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Reactions of podocarpic acid

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REACTIONS OF PODOCARPIC ACID

by

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Dean of Graduate College

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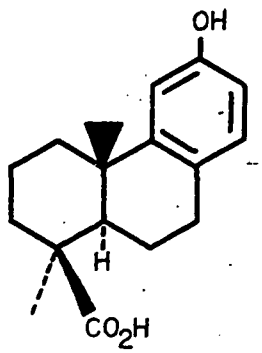
DEDICATION

To

Mickey

INTRODUCTION

In the last several decades the chemistry of podocarpic acid (I) has been investigated extensively, in part because of its possible use as an intermediate in the synthesis of other terpenes and steroids. However, a number of potentially interesting reactions have not been studied yet, and some unusual processes have been left unexplained. It is the purpose of the present study to investigate several of these reactions in some detail.



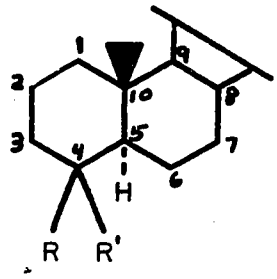
I

HISTORICAL

Catalytic Hydrogenations of Terpenes

The terpenes constitute a large and interesting class of natural products. One of the most challenging aspects of their chemistry is the attempt by the organic chemist to prepare these natural products in the laboratory from conventional starting materials. In these attempts much new organic chemistry of a general nature has evolved.

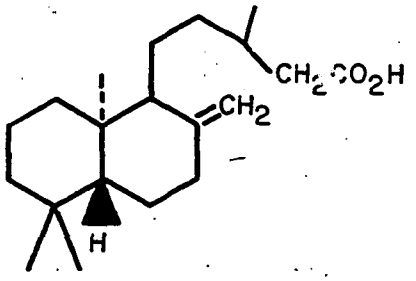
In particular, the synthesis of diterpenes is noteworthy. A general part structure of a majority of these C_{20} substances may be represented as follows:



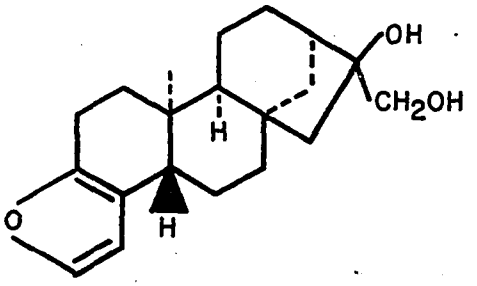
II

Several generalities are shown in II. C-4 is nearly always disubstituted. Usually R or R' is a methyl group, while the other substituent is either a methyl group or another one-carbon fragment in a higher state of oxidation. Another general feature is the A:B <u>trans</u> ring juncture of the absolute configuration shown in II. There are some exceptions, however. They include eperuic acid (III) and related derivatives

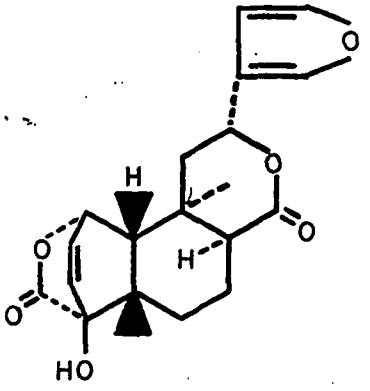
(1, 2), cafestol (IV), columbin (V), and andrographolide (VI).



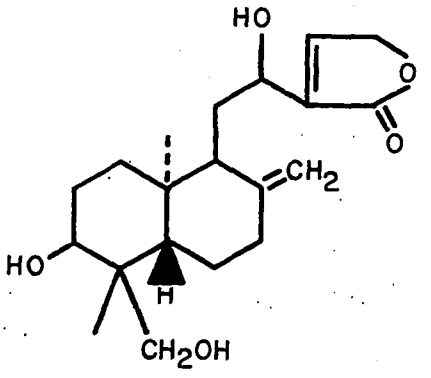
III



IV

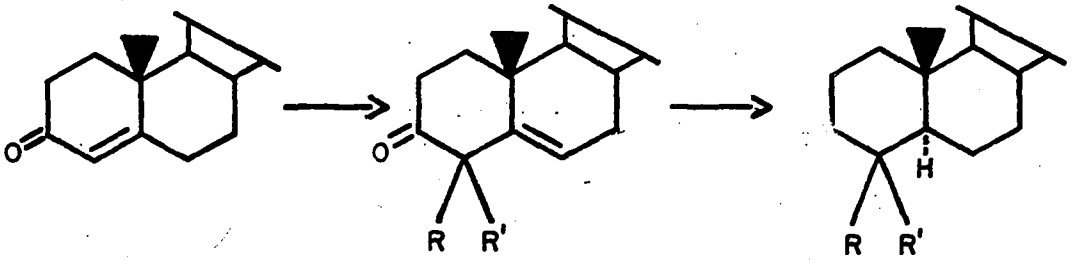


V



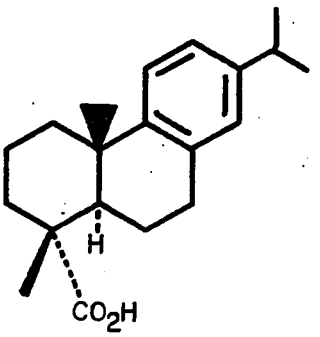
VI

One synthetic route for diterpenes involves the introduction of the C-4 substituents on a 2-octalone VII by the procedure of Woodward (3, 4). This is followed by removal of the keto group and catalytic hydrogenation of the $\Delta^{5,6}$ system VIII to give the decalin IX.

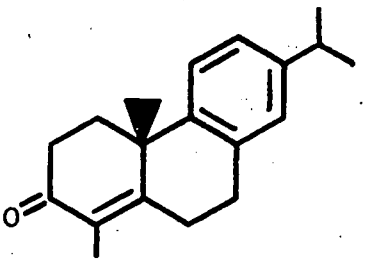


VII VIII IX

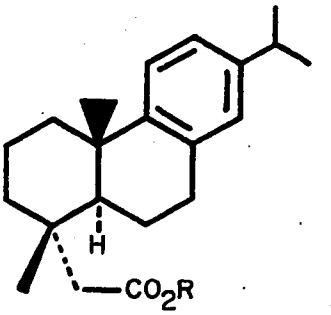
The first example of this type of reaction scheme for diterpenes was the total synthesis of dl-dehydroabietic acid (X) by Stork and Schulenberg (5). The second C-4 substituent was introduced by alkylation of the α, β -unsaturated ketone XI with ethyl bromoacetate to give the ester XII. After removal of the keto function via its thioketal and desulfurization with Raney nickel, the double bond was hydrogenated catalytically. Barbier-Wieland degradation of the acid XIII gave the desired natural product X, whose A:B ring juncture is known to be trans. This constituted proof that the double bond had been hydrogenated from the α-side.



X



XI

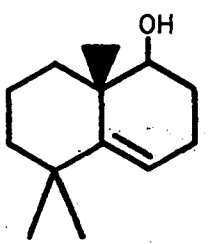


XII R = CH_2CH_3

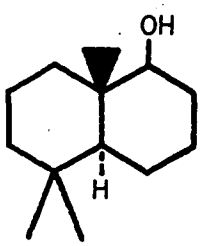
XIII R = H

A number of examples of similar schemes of alkylation and reduction are known. Sondheimer and Elad (6) reduced the octalol XIV and obtained the decalol XV in 73% yield. The stereochemistry of the A:B juncture was assigned on the basis of models of XV. These same investigators (7) effected the reduction of the ketone XVI to give the trans-decalone. This

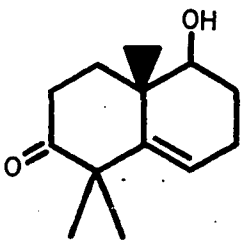
was proved by comparison of a derivative XVII with a compound prepared by Gaspert, Halsall, and Willis (8), to which configuration XVII had been assigned. This assignment had been made on the basis of the degradation of XVII to XVIII and comparison of the latter with the compound obtained from XIX by a series of reactions, the first of which was reduction with lithium-ammonia, a reaction known to give <u>trans</u> ring fusion (9).



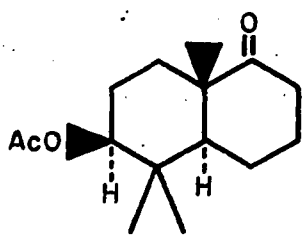
XIV



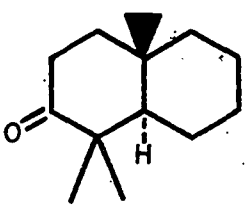
XV



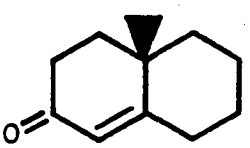
XVI



XVII

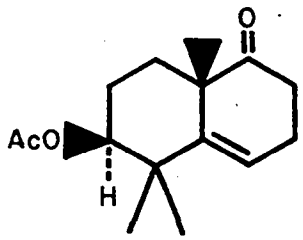


XVIII

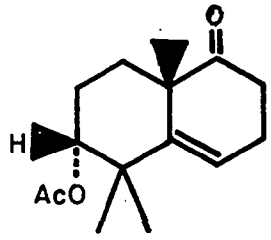


XIX

Kalvoda and Loeffel (10) did some careful studies on the catalytic hydrogenation of some octalone systems. They found that reduction of XX with platinum oxide in acetic acid gave 6:1.8 ratio of <u>trans</u>-:<u>cis</u>-decalones. However, hydrogenation of the epimeric acetate XXI gave 4.3:0.9 ratio of <u>cis</u>:<u>trans</u> products.

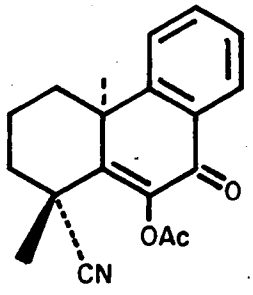


XX

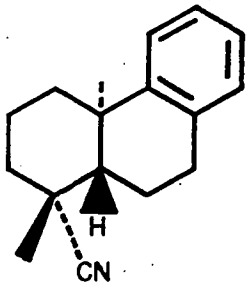


XXI

In proving the isomerization of the C-10 methyl group during the deisopropylation reaction of dehydroabietonitrile, Wenkert and Jackson (11) used a scheme which involved the hydrogenation of the enol-acetate XXII. Hydrogenation of this acetate furnished compound XXIII which was shown to be an enantiomer of desoxypodocarponitrile. This indicated that the hydrogenation of XXII had yielded a <u>trans</u> A:B ring juncture.



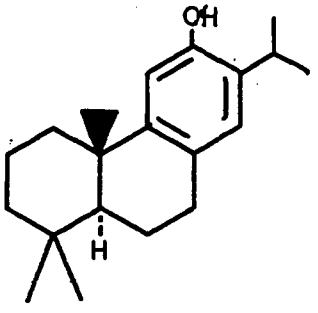
XXII



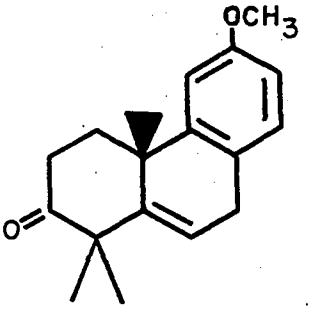
XXIII

In the stereospecific synthesis of ferruginol (XXIV), Rao and Raman (12) obtained the phenolic diterpene from a series of reactions which included catalytic reduction of the unsaturated compound XXV. The proof of the stereochemistry of this reduction is the fact that the compound isolated was

identical with naturally occurring ferruginol (XXIV).

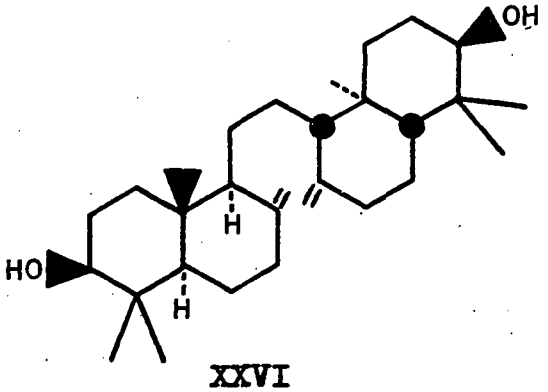


XXIV

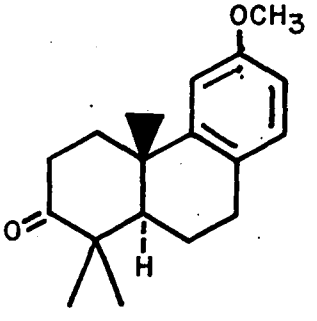


XXV

Stork et al. (13) reported the total synthesis of the triterpene ∝-onocerin (XXVI). The tricyclic intermediate XXVII was prepared by the catalytic hydrogenation of XXV.

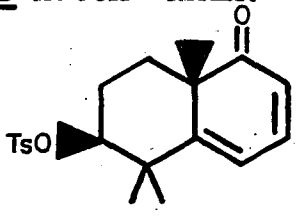


XXVI

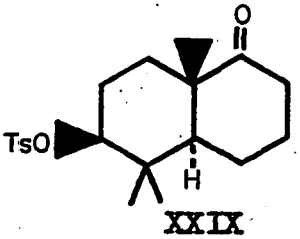


XXVII

In their preliminary studies into the synthesis of pentacyclic triterpenes, King, Ritchie, and Timmons (14) hydrogenated the conjugated dienone XXVIII and obtained the trans-ketone XXIX.

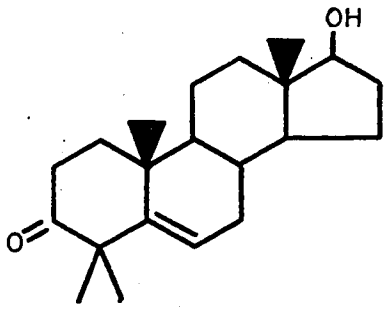


XXVIII

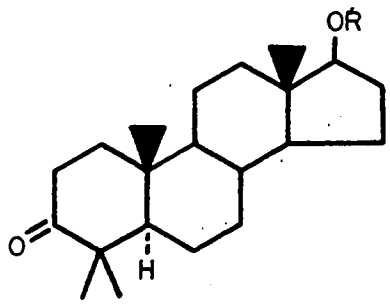


XXIX

This type of reduction has also been investigated in the steroid field. In synthesizing 4-methyl and 4,4-dimethyl hormone analogs, Ringold and Rosenkranz (15) reduced the steroid ketone XXX catalytically to give 4,4-dimethylandrostane-17-β-ol-3-one (XXXI) in 81% yield. Evidence for the trans A:B juncture was the optical rotatory dispersion curves of XXXI and XXXII which were identical with the known 4,4-dimethyl-3-keto-A:B trans terpenes. Similarly, Beton et al. (16) reduced XXXIII to give the cholestane derivative XXXIV whose 2-propylene dithio derivative XXXV was shown to be identical with the 4,4-dimethyl compound obtained by methylation of the cholestanone derivative XXXVI.

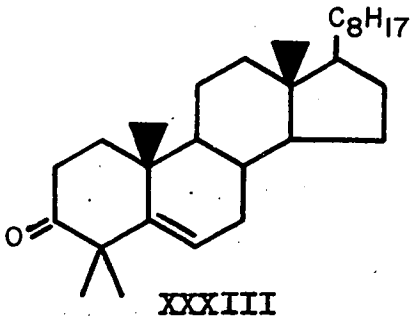


XXX

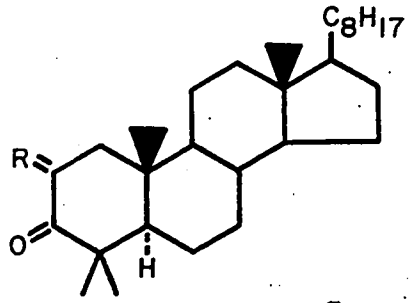


XXXII R = CH_3

XXXI R = H

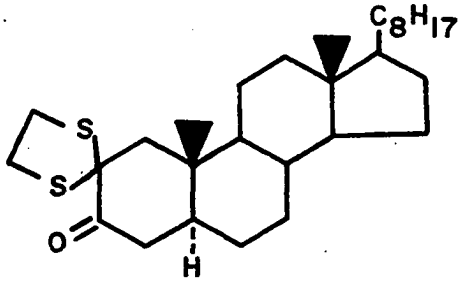


XXXIII



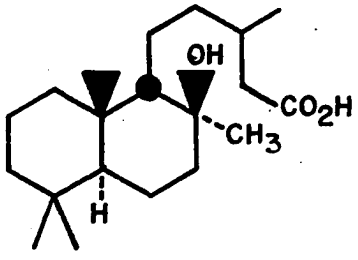
XXXV R = 

XXXIV R = H_2

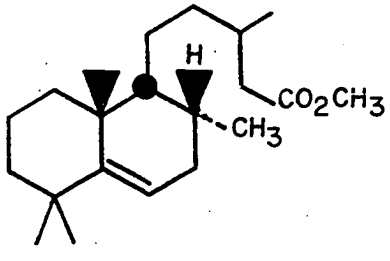


XXXVI

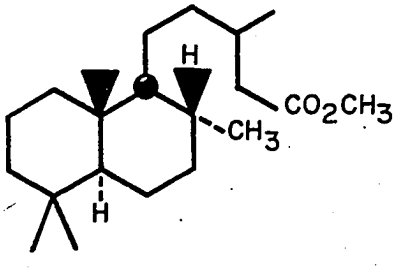
In preliminary investigations into the synthesis of labdanolic acid (XXXVII), Cocker and Halsall (17) prepared the decalol of Sondheimer and Elad XV by catalytic reduction of the octalol XIV. The trans ring juncture was inferred from the results of previous investigations (16). In later studies Halsall and Moyle (18) hydrogenated XXXVIII with Adams catalyst to give methyl-8- β (H)-labdan-15-oate (XXXIX).



