1957

Syntheses in the resin acid series

Billy Grinnell Jackson
Iowa State College

SYNTHESES IN THE RESIN ACID SERIES

by

Billy Grinnell Jackson

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 College
1957

TABLE OF CONTENTS

INTRODUCTION

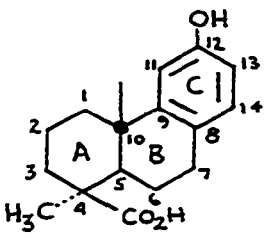
While syntheses of the known naturally occurring phenolic diterpenoids have been previously accomplished, only one such synthesis has been carried out in a stereospecific manner. None of the naturally occurring non-phenolic resin acids have been synthesized.

The purpose of the research here described was to attempt the total and stereospecific synthesis of the known phenolic diterpenoid podocarpic acid and to develop degradative and synthetic processes useful for the total synthesis of other resin acids.

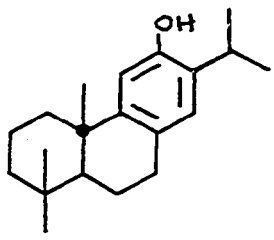
HISTORICAL

Isolation and structure determination of phenolic diterpenoids

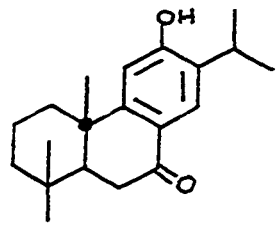
Six phenolic diterpenoid compounds have been isolated and characterized. The structures of podocarpic acid (I), ferruginol (II) and sugiol (III) are known; and synthetic interrelationships (1, 2, 3) have been demonstrated for these compounds.



I

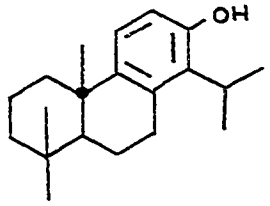


II

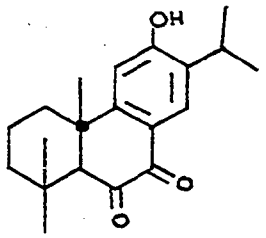


III

Totarol is isomeric with ferruginol and has the structure IV (4, 5). Hinokiol is a phenolic alcohol of unknown structure. Xanthoperol is a α-diketone to which the structure V has been tentatively assigned (6).



IV

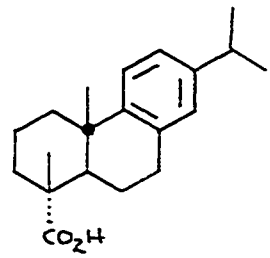


V

Podocarpic acid was isolated by Oudemans (7, 8, 9, 10) in 1873 as the major constituent of the resin from Podocarpus cupressina. Thirty-seven years thereafter, Easterfield and Aston (11) isolated the same substance from the resins of Podocarpus dacrydioides and Dacrydium cupressinum. All three sources are conifers indigenous to New Zealand.

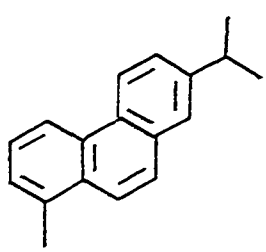
The structure of podocarpic acid was elucidated in essentially three stages. Oudemans' (7, 8, 9, 10) early experiments showed that the substance possessed a carboxyl and a phenolic hydroxyl group. The presence of a phenanthrenoid nucleus and the position of attachment of the phenolic hydroxyl to this nucleus were demonstrated by Sherwood and Short (12). These investigators dehydrogenated the acid and obtained 6-hydroxyl-methylphenanthrene, the structure of which was proven by synthesis. The correct structure and stereochemistry of podocarpic acid were reported in 1942 by Campbell and Todd (1, 2). Partial degradation and interrelationship with ferruginol (II) and dehydroabietic acid (VI) led these

workers to assign the structure I to the diterpenoid.

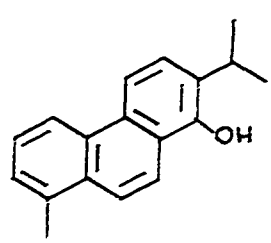


VI

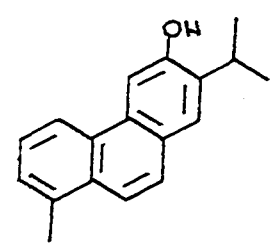
Brandt and Neubauer (13) reported in 1939 the isolation of ferruginol from the resin of Podocarpus ferruginea. These same workers characterized the compound as a phenol and degraded the phenol to retene (VII), a known degradation product of tricyclic diterpenes. Dehydrogenation of ferruginol gave a phenanthrol to which Brandt and Neubauer assigned the structure VIII. Campbell and Todd (14), however, showed that the phenanthrol was actually IX. The synthesis of ferruginol from podocarpic acid and dehydroabietic acid by Campbell and Todd (1, 2) substantiated their proposed structure II.



VII

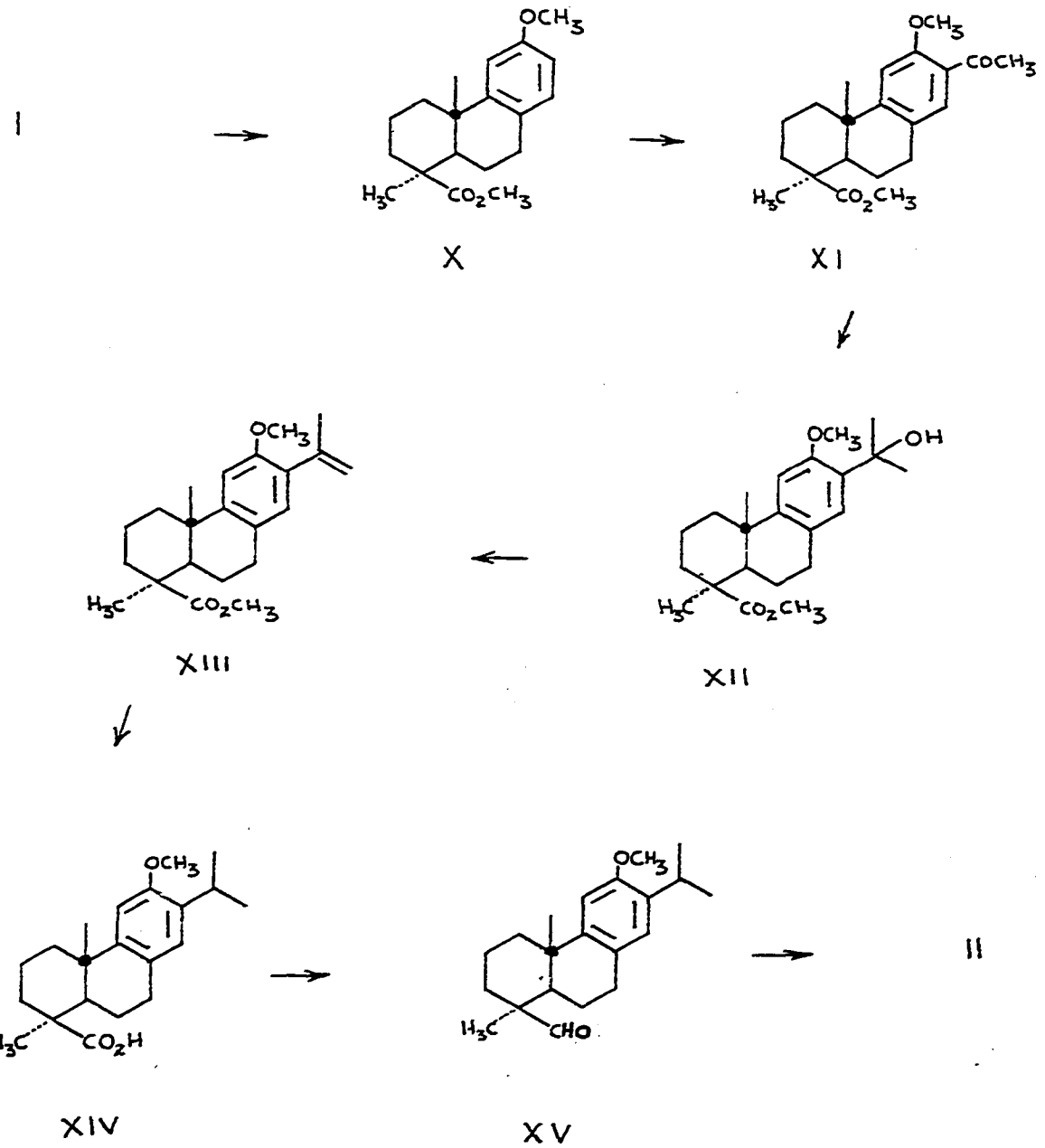


VIII



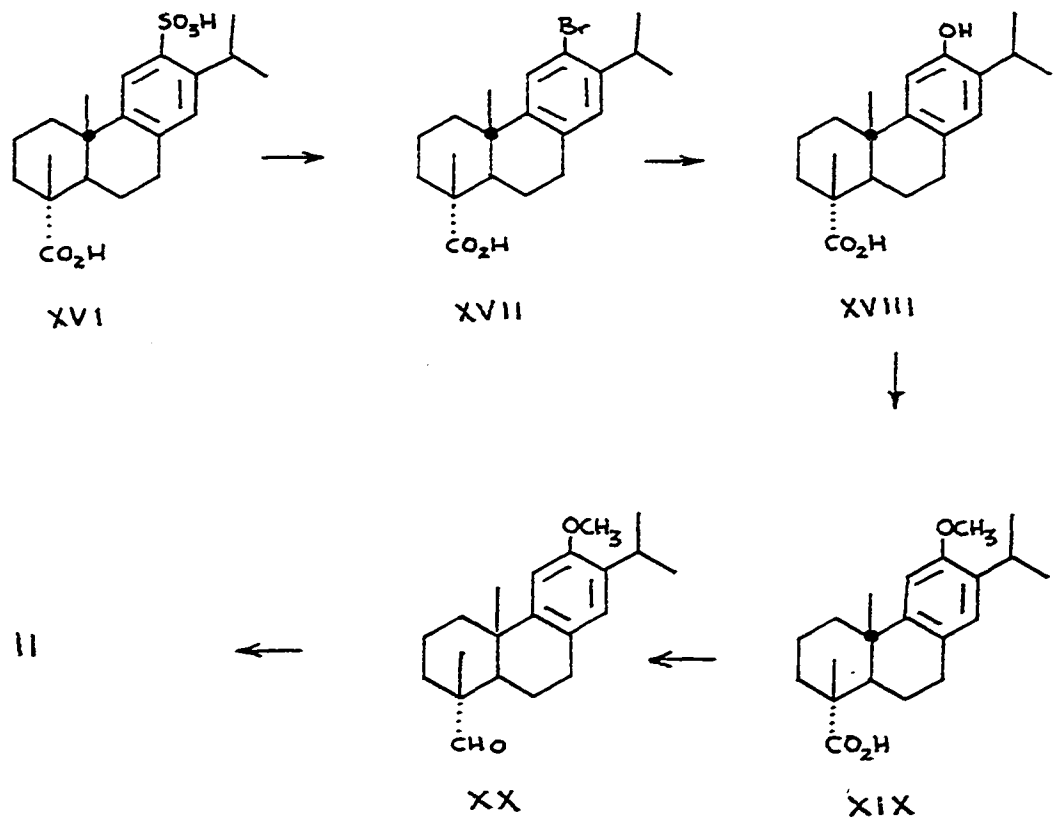
IX

The conversion of podocarpic acid to ferruginol is portrayed in the sequence X to XV.



Friedel-Crafts acetylation of methyl podocarpate methyl ether (X) afforded the ketone XI. Reaction of methylmagnesium chloride with XI gave the tertiary carbinol XII which was dehydrated to the styrene XIII. Catalytic reduction of XIII and subsequent hydrolysis produced the acid XIV. After Rosenmund reduction of the acid chloride of XIV, there was obtained the aldehyde XV which, by Wolff-Kishner reduction of its semicarbazone, yielded ferruginol.

Structures XVI to XX indicate the pathway from dehydroabietic acid to ferruginol.



Sulfuric acid and VI afforded the sulfonic acid XVI which reacted readily with bromine to give the bromide XVII. Hydrolysis of the bromo compound followed by reaction of the ensuing phenol with diazomethane yielded the methyl ester of XIX. Methylation of the phenolic hydroxyl with methyl sulfate and subsequent hydrolysis of the ester function produced the acid XIX. Rosenmund reduction of the acid chloride of XIX gave the aldehyde XX. Ferruginol was the product resulting from Wolff-Kishner reduction of XX.

Keimatsu et al. (15) reported in 1937 the isolation of sugiol from Cryptomeria japonica. The same workers characterized the diterpene as a phenolic ketone. Sugiol was found (16) to be identical to 7-ketoferruginol, isolated from Dacrydium cupressinum by Brandt and Thomas (16). Oxidation of ferruginyl acetate with chromic oxide or potassium permanganate was found to give sugiol acetate (3). Recently, Bredenberg and Gripenberg (17) have reported the isolation of sugiol from Juniperus communis.

From the wood of Podocarpus Totara, Easterfield and McDowell (18) in 1911 isolated the deterpene totarol. Short and Stromberg (19) degraded totarol to 1-methyl-8-isopropylphenan threne, the structure of which was proven by synthesis (20). Correlation of spectral and chemical data led Short et al. (4) to propose structure IV for the diterpene. The recent total synthesis (vide infra) of totarol by Barltrop and

Rogers (5) substantiated Short's structure.

Hinokiol occurs in the heartwood resin from Chamaecyparis obtusa (21). Early characterization experiments (21, 22, 23) showed the presence of a phenolic hydroxyl and an alcoholic hydroxyl in the molecule. Dehydrogenation of hinokiol gave retene (VII), a dihydroxyretene of unknown structure and 6-hydroxyretene (IX). Oxidation of hinokiol methyl ether with potassium permanganate gave a ketohinokiol methyl ether. Further oxidation of this ketone with chromic oxide produced a diketone which is not a α-diketone. Catalytic reduction of the diketone with palladium-on-charcoal catalyst afforded hinokione methyl ether. Reduction using platinum catalyst yielded hinokiol and isohinokiol.

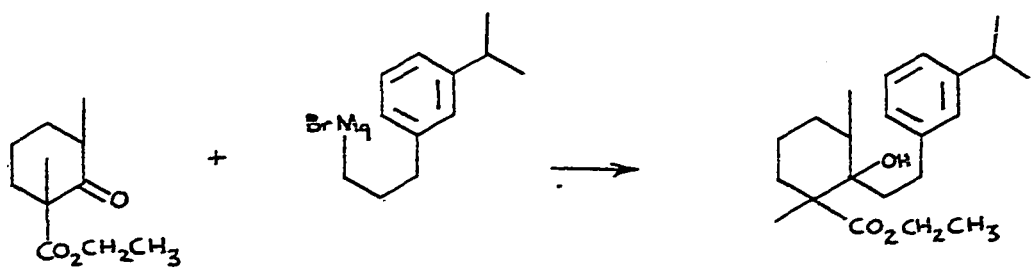
Bredenberg and Gripenberg (6) isolated xanthoperol after basic hydrolysis of resin constituents from Juniperus communis. These workers postulated that xanthoperol is an artifact since the yellow color of the diketone is not apparent in the crude resin extracts and does not appear until the extracts have been hydrolyzed with base. Co-occurrence with sugiol (III) led these investigators to propose structure V for xanthoperol.

Prior syntheses of ring-C-aromatic diterpenes

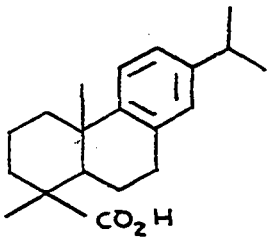
The gross structural similarities between the phenolic diterpenoids and dehydroabietic acid (VI) require that any

compendium of syntheses of the former type of compound include syntheses of the latter substance. These synthetic approaches are of two general types: cyclization of appropriate intermediates to give the tricyclic nucleus with all necessary substituents attached, or synthesis of a suitable tricyclic nucleus followed by attachment of required substituents. The most widely used synthetic pathway involves either a direct or modified Bogert (24) and Cook (25) synthesis of hydrophenanthrenes, in which a β-phenylethylmagnesium halide is condensed with a cyclohexanone to give a tertiary cyclohexanol. Dehydration to the corresponding β-phenylethylcyclohexene and cyclization with an acid catalyst produce the desired tricyclic nucleus.

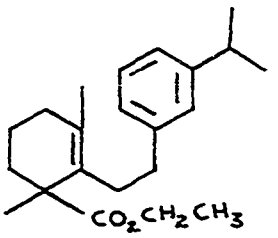
Haworth and Barker (26) in 1939 attempted the synthesis of dehydroabietic acid. Their synthetic acid was not resolved, and it was not shown which of the four possible diastereoisomers was obtained.



XXI



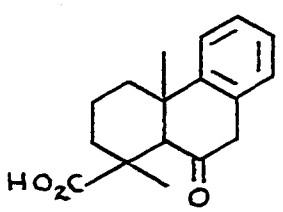
XXIII



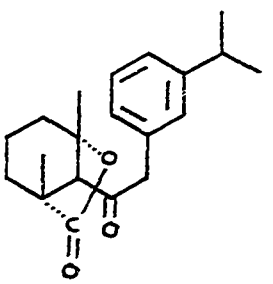
XXII

The synthesis by these workers involved dehydration of the tertiary alcohol XXI affording the olefin XXII which was then cyclized with sulfuric acid to give XXIII.

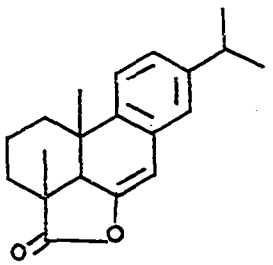
Parham et al. (27) attempted the synthesis of dehydroabietic acid using the ketolactone XXIV. Cyclization of XXIV with aluminum chloride afforded the deisopropyl compound XXV. The product obtained when XXIV was cyclized with polyphosphoric acid was assigned structure XXVI; however, no further work was done with this product.



XXV

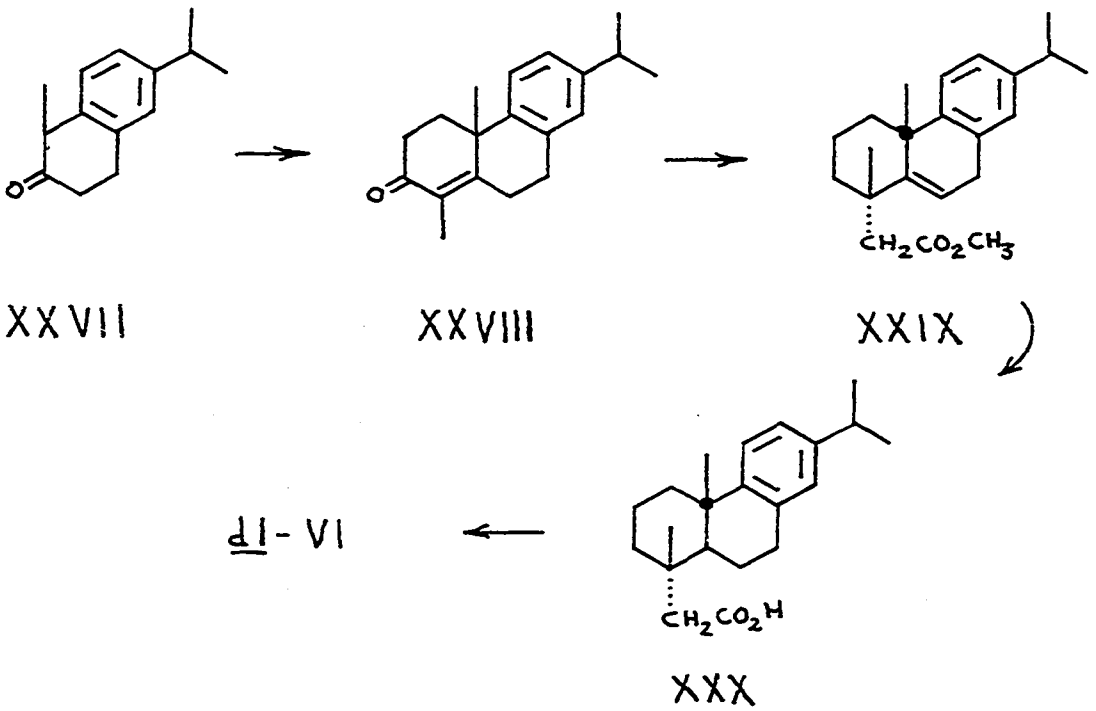


XXIV



XXVI

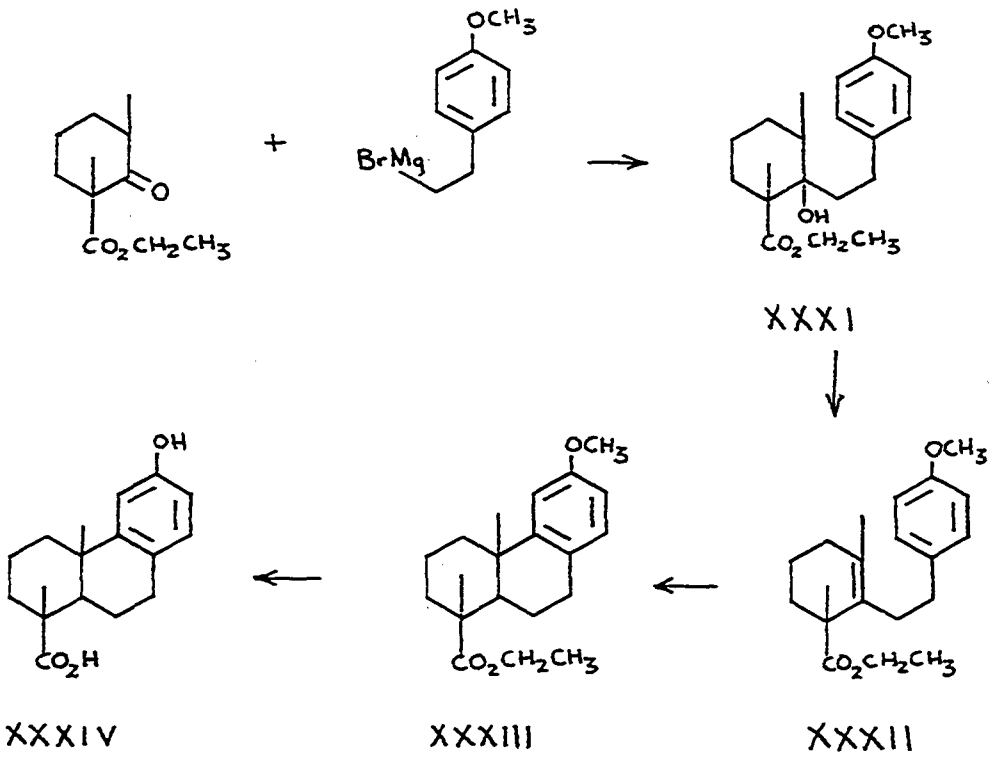
Stork and Schulenberg (28) reported in 1956 the stereospecific total synthesis of dl-dehydroabietic acid. The β-tetralone XXVII was made to react with ethyl vinyl ketone to produce the ketone XXVIII. The enolate anion of XXVIII upon treatment with methyl chloroacetate afforded the ketoester XXIX. Removal of the ketonic carbonyl via ethylenethioketal formation and Raney nickel desulfurization, catalytic hydrogenation of the olefinic double bond and hydrolysis of the ester gave the acid XXX. Arndt-Eistert homologation of dehydroabietic acid yielded a compound whose infrared spectrum was identical to the infrared spectrum of XXX. Barbier-Wieland degradation of XXX produced dl-dehydroabietic acid, identified by comparison of its infrared spectrum with that of the optically active material.



In the case of the first two of the three non-asymmetric syntheses of podocarpic acid reported herein, the dl-podocarpic acid was not then recognized as such. The authors of the last recorded synthesis of this compound demonstrated that the products obtained by the earlier workers were actually dl-podocarpic acid.

Bhattacharyya (29) in 1945 was first to report a non-stereospecific total synthesis of dl-podocarpic acid. Cyclization of the olefin XXXII obtained by dehydration of XXXI gave the acid XXXIII. A basic and subsequently an acid hydrolysis of XXXIII afforded the acid XXXIV. No resolution

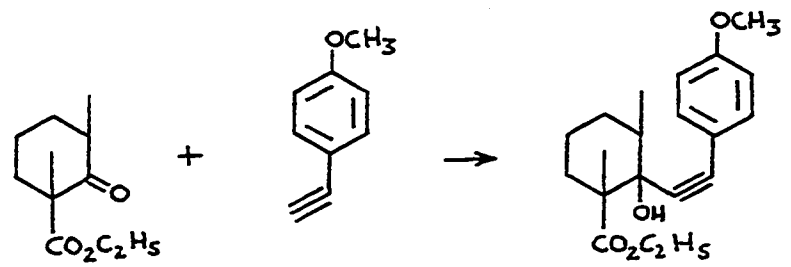
of the dl-acid (XXXIV) was achieved; and for this reason, it was not known which stereoisomer the synthesis had produced.



In 1946 Haworth and Moore (30) reported a nearly identical synthesis of dl-podocarpic acid. Again no resolution of the dl-product (XXXIV) was accomplished.

A communication of King et al. (31) in 1956 described a third synthesis of dl-podocarpic acid. The alcohol XXXI was prepared from the acetylenic carbinol XXXV and was cyclized directly to XXXIII with polyphosphoric acid. Fractional crystallization and chromatography resulted in the isolation of three of the four possible stereoisomers of

XXXIII. The saponification equivalent and solubility characteristics of one of these isomers were very similar to the corresponding properties of authentic methyl podocarpate methyl ether (X). Infrared spectra of X and the similar isomer of XXXIII were virtually identical. The dl-podocarpic acid methyl ether resulting therefrom was identical with the dl-methyl ether obtained by Haworth and Moore (30) and Bhattacharyya (29).

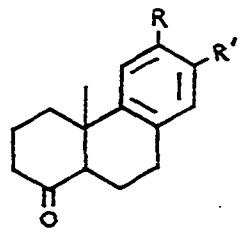


XXXV

XXXIV ← XXXI

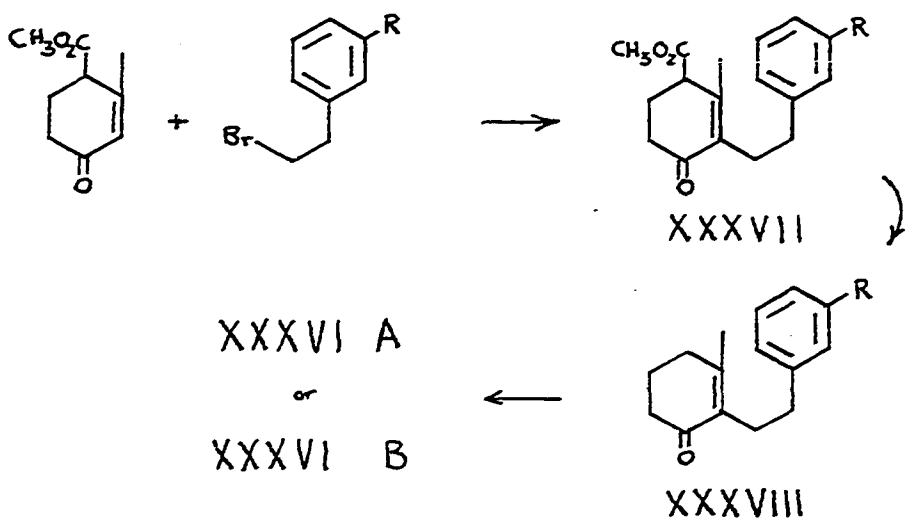
Since Campbell and Todd (1, 2) showed that dehydroabietic acid (VI) and podocarpic acid are epimeric at C-4, synthesis of a suitable intermediate might possibly lead to synthesis of either diterpenoid. Compound XXXVI A is an example of such

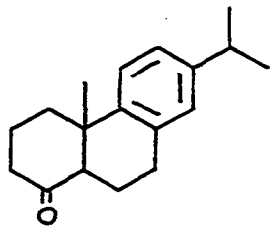
a synthetic intermediate.



XXXVI A R=R'=H
XXXVI B R=H, R' = $-CH(CH_3)_2$
XXXVI C R=OCH_3, R'=H

Stork and Burgstahler (32), in 1951, synthesized both XXXVI A and XXXVI B. The ketoester XXXVII was hydrolyzed and decarboxylated with alcoholic potassium hydroxide affording the enone XXXVIII which in turn was cyclized with phosphoric acid to yield the tricyclic ketone XXXIX.



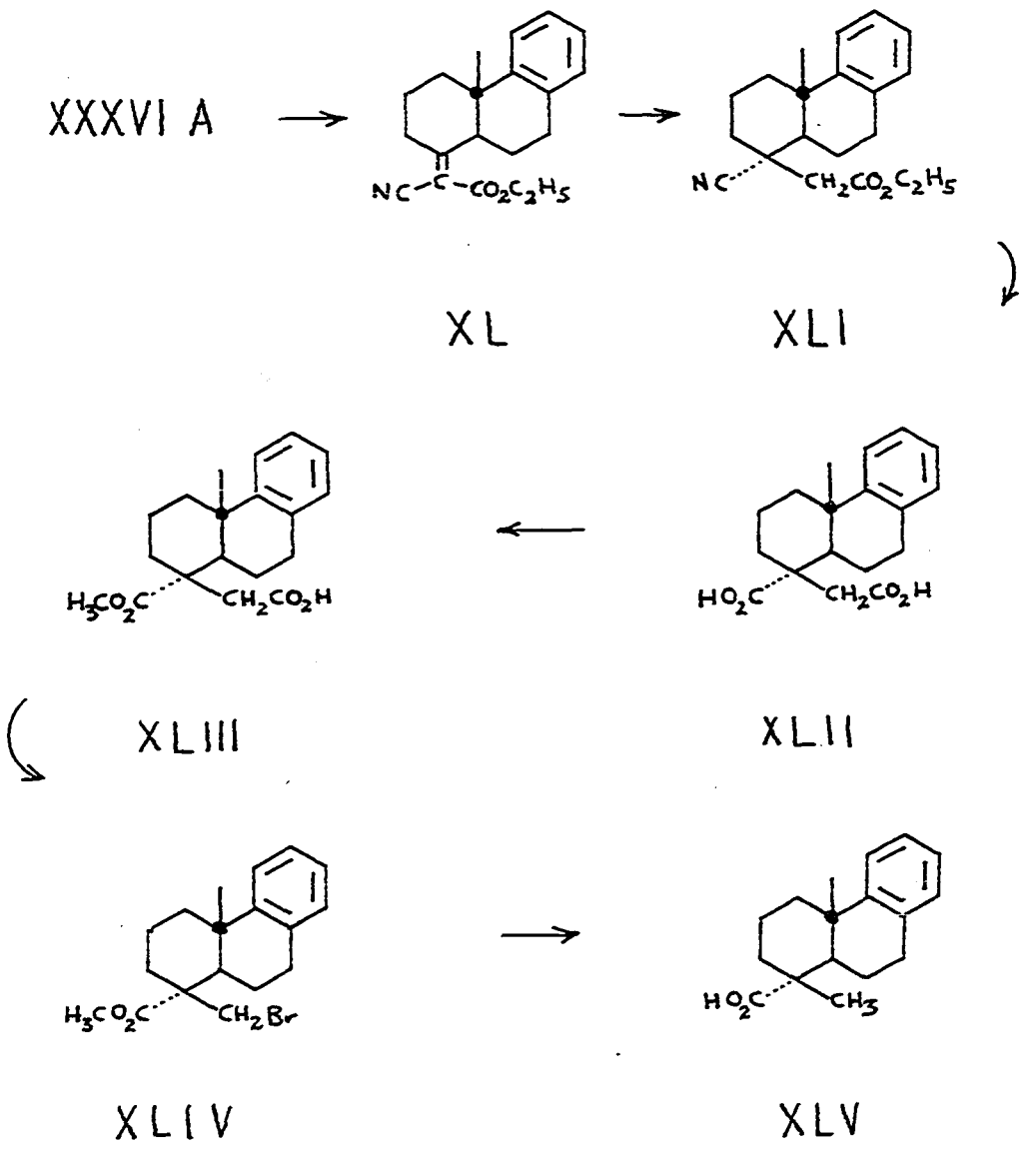


XXXVI B

The XXXVI B thus obtained was found to be identical with a degradation product from dehydroabietic acid having the same structural formula as XXXVI B.

Saha et al. (33, 34) synthesized the tricyclic ketone (XXXVI A) and the methoxy ketone XXXVI B, using a procedure very similar to that of Stork and Burgstahler (32).

