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Iowa State University of Science and Technology
Ph.D., 1960
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SUBSTITUTION REACTIONS OF AROMATIC RESIN ACIDS

by

Virgil Irvin Stenberg

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

1960

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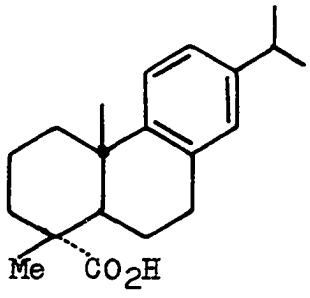
To

Helen and Beth

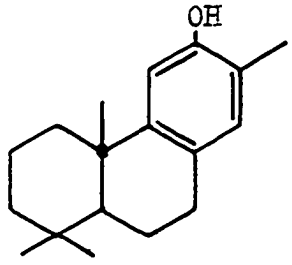
INTRODUCTION

The synthesis of naturally occurring compounds has provided a challenge to the chemist and has generated considerable interest in recent years. Because a fair number of compounds have already been synthesized, chemical correlation of newly discovered natural products with these synthetic substances has become inviting.

In light of the observation that most tricarbocyclic diterpenes have been found to be substituted at C-13, this work was devised to study various substitution reactions which may lead to useful synthetic intermediates. These reactions are to be applied toward the synthesis of abietic acid (I) and nimbiol (II).



I



II

HISTORICAL

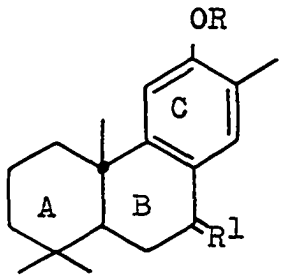
Isolation and Structure of Nimbiol

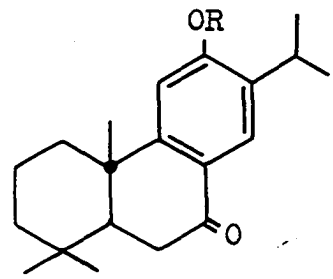
The leaves and bark of Melia azadirachta Linn. have been used in India as an antiseptic and for the treatment of a variety of skin diseases. This biological activity has encouraged several groups of workers (1, 2, 3) to attempt isolation of the active components in the leaves and bark.

Siddiqui et al. (2, 3) reported the isolation of two crystalline bitter constituents, nimbin and nimbinin, an amorphous constituent, nimbidin, containing sulfur, and a sterol, nimbosterol, from ethanolic extracts of the plant. Following a different isolation procedure, Sengupta et al. (1) were able to isolate three more crystalline substances. This procedure utilized benzene extraction followed by separation of the extract into phenolic, strongly acidic and neutral fractions.

Chromatography of the phenolic fraction led to sugiol (VII) and a new substance, nimbiol (II). The neutral fraction was partitioned between petroleum ether and aqueous methanol. The petroleum ether soluble material was saponified with methanolic potassium hydroxide and the unsaponifiable material chromatographed on alumina to yield two crystalline compounds, β-sitosterol and an unidentified alcohol. Acetylation and chromatography of the residue from the methanol extract led to the isolation of nimbin.

The structure proposed for nimbiol (II) by Sengupta et al. (1, 4, 5) was based largely on spectral data and only a small amount of chemical evidence. Nimbiol has the empirical formula $C_{18}H_{24}O_2$. Its infrared spectrum has absorption bands at 2.8, 3.05 and 6.03 microns as well as those characteristic of the benzene ring. The ultraviolet spectrum of nimbiol compared favorably with that of sugiol (VII) both in neutral and basic media. Hence, nimbiol had to contain a p-hydroxyphenylketone group.





II R = H, R^1 = O

III R = Me, R^1 = O

IV R = COMe, R^1 = O

V R = COMe, R^1 = H_2

VI R = H, R = H_2

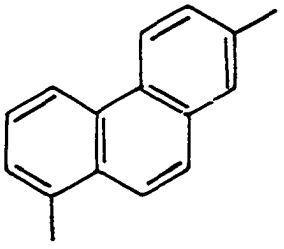
VII R = H

VIII R = Me

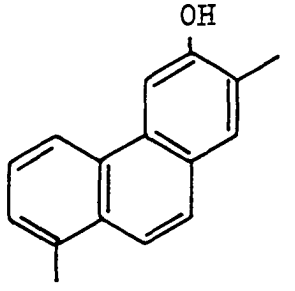
Nimbiol was converted to a monoacetate IV by pyridine and acetic anhydride. Catalytic hydrogenation of the acetate yielded desoxynimbiol acetate (V) which provided further evidence for the presence of a phenyl ketone. Base hydrolysis of V led to a resinous mass which could not be crystallized. The

main constituent of this mass appeared to be desoxynimbiol (VI).

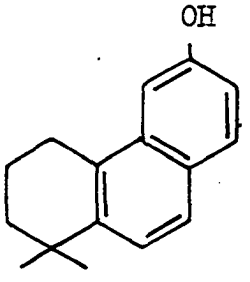
The basic ring skeleton could be surmised on the basis of selenium dehydrogenation experiments. Despite lack of crystallinity VI was used as the starting material in these studies. By varying conditions of the selenium treatment, four different products, IX, X, XI and XII, could be obtained in crystalline form. One of the products, $C_{16}H_{14}$, proved to be pimanthrene (IX) on comparison with an authentic sample. The other three products were not recorded in literature. However, the structures, X, XI and XII were assigned on the basis of comparing their ultraviolet spectra with those of known phenanthrenes, phenanthrols and the corresponding hydro-systems as well as on their empirical formulas derived from elemental analyses.



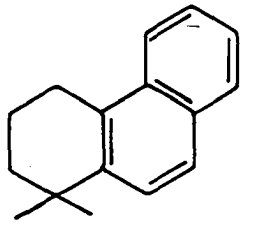
IX



X



XI



XII

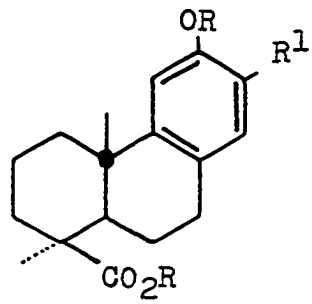
The isolation of pimanthrene was particularly profitable since this structure located two of the four methyl groups of nimbiol besides ascertaining the hydrophenanthrene nature of nimbiol. The location of the hydroxy and ketone groups at positions C-7 and C-12, respectively, was assumed on the basis of spectra of the phenanthrols, X and XI, and the similarity of the spectra of sugiol and nimbiol. The remaining two methyl groups most probably were located at quaternary centers because both were lost on selenium treatment. Only positions C-4, C-5 and C-10 remained as possibilities. However, the isolation of the tetrahydrophenanthrene XII indicated a gem-dimethyl function at C-4 leaving C-5 or C-10 as possible centers for the remaining methyl group. Biogenetic reasoning based on analogies with other diterpenic compounds suggested C-10 as the preferred site of the one-carbon unit.

The methyl ether of nimbiol (III) did not react with either furfural or ethyl formate in the presence of base indicating the trans nature of rings A and B (6). Sugiol methyl ether (VIII) also behaves similarly towards these reagents. The optical rotatory dispersion curves of sugiol and nimbiol are similar, substantiating the stereochemistry and adding proof to the location of the last methyl group mentioned above.

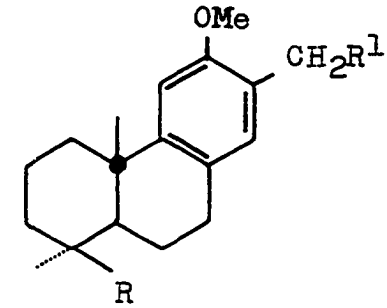
Syntheses of Nimbiol

Three research groups have synthesized the nimbiol skeleton within recent months (7, 8, 9).

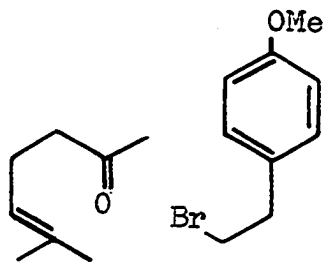
Bible (7) carried out an eleven-step partial synthesis of nimbiol utilizing podocarpic acid (XIII) as starting material. Podocarpic acid was converted to methyl O-methylpodocarpate (XIV) by base and dimethyl sulfate according to the procedure of Sherwood and Short (10). A Friedel-Crafts reaction was used to introduce the acetyl group at C-13, as in the synthesis of ferruginol from podocarpic acid by Campbell and Todd (11), leading to methyl 13-acetyl-O-methylpodocarpate (XV). Picha (12) utilized the haloform reaction to convert XV into the carboxy compound XVI. Bible treated XVI with lithium aluminum hydride yielding the diol XVII. Hydrogenation of XVII reduced the benzyl alcohol giving O,13-dimethylpodocarpinol (XVIII). Chromic acid oxidation of XVIII produced the corresponding aldehyde XIX which was reduced via its semicarbazone XX by the Wolff-Kishner method to a mixture of desoxynimbiol and desoxynimbiol methyl ether (XXI). Methylation of the crude reaction mixture gave desoxynimbiol methyl ether. Chromic acid oxidation of XXI produced nimbiol methyl ether (III) which proved identical with an authentic sample obtained from Sengupta. Subsequent demethylation yielded nimbiol (II).



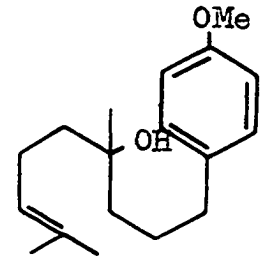
XIII R = R^1 = H
XIV R = Me, R^1 = H
XV R = Me, R^1 = COMe
XVI R = Me, R^1 = CO_2H



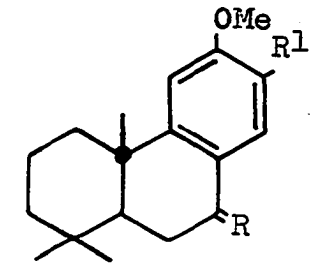
XVII R = CH_2OH, R^1 = OH
XVIII R = CH_2OH, R^1 = H
XIX R = CHO, R^1 = H
XX R = CHN_2HCONH_2, R^1 = H
XXI R = Me, R^1 = H



XXII XXIII



XXIV



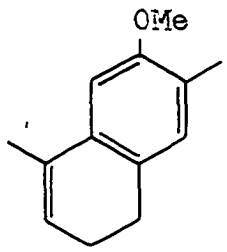
XXV R = H_2, R^1 = H
XXVI R = O, R^1 = H
XXVII R = O, R^1 = CH_2Cl
XXVIII R = O, R^1 = $CH_2SCNHNH_2HCl$
XXIX R = O, R^1 = CH_2SH

Fetizon and Delobelle (8, 13, see also 14) completed a total synthesis of dl-nimbiol methyl ether (III) by the cyclisation of the alcohol XXIV. This alcohol XXIV was prepared by the condensation of the ketone XXII with the Grignard reagent of β-(p-methoxyphenyl-)ethyl bromide (XXIII). The cyclisation to XXV was affected by both phosphoric and oxalic acids. Both A-B cis and trans fused ring junctures were formed. Oxalic acid gave a better yield of the trans isomer (13).

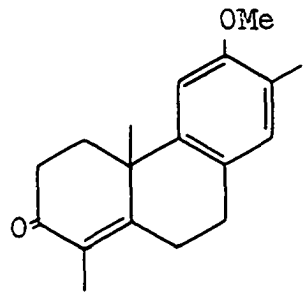
Chromic acid oxidation of XXV yielded the 7-keto derivative XXVI.

Introduction of the methyl group at C-13 was accomplished by chloromethylation of XXVI. Zinc reduction of the resulting chloromethyl compound XXVII failed to produce good yields of nimbiol methyl ether. Hence, a more indirect procedure of reduction was used. Treatment of XXVII with thiourea gave the thiouronium salt XXVIII whose hydrolysis with base yielded the mercaptan XXIX. Desulfurization with Raney nickel produced dl-nimbiol methyl ether (III) which had an infrared spectrum identical with that of an authentic sample.

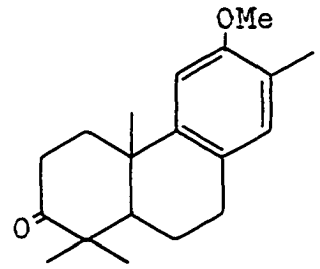
A second total synthesis of dl-nimbiol methyl ether has been reported more recently by Dutta and Ramachandran (9). Methyl magnesium iodide was reacted with 6-methoxy-7-methyl-1-tetralone forming XXX. Epoxidation of this product with perbenzoic acid followed by sulfuric acid-catalyzed rearrangement gave 1-methyl-6-methoxy-7-methyl-2-tetralone. This ketone was condensed with β-chloroethyl ethyl ketone in the presence of sodium methoxide producing the α,β-unsaturated ketone XXXI. Methylation and catalytic reduction gave XXXII. Huang-Minlon reduction and subsequent chromic acid oxidation produced dl-nimbiol methyl ether (III). This product was identical with the product obtained by Fetizon and Dellobelle (8).



XXX



XXXI



XXXII

Isolation of Dehydroabietic Acid

Literature on the isolation of the components in the oleoresin of Pinus palustris (15) has been quite confused until it was recognized that some components of this resin co-crystallized with others and some underwent isomerization during certain isolation procedures. Harris (15) designed a reliable method of isolation via amine salts and also utilized methods of ultraviolet absorption and Diels-Alder adduct formation for quantitative determination of components in the resin. Dehydroabietic acid was found spectroscopically to comprise about 4% of the oleoresin.

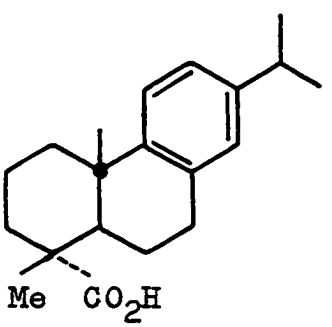
The method by which dehydroabietic acid is obtained is not through direct isolation, but usually by conversion from abietic acid (16, 17, 18, 19) by various oxidation-isomerization methods. A method developed by Fieser and Campbell (20, 21), later modified by Campbell and Morgana (22), involves the

sulfonation of pyroabietic acid, a mixture obtained on heating abietic acid above 200°. The sulfonated fraction is then isolated and the sulfonic acid group is removed by acid hydrolysis.

A later procedure involves the use of N-bromosuccinimide on methyl abietate followed by dehydrohalogenation and subsequent aromatization to methyl dehydroabietate (23). Dehydroabietic acid is formed also by treating abietic acid with a molar quantity of bromine followed by heating and distillation (24). Furthermore, dehydrogenation of abietic acid is affected by using either sulfur or nickel formate-charcoal catalyst (25).

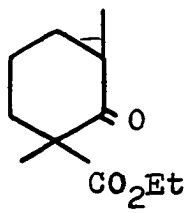
Synthesis of Abietic Acid and Its Derivatives

The synthesis of dehydroabietic acid (XXXIII) as well as other resin acids has been the object of numerous investigations over the last three decades.

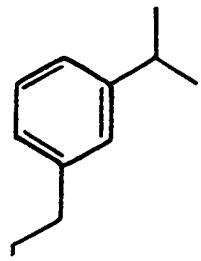


XXXIII

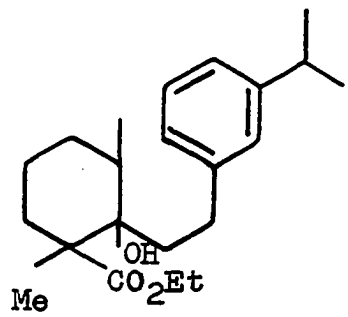
Haworth and Barker (26) reported the synthesis of a compound with the basic structure of dehydroabietic acid in 1939. The ketoester XXXIV was reacted with the Grignard reagent of β-(m-isopropylphenyl-)ethyl bromide (XXXVa) to yield the intermediate ester-alcohol XXXVI. This alcohol was dehydrated with potassium hydrogen sulfate and cyclized with acetic-sulfuric acids, yielding a compound thought to be methyl dl-dehydroabietate (XXXIII). The ultraviolet spectrum was consistent with the structure of the natural product; however, its stereochemistry remained in doubt. It is interesting to note that seven years later, Haworth and Moore (27) published a synthesis of 0-methylpodocarpic acid using the same route, exchanging only β-(p-methoxyphenyl-)ethyl bromide for XXXV.



XXXIV



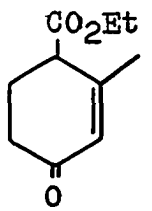
XXXVa



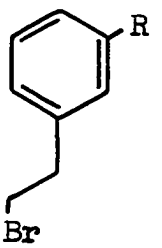
XXXVI

As part of a possible synthesis of resin acids, Stork and Burgstahler (28, see also 29) reported a synthesis of the hydrophenanthrone XXXIX. The sodium salt of XXXVII was reacted with XXXVb. Subsequent saponification and decarboxylation led

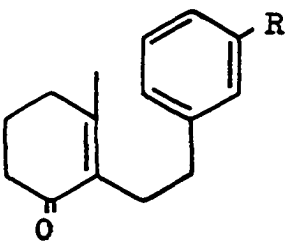
to the intermediate ketone XXXVIII. The hydrophenanthrone XXXIX was formed by the cyclization of XXXVIII with phosphoric and sulfuric acids. It was believed at the time that the stereochemistry of the A-B ring juncture was trans. When Burgstahler's early attempts to transform this ketone to dehydroabietic acid failed (30), this route was abandoned as unpromising.



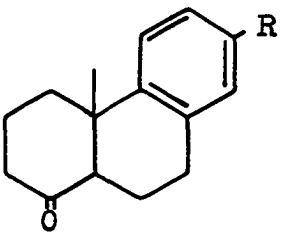
XXXVII



XXXVb



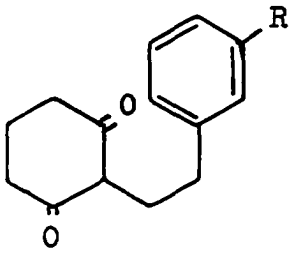
XXXVIII



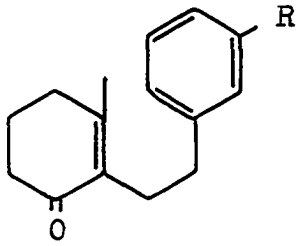
XXXIX

R = i-pr, H, OMe

After the Stork and Burgstahler publication, Dutta et al. (31, 32) devised a slightly different synthesis of the ketone XXXIX by utilizing dihydroresorinol and a β-(m-substituted-)-phenylethyl bromide to obtain the diketone XL. The mono-t-butyl enol ether of XL was prepared and treated with methyl magnesium iodide to give the intermediate XLI. Cyclization to XXXIX occurred on treatment of XLI with phosphoric acid.



XL

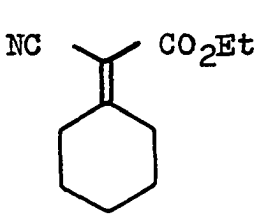


XLI

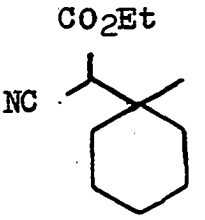
Dutta et al. (33) followed up the work by Stork and Burgstahler and their own group (31, 32) by forming gem-substituted compounds from model ketones. Simultaneous to this work similar studies were carried out by Parker and Raphael (34). The adduct XLII of cyclohexanone and cyanoacetic ester reacted with methyl magnesium iodide yielding XLIII. When XLIII was hydrolyzed and decarboxylated, 1-methylcyclohexylacetic acid was obtained. The Barbier-Wieland reaction applied to methyl 1-methylcyclohexylacetate gave 1-methylcyclohexanecarboxylic acid (XLIV).

A second pathway was chosen for the reverse to introduce the geminal substituents. Ethyl α-cyanocyclohexylideneacetate (XLII) was reacted with hydrocyanic acid to yield the intermediate (XLV). The latter was hydrolyzed and decarboxylated giving 1-carboxycyclohexylacetic acid (XLVI). This diacid was esterified, monohydrolyzed and exposed to a Hunsdiecker reaction. The resulting methyl 1-bromomethyl-

cyclohexanecarboxylate was reduced with zinc dust to the desired acid XLIV.

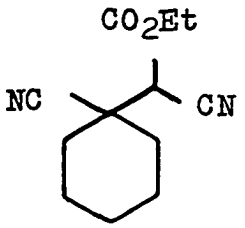


XLII

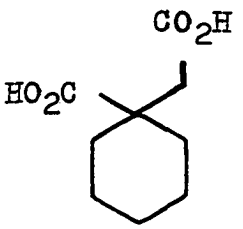


XLIII

XLIV



XLV

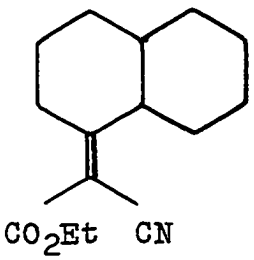


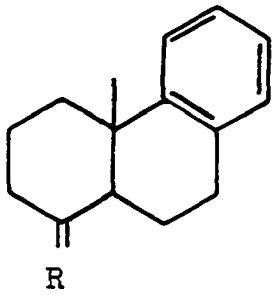
XLVI

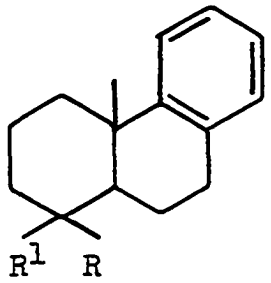
Dutta et al. (33) carried out an identical set of reactions on a bicyclic model system, but found that, although hydrocyanic acid could be added to the cyanoester-ketone condensation product XLVII as expected, the Grignard addition was anomalous.

Later Dutta et al. (35, 36) applied the model reactions to the previously synthesized ketone XXXIX: XXXIX → XLVIII → XLIX → L → LI → LII. When the final product was exposed to chromic acid oxidation, a diagnostic test for the stereochem-

istry of the A-B ring juncture, developed by Wenkert and Jackson (6), a diketone was found as the major product, indicating a cis-skeletal configuration. This dl-acid was not identical with that obtained by Haworth and Barker (26). Methyl magnesium iodide reacted with the cyanoacetate XLVIII abnormally, as with the model.







XLVII

XXXIX R = O

XLVIII R = $C(CN)CO_2Et$

XLIX R = CN, R^1 = $C(CN)CO_2Et$

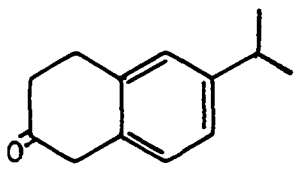
L R = CO_2Me, R^1 = CH_2CO_2Me

LI R = CO_2Me, R^1 = CH_2Br

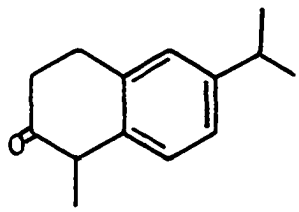
LII R = CO_2Me, R^1 = Me

Stork and Schulenberg (37) were the first to accomplish a total synthesis of stereochemically correct dl-dehydroabietic acid. The ketone LIII was synthesized from β-isopropyl naphthalene by sulfonation followed by potassium hydroxide fusion to yield 6-isopropyl-2-napthol. This was readily converted into its methyl ether which was reduced with lithium in liquid ammonia to yield 6-isopropyl-2-tetralone (LIII). The tetralone was methylated to LIV by means of its eneamine salt.