XXXVII

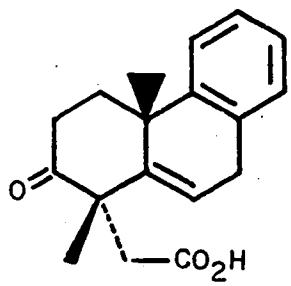


XXXVIII

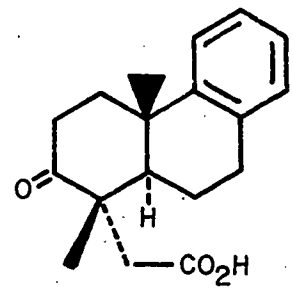


XXXIX

Ghatak *et al.* (19) reduced the homo-acid XL in the preparation of the stereoisomers of deisopropyldehydroabietic acid and obtained the A:B *trans* compound XLI in almost quantitative yield.

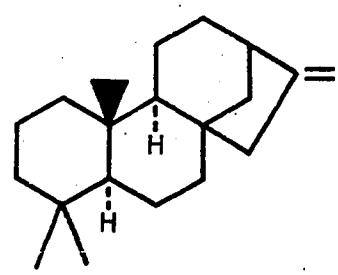


XL

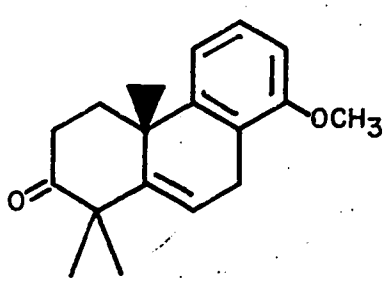


XLI

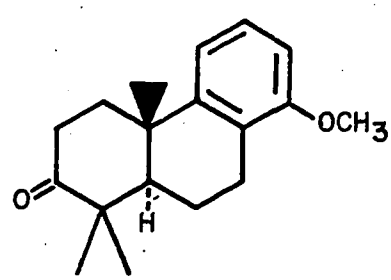
Turner and Shaw (20) synthesized a degradation product of phyllocladene (XLII) by the palladium-catalyzed reduction of the unsaturated ketone XLIII to the saturated *trans* tricycle XLIV.



XLII



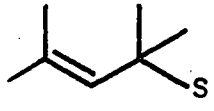
XLIII



XLIV

Raney Nickel Desulfurization

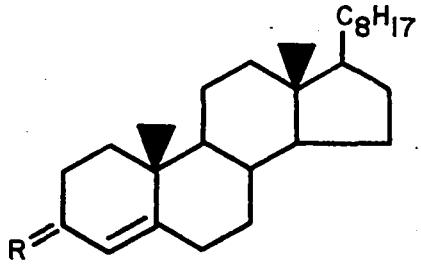
Since the use of Raney nickel for the desulfurization of organic thio compounds was first described by Bougault, Cattelain, and Chabrier (21), it has become a valuable synthetic tool for the organic chemist. The reaction involves the straightforward replacement of one or more sulfur atoms attached to carbon with one or more hydrogen atoms, yielding the parent hydrocarbon. However, because Raney nickel is also a hydrogenation catalyst (22, 23, 24), its behavior with compounds of general structure XLV, having the double bond allylic to the sulfur atom, may give mixed results. The sulfur atom may be removed with (a) no interaction with the double bond, (b) migration of the double bond to a thermodynamically more stable position, or (c) concomitant hydrogenation of the double bond.



XLV

Examples of this desulfurization have been previously reported. Hauptmann (25) prepared the unsaturated dibenzyl mercaptol XLVI with benzyl mercaptan, zinc chloride, and sodium sulfate. The product was desulfurized with Raney nickel in dioxane:water to give XLVII, identical in melting

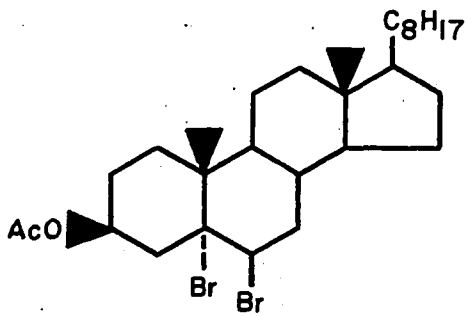
point and optical rotation with Δ^4-cholestene (XLVII).



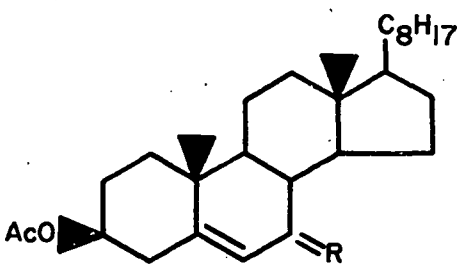
XLVI R = $(C_6H_5CH_2S)_2$

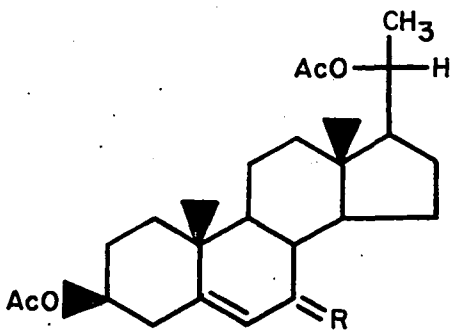
XLVII R = H_2

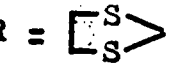
Other workers obtained similar results on steroid derivatives. Ralls, Dodson, and Riegel (26) prepared XLIX using ethanedithiol with dry hydrogen chloride as the catalyst. Desulfurization in dioxane:water gave L, which on bromination of the double bond gave a dibromo compound identical in all respects with XLVIII. This provided evidence that the double bond had neither migrated nor been reduced. Djerassi et al. (27) prepared the dithio diacetate LI and effected its desulfurization in acetone to give LII which was shown to be identical with authentic LII by mixed melting point and infrared comparison.



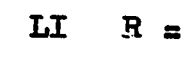
XLVIII





XLIX R = 

L R = H_2

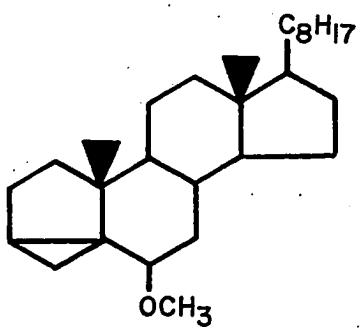
LI R = 

LII R = H_2

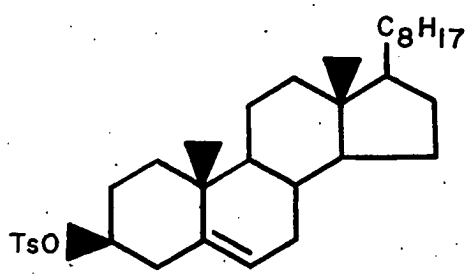
Neighboring Group Participation

In 1937 it was noted by Cowdrey et al. (28) that the hydrolysis of optically active α-bromo propionate with hydroxide ion gave the corresponding α-hydroxy propionate with unexpected retention of configuration. Two years later Winstein and Lucas (29) noted similar stereochemical results in the reaction of hydrogen bromide with the 3-bromo-2-butanols. According to Winstein these observations were best explained by considering that the atom attached to the α-carbon atom (in this case bromine) had participated in the reaction enabling the reaction center to retain its original stereochemistry. Further studies have added credence to this theory, now known as the theory of neighboring group participation.

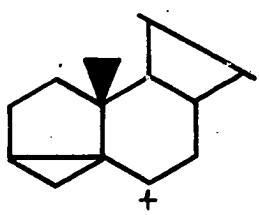
This type of interaction is well documented in the chemical literature. A celebrated example is the formation of i-cholesteryl ether (LIII) in the methanolysis of cholesteryl p-toluenesulfonate (-OTs = p-toluenesulfonate) (LIV) (30). Among the many investigators who have looked into this reaction has been Winstein (31) et al. who suggested that the reaction may involve the formation of intermediates such as LV or LVI. The fact that the i-ether LIII can be converted back to LIV with overall retention of configuration is evidence in favor of such intermediates.



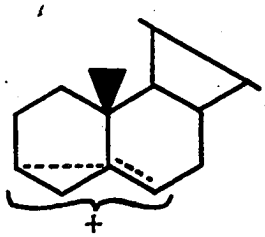
LIII



LIV



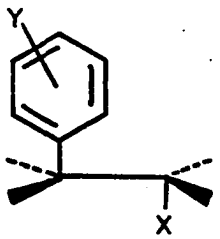
LV

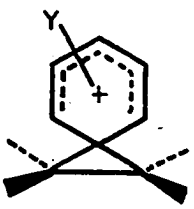


LVI

The theory of homoallylic rearrangements has been expounded and investigated by Winstein et al. using a series of 2-phenylethanol compounds of general structure LVII. Evidence gathered in these investigations has given rigorous

proof for the existence of symmetrical intermediates LVIII.



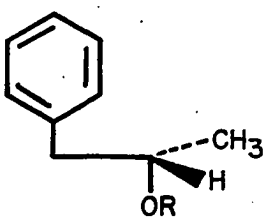


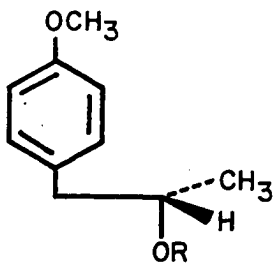
Y = H, OCH_3, NH_2, CH_3, etc.

X = Cl, Br, OTs, OAc, etc.

LVII LVIII

For instance, Winstein (32) investigated the formolysis of the optically pure p-toluenesulfonate LIX and observed that the product LX possessed 85% retention of configuration. These authors also showed that the presence of electron-donating groups on the aromatic ring enhanced the rate of this reaction, since the p-methoxy compound LXI gave formate LXII 37 times faster than the simple benzyl compound LIX.





LIX R = OTs

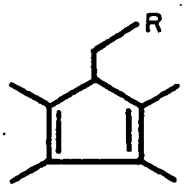
LX R = CHO

LXI R = OTs

LXII R = CHO

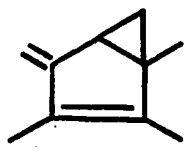
Homoallylic participation has also been observed in other unsaturated systems. Winstein and Battiste (33) solvolyzed

LXIII in acetic acid with added sodium acetate and obtained the cyclopropane LXV and the acetate LXIV in the ratio of 18:1, respectively. The structure of LXV was proved by comparison of the ultraviolet and infrared spectra with the spectra of authentic LXV prepared by another method (34).



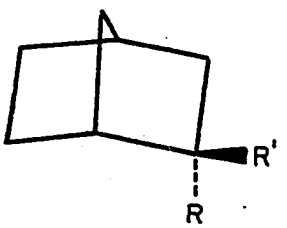
LXIII R = OTs

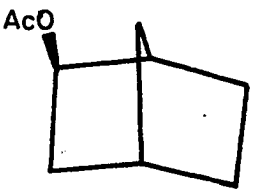
LXIV R = OAc

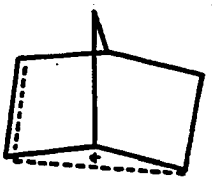


LXV

By observing the kinetics of some solvolyses in the norbornyl series, Winstein and co-workers obtained striking results which further indicated the existence of homoallylic interactions. These workers (35) treated the exo- and endo-5-bromobenzenesulfonates LXVI (-OBs = p-bromobenzenesulfonate) with acetic acid and obtained the same exo-acetate LXVII. Winstein postulated the non-classical carbonium ion LXVIII as the activated intermediate which gives rise to the observed behavior. Also, the relative solvolysis rates (36) of anti-7-norbornenyl p-toluenesulfonate (LXIX) and 7-norbornyl p-toluenesulfonate (LXX) are in the ratio of 10^{11}:1, respectively. The rate enhancement was explained again on the basis of participation of the homoallylic double bond as in LXXI.

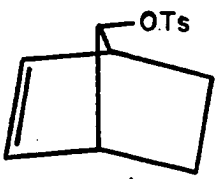


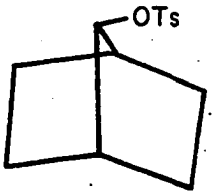


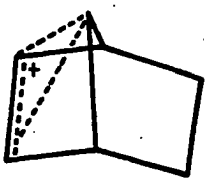


LXVIa R = H; R' = OBs LXVII LXVIII

LXVIb R = OBs; R' = H



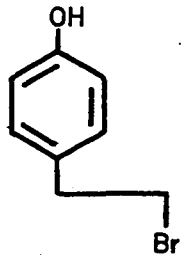




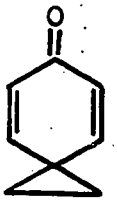
LXIX LXX LXXI

In all the cases reviewed thus far, the evidence for the cyclopropyl-type intermediate has been inferred from the examination of the products (e.g. their retention of configuration), and in no case has the actual isolation of such an intermediate been reported. However, in 1957, Winstein and Baird (37, 38) passed an ethereal solution of 2-p-hydroxyphenyl-1-ethyl bromide (LXXII) through a basic alumina column and obtained a solution of a compound which they postulated to have the spiro-structure LXXIII on the basis of the following evidence. The infrared spectrum was consistent with that expected for a highly conjugated carbonyl structure. It gave the correct carbon-hydrogen analysis for C_8H_8O. Chemically, catalytic hydrogenation gave p-ethylphenol in good yield.

When LXXIII is treated with ethereal hydrogen bromide, the parent compound LXXII is isolated.

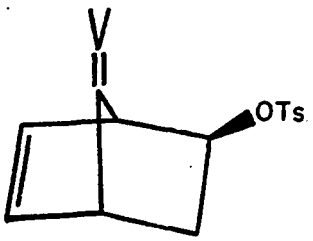


LXXII

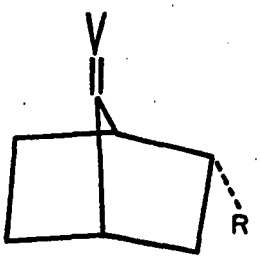


LXXIII

DePuy et al. (39) observed rate enhancement and complete stereospecificity in the acetolysis of the exo- and endo-tosylates, LXXIV and LXXVa, respectively. LXXIV gave the rearranged acetate LXXVI, and LXXVa gave the endo-acetate LXXVb as the sole product. The homoallylic interaction of the double bonds with the reaction center was cited as the explanation of both the accelerated rates and the stereospecificity. In work on the 5,6-dihydro compounds, LXXVIIa and LXXVIIb, DePuy and Story (40) noted similar results with regard to the relative rates and stereochemistry.

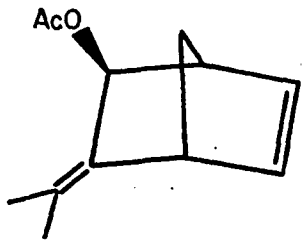


LXXIV

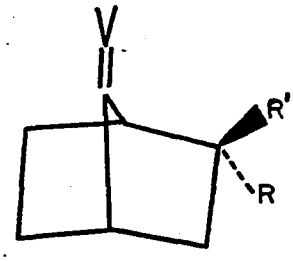


LXXVa R = OTs

LXXVb R = OAc



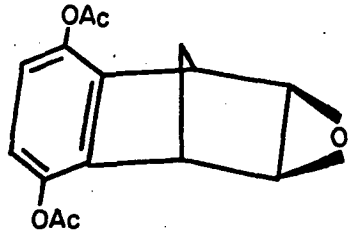
LXXVI



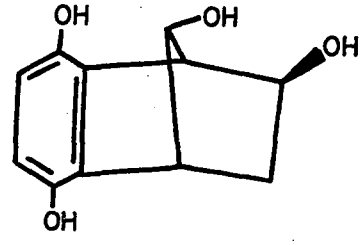
LXXVIIa R = H, R' = OTs

LXXVIIb R = OTs, R' = H

Meinwald and Wiley (41) observed an unusual rearrangement in a benzonorbornene system which was thought to involve group participation. When the epoxide LXXVIII was treated with mild base the product isolated was not the deacetylated epoxide but the tetraol LXXIX. This unexpected result was interpreted by the authors as a consequence of a homoallylic interaction of the hydroquinone ring with the epoxide. The reaction rate was high in contrast to the general inertness of such epoxides toward attack by base.