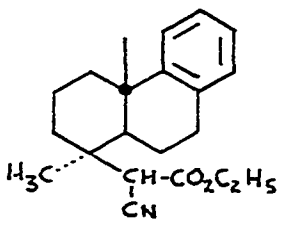
Compound XXXVI A was utilized by Saha et al. (35) as a model system in which to investigate the stereospecific attachment of methyl and carboxyl groups to the 4-position. The methods utilized to produce the two epimers were those which had been previously demonstrated by Parker and Raphael (36). The cyanoester XL resulting from the Knoevenagel-type condensation of XXXVI A and ethyl cyanoacetate was made to react with cyanide ion to give the adduct XLI. The stereochemistry of the cyanide addition product was assigned as indicated in XLI based on the assumption that the axial methyl group at C-10 would prevent axial addition of cyanide at C-4. Hydrolysis and decarboxylation of XLI afforded the



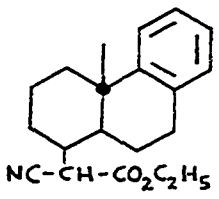
diacid XLII. The dimethyl ester of XLII could be selectively hydrolyzed to the half ester XLIII. The silver salt of XLIII reacted with bromine in refluxing carbon tetrachloride yielding the bromoester XLIV. Reductive debromination with zinc

followed by basic hydrolysis produced the acid XLV. The relative ease of hydrolysis was interpreted as further evidence that XLV possessed the abietic type stereochemistry at C-4.

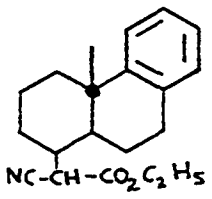
An attempt by the same investigators (35) to synthesize the C-4 epimer of XLV failed when the cyanoester XL did not add methylmagnesium iodide in a normal fashion to give XLVI. The products isolated instead were the saturated cyanoester XLVII and the tertiary alcohol XLVIII.



XLVI



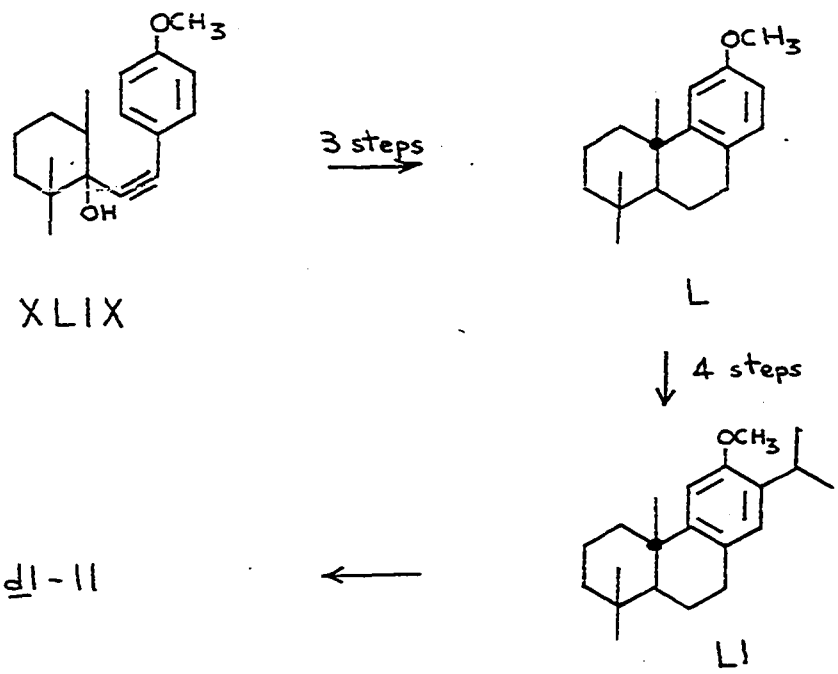
XLVII



XLVIII

King et al. (37, 38) reported the total synthesis of dl-ferruginol. The acetylenic carbinol XLIX was prepared in a manner analogous to that used to prepare XXXV (vide supra). Similarly, catalytic hydrogenation of the acetylenic linkage, dehydration of alcohol and cyclization of the resulting olefin produced the ether L. The isopropyl side chain was attached using the same procedure as that used by Campbell and Todd (2) in their conversion of podocarpic acid to ferruginol (see sequence X to XIV above), affording LI. dl-Ferruginol

was the product resulting from hydrobromic acid-acetic acid cleavage of the ether LI



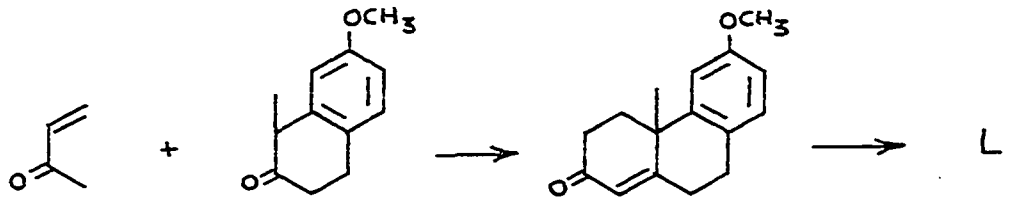
XLIX

L

LI

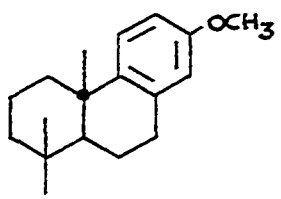
dl-II

Another synthesis of compound L was recently reported by Raman and Rao (39). The methoxy β-tetralone LII was made to react with methyl vinyl ketone to produce the enone LIII. Methylation of LIII with excess potassium t-butoxide and methyl iodide and subsequent catalytic hydrogenation of the resulting 4,5-double bond gave the desired L.

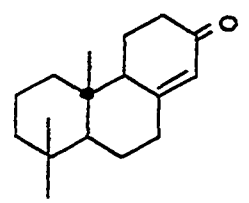


LII LIII

The total synthesis of totarol (IV) was reported by Barltrop and Rogers (5, 40). The tricyclic ether LIV was synthesized by means of a reaction sequence entirely analogous to that used for the preparation of XXXV (q.v.). Birch reduction of the ether afforded the enone LV.



LIV



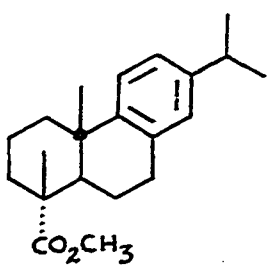
LV

Alkylation of LV with isopropyl iodide and potassium t-amyloxide followed by bromination and dehydrobromination with N-bromosuccinimide and γ-collidine respectively gave dl-totarol.

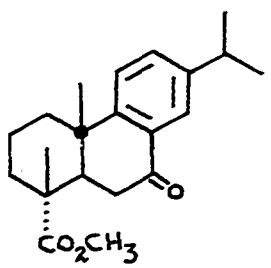
Oxidations of ring-C-aromatic diterpenoids

The oxidations which will be reviewed in this section will be limited to those which involve as a primary process the introduction of an oxygen function onto a carbon atom adjacent to the aromatic ring. Other oxidations of this class of compounds are not pertinent to the investigations undertaken in the study reported herein.

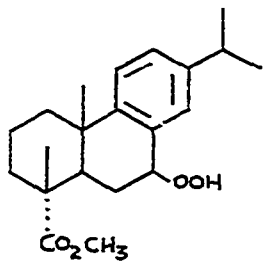
Oxidation with oxygen and free radical initiators gave rise to benzyl hydroperoxides and 7-keto compounds, the yield of the former predominating. Ritchie et al. (41) treated methyl dehydroabietate (LVI) with oxygen and benzoyl peroxide obtaining a 25% yield of methyl 7-ketodehydroabietate (LVII), 50% of the hydroperoxide LVIII and 6% of the isomeric hydroperoxide LIX.



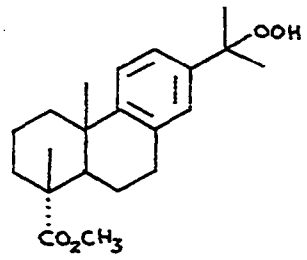
LVI



LVII

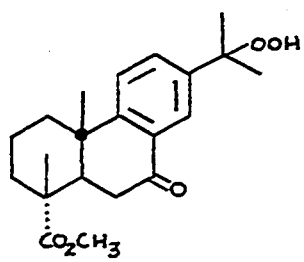


LVIII



LIX

Formation of the 15-hydroperoxide is facilitated where the 7-position is blocked by prior oxidation. The same investigators (42) exposed methyl 7-ketodehydroabietate (LVII) to oxygen and benzoyl peroxide whereupon the ketohydroperoxide LX resulted.



LX

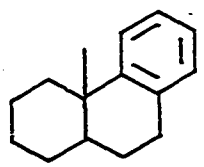
If the oxygen treatment is performed in a basic medium, the hydroperoxide disproportionates to the ketone. Drake (43) allowed methyl dehydroabietate and oxygen to react in a basic solution containing potassium peroxydisulfate giving the ketoester LVII.

Oxidation with chromic oxide under relatively mild

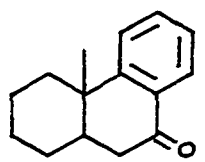
conditions effected transformation of the 7-methylene group to a ketonic function. Slightly more stringent conditions with isopropylated diterpenoids resulted in rupture of the C-15, C-16(17) bond and subsequent formation of 7,15-diketones. Drastic oxidation with the same oxidant cleaved the B ring and led to a variety of products. Examples of these stages of oxidation follow.

Ritchie et al. (42) found that methyl dehydroabietate (LVI) was oxidized by chromic oxide at 30-50° to methyl 7-ketodehydroabietate (LVII).

Likewise, the synthetic octahydrophenanthrene (LXI) was found (44) to yield its 7-keto derivative LXII when allowed to react with chromic oxide at room temperature.

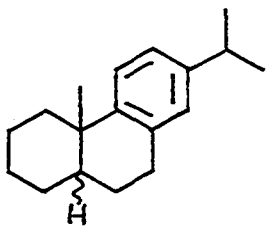


LXI

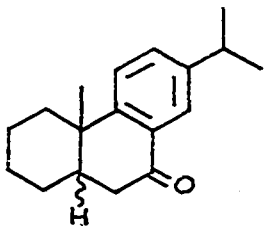


LXII

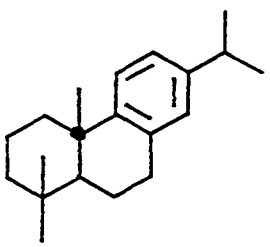
The diterpenoids LXIII and LXV, partial degradation products from dehydroabietic acid, afforded their 7-ketones LXIV and LXVI, respectively, with chromium trioxide at room temperature (45, 46).



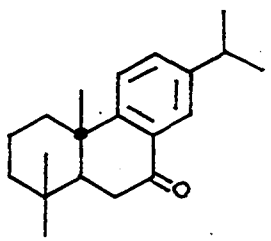
LXIII



LXIV

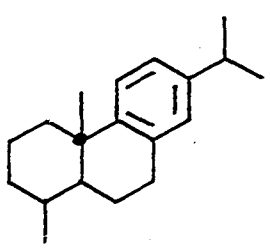


LXV

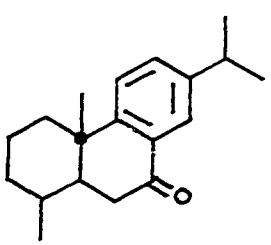


LXVI

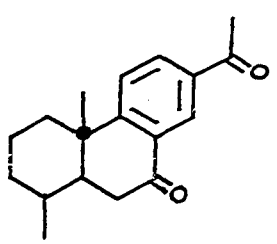
Brossi et al. (47) reacted the diterpenoid LXVII with chromic acid at 80° whereupon they obtained a mixture of the ketones LXIX and LXX.



LXVII



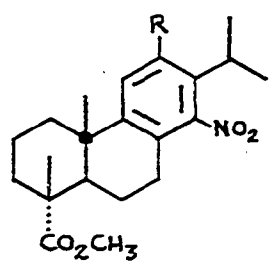
LXIX



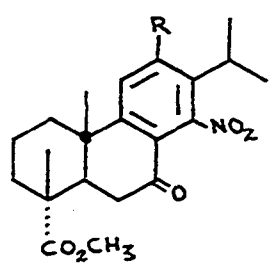
LXX

A 30% yield of acidic materials from this reaction was ignored.

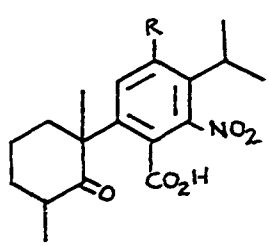
When either of the two nitrated dehydroabietic esters LXXI A or LXXI B was heated with chromic oxide for eight hours, a complex mixture of products was obtained (48, 49). Under these drastic conditions, only a small amount of the usually predominant 7-ketone LXXII was obtained, the major product being the keto acid LXXIII and the isomeric lactol LXXIV.



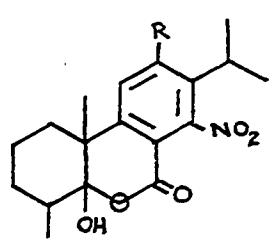
LXXI A R=H
LXXI B R=NO_2



LXXII

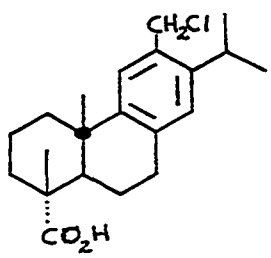


LXXIII

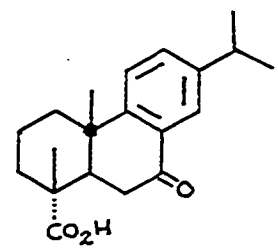


LXXIV

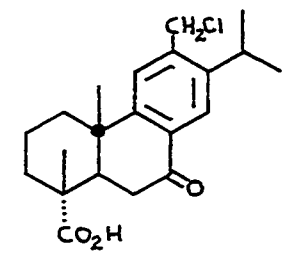
Potassium permanganate reacts with diterpenes in a manner entirely analogous to chromic oxide under mild conditions. Pratt (50) oxidized dehydroabietic acid (VI) and 12-chloromethyl dehydroabietic acid (LXXV) with this reagent and demonstrated that the products were the corresponding 7-ketones LXXVI and LXXVII, respectively.



LXXV



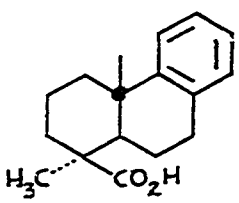
LXXVI



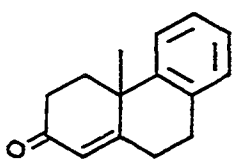
LXXVII

DISCUSSION

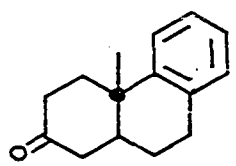
The total synthesis of podocarpic acid (I) was planned as a two stage program, the first stage being the degradation of the diterpenoid to desoxypodocarpic acid (LXXVIII) followed by conversion of this substance back to podocarpic acid. Synthesis of desoxypodocarpic acid from either of the two hydrophenanthrones LXXIX or LXXX would then complete the second phase of the process.



LXXVIII



LXXIX



LXXX

In order to prepare desoxypodocarpic acid it was merely necessary to remove the phenolic hydroxyl from podocarpic acid. Two methods for the removal of a phenolic hydroxyl have been developed by Kenner and co-workers (51, 52), one method (51) involving p-toluenesulfonate ester formation and subsequent aryl-oxygen fission with Raney nickel and the other (52) utilizing a lithium-liquid ammonia cleavage of a diethyl phosphate ester. Preliminary experiments established that the tosylate-Raney nickel deoxygenation was not satis-

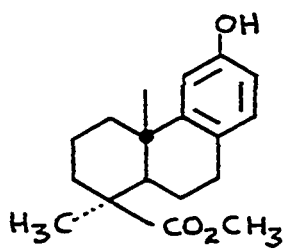
factory and that esterification of the carboxyl group of podocarpic acid was necessary for success of the phosphate method.

Podocarpic acid was quantitatively converted to its methyl ester (LXXXI) by treatment with an ether solution of diazomethane. Although excess diazomethane was employed, no methylation of the phenolic hydroxyl was observed during the short reaction time (ca. fifteen minutes).

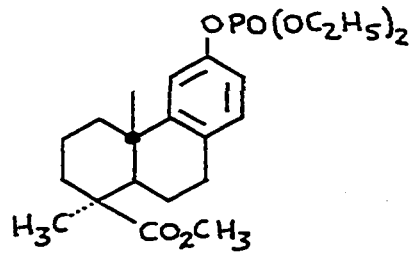
While Kenner and Williams (52) found that the diethyl phosphate esters of simple phenols could be readily formed at room temperature, it was observed that under his mild phosphorylation conditions, methyl podocarpate was recovered unchanged. Examination of a molecular model of podocarpic acid failed to show any steric hindrance to such ester formation. The nonmethylation of the phenolic oxygen by diazomethane might also be a similar anomaly.

Kenner's and Williams' (52) diethyl phosphate esters were prepared by mixing equimolar quantities of phenol, diethyl phosphite, and triethylamine in carbon tetrachloride solution. The low solubility of methyl podocarpate in carbon tetrachloride made necessary the use of tetrahydrofuran as a co-solvent. A successful metamorphosis from methyl podocarpate (LXXXI) to methyl podocarpate diethylphosphate (LXXXII) was effected by refluxing a carbon tetrachloride-tetrahydrofuran solution of the phenolester LXXXI with a three mole excess of

diethyl phosphite and triethylamine for six hours. The crude phosphorylated ester was obtained as a dark brown syrup possessing a pleasant, apple-like odor. This material was not purified further but was used directly for the lithium-ammonia treatment.



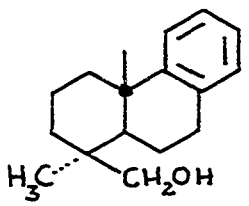
LXXXI



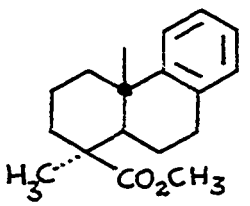
LXXXII

In contrast to Kenner's phosphates, LXXXII was insoluble in liquid ammonia, and use of tetrahydrofuran as a co-solvent was found desirable. The deoxygenation was effected by addition of lithium metal wire to an ammonia-tetrahydrofuran solution of the phosphate. Depending upon the mode of workup, the product from this reaction had two contrasting compositions. In the original procedure (52) and in early experiments, ethanol was added to the reaction mixture following solution of the lithium, after which the ammonia was allowed to evaporate. Using this procedure a 54% yield of desoxypodocarpic acid (LXXVIII) was obtained together with a 20% yield of desoxypodocarpinol (LXXXIII). None of the expected methyl desoxypodocarpate (LXXXIV) was obtained under these condi-

tions. When, in lieu of ethanol, ammonium chloride was used to quench the reaction, the major product was the expected ester LXXXIV in addition to some desoxy alcohol (LXXXIII) and desoxy acid (LXXVIII).



LXXXIII



LXXXIV

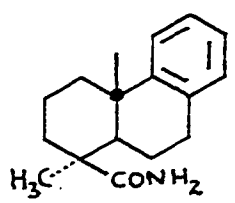
That the various products obtained were actually the desired desoxy compounds was evidenced by the typically characteristic (53, plate 13) tetralin chromophore in their ultraviolet spectra. Absorption maxima at 265 mμ and 272 mμ (ε ca. 600 and 550, respectively) were in sharp contrast to the maximum at 282 mμ (ε 2650) exhibited by the parent phenol.

The formation of the desoxy alcohol LXXXIII could be easily rationalized since lithium in liquid ammonia is known to be a reducing medium toward esters in the presence of suitable hydrogen donors.

The apparent hydrolysis of the ester function, giving rise to the acid LXXVIII, could not be accounted for with equal ease. Several explanations of this phenomenon could be dismissed without further experimentation. Since the reaction mixture was not protected from atmospheric moisture, there is

a possibility of hydroxide ion being present in the reaction medium. The isolation of grossly unequal amounts of alcohol and acid coupled with the non-isolation of aldehyde discouraged any attempt to account for the products by a Cannizzaro disproportionation. The known (1) difficultly hydrolyzable nature of the axial carbomethoxyl group in methyl podocarpate precludes any hydroxide ion catalyzed cleavage.

Since the base catalyzed hydrolysis of certain sterically hindered esters was found (54) to involve direct attack of hydroxide ion on the carbon atom of the alcohol bonded to the acyloxy function and since such a mode of cleavage would not be subject to great steric hindrance from the potential acid portion of the molecule, the possibility existed that amide ion, a product from the phosphate cleavage, directly attacked the ester methyl group displacing carboxylate anion and forming methylamine. However when the desoxy ester LXXXIV was exposed to lithium amide in liquid ammonia, only starting material and a 15% yield of the corresponding amide (LXXXV) were isolated.

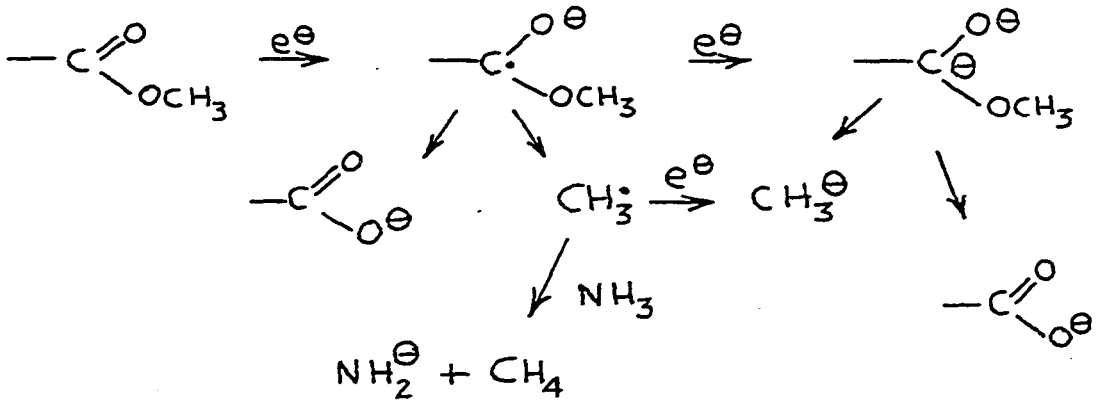


LXXXV

To test the possibility that the lithium solution in ammonia was the hydrolytic agent, methyl desoxypodocarpate (LXXXIV) was treated with the metal-ammonia mixture whereupon the product consisted of a 77% yield of the acid LXXVIII and a 23% yield of the alcohol LXXXIII. The formation of the acid then appears to be a result of a reductive hydrolysis, formulated thusly:

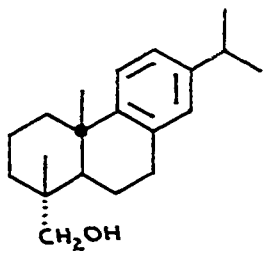
$$RCO_2Me + 2e^{\ominus} + NH_3 \longrightarrow RCO_2^{\ominus} + NH_2^{\ominus} + CH_4$$

No attempt will be made to portray the mechanism of this process other than to present the various possible reaction paths.

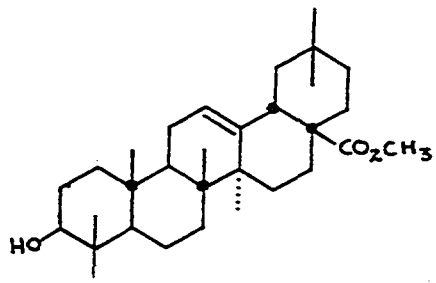


In order to test the scope and limitations of this reductive hydrolysis, several other sterically hindered esters were treated with lithium-ammonia. Methyl podocarpate (LXXXI) gave a 58% yield of podocarpic acid (I) and a 4% recovery of LXXXI. Methyl dehydroabietate (LVI) afforded 3% dehydroabietic acid (VI) together with 62% dehydroabietinol (LXXXVI). Methyl oleanolate (LXXXVII) yielded 68% oleanolic acid (LXXXVIII) and

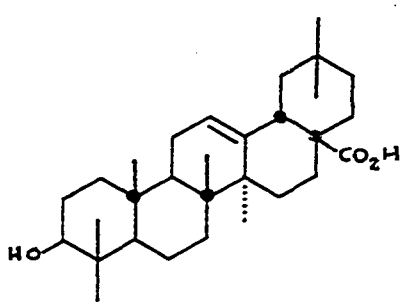
28% erythrodiol (LXXXIX). Methyl mesitoate (XC) was found to undergo reduction to 2,4,6-trimethylbenzyl alcohol (XCI).



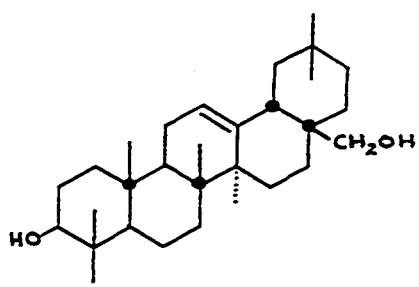
LXXXVI



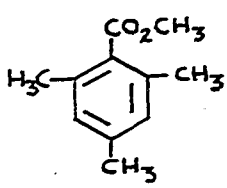
LXXXVII



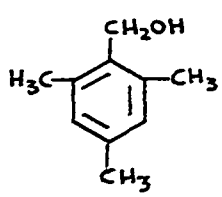
LXXXVIII



LXXXIX



XC



XCI

Examination of the conformation of the various esters tested showed that appreciable reductive hydrolysis occurred only when the carbomethoxyl group was axially oriented (compounds LXXXII, LXXXIV, LXXXVII). The equatorially oriented ester LVI as well as the hindered aromatic ester XC suffered reduction to their corresponding alcohols. It appears then that this procedure would be valuable as a diagnostic tool for assigning the stereochemistry to an unknown ester function.

Whereas reduction of an ester to an alcohol involves expansion of a trigonal sp^2 carbon to a tetrahedral sp^3 carbon and since in an axially oriented ester the reduced function would have a greater 1,3-diaxial interaction, it seems probable that reduction of an axial ester to an alcohol would be a fairly high energy process. The same transformation in an equatorial ester would not give rise to a similar increase in the non-bonded interactions. The experimental results obtained indicate that the energy of activation for the reductive hydrolysis is intermediate between the two reduction processes, for an ester of either conformation is given equal opportunity for reduction to an alcohol; and only in an equatorial ester, is the alcohol formed in preponderant yield.

The reductive hydrolyses which were run to test the spectrum of applicability of the reaction were performed without the addition of any hydrogen donor. However since no attempt

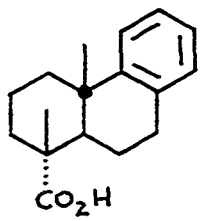
was made to protect the reaction mixture from atmospheric moisture, water was able to condense on the cold surface of the reaction vessel and was most likely the proton donor responsible for alcohol formation.

Quenching the reaction mixture with ammonium chloride irreversibly destroys the reducing power of the metal-ammonia solution. Ethanol, on the other hand, is a reversible proton donor and does not destroy the reducing power of the medium. Assuming that the reductive hydrolysis is a relatively slow process, the differences in product composition between the ammonium chloride quenched and the ethanol quenched reductions of the phosphate LXXXII is rationalized.

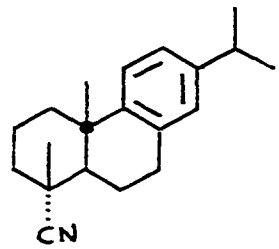
The reductive hydrolysis serves not only as a diagnostic tool but is useful for the mild hydrolysis of very sterically hindered esters. In contrast to the lithium-ammonia cleavage of methyl podocarpate wherein a 58% yield of podocarpic acid was obtained, heating the ester with sodium hydroxide and ethylene glycol at 160° for ten hours resulted in isolation of only 4% podocarpic acid.

Having prepared desoxypodocarpic acid (LXXVIII), it was desirable to have its C-4 epimer, deisopropyldehydroabietic acid (XCII) for possible use in the synthesis of abietic acid. Parham et al. (27) had found that dehydroabietic acid (VI) was transformed into a deisopropyl derivative when heated with aluminum chloride. The ready availability of dehydroabieto-

nitrile (XCIII) prompted the use of this material as a possible source of XCII via deisopropylation and subsequent hydrolysis.



XCII



XCIII

When dehydroabietonitrile was refluxed with anhydrous aluminum chloride and benzene for six hours, there was obtained a 39% yield of a new nitrile, m.p. 107-08°. That the isopropyl group had been removed was indicated by the changes in the ultraviolet and infrared spectra of the new compound. Its ultraviolet absorption maxima were at 265 and 272 mμ (ε 890 and 850, respectively), characteristic of the tetralin chromophore (53, plate 13) in contrast to that of the starting nitrile which showed absorption at 268 mμ and 276 mμ (ε 685 and 723, respectively). The infrared spectrum no longer showed the doublet at 7.27μ and 7.34μ attributable to an isopropyl group (55, p. 23). Elemental analyses were in accord with a $C_{17}H_{21}N$ formulation.

This C_{17} nitrile was found to be unusually resistant to base catalyzed hydrolysis. Drastic and prolonged base

treatment however gave a carboxylic acid $C_{17}H_{22}O_2$, melting 159-60°. Parham et al. (27) report the same melting point for the acid obtained by aluminum chloride treatment of dehydroabietic acid (VI).

Oxidation of the C_{17} nitrile with chromic oxide gave a mixture of acidic and neutral oxidation products. From the neutral fraction a yellow crystalline compound, $C_{17}H_{17}O_2N$, could be readily crystallized. Repeated recrystallization of this material failed to narrow the wide melting point range; but the optical rotation remained constant, and this physical property was used as a criterion of purity. The infrared spectrum of this substance showed absorption bands at 5.80μ and 5.93μ. This information coupled with the fact that it readily formed a quinoxaline derivative, m.p. 197-98°, suggests the presence of a α-diketone moiety of the sort Ar-CO-CO-CR_2. Chromatography of the remainder of the neutral fraction over alumina resulted in the isolation of colorless solid, $C_{17}H_{19}ON$. The ultraviolet spectrum of this compound was typical of a α-tetralone chromophore (53, plate 59), having ultraviolet maxima at 253 mμ (ϵ 12670), 294 mμ (ϵ 2420) and 296 mμ (ϵ 2390). Infrared absorption bands at 5.95μ and 6.24μ were consistent with the presence of a phenyl ketone moiety in the molecule.

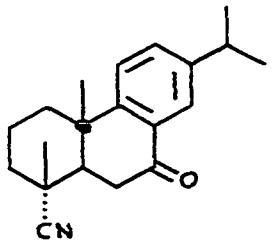
The acidic material was composed of a single substance $C_{16}H_{17}O_3N$. The infrared spectrum of this substance did not

show the usual diffuse carboxyl OH stretching frequency but possessed a sharp OH absorption band at 2.80μ together with a broad peak at 2.95μ-3.15μ. A wide peak at 5.77-5.82μ was also present. The spectral characteristics of this substance were very similar to those which Zeiss and co-workers (48, 49) described for compound LXXIV (see Historical section); and on this basis, the acid was assumed to be a similar lactol.

The formation of a α-diketone was unusual and unexpected since an examination of the literature (see Historical section) revealed that no 6,7-diketones had ever been obtained by chromic oxide oxidation of ring-C-aromatic diterpenoids. Since there was the possibility that such compounds were formed but not isolated or reported, several available diterpenoid compounds were treated with chromium trioxide under conditions identical to those used for the nitrile above and the product examined judiciously for possible α-diketone.

Since no 4-cyano diterpenoid had previously been exposed to chromic oxide, it was not known if the nitrile function could form a loose complex with the oxidant and thus facilitate further oxidative attack on the 7-ketone, forming a 6,7-diketone. In order to test this possibility, dehydroabietonitrile (XCIII) was oxidized with chromic oxide whereupon there was isolated a 44% yield of the 7-ketone XCIV. No 6,7-diketone or acidic material was present in the reaction

mixture.

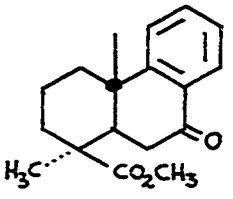


XCIV

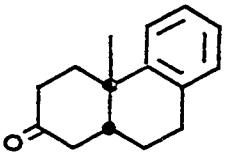
Dehydroabietic acid (VI) and methyl dehydroabietate were oxidized with chromic oxide resulting in the isolation of the corresponding 7-ketones (LXXVI and LVII) in 49% and 73% yields respectively. Again no α-diketone was found.

Oxidation of C-4 epimeric systems still produced no 6,7 diketone. Methyl desoxypodocarpate (LXXXIV) gave only the ketone XCV in 64% yield.