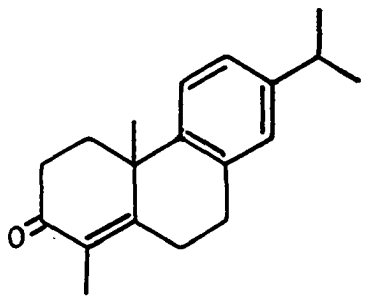
Either 1-diethylamino-3-pentanone methiodide or ethyl vinyl ketone reacted with LIV in the standard manner to give LV. The ketone LV was alkylated with ethyl bromoacetate to give the gem-substituted product LVI whose keto group was removed by conversion to its thioketal LVII and Raney nickel reduction. The resulting homolog of methyl dehydroabietate LVIII was degraded by a Barbier-Wieland degradation to dl-dehydroabietic acid (LIX) identical in infrared spectrum with the natural product.



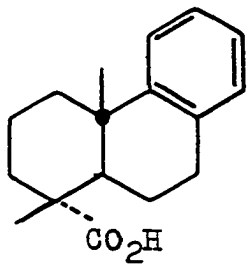
LIII



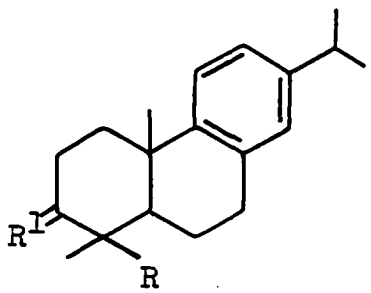
LIV



LV



LX



LVI R = CH_2CO_2Et, R^1 = O

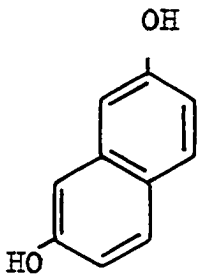
LVII R = CH_2CO_2Et, R^1 = $(SCH_2)_2$

LVIII R = CH_2CO_2Et, R^1 = H_2

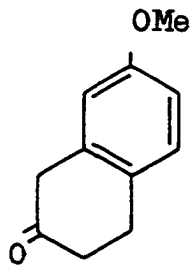
LIX R = CO_2H, R^1 = H_2

Recently Ghatak *et al.* (38) have used the Stork and Schulenberg scheme for the synthesis of dl-dehydrodeisopropylabietic acid (LX).

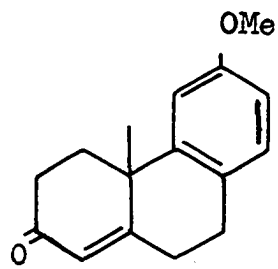
In an unsuccessful attempt to synthesize podocarpic acid, Kuehne (39) developed a synthetic route to abietic acid. Methylation of 2,7-dihydroxynaphthalene (LXI) and sodium-alcohol reduction gave 7-methoxy-2-tetralone (LXII). This was monomethylated via its pyrrolidine eneamine (40) and exposed to methyl vinyl ketone and base yielding the tricyclic ketone LXIII. Lithium-ammonia reduction afforded a saturated trans ketone, which was brominated via its eneamine and dehydrobrominated to the unsaturated ketone LXIV. Condensation with ethyl formate gave a hydroxymethylene derivative which was converted to the nitrile LXV by reaction with hydroxylamine and base.



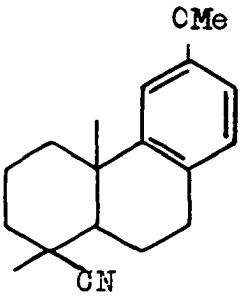
LXI



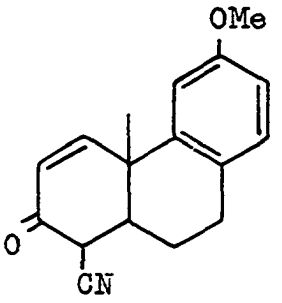
LXII



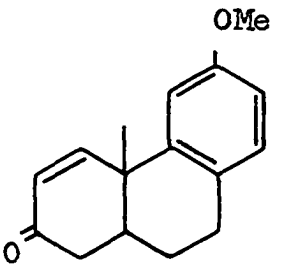
LXIII



LXVI



LXV

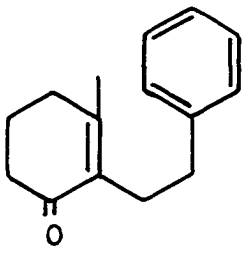


LXIV

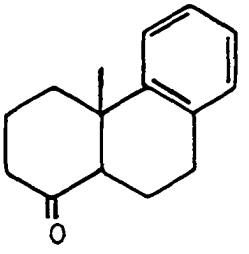
Alkylation of LXV with methyl iodide and potassium t-butoxide followed by reductive removal of the double bond and carbonyl group gave LXVI. The infrared spectrum of LXVI was found to differ from authentic O-methyl podocarponitrile obtained from the natural product. Apparently the methylation had occurred on the side of the molecule bearing the C-10 methyl group.

Recently Barltrop and Day (41) totally synthesized dl-dehydrodeisopropylabietic acid (LX) using a new procedure for the introduction of C-4 substituents. The ketone LXVII was cyclized with phosphoric acid to obtain the octahydrophenanthrene LXVIII. The first of the substituents at C-4 was introduced with lithium acetylide producing the condensation product LXIX. Isomerization with 90% formic acid gave rise to the ketone LXX. Hydrogenation followed by monobromination of the ketone gave LXXI, which on Favorski rearrangement with sodium methoxide in methanol yielded methyl dl-dehydrodeiso-

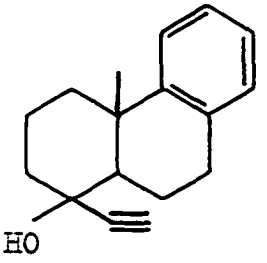
propylabietate (LXXII). Alkylation of C-4 directly on the α,β-unsaturated ketone LXX by methyl iodide and potassium t-butoxide failed, giving instead methyl-substituted products.



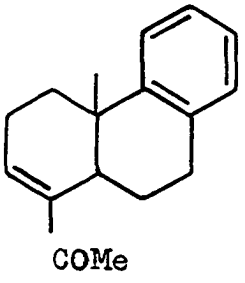
LXVII



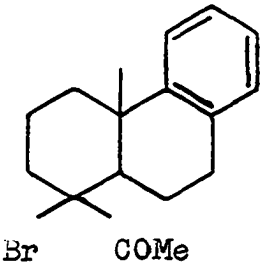
LXVIII



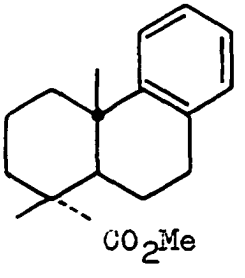
LXIX



LXX



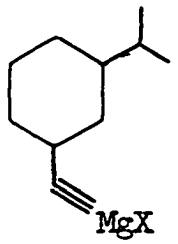
LXXI



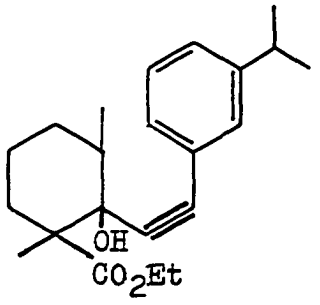
LXXII

An unsuccessful attempt to synthesize dehydroabietic acid was reported by Parham et al. (42, 43, 44). The keto-ester (XXXIV) previously used by Haworth and Barker (26) was treated with the Grignard reagent of m-isopropyl-phenylacetylene LXXIII to produce the intermediate alcohol LXXIV. This alcohol was reacted with hot formic acid to obtain a mixture from which a lactone with the proposed structure of LXXV was isolated.

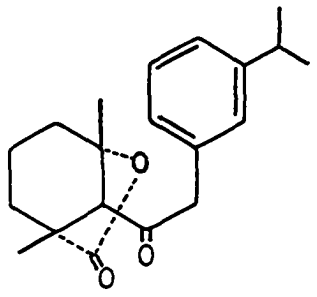
Attempted cyclization of LXXV with phosphoric acid gave anomalous results. Cyclisation with aluminum and hydrogen chlorides gave a single non-isomerizable keto-acid LXXVI. Wolff-Kishner reduction of the keto-acid LXXVI produced two acidic products LXXVII. Neither of these acids was identical with the product obtained from the aluminum chloride treatment of dehydroabietic acid.



LXXIII

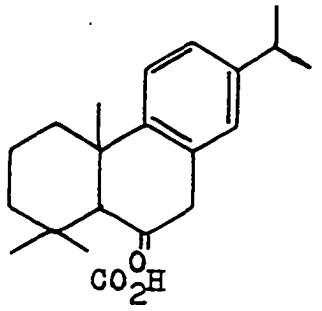


LXXIV



LXXV

LXXVII ⟵



LXXVI

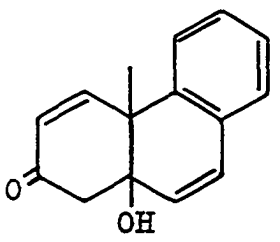
Ohta, Ohmori (45), Wenkert and Jackson (6) found that when dehydroabietic acid or its nitrile was treated with aluminum chloride, a deisopropylated compound of A-B cis config-

uration constituted the major product. Hence, Parham's compound (43) from the deisopropylation reaction may have suffered structural changes other than deisopropylation.

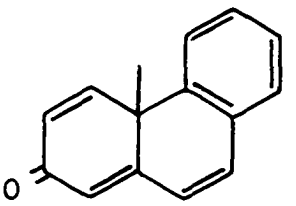
It is interesting that the melting point of one of Parham's acids is the same as that of a compound which Ghatak et al. (38) designated as the A-B cis system, dl-5-isodesoxypodocarpic acid. The absence of an authentic Parham sample for comparison left the problem of identity unsettled. The physical constants of the second Parham acid do not agree with those of the other three possible dl pairs (38).

The old synthetic compounds of Haworth and Barker (26) have recently been shown by Ghatak (38) to possess the skeleton of A-B cis and trans configuration in the podocarpic acid series.

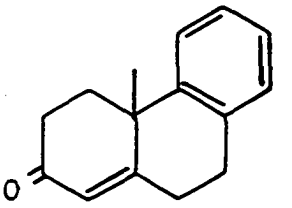
Wenkert and Stevens (46, 47) introduced two novel methods of synthesis of tricyclic ketones which can serve as intermediates in diterpene synthesis. In the first, 1-methyl-2-naphthol was condensed with methyl ethynyl ketone giving ketones LXXVIII and LXXIX and an O-alkylation product. Hydrogenation and dehydration of LXXVIII yielded the α,β-unsaturated ketone LXXX. The second method involved the condensation of the Reimer-Tieman product LXXXI with ethyl acetoacetate. Hydrolysis of the resulting product LXXXII and decarboxylation followed by reduction and cyclization with sodium triphenylmethyl gave ketone LXXXIII.



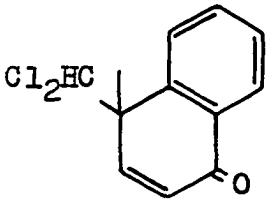
LXXVIII



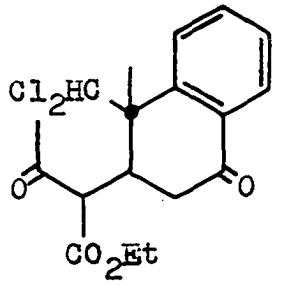
LXXIX



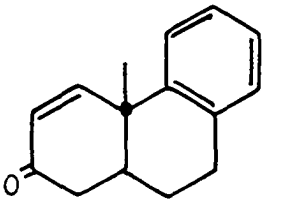
LXXX



LXXXI

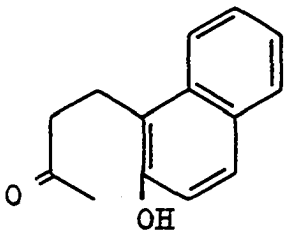


LXXXII

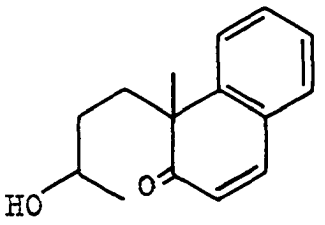


LXXXIII

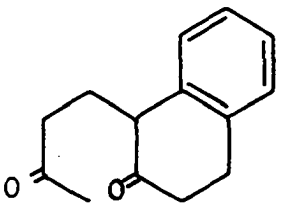
Wenkert and Youssefyeh (48) completed a third method of synthesis for hydrophenanthrones. Beta-naphthol was condensed with methyl vinyl ketone in the presence of base to give the ketone LXXXIV. It was reduced to an alcohol whose dry salt was methylated yielding LXXXV and an O-alkylation product. Reduction with lithium in liquid ammonia followed by chromic acid oxidation gave the diketone LXXXVI. Base-catalyzed cyclization of the latter led to the ketone LXXX.



LXXXIV

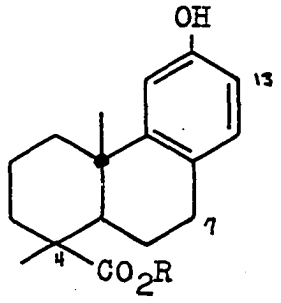


LXXXV



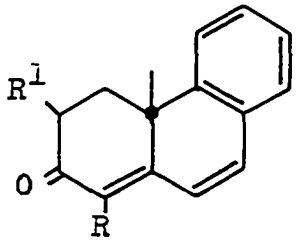
LXXXVI

Wenkert and Jackson (49) and Wenkert and Tahara (50) converted the ketone LXXX into dl-dehydrodeisopropylabietic acid (LX) and d-podocarpic acid (LXXXVII). Base-induced carbonation of LXXX and diazomethane treatment yielded two ketoesters, LXXXIX and XC. Methylation of LXXXIX with t-butoxide and methyl iodide gave a mixture of unresolved products.



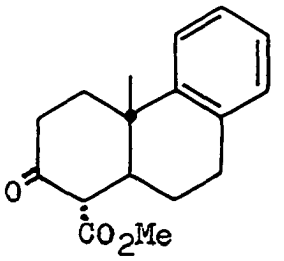
LXXXVII R = H

LXXXVIII R = Me



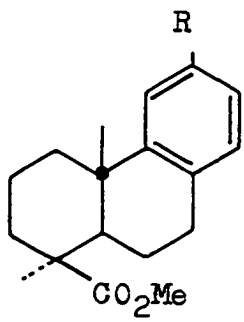
LXXXIX R = CO_2Me, R^1 = H

XC R = H, R^1 = CO_2Me



XCI

Catalytic hydrogenation of LXXXIX in acid medium led to XCI. Methylation of the latter with methyl iodide and potassium t-butoxide gave two products in a 2.4:1 yield ratio. Their reduction with zinc in dilute hydrochloric acid produced methyl dl-dehydrodeisopropylabietate (LXXII) and methyl dl-desoxypodocarpate (LXXXVIII), respectively. Base hydrolysis yielded their acids. dl-Desoxypodocarpic acid was resolved through its cinchonine salt. This constituted a total synthesis of the resin acid d-podocarpic acid since Wenkert and Jackson (51) had already converted methyl d-desoxypodocarpate to the natural product by acetylation to XCII, trifluoroperacetic acid treatment to XCIII and hydrolysis.



XCII R = COMe

XCIII R = OCOMe

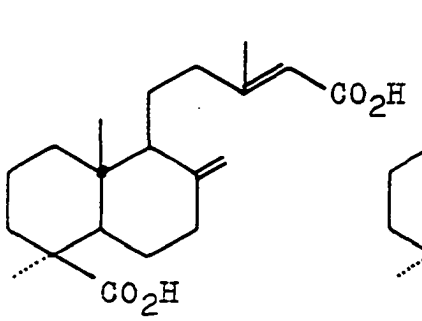
DISCUSSION

Aromatic Substitution Reactions of Podocarpic Acid

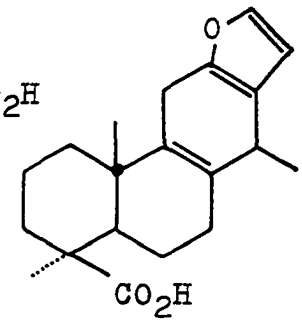
Podocarpic acid is a plant product which occurs abundantly in nature and can easily be isolated from the natural sources. The major sources of podocarpic acid are the resins of Podocarpus cupressina (52, 53, 54), a tree growing in Java and New Zealand, P. dacrydioides (55) and Dacrydium cupressium (56), both of which are indigenous to New Zealand.

Because of its properties and abundance, podocarpic acid serves as a desirable intermediate in natural product syntheses. Racemic podocarpic acid has already been synthesized through several different synthesis pathways (27, 38, 57, 58). Recently Wenkert and Tahara (49) resolved an intermediate and completed a new synthesis of d-podocarpic acid. As a result of this work, any chemical transformation of podocarpic acid to other natural products can formally be considered a total synthesis of those compounds.

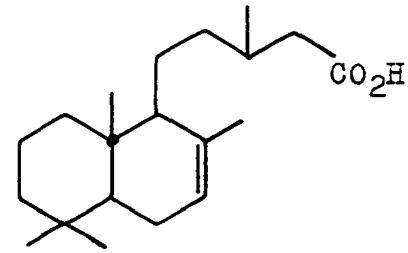
On inspection of the structures of various diterpenes, agathic acid (XCIV), vouacapenic acid (XCV), cativic acid (XCVI) and resononolactone (XCVII) appear as likely synthesis objectives.



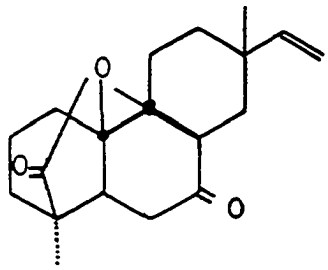
XCIV



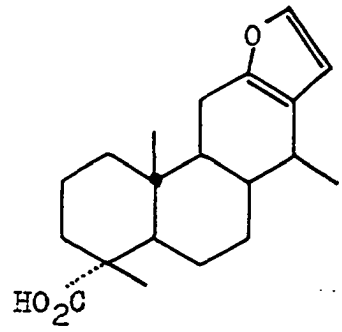
XCV



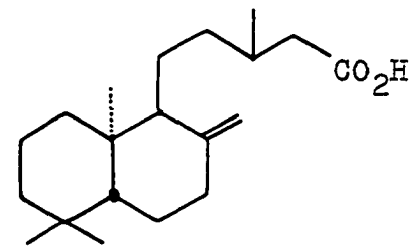
XCVI



XCVII



XCVIII

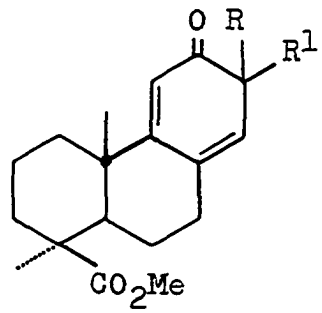


XCIX

One generalization that can be made about these as well as other diterpenic compounds not included in the above list is that all compounds have alkyl substituents at C-13 (podocarpic acid nomenclature). This is true also of compounds which are epimeric with podocarpic acid at C-4, e.g. vinhaticoic acid (XCVIII), and in compounds where the A-B ring juncture is of the unnatural configuration, e.g., eperuic acid (XCIX).

At the outset the purpose of the present investigations was to study various methods of substitution of C-13 of podocarpic acid. Hence, investigation of phenol alkylations became necessary. It was assumed that steric interference by the angular methyl and the C-1 methylene groups would prevent alkylation occurring at C-11 or C-8. Therefore, 13-alkyl-

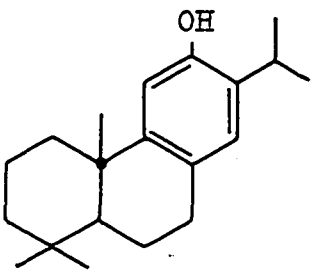
podocarpic acid systems and 13,13-dialkylcyclohexadienones (cf. C) represented the anticipated products.



C R = R^1 = alkyl groups

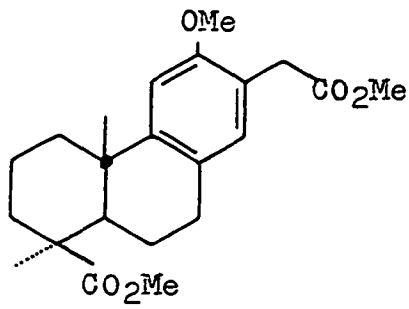
In recent years much active work has been pursued on the mechanistic aspects of the alkylation of phenol salts with alkyl halides (59, 60, 61) and such reaction has been used in organic synthesis (48). It was hoped to utilize these data for the alkylation of methyl podocarpate.

The sodium salt of methyl podocarpate reacts with methyl iodide in benzene at the latter's reflux temperature to give only the O-methylation product and starting material. Repeated trials failed to give any evidence for C-alkylation. Similarly, the reaction of sodium methyl podocarpate with isopropyl iodide, a procedure which, if successful, could replace the previous four-step synthesis of the ferruginol system (CI) (62) led only to methyl O-isopropylpodocarpate and starting material.

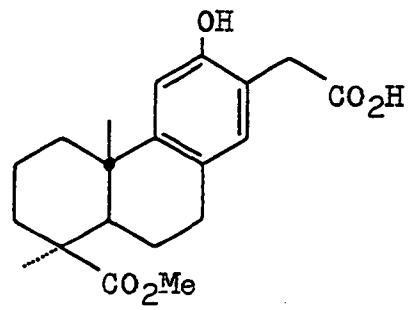


CI

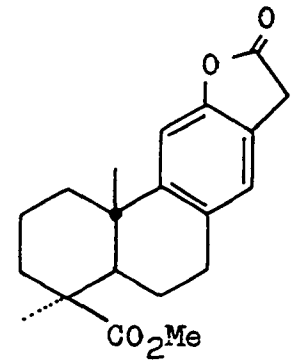
When ethyl bromoacetate was exposed to the sodium salt of methyl podocarpate, a new compound was isolated in good yield. It had infrared bands at 5.68 and 5.81 microns characteristic of a 5-membered lactone and an ester, respectively. The phenol O-H stretching band had disappeared. Figure CII illustrates the proposed structure of this lactone. This was confirmed by analysis. Despite a special search no O-alkylation product could be isolated. Repetition of the reaction with methanol as a co-solvent led to no new products. This was of interest since it provides evidence against the generality of the proposal that increasing the solvent polarity leads to more O-alkylation (63, 64). However, it is in agreement with the latest finding that the type of alkylation depends upon other properties of the solvent as well as polarity (59).