LXXVIII



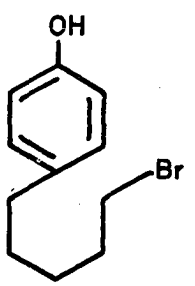
LXXIX

Internal Phenol Alkylations

Intramolecular phenol alkylations have been investigated recently as a method of attaching alkyl groups to an alicyclic

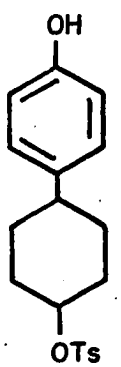
ring. The cases reported thus far have involved substituted phenols which underwent "desaromatization" (a word coined by Dreiding (42)) during the reaction.

The first instance in the literature of intramolecular phenol alkylation comes from the work of Dreiding (42). When a dilute t-butanol solution of the potassium salt of LXXX was heated in a sealed tube at 170°, there was realized an 88% yield of a dienone whose structure was shown to be LXXXI. The melting point and spectral properties of LXXXI and its 2,4-dinitrophenylhydrazone were identical with those of authentic LXXXI which had been prepared by an alternate method by Burnell and Taylor (43). The same investigator, together with Barner and Schmid (44), treated the hexahydrobiphenyl LXXXII under similar conditions and isolated the bridged compound LXXXIII in 8% yield. Two other products, LXXXIV (13%) and LXXXV (56%), were identified from the reaction mixture.

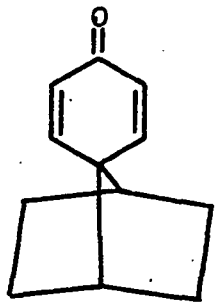


LXXX

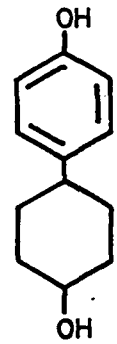
LXXXI



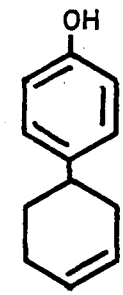
LXXXII



LXXXIII

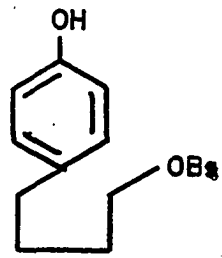


LXXXIV

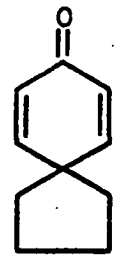


LXXXV

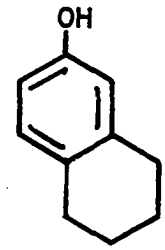
About the same time Winstein (45), in his extensive studies into neighboring group participation, heated the potassium salt of the p-bromobenzenesulfonate LXXXVI in t-butanol and obtained in more than 50% yield a dienone which was shown to be the gem-compound LXXXVII. This structure was validated by the elemental analysis, spectral properties, and uptake of 2 moles of hydrogen. Also, LXXXVII could be caused to undergo the known dienone-phenol rearrangement to give the tetrahydronaphthol LXXXVIII. With a compound of similar structure, Doring and Harley-Mason (46) observed a comparable product. When the ketal LXXXIX was treated with potassium t-butoxide in t-butanol, the bicyclic ketal XC was formed in 40% yield. The same product and yield were realized by pyrolysis of the sodium salt of LXXXIX. The structure of the product was proved by hydrolysis of the ketal and subjection of the diketone to the conditions of the dienone-phenol rearrangement (mineral acid in acetic anhydride). The diacetate that formed was aromatized, giving 2,6-diacetoxynaphthalene (XCI).



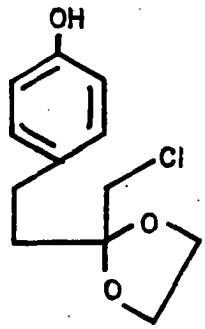
LXXXVI



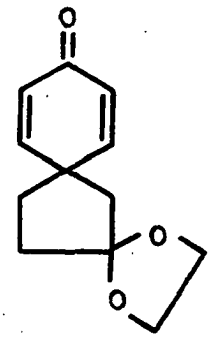
LXXXVII



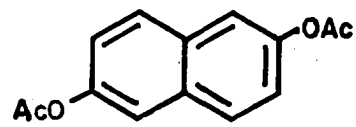
LXXXVIII



LXXXIX

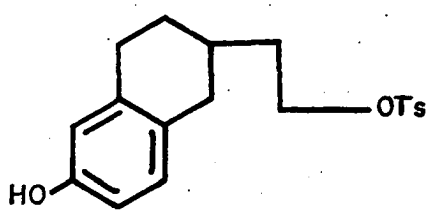


XC

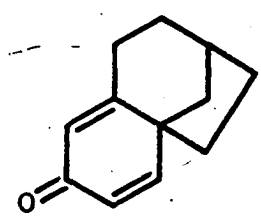


XCI

This reaction has been used in the formation of an intermediate toward the synthesis of a diterpene, phyllocladene (XLII). Masamune (47) prepared the p-toluenesulfonate XCII and heated its potassium salt to give the tricyclic ketone XCIII. Confirmation of the proposed structure was shown by the elemental analysis and its ultraviolet and infrared properties.



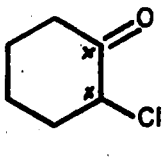
XCII



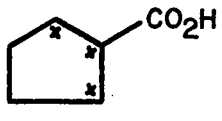
XCIII

The Favorskii Reaction

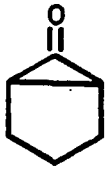
Since the original observation of the action of hydroxylic bases on α-haloketones by Favorskii (48), much effort has been put forth in determining reaction conditions, products, and stereochemistry. A thorough review of the Favorskii reaction has been assembled by Kende (49). A number of authors (50, 51, 52, 53, 54) have proposed mechanisms which have partially explained the results. Until recently, however, there was no rigorous proof for any one mechanism. An elegant investigation carried out by Loftfield (55) has disproved many of the existing theories and strongly supports the idea that the mechanism involves a symmetrical intermediate. The proof involved the use of C-14 tagging experiments. The α-chloroketone XCIV was prepared with equal proportions of radioactivity at carbons 1 and 2 (the asterisks indicate the labeled positions). When XCIV was treated with sodium isoamyloxide and the resulting ester hydrolyzed, the carboxylic acid XCV isolated contained <u>equal</u> amounts of C-14 at both the α- and β-carbon atoms. This was cited as conclusive proof for the formation of a symmetrical intermediate which Loftfield proposed to be the cyclopropanone XCVI.



XCIV

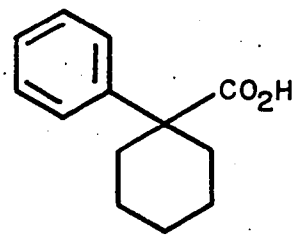


XCV

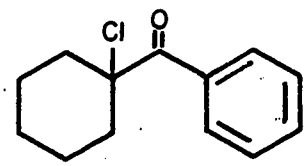


XCVI

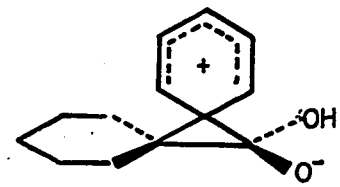
The Loftfield mechanism, however, does not explain those cases where α-haloketones with no α-hydrogen atoms undergo a Favorskii-type reaction. In 1939 Tchoubar and Sackur (56) noted the formation of the acid XCVII upon treatment of the haloketone XCVIII with powdered potassium hydroxide. The authors postulated a mechanism that involved the 1,2 migration of the phenyl group. Some years later Stevens and Farkas (57) studied the action of base on the same substrate. They found that 53% of the rearranged acid XCVII formed under optimum conditions. These investigators proposed a pinacol type rearrangement mechanism with the intermediate formation of the bridged ion XCIX.



XCVII

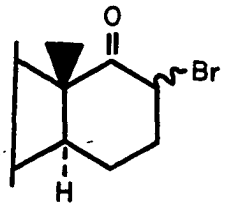


XCVIII

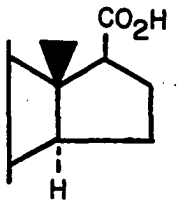


XCIX

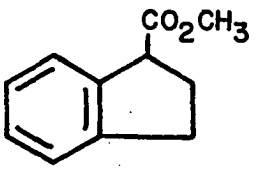
Several other examples of a similar reaction have been reported. Prins and Shoppee (58) treated the D-homoandrostane derivative C (partial structure as shown) with powdered sodium hydroxide in dioxane and isolated the acid CI in less than 1% yield. Mousseron and Phuoc Du (59) obtained methyl-1-indanoate (CII) from the reaction of sodium methoxide with 2-chloro-1-tetralone (CIII).



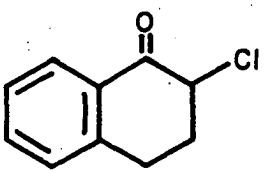
C



CI



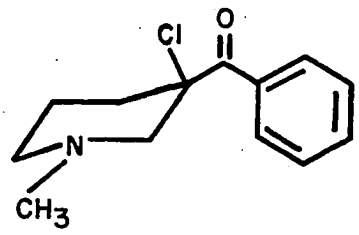
CII



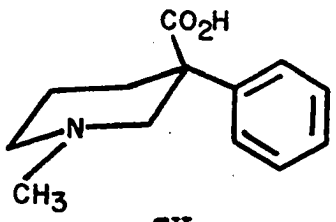
CIII

Smissman and Hite (60) investigated the so-called "quasi-Favorskii rearrangement" using the benzoylpiperdine CIV. They obtained evidence that the electron pair on the nitrogen atom was involved in the reaction pathway. When optically pure CIV was treated with powdered sodium hydroxide in refluxing xylene or Skelly E, there was formed the racemic acid CV and the dextrorotatory hydroxyketone CVI. Optical rotatory dispersion studies showed that the relative configuration of the original α-chloroketone CIV and CVI were the same, implying that the chloride ion had been replaced with retention of configuration. The ion pair CVII was proposed to explain this observation. CVII upon loss of a chloride ion could undergo racemization and phenyl migration to give the "quasi-cyclopropanone intermediate" CVIII. This cation could

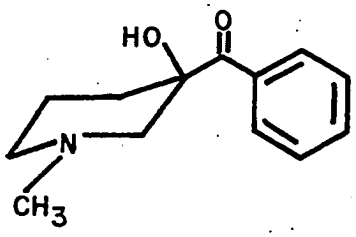
account for the racemic acid CV which was isolated from the reaction. Other evidence in favor of the formation of a cation was that optically pure CIV was racemized to the extent of 10% when refluxed for 30 minutes in xylene.



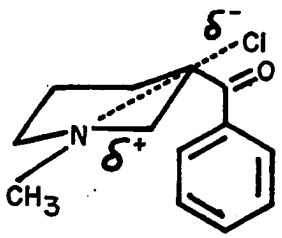
CIV



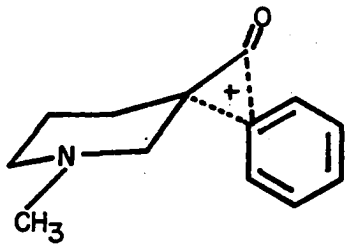
CV



CVI



CVII

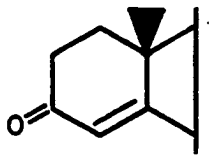


CVIII

Elimination Reactions of α-Haloketones

Because of the medicinal importance of steroids in modern times extensive chemical investigations have been carried out on the reactions and synthesis of these compounds. Whole areas of organic chemistry have their background in the studies of natural products such as the steroids. One such area is the reaction of bases with α-haloketones. The reason for extensive work in this particular area becomes apparent on the basis of the fact that most physiologically active steroids in the androgenic, progestational, and cortical hormone

series contain a Δ^4-3-keto grouping CIX. If the double bond is not already present, it is usually introduced by C-4 bromination of the appropriate 3-keto system and dehydrobromination. In the estrogenic series the feasibility of this same general method for obtaining an aromatic ring A has been investigated.

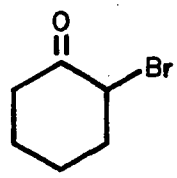


CIX

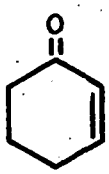
Unfortunately this method has its limitations. While in the "normal" steroid series (A:B cis-ring juncture) bromination leads to the C-4 derivative, the product obtained in the "allo" series (A:B trans-ring juncture) has the bromine at C-2 (61). Not all bases are suitable reagents for the dehydrobromination step. Simple hydroxylic bases will promote mainly undesirable condensations or initiate the Favorskii reaction. Therefore, nitrogen bases such as pyridine, collidine or various anilines have been used. More recently (62) 2,4-dinitrophenylhydrazine (2,4DNP) has been shown to be an excellent dehydrobrominating agent.

Kotz (63), as early as 1908, studied the transformation of hydroaromatic to aromatic compounds by this method. Bromination of cyclohexanone gave CX which, on treatment with aniline, gave the conjugated ketone CXI. However, aniline was

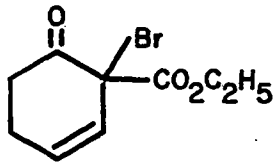
found to give poor yields and side reactions. It was found that simple distillation caused the evolution of hydrogen bromide, giving the same products. For instance, the bromo compound CXII gave the phenol CXIII by this procedure.



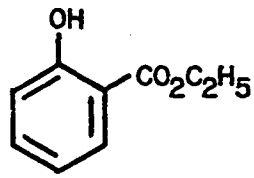
CX



CXI

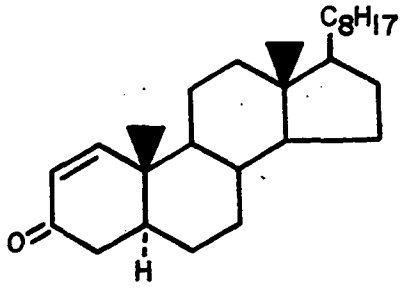


CXII

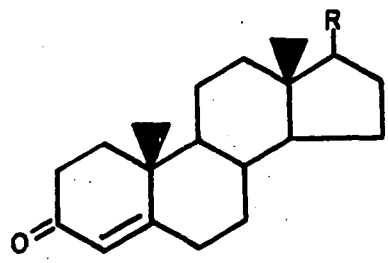


CXIII

Various investigators have studied this reaction extensively. Butenandt and Schmidt (64) found that treatment of CXVII with refluxing pyridine for 12 hours gave the desired enone CXV. The monobromo compound CXVII was obtained from the C-20 hydroxy compound which was oxidized to the diketone and then dehydrobrominated. Butenandt and Wolff (61) prepared 2-Br-cholestanone (CXVIII) and obtained the Δ^1-3-ketone CXIV by the use of potassium acetate and acetic acid under stringent conditions. The corresponding 4-bromo derivative CXIX with refluxing pyridine gave the enone CXVI (m.p. and mixed m.p.).

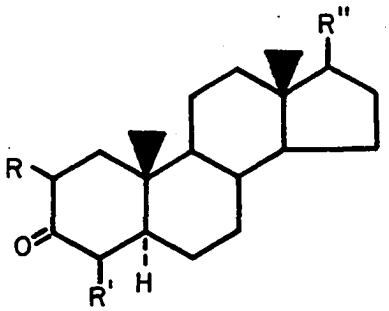


CXIV



CXV R = Ac

CXVI R = C_8H_{17}

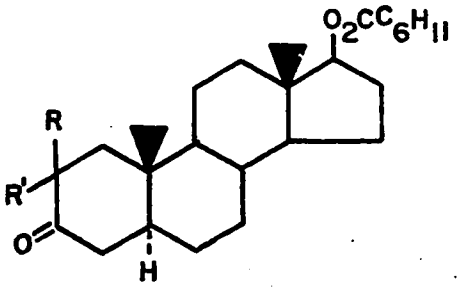


CXVII R = H; R' = Br; R'' = Ac

CXVIII R = Br; R' = H; R'' = C_8H_{17}

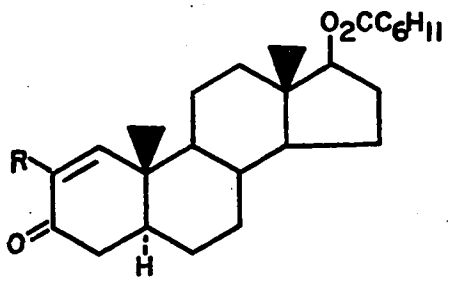
CXIX R = H; R' = Br; R'' = C_8H_{17}

Work carried out by Djerassi and Scholz (65) indicated that a mixture of products could form in this reaction. When the 2-bromo compound CXX was treated with collidine, both the Δ^1- and Δ^4-enones, CXXII and CXXIV, were formed, the latter in 20% yield. In preparing some estradiols from cholesterol, Djerassi and Wilds (66) found that the dibromo ketone CXXI formed the vinyl bromide CXXIII on treatment with refluxing collidine. The same ketone CXXI, when reacted with hydrogen bromide in acetic acid, gave the isomerized halide CXXV which was dehydrobrominated to the dienone CXXVI. The latter could be rearranged to the 1-methylphenol CXXVII. Using the same procedure Djerassi and Scholz (67) prepared 5-methyl-doisynolic acid (CXXVIII) from androstane-3,17-dione (CXXIX), after cleavage of ring D.