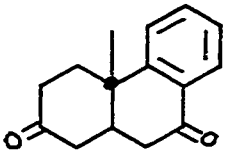
C-4 Unsubstituted hydropenanthrenes likewise yielded 7-ketones. Oxidation of the phenanthrones LXXX and XCVI afforded the diketones XCVII and XCVIII. While no α-diketone was formed, the predominant (52-62%) products in each case were acidic materials of unknown nature. The acids possessed typical carboxyl absorption in the infrared and hence were presumed not to be lactols like LXXIV. These acids were not examined further.



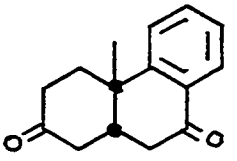
XCV



XCVI

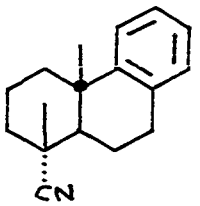


XCVII

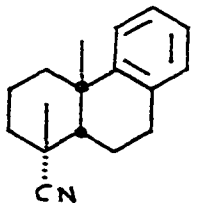


XCVIII

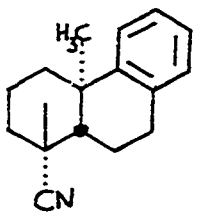
The α-diketone formation from the C_{17} nitrile coupled with the absence of α-diketone genesis among 4,4-disubstituted, A-B <u>trans</u> diterpenoids suggested that the C_{17} nitrile is not the expected deisopropyldehydroabietonitrile. Since the reverse Friedel-Crafts reaction which was used to obtain the deisopropyl nitrile could have resulted in a cleavage of the C-9, C-10 bond with subsequent recyclization, the stereochemistry of the A-B ring juncture might have been altered during the process. Thus the C_{17} nitrile might have any of four possible structures: XCIX, C, CI or CII.



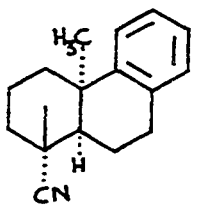
XCIX



C



CI

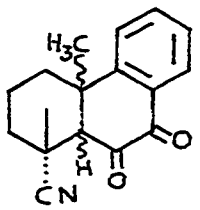


CII

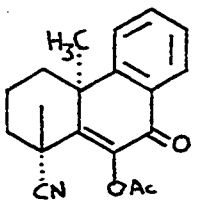
Of these various possibilities, CI may be eliminated. Examination of the stereoformula CI shows it to be enantiomeric to the normal podocarpic stereochemistry (cf. structure LXXVIII). Non identity of the physical and chemical properties and infrared spectra of the acid and methyl ester derived from the C_{17} nitrile with desoxypodocarpic acid (LXXVIII) and methyl desoxypodocarpate (LXXXIV) precludes that these substances are enantiomers. Hence the parent nitrile cannot be CI.

The α-diketone (CIII) is a suitable compound for use in

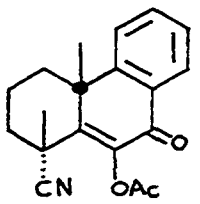
a stereochemical proof of structure of the deisopropyl nitrile. The diketone readily formed an enolacetate which must have been CIV or CV.



CIII



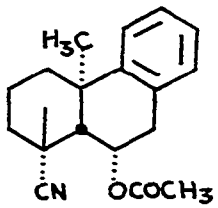
CIV



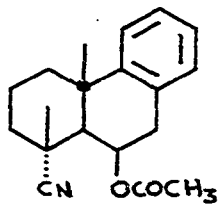
CV

Catalytic hydrogenation of a 5,6-double bond is known (28) (5) to give rise to an A-B trans ring juncture. If the product from catalytic hydrogenation of the enolacetate were then degraded to a $C_{17}H_{21}N$ compound, identity of this substance with the starting C_{17} nitrile would prove the presence of a A-B trans ring juncture in the latter compound. Non identity would indicate that the deisopropylation product possessed a cis A-B juncture.

When the enolacetate was subjected to catalytic hydrogenation in acid medium, a mixture of products was formed, the predominant one being a crystalline solid, $C_{19}H_{23}O_2N$, whose infrared spectrum was compatible with the structures CVI and CVII. The enolacetate CIV would give rise to the acetate CVI, whereas CV would catalytically reduce to CVII.



CVI



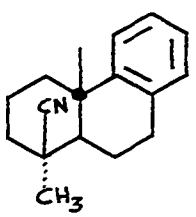
CVII

Conversion of the crystalline acetate to a $C_{17}H_{21}N$ compound was accomplished in two steps: by pyrolysis to a styrene and subsequent catalytic hydrogenation of the 6,7-double bond. Since the thermal elimination occurs by loss of a hydrogen atom cis to the acetoxy function and since there is no hydrogen at C-5 cis to the acetate (catalytic hydrogenation results in the C-5 and C-6 hydrogens being cis to one another), elimination must take place to give the 6,7-olefin exclusively. While it may be argued that there is a possibility of thermal rearrangement of the 6,7-double bond to a 5,6-position, experiments with appropriate model systems have shown that this does not occur (56-57). Notwithstanding such a possibility, catalytic hydrogenation of the 5,6-unsaturated linkage would still give the desired trans A-B nitrile.

The crystalline monoacetate smoothly lost acetic acid at 350° giving a liquid olefin. While the liquid was not analyzed for carbon and hydrogen, ultraviolet and infrared spectra indicated that it was the desired compound.

Catalytic hydrogenation of this olefin gave a crystalline, nitrile, $C_{17}H_{21}N$, m.p. 87-88°, which was not identical with the original deisopropyl nitrile, m.p. 107-08°. Thus the deisopropyl compound must have had a cis A-B ring juncture and was then either C or CII.

Since C would give rise to XCIX via the scheme outlined above and CII would yield CI by the same process, assignment of the correct structure to the lower melting C_{17} nitrile would reveal the correct stereoformula for the higher melting deisopropyl nitrile. It has been pointed out earlier that CI is enantiomeric with the normal podocarpic stereochemistry. Hence synthesis of desoxypodocarponitrile (CVIII) and comparison with the lower melting C_{17} nitrile would establish the stereochemistry of the latter substance. The isomeric desoxypodocarponitrile would either be the enantiomer or diastereomer of the lower melting C_{17} nitrile.

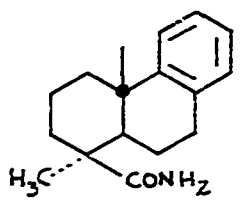


CVIII

Desoxypodocarpic acid (LXXVIII) was chosen as starting material for the synthesis of CVIII. Conversion of the desoxy acid to its acid chloride was accomplished by refluxing

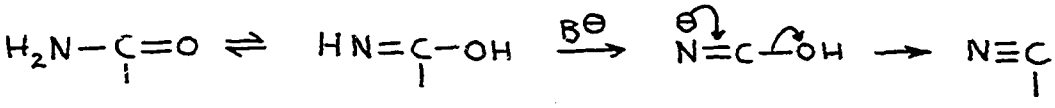
with thionyl chloride; but when the acid chloride was exposed to aqueous ammonia in the hope of converting it to the amide, no reaction took place, and the acid chloride was recovered unchanged. Apparently this is another example of the great resistance of the trigonal, axially oriented C-4 substituent in podocarpic systems to undergo expansion to a tetrahedral configuration.

The chloride could be made to react with sodamide in liquid ammonia whereupon, in addition to a 37% yield of the expected desoxypodocarpamide (CIX), there was obtained a 7% yield of desoxypodocarponitrile (CVIII). The base catalyzed dehydration of an amide to a nitrile was somewhat unusual.



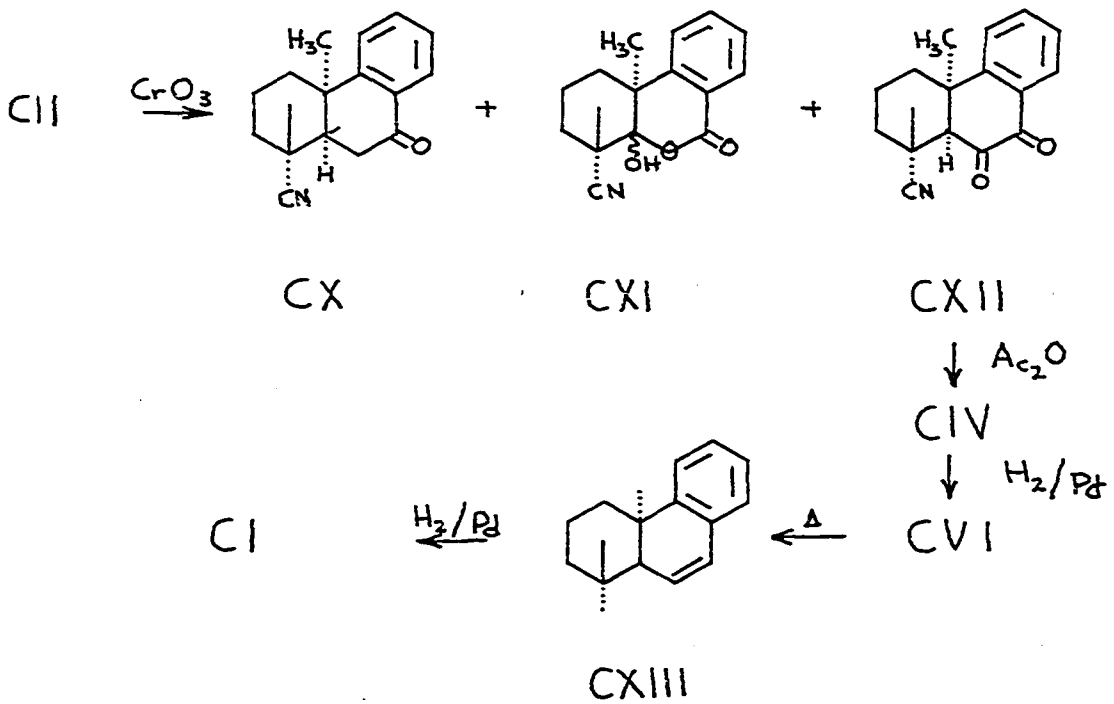
CIX

While this reaction has been observed before (58) the conditions were contrastingly drastic by comparison with the sodamide in liquid ammonia procedure. The dehydration may be mechanistically portrayed as a base catalyzed elimination of water from the iminol form of the amide:



In contrast to the extreme difficulty in expanding an axial C-4 trigonal carbon atom to a tetrahedral configuration, the relative ease of formation of the nitrile by base catalyzed dehydration of the amide may indicate the tendency for the axial C-4 substituent to become less sterically demanding by transformation from a trigonal to a linear function.

Dehydration of the amide CIX with thionyl chloride gave the expected desoxy nitrile CVIII. This nitrile had a melting point and infrared spectrum identical with those of the lower melting C_{17} nitrile obtained previously. The specific rotations of the two nitriles were of equal magnitude but of opposite sign. Comparison of these properties indicate that the two compounds are enanthiomers. Hence the deisopropylated nitrile has the stereoformula CII, and the reaction sequence involved in its structure proof may be now correctly stereoformulated:



Since the C-5 hydrogen in CXII is on the α-carbon of a ketone, the question of its stereochemistry remaining intact during the transformation from CII to CXII must be considered. The mechanism of formation of the α-diketone might of course influence the stereochemistry at C-5, but sufficient experimental evidence exists to preclude any epimerization or racemization occurring during the reaction.

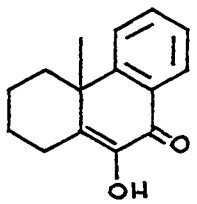
The α-diketone which was isolated directly from the reaction mixture gave no coloration with methanolic ferric chloride solution. Since fractional crystallization did not

remove all of the 6,7-diketone, some of this substance was adsorbed on alumina during the chromatographic separation of the oxidation products. The diketone which was eluted from the alumina was a semi-crystalline gum which could not be crystallized. It gave a brown coloration with ferric chloride, and furthermore its quinoxaline derivative, m.p. 157-59°, was different from the quinoxaline, m.p. 197-98°, obtained from the crystalline diketone. The presence of considerable enolic material in the gum was further substantiated by its infrared spectrum which showed strong enol double bond absorption at 6.05μ. It appears then that epimerization had occurred while the diketone was adsorbed on the column. The same epimerization could be brought about by heating the diketone at 150° for a few minutes. The heat treatment resulted in the same gummy enolic mixture as evidenced by its infrared spectrum and the formation of a quinoxaline melting at 157-59°. This heat-induced tautomerization undoubtedly explains the wide melting point range of the pure crystalline diketone.

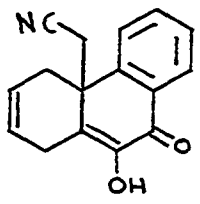
Had the enol been an intermediate in the formation of the α-diketone or had the C-5 hydrogen epimerized during oxidation, it should not have been possible to obtain the two different quinoxalines since any epimerization or enolization should give a diketone which would yield the lower melting quinoxaline. Hence the crystalline diketone must have the

same stereochemistry at C-5 as the initial deisopropyl nitrile.

The non-enolic character of the crystalline diketone is somewhat unusual since very similar α-diketones are known to be completely enolic, e.g. compounds CXIV (27) and CXV (59) exist entirely as enols.



CXIV

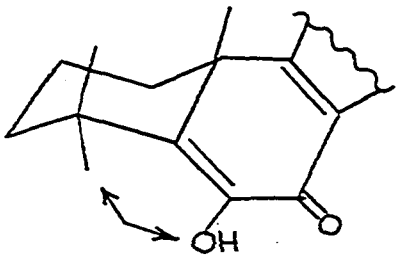


CXV

A similar apparent anomaly is observed with xanthoperol (V). It was reported (4) that this α-diketonic diterpenoid did not give any coloration with ferric chloride or possess any spectral characteristics expected for such an enol.

The major difference between the diketonitrile CXII and xanthoperol (V) on one hand and similarly constituted enolic α-diketones on the other appears to be the presence of two relatively bulky substituents at C-4. Examination of a molecular model of a C-4 disubstituted 6,7-diketone reveals that there is considerable non-bonded interaction between the quasi-equatorially oriented substituent at C-4 and the enolic hydroxyl. Ketonization of the enol removes this

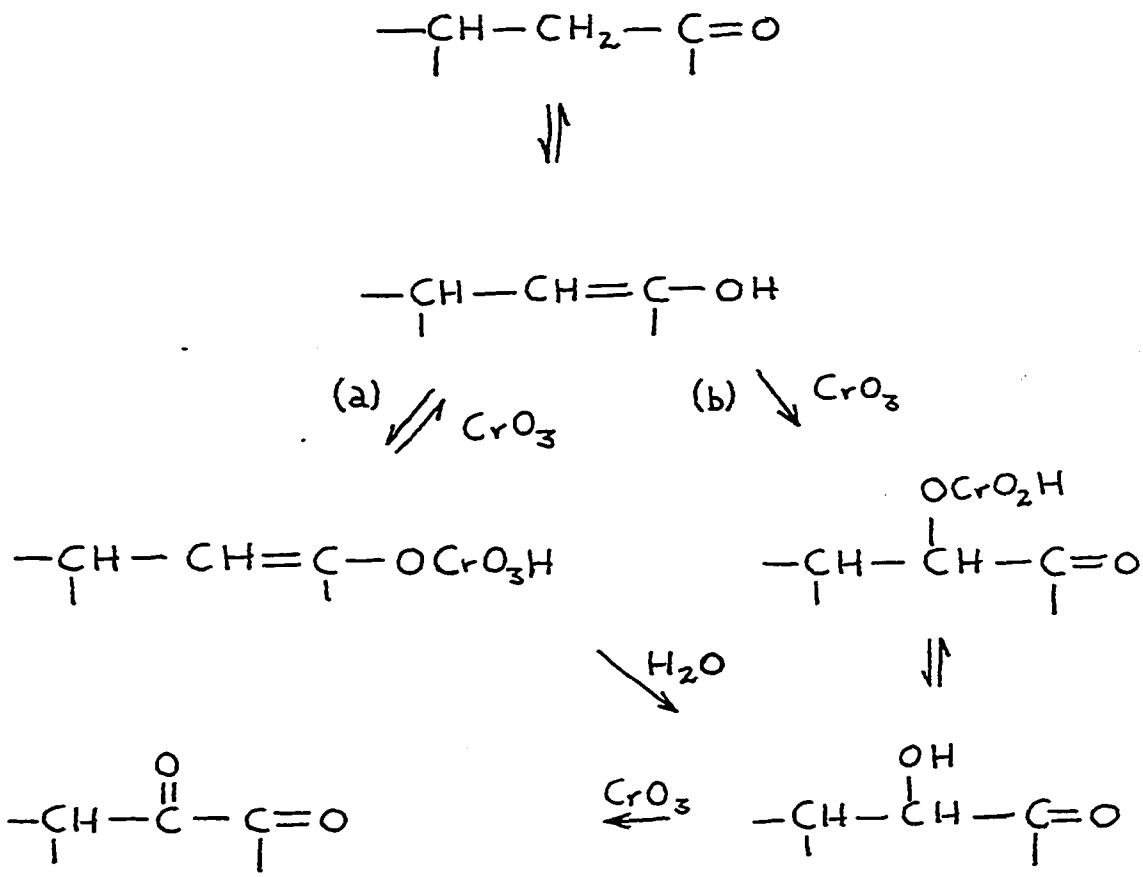
unfavorable interaction. A conformational picture of this steric influence is shown in structure CXVI.



CXVI

It has been mentioned previously that the formation of the α-diketone was unusual and unprecedented. Since the stereochemistry of the nitrile has been rigorously shown to be that indicated in CII, it should be possible to devise a rationale for the formation of the diketone based on the stereochemical differences between CII and diterpenoids which do not give rise to α-diketones. Before attempting such a rationalization, it is pertinent to discuss the general nature of chromic oxide oxidation of ketones, since undoubtedly the 7-ketone is formed prior to 6,7-diketone.

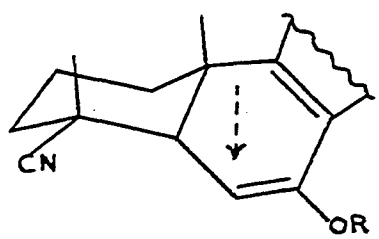
Further oxidation of a ketone most probably occurs via its enol. Two possible reaction paths from the enol to ultimate oxidation products may be postulated and are illustrated in the sequence below. One of the pathways (a) involves formation of an enol chromate as an intermediate which then adds solvent with concomitant cleavage of chromite.



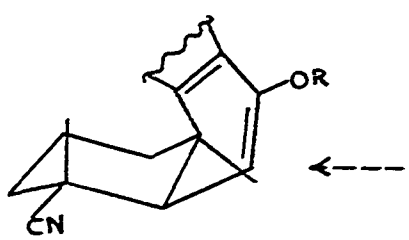
Sequence (b) embodies direct attack of chromate on the carbon atom of the enol giving a α-ketochromite. Solvolysis of the chromite yields a α-ketol. Oxidation of this α-ketol to a α-diketone doubtlessly occurs by the known (60) mechanism involving disproportionation of a chromate ester.

If the above mechanisms are correct, the resistance of the A-B trans 7-ketones to further oxidation may be attributed, a priori, to any of three factors: resistance of the 7-ketone toward enolization, inability to form an enol chromate ester or difficulty of direct attack on the enol or

enol chromate double bond. Inspection of molecular models of A-B trans and A-B cis 7-ketones fails to reveal any differences between the two systems with respect to ease of enolization or resistance to enol chromate formation, It is most likely that attack on the enol or enol chromate double bond occurs with the entering group approaching C-6 from an axial direction analogous to the kinetically controlled protonation (61) and bromination (62) of enols. Examination of conformational models reveals that there is strong interference to an axial attack at C-6 in A-B trans enols by virtue of the 1,3-diaxial interactions between the angular methyls at C-4 and C-10 with the axially oriented approaching reagent. In A-B cis systems the interference from the C-4 substituent is absent, and the interaction with the C-10 methyl is diminished. The nature of this effect is pictorially represented in structures CXVII (A-B trans) and CXVIII (A-B cis) in which the axial approach is indicated by an arrow.



CXVII R=H or CrO_3H

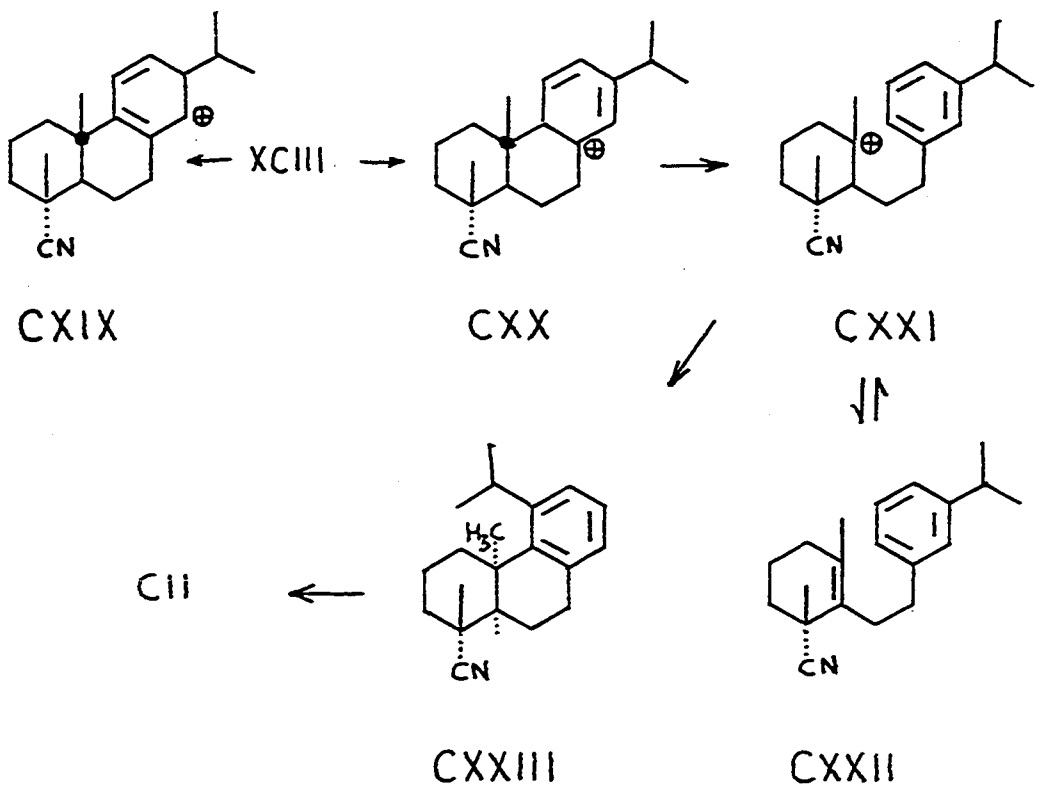


CXVIII R=H or CrO_3H

Hence the differences in the oxidative behavior between A-B trans and A-B cis 4,4-disubstituted, ring-C-aromatic diterpenoids may be rationalized by the contrasting ease of axial attack at C-6. An obvious exploitation of this difference would be the use of chromic oxide oxidation as a diagnostic tool to determine the stereochemistry of the A-B ring fusion of unknown 4,4-disubstituted, ring-C-aromatic diterpenoids.

Since the initial aluminum chloride treatment of XCIII not only cleaves the isopropyl group but results in a fission of the C-9, C-10 bond with accompanying reconversion to a cis enantiomeric podocarpic system, it is interesting to consider this reation from a theoretical standpoint. Formally, the deisopropylation appears to involve protonation at C-13 followed by loss of isopropyl cation. Since the carbonium ion so formed (CXIX) cannot be stabilized by hyperconjugation with the C-7 methylene group, it would be energetically more favorable to protonate at C-9 to give a carbonium ion (CXX) which could be stabilized by hyperconjugation with both the C-7 methylene and C-15 methine. Formation of this C-8 carbonium ion also facilitates breaking the C-9, C-10 bond which undoubtedly must occur prior to the epimerization at C-10. The carbonium ion which results from the C-9, C-10 scission is a stable tertiary carbonium ion (CXXI). Cyclization of the 9,10-seco structure CXXI or CXXII may occur in several ways to give a variety of position and stereoisomers. While

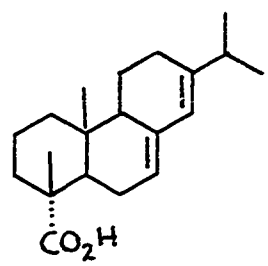
cyclization could take place either ortho or para to the isopropyl group, ortho attack would give a product (CXXIII) in which the isopropyl group is in an unfavorable steric situation with respect to the C-10 methyl group and hence should be easily lost via a reverse Friedel-Crafts reaction to give the deisopropyl nitrile.



Attack of the benzene ring on the C-10 carbonium ion may occur on either side of the potential A ring to give a tricyclic system either of the podocarpic stereochemistry, in which attack has taken place on the side of the C-4 methyl group, or of the abietic series in which attack has occurred

on the side of the C-4 cyano group. Since the major isolable product has the cis enantiomeric podocarpic stereochemistry, attack at C-10 must be preferred on the side of the C-4 methyl group. Complexing of the C-4 cyano group with aluminum chloride would increase its steric requirements, and this phenomenon may be responsible for the preferential attack on the side of the methyl function.

While the stereochemistry of the deisopropyl nitrile CII precludes its conversion to dehydroabietic acid (VI) or abietic acid (CXXIV), desoxypodocarpic acid (LXXVIII) may be readily transformed to podocarpic acid (I).



CXXIV

Since there is no direct method for the introduction of a phenolic oxygen onto such an aromatic system, it is necessary to substitute an appropriate functional group which can be ultimately converted to a phenolic hydroxyl. While a nitro group possesses the desired characteristic of being easily convertible to a hydroxyl, the known (63) ease of dinitration

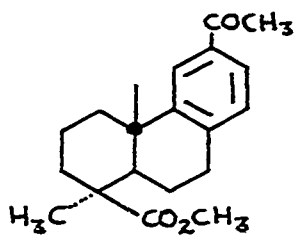
of tetrahydronaphthalene systems discourages the use of this method for oxygenation of desoxypodocarpic acid. Barnes and Gottesman (64) have demonstrated that only monoacetylated products are obtained when octahydrophenanthrene systems, structurally similar to desoxypodocarpic acid, are exposed to acetyl chloride and aluminum chloride. Since acetophenones may be oxidatively rearranged to the corresponding phenyl acetates which in turn may be hydrolyzed to phenols, the sequence acetylation, oxidation and hydrolysis appears to be satisfactory for the synthesis of podocarpic acid from its desoxy counterpart.

Although Friedel-Crafts acetylation gives only monosubstituted products, there remains the question of where the electrophilic attack will occur. Diterpenoids with a C-13 isopropyl substituent substitute electrophilically at C-12 (1). Barnes and Gottesman (64) likewise assign a C-12 position of substitution to his acetylated octahydrophenanthrene, but conclusive evidence is lacking in this latter example. Since C-12 substitution is desired, the above experimental evidence is encouraging.

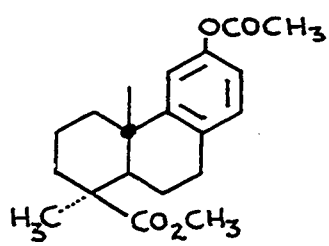
Methyl desoxypodocarpate (LXXXIV) reacted with acetyl chloride and anhydrous aluminum chloride in carbon disulfide to give a fair yield of acetylated product. Neither heating the reaction mixture nor increasing the reaction time gave higher yields. The acetyl compound exhibited ultraviolet

absorption at 258 mμ (ε 19,200) and had a band in its infrared spectrum at 5.95μ both spectral characteristics suggesting the presence of a phenyl ketone (53, plate 59), (65, p. 114).

Treatment of the acetylated methyl desoxypodocarpate with trifluoroperacetic acid, according to the procedure of Emmons and Lucas (65-66), gave a crystalline compound identical in all respects with methyl podocarpate acetate (CXXVI) prepared independently from methyl podocarpate and acetic anhydride. Thus the structure of the acetyl compound is correctly represented by structure CXXV.



CXXV



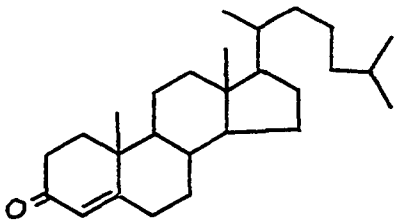
CXXVI

Hydrolysis of CXXVI to podocarpic acid was accomplished in two steps. Treatment of the acetate CXXVI with aqueous sodium hydroxide gave a quantitative yield of methyl podocarpate (LXXXI). Hydrolysis of the latter ester was achieved by a reductive hydrolysis using lithium in liquid ammonia.

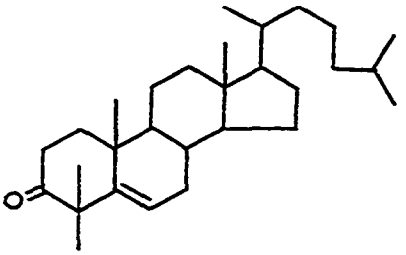
Having completed the first phase of the synthesis of podocarpic acid (I) by its partial synthesis from desoxypodo-

carpic acid (LXXVIII), it now remains to synthesize desoxy-podocarpic acid. Starting with the available phenanthrones LXXIX and LXXX the syntheses of which have been reported recently by Wenkert and Stevens (67, 68), it is necessary to introduce a carboxy and a methyl at C-4 and to remove the ketone at C-3 in order to convert them to LXXVIII. Use of compound LXXIX requires an additional step; i.e., the reduction of the 4,5-double bond so as to give a trans A-B ring fusion.

Direct carbonation of the enone LXXIX via enolate anion formation and reaction of the anion with carbon dioxide was used to introduce a carboxyl at C-4. While there is a possibility of anion formation at three positions on the enone: at C-2, C-4 and C-6, there is available experimental evidence to attest to the fact that reaction occurs preferentially at C-4. Woodward et al. (69) treated cholestenone (CXXVII) with excess methyl iodide and potassium t-butoxide and obtained the ketone CXXVIII. In the synthesis of dl-dehydroabietic acid described above (see Historical section), Stork and Schulenberg (28) found that the enone XXVIII reacted with methyl chloroacetate to give a C-4 alkylated product (XXIX).



CXXVII

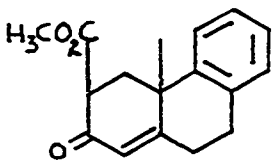


CXXVIII

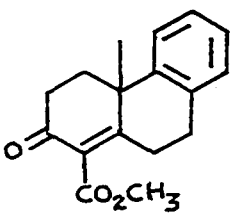
The procedure (70) used for the carbonation of the phenanthrones was that developed by the school of Sir Robert Robinson during an extended study of steroid syntheses. Enolate anion formation was accomplished by using sodium triphenylmethide, and the ensuing carbanion was carbonated using Dry Ice. The resulting β-ketocarboxylate was acidified and rapidly esterified with diazomethane to avoid decarboxylation during the workup.

When the enone LXXIX was carbonated using the above (70) procedure and the crude product carefully chromatographed over Celite-silicic acid, there were obtained two crystalline ketoesters, both having the empirical formula $C_{17}H_{18}O_3$, one melting at 111° and the other at 117°. The ultraviolet spectra of the two substances were practically identical, the lower melting compound having an absorption maximum at 238 mμ (ε 18,500) while the material melting at 117° showed maximum absorption at 239 mμ (ε 14,300).

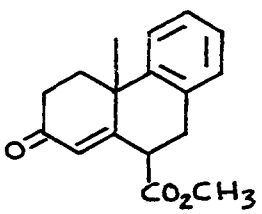
Infrared spectra of the two ketoesters were very similar, being characterized by sharp bands at 5.77 μ, 5.95 μ and 6.15 μ. The lower melting material gave a blue color with methanolic ferric chloride solution, but the higher melting compound gave no color with this reagent. It was assumed that these compounds were two of the three possible isomers (CXXIX, CXXX or CXXXI) resulting from carbonation at C-2, C-4 or C-6.



CXXIX



CXXX

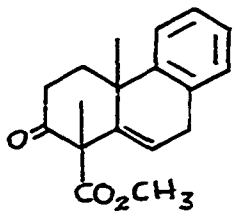


CXXXI

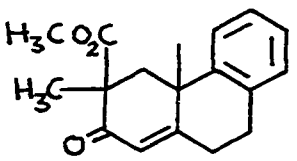
In order to ascertain which of the three possible isomers were obtained, the two crystalline ketoesters were subjected to catalytic hydrogenation whereupon there was obtained, in each case, an enolic product. The enolic nature of the products resulting from reduction of the 4,5-double bond immediately rules out the 6-ester which would give rise to a non-enolizable δ-ketoester in contrast to the 2- and 4-esters which would give enolizable β-ketoesters.