CIII



CIV



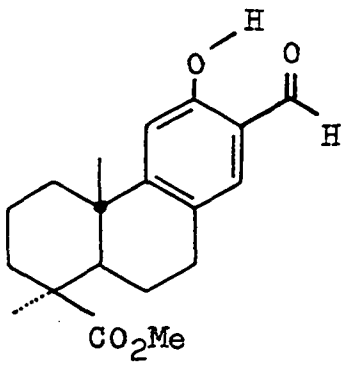
CII

Attempted decarboxylation of the lactone CII to methyl 13-methylpodocarpate failed. Heating the lactone with a solution of glycerol and water (65) at temperatures from 150° to 200°C for 51 hours gave a nearly quantitative yield of the starting lactone.

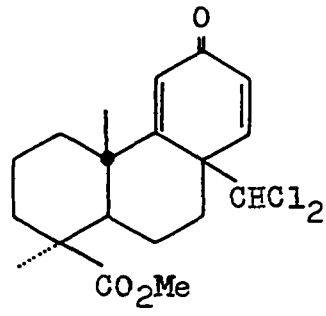
Methylation of the lactone by sodium methoxide and methyl iodide gave only the O-alkylation product CIII and the acid CIV, most probably formed in the work-up.

When during the present work the structure of nimbiol was shown to contain a 13-methyl group (5), methyl 13-methylpodocarpate became a desired product. Methods other than direct alkylation were attempted for its synthesis. Sodium hydroxide and chloroform reacted with methyl podocarpate to give a low yield (0-9%) of an aldehyde (CV). The aldehyde was extracted from the reaction mixture by means of the Girard reagent and obtained crystalline. None of the abnormal Reimer-Tiemann

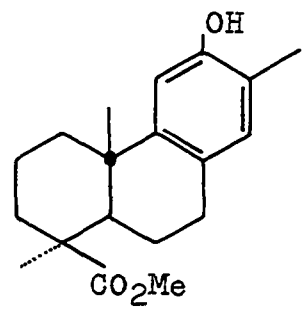
product CVI was observed. Alumina chromatography proved equally efficient as the Girard reagent procedure in the isolation of the aldehyde. The infrared spectrum of the aldehyde indicated a strong hydrogen bond between the phenolic hydroxyl and the aldehydic carbonyl group by weak O-H stretching bands and an intense broad band in the region of 3.05 microns.



CV



CVI

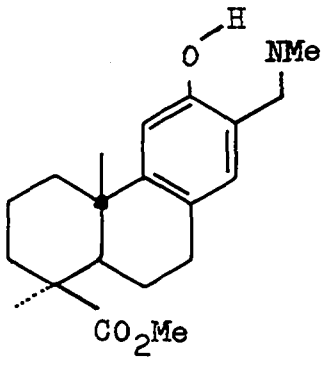


CVII

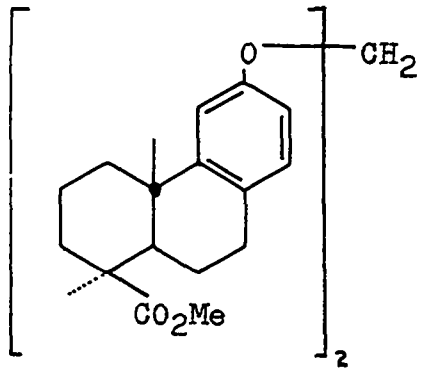
The aldehyde CV could be reduced by the Clemmensen method, although hydrogenation over palladium-charcoal was more facile and gave higher yields of the desired methyl 13-methylpodocarpate (CVII).

The low yield of the aldehyde prompted further investigation of other methods of synthesis of the 13-methyl compound. The Gattermann aldehyde reaction on methyl podocarpate gave no aldehyde products. The Mannich reaction gave low yields of a crystalline amine (ca. 2-3%) under the usual conditions of limiting the reactants to molar ratios. While an increased quantity of reagents has been known to give disubstitution

(66) with phenols, the use of a three-fold excess of formaldehyde and dimethylamine gave the same amine CVIII in an 89% yield. Its infrared spectrum also exhibited evidence for a strong hydrogen bond.

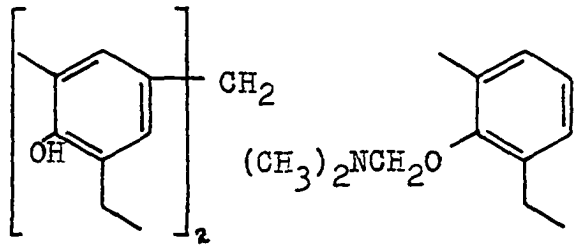


CVIII



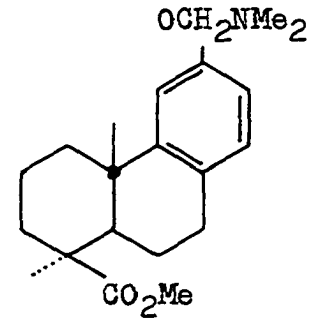
CIX

A neutral crystalline side product of the Mannich reaction showed no infrared O-H peaks and possessed a molecular weight in agreement with the structure CIX. Its formation can be rationalized in terms of the mechanism proposed by Wagner (67) for a similar reaction. Décombe (68) reported the isolation of two interesting products, CX and CXI, in the reaction of 2-methyl-6-ethylphenol with dimethylamine and formaldehyde. Compound CXII, analogous to CXI, may be an intermediate in the formation of CIX.



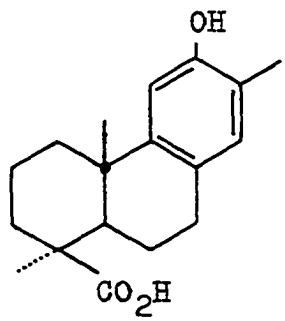
CX

CXI

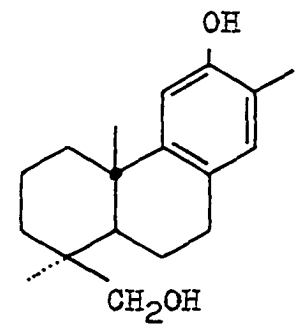


CXII

Methyl 13-dimethylaminomethylpodocarpate could be converted into 13-methylpodocarpic acid (CXIII) by formation of a methiodide and reduction with lithium in liquid ammonia. The quaternary salt was obtained in crystalline form, but was unstable to light.



CXIII



CXIV

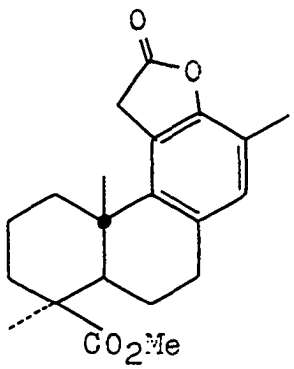
The lithium-ammonia reduction accomplished two steps in one, the reductive cleavage of the quaternary ammonium group and the reductive hydrolysis of the methoxycarbonyl group at C-4. The side product from this reaction was 13-methylpodocarpinol (CXIV). Similar products of lithium-ammonia reductions of sterically hindered esters have been observed and discussed previously by Wenkert and Jackson (51). No amine derivatives of podocarpic acid were isolated, indicating all the methyl dimethylaminomethylpodocarpate had reacted with methyl iodide in the formation of the quaternary ammonium salt and reduction of the quaternary salt had occurred exclusively at the benzylic position.

Esterification of 13-methylpodocarpic acid with diazomethane gave methyl 13-methylpodocarpate (CVII) in quantitative yield. This compound was identical with that obtained from catalytic hydrogenation of the aldehyde CV.

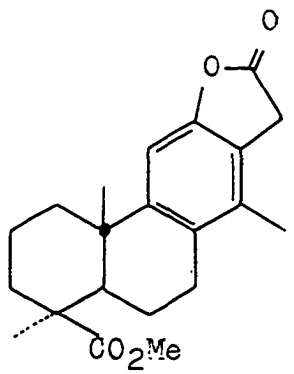
With the introduction of a methyl group at C-13, the probability of obtaining a dienone of type C by alkylation with ethyl bromoacetate seemed likely. The previous case where the lactone was alkylated with methyl iodide was not as favorable because of steric factors as well as halide reactivity. Ethyl bromoacetate reacted with the sodium salt of 13-methylpodocarpate to give a new 5-membered lactone in high yield and starting material. There was no evidence for the expected dieneone. The lactone had infrared bands at 5.72 and 5.81 microns, characteristic of 5-membered lactone and

ester carbonyl groups respectively.

Structures CXV or CXVI may be proposed for the lactones. Unfortunately, neither has been substantiated. Structure CXV is unlikely for the steric reasons already cited, while CXVI could only have arisen by a dienone-phenol rearrangement which usually requires acid catalysis. Not even heat (reaction temperature of 159°) could have been responsible for a rearrangement, since the lactone also proved to be the product of the reaction at room temperature.



CXV

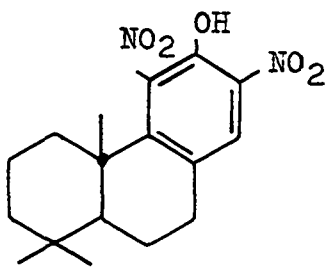


CXVI

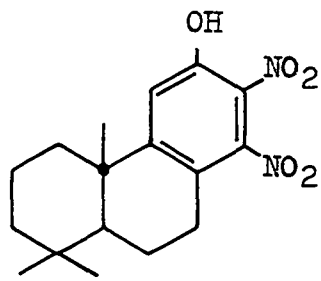
In light of the above discussion the proposed structures of dinitration products of podocarpic acid systems are open to question. Oudemans (69) reported that both mono and dinitro derivatives could be obtained on nitration of podocarpic acid. Recently, Hodges and Raphael (70) discussed the nitration of O-methylpodocarpane in which they obtained a mixture of mono

and dinitrated derivatives.

Their proposed structure for the dinitration product is shown in figure CXVII. However, in the absence of any unambiguous proof, structure CXVIII can be suggested as an alternate possibility.



CXVII



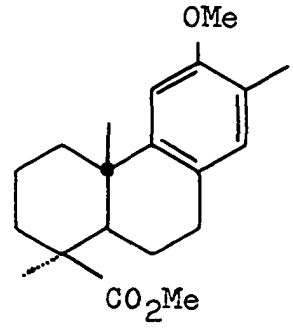
CXVIII

Both mono and dinitro derivatives of methyl podocarpate have been prepared for the initial steps in the structure proof of the dinitration product. Attempted reduction with tin in hydrochloric acid was unsuccessful.

Earlier results with the alkylation of methyl 13-methyl-podocarpate with ethyl bromoacetate prompted the alkylation of the lactone CII with the same reagent. Three products were obtained, an O-alkylation product, a 5-membered lactone in largest yield and an acid. The products have been difficult to purify and as yet have eluded identification. Again no dieneone could be found.

To complete this series of alkylations it was desirable

to alkylate the sodium salt of methyl 13-methylpodocarpate with methyl iodide. Only the O-alkylation derivative CXIX and starting material were obtained.



CXIX

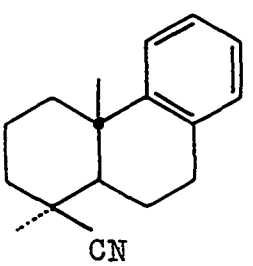
Partial Synthesis of Nimbiol

After the present work on the partial synthesis of nimbiol was reported (71), several other groups (7, 8, 9) of workers published their experiments on the partial and total synthesis of the nimbiol system. These have been described already in the Historical Section.

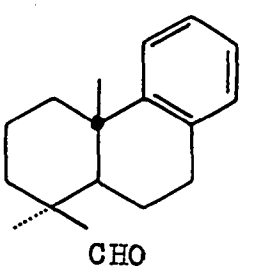
The conversion of podocarpic acid into nimbiol can be considered in the form of three separate problems: the introduction of the methyl group had already been accomplished, as described in the preceding section. The introduction of a ketone at C-7 was left till the end to keep the number of reactive centers in the molecule to a minimum during earlier

parts of the synthesis.

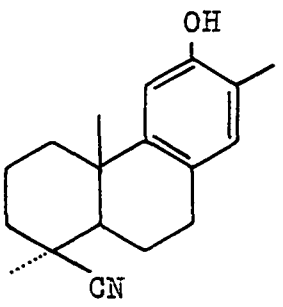
Three methods of reduction of C-4 carboxylic acid derivatives to methyl groups had been recorded for related diterpenoid systems. O-Methylpodocarpic acid has been converted to the acid chloride and reduced by the Rosenmund method to O-methylpodocarpal, which, in turn, has been reduced further (64) by the Wolff-Kishner method to O-methylpodocarpane. An ester can be reduced to an alcohol, oxidized with chromic acid to the aldehyde and reduced to the hydrocarbon by the Huang-Minlon modification of the Wolff-Kishner procedure (72). Finally, by the recent method of Wenkert and Tahara (73) desoxypodocarponitrile (CXX) could be reduced with lithium aluminum hydride to an imine which yielded desoxypodocarpal (CXXI) on mild acid hydrolysis. Its further reduction could be accomplished by the aforementioned means.



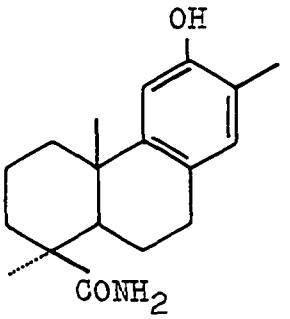
CXX



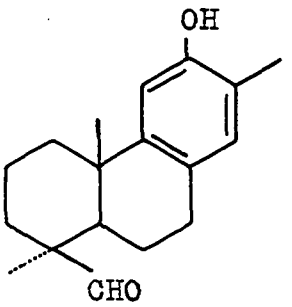
CXXI



CXXII

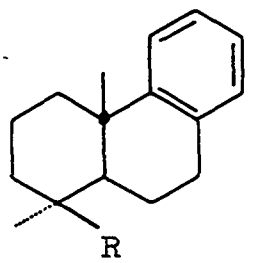


CXXIII



CXXIV

The last method appeared most attractive for the present problem. For this reason 13-methyl-podocarpic acid had to be converted first into its nitrile. The formation of the nitrile CXXII was accomplished in one step by acetylation of 13-methylpodocarpic acid, conversion of the ester-acid to its acid chloride with thionyl chloride and permitting the unisolated intermediate to react with a lithium amide solution for 46 hours. A mixture of the nitrile CXXII and the amide CXXIII were obtained, in conformity with similar results by Jackson (74) in the conversion of desoxypodocarpic acid (CXXV) to its amide (CXXVI) and nitrile (CXXVII) by lithium amide. Undoubtedly the reaction would have gone to completion if a longer reaction time had been provided, because earlier quenching of the reaction gave smaller yields of the nitrile.



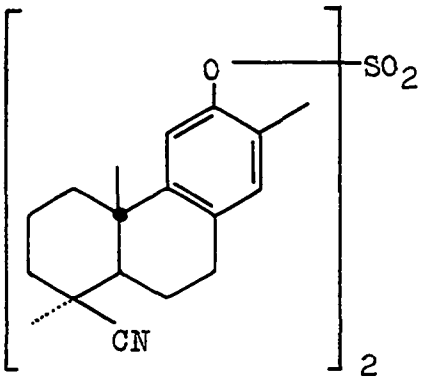
CXXV R = CO_2H

CXXVI R = $CONH_2$

CXXVII R = CN

The previous work-up of the lithium amide reaction had to be modified in the present case. The iron salts, which are present in solution because of the in situ conversion of ammonia into amide, apparently complexed with the phenolic products. The addition of tartaric acid and adjustment of the aqueous solutions to pH7 during work-up were necessary to obtain better yields of products.

More 13-methylpodocarponitrile (CXXII) could be made from the amide CXXIII either by acetylation, dehydration with thionyl chloride and mild basic hydrolysis or by direct dehydration with thionyl chloride and basic hydrolysis of the intermediate sulfite-nitrile CXXVIII.



CXXVIII

In the conversion of 13-methylpodocarponitrile to the corresponding aldehyde CXXIV, the optimum conditions (1:7 molar ratio of nitrile to lithium aluminum hydride) were discovered empirically. The yields were nearly quantitative.

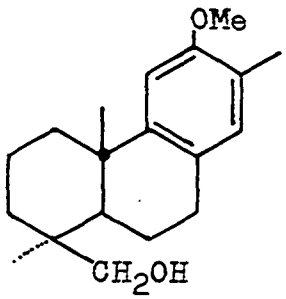
Reduction of the aldehyde to the hydrocarbon proved unsuccessful. A modification of the Huang-Minlon reduction method was employed, whereby the aldehyde was reacted with hyrazine prior to the addition of base. The yield of desoxynimbiol was low. However, acetylation of the chromatographic fraction corresponding to desoxynimbiol did give crystalline desoxynimbiol acetate. Only a small amount was obtained which was identified by its melting point.

The reason for the failure of the Huang-Minlon reduction is obscure. It is conceivable that the phenol interferred in the decomposition of the hydrazone.

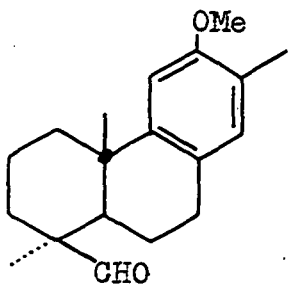
Attempts to improve the yield of desoxynimbiol by the

formation of a thioacetal and reduction with Raney Nickel failed when crystalline 13-methylpodocarpal was recovered from the initial ethanedithiol reaction mixture. The Clemmensen reduction of 13-methyl podocarpal also failed.

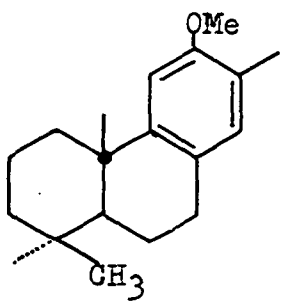
Further proof that the free phenol did participate in the Huang-Minlon reduction was given by the fact that the procedure worked well when the phenolic function was protected by a methyl group. The diol CXIV obtained previously as a side product was methylated with dimethyl sulfate in base to produce 13,O-dimethylpodocarpinol (CXXIX). Oxidation with chromic acid in pyridine gave 13,O-dimethylpodocarpal (CXXX) identified by its spectrum. The aldehyde was reduced by the modified Huang-Minlon method to give 13,O-dimethylpodocarpane (CXXXI) as an oil. This oil was submitted to oxidation with chromic acid in acetic acid to produce crystalline nimbiol methyl ether (III) identified by its melting point, optical rotation and infrared spectrum. This constituted a seven-step partial synthesis of nimbiol methyl ether.



CXXIX



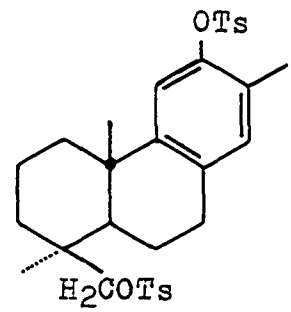
CXXX



CXXXI

The synthesis of nimbiol methyl ether constituted the first correlation by synthesis of the structures podocarpic acid and nimbiol. This also confirmed that the introduction of the methyl group on the phenol ring via the Mannich and Reimer-Tiemann methods had occurred at C-13 rather than at C-11 in agreement with prediction.

In regard to the synthesis of nimbiol, 13-methylpodocarpinol (CXIV) was an attractive intermediate from another viewpoint. If the 13-methylpodocarpinol ditosylate were prepared and reduced with lithium aluminum hydride, desoxynimbiol (VI) might be formed directly. The diol CXIV reacted with excess p-toluenesulfonyl chloride to give a crystalline ditosylate CXXXII. Lithium aluminum hydride reduction of the ditosylate yielded two products, desoxynimbiol in yields up to 75% and the starting diol CXIV. Acetylation of the synthesized desoxynimbiol gave crystalline desoxynimbiol acetate. The optical rotation agreed with that of the authentic desoxynimbiol acetate and the infrared spectra were identical. However, the melting point was low. Recrystallization from aqueous methanol failed to raise the melting point sufficiently. The synthetic material was oxidized by chromic acid in acetic acid to crystalline nimbiol acetate (IV) and hydrolyzed to nimbiol (II). The melting point agreed for nimbiol and the mixed melting point with nimbiol gave no depression proving the identity of the product. This constituted a nine-step synthesis of nimbiol from podocarpic acid.

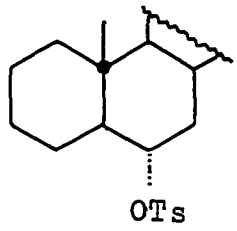


CXXXII

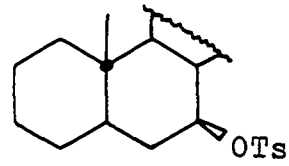
The unique aspect of this synthesis was the difference in mode of reduction of the two sulfonate esters of the ditosylate. It is impossible to displace an aromatic tosylate with hydride or other nucleophiles unless the aromatic ring is substituted with electron withdrawing groups at ortho and para positions. Hence, the reduction of phenyl tosylates with lithium aluminum hydride proceeds by cleavage of the sulfur-oxygen bond rather than the carbon-oxygen bond (75, 76).

In contrast, aliphatic p-toluenesulfonates have been known to cleave either bond. The results vary considerably depending on the compound. For example, lithium aluminum hydride reduction of cholestan-6-ol tosylate (CXXXIII) gave 38% of cholestane and 37% of cholestan-6-ol (77, 78). The tosylate CXXXIII was originally considered as the β-tosylate (77), but this was later changed to the 6 α-configuration (78). The reduction of cholestan-7-ol tosylate (CXXXIV)

yielded 92% of cholestane (77, 78). In light of these and other examples it is evident steric factors exercise a major role in the reduction.

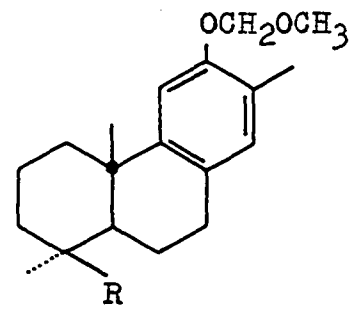


CXXXIII



CXXXIV

Since the failure of the Huang-Minlon reduction of 13-methylpodocarpal had been attributed to the presence of the phenolic group, it appeared possible to convert 13-methylpodocarponitrile into desoxynimbiol by first masking the phenol with a protecting group. The methyl ether was undesirable because of the difficulty that would be encountered in removing the methyl group at the end of the synthesis. Tetrahydropyranyl derivative formation with dihydropyran proved unsuccessful. However, the methoxymethyl derivative of 13-methylpodocarponitrile could be made. Reaction of the nitrile in acetone with potassium carbonate and chloromethyl ether gave no alkylation. But the dry potassium salt of the phenol reacted with chloromethyl ether to give the alkylated product CXXXV and starting material.