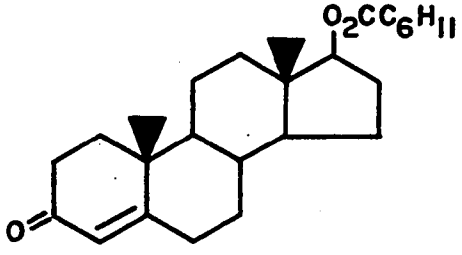
CXX R = H; R' = Br

CXXI R = R' = Br

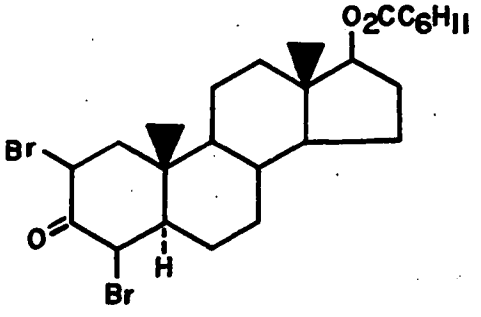


CXXII R = H

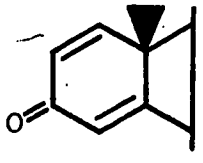
CXXIII R = Br



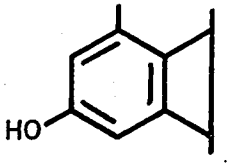
CXXIV



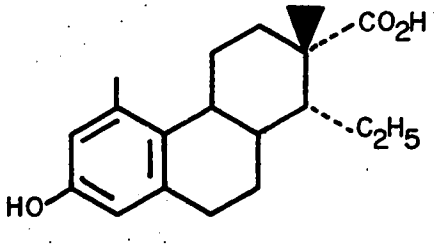
CXXV



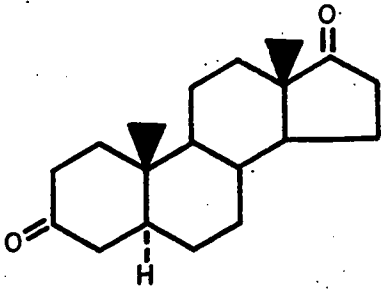
CXXVI



CXXVII

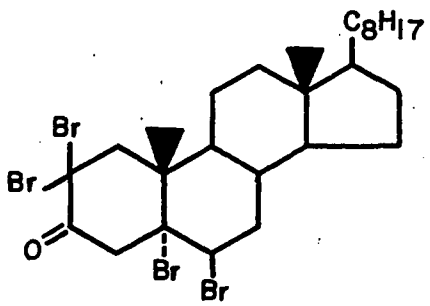


CXXVIII

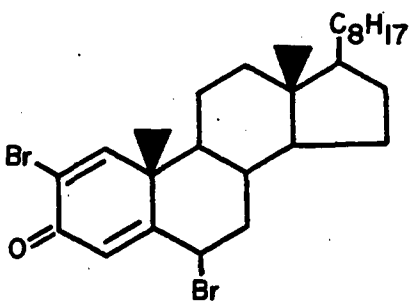


CXXIX

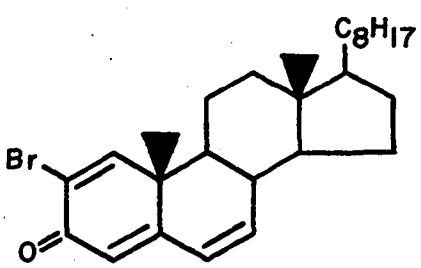
Collidine has been found to react at different rates in dehydrobrominations depending upon the position of the bromine atom. Fieser, Romero, and Fieser (68) determined the reactivities of the bromine atoms in CXXX. The dienone CXXXI was formed after 5 minutes with refluxing collidine, which on longer treatment with the same reagent, gave the trienone CXXXII. Also, the 2,5-dibromocholestanone (CXXXIII) gave the unsaturated bromide CXXXIV by selective treatment with collidine.



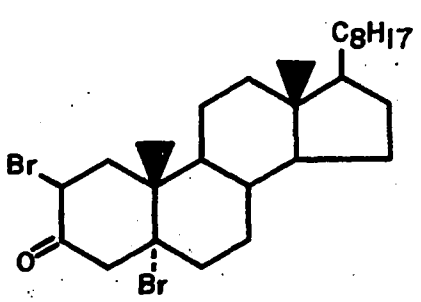
CXXX



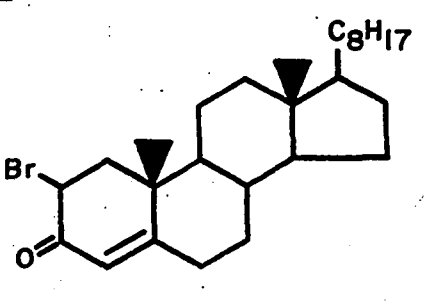
CXXXI



CXXXII

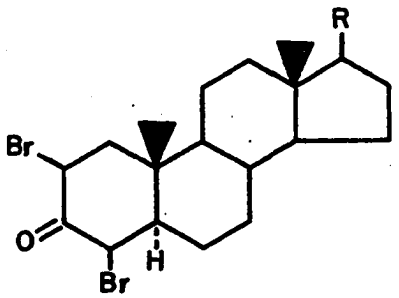


CXXXIII



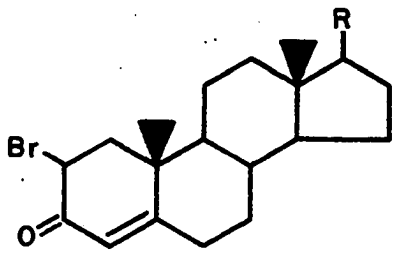
CXXXIV

Similar reactivity differences were noted by Inhoffen and Zühlsdorff (69). Treatment of CXXXV with collidine formed the enone CXXXVII after 5 minutes, and the benzoate CXXXVI gave the Δ^4-ketone CXXXVIII in only 2 minutes. Treatment of CXXXIX for ½ hour with the same base formed the dienone CXL.



CXXXV R = $OCOC_6H_{11}$

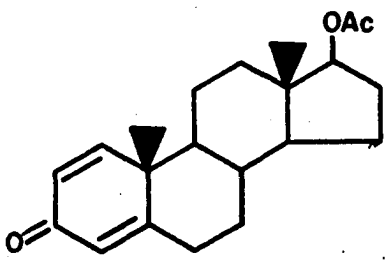
CXXXVI R = $OCOC_6H_5$



CXXXVII R = $OCOC_6H_{11}$

CXXXVIII R = $OCOC_6H_5$

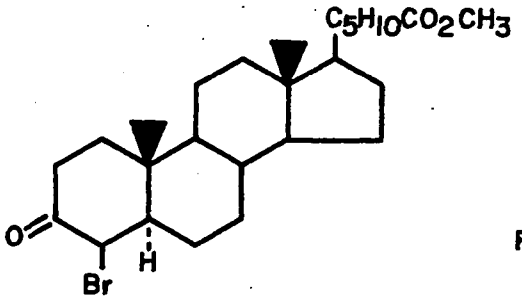
CXXXIX R = OAc



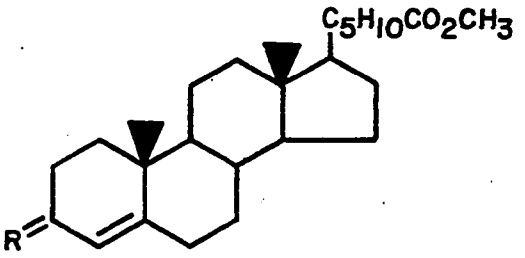
CXL

Although collidine has been employed extensively as a base, Mattox and Kendall (62) have shown that 2,4DNP is a useful reagent. Treatment of the bromoketo ester CXLI with the hydrazine derivative gave the unsaturated hydrazone CXLII. The ketone CXLIII could be regenerated by hydrazone exchange with pyruvic acid. CXLIII proved to be identical with the

product made by pyridine dehydrobromination of CXLI. Using the same reagent Djerassi (70) obtained the Δ^1-ketones CXLV from the 2-bromides CXLIV in 80-90% yield in the A:B *trans* series.

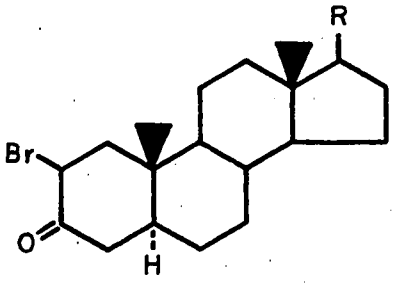


CXLI

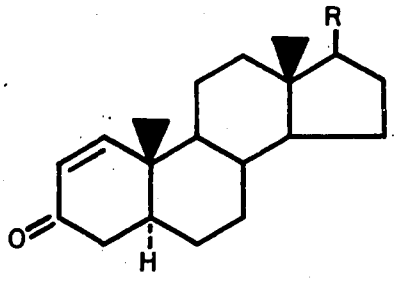


CXLII R = $NN(H)C_6H_3(NO_2)_2$

CXLIII R = O



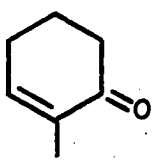
CXLIV R = C_8H_{17} or CO_2CH_3



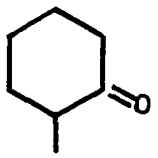
CXLV R = C_8H_{17} or CO_2CH_3

Work has also been carried on with mono- and bicyclic compounds. Rinne *et al.* (71) prepared the conjugated ketone CXLVI from 2-methyl-1-cyclohexanone (CXLVII) by making the intermediate bromide and treating with 2,4DNP to obtain the hydrazone of CXLVI in 78% yield. Ramirez and Kirby (72) observed the same reactions with substituted cyclohexanones. Treatment of the 2,4DNP derivative of CXLVIII with boiling

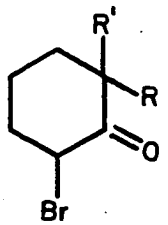
acetic acid for 5 minutes gave the unsaturated compound CXLIX. However, 2-bromo-1-tetralone (CL) and the tetrahydrophenanthrone CLI did not eliminate the elements of hydrogen bromide under identical conditions. The authors explained this on the basis of the extra resonance energy stabilization of the benzene ring to the ground state of the molecule.



CXLVI

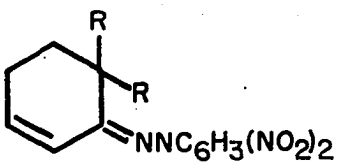


CXLVII



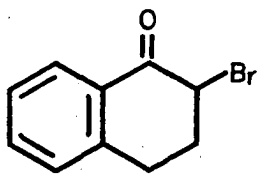
CXLVIII R = R' = H

or R = R' = CH_3

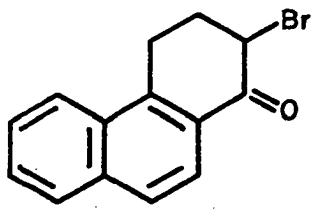


CXLIX R = R' = H

or R = R' = CH_3

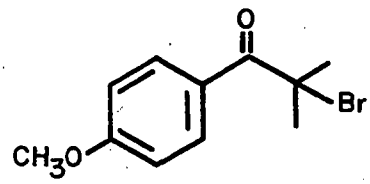


CL

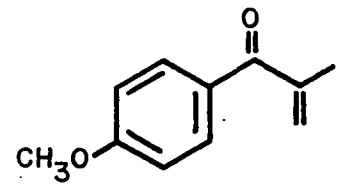


CLI

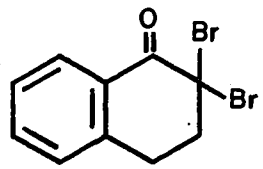
In the formation of pyridinium salts of phenacyl bromides Krollpfeiffer and Müller (73) isolated the unsaturated ketone CLIII in 1-2% from the reaction of pyridine with the halide CLII. Using the same base or dimethylaniline, the α, α-dibromide CLIV was converted to the naphthol CLV in 40% yield.



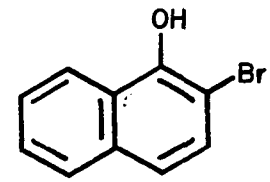
CLII



CLIII

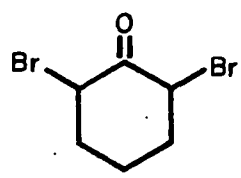


CLIV

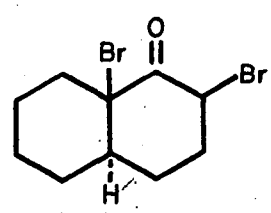


CLV

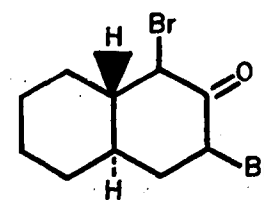
Galinovsky (74), working with α, α'-dibromides, synthesized the corresponding aromatic compounds by this method. The dibromocyclohexanone CLVI gave phenol in high yield, while the dibromodecalones, CLVII and CLVIII, formed the corresponding naphthols, CLIX and CLX, respectively, in 50-60% yield.



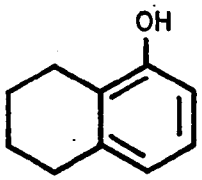
CLVI



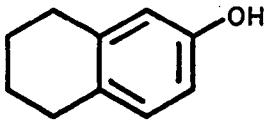
CLVII



CLVIII

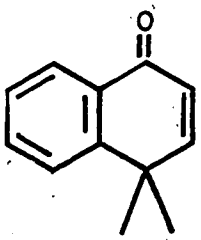


CLIX

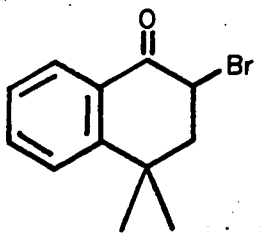


CLX

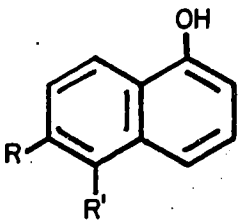
Much work has been done on α-tetralones. Arnold et al. (75) formed the unsaturated ketone CLXI from the α-bromide CLXII in 60% yield with refluxing collidine. Coulson (76) obtained the naphthol CLXIII via the bromide CLXV using refluxing diethylaniline. Finally, Fieser and Dunn (77) reacted a similar tetralone CLXVI with the same base and isolated the aromatic compound CLXIV in greater than 50% yield.



CLXI

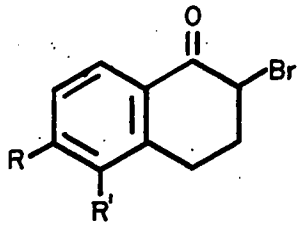


CLXII



CLXIII R = R' = CH_3

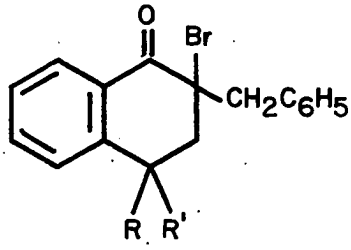
CLXIV R = H; R' = CH_3



CLXV R = R' = CH_3

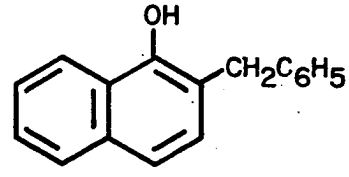
CLXVI R = H; R' = CH_3

Hassner et al. (78) in some recent work ran some competition studies on the directional preference of this elimination. Using the benzyl tetralone CLXVII and morpholine, they obtained the naphthol CLXIX in 60% yield with no report that the benzylidene compound had formed. In similar studies on the 4,4-dimethyltetralone CLXVIII and a series of amine bases (79), they isolated CLXX and CLXXI, the latter being formed predominantly. For example, with piperidine the yield of CLXX and CLXXI was 14 and 86%, respectively.

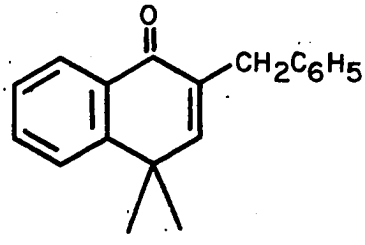


CLXVII R = R' = H

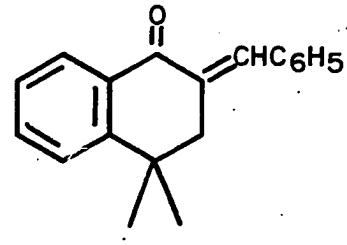
CLXVIII R = R' = CH_3



CLXIX



CLXX



CLXXI

DISCUSSION

α-Haloketones

As has already been noted in the literature survey, participation of neighboring groups in solvolysis reactions has been proved by many studies involving mainly reaction kinetics (32). Participation mechanisms are often operative in cases involving rigid structures (e.g. fused ring compounds). One such compound, whose solvolysis could proceed a priori in several directions, is a derivative of podocarpic acid, the bromoketone CLXXV. The chemistry of this ketone was selected for the present study.