In order to differentiate the C-2 ester from the C-4 ester, the two enone esters were alkylated with potassium

t-butoxide and methyl iodide. Methylation of the 4-carbomethoxy compound would be expected to give an alkylation product (CXXXII) in which the double bond has shifted out of conjugation with the C-3 carbonyl. Conversely, the methylated 2-carbomethoxy enone CXXXIII should still possess a conjugated Δ^4-3-ketone. These differences would be readily discernable in the ultraviolet and infrared spectra of the methylated products.



CXXXII



CXXXIII

Methylation of the lower melting carbonation product gave a $C_{18}H_{20}O_3$ compound which had an ultraviolet absorption maximum at 239 mμ (ε 15,000) and carbonyl stretching frequencies at 5.78 μ and 5.97 μ. Both spectra are similar to the starting enone ester and are characteristic (67), (71, p. 192) of an α,β-unsaturated ketone. Hence the ketoester melting at 111° corresponded to the 2-carbomethoxy enone CXXIX, and the higher melting carbonation product was the desired 4-carbomethoxy ketoester CXXX. Alkylation of CXXX afforded a mixture of unidentifiable products.

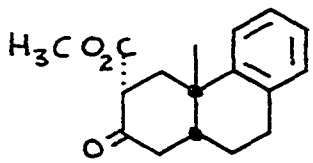
Since the use of CXXX as a precursor to desoxypodocarpic

acid requires stereospecific reduction of the 4,5-double bond, it is of interest to examine the products from catalytic hydrogenation of the enone esters CXXIX and CXXX to see if the reduction had occurred to give a cis or a trans A-B ring fusion. It was expected that the reduction had occurred to give a cis product since it has been demonstrated (67) that hydrogenation of the enone LXXIX gives predominantly the cis isomer. Hydrolysis and decarboxylation of the saturated β-ketoesters would give either the cis or trans phenanthrones (XCVI or LXXX, respectively) depending upon the stereochemistry of the reduction process.

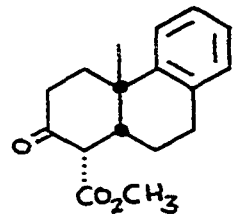
The crude product from the hydrogenation of the 2-carbomethoxy enone ester CXXIX was refluxed in ethanol-hydrochloric acid. Chromatography of the crude product over alumina gave only the cis ketone XCVI. Hence the saturated β-ketoester from CXXIX was represented correctly by structure CXXXIV.

Trituration of the crude product from the catalytic hydrogenation of the isomeric 4-ester CXXX with petroleum ether afforded a solid crystalline ketoester. Acid hydrolysis of a pure sample of this solid produced the trans ketone LXXX. Acid catalyzed decarbalkoxylation of the mother liquors from the crystallization of the aforementioned solid gave a mixture of the cis (XCVI) and the trans (LXXX) phenanthrones. Thus in contrast to the 2-ester CXXIX, catalytic hydrogenation

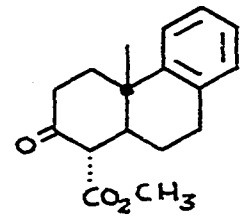
of CXXX gave a mixture of the cis and trans ketoesters CXXXV and CXXXVI, respectively. Therefore catalytic hydrogenation



CXXXIV



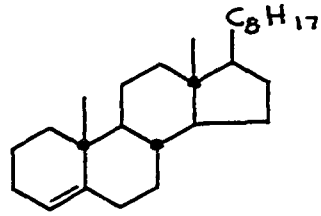
CXXXV



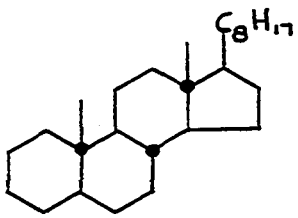
CXXXVI

of the enone ester CXXX gave a product potentially useful for the synthesis of desoxypodocarpic acid.

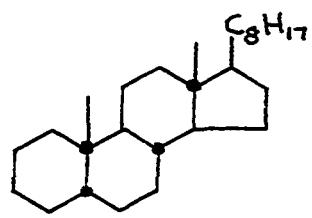
It has been demonstrated that the stereochemistry of catalytic hydrogenation of Δ^4-hydrophenanthrenoid systems is susceptible to changes in the pH of the reduction medium. Δ^4-Cholestene (CXXXVII) was found (71, p. 249) to give cholestane (CXXXVIII) when hydrogenated in an acidic medium in contrast to the formation of coprostane (CXXXIX) when the reduction was carried out in neutral or basic solution.



CXXXVII



CXXXVIII



CXXXIX

Since hydrogenation of CXXX in neutral solution gave a mixture of cis and trans products, the reduction was performed in acid solution in the hope of obtaining high yields of the desired trans ketoester CXXXVI. Addition of a small amount of sulfuric acid to the reduction medium resulted in an 80% yield of the trans ester.

It appears that the presence of a substituent other than hydrogen at C-4 is necessary in order to obtain a predominant yield of trans fused A-B rings when a 4,5-double bond is catalytically hydrogenated in acid medium. When the enone LXXIX was reduced in acid medium with hydrogen and palladium-on-charcoal, an equimolar mixture of the C-5 epimers LXXX and XCVI were obtained. When the same enone was hydrogenated in a basic medium, the cis isomer XCVI was the sole product.

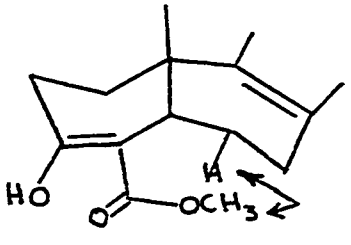
It was observed that the trans ketoester CXXXVI was not enolic as were the other β-ketoesters prepared during the course of this study. The driving force for enolization of β-dicarbonyl systems is twofold: formation of an enol double bond stabilizes the system by its being part of an α,β-unsaturated carbonyl moiety, and intramolecular hydrogen bonding between the enolic hydroxyl and the carbonyl function decreases the unfavorable dipole interactions between these groups.

Since enolization of CXXXVI involves removal of the C-4 hydrogen atom, one possible explanation of this apparent anomaly might be that the C-4 hydrogen is equatorially oriented, in which case its abstraction would be somewhat more difficult than it would be if axially oriented. Abstraction of an axial hydrogen α to a carbonyl group forms a carbanion whose unbonded orbital is coplanar with the π-orbital of the carbonyl group permitting stabilizing overlap. An equatorially oriented orbital must first invert before interaction with the carbonyl group can take place.

When the saturated ester CXXXVI was equilibrated with base, it was recovered unchanged. If the C-4 hydrogen were equatorial, the C-4 carbomethoxyl would be in the thermodynamically unstable axial orientation. Base-catalyzed equilibration of such an axial ester function would isomerize it to the more stable equatorial conformation. The non-isomeriza-

tion of CXXXVI indicates that the C-4 hydrogen is axially oriented and that enolization is not precluded by the conformation of the C-4 hydrogen.

Examination of a model of CXXXVI shows that the C-6 hydrogen atom interferes with free rotation of the peri C-4 carbomethoxyl group forcing the ester carbonyl group out of the plane of the enol double bond. Resonance involving the α,β-unsaturated carbonyl group would then be minimized. Furthermore the hydrogen bonded ester has a poor steric interference between the ester methoxyl and the C-6 hydrogen as shown in structure CXXXX. Cis fusion of the A and B rings

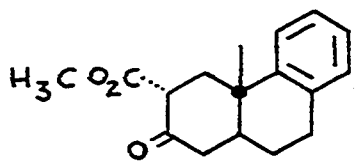


CXXX

removes this peri interaction. It is interesting to note that this is the second case encountered where such a peri non-bonded interaction gives rise to an apparently anomalous situation. The non-enolic character of the diketone CXII was rationalized in a similar fashion.

Another possible route to the ketoester CXXXVI would be carbonation of the trans phenanthrone LXXX. When this ketone

was carbonated using the procedure of Cardwell et al. (70), the major product was the trans 2-carbomethoxy compound CXXXI. Only a small amount (6%) of the isomeric 4-ester (CXXXVI) was produced.



CXLI

The product composition from the two carbonation reactions gives some insight into the nature of the transition state of proton removal from the ketones with triphenylmethyl anion. If, in the case of the anone LXXX, the transition state had appreciable enolate anion character, then one would expect the most stable enolate ion to be formed. On the other hand, if the transition state has more character of the starting material, then the enolate anions formed would be the products of abstraction of the most acidic proton, and both possible enolate anions would be formed with equal probability. Leffler (72-73, p. 221) has pointed out that when proton removal is fast as in the case of the use of a strong base like triphenylmethyl anion, then that enolate anion is formed which has the most acidic proton.

It has been demonstrated (71, p. 262) that enolization of

enolization of 3-ketones in hydrophenanthrene systems containing trans fused A and B rings occurs preferentially in the 2,3-direction rather than in the 3,4-direction. Since the preponderant product from carbonation of the ketone LXXX resulted from a 2-enolate anion, the more stable of the two possibilities, the transition state had considerable enolate anion character.

The acidity of the hydrogens which could be abstracted from the enone LXXIX however are not equal. Due to the proximity of the carbonyl group, the 2-hydrogen is more acidic than the 6-hydrogen. On the other hand, the enolate anion resulting from proton loss at C-6 is more stable because of greater resonance stabilization, the negative charge being distributed over the carbons at C-4 and C-6 as well as the ketonic oxygen. The ratio of products from the carbonation of LXXIX was four to three in favor of the 4-ester. Since the 4-ester was derived from the most stable enolate anion, it appears the transition state of proton removal again had appreciable enolate anion character.

While irreversible conditions were used to produce the enolate anions described above, there is a short time (one minute or less) during the addition of triphenylmethyl anion to the ketone when the enolate anion is in contact with unreacted ketone. Such a condition could possibly lead to an equilibrium mixture of enolate anions regardless of the

transition state of proton removal. The product composition from the carbonation of the anone LXXX could be equally well explained by equilibrium considerations since an equilibrium mixture would be composed principally of the most stable enolate anion.

That complete equilibrium was never attained was evidenced by the results from the carbonation of the unsaturated ketone LXXIX. The methylation of cholestenone (CXXVII), reported by Woodward et al. (69), resulted in methylation only at C-4. Since this reaction formed solely the thermodynamically most stable anion (by proton removal at C-6), it was probable that such anion formation was the result of complete equilibration of the two possible enolate anions. The isolation of the 2-carbomethoxyl ester CXXIX from the carbonation of LXXIX thus precludes complete equilibration.

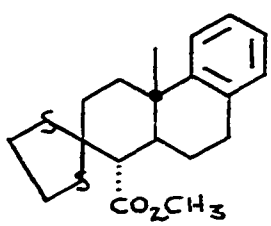
The synthesis of dl-desoxypodocarpic acid from the enone ester CXXX may be accomplished, a priori, by several reaction paths. Since the synthesis is to be accomplished in a stereospecific manner, the 4,5-double bond must be reduced to give an A-B trans ring fusion. Introduction of the methyl group at C-4 must be done so that the methyl group enters the A ring on the side opposite to the C-10 methyl group. Since the A-B trans ring system must have an axial C-10 methyl group, attack at C-4 in such a molecule would not occur axially because of the strong 1,3-diaxial interaction between the C-10

methyl and the attacking reagent.

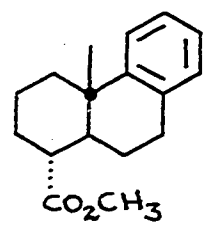
Removal of the C-3 ketone function from the trans ester CXXXVI via ethylenethioketal formation (74-75) and Raney nickel desulfurization (76) would give an ester which would yield dl-methyl desoxypodocarpate (LXXXIV) after methylation at C-4.

The ketoester did form a thioketal (CXLII) which gave rise to ester CXLIII upon treatment with Raney nickel. Whereas the ester CXLIII was a liquid it was characterized by hydrolysis to the solid crystalline acid CXLIV. However, methylation of this ester could not be accomplished.

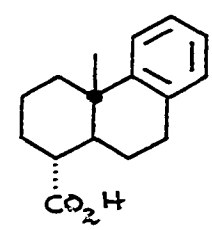
Non-methylation of this ester may be due to either of two factors: a low concentration of enolate anion due to incomplete proton abstraction by the base employed (potassium t-butoxide) or a slow rate of methylation of enolate anion



CXLII



CXLIII



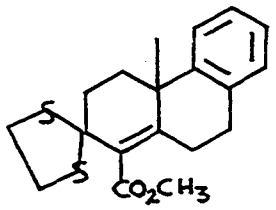
CXLIV

compared to the rate of methylation of t-butoxide anion. Since methylation of the anion from CXLIII results in the C-4 carbomethoxy function being pushed into an axial orientation as the methyl iodide is being attacked, the 1,3-diaxial

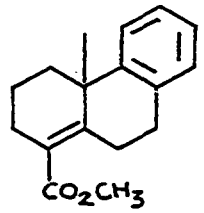
interaction of the C-10 methyl and the C-4 carbomethoxy might be sufficient to decrease the rate of attack on methyl iodide by ester anion so that the rate of t-butoxide attack upon methyl iodide becomes the predominant reaction.

If the non-methylation of the ester CXLIII is due to the latter of the two possible reasons, then use of an ester in which the steric effect of the C-10 methyl group is somewhat diminished might be the solution to the methylation problem. One cannot decrease the steric control of the methyl group too far or else stereoelectronic control of the stereochemistry of methylation will occur. Johnson (77) and Johnson and Allen (78) have demonstrated that attack on enolate anions occurs axially in the absence of steric factors. Such as axial attack on any ester similar to CXLIII would give rise to an ester possessing the abietic stereochemistry (cf. structure XCII).

The unsaturated ester CXLV was obtained by Raney nickel treatment of the thioketal CXLVI which in turn was prepared from ethanedithiol and the enone ester CXXX. The olefinic ester CXLV would fit the requirements outlined above for an ester in which the steric effect of the C-10 methyl group is slightly reduced. The 4,5-double bond causes the C-10 methyl group to be pseudo-axially oriented thus causing less interference with substitution at C-4.



CXLV



CXLVI

Since it is known (79) that ketal formation from Δ^4-3-ketosteroids occurs with concomitant migration of the double bond to the 5,6-position, it is pertinent to examine the thioketal CXLVI to determine whether or not an analogous double bond migration had occurred. The infrared spectrum of this compound shows carbonyl absorption at 5.82 μ. This slight shift from the usual saturated ester band at 5.78 μ is indicative of a conjugated ester. The strong end absorption in its ultraviolet spectrum also suggests that the double bond had not migrated. The ester CXLV likewise possessed the same spectral properties.

An attempt to characterize the liquid ester failed when the acid obtained by hydrolysis of the ester could not be crystallized.

Methylation of the olefinic ester was attempted using potassium t-butoxide and methyl iodide. The infrared spectrum of the crude methylation product indicated that some methylation had occurred, the carbonyl stretching absorption

having dropped from 5.82μ to 5.78μ indicating that the double bond had shifted out of conjugation as would have been expected in the methylated product. However no substance having the spectral characteristics of the desired ester could be isolated from the crude reaction mixture.

Methylation of the trans ketoester and subsequent removal of the C-3 carbonyl group would probably yield dl-methyl desoxypodocarpate. This reaction sequence followed by a reductive hydrolysis of the dl-desoxy ester is suggested as an alternate synthetic route to dl-desoxypodocarpic acid.

SPECTRA

Ultraviolet spectra were run in 95% ethanol using a Beckman model DU quartz spectrophotometer. All infrared absorption spectra were recorded using a Baird Double Beam infrared spectrophotometer. Special thanks are due the Institute for Atomic Research, Iowa State College, for the use of the infrared spectrophotometer.

Fig. 1 Ultraviolet Spectra.

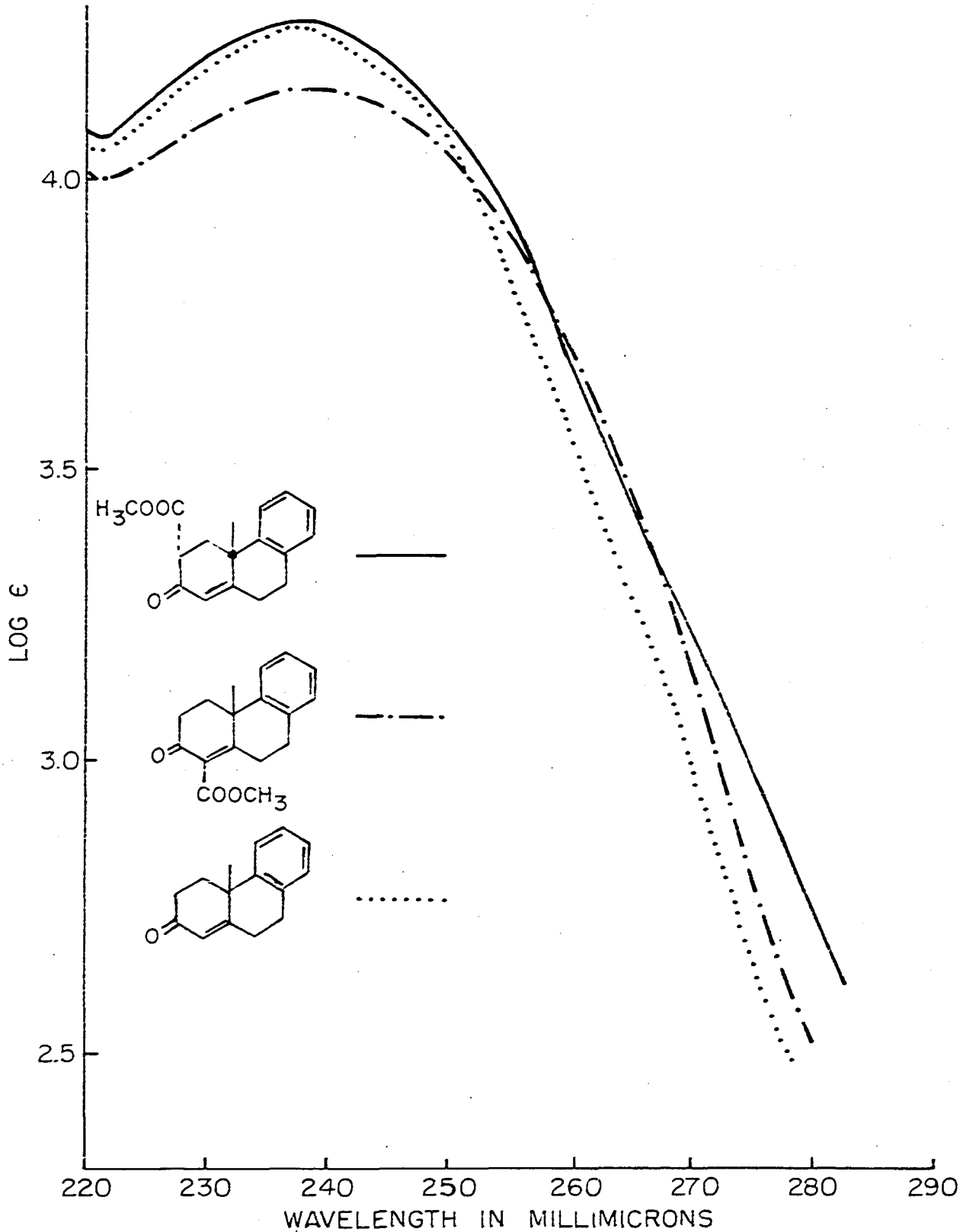

4.0
3.5
3.0
2.5
LOG ε
H3COOC
O
O
COOCH3
O
220
230
240
250
260
270
280
290
WAVELENGTH IN MILLIMICRONS

Fig. 2 Ultraviolet Spectra.

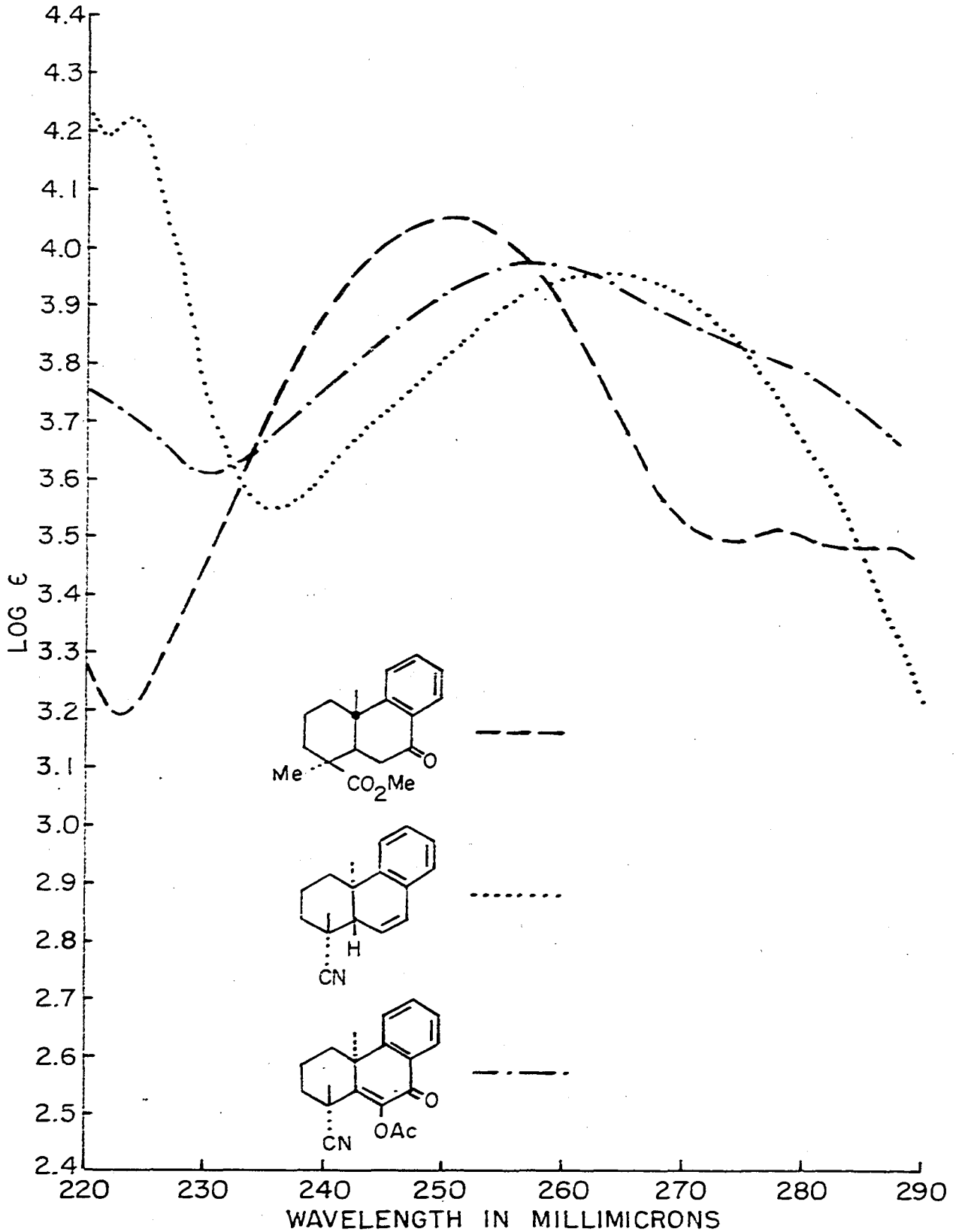

4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
LOG ε
220
230
240
250
260
270
280
290
WAVELENGTH IN MILLIMICRONS
Me
CO2Me
O
H
CN
CN
OAc
O

Fig. 3 Ultraviolet Spectra.

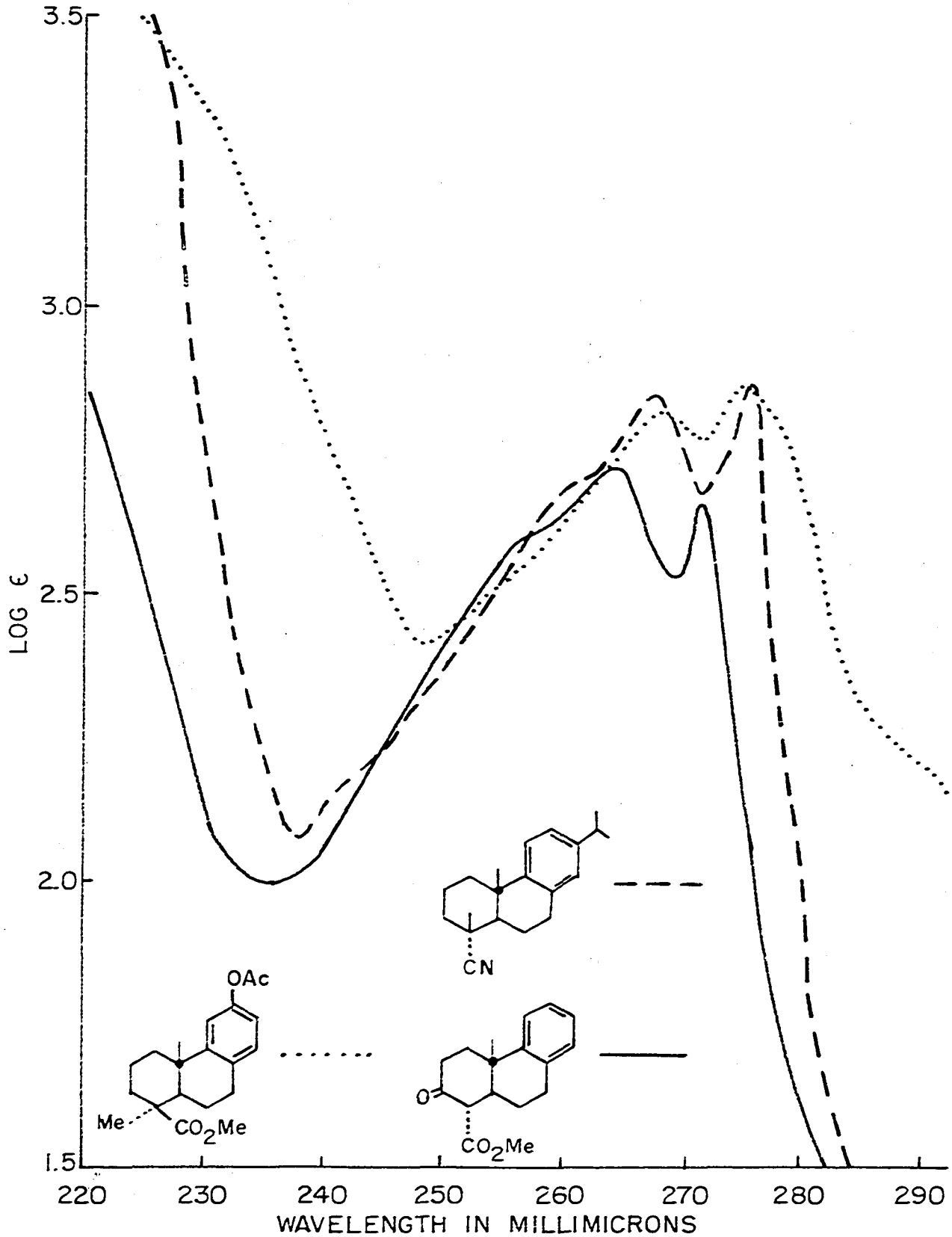

3.5
3.0
2.5
2.0
1.5
LOG ε
220
230
240
250
260
270
280
290
WAVELENGTH IN MILLIMICRONS
CN
OAc
Me
CO2Me
O
CO2Me

Fig. 4 Ultraviolet Spectra.

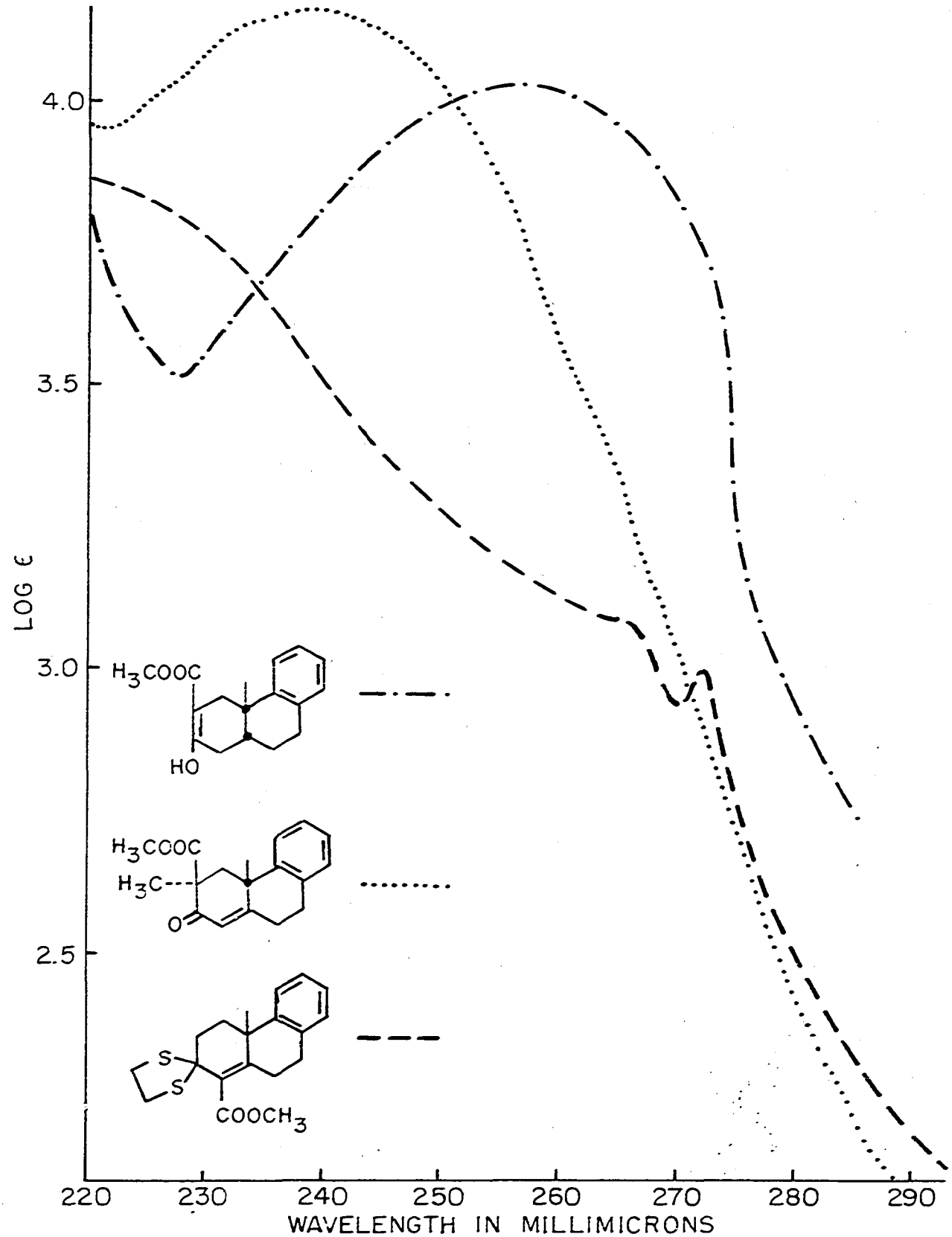

4.0
3.5
3.0
2.5
LOG ε
H3COOC
HO
H3COOC
H3C
O
S
S
COOCH3
220
230
240
250
260
270
280
290
WAVELENGTH IN MILLIMICRONS

Fig. 5 Ultraviolet Spectra.