CXXXV R = CN

CXXXVI R = CHO

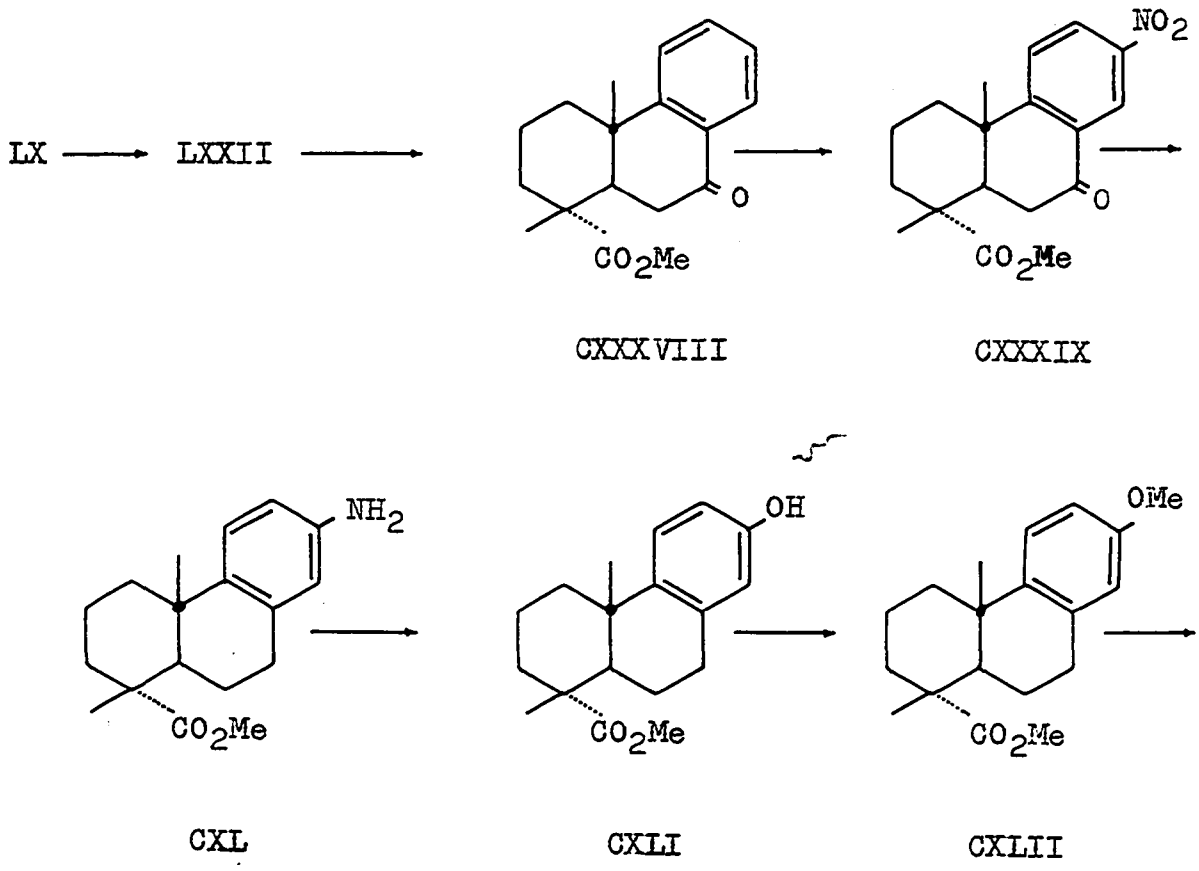
CXXXVII R = CH_2OH

After again modifying the ratio of nitrile to lithium aluminum hydride, reduction of CXXXV gave the aldehyde CXXXVI identified by its infrared spectrum. The Huang-Minlon reduction followed by dilute sulfuric acid hydrolysis gave desoxynimbiol as an oil. Acetylation with acetic anhydride gave crystalline desoxynimbiol acetate (VI) identical with the authentic compound. This completed the third method of partial synthesis of nimbiol.

The same aldehyde obtained from lithium aluminum hydride reduction of CXXXV was obtained by chromic acid oxidation of 13-methyl-O-methoxymethylpodocarpinol (CXXXVII). The mono ether was obtained by alkylation of the potassium salt of 13-methylpodocarpinol. The diether and diol CXIV were also obtained as side products.

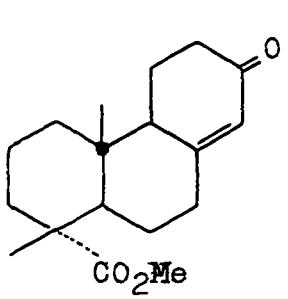
On the Synthesis of Abietic Acid

The synthesis of dl-deisopropyldehydroabietic acid (LX) by Wenkert and Tahara (50), as previously described in the Historical Section, prompted attempts to complete the synthesis of d-abietic acid (I). For this project dl-deisopropyldehydroabietic acid must be resolved and the d-form be converted to abietic acid. The proposed synthesis pathway is illustrated in the following diagram.

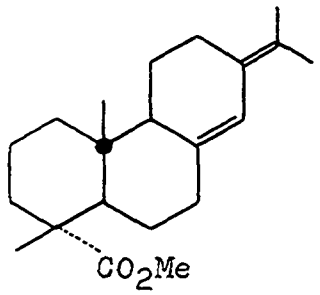


CXXXVIII CXXXIX

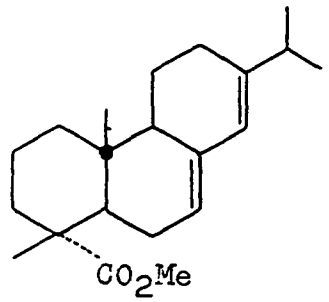
CXL CXLI CXLII



CXLIII

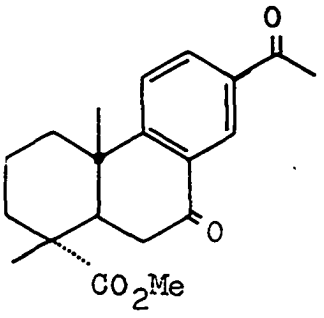


CXLIV

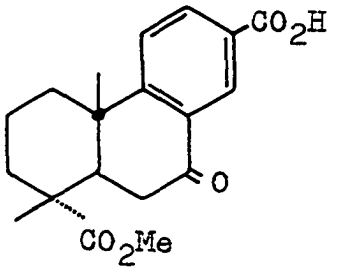


CXLV

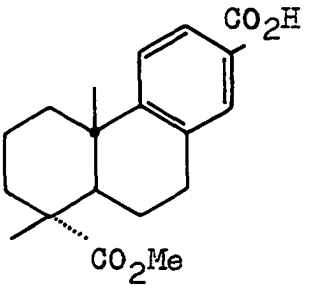
New sources of starting materials had to be found, since the supply of deisopropyldehydroabietic acid (LX) was small. The diketoester CXLVI was available in sufficient quantity to make it a desirable starting material. Ohta (79) and Ohta and Ohmori (80) had previously converted the diketoester CXLVI into the acid-ester CXLVII by iodine and pyridine. A Huang-Minlon reduction, esterification and monohydrolysis had given CXLIII. The Curtius rearrangement applied to CXLVIII had produced the aminoester CXL, an intermediate in the proposed synthesis scheme. This compound has been reacted with nitrous acid, base and formaldehyde to give methyl deisopropyldehydroabietate LXXII, another intermediate (80).



CXLVI



CXLVII

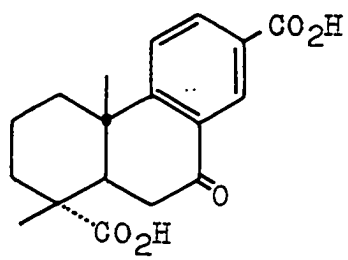


CXLVIII

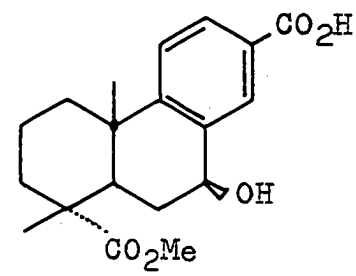
When the iodine-pyridine reaction was repeated on CXLVI, two products were obtained, the desired acid CXLVII and a second acid CXLIX. Ohta (79) also isolated the second acid CXLIX and proposed that it was the hydrolyzed ester of CXLVII but gave no chemical evidence. To obtain maximum yield of the acid CXLVIII, an attempt was made to convert CXLIX into CXLVIII. Esterification of CXLIX, catalytic hydrogenation over palladium-charcoal catalyst and monohydrolysis gave a new crystalline product CL different from the expected acid-ester CXLVIII. Elemental analysis indicated the presence of an extra hydroxyl group in the molecule.

Most likely the hydrogenation of CXLIX had been incomplete leaving a hydroxyl group at C-7. Indeed, exhaustive hydrogenation with palladium-charcoal catalyst gave CXLVIII. The mixed melting point with a sample of CXLVIII prepared directly from CXLVI was not depressed proving the identity of

the hydrogenation products. Hence, the structure of CXLIX must be the hydrolyzed ester of CXLVII, and CL must have a hydroxy group at C-7. The configuration of the hydroxyl group is most probably β since the α-side of the molecule is least hindered for catalyst approach.



CXLIX

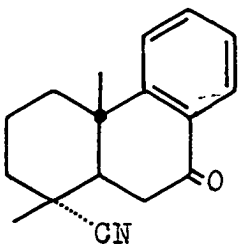


CL

Ohta's procedures were modified to include a catalytic hydrogenation of the ketone CXLVII to CXLVIII. This alteration simplified the previously cumbersome procedure and gave quantitative yields of CXLVIII. The yields of the Curtius rearrangement to the aminoester CXL, however, were low compared with those reported (79).

Another method was devised to obtain deisopropyldehydroabietic acid from a second available compound CLI. This nitrile was obtained from deisopropylation of dehydroabietonitrile by Wenkert and Chamberlin (81). Huang-Minlon reduction and subsequent addition of more base and water with prolonged heating produced the desired acid LX. Reduction of the

ketone and hydrolysis of the nitrile were incorporated into one step by this procedure. The acid LX was esterified with diazomethane to give LXXII. Chromic acid-acetic acid oxidation of LXXII produced the ketone CXXXVIII.



CLI

This completes three of the ten steps of the proposed conversion of deisopropyldehydroabietic acid to abietic acid. Another intermediate, the amine CXL, has been synthesized and can be used for further work.

Figure 1. Ultraviolet spectra

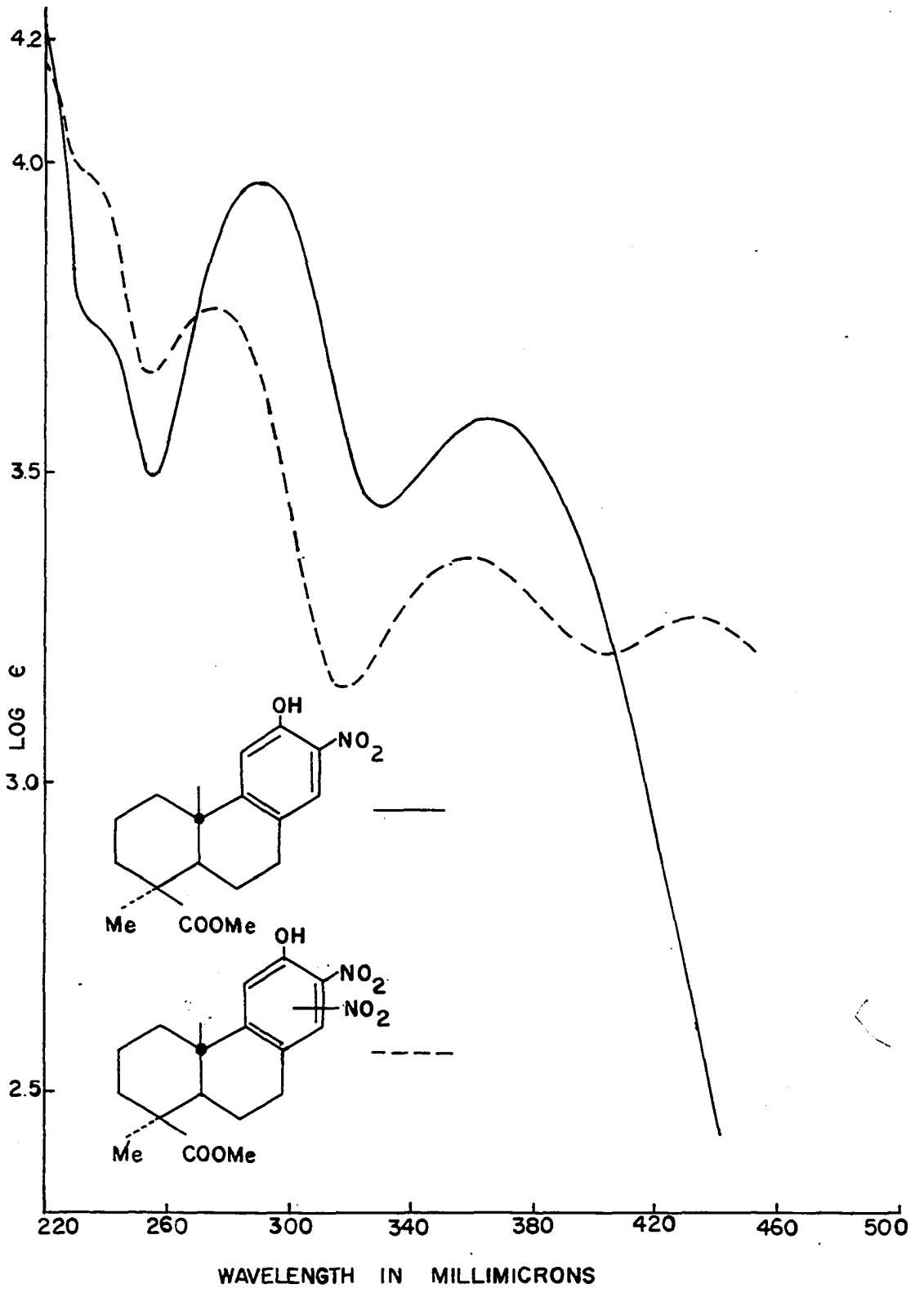

4.2
4.0
3.5
3.0
2.5
LOG ε
OH
NO2
Me
COOMe
OH
NO2
NO2
Me
COOMe
220
260
300
340
380
420
460
500
WAVELENGTH IN MILLIMICRONS

Figure 2. Ultraviolet spectra

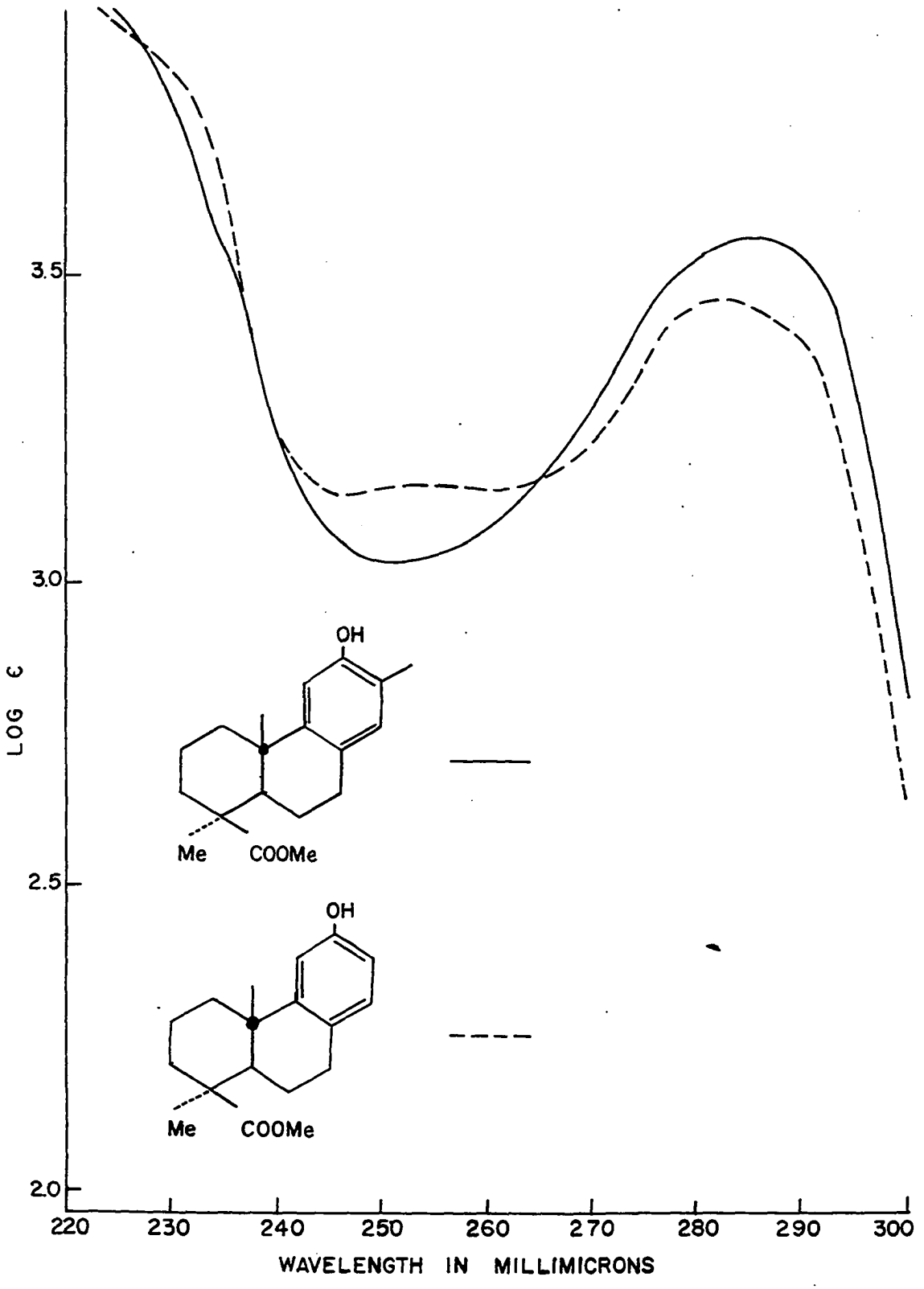
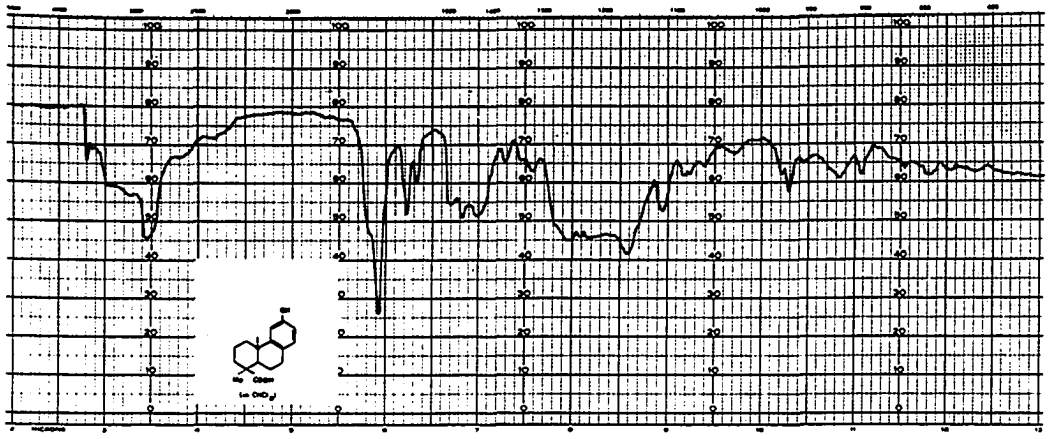
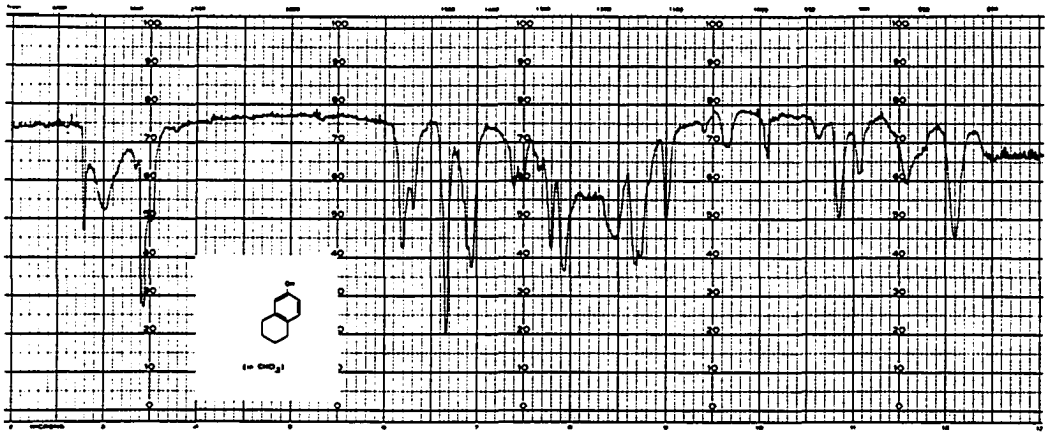

3.5
3.0
2.5
2.0
LOG ε
OH
Me
COOMe
OH
Me
COOMe
220
230
240
250
260
270
280
290
300
WAVELENGTH IN MILLIMICRONS

Figure 3. Infrared spectra





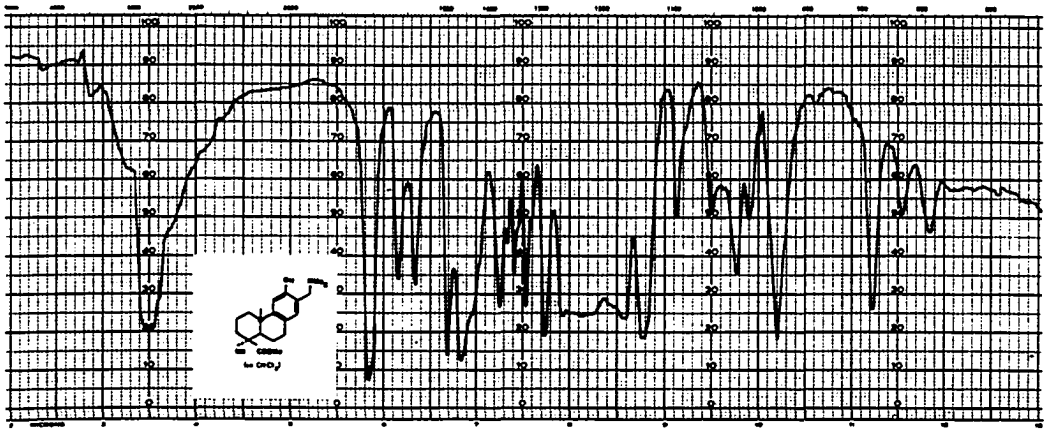
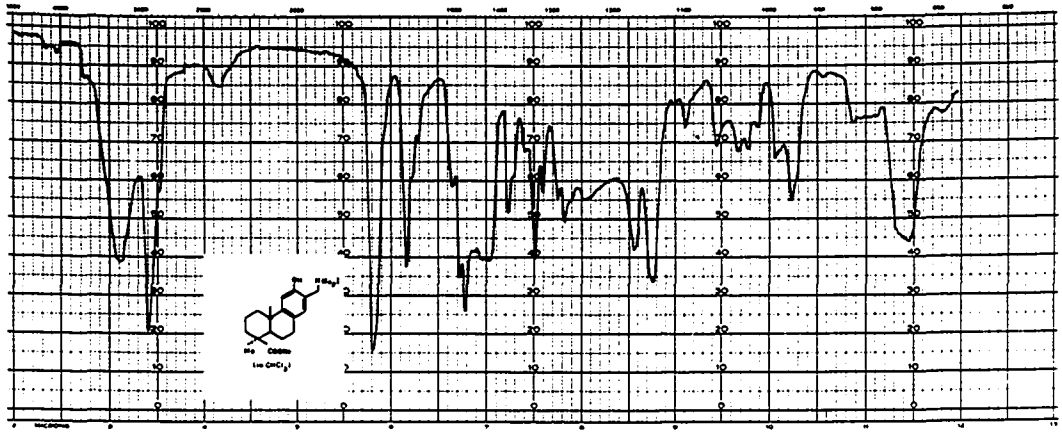
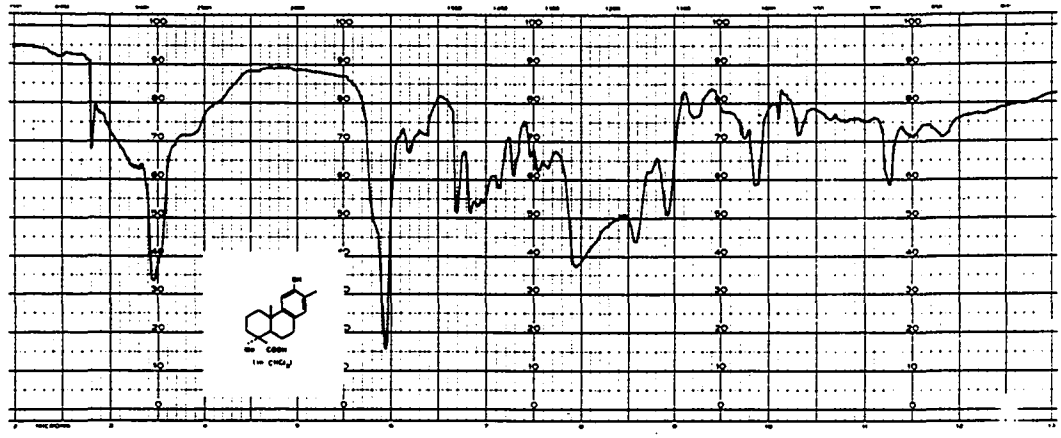