The required ketone CLXXV was obtained from podocarpic acid in a four-step synthesis. Podocarpic acid was first acetylated with acetic anhydride and sodium acetate to give O-acetylpodocarpic acid (CLXXII). The results of the analytical sample indicated that CLXXII contained one mole of water of crystallization.

Methyl O-acetylpodocarpate (CLXXIII) was next prepared by treatment of CLXXII with diazomethane and the crystalline material was used for the subsequent reaction without purification.

The third step involved chromic acid oxidation which proved more unpredictable than the other steps. The yield of

methyl O-acetyl-7-ketopodocarpate (CLXXIV) appeared to be somewhat dependent on the age of the chromic acid employed. The best yields were obtained with fresh oxidizing agent. In order to obtain pure CLXXIV the crude product was chromatographed on hydrochloric acid washed alumina. This removed the chromium (III) salts which were present in the chloroform extract. After a series of runs it was found that the chromatography was most successful if completed in approximately thirty minutes after the material was added to the column. As is true of phenyl acetates in general, this compound was extremely labile toward base hydrolysis, and some deacetylated product was always obtained from the column. That this latter product had not been formed during the reaction or its work-up was shown in the following manner. The chloroform extracts containing CLXXIV were washed with dil. sodium hydroxide as part of the purification procedure. The washings were examined carefully for the presence of free phenol but no trace of organic material was ever found. The hydrolysis must have occurred on the column.

The bromination step was carried out according to the procedure of Ohta and Ohmori (80). This reaction proceeded smoothly and gave methyl O-acetyl-6-bromo-7-ketopodocarpate (CLXXV) in good yields. Here again chromatography on hydrochloric acid washed alumina gave partial hydrolysis. In a typical run there was isolated the acetate and the free phenol

in 7:1 ratio.

Having obtained pure CLXXV it appeared worthwhile to study its behavior on acid and base hydrolyses. Several interesting facts were uncovered in this investigation. The first such reaction involved the treatment of CLXXV with two moles of sodium methoxide. It was noted that upon addition of the base there was formed a bright yellow color which was most likely due to the phenoxide ion. In these studies it was found to be generally true that those podocarpic acid derivatives which contained a 7-keto function gave yellow colored solutions in the presence of base. A good yield of the enone CLXXVI was obtained.

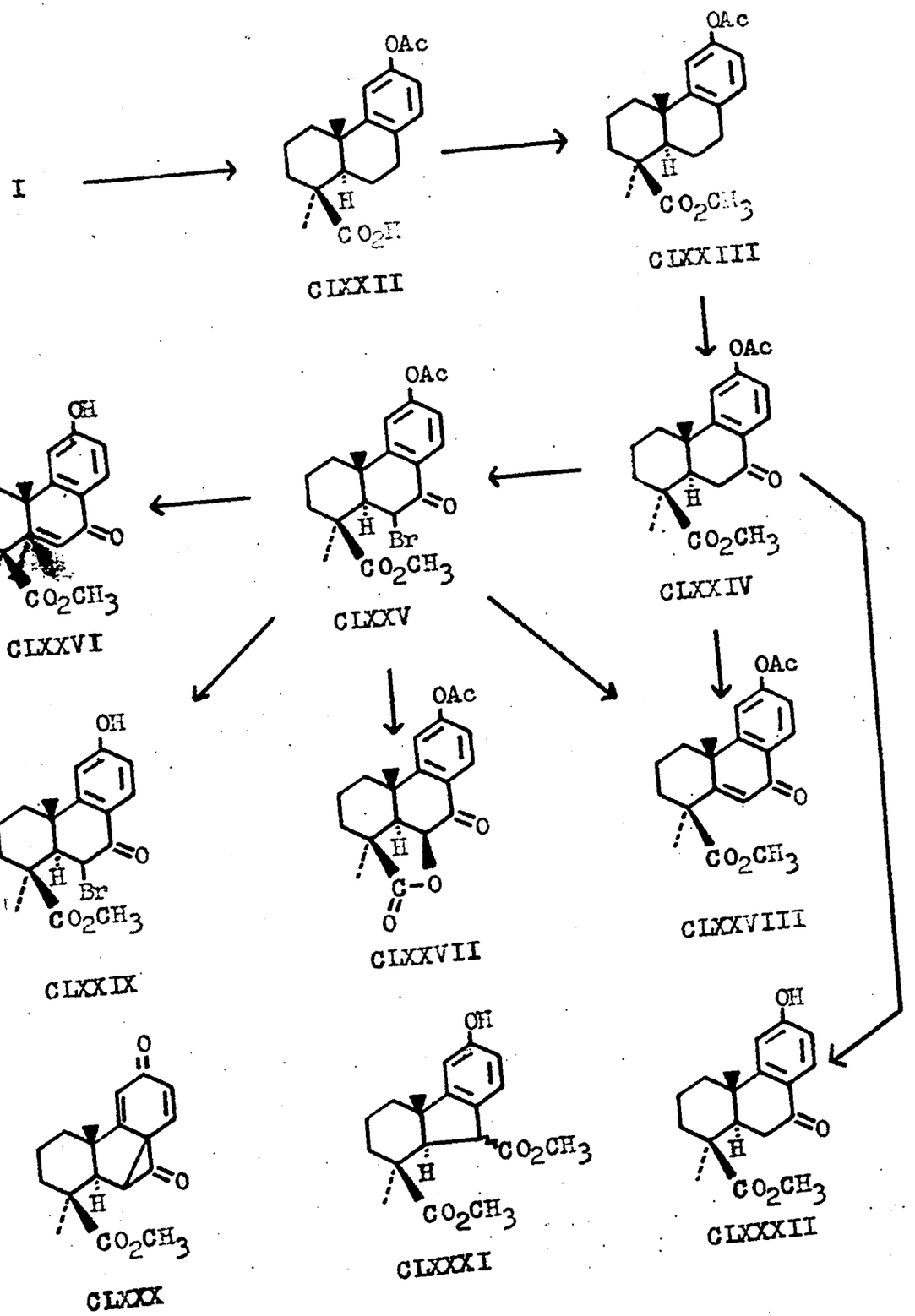
Collidine was the second base to which CLXXV was exposed. A procedure had been reported previously by Bible (81) involving the reaction of collidine with other 6-bromo-7-keto-podocarpic acid derivatives. Employing this method CLXXV was found to give a mixture of two products. These products were the lactone acetate CLXXVII and the enone acetate CLXXVIII in roughly equal amounts. The infrared spectrum of the crude reaction mixture clearly indicated the presence of such compounds, but it proved more difficult to effect a clean separation of them. Selective crystallization failed. In fact, the crude product could not be made to solidify. Separation by chromatography was attempted next. Both alumina and silica gel failed as adsorbents. They caused hydrolysis of

the acetate and no usable material could be eluted from the column. Finally, chromatography was tried on a Bentonite-Celite column according to a method first described by Elvidge and Whalley (82) for the separation of 2,4-dinitrophenylhydrazones. Even though a short column (3-4 centimeters) was used, this chromatography proved to be an efficient method of separation. The enone was eluted first, while the lactone came off the column in a more polar solvent mixture.

A point for discussion arises here. Can a suitable mechanism be found to explain the formation of both compounds? Before possible mechanisms for the formation of these products can be discussed, it is necessary to consider various pathways of bromination of the keto compound CLXXIV. An explanation of the reaction mechanism of CLXXV with collidine is dependent on the stereochemistry of the bromine atom in the haloketone.

Recently, Corey (83) has examined the stereochemistry of a series of steroidal α-haloketones. On the basis of his work he has formulated a rule that the kinetically controlled bromination of steroid ketones always gives the axially brominated product. He determined experimentally that the stereochemistry of a 6-bromo-7-keto steroid formed by kinetic control contained an axial bromine atom. On the basis of this rule the bromination of CLXXIV (somewhat analogous to the

Figure 1. Reaction scheme


I
OAc
H
CO2H
CLXXII
OAc
H
CO2CH3
CLXXIII
OAc
H
CO2CH3
O
CLXXIV
OAc
H
Br
CO2CH3
O
CLXXV
OH
O
CO2CH3
CLXXVI
OH
H
Br
CO2CH3
O
CLXXIX
OAc
H
C-O
O
O
CLXXVII
OAc
H
CO2CH3
O
CLXXVIII
O
H
CO2CH3
O
CLXXX
OH
CO2CH3
H
CO2CH3
CLXXXI
OH
H
CO2CH3
O
CLXXXII

7-keto steroids) would be expected to give the 6 β (axial) -bromo compound.

After the examination of the stereochemistry of some α-haloketones Djerassi (84, 85, 86) reached a significantly modified conclusion from that stated in Corey's rule. He examined the 2-bromo steroid obtained from the bromination of 2 α-methylcholestan-3-one enol acetate (CLXXXIII). The ultraviolet and infrared spectra showed the bromine atom to be axial. However, the optical rotatory dispersion curve was the opposite of that predicted by the axial haloketone rule (87). He repeated the bromination of CLXXXIII under kinetically controlled conditions and obtained the same product with its unexpected dispersion curve.

Djerassi proposed that the optical rotatory dispersion curve could only be explained if ring A in CLXXXIV was in the boat form. There are several possible explanations for this particular conformation. Ring A could have been brominated after it had assumed the boat form. This would agree with Corey's proposal as far as axial bromination is concerned. However, there exists the possibility that CLXXXIII was brominated by equatorial approach of the bromine atom following which ring A had "flipped" into the boat form. Djerassi preferred the latter explanation and presented experimental data in support of this viewpoint.

Kinetically controlled bromination was carried out on

CLXXXV to see if the keto compound would give the same results as its enol acetate. This was found to be true. It was also shown that 3-keto steroids lacking the 2 α-methyl group under identical bromination conditions gave the equatorial 2-bromo compound (ring A in chair form). When equilibration studies were run on a 2 α-bromo-2 β-methylandrostane derivative CLXXXVI, its 17-acetate, and its 17-acetate enol acetate, the thermodynamically stable isomer was shown to be the 2 β-bromo (axial) derivative.

Bromination was also carried out on C-19 norsteroids as CLXXXVII in order to gain some information on the stereochemical role of the C-10 methyl group. It was found that in these cases both axial and equatorial 2-bromo derivatives were formed under kinetically controlled conditions, indicating that there is significant steric influence of this methyl group under these conditions.

These results are not in complete accord with those stated by Corey, and Djerassi considers other possible mechanisms to explain his observations. For instance, Barton and Cookson (88) have suggested that the bromination of cyclohexanones is mechanistically similar to the bromination of cyclohexenes. This is pictured as involving the formation of an intermediate bromonium ion. Djerassi tested this theory by carrying out the halogenation of a series of 3-keto steroids and their enol acetates with Br-Cl. In no case was

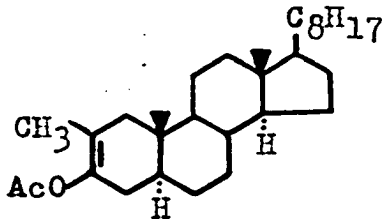
the chloroketone obtained. This makes the Barton-Cookson mechanism appear very unlikely.

Djerassi favors the idea that bromination of 3-keto steroids may occur via equatorial attack by the bromine. In support of this the steroids CLXXXVIII and its enol acetate were brominated under kinetically controlled conditions. Their bromination products were shown to be almost exclusively the equatorial isomers, and this would seem to be the preferred path in the presence of steric hindrance. The unfavorable 1,3 interaction of the C-10 methyl group with a bromine atom approaching axially at C-2 is circumvented by the attack of an equatorially approaching bromine to give the conformation CLXXXIX. However, the C-2 and C-10 methyl groups now experience a similar 1,3 interaction, and the equatorially located bromine atom has a repulsive dipolar interaction with the 3-keto group. To alleviate these unfavorable interactions the ring then "flips" into the boat form as pictured in CXC.

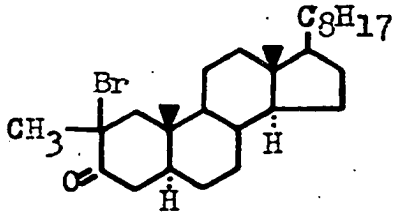
Finally, there is the possibility that the mechanisms of both Corey and Djerassi are operating. This would result in the formation of both the equatorial and axial bromoketones.

The reaction conditions employed for the bromination of the ketone CLXXIV were essentially those used by Djerassi in the formation of the kinetically controlled brominated keto steroids. The product CLXXV could be expected to be the kinetically controlled isomer.

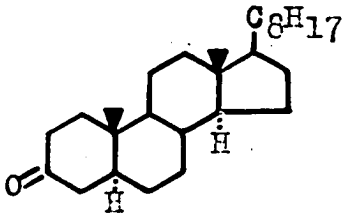
Figure 2. Compounds involved in Djerassi's proof



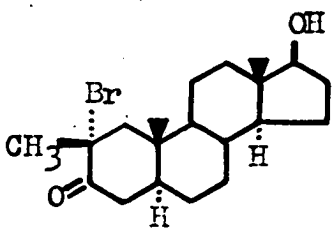
CLXXXIII



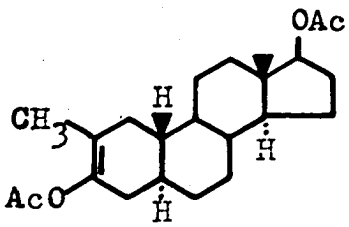
CLXXXIV



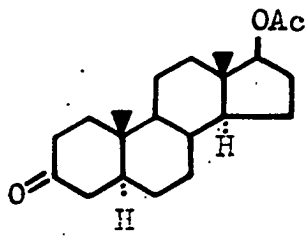
CLXXXV



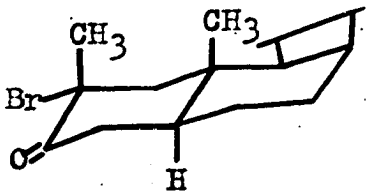
CLXXXVI



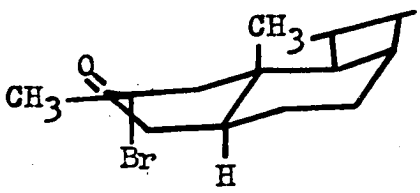
CLXXXVII



CLXXXVIII



CLXXXIX



CXC

Would the axial or equatorial bromine be expected *a priori*? Consider each separate situation. With an axial bromine atom there are two unfavorable 1,3 interactions with the bromine. These involve the C-10 methyl group and the carbomethoxy group at C-4. In the case of an equatorially oriented bromine atom there is the unfavorable dipolar interaction between the C-Br bond and the keto group along with a *peri* interaction with the C-4 methyl. There are, however, no axial 1,3 interactions. At first glance the equatorially brominated product would be expected.

Can anything be gained from the experimental results concerning the stereochemistry of CLXXV? There are several pieces of evidence that give some indication of the orientation of the C-Br bond. An equilibration reaction was carried out (89) on CLXXV using hydrogen bromide in ether solution. After twelve hours at room temperature the product was examined and the material isolated (43% of the starting material) gave a m.p. and mixed m.p. identical with the starting material. If the starting material had contained an axial bromine, it would appear likely that the thermodynamically stable product (bromine atom equatorial) would have been formed.

The spectral data of CLXXV should provide more concrete evidence concerning the stereochemistry of the C-6 bromine atom. According to Jones *et al.* (90) the carbonyl absorption in the infrared spectrum of an α-haloketone is changed little

from that of the parent ketone if the halogen atom is axially oriented. However, an equatorial halogen atom displaces the carbonyl absorption 20 cm^{-1} toward higher frequency. The carbonyl band of the parent ketone CLXXIV is located at 1670 cm^{-1}, but the same band in CLXXV is at 1687 cm^{-1}. On the basis of Jones' rule it would appear that CLXXV contains predominantly the equatorial product. The ultraviolet spectrum is also informative. Cookson (91) has shown that the position of the λ max. in the ultraviolet spectrum of α-haloketones is a function of the angle between the carbonyl group and the C-X bond. If the angle is large (axial halogen atom) the maximum is displaced + 28 mμ from that of the parent ketone. With an equatorially oriented halogen atom (small angle) the displacement is much smaller. In the case of CLXXV the spectrum shows a shift of + 5 mμ suggesting strongly that the C-6 bromine atom is attached predominantly in an <u>equatorial</u> orientation. One may conclude that CLXXV contains an equatorial bromine atom.