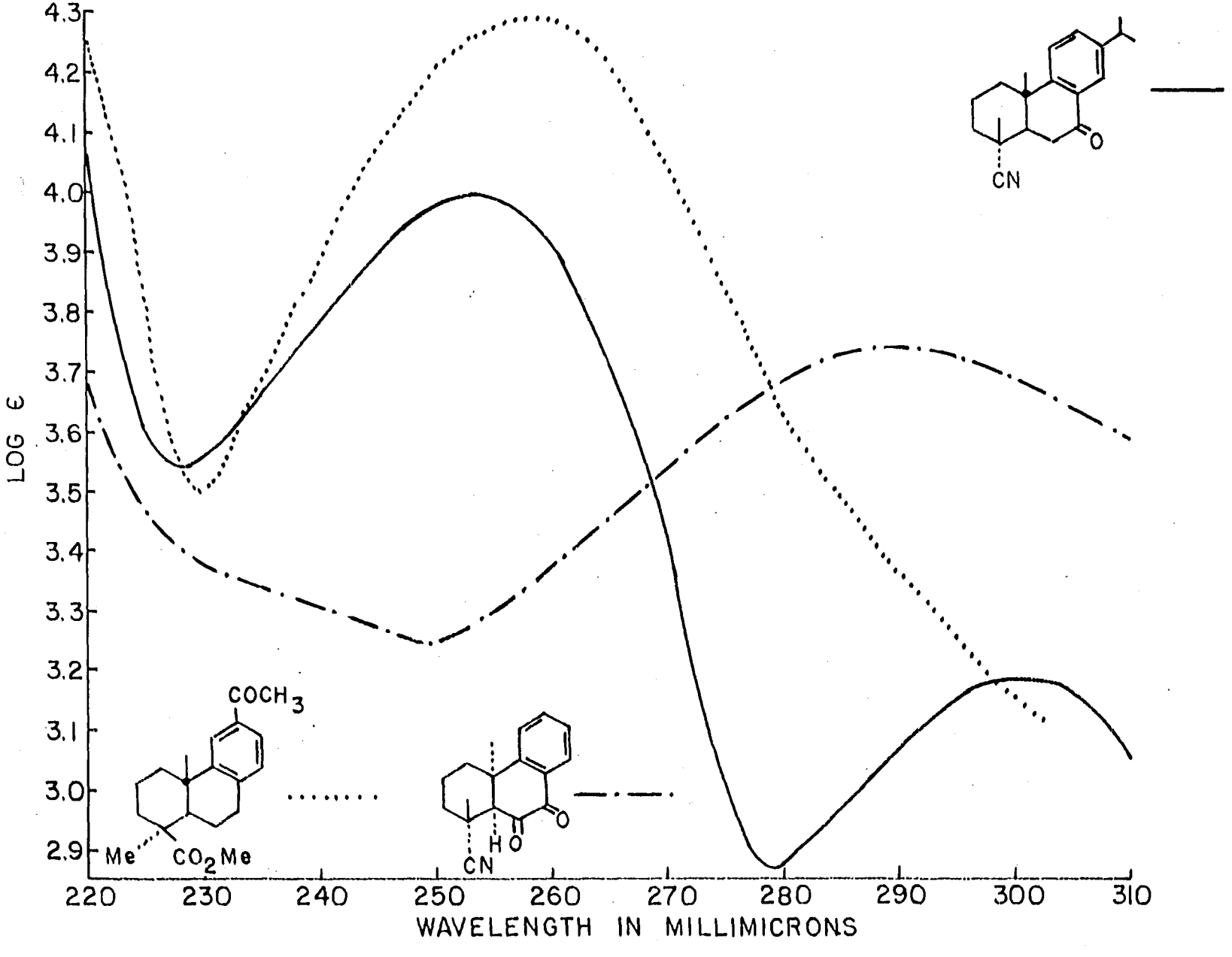
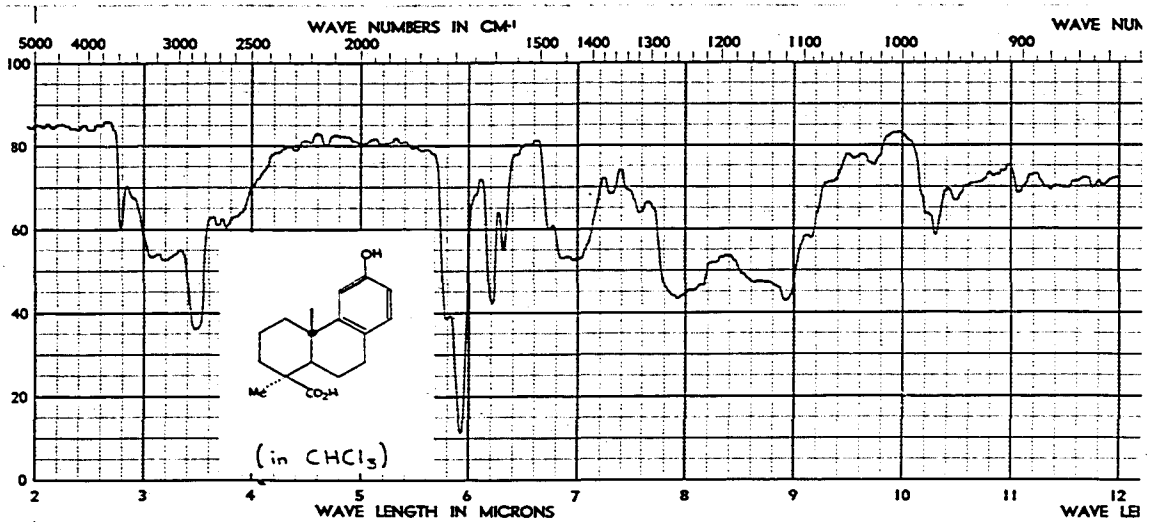
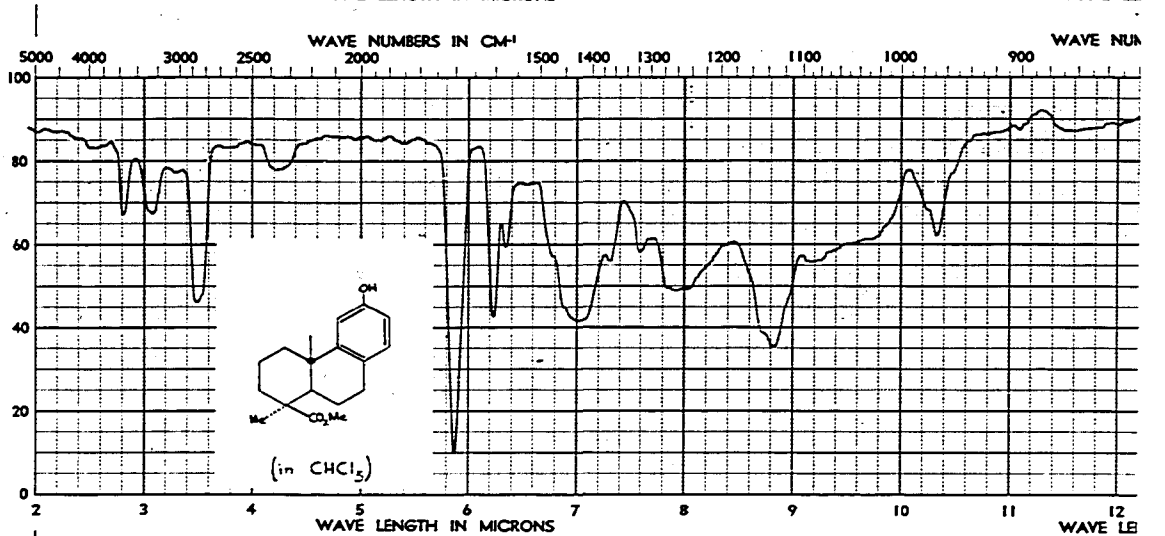

LOG ε
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
220
230
240
250
260
270
280
290
300
310
WAVELENGTH IN MILLIMICRONS
COCH3
Me
CO2Me
CN
H
O
O
CN

Fig. 6 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
OH
Me
CO2H
(in CHCl3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
OH
Me
CO2Me
(in CHCl3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

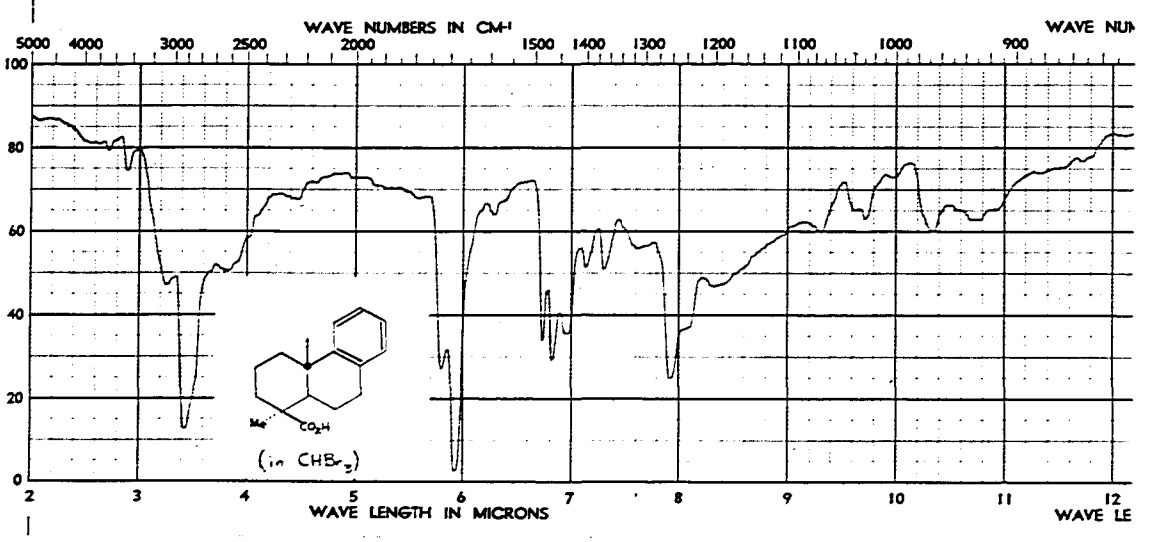
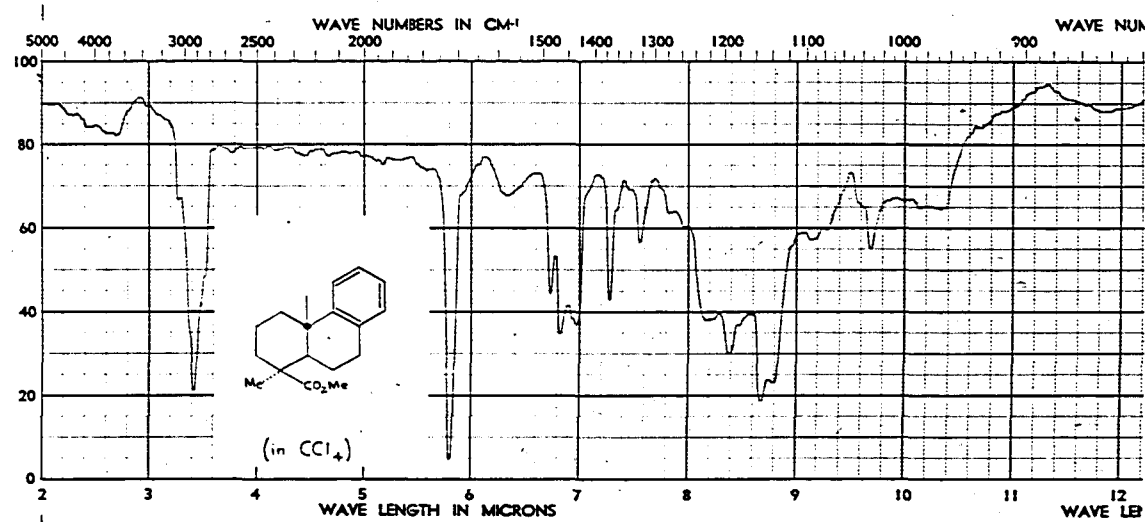
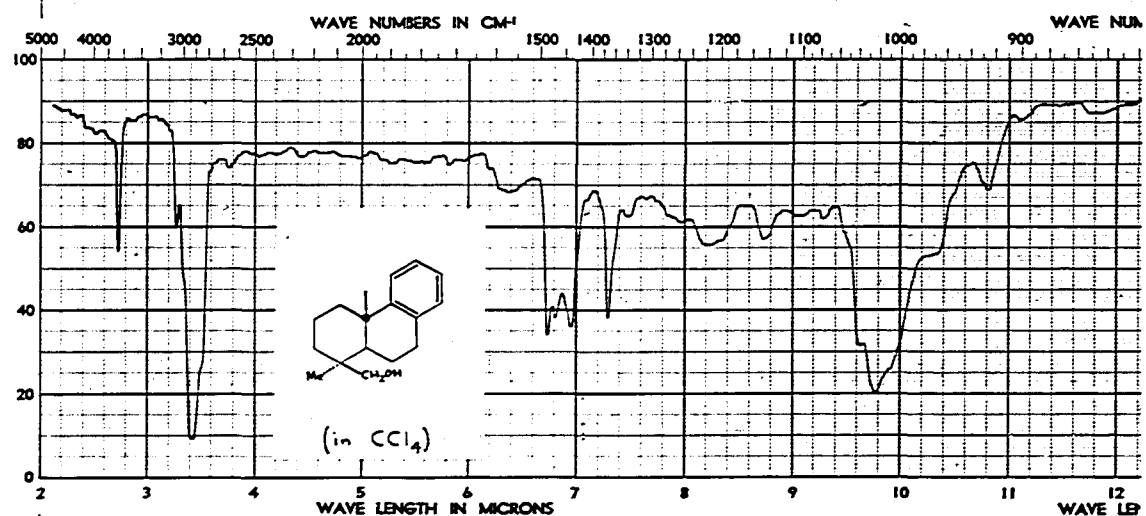

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me
CO2H
(in CHBr3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

Fig. 7 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me CO2Me
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me CH2OH
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

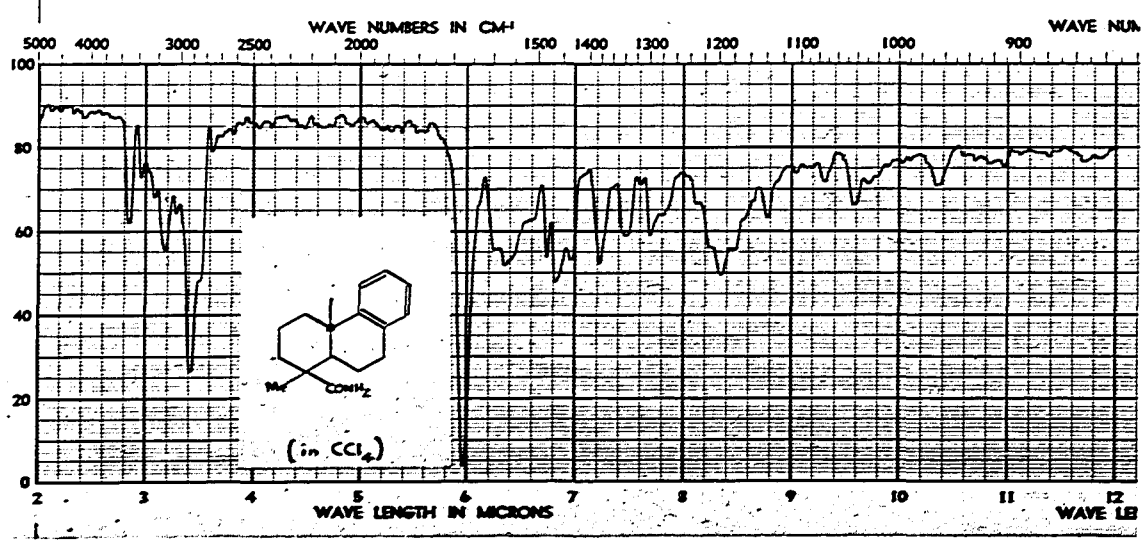
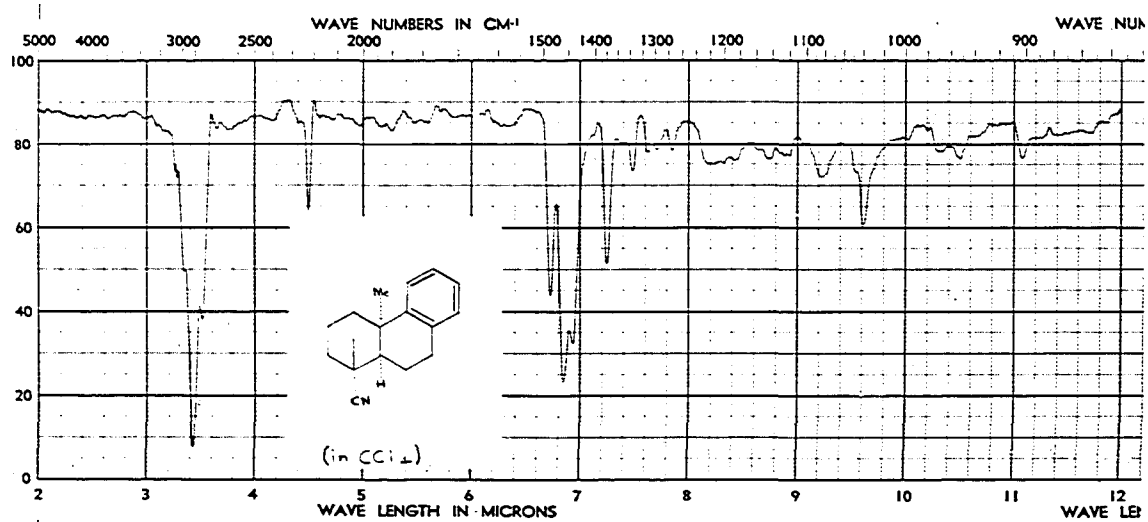
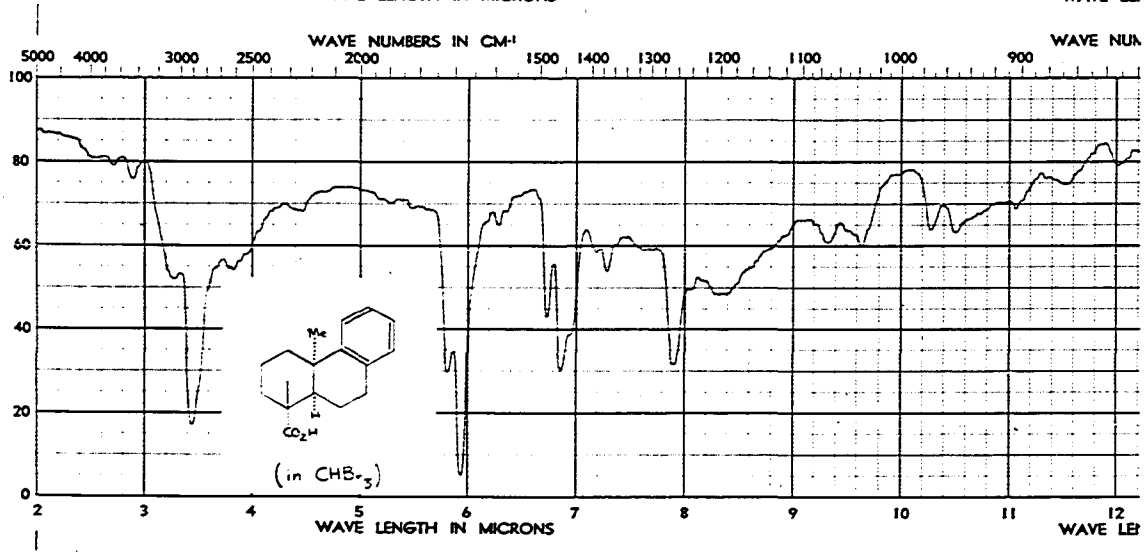

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me CONH2
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

Fig. 8 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me
H
CN
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me
H
CO2H
(in CHBr3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

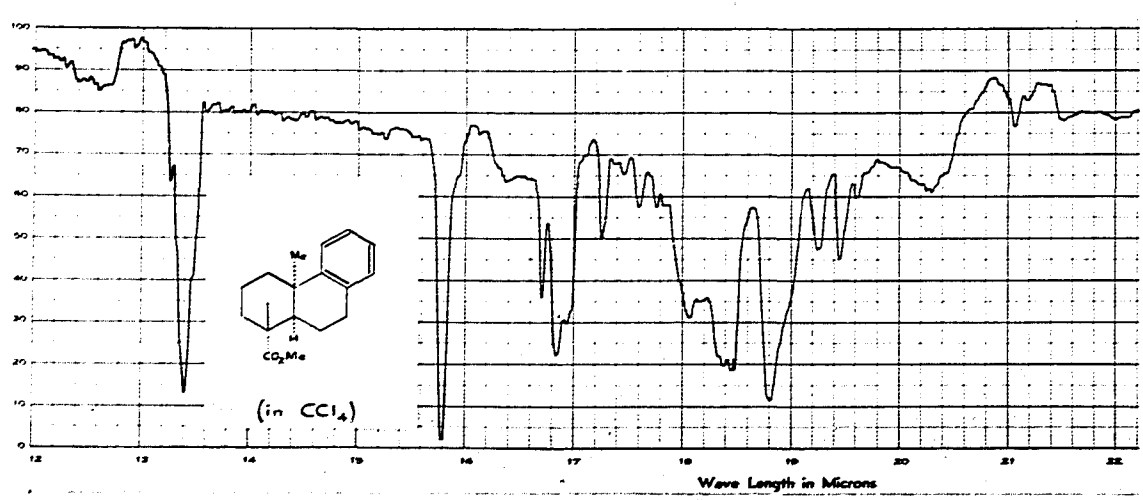
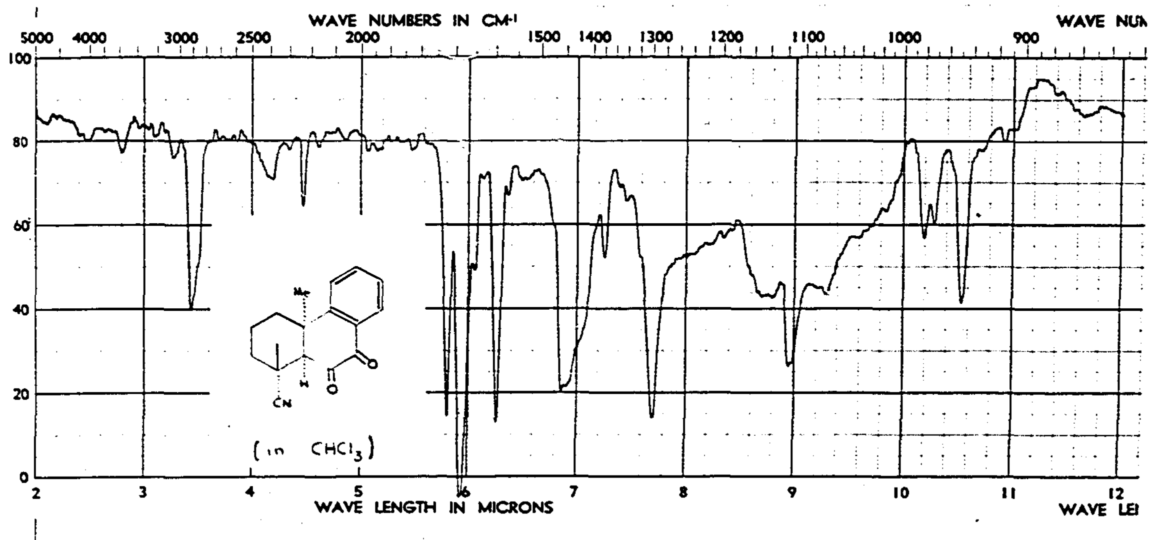
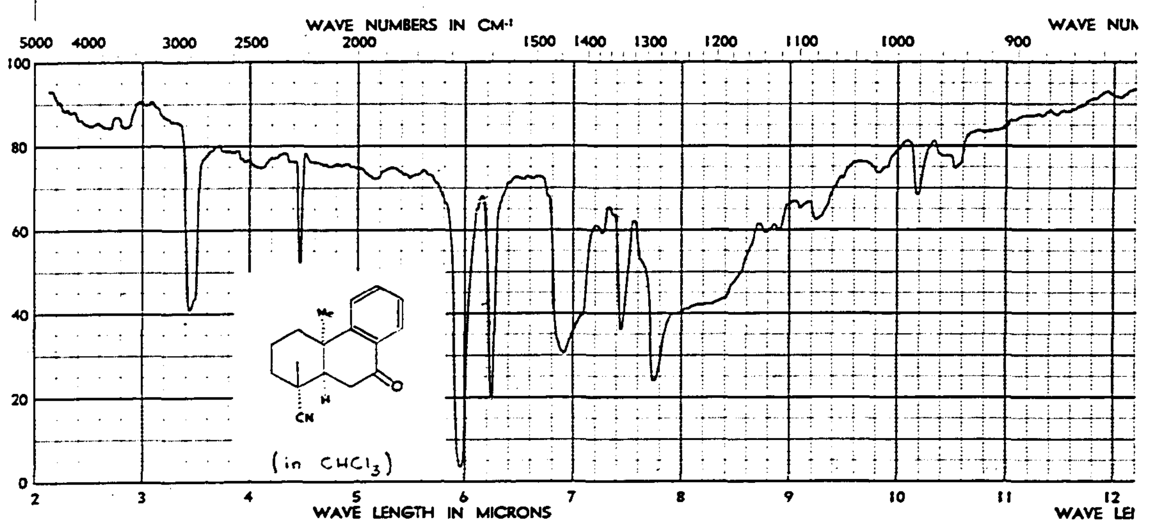

Me
H
CO2Me
(in CCl4)
Wave Length in Microns

Fig. 9 Infrared Spectra.


WAVE NUMBERS IN CM-1
WAVE NUMBERS
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me
H
CN
(in CHCl3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LENGTH


WAVE NUMBERS IN CM-1
WAVE NUMBERS
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
Me
H
CN
(in CHCl3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LENGTH

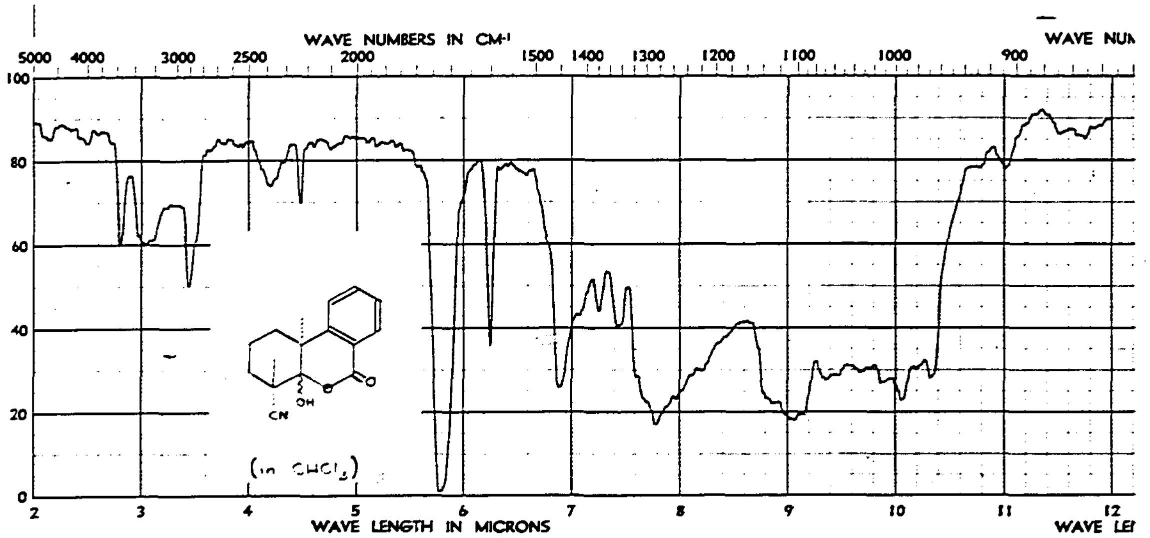
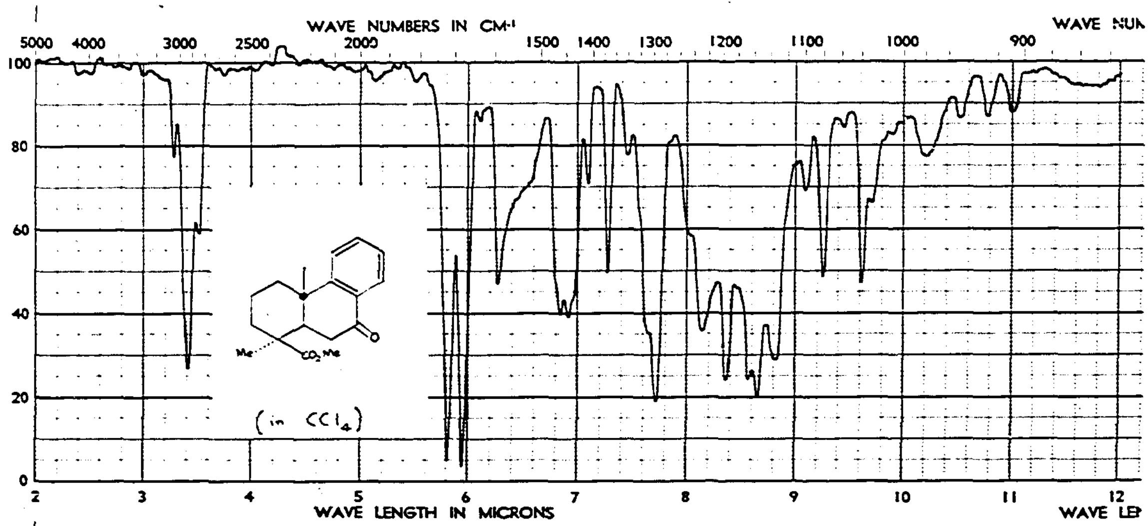
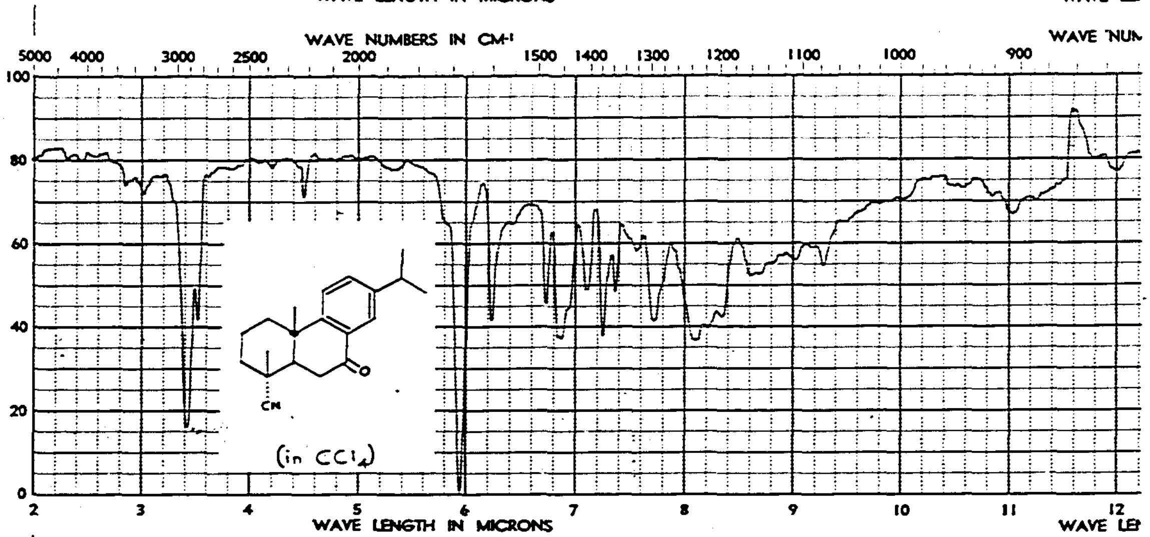

WAVE NUMBERS IN CM-1
WAVE NUMBERS
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
OH
CN
(in CHCl3)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LENGTH

Fig. 10 Infrared Spectra.