Figure 4. Infrared spectra





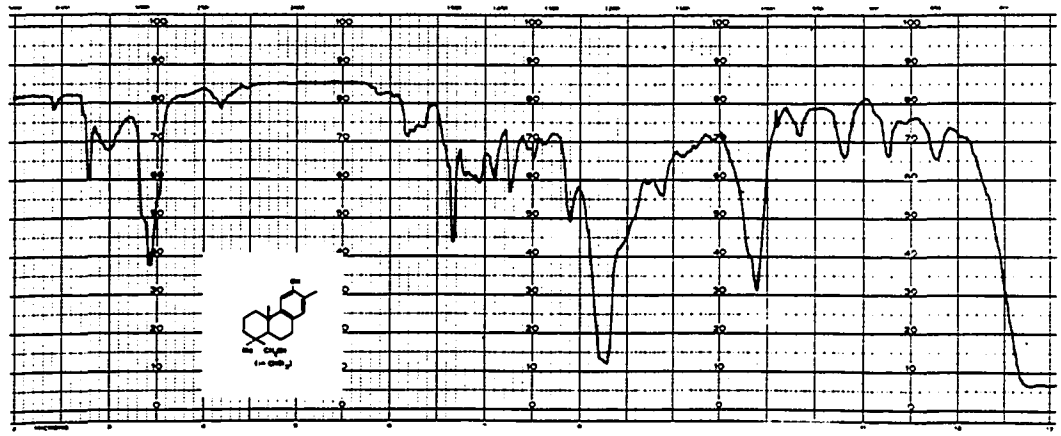
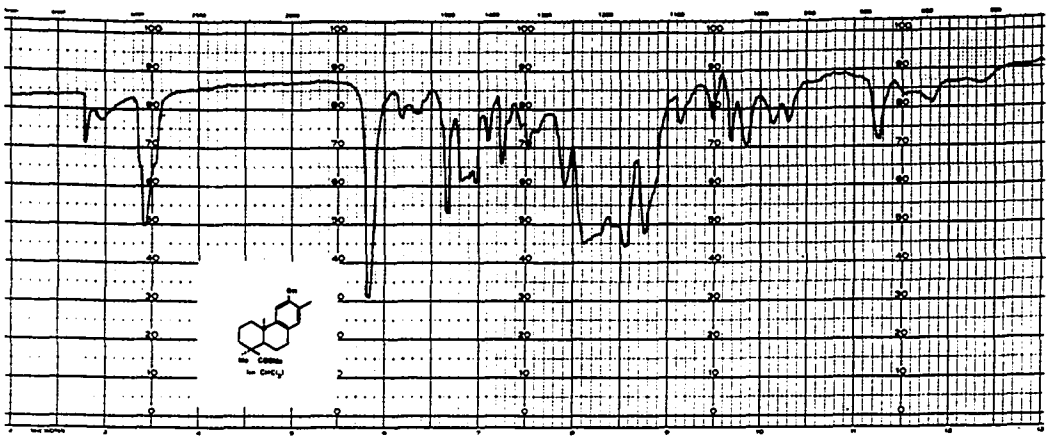
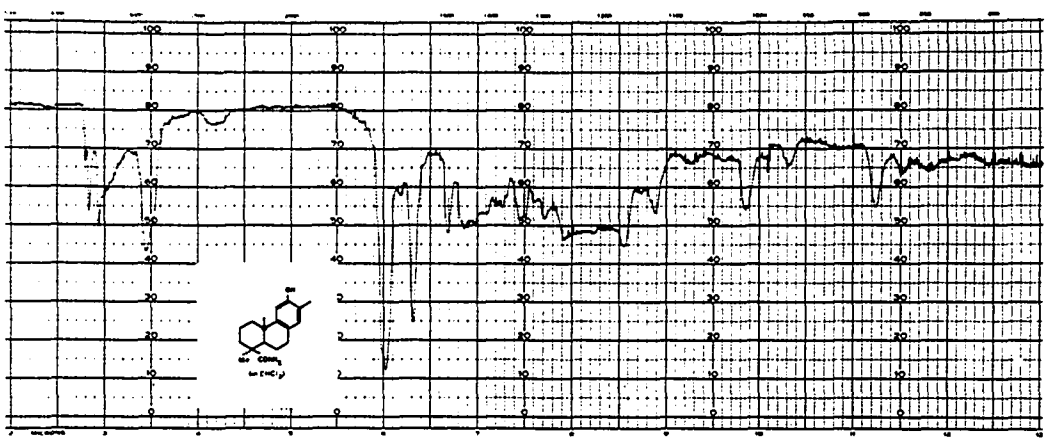


Figure 5. Infrared spectra





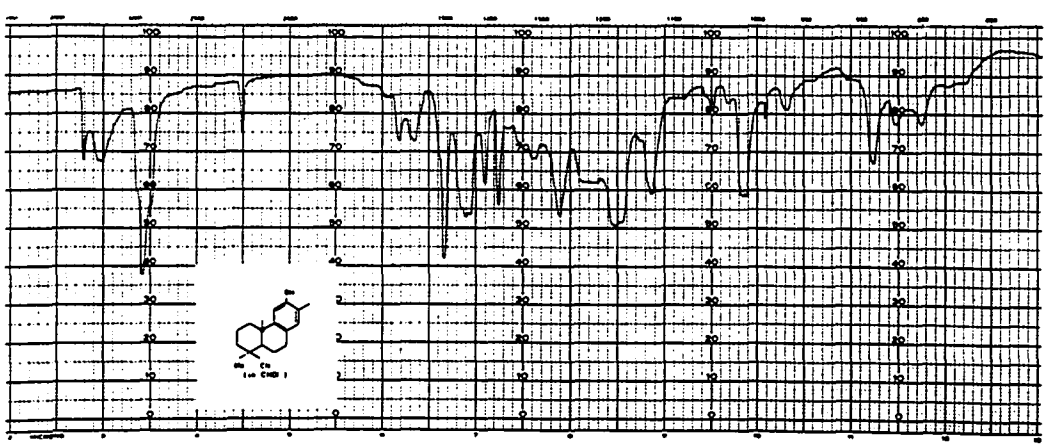
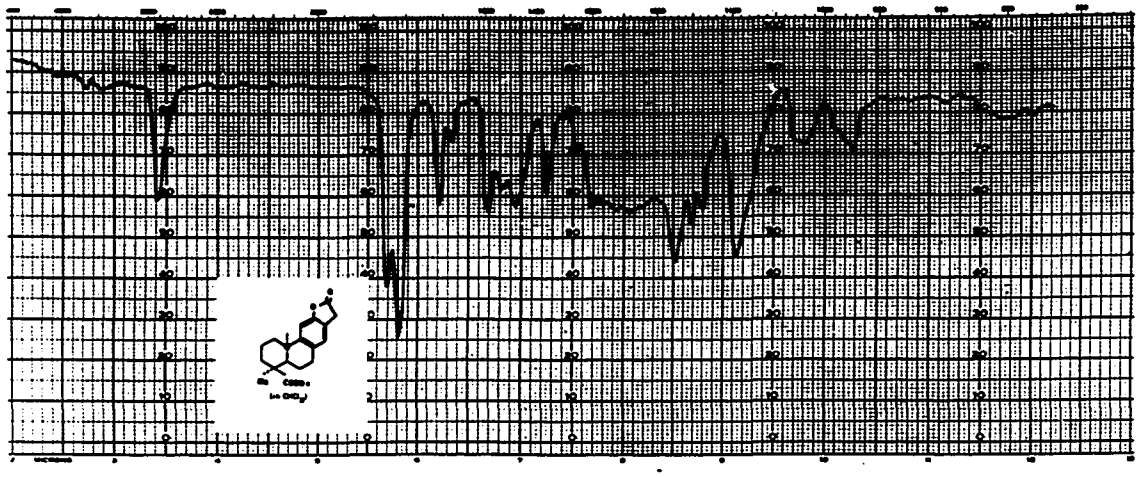
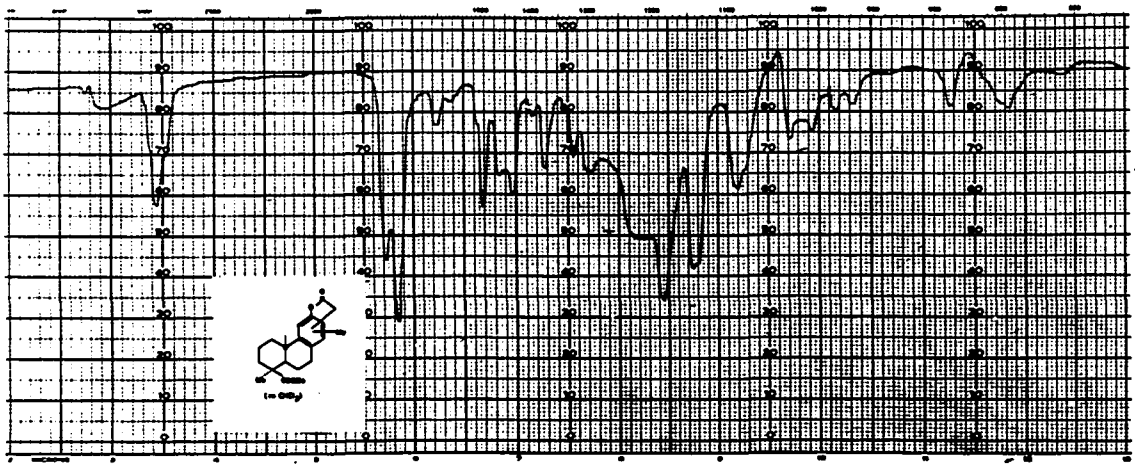


Figure 6. Infrared spectra





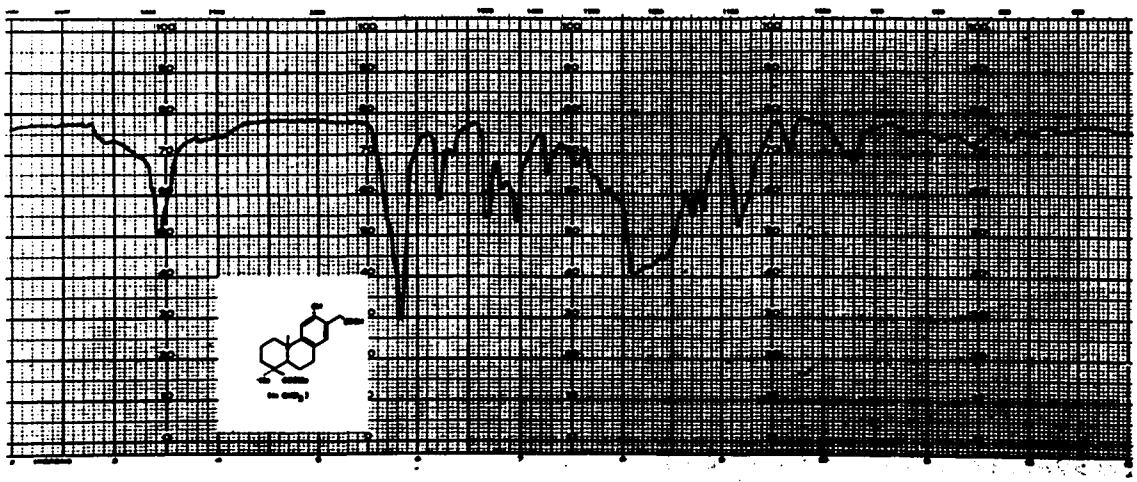
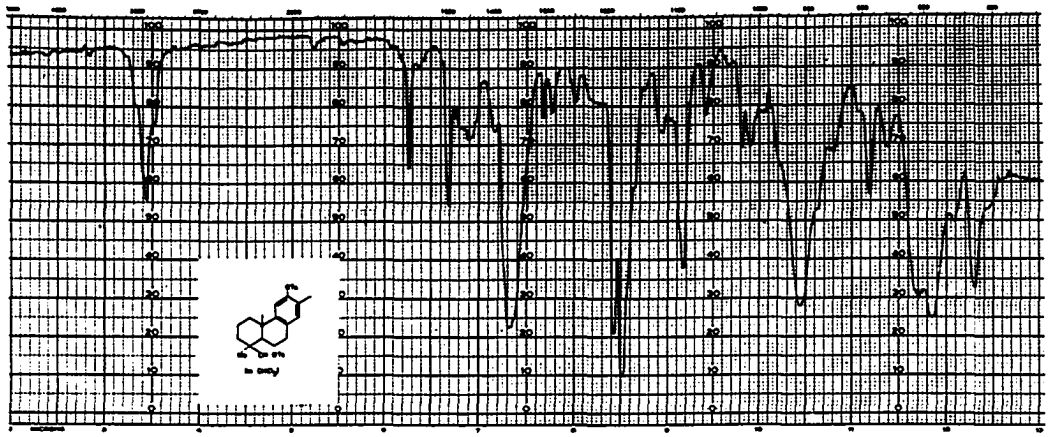
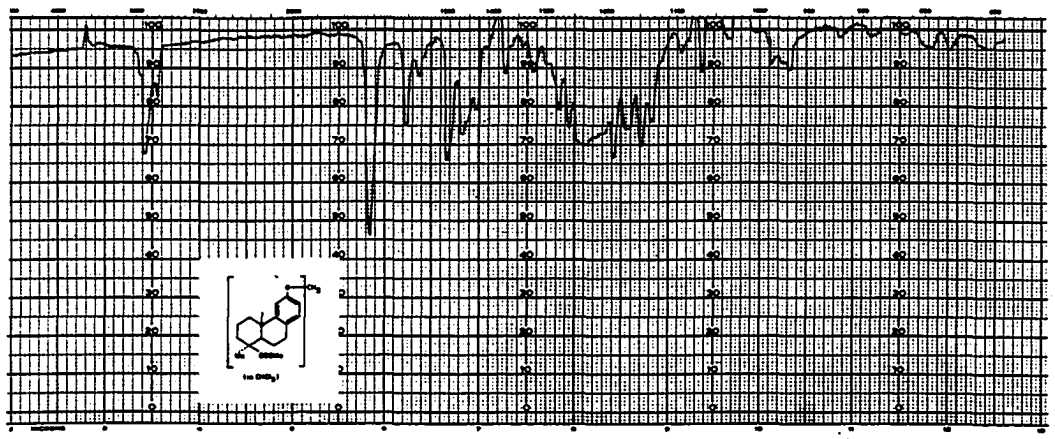


Figure 7. Infrared spectra





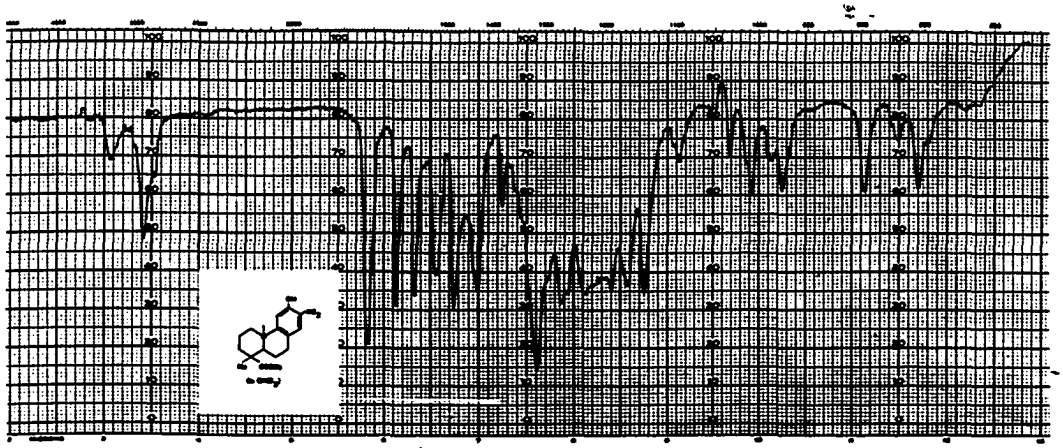
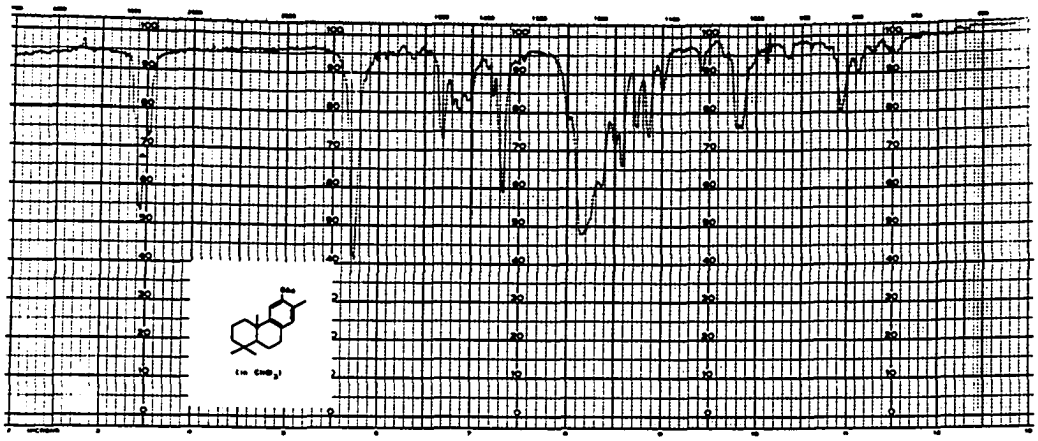
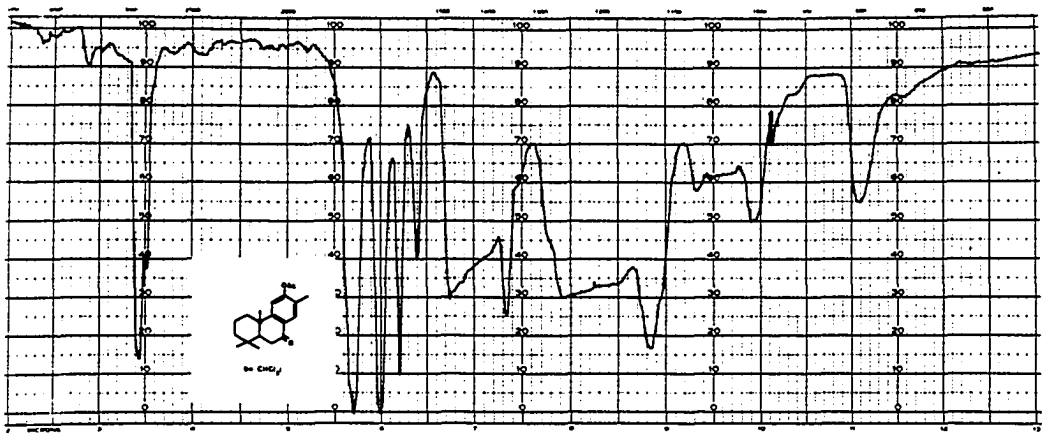


