. Lawson and J. E. C. Topps, Aconitine, Part II, The Relationship between Aconitine and Atisine and Some Degradation Products of the Latter, *J. Chem. Soc. (London)*, 1640 (1937).

5. O. E. Edwards and L. Marion, *Canad. J. Chem.*, *30*, 627 (1952).

6. O. E. Edwards and L. Marion, *ibid.*, *32*, 195 (1954).

7. O. E. Edwards and L. Marion, *ibid.*, *32*, 1146 (1954).

8. O. E. Edwards, L. Marion and R. A. McIvar, *ibid.*, *32*, 708 (1954).

9. O. E. Edwards, L. Marion and D. K. R. Stewart, *ibid*, *34*, 1315 (1956).

10. A. Lawson and J. E. C. Topps, *J. Chem. Soc.*, 1640 (1937).

11. W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, *143*, 589 (1942).

12. K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, *Experientia*, *11*, 255 (1955).

13. D. Dvornik and O. E. Edwards, *Chem. and Ind.*, 248 (1956).

14. D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, *35*, 860 (1957).

15. D. Dvornik and O. E. Edwards, *Chem. and Ind.*, 623 (1958).

16. H. Vorbrüggen and Carl Djerassi, *Tetrahedron Letters*, No. 3, 119 (1961).

17. Erich Mosettig, Peter Quitt, Urs Beglinger, James A. Waters, Helmut Vorbrüggen, and Carl Djerassi, *J. Am. Chem. Soc.*, *83*, 3163 (1961).