WAVE NUMBERS IN CM-1
WAVE LENGTH IN MICRONS
(in CCl4)


WAVE NUMBERS IN CM-1
WAVE LENGTH IN MICRONS
(in CCl4)

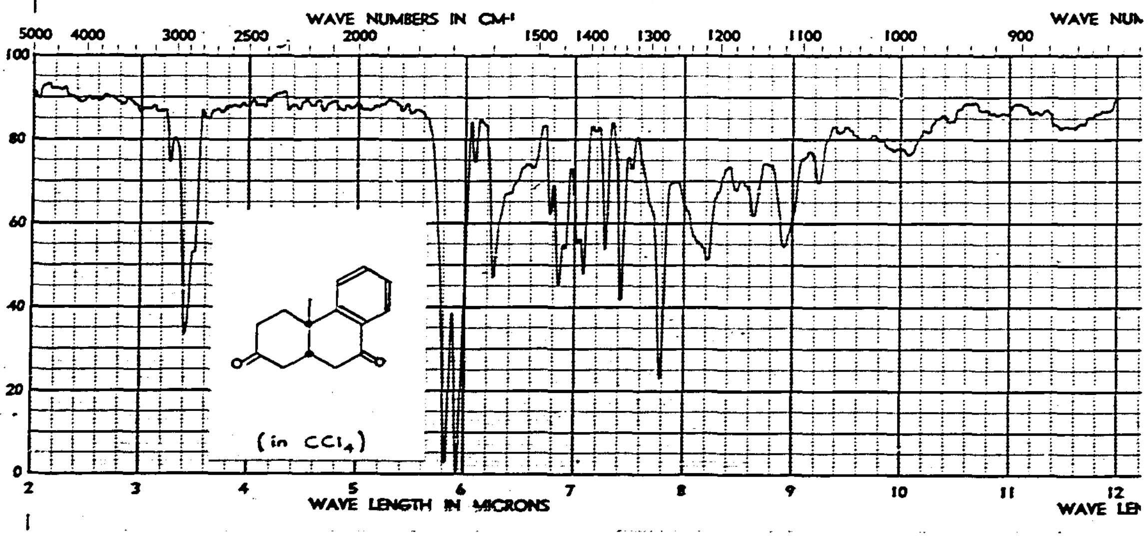
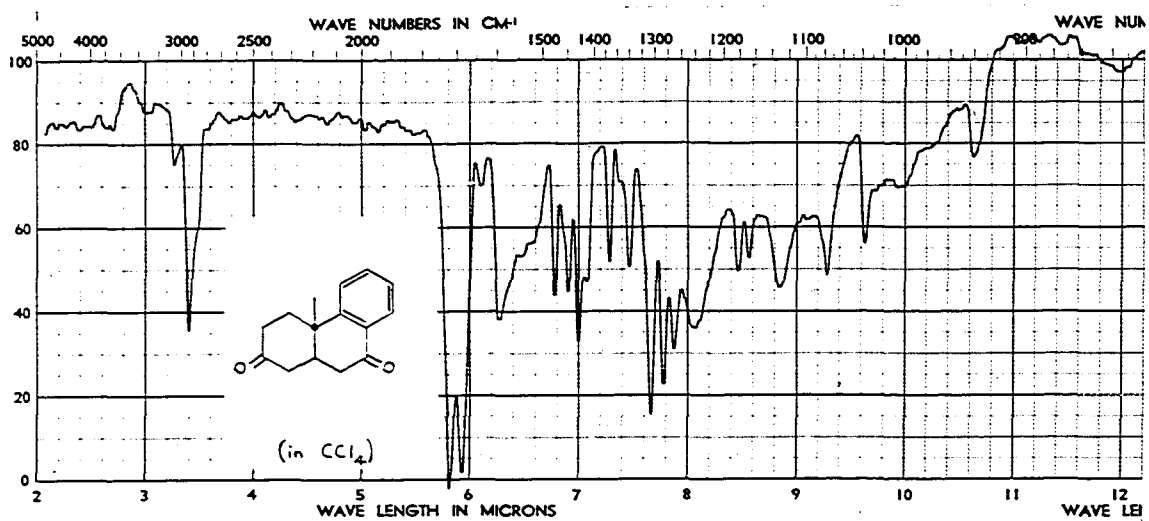
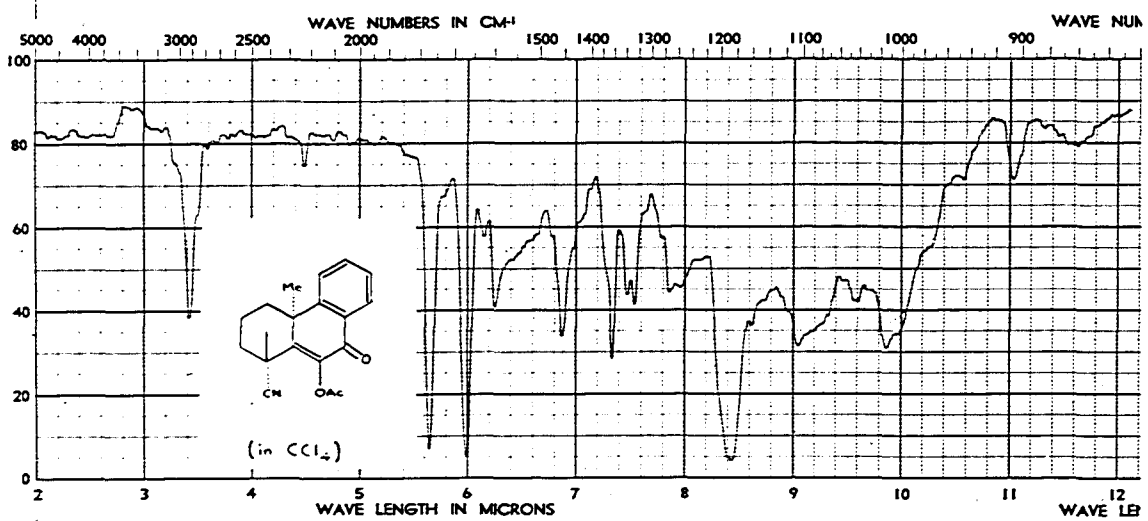

WAVE NUMBERS IN CM-1
WAVE LENGTH IN MICRONS
(in CCl4)

Fig. 11 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000
WAVE NUM
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LEN
(in CCl4)


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
WAVE NUM
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LEN
Me
CN
OAc
(in CCl4)

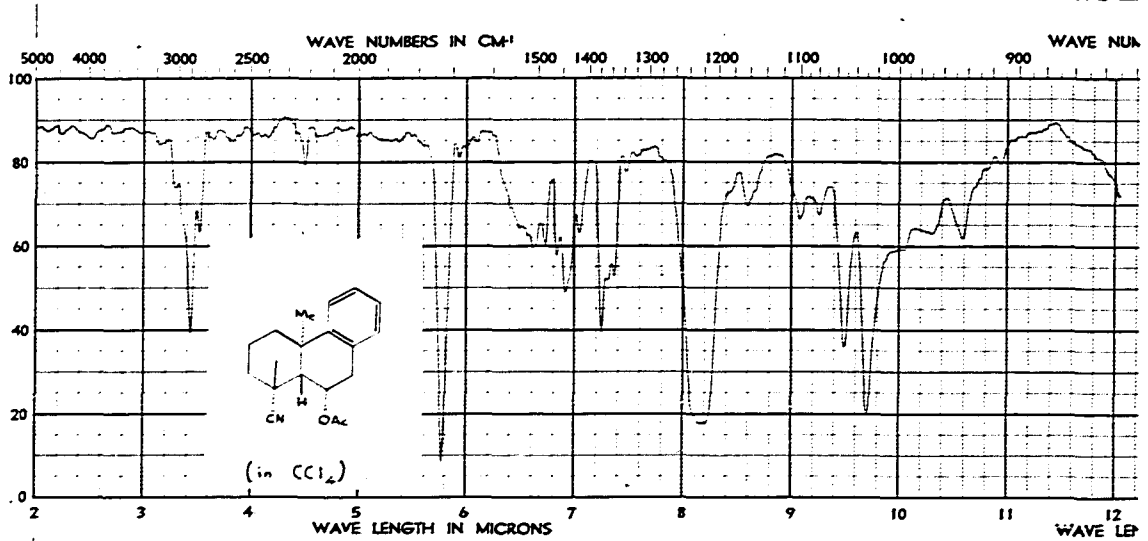
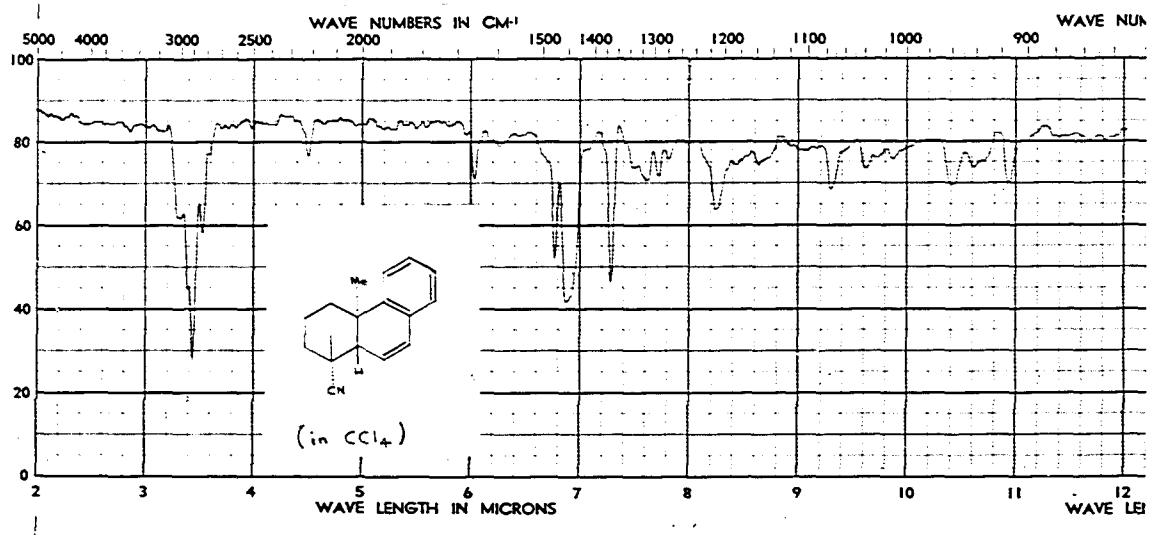
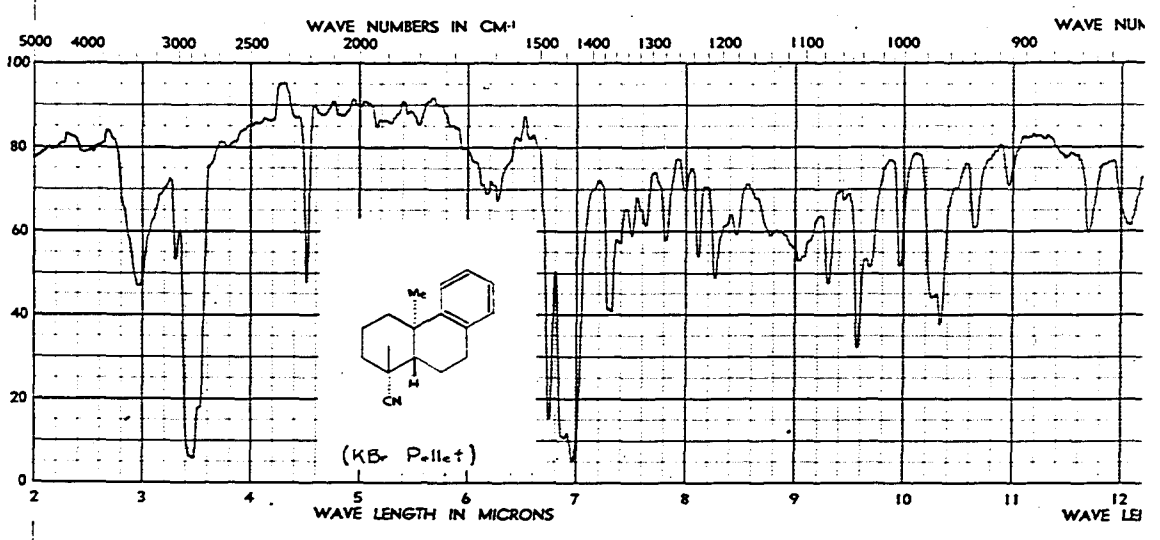

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
WAVE NUM
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE LEN
Me
H
CN
OAc
(in CCl4)

Fig. 12 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
Me
H
CN
(in CCl4)


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
Me
H
CN
(KBr Pellet)

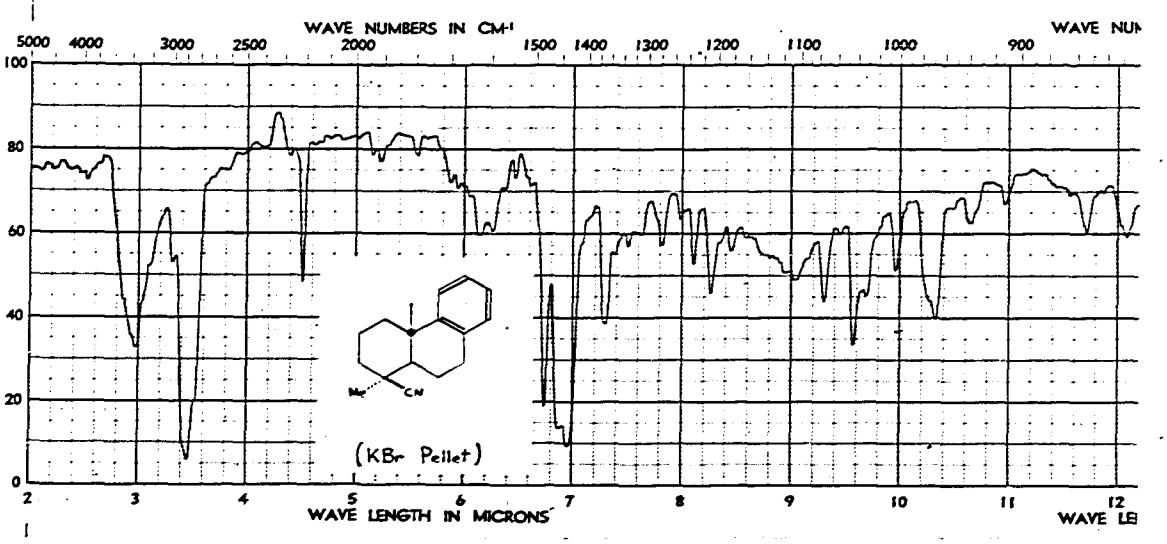
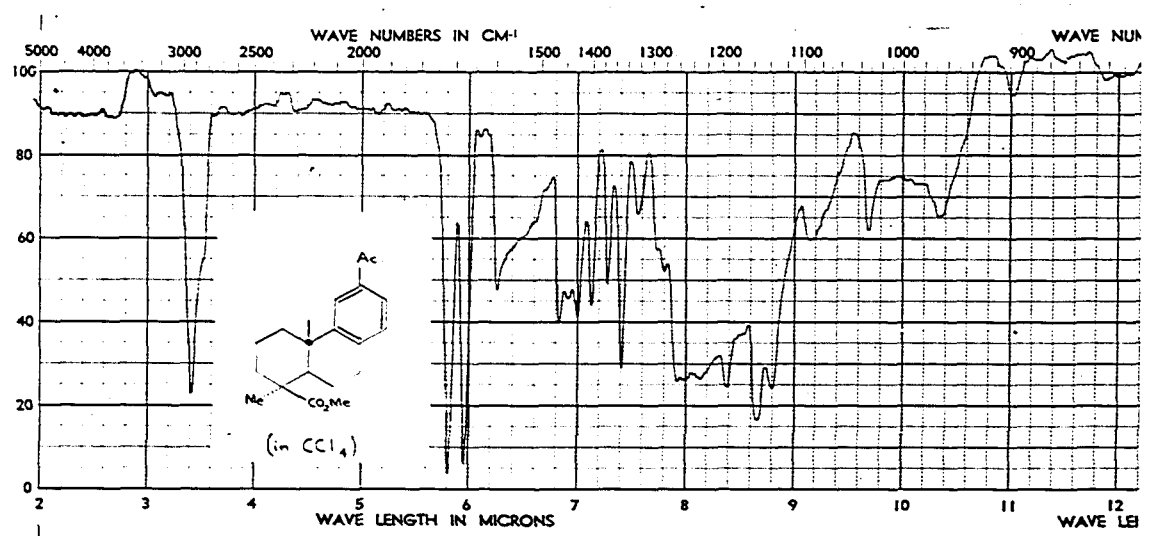
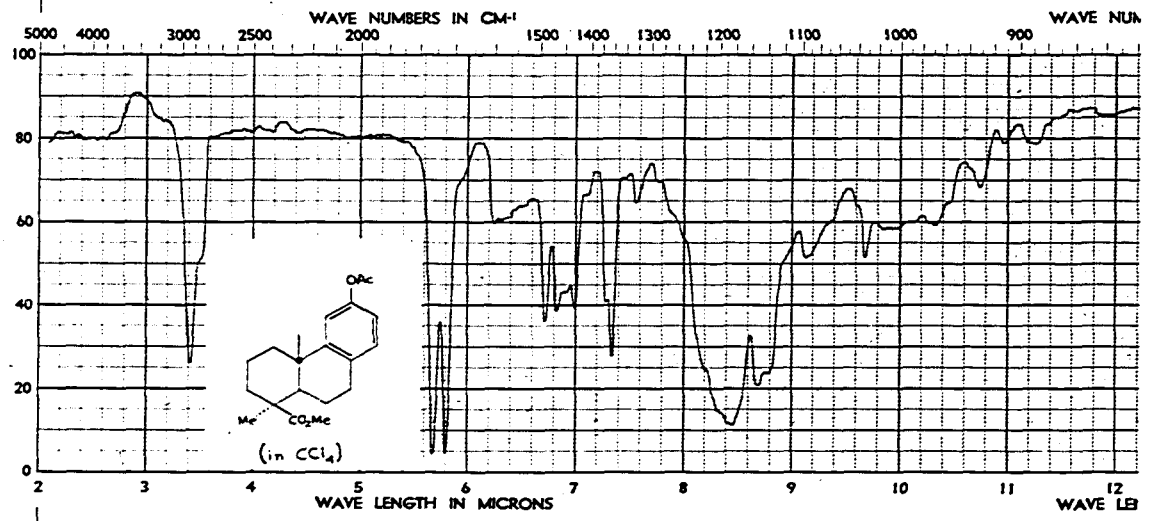

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
Me
CN
(KBr Pellet)

Fig. 13 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100
80
60
40
20
0
Ac
Me
CO2Me
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100
80
60
40
20
0
OAc
Me
CO2Me
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

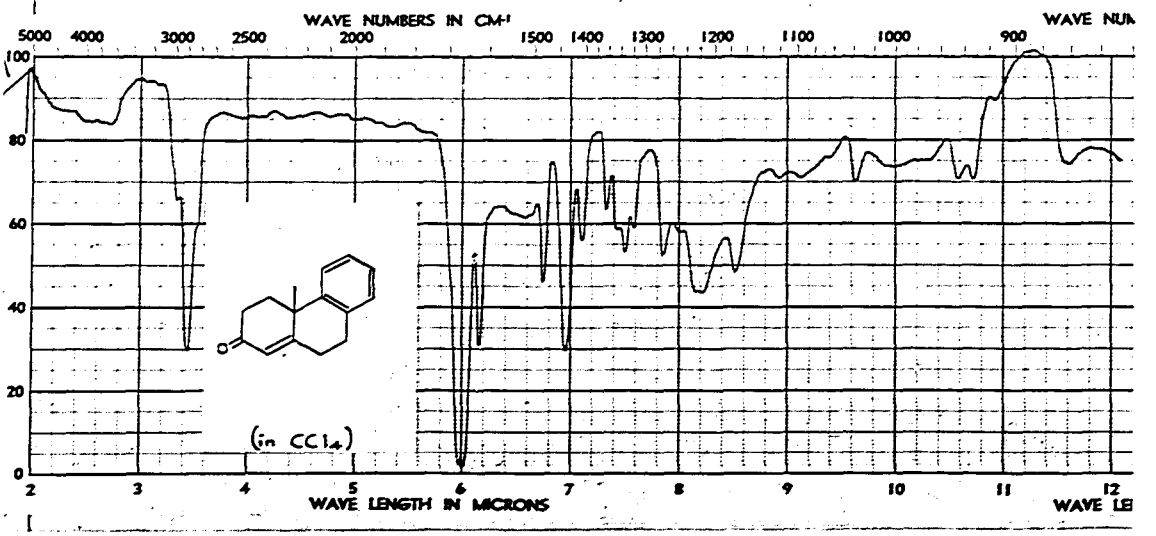
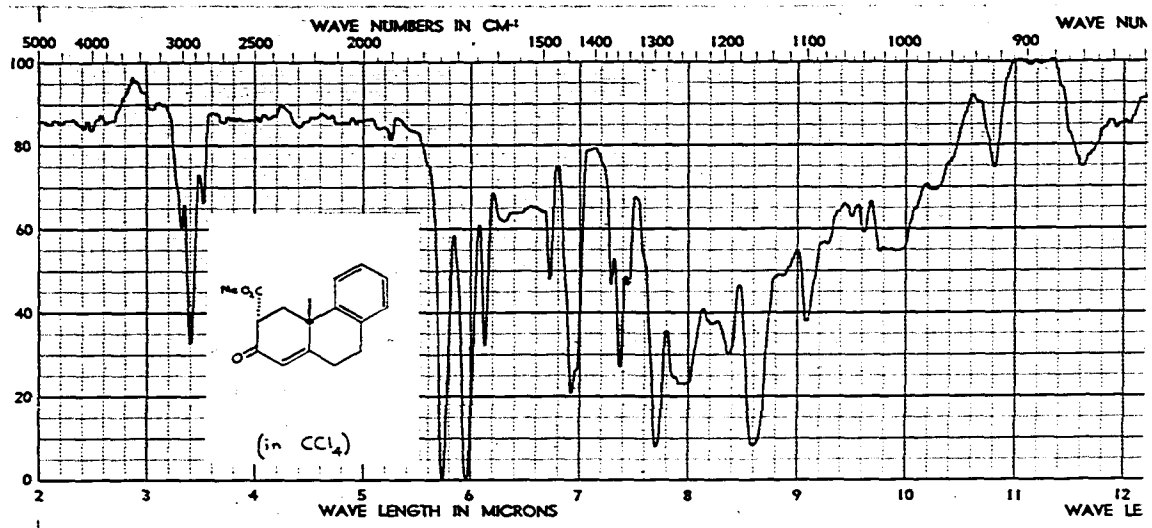
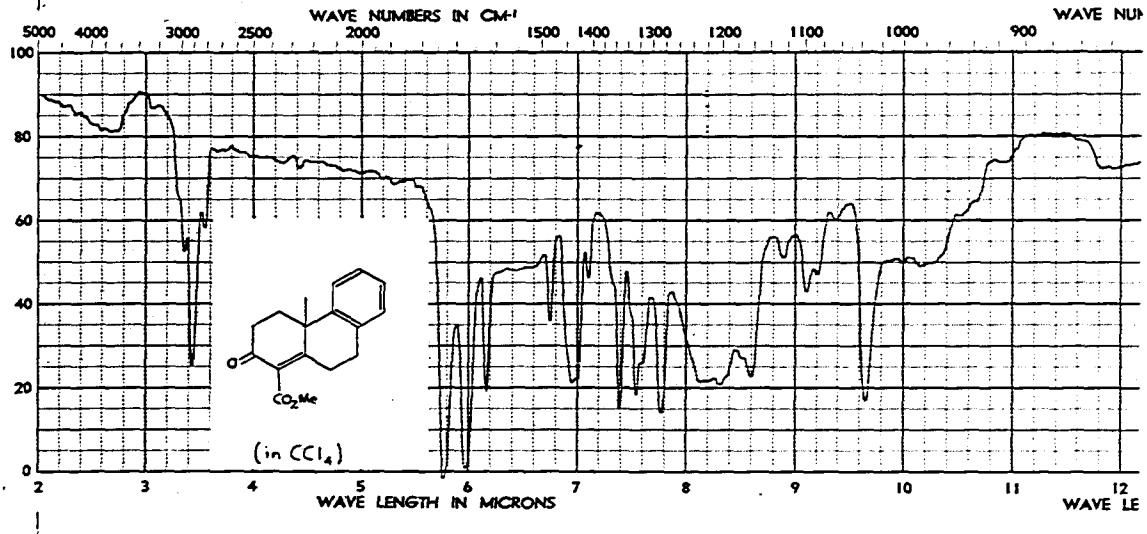

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100
80
60
40
20
0
O
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS

Fig. 14 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
(in CCl_4)


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO_2Me
(in CCl_4)

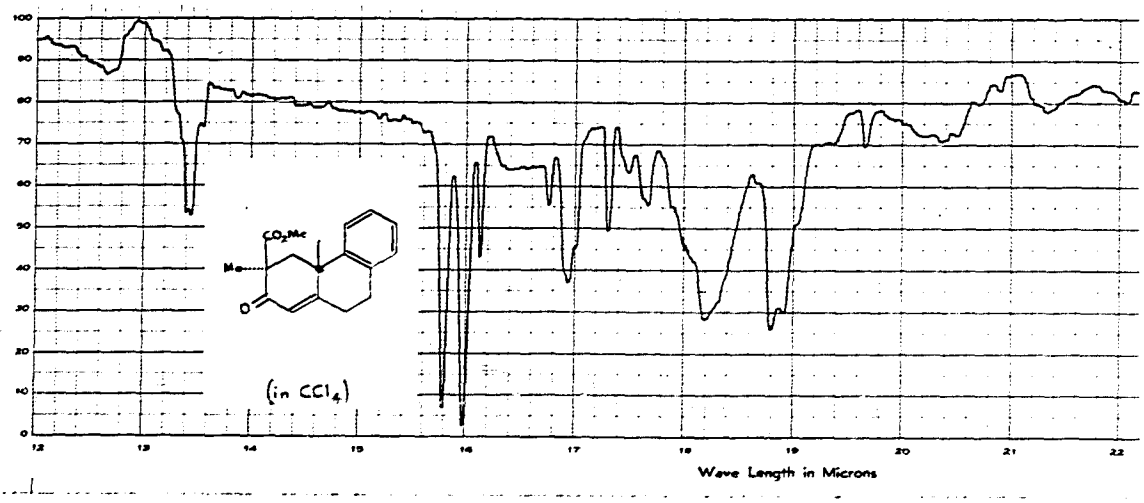
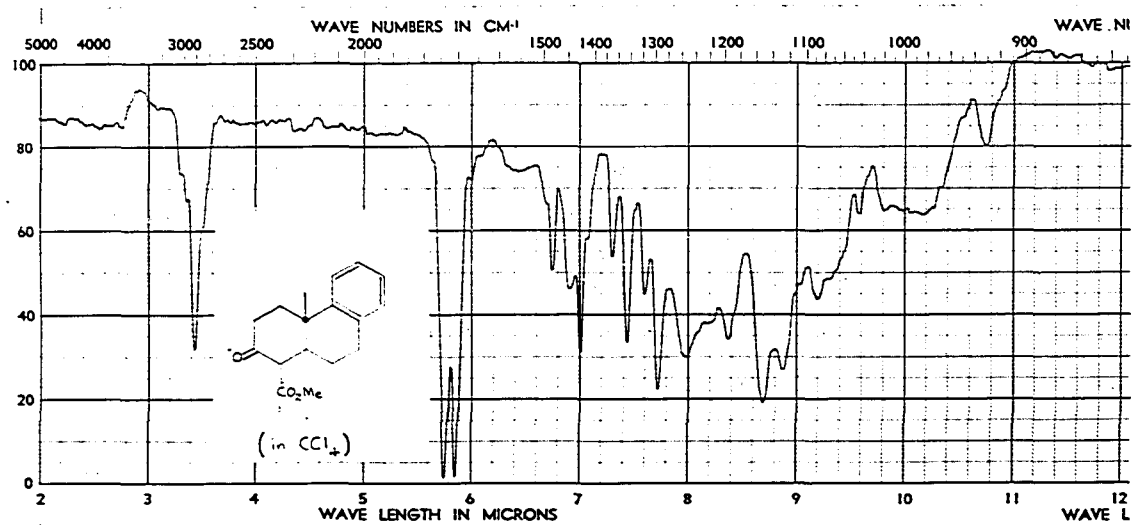
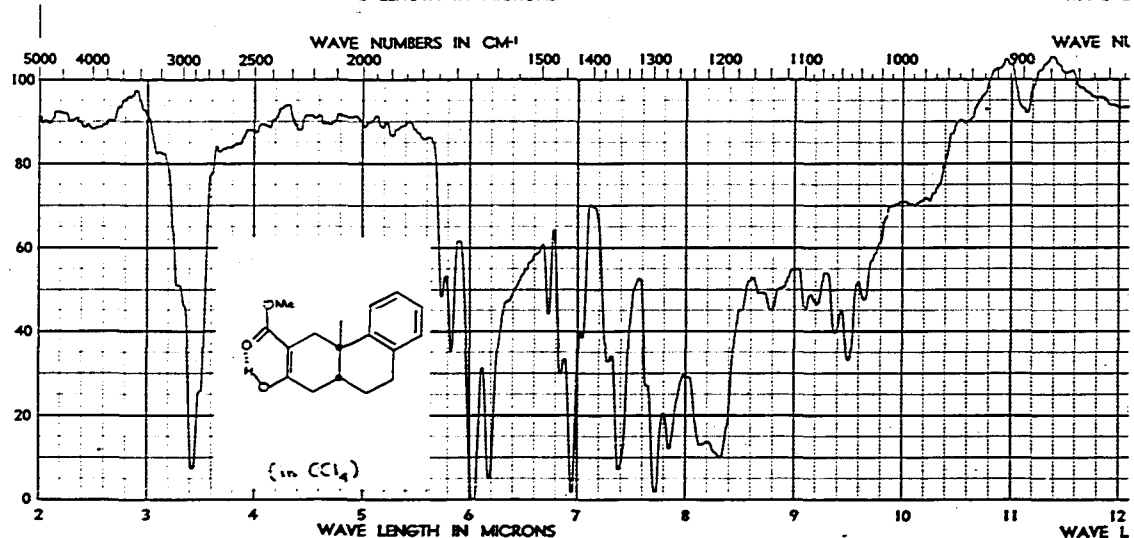

100 90 80 70 60 50 40 30 20 10 0
12 13 14 15 16 17 18 19 20 21 22
Wave Length in Microns
CO_2Me
Me
O
(in CCl_4)

Fig. 15 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO2Me
(in CCl4)


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
OMe
(in CCl4)

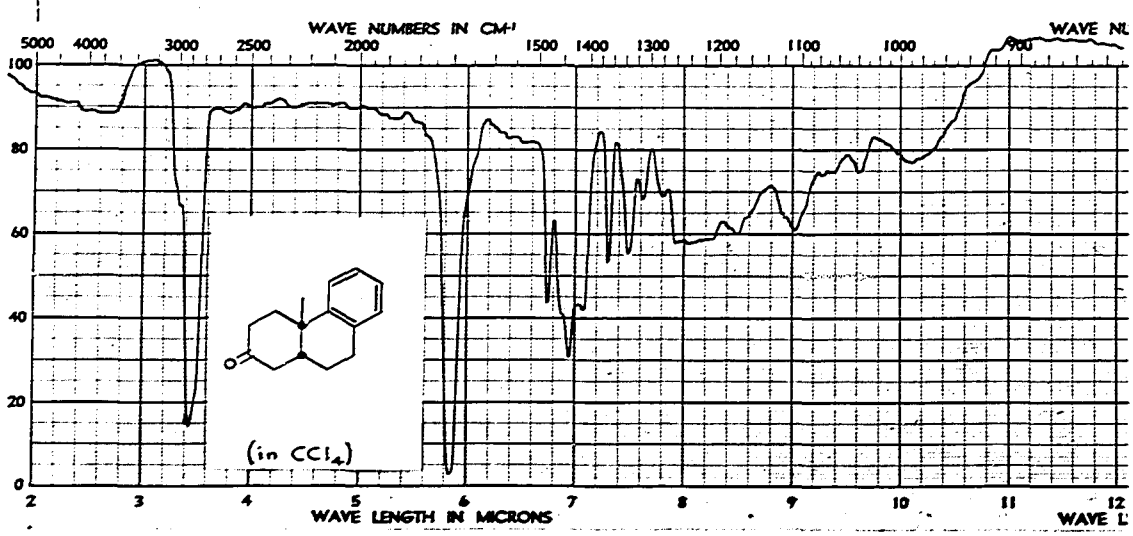
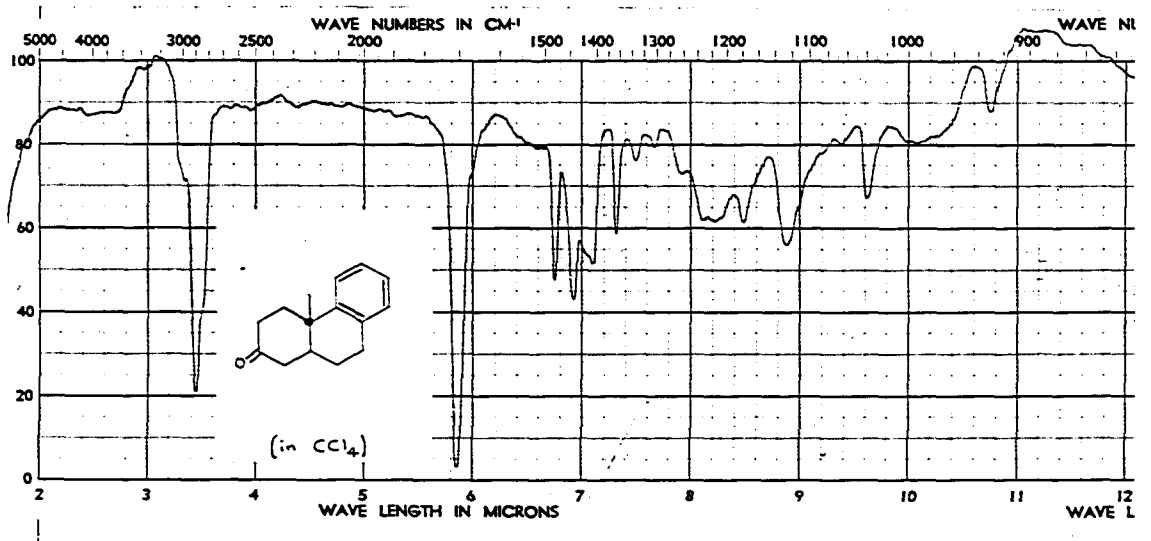
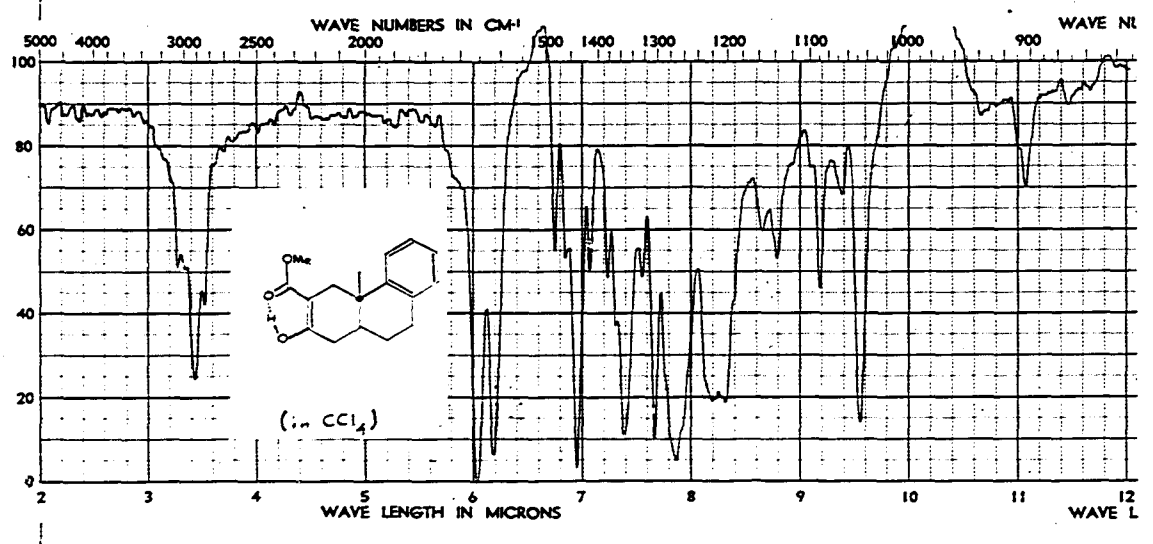