Figure 8. Infrared spectra





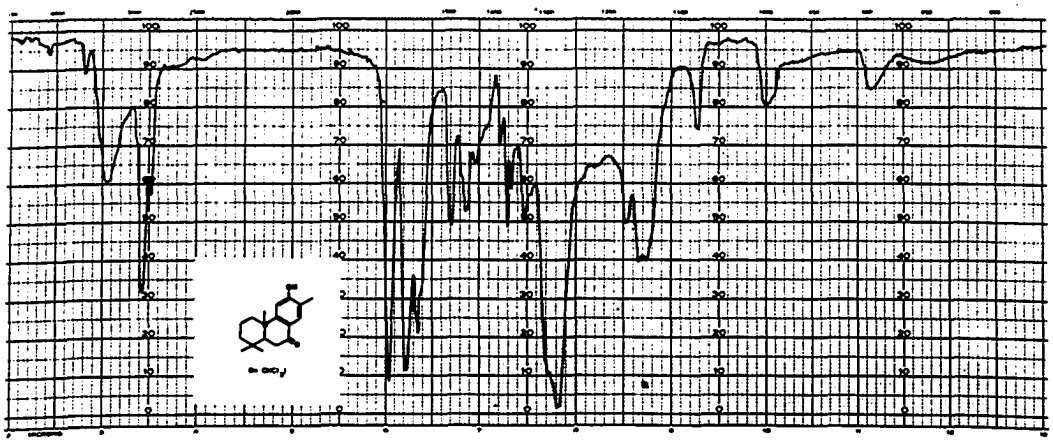
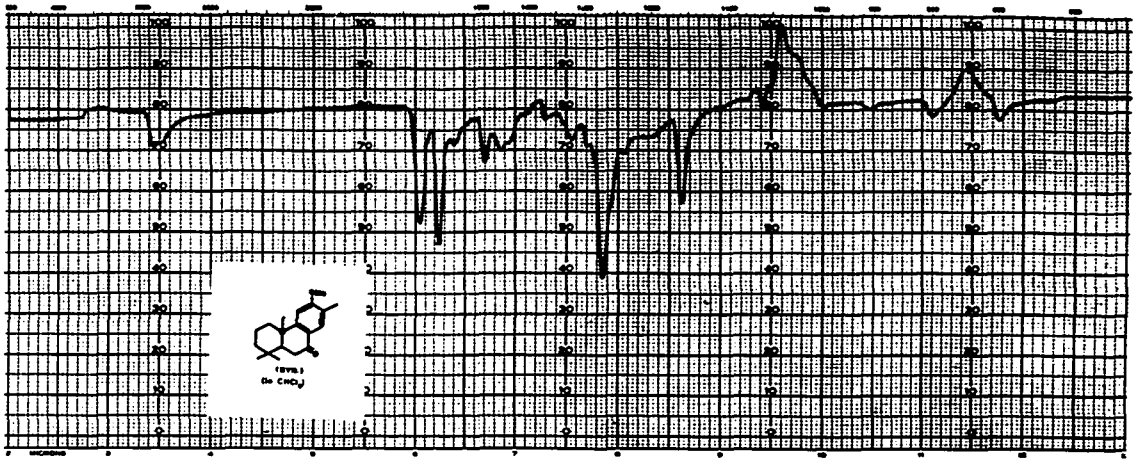
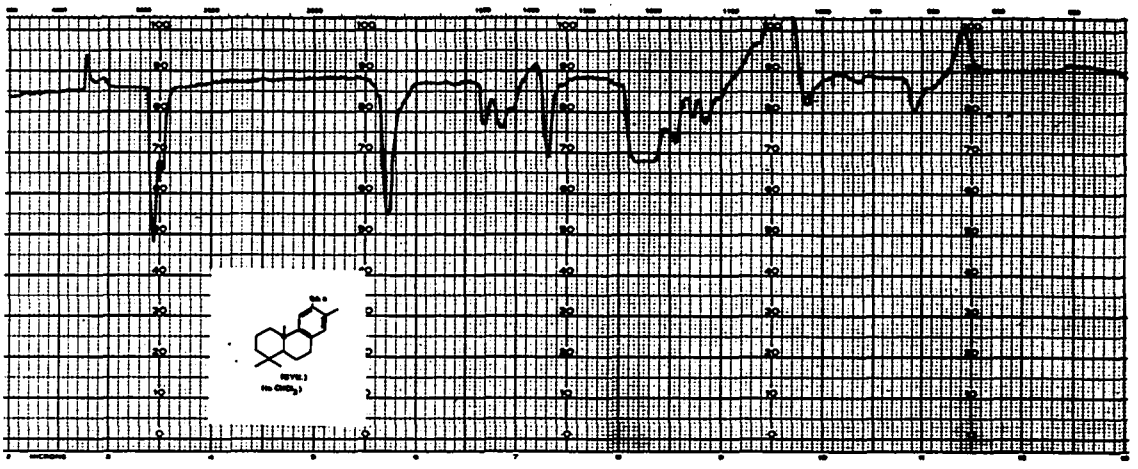


Figure 9. Infrared spectra





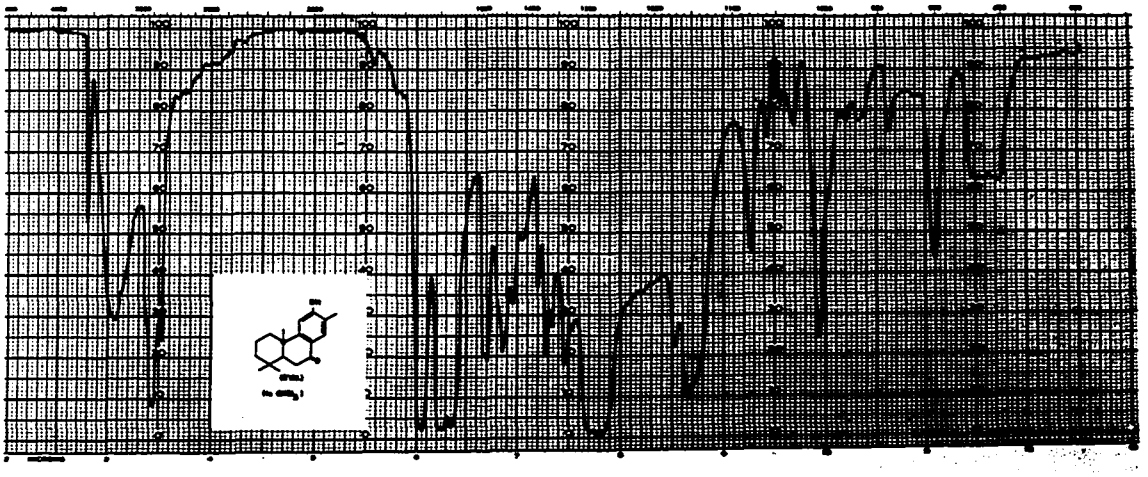
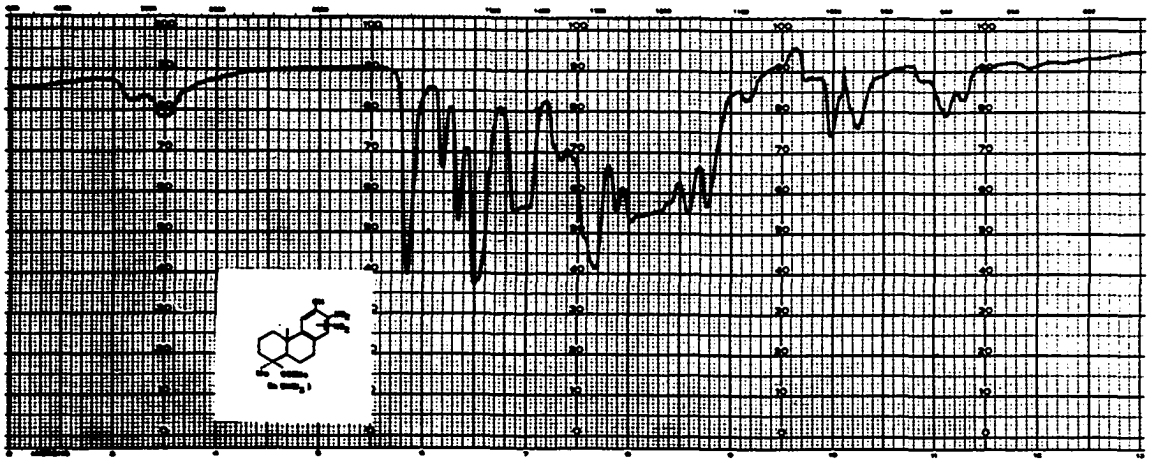
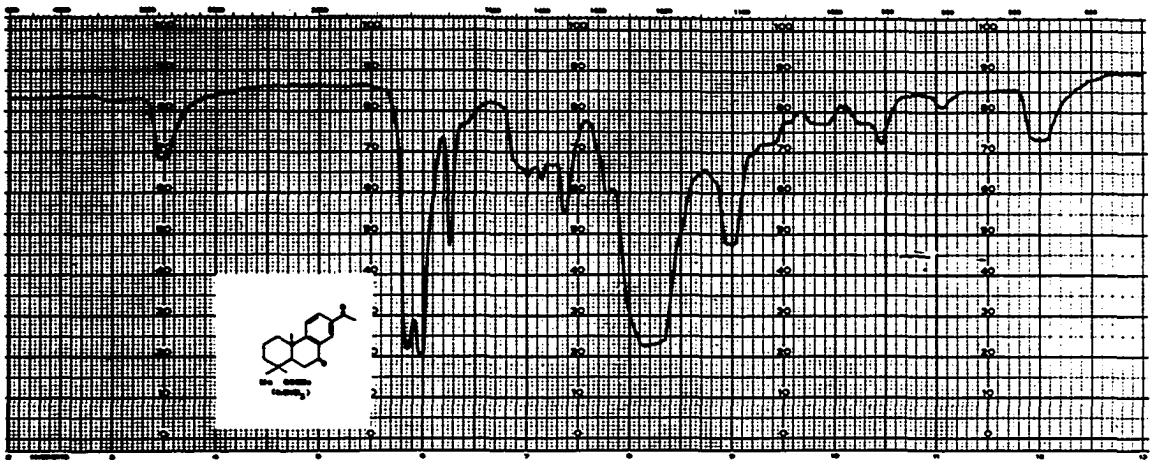


Figure 10. Infrared spectra





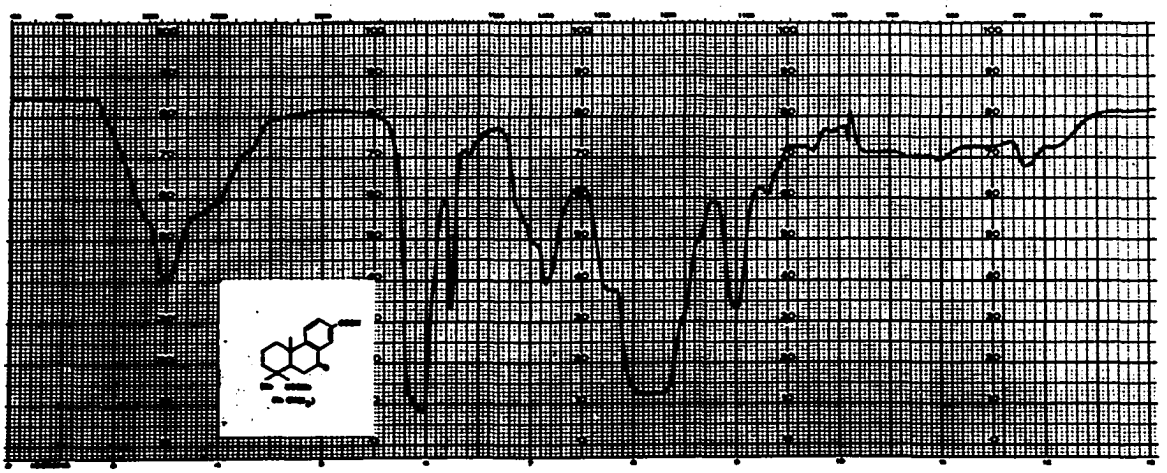
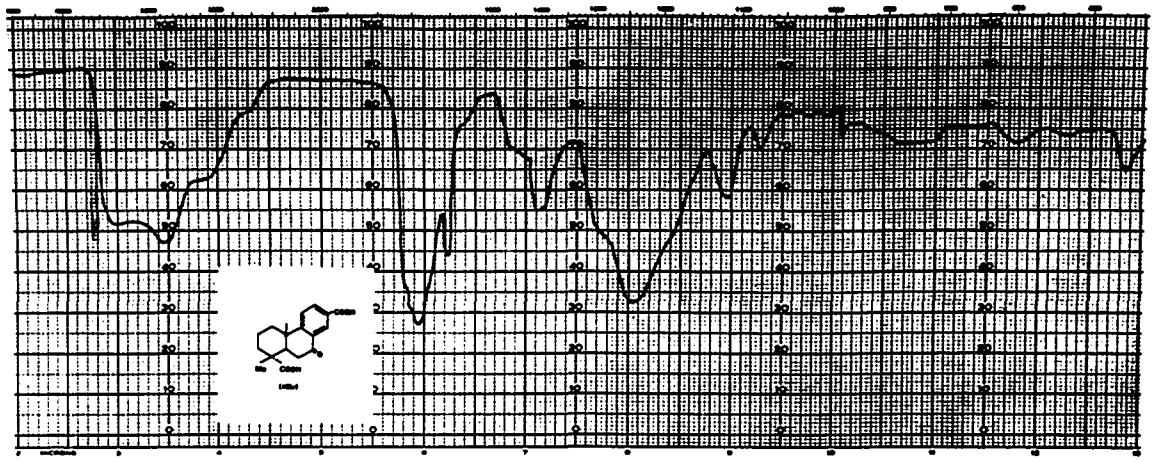
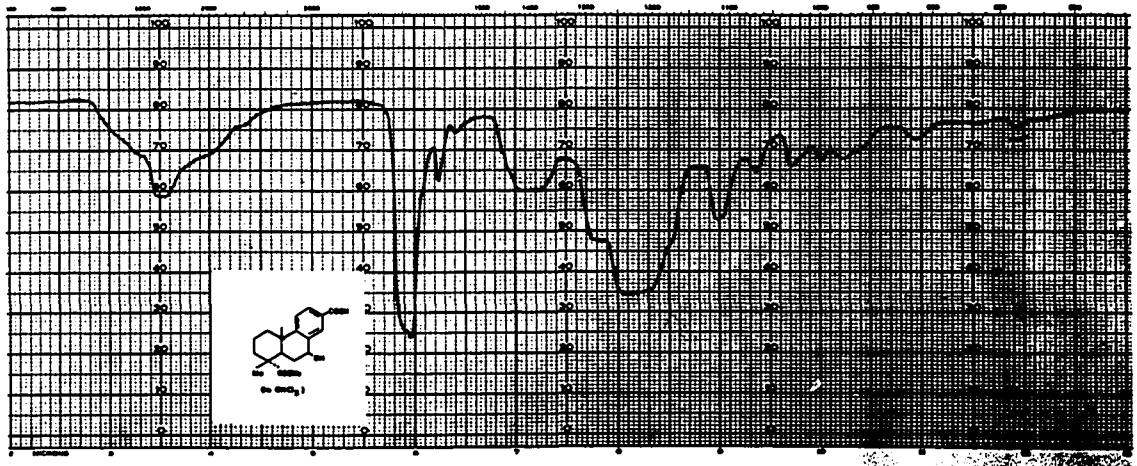


Figure 11. Infrared spectra





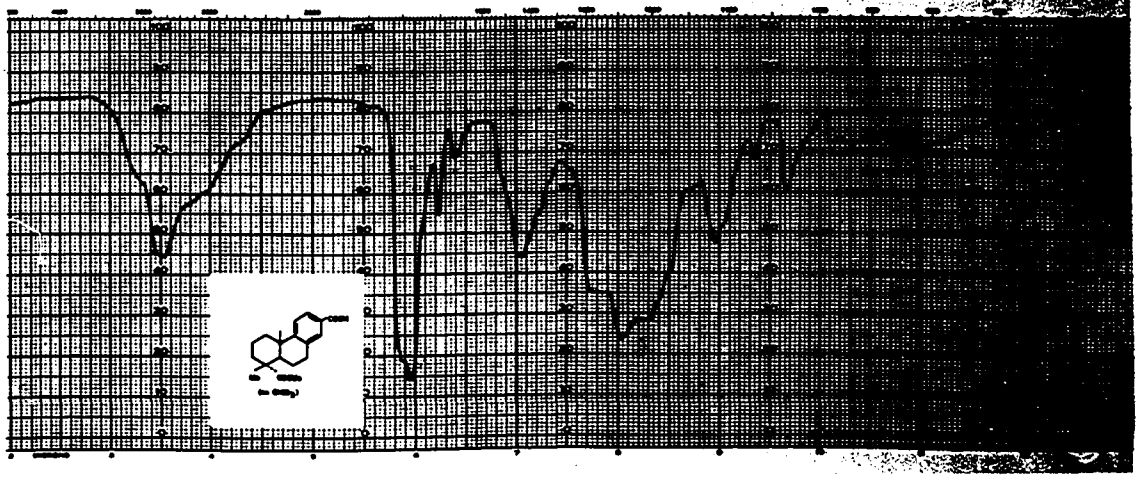
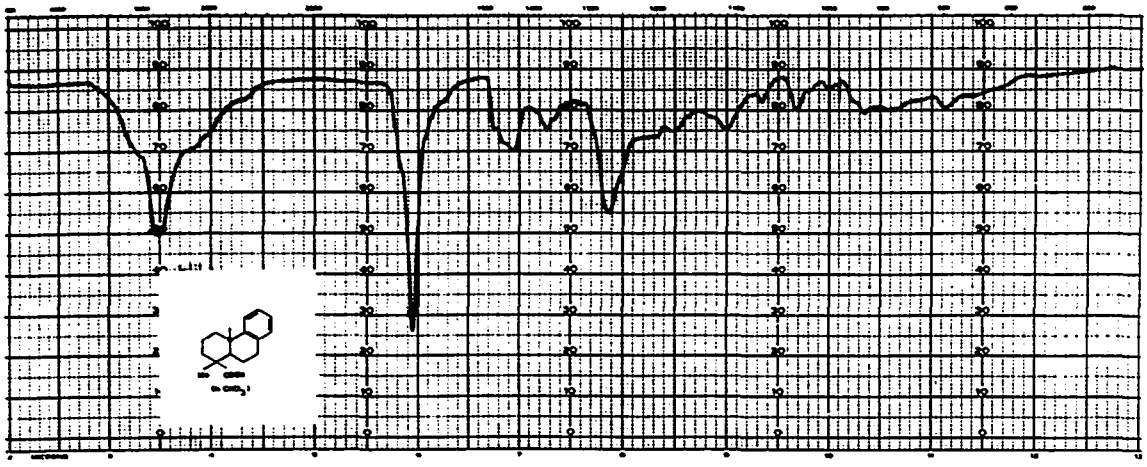
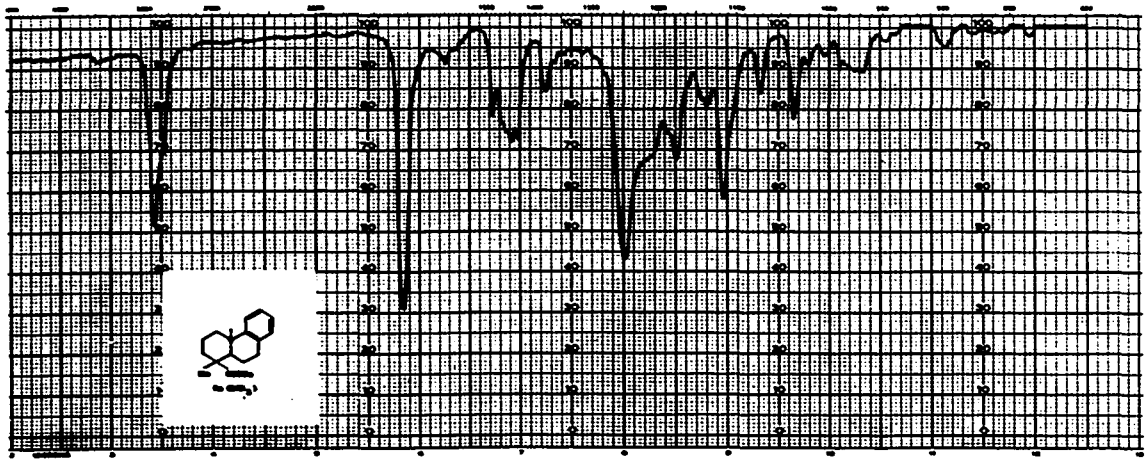
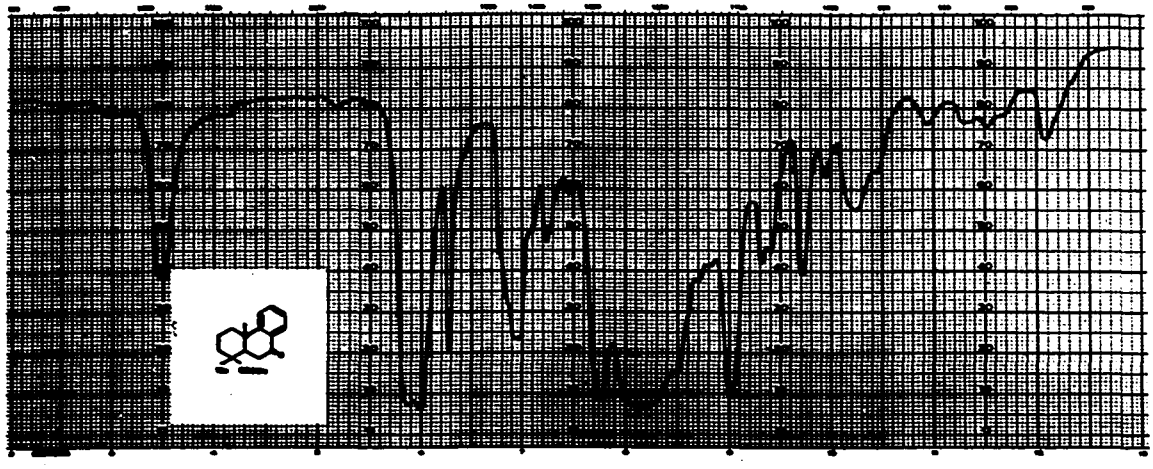


Figure 12. Infrared spectra







EXPERIMENTAL

Procedure Notes

All melting points are corrected. The term petroleum ether refers to a petroleum distillate boiling at 66-70°. The microanalyses were performed by Strauss and Weiler Microanalytical Laboratory, Oxford, England, Midwest Microlab, Indianapolis, Indiana and Alfred Bernhardt of the Max Planck Institute, Mulheim (Ruhr), Germany. The optical rotations were measured in chloroform solution unless otherwise stated, using an O. C. Rudolpf polarimeter.

The chromatography was done on two adsorbants, activated alumina and silica. The alumina was 80-200 mesh, prepared by allowing it to stand with ethyl acetate for 48 hours, then washed with water and methanol and dried at 50° for 48 hours. Commercial silica, 50-200 mesh, was used directly for chromatography.

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

Esterification of Podocarpic Acid

To a solution of 5.0 g. of podocarpic acid in 50 ml. of methanol was added an ether solution of excess diazomethane.

The diazomethane solution was prepared from 14 g. of N-nitroso-N-methylurea. The reaction solution was permitted to stand for 5 minutes after which time the gas evolution had nearly stopped. The excess diazomethane and solvents were removed under vacuum in a water bath at 40-50°. As the solvents distilled off, methyl podocarpate began crystallizing, giving 5.2 g. (99%) of methyl podocarpate after all the solvent was removed. Crystallization from aqueous methanol produced needles melting at 212.5-213°.

Ultraviolet spectrum

See figure 1.

Alkylation of Methyl Podocarpate with Methyl Iodide

Dry benzene was twice distilled from 100 mg. of methyl podocarpate (0.35 mmole) in a predried vessel and the dry methyl podocarpate dissolved in 10 ml. of dry methanol. The sodium salt of methyl podocarpate was prepared by reacting 8 mg. of sodium (0.35 mmole) with the methanol solution and distilling off the excess methanol in vacuum. The reaction was completed by adding 15 ml. of dry toluene and 0.6 ml. of methyl iodide and refluxing for 25 hours. After cooling, the salt was filtered off and washed with ether. Evaporation of the ether left a semicrystalline residue. The mixture was fractionally crystallized from aqueous methanol to give 35 mg. of

methyl podocarpate methyl ether, m.p. 104-107°. Recrystallization from aqueous methanol produced crystals, m.p. 127-129°. The mixed m.p. with methyl podocarpate methyl ether prepared directly from podocarpic acid was not depressed. The residues were chromatographed on alumina. Elution with petroleum ether gave 42 mg. (74% total) of methyl podocarpate methyl ether and 14 mg. (14%) of methyl podocarpate, m.p. 196-204°. Recrystallization of the latter from aqueous methanol once led to crystals of m.p. 201-204°.

Infrared spectrum

λ max. 3.41 (s), 5.81 (s), 6.23 (m) and 6.39 (w) microns.