18. Carl Djerassi, Peter Quitt, Erich Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *ibid.*, 83, 3720 (1961).

19. J. W. ApSimon and O. E. Edwards, *Proc. Chem. Soc.*, 461 (1961).

20. J. W. ApSimon and O. E. Edwards, *Canad. J. Chem.*, *40*, 896 (1962).

21. I. Iwai, A. Ogiso and B. Shimizu, *Chem. and Ind.*, *28*. 1288 (1962).

22. Ernest Wenkert and Bill G. Jackson, *J. Am. Chem. Soc.*, *80*, 211 (1958).

23. E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, *81*, 688 (1959).

24. Michitoshi Ohta and Lara Ohmori, *Pharm. Bull.* (Tokyo), 5, 91 (1957).

25. Michitoshi Ohta and Lara Ohmori, *ibid.*, *5*, 96 (1957).

26. Michitoshi Ohta, *ibid.*, *5*, 256 (1957).

27. Usha Ranjan Ghatak, *Tetrahedron Letters*, No. 1, 19 (1959).

28. Usha R. Ghatak, Dilip K. Datta and Suvas C. Ray, *J. Am. Chem. Soc.*, *81*, 3670 (1959).

29. Marcel Fétizon, Jacques Delobelle and M. Jacques Tre Trefovel, *Comptes rendus.*, *246*, 2774 (1958).

30. M. Fétizon and J. Delobelle, *Tetrahedron Letters*, No. 9, 16 (1960).

31. J. A. Barltrop and A. C. Day, *J. Chem. Soc.*, 671 (1959).

32. Narendra N. Saha, Bejoy K. Ganguly and Phanindra C. Dutta, J. Am. Chem. Soc., 81, 3670 (1959).

33. Jacques Delobelle and Marcel Fétizon, Bull. Chem. Soc. France, 1894 (1961).

34. Jacques Delobelle and Marcel Fétizon, ibid., 1632 (1961).

35. Ernest Wenkert and B. G. Jackson, J. Am. Chem. Soc., 80, 217 (1958).

36. Ernest Wenkert and Peter Beak, Tetrahedron Letters, No. 11, 358 (1961).

37. L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, London, 1959.

38. R. C. Cambie and L. N. Mander, Chem. and Ind., 1877 (1961).

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

40. I. R. Sherwood and W. F. Short, ibid., 1006 (1938).

41. T. J. King and J. P. Yardley, ibid., 4308 (1961).

42. F. E. King and T. J. King, ibid., 4158 (1953).

43. Ernest Wenkert and Akira Tahara, Unpublished observations, Iowa State University of Science and Technology, 1960.

44. J. W. ApSimon and O. E. Edwards, Proc. Chem. Soc., 461 (1961).

45. J. W. ApSimon and O. E. Edwards, Canad. J. Chem., 40, 896 (1962).

46. D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pecket, J. Am. Chem. Soc., 82, 2640 (1960).

47. Ernest Wenkert and Johan B-Son Bredenberg, unpublished observations, Indiana University, 1962.

48. Peter Kabasahalian and Edward R. Townley, _J. Am. Chem. Soc._, _84_, 2711 (1962).

49. Peter Kabasahalian, Edward R. Townley, and Milton D. Yudis, _ibid._, _84_, 2716 (1962).

50. Peter Kabasahalian, Edward R. Townley, and Milton D. Yudis, ibid., 84, 2718 (1962).

51. Peter Kabasahalian and Edward R. Townley, _ibid._, _84_. 2723 (1962).

52. Peter Kabasahalian and Edward R. Townley, _ibid._, _84_, 2724 (1962).

53. Huang-Minlon, _J. Am. Chem. Soc._, _68_, 2487 (1946).

54. Thomas F. Sanderson, Derivatives of Dehydroabietonitrile, U. S. Patent 2,750,367, 1956.

55. A. B. Burns, A. R. H. Cole, B. J. Parkes, and D. E. White, _Aust. J. Chem._, _9_, 406 (1956).

56. Michitoshi Ohta, _Pharm. Bull._ (Tokyo), 4, 273 (1956).

57. L. F. Fieser, Experiments in Organic Chemistry. 3rd Ed. Boston, Mass., D. C. Heath and Co., 1955.

58. E. Mosettig, Organic Reactions, Vol. VIII, John Wiley and Sons, Inc., New York, N.Y., 1954.

59. Herbert C. Brown, Charles J. Shoaf and C. P. Gary, _Tetrahedron Letters_, No. 3, 9 (1959).

60. W. Nagata, _Tetrahedron_ _13_, 287 (1961).

61. F. Elsinger, J. Schreiber and A. Eschenmoser, _Helv. Chim. Acta._, _43_, 113 (1960).

62. Ernest Wenkert, Richard W. J. Carney, and Chikara Kaneko, _J. Am. Chem. Soc._, _83_, 4440 (1961).

63. R. Dulon and G. Defage-Duchateau, _Comptes rendus._, _250_, 1288 (1960).

64. R. H. Bible, Jr., Lactones of 1,12-Dimethyl-6,10-Dihydroxy-9-oxo-1,2,3,4,9,10,11,12-Octahydropenanthrene-1-Carboxylic Acid, U. S. Patent 2,753,357, 1956.

65. N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Am. Chem. Soc.*, 79, 6562 (1957).

66. Elmore L. Martin, Organic Reactions, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

67. Shiba N. Mahapatra and R. M. Dodson, Private communication, University of Minnesota, 1962.

68. M. Karplus, *J. Chem. Phys.*, 30, 11 (1959).

69. Kenneth L. Williamson and William S. Johnson, *J. Am. Chem. Soc.*, 83, 4623 (1961).

70. J. B. Brendenberg and J. N. Shoolery, *Acta. Chem. Scand.*, 14, 556 (1960),

71. James C. W. Chien, *J. Am. Chem. Soc.*, 82, 4762 (1960).

72. E. Wenkert and P. Beak, *Chem. and Ind.*, 1574 (1961).

73. E. Wenkert and P. Beak, *J. Am. Chem. Soc.*, 83, 998 (1961).

74. Walter L. Meyer and Robert W. Huffman, *Tetrahedron Letters*, No. 16, 691 (1962).

75. Peter Beak, Unpublished observations, Iowa State University of Science and Technology, 1961.

76. J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, 80, 5121 (1958).

77. W. E. Rosen, J. B. Zieglar, D. C. Shabria and J. N. Shoolery, *J. Am. Chem. Soc.*, 81, 1081 (1959).

78. G. Slomp, Jr. and B. R. McGarvey, *J. Am. Chem. Soc.*, 81, 2020 (1959).

79. J. S. G. Cox, E. O. Bishop and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).

80. J. I. Mucher, J. Am. Chem. Soc., 83, 1146 (1961).

81. J. A. Pople, W. G. Schneider and H. J. Bernstein, High Resolution Nuclear Magnetic Resonance, New York, New York, McGraw-Hill Book Co., Inc., 1959.

82. James C. W. Chien, *J. Am. Chem. Soc.*, *82*, 4762 (1960).

83. Walter L. Meyer, Private communication, Indiana University, 1962.

84. William P. Campbell and David Todd, *J. Am. Chem. Soc.*, *64*, 928 (1942).

85. Andrejs Zvejnieks, *Svensk Kem. Tidski.*, *66*, 316 (1954) *C. A.*, *49*, 15809 (1955).

86. E. Wenkert and P. Beak, Unpublished results in research notes (1961).

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