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
(in CCl4)

Fig. 16 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
WAVE NU
100 80 60 40 20 0
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE L


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
WAVE NU
100 80 60 40 20 0
OMe
H
O
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE L

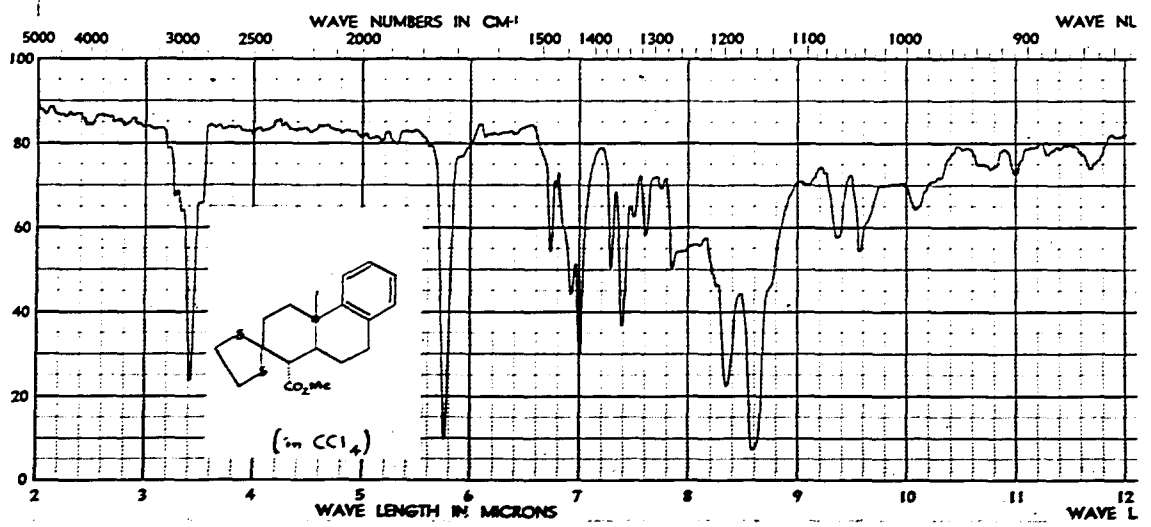
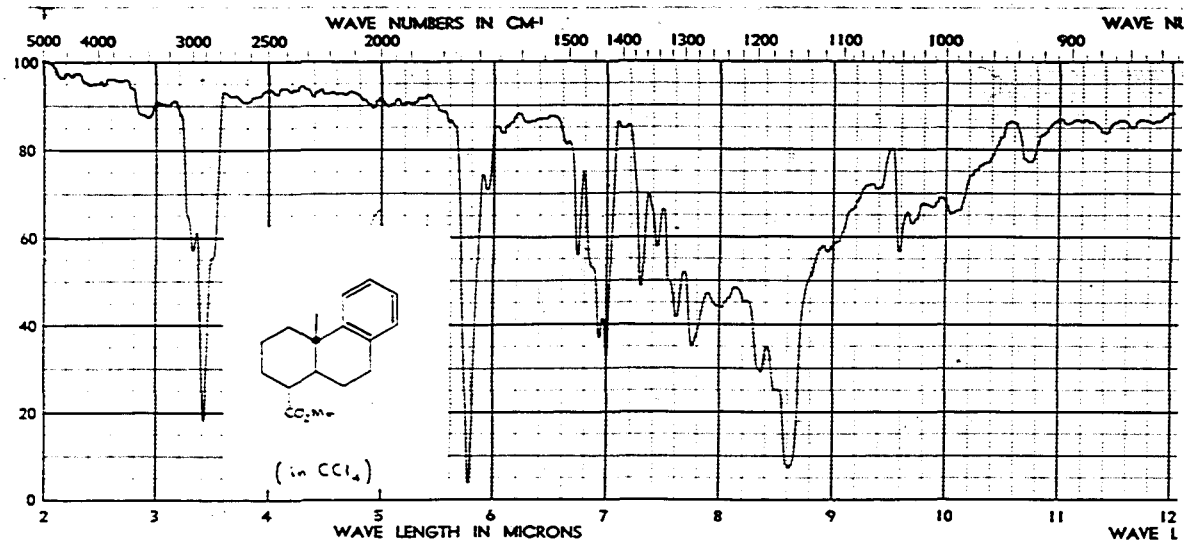

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
WAVE NU
100 80 60 40 20 0
S
CO2Me
(in CCl4)
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
WAVE L

Fig. 17 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO2Me
(in CCl4)

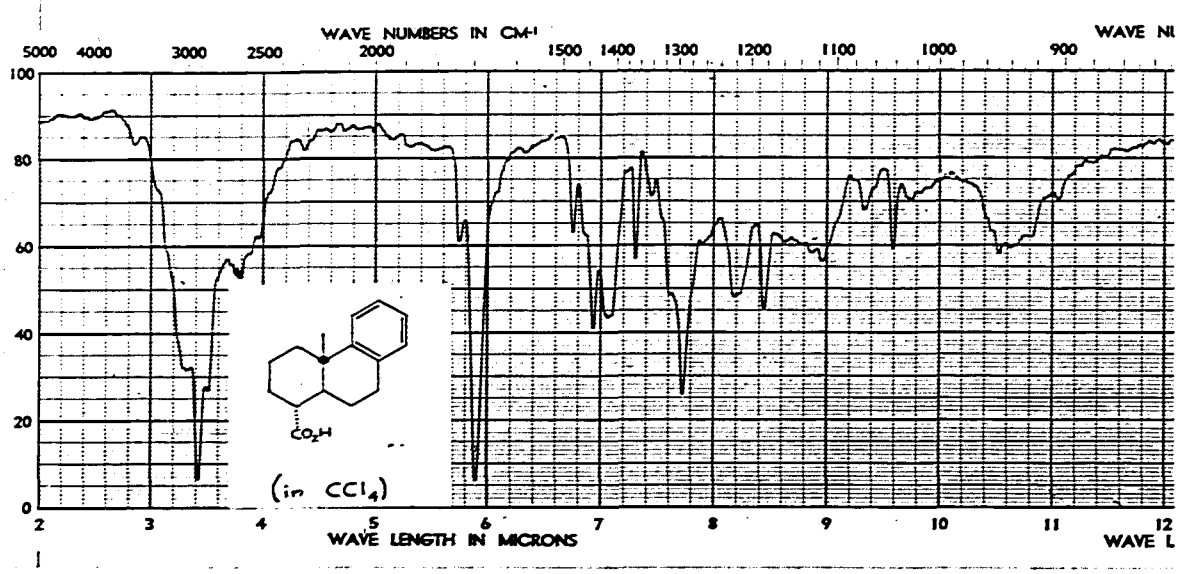
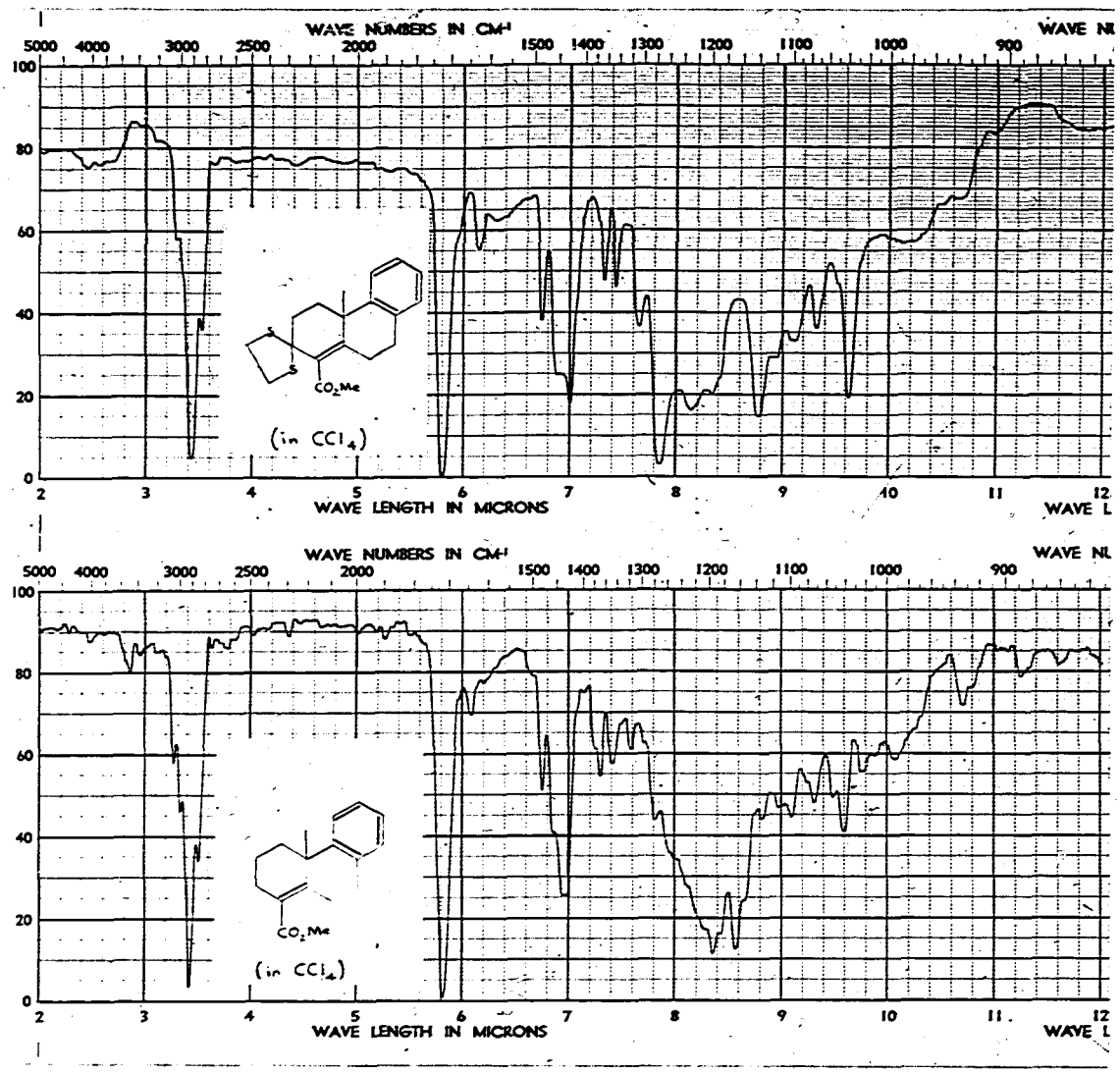

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO2H
(in CCl4)

Fig. 18 Infrared Spectra.


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO2Me
(in CCl4)
WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900
100 80 60 40 20 0
2 3 4 5 6 7 8 9 10 11 12
WAVE LENGTH IN MICRONS
CO2Me
(in CCl4)

EXPERIMENTAL

All melting and boiling points are uncorrected. The term petroleum ether refers to the fraction b.p. 60-70°. Microanalyses were performed by Strauss and Weiler Microanalytical Laboratory, Oxford, England, and Midwest Microlab, Indianapolis, Indiana. Optical rotations were measured in 95% ethanol solution using an O. C. Rudolph polarimiter.

Adsorbents for chromatography

Activated alumina, 80-200 mesh, was allowed to stand with ethyl acetate for 48 hours, then washed with water and methanol, and dried at 50° for 48 hours.

The Celite-silicic acid adsorbent was prepared by mixing equal weights of Celite and 100 mesh silicic acid.

Methyl podocarpate (LXXXI)

To a solution of 2.00 g. of podocarpic acid in 15 ml. of ether was added an ether solution of ca. 1 g. of diazomethane. After allowing the resulting mixture to stand for 10 minutes, ether and excess diazomethane were removed by evaporation under reduced pressure at room temperature. The resulting crystalline residue was recrystallized once from methanol-

water giving 2.082 g. (99%) of the ester, m.p. 212.5-13°.

Optical rotation. $[\alpha]_D^{25^\circ}$ +104.6

Diethyl phosphite

This compound was prepared from phosphorus trichloride and ethanol as described by McCombie et al. (80). Fractional distillation of the crude product gave a 76% yield of diethyl phosphite, b.p. (17 mm.) 78-81°.

Methyl podocarpate diethyl phosphate (LXXXII)

A mixture of 700 mg. (2.43 millimoles) of methyl podocarpate, 5 ml. of anhydrous tetrahydrofuran, 25 ml. of carbon tetrachloride, 1.3 ml. (10 millimoles) of diethyl phosphite and 1.5 ml. (10 millimoles) of anhydrous triethylamine was refluxed for 6 hours. When the refluxed mixture had cooled, it was washed first with 5% hydrochloric acid, then with 5% aqueous sodium hydroxide solution, and finally with water. After drying ($MgSO_4$) and evaporating the solvent, there was obtained 1.211 g. of a dark brown gum. This gum was presumed to be the phosphorylated ester LXXXII and was used directly for the next reaction without further purification.

Lithium-liquid ammonia reduction (rapid quenching) of methyl podocarpate diethyl phosphate (LXXXII)

To 500 ml. of liquid ammonia was added a solution of 5.68 g. (13.4 millimoles) of the ester LXXXII in 50 ml. of anhydrous tetrahydrofuran. Then 0.35 g. (50.5 millimoles) of lithium metal wire was added to the ammonia solution. As soon as the lithium had dissolved, 5 g. of ammonium chloride were added, and the mixture was allowed to stand until the ammonia had evaporated. The resulting residue was dissolved in a mixture of chloroform and 5% hydrochloric acid, the chloroform layer separated and the aqueous layer extracted three times with chloroform. The combined chloroform solutions were washed with 5% aqueous sodium hydroxide solution, dried ($MgSO_4$), and evaporated. Recrystallization of the resulting colorless solid from methanol-water gave 1.59 g. (54% based on methyl podocarpate) of methyl-1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrene carboxylate (LXXXIV), m.p. 140-41°. The analytical sample was obtained as colorless needles, m.p. 141-42°, after four recrystallizations from methanol-water.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.55; H, 8.99.

Ultraviolet spectrum. $\lambda_{max.}$ 265 mμ (ε 460) and 272 mμ (ε 436).

Optical rotation. $[\alpha]_D^{25^\circ}$ +138.2°

When the above sodium hydroxide washings were acidified and extracted with chloroform, there was obtained, after drying ($MgSO_4$) and evaporating the chloroform, a colorless solid. Recrystallization of this material from methanol-water gave 0.295 g. (10% based on methyl podocarpate) of 1,2,3,4,4a,9,10,10aα- octahydro-1α,4aβ-dimethyl-1β-phenanthrene-carboxylic acid (LXXVIII), m.p. 195-97°. Recrystallization from methanol-water four times gave the analytical sample as colorless needles, m.p. 197-98°.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.16; H, 8.67.

Ultraviolet spectrum. $\lambda_{max.}$ 265 mμ (ε 670) and 272 mμ (ε 640).

Optical rotation. $[\alpha]_D^{26^\circ}$ +40.8°

The mother liquors from the crystallization of the ester LXXXIV were combined and chloroform extracted. The residue obtained after drying ($MgSO_4$) and evaporating the chloroform was chromatographed over 5 g. of alumina. Elution with petroleum ether gave an additional 0.020 g. of LXXXIV. Elution with petroleum ether-ether (20:1) gave 0.063 g. (2.5% based on methyl podocarpate) of 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenemethanol (LXXXIII), m.p. 88-91°. The analytical sample was obtained as colorless needles, m.p. 93.5-94°, after three recrystallizations from methanol-water.

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.26; H, 9.66.

Optical rotation. $[\alpha]_D^{26^\circ}$ $+29.3^\circ$

Lithium-liquid ammonia treatment (alcohol quenching) of methyl podocarpate diethyl phosphate (LXXXII)

When the phosphate ester LXXXII was treated with lithium-ammonia in a manner exactly like the preceding experiment except that alcohol was used in the place of ammonium chloride, the products consisted of only the desoxy acid LXXVIII and the desoxy alcohol LXXXIII. The phosphate from 700 mg. of methyl podocarpate gave 338 mg. of LXXVIII and 118 mg. of LXXXIII.

Lithium amide treatment of methyl 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylate (LXXXIV)

To a suspension of 490 mg. of lithium amide in ca. 75 ml. of liquid ammonia was added a solution of 100 mg. of the ester LXXXIV in 25 ml. of anhydrous tetrahydrofuran. The resulting mixture was allowed to stand at room temperature until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid, the organic phase separated and the aqueous layer extracted with chloroform.

The combined chloroform extracts were washed with 10% sodium hydroxide, dried ($MgSO_4$), and evaporated. This non-acidic material was chromatographed over 10 g. of alumina. Elution with petroleum ether gave 58 mg. of starting material (LXXXIV). In the methanol eluates there was obtained 15 mg. of 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxamide (LXXXV), m.p. 191-95°.

General method for reductive hydrolyses

To approximately 75 ml. of liquid ammonia was added a solution of the appropriate ester in 25 ml. of tetrahydrofuran. Sufficient lithium metal to cause a persistent blue color was then added to the solution of the ester. The mixture was then allowed to stand at room temperature until the ammonia had evaporated. The residue was dissolved in 10% hydrochloric acid and chloroform. After separating the organic layer, the aqueous phase was extracted with chloroform three times. The combined chloroform extracts were washed with four 25 ml. portions of 5% sodium hydroxide solution, dried over $MgSO_4$ and evaporated giving the crude neutral fraction. The sodium hydroxide washings were collected, acidified with concentrated hydrochloric acid and extracted thrice with chloroform. The chloroform solution of the acidic products was dried ($MgSO_4$) and evaporated.

Reductive hydrolysis of methyl 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylate (LXXXIV)

To a solution of 100 mg. of the ester LXXXIV, 25 ml. of anhydrous tetrahydrofuran and ca. 100 ml. of liquid ammonia was added 10 mg. of lithium metal wire. The resulting solution was allowed to stand until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid, the organic layer then being separated and the aqueous portion extracted with chloroform. The combined extracts were washed with three 25 ml. portions of 5% sodium hydroxide, dried ($MgSO_4$) and evaporated. Chromatography of the resulting non-acidic products over alumina afforded, in the ether eluates, 21 mg. of the alcohol LXXXIII, m.p. 90-93°.

The chloroform extracts of the acidified sodium hydroxide washings were dried ($MgSO_4$) and evaporated yielding 75 mg. of the acid LXXVIII, m.p. 195-99°.

Reductive hydrolysis of methyl podocarpate (LXXXI)

When 200 mg. of the ester LXXXI was exposed to lithium in liquid ammonia, there was obtained 192 mg. of acidic products. Crystallization of the crude acidic material from methanol-water gave 111 mg. (58%) of podocarpic acid, m.p. 179-92°. Another recrystallization from the same solvent

mixture gave material melting at 192-94° which had an infrared spectrum identical to that of authentic podocarpic acid. The neutral material was crystallized from methanol-water giving 9 mg. of methyl podocarpate, m.p. 205-10°. The infrared spectrum of this neutral product was identical to that of authentic methyl podocarpate.

Reductive hydrolysis of methyl oleanolate (LXXXVII)

The neutral fraction from a 55 mg. run was crystallized from methanol-water giving 15 mg. of erythrodiol (LXXXIX), m.p. 215-30°. Further recrystallization of the diol from the same solvent mixture gave material melting at 233-37°. The infrared spectrum of this material was identical to that of authentic erythrodiol.

The crude acid was crystallized from methanol-water affording 37 mg. of oleanolic acid (LXXXVIII), m.p. 308-10°. The infrared spectrum of this acid was identical to that of authentic oleanolic acid.

Reductive hydrolysis of methyl mesitoate (XC)

Lithium-ammonia treatment of 450 mg. of the ester yielded 422 mg. of a semi-crystalline neutral material. Trituration with petroleum ether and filtration afforded 182 mg. of

2,4,6-trimethyl benzyl alcohol, m.p. 85-88°. Infrared spectra of the crude neutral fraction and the benzyl alcohol were practically identical.

The acid products amounted to 12 mg. and were ignored.

Reductive hydrolysis of methyl dehydroabietate (LVI)

When 200 mg. of the ester LVI were treated with lithium in liquid ammonia, there was obtained 177 mg. of neutral material. Chromatography of the crude neutral fraction over alumina gave 118 mg. of dehydroabietinol (LXXXVI). The 3,5-dinitrobenzoate of this alcohol melted at 123-24°. Fieser and Campbell (81) report the same melting point for anthentic dehydroabietinol 3,5-dinitrobenzoate.

The acidic material amounted to 17 mg. and could be crystallized from methanol-water to give 6 mg. of dehydroabietic acid, m.p. 165-68°.

1,2,3,4,4a,9,10,10aα-Octahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CII)

A mixture of 5.0 g. of dehydroabietonitrile, 12.5 g. of anhydrous aluminum chloride and 50 ml. of benzene was refluxed for 6 hours. The refluxed mixture was allowed to cool and was decomposed with ice and concentrated hydrochloric

acid. The organic products were extracted from the acid mixture with ether, the extracts combined, dried ($MgSO_4$) and evaporated. The resulting dark brown gum slowly crystallized. Trituration with petroleum ether and filtration yielded 1.64 g. (39%) of the deisopropyl nitrile CII, m.p. 107-08°. The analytical sample, m.p. 107-08°, was obtained as colorless needles after two recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 85.07; H, 8.79.

Ultraviolet spectrum. $\lambda_{max.}$ 266 mμ (ε 890) and 273 mμ (ε 850).

Optical rotation. $[\alpha]_D^{25°}$ +16.5°

1,2,3,4,4a,9,10,10aα-Octahydro-1β,4aα-dimethyl-1α-phenanthrenecarboxylic acid

A mixture of 1.0 g. of the nitrile CII, 5 g. of potassium hydroxide, 25 ml. of diethylene glycol and 3 ml. of water was heated at 160° for 21 days. After the reaction mixture had cooled, it was poured into 200 ml. of water and extracted with chloroform. The aqueous phase was then acidified with 10% hydrochloric acid and again extracted with chloroform. The combined chloroform extracts of the acid solution were dried ($MgSO_4$) and evaporated to dryness. The resulting dark brown residue was extracted with hot petroleum

ether. Evaporation of the combined petroleum ether extracts gave 0.915 g. (87%) of the acid, m.p. 156-58°. The analytical sample was obtained as colorless plates, m.p. 159-60°, after three recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.27; H, 8.75.

Optical rotation. $[\alpha]_D^{24^\circ}$ +8.2°

Methyl-1,2,3,4,4a,9,10,10aα-octahydro-1β,4aα-dimethyl-1α-phenanthrenecarboxylate

To an ether solution of 75 mg. of the acid was added an ether solution of ca. 200 mg. of diazomethane. After the resulting solution had stood for two hours, the ether and excess diazomethane were removed by evaporation under reduced pressure at room temperature. Crystallization of the resulting solid from methanol-water gave 65 mg. (82%) of the ester, m.p. 70-78°. Recrystallization from methanol-water four times gave colorless needles of the analytical sample, m.p. 90-90.5°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.67; H, 8.94.

Optical rotation. $[\alpha]_D$ +19.4°

General procedure for chromic acid oxidations

To a solution of the appropriate substrate in acetic acid (usually 10% w/v) was added a solution of chromic oxide in acetic acid-water (4:1). The weight of chromic acid employed was 1.25 times the weight of the substrate, and its concentration in the 80% acetic acid varied from 5% to 25%, the more dilute solutions being necessary to facilitate the handling of small amounts of oxidant used when the experiment was carried out on a semimicro scale. After the mixed solutions had stood at room temperature for 15-18 hours, the mixture was diluted with a fivefold volume of saturated sodium chloride solution and extracted with chloroform. The extracts were then washed with 5% sodium hydroxide to separate the acidic products. These acids were recovered by acidifying the aqueous solution with 10% hydrochloric acid and extracting with chloroform. The solutions of both the acidic and non-acidic products were dried over $MgSO_4$ and evaporated.

Chromic acid oxidation of 1,2,3,4,4a,9,10,10aα,octahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CII)

The neutral portion from a 5.00 g. run was crystallized from petroleum ether-benzene giving 1.36 g. of 1α-cyano-1,2,3,4,4aα,10aα-hexahydro-1β,4aα-dimethyl-9,10-phenanthrenedione (CXII), m.p. 150-67°. An alcoholic solution of this diketone gave no coloration to a methanolic solution of ferric chloride. The analytical sample was obtained as bright yellow needles, m.p. 125-64°, after four recrystallizations from petroleum ether-benzene.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.10; H, 6.43; N, 5.37.

Ultraviolet spectrum. (Fig. 5) $\lambda_{max.}$ 290 mμ (ε 5500).

Optical rotation. $[\alpha]_D^{27°}$ -267°

The colorless quinoxaline derivative was recrystallized from methanol-water, m.p. 196-97°.

Anal. Calcd. for $C_{23}H_{21}N$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.22; H, 6.32; N, 12.3.

Optical rotation. $[\alpha]_D^{26°}$ -206°

The filtrates from the crystallization of the diketone were chromatographed over alumina. Elution with petroleum ether afforded 1.10 g. of starting material (CII). In the petroleum ether-ether eluates (3:1), there was obtained 1.38 g. of 1α-cyano-1,2,3,4,4a,10aα-hexahydro-1β,4aα-dimethyl-

9(10H)-phenanthrone (CX), m.p. 154-57°. Colorless needles of the analytical sample, obtained after three recrystallizations from petroleum ether, melted at 156-57°.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.55; H, 7.58; N, 5.55.

Ultraviolet spectrum. $\lambda_{max.}$ 253 mμ (ε 12,600) and 294 mμ (ε 2,420).

Optical rotation. $[\alpha]_D^{25°}$ -107°

In another experiment, the diketone was not first separated by fractional crystallization, and the whole of the neutral material was chromatographed over alumina. The diketone which was recovered by elution with methanol could not be crystallized. This gum, in contrast to the crystalline diketone isolated prior to chromatography, gave a brown coloration with methanolic ferric chloride.

The quinoxaline derivative from the partially enolic diketone melted at 157-59°. A mixture of this quinoxaline and the previously obtained quinoxaline from the crystalline diketone melted at 138-60°.

Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24. Found: C, 80.96; H, 6.44.

Optical rotation. $[\alpha]_D^{28°}$ -357°

Heating or subliming the crystalline diketone converted it to a semi-crystalline gum. The quinoxaline derivative of this gum melted at 157-59°. Admixture with the lower melting

quinoxaline obtained above produced no depression in melting point.

Chromic acid oxidation of dehydroabietonitrile (XCIII)

The acidic material from the oxidation of 200 mg. of the nitrile amounted to 3 mg. and was ignored. The neutral material was chromatographed over 15 g. of alumina. Elution with petroleum ether gave 17 mg. of starting material. In the petroleum ether-ether (10:1) eluates, there was obtained 85 mg. of 7-ketodehydroabietonitrile (XCIV).

Ultraviolet spectrum. (Fig. 5) $\lambda_{max.}$ 254 mμ (ε 9,950) and 300 mμ (ε 1,510).

Optical rotation. $[\alpha]_D^{25^\circ}$ $+145^\circ$

Further elution with more polar solvents gave 29 mg. of unidentifiable substances.

Chromic acid oxidation of methyl 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylate (LXXXIV)

No acidic substances were produced during the oxidation of 200 mg. of the ester. After adsorption of the neutral products on alumina, elution with petroleum ether afforded 37 mg. of the starting ester LXXXIV. In the petroleum ether-ether eluates (4:1), there was obtained 110 mg. of 1β-carbo-

methoxy-1,2,3,4,4a,10aα-hexahydro-1α,4aβ-dimethyl-9(10H)-phenanthrone (XCV), m.p. 147-53°. The analytical sample was obtained as colorless needles, m.p. 152-53°, after four recrystallizations from methanol-water.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.66; H, 7.73.

Ultraviolet spectrum. (Fig. 2) $\lambda_{max.}$ 250 mμ (ε 11,200) and 286 mμ (ε 3,040).

Optical rotation. $[\alpha]_D^{25°}$ +84.5°

Chromic acid oxidation of methyl dehydroabietate (LVI)

No acidic materials were isolated when 200 mg. of this ester were oxidized. Chromatography of the non-acidic material over 15 g. of alumina gave, in the petroleum ether eluates, 91 mg. of the starting ester. Elution with petroleum ether-ether (4:1) afforded 84 mg. of methyl 7-ketodehydroabietate (LVII).

Ultraviolet spectrum. $\lambda_{max.}$ 254 mμ (ε 10,800) and 302 mμ (ε 1,770).

Optical rotation. $[\alpha]_D^{26°}$ +7.9° Reported (42) +6.6°

The 2,4-dinitrophenylhydrazone derivative of LVII melted at 185-86°. The reported (42) melting point was 184.5-85.5°.

Chromic acid oxidation of 3,4,4a,9,10,10aβ-hexahydro-4aβ-methyl-2(1H)-phenanthrone (XCVI)

Oxidation of 140 mg. of this ketone gave 65 mg. of acidic material and 40 mg. of neutral substances. When the latter was chromatographed over alumina, there was obtained, in the petroleum ether eluates, 15 mg. of the starting ketone XCVI. Elution with ether afforded 22 mg. of 1,3,4,4a,10,10aβ-hexahydro-4aβ-methyl-2,9-phenanthrenedione (XCVIII), m.p. 107-08°. The analytical sample was obtained as fluffy needles after three recrystallizations from methanol-water and melted at 110-11°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.04. Found: C, 78.66; H, 7.46.

Ultraviolet spectrum. $\lambda_{max.}$ 249 mμ (ε 14,100) and 288 mμ (ε 2,640).

Chromic acid oxidation of 3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (LXXX)

Oxidation of 200 mg. of this material afforded 98 mg. of acidic material and 90 mg. of non-acidic material. Chromatography of the latter over alumina gave, in the petroleum ether-ether (20:1) eluates, 31 mg. of the starting phenanthrone LXXX. Elution with ether yielded 25 mg. of 1,3,4,4a,

10, 10aα-hexahydro-4aβ-methyl-2,9-phenanthrenedione (XCVII), m.p. 117-24°. Colorless needles of the analytical sample, m.p. 125-26°, were obtained after four recrystallizations from petroleum ether.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.04. Found: C, 78.83; H, 6.98.

Ultraviolet spectrum. $\lambda_{max.}$ 250 mμ (ε 11,500) and 290 mμ (ε 1,850).

Elution with methanol gave 21 mg. of unidentifiable substances.