This conclusion is in agreement with the results obtained by other investigators on compounds of similar structure. Hassner and Cromwell (92) concluded from the infrared and ultraviolet spectra of CXCI that this compound was predominantly the equatorial isomer. Recent work carried out in these laboratories by Wenkert <u>et al.</u> (93) indicated that a closely related compound in the abietic acid series, namely CXCII,

contained an equatorially oriented halogen atom. This conclusion was reached on the following piece of evidence. CXCII could be converted to CXCIII by the action of dimethyl sulfoxide but only after a reaction time of ten days had elapsed. The long reaction time suggests that the dimethyl sulfoxide molecule had to approach CXCII from the β-side (axial approach). This is very unfavorable because of the 1,3 interactions. α-Approach should have been much less hindered and not required such extended reaction time.

It is now necessary to explain the formation of both CLXXVII and CLXXVIII from the bromoketone CLXXV. Here the stereochemistry of the C-6 bromine atom becomes crucial. On the basis of the available evidence it will be assumed that CLXXV contains predominantly an equatorial bromine.

Formation of the lactone can best be considered as involving internal displacement of the bromine atom by the C-4 ester via transition state CXCIX or CCV and intermediate CC or CCVI, respectively, followed by collidine-induced demethylation. Although there is strain associated with the lactone ring, the stereochemistry is favorable for the intramolecular displacement. However, the hydrogen bromide elimination giving CLXXVIII is more difficult to explain. Because of the equatorial nature of the bromine atom an E2 elimination cannot occur with collidine as the base. It is possible that equilibration of the bromine atom could occur in CLXXV resulting in

the formation of some of the axial bromine isomer which could readily eliminate hydrogen bromide. However, similar products were observed with the bromophenol CLXXIX and there is little chance that equilibration could occur here (though there is the possibility of equilibration in the formation of CLXXIX). The possibility of an E1 elimination is unlikely because the carbonium ion that would be formed would be adjacent to a carbonyl group. This is energetically unfavorable.

Recently Winstein, Darwish, and Holness (94) developed a mechanism which may give an answer to the above dilemma. They studied the reaction of trans-4-t-butylcyclohexyl p-toluenesulfonate (CXCV) with bromide ion. They noted that two products, CXCVI and CXCVII were formed. The reaction was known to involve an equatorial p-toluenesulfonate group since the presence of a tert-butyl group in the 4-position keeps 1,4 trans substituents in cyclohexane oriented equatorially. The formation of the cyclohexene CXCVII was shown not to involve the standard elimination reactions both on the basis of steric factors and reaction rates. Therefore, they formulated a "merged bimolecular nucleophilic substitution" mechanism to explain their results. Their mechanistic intermediate is shown in CXCVIII. As pictured the intermediate is the one which is generally ascribed to the transition state in the SN2 reaction. The figure indicates approximately equal bonding between both the approaching bromide ion and the leaving

tosylate group with the C-1 carbon atom. The formation of the bromide CXCVI is self-explanatory. To explain the formation of CXCVII Winstein proposed that the leaving tosylate group could assist in the removal of the axial hydrogen at C-2 thereby facilitating the formation of the olefin.

One can note a number of similarities between the reaction of collidine with CLXXV and Winstein's reaction. In both cases an equatorial leaving group is involved. With the C-4 axial carbomethoxy group acting in the capacity of Winstein's bromide ion, transition states CXCIX or CCV become analogous to CXCVIII. Therefore, not only can the afore-described displacement leading to lactone CLXXVII via intermediate CC or CCVI take place, but also an olefin yielding elimination induced by collidine abstraction of the 5 α (axial)-hydrogen atom can occur. Should the carbon-bromine bond in CXCIX be broken first, the resulting oxonium ion CC or CCVI would undergo an E2-type elimination.

The reaction of CLXXV with 2 moles of sodium methoxide merits further discussion. In this case the major product is the enone CLXXVI. However, there is less likelihood of an E2 elimination here. The reason is the following. It could be shown that hydrolysis of the acetate of CLXXV occurs much faster and under milder conditions than the elimination of hydrogen bromide. In the presence of sodium methoxide (2 moles) the acetate was hydrolyzed completely in only one

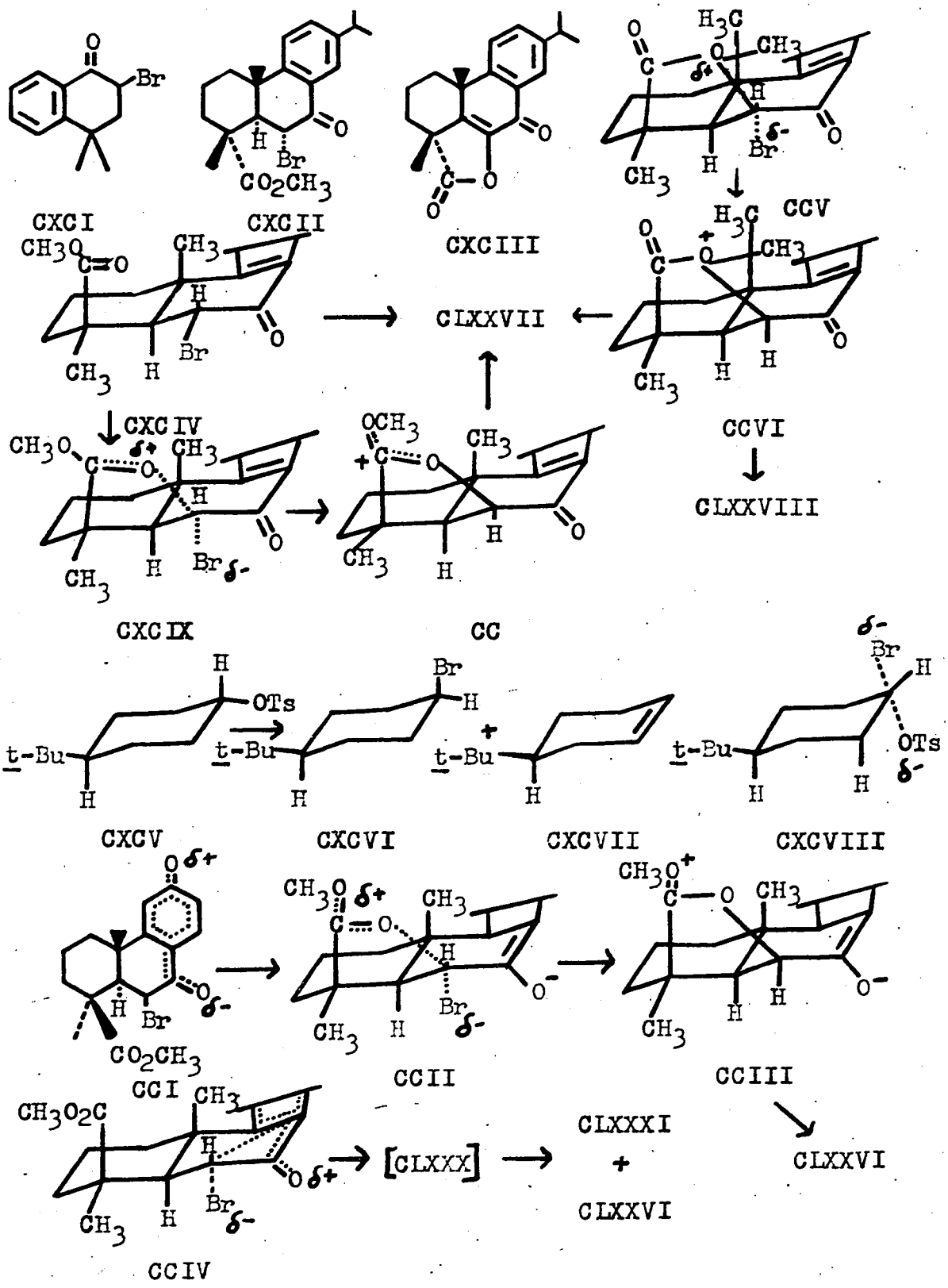
minute at room temperature, while the dehydrobromination was completed after only two hours in refluxing methanol. This indicates that the anion of CLXXIX (see CCI) is present preponderantly in the reaction mixture. It is possible that the quasi-allylic bromide CCI suffers halide loss by carbomethoxy participation (see CCII and CCIII or the anion equivalents of CCV and CCVI) in a manner similar to the elimination CLXXV-CLXXVIII. Alternatively transition state CCIV may be operative, leading as a consequence to the cyclopropanone CLXXX. This intermediate may react in two different ways. First, the ring may be opened by 5-H removal to give the major product CLXXVI. Second, since CLXXX is an intermediate comparable with that proposed by Loftfield (55) for the Favorskii reaction, the ketone could undergo ring opening by reaction with either sodium methoxide or methanol with the formation of the B-nordiester CLXXXI.

The mother liquors from the sodium methoxide reaction were reduced in volume until most of the CLXXVI had precipitated. The remaining residue was taken up in chloroform and dried. The solvent was evaporated and the dried residue was chromatographed on an alumina column in an attempt to separate the oil into fractions and examined to see if any CLXXXI could be identified. The residual enone CLXXVI was strongly adsorbed by the alumina and could not be eluted from the column. With chloroform as the eluent a colorless oil (approximately

1% yield) was obtained from the column. Its infrared spectrum showed the presence of a peak in the carbonyl region at 5.85μ with no trace of a peak at 6.05μ where the 7-keto function would be expected to absorb. The observed peak is due in part to the C-4 methyl ester. However, it is unlikely that the material from the column is methyl podocarpate (CCXVI) although their infrared and ultraviolet spectra were similar. However, it is difficult to imagine that any CCXVI could have survived the entire reaction sequence leading to the bromoketone CLXXV. The oil obtained from the chromatography of the enone mother liquors could not be crystallized although CCXVI is easily purified by crystallization. Proof is yet lacking that the oil has the structure CLXXXI. However, the spectral data obtained are consistent with such a structure. Further work with larger quantities of the bromoketone CLXXV are necessary for proper isolation and characterization of the oily product.

After determining the products in the reaction of the bromoketone CLXXV with collidine, it seemed worthwhile to reexamine the reaction of collidine with the methyl ether CCIX which had been previously described by Bible (81). CCIX was synthesized according to the procedures of Bible starting with methyl O-methylpodocarpate (CCVII). The oxidation of this compound with chromium trioxide-acetic acid proceeded smoothly to give methyl O-methyl-7-ketopodocarpate (CCVIII)

Figure 3. Reaction scheme


CXCI
CXCII
CXCIII
CCV
CLXXVII
CXCIV
CCVI
CLXXVIII
CXCIX
CC
CXCV
CXCVI
CXCVII
CXCVIII
CCII
CCIII
CCI
CCIV
[CLXXX]
CLXXXI
+
CLXXVI
CLXXVI

in good yield. The physical properties agreed with those obtained by Bible. The elemental analysis gave further proof for its structure.

The bromination of CCVIII was carried out and a product was obtained which appeared to be pure, judging from its melting point. However, the m.p. was 20° lower than that reported by Bible, and its infrared spectrum showed three peaks in the carbonyl region. The pure material was analyzed twice but did not give values in agreement with the structure CCIX. These facts are difficult to explain. However, further reactions which were run on assumed pure CCIX gave unambiguous proof that this bromoketone had been synthesized.

In order to prove that the bromoketone CCIX had been prepared, the material was refluxed with one mole of sodium methoxide in methanol. The product was an unsaturated ketone obtained in 84% yield. Its infrared and ultraviolet spectra together with the analysis were in agreement with the enone structure CCX.

Pure CCIX was then reacted with collidine under the conditions which had been used for the bromoketone CLXXV. The work-up gave an oily product whose infrared spectrum clearly indicated that it was a mixture of products. Crystallization proved fruitless. Therefore, chromatography on a Bentonite-Celite column was tried. Again separation was effected smoothly and two products were obtained. The first to come

off the column was an unsaturated ketone and proved to be methyl O-methyl- $\Delta^{5,6}$-7-ketopodocarpate (CCX). This was shown by m.p. and mixed m.p. with authentic CCX prepared by treatment of enone CLXXVI with dimethyl sulfate and sodium hydroxide with heating. The second product was eluted with chloroform and gave an infrared absorption peak at 5.60μ characteristic of five-membered lactones. Comparison of its physical properties with those described by Bible and an elemental analysis proved that the compound was the lactone CCXI. It is interesting that in Bible's patent no isolation of any enone CCX is mentioned. Both compounds were isolated in approximately the same quantities. The arguments used to explain the formation of the products in the reaction of collidine with the lactone acetate CLXXV are valid for the above reaction also.

To complete the series the collidine reaction was run on the bromophenol CLXXIX. Similar results were noted in this reaction. After unsuccessful attempts at crystallization the crude material was chromatographed on a Bentonite-Celite column. The products obtained were those expected on the basis of the previous collidine reactions. The enone CLXXVI was eluted first and its structure was proved by the infrared and ultraviolet spectra and its conversion to the known acetate CLXXVIII.

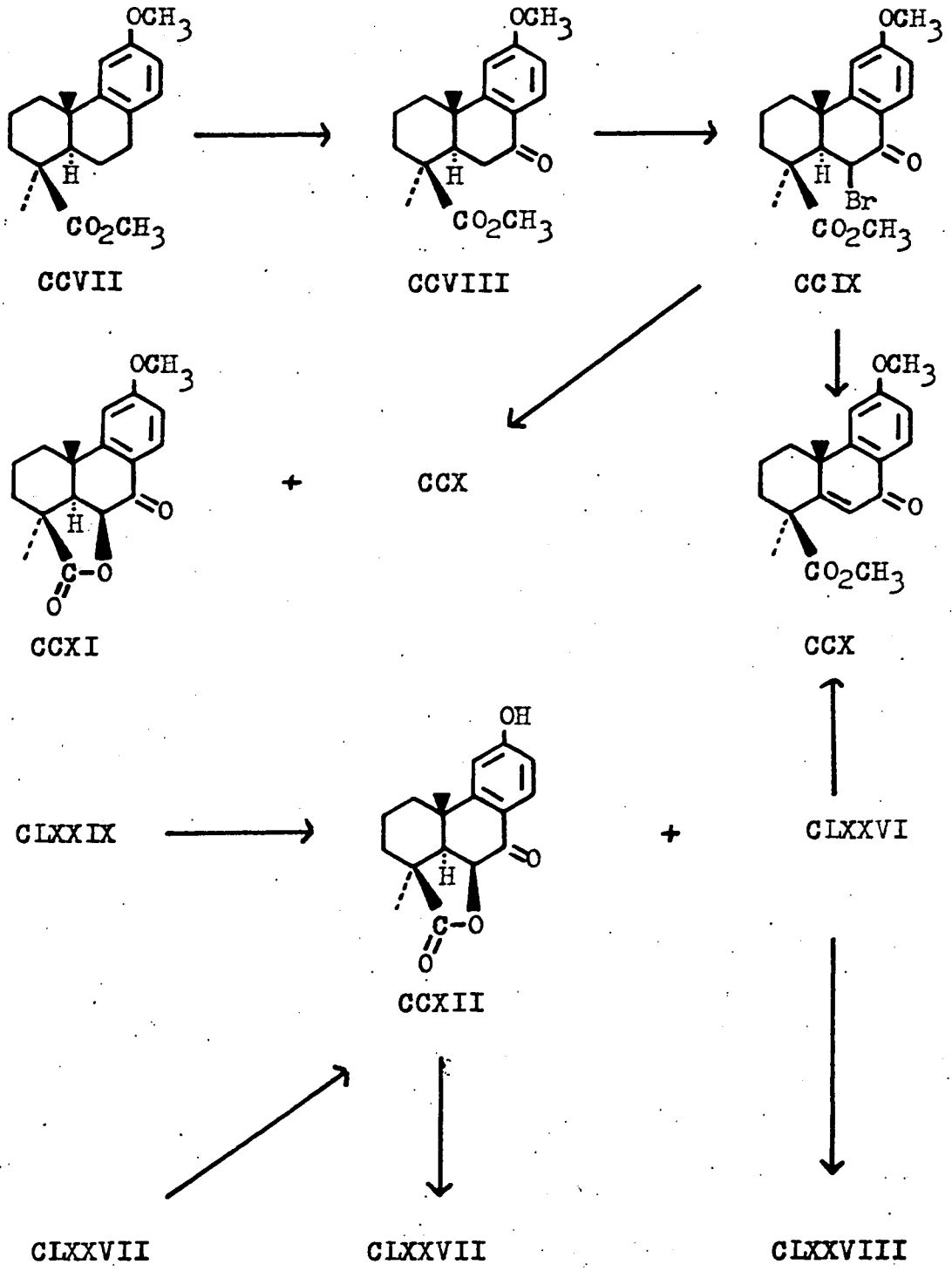
A lactone was next eluted and, although numerous attempts

were made to bring about crystallization, it was not possible to do so. The oil was finally converted to the lactone acetate CLXXVII with acetic anhydride-pyridine. Its identity with authentic CLXXVII was shown by m.p., mixed m.p., and infrared and ultraviolet spectra. Therefore, the lactone CCXII must have been formed in the reaction with collidine. The formation of these two products is explained by a mechanism similar to that described in the reaction of the bromoketone CLXXV with sodium methoxide.