Alkylation of Methyl Podocarpate with Isopropyl Iodide

Dry benzene was twice distilled from 100 mg. of methyl podocarpate (0.35 mmole) in a predried vessel and the dry methylpodocarpate dissolved in 10 ml. of dry methanol. The dry sodium salt was prepared by reacting 8 mg. of sodium with the methanol solution and distilling off the excess methanol in vacuum. The alkylation was completed by adding 10 ml. of isopropyl iodide and refluxing for 48 hours. The reaction mixture was stripped of solvent under reduced pressure and the tan residue taken up in water and extracted with ether. After drying over sodium sulfate, the ether was evaporated, leaving an oil which partly crystallized. The oil was dissolved with

petroleum ether leaving 41 mg. of methyl podocarpate, m.p. 200-207°. Recrystallization from aqueous methanol gave crystals, m.p. 208-209°.

Optical rotation

$[\alpha]_D^{23^\circ}$ + 141.5°. Methyl podocarpate: $[\alpha]_D^{23^\circ}$ + 136°.

The petroleum ether soluble fraction crystallized on standing, m.p. 114-119°. Recrystallization from aqueous methanol to give an analytical sample of methyl podocarpate isopropyl ether, m.p. 131.5-133°.

Analysis

Calculated for $C_{21}H_{30}O_3$: C,76.5; H,9.1. Found: C, 76.30; H,9.13.

Infrared spectrum

λmax. 4.38 (s), 5.81 (s), 6.24 (m) and 6.38 (w) microns.

Chromatography of the mothor liquor residues on alumina produced 40 mg. of methyl podocarpate isopropyl ether (total of 40%) and 14.6 mg. of methyl podocarpate (total 56%).

Alkylation of Methyl Podocarpate with Ethyl Bromoacetate

A solution of 1.893 g. (6.6 mmoles) of dry methyl podocarpate in 10 ml. of dry methanol was reacted with 166 mg. (7.2 mmoles) of sodium. After the reaction was completed, the excess methanol was distilled off under vacuum. Dry benzene was distilled from the residue twice. The dry salt was mixed with 5 ml. of ethyl bromoacetate and refluxed for 6 hours. The excess ethyl bromoacetate was removed under reduced pressure and the residue taken up in water and extracted with ether. The combined ether solutions were washed with water and filtered through anhydrous sodium sulfate. Evaporation of the ether solution left 2.58 g. of a light yellow semi-crystalline residue. The oil was washed away leaving 662 mg. (35%) of crystalline methyl podocarpate, m.p. 179-201°.

Infrared spectrum

Identical with that of methyl podocarpate.

The petroleum ether fraction was chromatographed on 60 g. of silica. Elution with benzene-ether gave 1.388 g. (64%) of the lactone CII as an oil. This lactone crystallized from aqueous methanol with difficulty to yield an analytical fraction, m.p. 81.5-83°.

Analysis

Calculated for $C_{20}H_{24}O_4 \cdot CH_3OH$: C,69.97; H,7.83. Found: C,69.80; H,8.08.

Infrared spectrum

See figure 6.

Alkylation of the Lactone CII with Methyl Iodide

In a predried flask 200 mg. (0.61 mmole) of the lactone was dissolved in 10 ml. of absolute methanol. The sodium salt of the phenol was prepared by reacting 16 mg. (0.69 mmole) of sodium with the methanol solution and distilling off the excess alcohol under vacuum on a steam bath. The reaction was completed by adding 10 ml. of dry benzene, 1.5 ml. of methyl iodide and refluxing for 24 hours. The solvents were distilled under reduced pressure and the residue taken up in water, neutralized with 10% hydrochloric acid and extracted with ether. The combined ether solutions were extracted with 5% sodium hydroxide, filtered through anhydrous sodium sulfate and evaporated, leaving 32 mg. (14%) of O-methylated ester CIII, m.p. 167-195°.

Infrared spectrum

λ max. 5.80 (s) microns, no O-H stretching band.

The base extract was neutralized with 10% hydrochloric acid and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 131 mg. (62% of an acid, m.p. 138.5-142°). Crystallization from aqueous methanol gave a solid which appeared to have no definite crystalline pattern, m.p. 143-146°. The analytical sample was prepared by sublimation of this product.

Analysis

Calculated for $C_{20}H_{26}O_5$: C,69.34; H,7.64. Found: C,69.41; H,7.64.

Infrared spectrum

See figure 6.

Reimer-Tiemann Reaction on Methyl Podocarpate

A solution of 257 mg. of methyl podocarpate in 3 ml. of 95% ethanol was added to a base solution prepared by dissolving 1 g. of sodium hydroxide in 2 ml. of water. After the dropwise addition of ½ ml. of chloroform, the solution was refluxed for 1 hour. As the chloroform was added, the solution

turned blue. When the reaction was complete, the solution was neutralized with 10% hydrochloric acid and extracted with ether. The ether was dried by filtering through anhydrous sodium sulfate and evaporated, leaving a brown gum. The gum was separated into its aldehyde and non-aldehyde components by use of Girard's reagent T (82). The gum and 0.125 g. of Girard's reagent T were dissolved in 0.25 ml. of acetic acid and 2.5 ml. of 95% ethanol. The mixture was refluxed for 1 hour under a cold finger condenser. The solution was cooled and diluted with a mixture of 13 ml. of ether, 13 ml. of water and 5 ml. of saturated sodium chloride solution. Further extractions with ether removed the non-aldehydic components. The aqueous layer was treated with 0.5 ml. of concentrated hydrochloric acid and heated for 10 minutes on a steam bath. The cloudy mixture was cooled and extracted with ether. On drying and evaporating the ether solution of the aldehyde fraction, 20.8 mg. (7%) of crystals formed, m.p. 121-127°.

Infrared spectrum

λ max. 3.05 (m), 3.51 (s), 5.82 (s) and 6.04 (s) microns. (Infracord)

Methyl 13-Methylpodocarpate from the Aldehyde CV

The reaction mixture was prepared by dissolving 20.8 mg. of the crystalline aldehyde CV in 2 ml. of acetic anhydride.

The acetate was formed by refluxing this solution for 1½ hours. After cooling, 40 mg. of 10% palladium on charcoal was added and the mixture hydrogenated at atmospheric pressure for 22½ hours. The reduction mixture was filtered and the solvent removed. The infrared spectrum of the residual oil indicated complete removal of the aromatic aldehyde by the disappearance of the carbonyl band at 6.04 microns. The acetate was hydrolyzed by refluxing 2 hours with 7.5 ml. of isopropyl alcohol and 2.5 ml. of 2 N potassium hydroxide. The basic solution was extracted with ether, the ether layer washed with water and filtered through anhydrous sodium sulfate. After removal of the solvent under reduced pressure, 11.2 mg. of a semicrystalline oil was obtained. Chromatography of this oil on 1 g. of alumina produced crystals, m.p. 112-130°. Repeated crystallizations from aqueous methanol produced crystals melting at 160-172°. Further recrystallization was difficult because of the amount of crystals remaining.

Mannich Reaction on Methyl Podocarpate

A solution of 200 mg. (0.69 mmole) of methyl podocarpate, 2 ml. of dioxane and 2 ml. of 95% ethanol was reacted a three fold excess each of 37% formaldehyde and 35% dimethylamine. The formaldehyde was added dropwise after the addition of dimethyl amine. The solution was allowed to react at room temperature for 3½ hours with stirring and at the boiling point

for 5½ hours. The solvents were removed under reduced pressure. The residue was taken up in 10% hydrochloric acid and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 25 mg. (12%) of a solid. Trituration with methanol produced crystals of CIX, m.p. 68-75°. Subsequent sublimation and recrystallization from methanol gave colorless needles, m.p. 129.5-130.5°.

Analysis

Calculated for $C_{37}H_{48}O_6$: C,75.48; H,8.22. Found: C,75.13; H,8.53.

Infrared spectrum

See figure 7.

Optical rotation

$$[\alpha]_D^{22^\circ} + 116^\circ$$

Molecular weight

The molecular weight of CIX and methyl podocarpate was determined by melting point depression of camphor to be 484 and 295 respectively.

The acid solution was neutralized and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 203 mg. (85%) of white crystals of methyl 13-dimethylaminomethylpodocarpate (CVIII), m.p. 148-152°. Recrystallization from aqueous methanol gave an analytical sample, m.p. 152-153°.

Analysis

Calculated for $C_{21}H_{31}O_3N$: C,73.00; H,9.05; N,4.05. Found: C,73.10; H,8.87; N,4.20.

Infrared spectrum

See figure 3.

Optical rotation

$$[\alpha]_D^{24^\circ} = +116^\circ$$

Quaternary Salt of CVIII

A solution was prepared by dissolving 4.535 g. (13.1 mmoles) of the tertiary amine CVIII in 175 ml. of dry ether (minimum for dissolution) and adding 18.3 ml. of methyl iodide. This solution was stirred at room temperature for 17 hours. A precipitate of the methiodide began forming almost immediately

after the addition of methyl iodide. After the allowed time, the liquids were removed under reduced pressure, leaving a quantitative yield of light yellow methiodide, m.p. 209-211°. Three crystallizations from absolute ethanol-petroleum ether gave an analytical sample of colorless rectangular plates, m.p. 210-211°.

Analysis

Calculated for $C_{22}H_{34}O_3NI$: C,54.39; H,7.02; N,2.86. Found: C,53.29; H,7.08; N,2.63.

Infrared spectrum

See figure 4.

The salt was unstable, particularly in the presence of light, and decomposed to a second unidentified product, m.p. 168-169°.

13-Methylpodocarpic Acid

One liter of liquid ammonia solution was reacted with 1 g. of lithium wire in small pieces to give a deep blue solution. A slurry of 5 g. of the quaternary salt and 300 ml. of tetrahydrofuran was prepared and added rapidly to the lithium-ammonia solution with rapid stirring. After the addition, the blue color of the ammonia solution disappeared. Another 1.2 g.

of lithium was added in portions of 500, 300, 200, 100 and 100 mg. portions with stirring. Decolorization occurred between each addition except the last after which the color remained for ½ hour. Water was added dropwise until the blue color disappeared and the ammonia was permitted to evaporate at room temperature. The last traces of ammonia were removed by heating on a steam bath. The residue was taken up in 10% hydrochloric acid and, after cooling, extracted with ether. The ether layer was extracted with 1% sodium hydroxide, washed with water and filtered through anhydrous sodium sulfate. The ether was evaporated, leaving 0.915 g. (33%) of a gum which consisted mainly of the diol CXIV. When insufficient lithium was used, methyl 13-methyl podocarpate was obtained as a contaminant. The diol was purified by fractional distillation to give a solid, m.p. 87-88.5°.

Analysis

Calculated for $C_{18}H_{26}O_2$: C,78.79; H,9.55. Found: C,79.13; H,9.70.

Infrared spectrum

See figure 4.

Optical rotation

$$[\alpha]_D^{24^\circ} + 52.7^\circ \ (CHCl_3)$$

The basic solution was neutralized and extracted with ether. The ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated under vacuum producing 1.891 g. (64%) of a gum of which the predominant product was 13-methylpodocarpic acid. This acid crystallized with difficulty from ether-petroleum ether. The analytical sample was prepared by fractional distillation to yield a solid, m.p. 109-110°.

Analysis

Calculated for $C_{18}H_{24}O_3$: C,74.97; H,8.39. Found: C,74.74; H,8.39.

Infrared spectrum

See figure 4.

Optical rotation

$$[\alpha]_D^{24^\circ} + 84^\circ \ (CHCl_3)$$

Esterification of 13-Methylpodocarpic Acid

An ether solution of diazomethane, prepared from 2.9 g. of N-methyl-N-nitrosourea, was added to a solution of 1 g. of 13-methylpodocarpic acid dissolved in 15 ml. of methanol. The reaction was permitted to proceed for 5 minutes and the excess diazomethane was stripped under vacuum in a water bath of 40-50° producing 1.038 g. (99%) of crystalline methyl 13-methylpodocarpate (CVII). An analytical sample was prepared by crystallization from aqueous methanol, m.p. 179-181°. Preliminary melting occurs at 173° and a new crystalline form appears which melts at 179-181°.

Analysis

Calculated for $C_{19}H_{26}O_3$: C,75.46; H,8.67. Found: C,75.42; H,8.71.

Infrared spectrum

See figure 5.

Ultraviolet spectrum

See figure 1.

Optical rotation

$$[\alpha]_D^{25^\circ} + 128^\circ \ (CHCl_3)$$

Mixed melting point with the reduction product of CV

The mixed melting point was 164-173°. The melt crystallized as needles. Crystallization from aqueous methanol gave needles, m.p. 174-178.5°.

Alkylation of CVII with Ethyl Bromoacetate

In a predried flask 200 mg. (0.66 mmoles) of methyl 13-methylpodocarpate (CVII) was dissolved in 10 ml. of dry methanol. The sodium salt of the phenol was prepared by reacting 18 mg. (0.78 mmoles) of sodium with the methanol and distilling off the excess solvent under reduced pressure. Dry benzene was distilled from the salt twice. The reaction was completed by adding 3 ml. of ethyl bromoacetate to the dry salt and refluxing the mixture for 4 hours. The solvent was removed under reduced pressure and the residue taken up in water and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated. The residual oil was chromatographed on 8 g. of alumina. Elution with petroleum ether produced 153 mg. (68%) of the lactone CXV or CXVI, m.p. 70-90°. Crystallization from meth-

anol gave an analytical sample as crystals in the form of needles, m.p. 87-88.5°.

Analysis

Calculated for $C_{21}H_{26}O_4$: C,71.10; H,8.30. Found: C,70.82; H,8.16.

Infrared spectrum

See figure 6.

Optical rotation

$[\alpha]_D^{25°}$ + 105° ($CHCl_3$)

Further elution with benzene led to 55 mg. (27%) of methyl 13-methylpodocarpate, m.p. 171-176°. Recrystallization from aqueous methanol gave crystals in the form of plates, which exhibit dimorphism as does the starting material, m.p. 172-179°, mixed m.p. 174.5-180.5°.

Infrared spectrum

Identical with that of methyl 13-methylpodocarpate, figure 5.

Alkylation of CII with Ethyl Bromoacetate

Dry benzene was twice distilled from 200 mg. (0.61 mmole) of the lactone CII and the dry lactone dissolved in 10 ml. of dry ethanol. The sodium salt of the opened lactone was formed by reacting 14 mg. (0.61 mmole) of sodium with the alcohol solution and the excess ethanol removed under vacuum. Dry benzene was distilled from the salt and the reaction was completed by the addition of 5 ml. of ethyl bromoacetate and refluxing for 6 hours. The solvent was removed under vacuum and the residue taken up in water and extracted with ether. The combined ether layers were filtered through anhydrous sodium sulfate and evaporated, leaving 277 mg. of residue. The residue was chromatographed on 9 g. of alumina. Elution with petroleum ether gave 44 mg. (16%) of crystals, m.p. 70-84°. Sublimation raised the m.p. to 113.5-123°.

Infrared spectrum

λ max. 3.35 (s), 5.81 (s), 6.22 (m) and 6.38 (m) microns. (Infracord)

Repetition of the above experiment and chromatography on silica led to two new products. Elution with petroleum ether-benzene gave 94 mg. of a partially crystalline lactone fraction, m.p. 150-180°. Further elution with benzene-ether gave 74 mg. of an acid as an oil.

Methylation of Methyl 13-Methylpodocarpate

In a predried flask 200 mg. (0.66 mmole) of methyl 13-methylpodocarpate was dissolved in 8 ml. of dry methanol. The sodium salt of the phenol was formed by reacting 23 mg. (1 mmole) of sodium with the methanol solution and removing the excess solvent under reduced pressure. Dry benzene was distilled from the salt twice. The reaction was completed by adding 10 ml. of dry benzene and 0.5 ml. of methyl iodide to the dry salt and refluxing the mixture for 8 hours. The solvents were removed under reduced pressure, leaving a gummy residue. The residue was chromatographed on 8 g. of alumina. Elution with petroleum ether gave 64 mg. (30%) of methyl 13-methylpodocarpate methyl ether (CXIX), m.p. 113-125°. Recrystallization from aqueous methanol failed to raise the melting point. The analytical sample was prepared by sublimation 3 times at a bath temperature of 95-100°.

Analysis

Calculated for $C_{20}H_{28}O_3$: C,75.91; H,8.92. Found: C,75.58; H,8.98.

Infrared spectrum

λ max. 3.35 (s), 5.81 (s) and 6.21 (w) microns. (Infracord)

Elution with benzene-ether produced 114 mg. (57%) of methyl 13-methylpodocarpate, m.p. 176-180°.

Infrared spectrum

Identical with that of methyl 13-methylpodocarpate, figure 5.

13-Methylpodocarponitrile (CXXII)

A mixture of 10 ml. of acetic anhydride, 4 g. of 13-methyl podocarpic acid and 100 mg. of anhydrous sodium acetate was refluxed for 2 hours. The solvent was stripped under vacuum, taken up in water and extracted with ether. The combined ether layers were evaporated and the crude gum refluxed 2 hours with 15 ml. of thionyl chloride. The solvent was removed from the crude acid chloride under vacuum. This crude brown gum was added to a gray lithium amide paste prepared by adding 6.6 g. of lithium to 500 ml. of liquid ammonia together with a few crystals of ferric nitrate. The ammonia was permitted to evaporate over a 46-hour period. The remainder of the ammonia was driven off by steam heating the flask. The white residue was decomposed with 10% hydrochloric acid until the water layer was acid. The mixture was filtered and the brown residue washed with ether. The water layer was extracted with ether. The remaining brown oil after removal of the ether was chromatographed on alumina. Elution with benzene-ether first

produced 488 mg. (13%) of 13-methylpodocarponitrile (CXXII) followed by 926 mg. (23%) of 13-methylpodocarpamide (CXXIII). Treatment of the aqueous layer of the ether extraction with excess tartaric acid with subsequent neutralization produced 721 mg. of a crude oil consisting mainly of 13-methylpodocarpamide.

An analytical sample of the amide was prepared by crystallization from aqueous methanol and aqueous acetone to yield needles, m.p. 109-110°.

Analysis

Calculated for $C_{18}H_{25}O_2N \cdot C_3H_6O$: C,73.00; H,9.05; N,4.05. Found: C,72.89; H,9.04; N,4.49.

Infrared spectrum

λmax. 2.59 (s), 2.64 (s), 2.73 (s), 3.23 (s), 5.82 (s) and 6.10 (m) microns.

On heating the solvated amide to its melting point, the acetone of solvation was driven off.

Analysis

Calculated for $C_{18}H_{25}O_2N$: C,75.22; H,8.77. Found: C,74.97; H,8.85.

Infrared spectrum

See figure 5.

Optical rotation

$[\alpha]_D^{23^\circ} + 142^\circ.$

The nitrile on recrystallization from aqueous acetone and aqueous methanol produced an analytical fraction, m.p. 183-184°.

Analysis

Calculated for $C_{18}H_{23}ON$: C,80.25; H,8.61; N,5.20. Found: C,80.43; H,8.71; N,5.09.

Infrared spectrum

See figure 5.

Optical rotation

$[\alpha]_D^{24^\circ} + 49.6^\circ.$

13-Methylpodocarpamide (CXXIII) Dehydration

A solution of 400 mg. of the acetone-solvated 13-methylpodocarpamide (CXXIII) and 20 ml. of freshly distilled thionyl chloride was refluxed for 8 hours. The excess solvent was removed from the dark reaction mixture under reduced pressure. The remaining oil was hydrolyzed by refluxing 4 hours with 18 ml. of ethylene glycol and 4 g. of potassium hydroxide under nitrogen. The hydrolysate was diluted with 40 ml. of water and extracted with ether to yield 372 mg. of crude brown crystals. Chromatography on alumina produced 291 mg. (78%) of crystalline nitrile, m.p. 181-183°.

Lithium Aluminum Hydride Reduction of 13-Methylpodocarponitrile (CXXII)

A solution of 38.7 mg. (0.14 mmole) of 13-methylpodocarponitrile and 3.5 ml. of dry tetrahydrofuran was refluxed for 2 hours after dropwise addition a suspension of 38.7 mg. (1.02 mmoles) of lithium aluminum hydride in 3.5 ml. of tetrahydrofuran. The solvent was removed under vacuum, leaving a residue, which was hydrolyzed with 10 ml. of a 10% hydrochloric acid solution (10 ml. of concentrated hydrochloric acid, 12 ml. of water and 20 ml. of 95% ethanol) on a steam bath for 10 minutes. The hydrochloric acid solution was extracted with chloroform. The combined chloroform layers were washed with water, filtered through anhydrous sodium sulfate

and the chloroform distilled off under reduced pressure, leaving 38.7 mg. (99%) of an oil for which the infrared spectrum indicated almost pure 13-methylpodocarpal (CXXIV). The aldehyde crystallized on standing, m.p. 149-150°. No further attempt was made to purify the crystals due to the known instability of compounds of this type (73).

Infrared spectrum

λ max. 3.55 (w), 5.79 (s), 6.15 (m) and 6.29 (m) microns. (Infracord)

The acid layer was neutralized and extracted with chloroform. After filtering the combined chloroform layers through anhydrous sodium sulfate and evaporation of the solvent, 1.8 mg. of acid soluble oil remained. The latter was not investigated further. The study of the necessary ratio of lithium aluminum hydride to nitrile for optimum yields is summarized on the accompanying chart.

Am't. of nitrile X	Am't. of $LiAlH_4$	% aldehyde T
25 mg.	10 mg.	34%
25	11.5	54
25	15	43,60
25	20	22,49
25	25	99

T estimated on the basis of the intensity of the 5.79 M infrared band intensity.

X converted to the basis of 25 mg.

13-Methylpodocarpinol Methyl Ether (CXXIX)

To a stirred mixture of 0.953 g. of 13-methylpodocarpinol (CXIV) dissolved in 15 ml. of 95% ethanol and 0.465 g. of sodium hydroxide dissolved in 15 ml. of water was added 0.2 ml. of dimethyl sulfate. The mixture was stirred at room temperature for 10 minutes, 70° for 15 minutes and 120° for 15 minutes. The pH of the mixture was adjusted to 11 by 10% hydrochloric acid and the solution extracted with ether. The combined ether layers were washed with water, 2% base and 10% hydrochloric acid. The ether solution was dried and evaporated, leaving 0.914 g. of an oily residue. This residue was chromatographed on alumina. Elution with petroleum-ether-benzene gave 13-methylpodocarpinol methyl ether (CXXIX) as an oil. Sublimation of this oil gave a solid, m.p. 60-78°.

Infrared spectrum

λmax. 2.62 (w), 2.76 (w), 3.35 (w), 6.15 (m) and 6.34 (w) microns. (Infracord)

13-Methylpodocarpal Methyl Ether (CXXX)

A solution of 150 mg. of 13-methylpodocarpinol methyl ether (CXXIX) in 1 ml. pyridine was added to a solution of 264 mg. of chromic anhydride dissolved in 2 ml. of pyridine at 15-20°. The combined solutions were mixed and allowed to stand at room temperature for 1 hour and 20 minutes. The chromic oxide oxidation mixture was diluted with water and extracted with ether. The ether layer was washed with water, filtered through anhydrous sodium sulfate and the ether distilled under vacuum, leaving 87.4 mg. (58%) of CXXX as an oil.