10-Acetoxy-1α-cyano-2,3,4,4a-tetrahydro-1β,4aα-dimethyl-9(1H)-phenanthrone (CIV)

A mixture of 200 mg. of the diketone CXII, 5 ml. of acetic anhydride and 82 mg. of anhydrous sodium acetate were refluxed for one hour. The solvent was evaporated in vacuo and the resulting residue was dissolved in chloroform and water. The organic layer was separated, and the aqueous phase was further extracted with chloroform. The combined chloroform extracts were washed with 10% sodium bicarbonate solution, dried ($MgSO_4$) and evaporated in vacuo. The resulting crude enolacetate weighed 216 mg. and was not further purified prior to catalytic hydrogenation.

Ultraviolet spectrum. (Fig. 2) $\lambda_{max.}$ 257 mμ (ε 9,400).

Catalytic hydrogenation of 10-acetoxy-1α-cyano-2,3,4,4a-tetrahydro-1β,4aα-dimethyl-9(1H)-phenanthrone (CIV)

A mixture of 214 mg. of the enolacetate CIV, 75 mg. of 5% palladium-on-charcoal, 15 ml. of ethyl acetate and 0.1 ml. of concentrated sulfuric acid was hydrogenated at room temperature and atmospheric pressure. Approximately two molar equivalents of hydrogen were absorbed before uptake ceased. After removal of the catalyst by filtration, the filtrate was washed with 10% sodium bicarbonate solution, dried over $MgSO_4$ and evaporated. Chromatography of the resulting residue over alumina gave, in the petroleum ether eluates, 11 mg. of 1,2,3,4,4a,9,10,10aβ-octahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CI), m.p. 70-80°. Elution with petroleum ether-ether (20:1) afforded 91 mg. of 10α-acetoxy-1,2,3,4,4a,9,10,10aβ-octahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CVI), m.p. 116-117°. The analytical sample was obtained as colorless needles, m.p. 118-118.5° after three recrystallizations from methanol-water.

Anal. Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80. Found: C, 76.93; H, 7.96.

Optical rotation. $[\alpha]_D^{27^\circ}$ -15.5°

Elution with petroleum ether-ether (4:1) gave 18 mg. of a compound which melted at 213-14°. The infrared spectrum of this substance was compatible that expected for 1α-cyano-

1,2,3,4,4a,10aβ-hexahydro-1β,4aα-dimethyl-9(10H)-phenanthrone. This ketone was not further characterized.

1,2,3,4,4a,10aβ-Hexahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CXIII)

Under an atmosphere of nitrogen, 91 mg. of the acetate CVI was heated at 250° for 5 minutes. The resulting gum was dissolved in chloroform and the solution washed with 10% sodium bicarbonate solution. The crude product, obtained after drying ($MgSO_4$) and evaporating the solvent, was chromatographed over alumina. Elution with petroleum ether gave 48 mg. (6%) of the styrene CXIII as a colorless gum. The compound was not further purified before hydrogenation.

Ultraviolet spectrum. (Fig. 2) $\lambda_{max.}$ 224 mμ (ε 16,600) and 263 mμ (ε 8,800).

Optical rotation. $[\alpha]_D^{27^\circ}$ +86.5°

1,2,3,4,4a,9,10,10aβ-Octahydro-1β,4aα-dimethyl-1α-phenanthrenecarbonitrile (CI)

A mixture of 46 mg. of the styrene CXIII, 25 mg. of 5% palladium-on-charcoal and 15 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake was complete in 3 hours and corresponded to one molar

equivalent. The residue obtained after filtration of the catalyst and evaporation of solvent from the filtrate was chromatographed over alumina. Elution with petroleum ether and subsequent crystallization from methanol-water gave 19 mg. of the nitrile CI, m.p. 71-83°. The analytical sample melted at 87-88° after two recrystallizations from methanol-water.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 85.30; H, 8.53.

Optical rotation. $[\alpha]_D^{27°}$ -85°

1,2,3,4,4a,9,10,10aα-Octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxamide (LXXXV)

A mixture of 300 mg. of 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylic acid (LXXVIII) and 5 ml. of thionyl chloride was refluxed for one hour. The residue of crude acid chloride obtained after evaporating the excess solvent in vacuo was dissolved in 10 ml. of tetrahydrofuran and added to a suspension of sodium amide (from 1 g. of sodium metal) in ca. 75 ml. of liquid ammonia. The resulting mixture was allowed to stand until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid, the organic layer separated and the aqueous phase extracted with chloroform. The crude product obtained after

drying ($MgSO_4$) and evaporating the combined chloroform extracts was crystallized from methanol-water giving 76 mg. of the amide LXXXV, m.p. 160-71°. The filtrate was evaporated *in vacuo* and the residue chromatographed over alumina. Elution with petroleum ether afforded, after crystallization from methanol-water, 20 mg. of 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarbonitrile (CVIII), m.p. 82-86°. After two recrystallizations from methanol-water and subsequent sublimation, the material melted at 81-89°.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 84.99; H, 8.59.

Optical rotation. $[\alpha]_D^{27°}$ +90°

Elution with methanol gave 35 mg. of the amide, m.p. 190-93°. Three recrystallizations from methanol-water gave fluffy needles of the analytical sample, melting at 191-95°.

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.35; H, 9.21.

Optical rotation. $[\alpha]_D^{25°}$ +157°

1,2,3,4,4a,9,10,10aα-Octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarbonitrile (CVIII)

A mixture of 75 mg. of 1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxamide (LXXXV), 4 ml. of benzene and 1 ml. of thionyl chloride was refluxed for 6

hours. The residue obtained after evaporating the solvents was dissolved in chloroform. This solution was then washed with 10% sodium bicarbonate solution, dried over $MgSO_4$ and evaporated *in vacuo*. The resulting crude product was adsorbed on 5 g. of alumina. Elution with petroleum ether and subsequent crystallization from methanol-water gave 41 mg. of the nitrile CVIII, m.p. 83-87°. A mixture of the nitrile obtained from this reaction and the one obtained in the preceding experiment melted at 83-87°. The infrared spectra of the two samples of nitrile were identical.

Methyl-6-acetyl-1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylate (CXXV)

To a stirred suspension or 0.65 g. of anhydrous aluminum chloride in 25 ml. of carbon disulfide was added a solution of 1.0 g. of the ester LXXXIV and 0.30 ml. of acetyl chloride in 15 ml. of carbon disulfide. After refluxing and stirring this mixture for one hour, the solvent was evaporated and the resulting residue was taken up in 5% hydrochloric acid and chloroform. The chloroform layer was separated and the aqueous layer was extracted three times with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to dryness. The crystalline crude product was then chromatographed over 30 g. of alumina. Elution with

petroleum ether gave 0.565 g. of the starting material (LXXXIV). Elution with petroleum ether-ether (9:1) gave 0.219 g. (43% based on recovered starting material) of the acetyl compound (CXXIV), m.p. 147-57°. The analytical sample was obtained as colorless needles, m.p. 160.5-61.5°, after five recrystallizations from methanol-water.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.61; H, 7.94.

Ultraviolet spectrum. (Fig. 5) $\lambda_{max.}$ 258 mμ (ε 19,200)

Optical rotation. $[\alpha]_D$ +157°

Trifluoroperacetic acid treatment of methyl-6-acetyl-1,2,3,4,4a,9,10,10aα-octahydro-1α,4aβ-dimethyl-1β-phenanthrenecarboxylate (CXXV)

A solution of the per acid in methylene chloride was prepared by the addition of 0.085 ml. of trifluoroacetic anhydride to an ice cold, stirred suspension of 0.014 ml. of 90% hydrogen peroxide in 10 ml. of methylene chloride. The resulting solution of the acid was then added to a stirred mixture of 0.35 g. of anhydrous disodium hydrogen phosphate, 100 mg. of the keto ester (CXXV), and 20 ml. of methylene chloride. After refluxing this mixture for three hours, it was allowed to cool and then filtered. The filtrate was washed with 10% sodium carbonate solution, dried (Na_2SO_4),

and evaporated to dryness. Recrystallization of the crude crystalline product from methanol-water gave 86 mg. (74%) of methyl podocarpate acetate (CXXVI), m.p. 117-21°. After two recrystallizations from methanol-water, the material melted at 125-125.5°. The melting point was undepressed when admixed with a sample of authentic methyl podocarpate acetate (m.p. 124-25°). The infrared spectra of the two samples of methyl podocarpate acetate were identical.

Methyl podocarpate acetate (CXXVI)

A mixture of 288 mg. of methyl podocarpate, 70 mg. of anhydrous sodium acetate, and 20 ml. of acetic anhydride was refluxed for three hours. The residue remaining after the removal of the acetic anhydride by evaporation under reduced pressure was lixiviated with ethyl ether. The ether solution was washed with 5% sodium hydroxide solution, dried ($MgSO_4$), and evaporated to dryness. The resulting crystalline mass was recrystallized once from methanol-water giving 300 mg. (91%) of CXXVI, m.p. 124-25°. The analytical sample was obtained as fluffy white needles, m.p. 125-25.5°, after three recrystallizations from methanol-water.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 73.10; H, 8.09.

Ultraviolet spectrum. (Fig. 3) $\lambda_{max.}$ 268.5 mμ (ε 680)

and 275 mμ (ε 740).

Optical rotation. $[\alpha]_D^{23^\circ}$ +113°

Hydrolysis of methyl podocarpate acetate

A mixture of 100 mg. of methyl podocarpate acetate, 15 ml. of ethanol, 150 mg. of potassium hydroxide, and 10 ml. of water was refluxed for 4 hours. The refluxed solution was allowed to cool and was poured into 50 ml. of 10% hydrochloric acid. The acid solution was then extracted with chloroform three time. The combined and dried ($MgSO_4$) extracts were evaporated to dryness. The resulting methyl podocarpate was recrystallized once from methanol-water giving 86 mg. (99%) of fluffy, colorless needles, m.p. 210-13°. Another recrystallization gave material melting at 212-13°. The melting point was undepressed when admixed with authentic methyl podocarpate (m.p. 212.5-13°). The infrared spectra of the two samples of methyl podocarpate were identical.

Carbonation of 4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (LXXIX)

An ether solution of sodium triphenylmethyl was prepared and standardized as follows. The pressure bottle from a Parr hydrogenation apparatus was charged with a mixture of 600 g.

of 1% sodium amalgam, 20 g. of triphenylmethyl chloride, and 200 ml. of anhydrous ether. The mixture was placed on the hydrogenation apparatus and was shaken for 4 hours. After allowing the suspension of sodium chloride to settle, a 2 ml. aliquot of the sodium triphenylmethyl solution was removed and run into water. The resulting basic solution was then titrated with standardized hydrochloric acid.

The carbonation reaction was carried out in a 250 ml. round-bottomed, three necked flask. All glassware used in this experiment had been dried at 160° for 24 hours and was allowed to cool in a dry nitrogen atmosphere. The carbon dioxide used was generated from Dry Ice and was dried by passing it through a gas trap at -80°.

To a stirred, nitrogen-blanketed solution of 5.00 g. of the enone LXXIX in 20 ml. of ether was added a molar equivalent of the previously prepared sodium triphenylmethyl solution. After the base had been added, a stream of dry carbon dioxide was bubbled through the suspension of the sodium enolate for a period of one hour. At the end of this time, the reaction mixture was decomposed with ice; and the organic phase was quickly extracted with four 75 ml. portions of ice cold 5% sodium hydroxide solution. The combined basic extracts were rapidly neutralized with ice cold 10% hydrochloric acid and the acid solution immediately extracted with ether. The combined ether extracts of the acid solution were

then poured into an ether solution of ca. 1.5 g. of diazomethane, and the resulting solution was allowed to stand for 10 minutes. Excess diazomethane was removed by washing the ether solution with 10% hydrochloric acid. The ether solution of the ketoesters was washed with sodium bicarbonate solution, dried ($MgSO_4$), and evaporated to dryness giving 3.96 g. of a yellow gum. This yellow gum was carefully chromatographed over 150 g. of silicic acid-Celite. Elution with petroleum ether-benzene (1:1) gave 0.075 g. of triphenylmethane, m.p. 79-80°. Elution with petroleum ether-ether (20:1) gave 1.106 g. of a keto-enol mixture of 3-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXIX), m.p. 90-107°. The analytical sample of the ketonic form was obtained as colorless prisms, m.p. 111-12°, after three recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.55; H, 6.63.

Ultraviolet spectrum. (Fig. 1) $\lambda_{max.}$ 238 mμ (ε 18,500)

Elution with petroleum ether-ether (10:1) gave 1.183 g. of 1-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXX), m.p. 116-18°. Colorless prisms of the analytical sample, m.p. 117-18°, were obtained after two recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.70; H, 6.60.

Ultraviolet spectrum. (Fig. 1) $\lambda_{max.}$ 239 mμ (ε 14,300)

Continued elution with more polar solvents gave 1.07 g. of a yellow brown gum.

The ether solution of the non-acidic products; i.e. that material remaining in the ether after the initial sodium hydroxide extraction, was dried ($MgSO_4$) and evaporated to dryness. Chromatography of the resulting semi-crystalline gum gave, in the petroleum ether-benzene eluates, triphenylmethane, m.p. 79-80°. Elution with petroleum ether-ether (10:1) gave 1.22 g. of starting material (LXXIX), m.p. 87-89°.

Methylation of 3-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXIX)

To a stirred, nitrogen-blanketed solution of 35 mg. of potassium in 100 ml. of t-butanol was added a solution of 200 mg. of the ketoester in 100 ml. of t-butanol. The resulting solution was stirred for ten minutes to complete formation of the enolate anion. To the stirred solution of the enolate anion was then added 3.0 ml. of methyl iodide. The reaction was allowed to proceed at room temperature for ten minutes and then was refluxed for three hours. The cooled refluxed solution was filtered, and the filtrate was evaporated to dryness. The residue thus obtained was taken up in chloroform and water, the chloroform separated and the aqueous

phase extracted twice with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to dryness. The resulting crystalline residue was triturated with petroleum ether and filtered to give 110 mg. of 3-carbomethoxy-4, 4a,9,10-tetrahydro-3,4a-dimethyl-2(3H)-phenanthrone (CXXXIII), m.p. 153-56°. The analytical sample was obtained as colorless prisms, m.p. 157-58° after four recrystallizations from methanol.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 7.44.

Ultraviolet spectrum. (Fig. 4) $\lambda_{max.}$ 239 mμ (ε 15,000).

Catalytic hydrogenation of 3-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXIX)

A mixture of 200 mg. of the ester CXXIX, 75 mg. of 5% palladium-on-charcoal and 20 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake was measured dolumetrically, and absorption ceased after a volume corresponding to one mole had been used. After filtration of the catalyst, the solvent was evaporated, giving 200 mg. of a colorless gum. Half of the crude product was removed at this stage for the decarboxylation described below. Crystallization of the remainder from methanol-water gave 76 mg. of the saturated ketoester CXXXIV, m.p. 88-93°. An alcoholic

solution of this solid gave a violet color with alcoholic ferric chloride solution. Colorless fluffy needles of the analytical sample, m.p. 102-03°, were obtained after five recrystallizations from methanol-water.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.11.

Ultraviolet spectrum. (Fig. 4) $\lambda_{max.}$ 256 mμ (ε 10,800).

Catalytic hydrogenation (acid medium) of 1-carbomethoxy-4,4a, 9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXX)

A mixture of 370 mg. of the enone ester CXXX, 15 ml. of ethyl acetate, 150 mg. of palladium-charcoal (5%) and 0.2 ml. of 80% sulfuric acid was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake stopped after one molar equivalent of hydrogen had been absorbed. The catalyst was then filtered and the filtrate washed with 10% sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness. The resulting semi-crystalline residue was recrystallized from petroleum ether giving 295 mg. (79%) of the saturated keto ester CXXXVI, m.p. 126-27°. The analytical sample was obtained as colorless prisms, m.p. 127-28°, after three recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.76; H, 7.12.

Ultraviolet spectrum. (Fig. 3) $\lambda_{max.}$ 265 mμ (ε 525) and 272 mμ (ε 465).

Hydrolysis and decarboxylation of the crude product obtained by catalytic hydrogenation of 3-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXIX)

A mixture of 100 mg. of the crude ketoester, 7 ml. of ethanol and 5 ml. of concentrated hydrochloric acid was refluxed for 18 hours. The cooled acid solution was diluted with 50 ml. of water, saturated with sodium chloride and extracted with chloroform. After drying and evaporating the extracts, there was obtained 75 mg. of a yellow gum. Chromatography of this gum over 25 g. of alumina gave, in the petroleum ether eluated, 43 mg. of the cis-ketone XCVI. Elution with petroleum ether-ether (99:1) gave 19 mg. of a colorless oil, the infrared spectrum of which showed it to be neither the cis-ketone nor the trans-ketone LXXX. This latter oil was not further characterized.

Hydrolysis and decarboxylation of 1-carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (CXXXVI)

A mixture of 75 mg. of the keto ester CXXXVI, 7 ml. of ethanol, and 5 ml. of concentrated hydrochloric acid was

refluxed for 18 hours. The cooled reaction mixture was diluted with 50 ml. of water, saturated with sodium chloride, and extracted with chloroform. The combined and dried ($MgSO_4$) extracts were evaporated giving a slowly crystallizing oil. Recrystallization of the crude product from petroleum ether gave 37 mg. (63%) of the trans ketone LXXX, m.p. 98-103°. Recrystallization from petroleum ether raised the melting point to 107-08°. No depression was observed when the hydrolysis product was admixed with authentic LXXX. The infrared spectra of the two samples of hydrophenanthrene ketone were identical.

Catalytic hydrogenation (acid medium) of 4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (LXXIX)

A mixture containing 100 mg. of the phenanthrone LXXIX, 50 mg. of 5% palladium-on-charcoal, 10 ml. of ethyl acetate and 0.1 ml. of concentrated sulfuric acid was hydrogenated at atmospheric pressure and room temperature. Hydrogen absorption, measured volumetrically, ceased in 45 minutes, with an uptake corresponding to one double bond. The solution was filtered, washed with 10% sodium bicarbonate solution and evaporated. The residue was chromatographed over 15 g. of alumina. Elution with petroleum ether gave, in the early fractions, 32 mg. of the cis phenanthrone XCVI. Later

fractions contained a total of 30 mg. of the trans phenanthrone LXXX. Further elution with the same solvent gave 18 mg. of an unidentifiable substance.

Catalytic hydrogenation (basic medium) of 4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (LXXIX)

A mixture of 200 mg. of the phenanthrone LXXIX, 15 ml. of methanol, 15 mg. of potassium hydroxide and 75 mg. of 5% palladium-on-charcoal was hydrogenated at atmospheric pressure and room temperature. Hydrogen absorption was measured volumetrically and uptake ceased after a volume corresponding to one mole had been absorbed. The catalyst was filtered, the filtrate neutralized with 10% hydrochloric acid and the solvent removed in vacuo. A chloroform solution of the residue was washed with water, dried over $MgSO_4$, and evaporated. The crude product was chromatographed over 5 g. of alumina affording, in the petroleum ether-ether (99:1) eluates, 140 mg. (70%) of 3,4,4a,9,10,10a -hexahydro-4a -methyl-2(1H)-phenanthrone (XCVI).

Sodium methoxide treatment of 3-carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone (CXXXVI)

A mixture of 200 mg. of the ketoester CXXXVI, 20 mg. of sodium metal and 20 ml. of anhydrous methanol was refluxed for 18 hours. The cooled mixture was poured into 150 ml. of water, and the aqueous solution was acidified with acetic acid. The chloroform extracts were dried over $MgSO_4$ and evaporated. Since the infrared spectrum of the resulting residue was virtually identical to that of the starting material, the crude product was not further treated.

Carbonation of 3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (LXXX)

An ether solution of 1.00 g. of the phenanthrone LXXX was carbonated using the same procedure as described previously for the enone LXXIX. Chromatography of the crude products over 50 g. of silicic acid-celite gave, in the petroleum ether-ether (99:1) eluates, 515 mg. of the enolic form of 3-carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (CXLI), m.p. 75-77°. Recrystallization from methanol-water gave colorless prisms, melting at 77-85°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.24; H, 7.65.

Ultraviolet spectrum. $\lambda_{max.}$ 255 mμ (ϵ 13,800)

Elution with petroleum ether-ether (10:1) yielded 72 mg. of a keto-enol mixture of 1-carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (CXXXVI), identified by infrared spectrum.

Chromatography of the neutral products over alumina afforded, in the petroleum ether-ether (10:1) eluates, 267 mg. of the starting phenanthrone LXXX.

1α- Carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone ethylene dithioketal (CXLII)

A mixture of 100 mg. of 1α-carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone (CXXXVI), 100 mg. of freshly fused zinc chloride, 200 mg. of anhydrous sodium sulfate, 10 ml. of benzene and 0.1 ml. of ethanedithiol was stirred at room temperature for 48 hours. The reaction mixture was then filtered, the filtrate washed with 5% sodium hydroxide solution, dried ($MgSO_4$) and evaporated. The resulting crude product was crystallized from petroleum ether to give 94 mg. (73%) of the thioketal, m.p. 163-66°. The filtrate was evaporated and the residue chromatographed over 5 g. of alumina. Elution with petroleum ether-ether (10:1) yielded an additional 10 mg. (8%) of the thioketal, m.p. 165-67°. The analytical sample was obtained as colorless

prisms, m.p. 165.5-66.5°, after four recrystallizations from petroleum ether.

Anal. Calcd. for $C_{19}H_{24}O_2S_2$: C, 65.50; H, 6.94. Found: C, 65.18; H, 7.06.

Desulfurization of 1α-carbomethoxy-3,4,4a,9,10,10aα-hexahydro-4aβ-methyl-2(1H)-phenanthrone ethylene dithioketal (CXLII)

A mixture of 160 mg. of the thioketal CXLII, 2 g. of Raney nickel and 15 ml. of ethanol was refluxed for 10 hours. The catalyst was filtered and the filtrate evaporated *in vacuo*. The crude product was filtered through s short (2 x 6 cm.) alumina column and washed off with petroleum ether. In this manner 105 mg. (88%) of the ester CXLIII was obtained.

1,2,3,4,4a,9,10,10aα-Octahydro-4aα-methyl-1β-phenanthrenecarboxylic acid (CXLIV)

A mixture of 75 mg. of the ester CXLIII, 10 ml. of 95% ethanol and 10 ml. of 10% sodium hydroxide solution was refluxed for eight hours. The reaction mixture was diluted with 100 ml. of water and extracted with chloroform to remove any unhydrolyzed ester. The aqueous phase was then acidified with hydrochloric acid and extracted with chloro-

form. Drying ($MgSO_4$) and evaporating the solvent and subsequent crystallization of the crude product afforded 43 mg. (61%) of the acid CXLIV. The analytical sample, m.p. 153-54°, was obtained as colorless needles after three recrystallizations from methanol-water.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.71; H, 8.42.

1-Carbomethoxy-4,4a,9,10-tetrahydro-4a-methyl-2(3H)-phenanthrone ethylene dithioketal (CXLVI)

A mixture of 510 mg. of the keto ester (CXXX), 510 mg. of freshly fused zinc chloride, 1.02 g. of anhydrous sodium sulfate, 0.5 ml. of ethanedithiol, and 20 ml. of anhydrous benzene was stirred for 48 hours at room temperature. The reaction mixture was taken up in ether and water, the water layer separated and the organic layer washed twice with 5% sodium hydroxide solution. After a final wash with water, the benzene-ether solution was dried ($MgSO_4$) and evaporated. The resulting yellow gum was chromatographed over 15 g. of alumina. Elution with benzene gave 490 mg. (74%) of the thioketal CXLVI, m.p. 120-22°. Colorless prisms of the analytical sample, m.p. 124.5-25.5°, were obtained after three recrystallizations from methanol-water.

Anal. Calcd. for $C_{19}H_{22}O_2S_2$: C, 65.88; H, 6.40.

Found: C, 66.09; H, 6.26.

Ultraviolet spectrum. (Fig. 4) $\lambda_{max.}$ 272 mμ (ε 990).

Methyl-2,3,4,4a,9,10-hexahydro-4a-methyl-1-phenanthrenecarboxylate (CXLV)

A mixture of 490 mg. of the thioketal CXLVI, 1 g. of Raney nickel, and 25 ml. of ethanol was refluxed for 12 hours. After removal of the catalyst by filtration, the filtrate was evaporated giving 306 mg. of a colorless oil. Chromatography of this oil over 5 g. of alumina gave 244 mg. (68%) of the ester CXLV.

Ultraviolet spectrum. $\lambda_{max.}$ 265 mμ (ε 720) and 272 mμ (ε 575).

SUMMARY

The conversion of podocarpic acid to desoxypodocarpic acid and the transformation of the latter substance back to podocarpic acid are described. This transformation resulted in the discovery of a new method for the hydrolysis of very sterically hindered esters. The scope and limitations of this hydrolytic method are discussed.

The attempted degradation of dehydroabietonitrile to deisopropyldehydroabietic acid is reported. Stereochemical proofs of structures for the products obtained in this phase of the study are presented.

Syntheses of compounds useful for the synthesis of desoxypodocarpic acid are described, and the stereochemistry of these intermediates is discussed.

LITERATURE CITED

1. W. P. Campbell and D. Todd, J. Am. Chem. Soc., 64, 928 (1942).
2. _____ and _____, ibid., 62, 1287 (1940).
3. C. W. Brandt and B. R. Thomas, J. Chem. Soc. (London), 1952, 2442.
4. W. F. Short, H. Wang and J. D. S. Goulden, ibid., 1951, 2979.
5. J. A. Barltrop and N. A. J. Rogers, Chem. and Ind. (London), 1957, 397.
6. J. B. Bredenberg and J. Gripenberg, Acta Chem. Scand., 10, 1511 (1956).
7. A. C. Oudemans, Jr., Ber., 6, 1122 (1873).
8. _____, ibid., 6, 1125 (1873).
9. _____, Ann., 170, 214 (1873).
10. _____, J. Prakt. Chem., 9, 385 (1873).
11. T. H. Easterfield and B. C. Aston, Trans. Proc. Roy. Soc. New Zealand, 42, 53 (1910).
12. I. R. Sherwood and W. F. Short, J. Chem. Soc. (London), 1938, 1006.
13. C. W. Brandt and L. G. Neubauer, ibid., 1939, 1031.
14. W. P. Campbell and D. Todd, J. Am. Chem. Soc., 62, 1287 (1940).
15. S. Keimatsu, T. Ishiguro and G. Fukuri, J. Pharm. Soc. Japan, 57, 69 (1937) [C. A. 31, 3932 (1938)].
16. C. W. Brandt and B. R. Thomas, New Zealand J. Sci. Technol. B., 33, 30 (1951).
17. J. B. Bredenberg and J. Gripenberg, Acta Chem. Scand., 8, 1728 (1954).

18. T. H. Easterfield and F. H. McDowell, Trans. Proc. Roy. Soc. New Zealand, 43, 55 (1911).

19. W. F. Short and H. Stromberg, J. Chem. Soc. (London), 1937, 516.

20. W. F. Short and H. Wang, ibid., 1950, 991.

21. Y. Yoshiki and T. Ishiguro, J. Pharm. Soc. Japan, 53, 11 (1933) [C. A., 27, 4530 (1933)].

22. S. Keimatsu and T. Ishiguro, ibid., 55, 45 (1935) [C. A., 29, 7323 (1935)].

23. G. Hukui and T. Tikamori, ibid., 59, 116 (1939) C. A., 33, 4592 (1939).

24. M. T. Bogert, Science, 77, 289 (1933).

25. J. W. Cook and C. L. Hewett, J. Chem. Soc. (London), 1933, 1098.

26. R. D. Haworth and R. Barker, ibid., 1939, 1299.

27. W. E. Parham, E. L. Wheeler and R. M. Dodson, J. Am. Chem. Soc., 77, 1166 (1955).

28. G. Stork and J. W. Schulenberg, ibid., 78, 250 (1956).

29. B. K. Bhattacharyya, J. Indian Chem. Soc., 22, 165 (1945).

30. R. D. Haworth and B. P. Moore, J. Chem. Soc. (London), 1946, 633.

31. F. E. King, T. J. King and J. G. Topliss, Chem. and Ind. (London), 1956, 113.

32. G. Stork and A. Burgstahler, J. Am. Chem. Soc., 73, 3544 (1951).

33. N. N. Saha, P. Bagchi and P. C. Dutta, Chem. and Ind. (London), 1954, 1143.

34. _____, _____ and _____, J. Am. Chem. Soc., 77, 3408 (1956).

35. N. N. Saha, B. K. Ganguly and P. C. Dutta, Chem. and Ind. (London), 1956, 412.

36. W. Parker and R. A. Raphael, J. Chem. Soc. (London), 1955, 1723.

37. F. E. King, T. J. King and J. G. Topliss, Chem. and Ind. (London), 1954, 108.

38. _____, _____ and _____, J. Chem. Soc. (London), 1957, 573.

39. K. Raman and P. N. Rao, Experientia, 12, 472 (1956).

40. J. A. Barltrop and N. A. J. Rogers, Chem. and Ind. (London), 1957, 20.

41. P. F. Ritchie, T. F. Sanderson and L. F. McBurney, J. Am. Chem. Soc., 75, 2610 (1953).

42. _____, _____ and _____, ibid., 76, 723 (1954).

43. A. E. Drake, Oxidation of an Alkali Metal Salt of Dehydroabietic Acid, U. S. Patent 2,434,643 [C. A., 42, 2786 (1948)].

44. R. A. Barnes and M. T. Beachem, J. Am. Chem. Soc., 77, 5388 (1955).

45. D. Arigoni, J. Kalvoda, H. Heusser, O. Jeger and L. Ruzicka, Helv. Chim. Acta, 38, 1857 (1955).

46. K. Schaffner, R. Viterbo, D. Arigoni and O. Jeger, ibid., 39, 174 (1956).

47. A. Brossi, H. Gutmann and O. Jeger, ibid., 33, 1730 (1950).

48. E. S. Hansen and H. H. Zeiss, J. Am. Chem. Soc., 77, 1643 (1955).

49. H. H. Zeiss and M. Tsutsui, ibid., 77, 6707 (1955).

50. Y. T. Pratt, ibid., 73, 3803 (1951).

51. G. W. Kenner and M. A. Murray, J. Chem. Soc. (London), 1949, 5178.

52. G. W. Kenner and N. R. Williams, ibid., 1955, 522.

53. R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, New York, N. Y., 1951.

54. H. L. Goering, T. Rubin and M. S. Newman, J. Am. Chem. Soc., 76, 787 (1954).

55. L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1954.

56-57. C. H. DePuy, Ames, Iowa, Information concerning equilibria of styrenes and phenylallyl systems. (Private communication.) 1957.

58. L. Tsai, T. Miwa and M. S. Newman, J. Am. Chem. Soc., 79, 2530 (1957).

59. M. Gates and W. F. Newhall, ibid., 70, 226 (1948).

60. A. Leo and F. H. Westheimer, ibid., 74, 4383 (1952).

61. H. E. Zimmerman and H. J. Giallombardo, ibid., 78, 6259 (1956).

62. E. J. Corey, ibid., 76, 175 (1954).

63. G. Schroeter, Ann., 426, 17 (1922).

64. R. A. Barnes and R. T. Gottesman, J. Am. Chem. Soc., 74, 35 (1952).

65-66. W. B. Emmons and G. B. Lucas, J. Am. Chem. Soc., 77, 2287 (1955).

67. E. Wenkert and T. E. Stevens, ibid., 78, 2318 (1956).

68. _____ and _____, ibid., 78, 5627 (1956).

69. R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, ibid., 76, 2853 (1954).

70. H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Halterman and R. Robinson, J. Chem. Soc. (London), 1953, 373.

71. L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrenes," 3rd. ed., Reinnold Publishing Corporation, New York, N. Y., 1949.

72-73. J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc. New York, N. Y., 1956.

74-75. R. Antonucci, S. Bernstein, R. Littel, K. J. Sax and J. H. Williams, J. Org. Chem., 17, 1341 (1952).

76. H. Hauptmann, J. Am. Chem. Soc., 69, 562 (1947).

77. W. S. Johnson, Chem. and Ind. (London), 1956, 167.

78. _____ and D. S. Allen, Jr., J. Am. Chem. Soc., 79, 1261 (1957).

79. C. Djerassi and M. Gorman, ibid., 76, 3704 (1954).

80. H. McCombie, B. C. Saunders, and G. J. Stacey, J. Chem. Soc. (London), 1945, 380.

81. L. F. Fieser and W. P. Campbell, J. Am. Chem. Soc., 61, 2528 (1939).

ACKNOWLEDGEMENTS

The author is indebted to Dr. Ernest Wenkert for suggestion of the problem and for helpful guidance throughout the course of the investigation.

He wishes to thank Messrs. W. A. Bappe and R. O. Reinhart for valuable technical assistance, and he is grateful to Drs. R. L. Bible, W. M. Hoehn, H. H. Zeiss and R. W. Ivett for supplying natural products used in this study.