Infrared spectrum

λmax. 3.33 (s), 3.56 (w), 5.78 (s), 6.00 (w), 6.15 (s) and 6.32 (w) microns. (Infracord)

Desoxynimbiol Methyl Ether (CXXXI)

In a predried flask 87.4 mg. of 13-methylpodocarpal methyl ether was reacted with 1 ml. of 95% anhydrous hydrazine in 8.7 ml. of anhydrous diethylene glycol for 2 hours at 100°. After the hydrazone had formed, 472 mg. of potassium hydroxide was

added and the solution heated at 150-160° for 5½ hours. The solution was diluted with 40 ml. of water and extracted with ether. The combined ether layers were washed with 2 N hydrochloric acid, water and dried. Evaporation of the solvent left 76 mg. of an oil. The oil was chromatographed on alumina. Eluting with petroleum ether gave 45 mg. (49%) of desoxynimbiol methyl ether (CXXXI) as an oil.

Infrared spectrum

λ max. 3.29 (s), 6.12 (m) and 6.29 (w) microns. (Infracord)

Nimbiol Methyl Ether (III)

A solution of 44.6 mg. of chromic oxide was dissolved in 0.9 ml. of 80% acetic acid and added to a solution of 35.6 mg. of desoxynimbiol methyl ether (CXXXI) in 1 ml. of acetic acid. The solutions were mixed and permitted to stand at room temperature for 15½ hours. The oxidation solution was diluted with a five-fold volume of a saturated salt solution and extracted with chloroform. The combined chloroform layers were washed with 5% sodium hydroxide, water and dried over anhydrous sodium sulfate. After filtration, the chloroform was evaporated, leaving 27.2 mg. (58%) of crystalline nimbiol methyl ether, m.p. 110-120°. The ether was further purified by chromatography on 3 g. of alumina to give crystals, m.p.

110-136°. Recrystallization from methanol gave needles, m.p. 139-141°. Literature value is m.p. 142-143°.

Infrared spectrum

See figure 9.

Optical rotation

$[\alpha]_D^{24^\circ}$ + 34.2°. Literature: $[\alpha]_D$ + 43.7°.

13-Methylpodocarpinol Ditosylate (CXXXII)

A solution of 274 mg. of the diol, 2 ml. of dry analytical reagent pyridine and 762 mg. of freshly recrystallized tosyl chloride (4-fold molar excess) was prepared in predried equipment in an ice-salt bath (-5°). The tosyl chloride was dissolved by gently swirling the flask. A precipitate of pyridine hydrochloride began forming, making the point of complete dissolution of tosyl chloride obscure. The reaction mixture was permitted to stand at zero degrees for 36 hours. The solvent was removed at room temperature under vacuum and the residue taken up in ether and 10% sodium bicarbonate. The ether layer was washed with water, filtered through anhydrous sodium sulfate and the solvent removed under vacuum, leaving a brown gum which crystallized on trituration with benzene.

Recrystallization from benzene-petroleum ether produced 323 mg. (56%) of crystals, m.p. 113-116°. The analytical sample, m.p. 117-118.5°, was prepared by 4 more recrystallizations from benzene-petroleum ether.

Analysis

Calculated for $C_{32}H_{38}O_6S_2$: C,65.95; H,6.57. Found: C,65.87; H,6.76.

Infrared spectrum

See Figure 7.

Optical rotation

$$[\alpha]_D^{25^\circ} + 35.5^\circ \ (CHCl_3).$$

Lithium Aluminum Hydride Reduction of 13-Methylpodocarpinol Ditosylate (CXXII)

In a predried vessel 200 mg. (0.35 mmole) of 13-methylpodocarpinol ditosylate (CXXII) was dissolved in 4 ml. of dry tetrahydrofuran. Slowly, 268 mg. (7.0 mmoles) of lithium aluminum hydride was added in powder form. This mixture was refluxed for 46 hours. The excess lithium aluminum hydride

was decomposed by the dropwise addition of water. The mixture was made acidic with 10% hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, filtered through anhydrous sodium sulfate and the solvent evaporated, leaving 118 mg. of a light yellow oil. The oil was chromatographed on 12 g. of alumina. Elution with benzene gave 67 mg. (76%) of desoxynimbiol (VI) as an oil which had a slight odor of a thiol.

Infrared spectrum

λ max. 2.79 (m), 3.00 (w), 3.43 (s), 6.23 (w) and 6.38 (w) microns. (Infracord)

Further elution with 9:1 benzene-ether produced 30.9 mg. (33%) of 13-methylpodocarpinol (CXIV). Repetition of this reaction gave 44% of the diol.

Infrared spectrum

Identical with that of 13-methylpodocarpinol (CXIV), figure 4.

Desoxynimbiol Acetate (V)

A mixture of 8.5 mg. of desoxynimbiol (VI), 1 ml. of acetic anhydride and 20 mg. of sodium acetate was refluxed for 8 hours. The solvent was stripped under vacuum, water added and

extracted with ether. The ether solution was washed with a 10% sodium bicarbonate solution, water and filtered through anhydrous sodium sulfate. On removing the solvent, 8.9 mg. of a gum remained. The gum was chromatographed on 1 g. of alumina. Elution with petroleum ether gave 7.2 mg. (73%) of an oil which crystallized, m.p. 90-100°, on seeding with authentic desoxynimbiol acetate. Further attempts to purify this compound were unsuccessful.

Infrared spectrum

See figure 9, compare with figure 8.

Optical rotations

$[\alpha]_D^{23^\circ}$ + 71.0° ($CHCl_3$) (authentic desoxynimbiol acetate).

$[\alpha]_D^{29^\circ}$ + 69.7° ($CHCl_3$) (synthetic desoxynimbiol acetate).

$[\alpha]_D$ + 56.4° ($CHCl_3$) (reported in literature for desoxynimbiol acetate).

13-Methylpodocarponitrile Methoxymethyl Ether (CXXXV)

A solution of 3 ml. of dry t-butanol and 71.3 mg. (0.27 mmole) of 13-methylpodocarponitrile was reacted with 72 mg.

(3.1 mmole) of sodium. The excess solvent was removed under vacuum. The reaction was completed by adding 5 ml. of dry benzene and 0.75 ml. of chloromethyl ether to the dry salt and refluxing for 18 hours. After cooling, the solvent was removed under vacuum. The residue was taken up in water and extracted with ether. The combined ether layers were washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 93.5 mg. of a yellow-orange semi-solid. This mixture was chromatographed on 4 g. of alumina. Elution with petroleum ether produced 50.7 mg. (61%) of 13-methylpodocarponitrile methoxymethyl ether as an oil. Attempts to crystallize this oil were unsuccessful.

Infrared spectrum

λ max. 3.32 (s), 4.47 (m), 6.22 (m) and 6.40 (w) microns. (Infracord)

Further elution with benzene-ether produced 24 mg. (34%) of 13-methylpodocarponitrile (CXXII), m.p. 160-170°.

Infrared spectrum

Identical with that of figure 5.

O-Methoxymethyl-13-Methylpodocarpal (CXXXVI)

A slurry of 27.5 mg. of lithium aluminum hydride in 4 ml. of dry tetrahydrofuran was added to a solution of 90.6 mg. of 13-methylpodocarponitrile methoxymethyl ether (CXXXV) in 7 ml. of dry tetrahydrofuran in a predried flask. The stirred mixture was refluxed for 2 hours. Water was added dropwise to decompose the excess lithium aluminum hydride. The solvent was removed under reduced pressure and the residue heated on a steam bath with 10% hydrochloric acid for 10 minutes. The solution was diluted and extracted with ether producing 69 mg. of an oil. The infrared absorption spectrum indicated a small amount of the aldehyde and a predominance of starting material. The 69 mg. of partially reduced mixture was dissolved in 5 ml. of diethylene glycol and 0.2 ml. of 95% anhydrous hydrazine and heated at 90-110° for 2 hours. Then 90 mg. of KOH pellets were added and the temperature raised to 140° for 5½ hours. The cooled solution was extracted with ether and the combined ether layers washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving a residue. This residue was taken up in 5 ml. of dry tetrahydrofuran and again reacted with 30 mg. of lithium aluminum hydride in 3 ml. of dry tetrahydrofuran according to the first procedure producing 49 mg. of an oil.

Infrared spectrum

λmax. 3.37 (s), 5.79 (s) and 6.27 (m) microns. (Infracord)

On neutralization of the hydrochloric acid solution, 4.1 mg. of the amine was extracted in the form of an oil. This fraction was not examined further.

O-Methoxymethyl-13-Methylpodocarpinol (CXXXVII)

The potassium salt of 13-methylpodocarpinol (CXIV) was prepared by dissolving 300 mg. (1.09 mmoles) of the diol in 8 ml. of dry t-butanol and reacting 47 mg. (1.2 mmoles) of potassium with the alcohol solution under an atmosphere of nitrogen. When the potassium had completely reacted, the excess solvent was distilled off under reduced pressure. The reaction was completed by adding 5 ml. of dry benzene and 0.32 ml. of chloromethyl ether to the dry salt and refluxing the mixture for 13 hours. After cooling, water was added to the reaction mixture and the contents extracted with ether. The combined ether layers were washed with water, filtered through anhydrous sodium sulfate and the solvent removed under vacuum, leaving 380 mg. of residue. The residue was chromatographed on 12 g. of alumina. Elution with petroleum ether produced 151 mg. (38%) of 13-methylpodocarpinol dimethoxymethyl ether as an oil.

Infrared spectrum

λmax. 3.37 (s), 6.19 (m) and 6.37 (w) microns. (Infracord)

Further elution with methylene chloride gave 172.4 mg. of an oil in a very broad band. The latter oil was rechromatographed on alumina. Elution with benzene-petroleum ether gave 89 mg. (26%) of 0-methoxymethylpodocarpinol (CXXXVII) as an oil. Attempts at crystallization were unsuccessful.

Infrared spectrum

λmax. 2.63 (w), 2.85 (w) and 6.22 (m) microns. (Infracord)

Further elution with benzene-ether produced 79 mg. (26%) of 13-methylpodocarpinol (CXIV) as an oil.

Infrared spectrum

Identical with that of 13-methylpodocarpinol, figure 4.

13-Methylpodocarpal Methoxymethyl Ether (CXXXVI)

A solution of 59 mg. (0.18 mmole) of 0-methoxymethylpodocarpinol (CXXXVII) and 0.4 ml. of anhydrous pyridine were added to a yellow mixture made by dissolving 94 mg. of chromic oxide to 1.4 ml. of pyridine while in an ice bath. The mixture was stirred thoroughly. Soon the mixture obtained a deep

red color. It was permitted to stand for 1½ hours at room temperature. The mixture was then poured into a five-fold volume saturated salt solution and extracted with ether. The ether layer was filtered through anhydrous magnesium sulfate and the ether evaporated, leaving 44 mg. (72%) of non-crystalline aldehyde (CXXXVI). No attempt was made at crystallizing this intermediate.

Infrared spectrum

λ max. 5.81 (s), 6.03 (w), 6.25 (m) and 6.36 (w) microns. (Infracord)

Huang-Minlon Reduction of 13-Methylpodocarpal Methoxymethyl Ether (CXXXVI)

The reduction was completed by dissolving 44 mg. of 13-methylpodocarpal methoxymethyl ether (CXXXVI) in 5 ml. of anhydrous diethylene glycol and 0.6 ml. of 95% anhydrous hydrazine. The solution was heated to 100° for 2 hours when 270 mg. of potassium hydroxide pellets were added and the temperature raised to 155-160° for 5½ hours. The solution was cooled, diluted with water and extracted with ether. The combined ether solutions were washed with dilute hydrochloric acid and water. The ether solution was dried by filtering through anhydrous sodium sulfate and evaporated, leaving an oily residue. The residue was hydrolyzed by refluxing for

2 hours in a homogeneous aqueous 5% sulfuric acid-dioxane solution. The hydrolysis solution was extracted with ether and the combined ether solutions were filtered through anhydrous sodium sulfate, evaporated and the residue chromatographed on 1.5 g. of alumina. Elution with benzene-ether gave 8.5 mg. (24%) of desoxynimbiol (VI) as an oil.

Infrared spectrum

λ max. 2.72 (m), 2.81 (w) and 3.42 (s) microns. (Infracord)

Nimbiol Acetate (IV)

Oxidation occurred by dissolving 4 mg. of desoxynimbiol acetate (V) in a few drops of glacial acetic acid and adding 5 mg. of chromic anhydride dissolved in 0.5 ml. of 80% glacial acetic acid. The solution was permitted to stand at room temperature for 15 hours. The deep red reaction solution was diluted with a five-fold volume of a saturated salt solution and extracted with chloroform. The chloroform layer was washed with water, dried by filtering through anhydrous sodium sulfate and stripped, yielding 2.6 mg. (62%) of nimbiol acetate. The melting point after one recrystallization from aqueous methanol was 107-109°. The melting point of authentic nimbiol acetate is 108-111°.

Nimbiol (II)

Hydrolysis was effected by dissolving 4 mg. of nimbiol acetate (IV) in 2.5 ml. of isopropyl alcohol and 0.8 ml. of 2 N potassium hydroxide and refluxing for 2 hours. The reaction solution was cooled and extracted with ether. The remaining yellow aqueous layer was neutralized, whereby it became colorless, and again extracted with ether. The ether layer was washed with water, dried and stripped, yielding 2.8 mg. (71%) of crystalline nimbiol, m.p. 220-235°. Recrystallization from methanol twice raised the melting point to 244.5-246°. Mixed melting point with authentic nimbiol, m.p. 248-249° was 245-248°.

1-Methoxymethylcarbonyl-7-carboxy-1,12-dimethyl-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene (CXLVII)

The reaction was completed according to the procedure of Ohta (79) with 1.51 g. of the diketone CXLVI. On completion of the reaction 3 ml. of water was added and the pyridine was distilled off under reduced pressure. More water was added to the residue and the mixture was extracted with chloroform. The solvent was removed from the combined chloroform layers by distillation under reduced pressure. The residue was heated on the steam bath for 2 hours with 11.9 ml. of 1 N sodium hydroxide and 29 ml. of 95% ethanol. The hydrolysis solution

was acidified by 10% hydrochloric acid and extracted with ether. The combined ether layers were washed with 5% sodium hydroxide and with water. The ether solution was dried over sodium sulfate, filtered and evaporated, leaving 397 mg. of an oil. The base solution was neutralized and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 1.293 g. of a semi-crystalline oil. This residue was chromatographed on 45 g. of silica. Elution with 4:1 benzene-ether gave 1.144 (75%) of the desired compound CXLVII, m.p. 200-208°. Literature value is 195-200°.

Infrared spectrum

See figure 10.

Further elution with 4:1 benzene-ether gave 89 mg. (6%) of CXLIX, m.p. 285-288°. Crystallization from aqueous methanol gave crystals, m.p. 294-296°.

Infrared spectrum

See figure 11.

1-Methoxycarbonyl-7-carboxy-1,12-dimethyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (CXLVIII)

To a solution of 50 mg. of CXLVII and 5 ml. of ethyl ace-

tate was added 50 mg. of 10% palladium-charcoal catalyst. The stirred solution was hydrogenated at atmospheric pressure for 21½ hours. The catalyst was filtered and washed with more ethyl acetate. The ethyl acetate solution was evaporated, leaving 45 mg. (95%) of crystalline CXLVIII, m.p. 176-179°. One recrystallization from aqueous methanol produced crystals, m.p. 180-182°. Literature value for the melting point is 179-181°.

Infrared spectrum

See figure 11.

1-Carboxy-1,12-dimethyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (LX)

In a predried flask 250 mg. of 1-cyano-1,12-dimethyl-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene (CLI) was dissolved in 20 ml. of diethylene glycol and 3 ml. of 95% anhydrous hydrazine. This solution was heated at 100-110° for 2 hours after which 1.33 g. of potassium hydroxide was added and the reaction heated to reflux temperature. After 16 hours of reflux 1 ml. of water was added and after 36 hours the potassium hydroxide content was raised to 40% by the addition of more potassium hydroxide pellets. At the end of 72 hours at reflux temperature, the solution was taken up in water and extracted with ether. The basic layer was neutralized and

extracted with ether. The combined ether layers of the latter extraction were washed with water, filtered through anhydrous sodium sulfate and evaporated, yielding 224 mg. (99%) of the acid LX which crystallized on standing, m.p. 135-140°. Recrystallization from petroleum ether gave crystals, m.p. 169-170°, which exhibited dimorphism by recrystallizing to melt again at 173-174°. Literature value is 172-173°. The mixed melting point gave no depression.

Infrared spectrum

See figure 12.

1-Methoxycarbonyl-1,12-dimethyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (LXXII)

A solution of 140 mg. of LX was dissolved in 3 ml. of dry ether and added to an ether solution of excess diazomethane (prepared from 1.45 g. of N-methyl-N-nitrosourea). The reaction solution was allowed to stand for 2 hours at room temperature. The excess diazomethane and ether were distilled off under reduced pressure in a 40° water bath. As the ether was distilling, crystals of LXXII began to form, amounting to 145 mg. (99%) after complete removal of the ether, m.p. 93-100°. Recrystallization from aqueous methanol gave crystals, m.p. 108-109°. Literature (81) value is 108-109°.

1-Methoxycarbonyl-1,12-dimethyl-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene (CXXXVIII)

A solution of 177 mg. of chromic oxide and 3.5 ml. of 80% acetic acid was added to a solution of 142 mg. of LXXII and 1.4 ml. of glacial acetic acid. The two solutions were mixed thoroughly and allowed to stand at room temperature for 15 hours. The reaction solution was diluted with a five-fold volume of a saturated salt solution and extracted with chloroform. The chloroform solution was washed with 5% sodium hydroxide, water and filtered through anhydrous sodium sulfate. On evaporation 133 mg. (72%) of an oil was obtained. The oil was crystallized from petroleum ether, m.p. 43-45°.

Infrared spectrum

See figure 12.

1-Methoxycarbonyl-7-carboxy-1,12-dimethyl-9-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (CL)

An ether solution of 684 mg. of the diacid CXLIX was added to an ether solution of excess diazomethane (prepared from 1.45 g. of N-nitroso-N-methylurea). The combined solutions were permitted to react at room temperature for 5 minutes. The excess diazomethane and ether were distilled off under vacuum in a 40° water bath. The residue was dissolved

in 10 ml. of ether and extracted with 2% sodium hydroxide. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated. The residual oil weighed 671 mg.

Infrared spectrum

λmax. 5.81 (s), 5.94 (s) and 6.24 (m) microns. (Infracord)

The oil was dissolved in 40 ml. of ethylacetate and 167 mg. of 10% palladium-charcoal catalyst was added. The mixture was reduced for 45 hours in hydrogen of 1 atmosphere pressure. The catalyst was filtered off and the ethyl acetate evaporated, leaving 739 mg. of an oil.

Infrared spectrum

5.81 (s) and 6.25 (w) microns. (Infracord)

A solution of the oil obtained from the hydrogenation, 20 ml. of 95% ethanol and 2.24 ml. of I N sodium hydroxide, was boiled on a steam bath for 1 hour. The ethanol was distilled under reduced pressure. The aqueous layer was neutralized and extracted with ether. The ether layer was extracted with 10% sodium hydroxide. After drying over sodium sulfate and evaporating, the ether layer gave 256 mg. of neutral oil. The sodium hydroxide layer was neutralized and extracted with ether. The ether layer was filtered through anhydrous sodium

sulfate and evaporated, leaving 281 mg. of residual oil. This oil was chromatographed on 9 g. of silica. Elution with benzene-ether gave 180 mg. of semicrystalline product. Fractional crystallization from aqueous methanol gave CL as plates which exhibit dimorphism at the melting point, 195-206°.

Analysis

Calculated for $C_{19}H_{26}O_5$: C,68.24; H,7.84; Found: C,68.45; H,7.74.

Infrared spectrum

See figure 12.

Structure Proof of CL

To a solution of 20.5 mg. of CL in 2 ml. of ethyl acetate was added 20.5 mg. of 10% palladium-charcoal catalyst. The mixture was hydrogenated for 21 hours under an atmosphere of hydrogen at atmospheric pressure. The catalyst was filtered and washed with ethyl acetate. The solvent was evaporated, leaving 17.7 mg. (91%) of crystalline CXLVIII, m.p. 177-178°. Crystallization from aqueous methanol produced crystals, m.p. 177-179°. The mixed melting point with CXLVIII was 177.5-179°.

Methyl 13-Nitropodocarpate

To solution of 300 mg. (1.04 mmoles) of methyl podocarpate, dissolved in 20 ml. of acetic anhydride was added 0.1 ml. (1.57 mmoles) of 70% nitric acid. The solution turned to a light yellow color on heating in an oil bath at 70° for 10 minutes. The solution was diluted with 140 ml. of water. As the acetic anhydride decomposed, a yellow precipitate began forming. After hydrolysis was complete, the solution was extracted with ether. The ether layer was filtered through anhydrous sodium sulfate and the ether distilled under reduced pressure on a steam bath giving 350 mg. (90%) methyl 13-nitropodocarpate acetate as an oil. The oil was dissolved in ether and extracted exhaustively with Claisen's alkali gave a red alkali soluble fraction. The alkali solution was neutralized and extracted with ether. The ether solution was washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving yellow crystals of methyl 13-nitropodocarpate. Four recrystallizations from methanol-ether gave crystalline plates for an analytical sample, m.p. 141.5-142.5°. On evaporation of the initial ether solution the alkali insoluble fraction was found to be negligible.

Analysis

Calculated for $C_{18}H_{23}O_5N$: C,64.82; H,6.96; N,4.20.
Found: C,64.73; H,7.12; N,3.94.

Infrared spectrum

See figure 7.

Ultraviolet spectrum

See figure 2.

Methyl Dinitropodocarpate (CXVIII or CXIX)

A rapidly stirred suspension was prepared by adding 300 mg. of methyl podocarpate to 75 ml. of water. The mixture was heated to 70°. Dilute nitric acid (35%) was added dropwise to the mixture until the developing yellow color remained about the same intensity. The reaction solution was neutralized with 10% sodium hydroxide to pH 7 and extracted with ether. The combined ether layers were washed with water, filtered through anhydrous sodium sulfate and evaporated, leaving 242 mg. (48%) of methyl dinitropodocarpate as yellow crystals. Four recrystallizations from aqueous methanol gave an analytical sample, m.p. 184-185°.

Analysis

Calculated for $C_{18}H_{22}O_7N_2$: C,57.13; H,5.86; N,7.40. Found: C,57.54; H,5.92; N,7.83.

Infrared spectrum

See figure 10.

Ultraviolet spectrum

See figure 2.

SUMMARY

1. C-Alkylation at C-13 with ethyl bromoacetate and methyl iodide have been applied to methyl podocarpate to explore new chemical pathways for diterpenoid syntheses. Conventional aromatic substitution reactions, as the Reimer-Tiemann reaction and the Mannich reaction, have also been utilized.

2. As a result of an intermediate prepared in the alkylation studies, the partial synthesis of nimbiol from podocarpic acid has been accomplished by several routes.

3. Three synthesis steps have been completed in the effort to convert deisopropyldehydroabietic acid into abietic acid and two synthesis intermediates have been prepared.

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