Little has been mentioned concerning the properties of these lactones. Some further experiments were carried out to determine some of these characteristics (89). Catalytic hydrogenation of the lactone acetate CLXXVII over long periods of time gave evidence that the lactone was slowly opened. The products, however, were never fully characterized. Base hydrolysis of CLXXVII at elevated temperatures opened the lactone ring. However, treatment of the lactone acetate with sodium hydroxide at room temperature for one minute gave infrared evidence for the presence of a phenol. The lactone peak at 5.60 μ was still strong.

The hydrolysis of CLXXVII in the presence of two moles of sodium methoxide was examined more closely. In one run the hydrolysis was carried out for two minutes at room temperature. The product had the same physical properties as the lactone obtained from the reaction of the bromophenol CLXXIX

Figure 4. Reaction scheme


OCH3
CO2CH3
H
O
Br
C-O
OH
CCVII
CCVIII
CCIX
CCX
CCXI
CLXXIX
CLXXVI
CCXII
CLXXVII
CLXXVII
CLXXVIII

with collidine. The hydrolyzed product could not be crystallized. Acetylation was attempted in the hope of obtaining the starting material back. The crude hydrolysis product was heated with acetic anhydride with a trace of pyridine. The acetylated product was easily crystallized and had spectral properties, m.p., and mixed m.p. identical with authentic CLXXVII.

Catalytic Hydrogenations

The literature abounds with examples of catalytic hydrogenations of many types, and various explanations have been proposed to explain the observed facts. It is well known that one of the major factors affecting the course of catalytic hydrogenation is the size and relative stereochemistry of groups in the vicinity of the double bond. Other things being equal, catalytic hydrogenation will occur on that side of the molecule which is less hindered sterically. Among the systems that have been carefully examined have been polycyclic molecules whose partial structures are represented by CCXIX. In the majority of the cases studied the hydrogenation has given A:B *trans* products. Because of the availability of compounds with partial structure CCXIX it appeared worthwhile to carry out some similar hydrogenations and examine the results.

The enone CLXXVI was an appropriate starting material.

However, to minimize any polar effects that might influence the direction of hydrogenation, removal of the 7-keto function was carried out. Accordingly CLXXVI was reacted with ethanedithiol using boron trifluoride etherate as the catalyst in the hope of obtaining the thioketal CCXIII. It was noted after the mixture had been standing for several hours that a bright burgundy color had formed. This color was probably due to oxidation products since the 7-position of CLXXVI is both benzylic and allylic and therefore highly susceptible to air oxidation. The color proved difficult to remove, and the desired thioketal was obtained as pure crystals only after a number of recrystallizations.

The desulfurization was carried out using the standard Raney nickel procedures. However, it was soon found that the different types of Raney nickel yielded different products. If W-2 Raney nickel was employed in the reaction without any deactivation, not only was the thioketal desulfurized, but the double bond was also saturated giving methyl podocarpate (CCXVI). Nevertheless, the unsaturated compound could be obtained by two methods which differed only in slight detail.

The first procedure was that of Spero *et al.* (95) which involved deactivation of the catalyst by refluxing it in acetone before the addition of the thioketal. The second procedure was the method of Romo *et al.* (96) who added the nickel catalyst and the thioketal to the acetone at the same

time. Both methods gave comparable results although the latter was most frequently used. The structure of the product was assumed to be CCXIV. Crystallization of the oily product was unsuccessful. Sublimation gave a brown colored solid which on resublimation gave a colorless product whose purity was questionable as judged from its melting point range.

The oil was subjected to catalytic hydrogenation and a product was obtained which was easily crystallized and proved to be methyl podocarpate by m.p. and ultraviolet and infrared spectra. This was shown by comparison of the hydrogenation product with authentic CCXVI obtained by the action of diazomethane on podocarpic acid (I). Obviously, the hydrogenation had given the A:B trans ring juncture in agreement with reported observations on other similar systems.

However, there is another possible explanation for these results. Raney nickel could possibly have caused migration of the double bond to give the isomeric unsaturated compound CCXVII. Since this possibility cannot be ruled out, a series of reactions was undertaken to clear up this point.

The scheme involved the synthesis of the $\Delta^{6,7}$ compound CCXVII in a clear-cut fashion and comparison of its physical properties with those of the desulfurized product. The starting point was the ketodiester CLXXIV. It was hoped that the carbonyl group could be reduced to the alcohol, and an elimination reaction then carried out to give authentic CCXVII.

The ketodiester was treated with sodium borohydride using sodium carbonate as the buffering agent. An infrared analysis of the product showed several things. First, the appearance of phenolic peaks around 3.0 μ indicated that the acetate had been hydrolyzed during the reduction. Second, there was no trace of a peak at 5.98 μ where the 7-keto function would have absorbed. Its structure was assumed to be CCXV. The product was a colorless oil which resisted all attempts at crystallization. It was used for the next reaction without further purification. The optical rotation of the oil gave a value of $+65^{\circ}$ (in chloroform). The significance of this value will become apparent later.

Although the borohydride reduction went smoothly with CLXXIV, it appeared worthwhile to determine whether the free phenol CLXXXII would react in the same manner or the presence of the acetate was necessary. The desired phenol was obtained quantitatively by treatment of CLXXIV with sodium hydroxide at room temperature for three hours. The spectral data and elemental analysis proved that the phenol had the structure CLXXXII.

A general property of these 7-ketophenols was brought out in this experiment. The chloroform extracts of the crude phenol contained traces of hydrochloric acid from the work-up. In attempting to remove this acid with dilute sodium carbonate solution it was found that the product was also extracted by

the carbonate solution. This is in sharp contrast to compounds such as methyl podocarpate (CCXVI) which are difficultly soluble even in aqueous potassium hydroxide solution.

The phenol CLXXXII was treated with sodium borohydride under the same conditions to which the acetate had been subjected previously. After the reaction had gone for two hours, the infrared spectrum showed that the carbonyl group had completely disappeared indicating that the reduction had proceeded smoothly. The crude product was hydrogenolyzed, and the final compound proved to be methyl podocarpate.

Conditions were now explored for the dehydration of the 7-hydroxy compound CCXV. After trying several different procedures the following conditions were chosen for the reaction. CCXV was dissolved in methanol, conc. hydrochloric acid was added, and the solution was refluxed for eight hours. The oily product was sublimed twice and gave pure material whose elemental analysis was consistent with the structure CCXVII. Of significance, too, was the fact that the optical rotation of this compound was -74° (in chloroform). Of all the podocarpic acid derivatives investigated in this work CCXVII was the only compound that gave a negative rotation.

The $\Delta^{6,7}$ compound CCXVII was subjected to the previous conditions of catalytic hydrogenation, and the product obtained was methyl podocarpate (CCXVI). The hydrogen uptake of CCXVII was quite rapid. Approximately 75% of the total volume

was absorbed in the first five minutes of reaction.

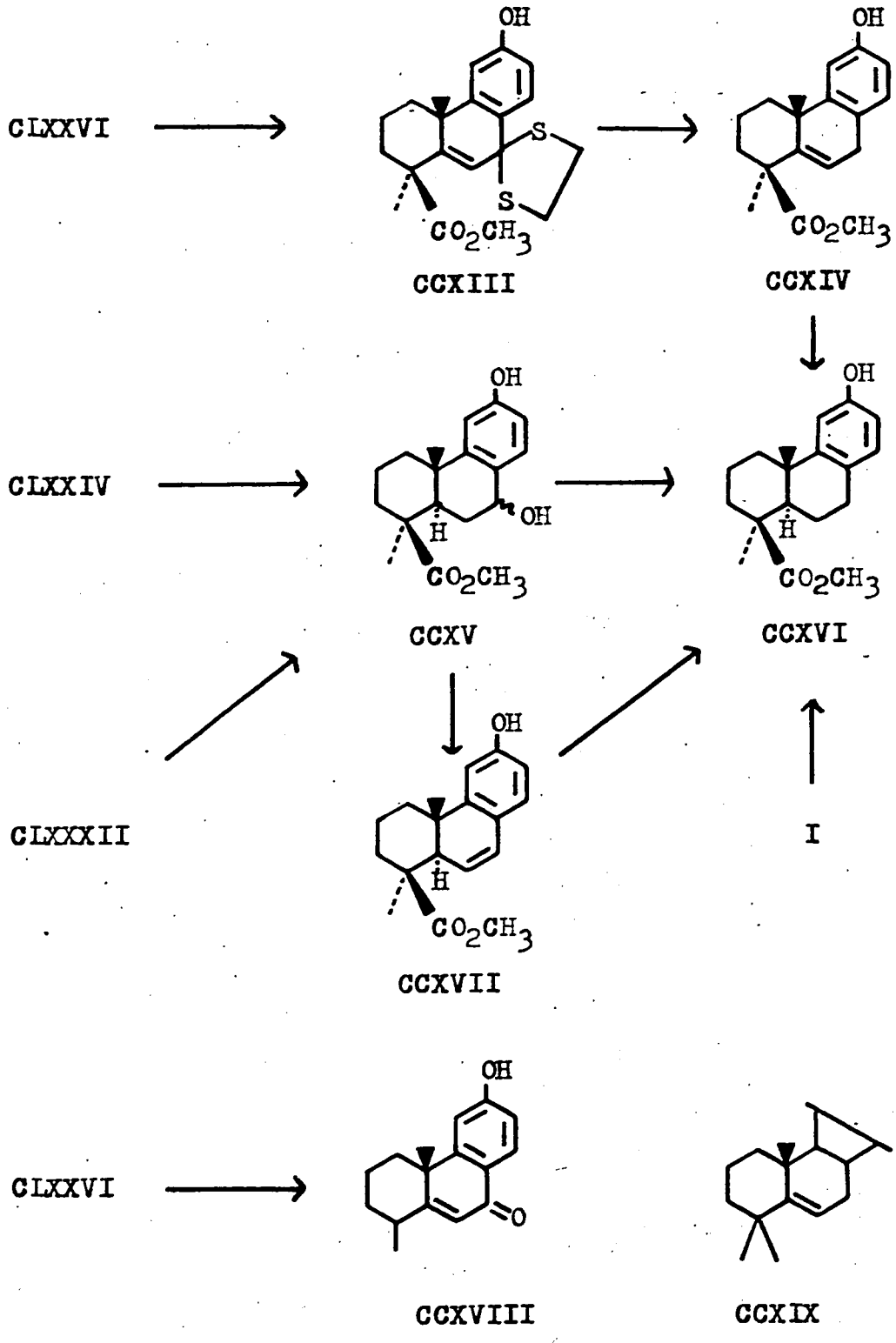
One other hydrogenation was carried out that deserves comment here. It was hoped that some significant difference would show up in attempted hydrogenation of the 7-hydroxy compound CCXV to help differentiate it from its dehydration product CCXVII. Catalytic hydrogenation of CCXV showed essentially the same rate of hydrogen uptake as was observed for CCXVII. This is not too surprising since similar benzyl-type alcohols are known to hydrogenolyze readily under the reaction conditions used.

This scheme provided the needed evidence that the original Raney nickel treated thioketal had the structure CCXIV, and its catalytic hydrogenation had proceeded in the same manner as similar systems reported in the literature.

Decarboxylation and Oxidation in the Presence of the 7-Keto Function

The utility of tricyclic diterpenes as intermediates in the synthesis of other natural products has certain limitations. One of the limiting factors is the structure of ring A of many of these diterpenes. Almost without exception they contain methyl groups at C-4 and C-10, with either another methyl group or other oxidized one-carbon fragment attached at C-4. The result is that the carbon atoms in ring A in

Figure 5. Reaction scheme


CLXXVI
OH
S
S
CO_2CH_3
CCXIII
OH
CO_2CH_3
CCXIV
CLXXIV
OH
OH
H
CO_2CH_3
CCXV
OH
H
CO_2CH_3
CCXVI
CLXXXII
OH
H
CO_2CH_3
CCXVII
I
CLXXVI
OH
O
CCXVIII
CCXIX

most diterpenes are rather inert chemically. Unfortunately, it is this same ring in the steroids which usually contains an oxygen function at C-3 and, many times, a double bond or aromatic ring. The introduction of these functions into ring A of diterpenes presents some problems. For one thing the gem-disubstitution at C-4 has to be removed or altered.

One of the reactions which was investigated was the hydrolysis of the enone CLXXVI. Preliminary work with aqueous potassium hydroxide indicated that no hydrolysis was accomplished under these conditions. This was not too surprising because it is well known that reactions which involve neopentyl carbon atoms, as the ester carbonyl carbon, are very sluggish. A new method for the hydrolysis of such hindered esters has recently appeared in the literature. This procedure (97, 98) involves treatment of the ester with lithium iodide-collidine at high temperatures. The reaction was carried out under nitrogen in refluxing collidine for 8-10 hours. An infrared spectrum of the product showed only one peak in the carbonyl region, and that was located at 6.07μ. This suggested a highly conjugated ketone structure and, in fact, the position of this peak was identical with the position of the 7-keto absorption in the parent enone CLXXVI. It was evident not only that the C-4 ester had been hydrolyzed (no peak at 5.85μ) but decarboxylation must also have occurred. This decarboxylation occurs because of the presence of

the vinylogous β-carbonyl at C-7. The product was relatively easy to crystallize, but removal of the brown colored impurities did not occur with recrystallization. This was only accomplished after chromatography of the crude solids on an alumina column. Sublimation of the slightly yellow solid product in a high vacuum gave colorless platelets which melted at 234-237° (crystal change to needles at 200°). While the reaction was not investigated further, it appears to represent a possible route not only for the elimination of the C-4 carboxyl group, but also for opening ring A of podocarpic acid for the introduction of other functions.

It was of interest to investigate the behavior of the 7-keto function of a podocarpic acid derivative toward selenium dioxide. Previous work in these laboratories (93) with selenium dioxide in the abietic acid series had shown that 7-keto compounds undergo oxidation mostly to $\Delta^{5,6}$ enones. This reaction was tried on the keto diester CLXXIV and the product, which was obtained in good yield was the enone CLXXVIII as shown by elemental analysis and by comparison with authentic CLXXVIII, which had been prepared by acetylation of CLXXVI.

Figure 6. Ultraviolet spectra

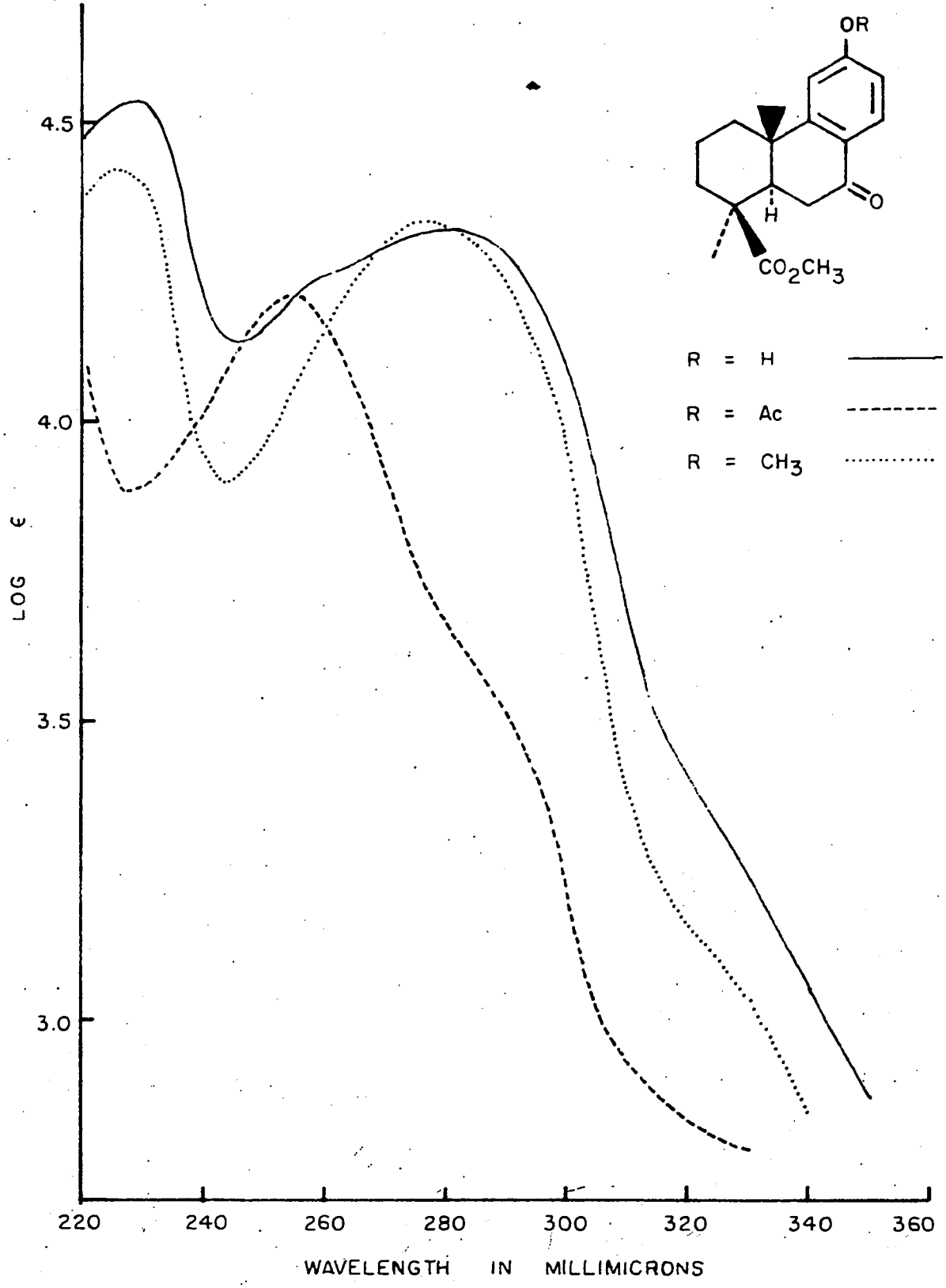

OR
O
H
CO_2CH_3
R = H
R = Ac
R = CH_3
LOG ε
4.5
4.0
3.5
3.0
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS

Figure 7. Ultraviolet spectra

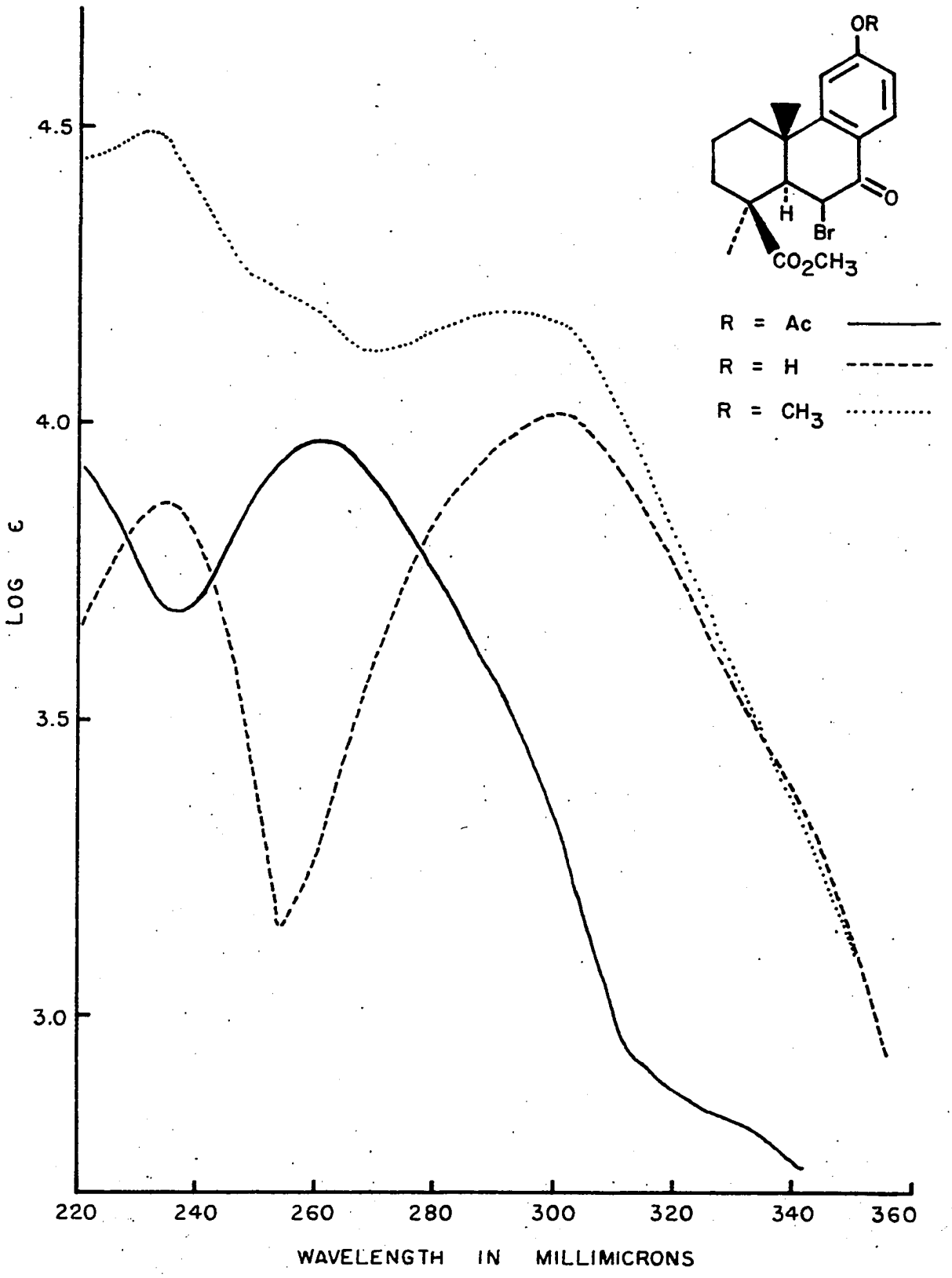

OR
O
H
Br
CO2CH3
R = Ac
R = H
R = CH3
4.5
4.0
3.5
3.0
LOG ε
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS

Figure 8. Ultraviolet spectra

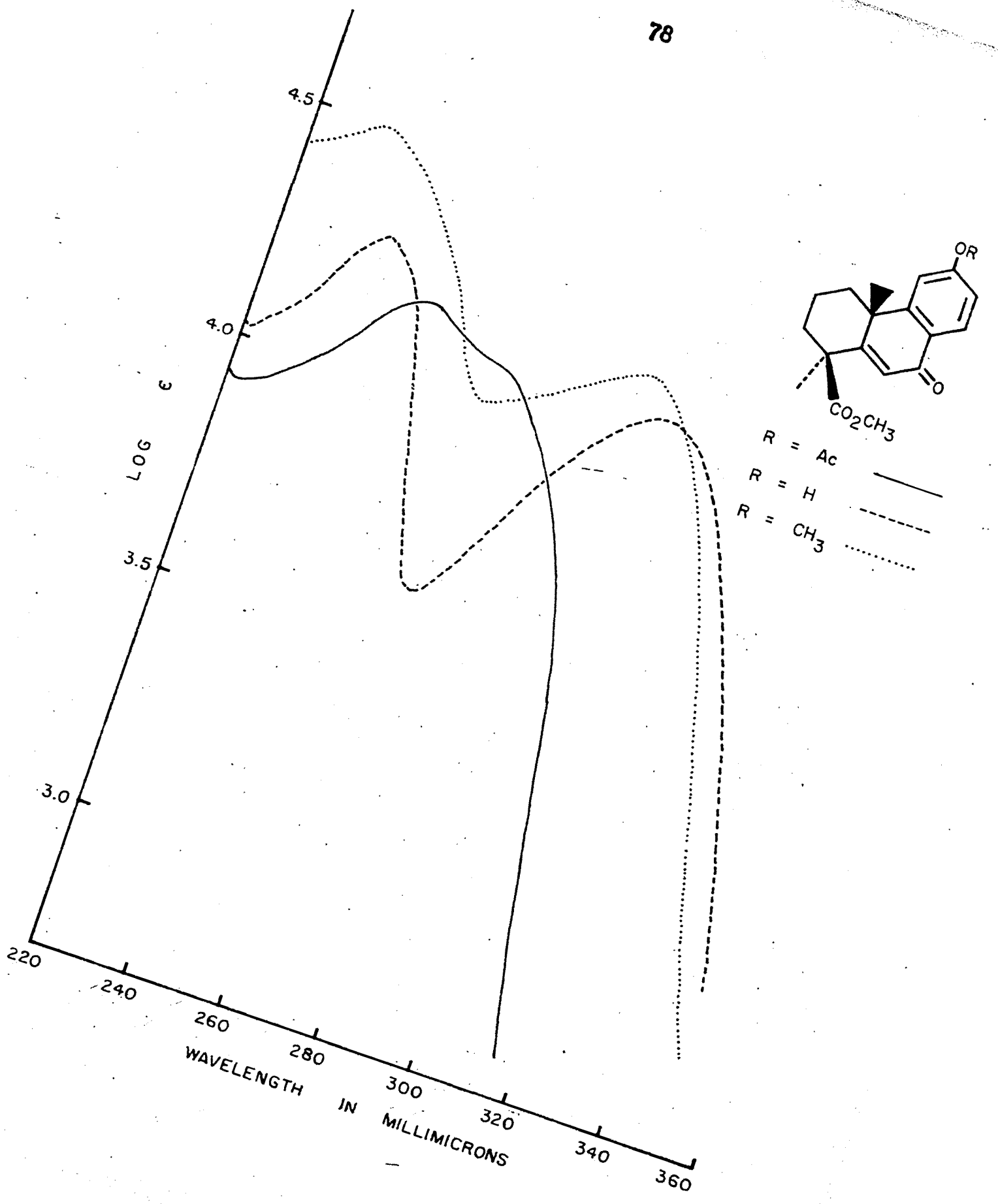

4.5
4.0
3.5
3.0
LOG ε
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS
OR
O
CO2CH3
R = Ac
R = H
R = CH3

Figure 9. Ultraviolet spectra

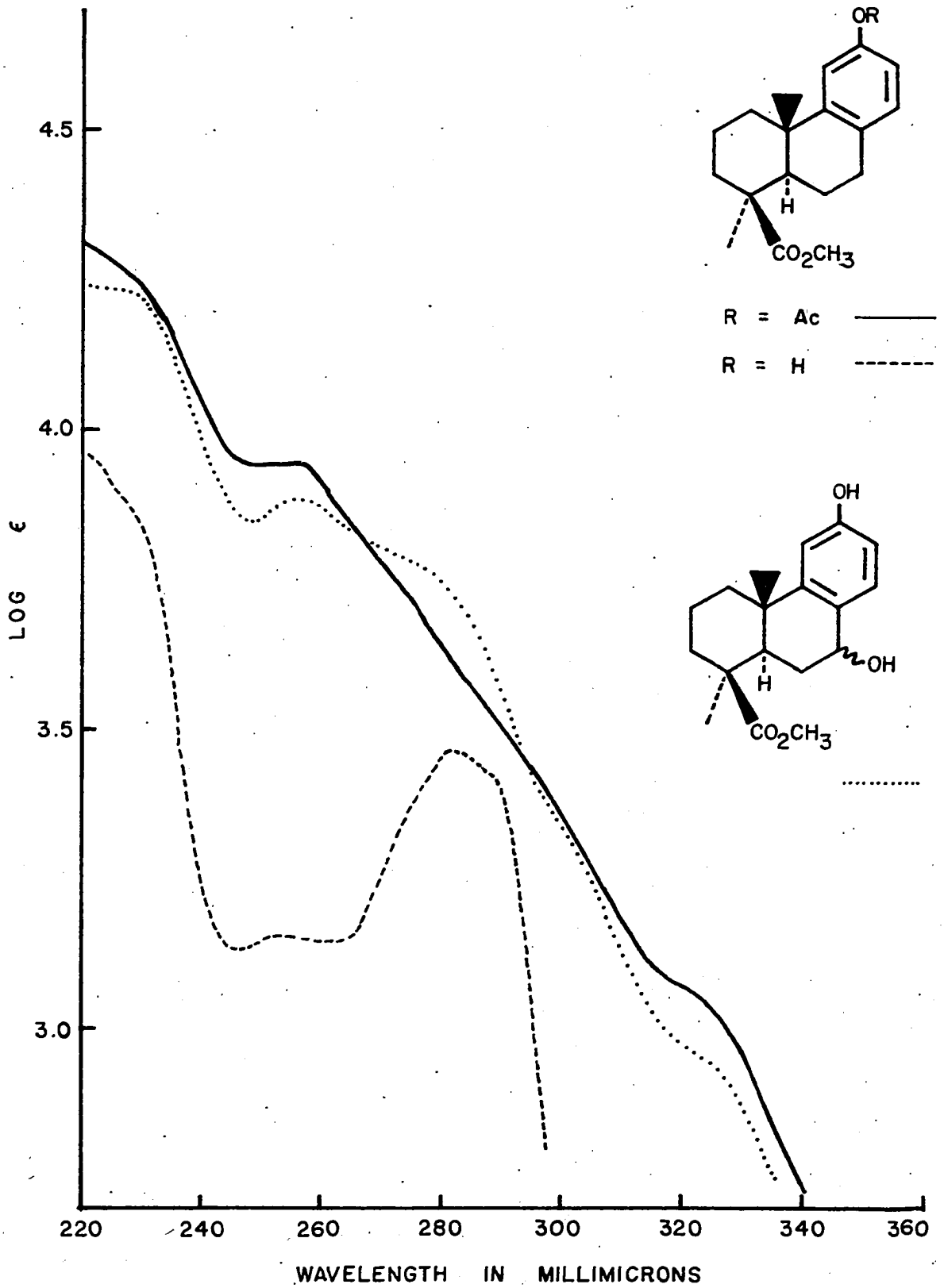

OR
H
CO2CH3
R = Ac
R = H
OH
OH
H
CO2CH3
4.5
4.0
3.5
3.0
LOG ε
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS

Figure 10. Ultraviolet spectra

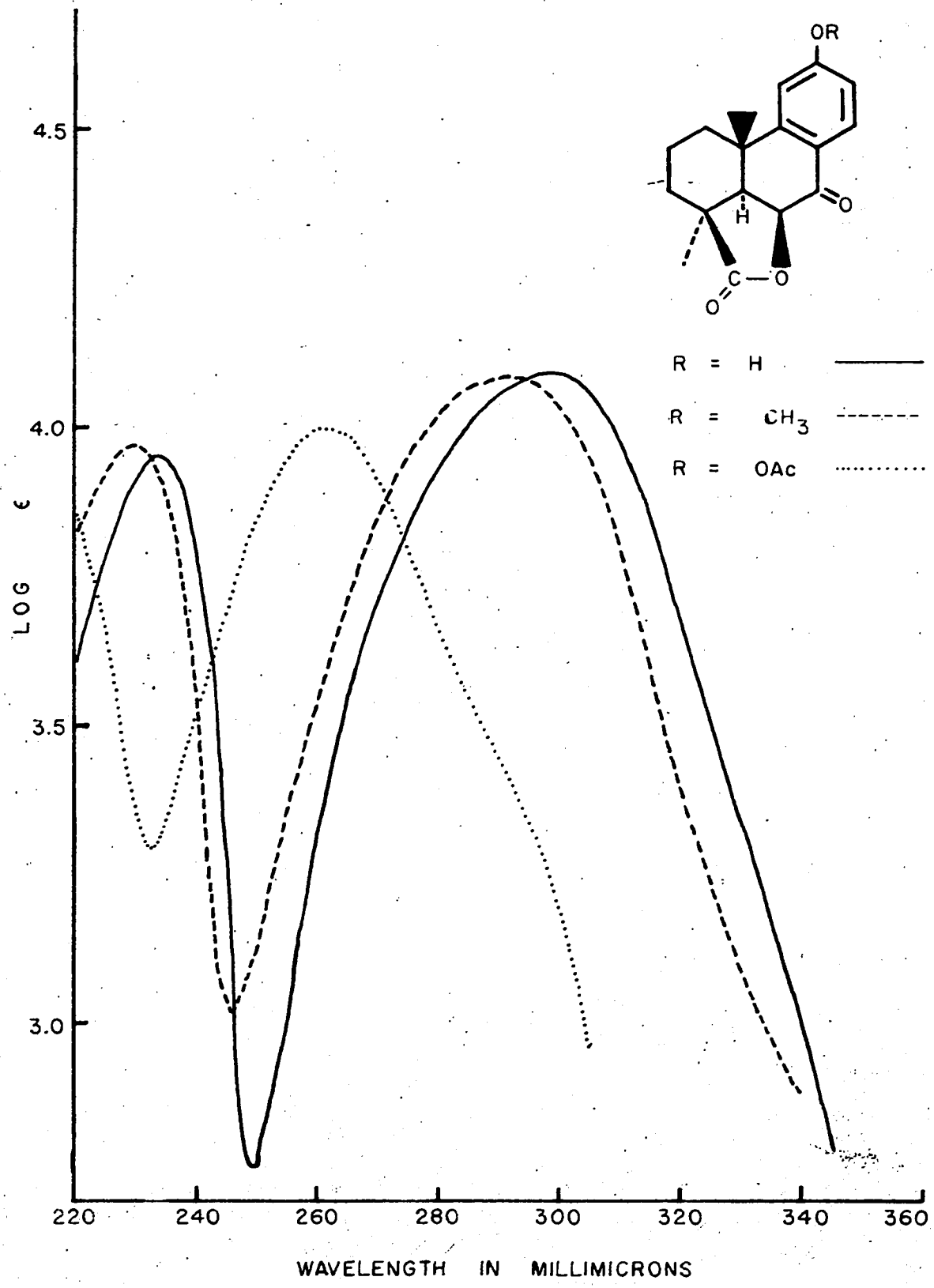

OR
O
H
C—O
O
R = H
R = CH3
R = OAc
4.5
4.0
3.5
3.0
LOG ε
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS

Figure 11. Ultraviolet spectra

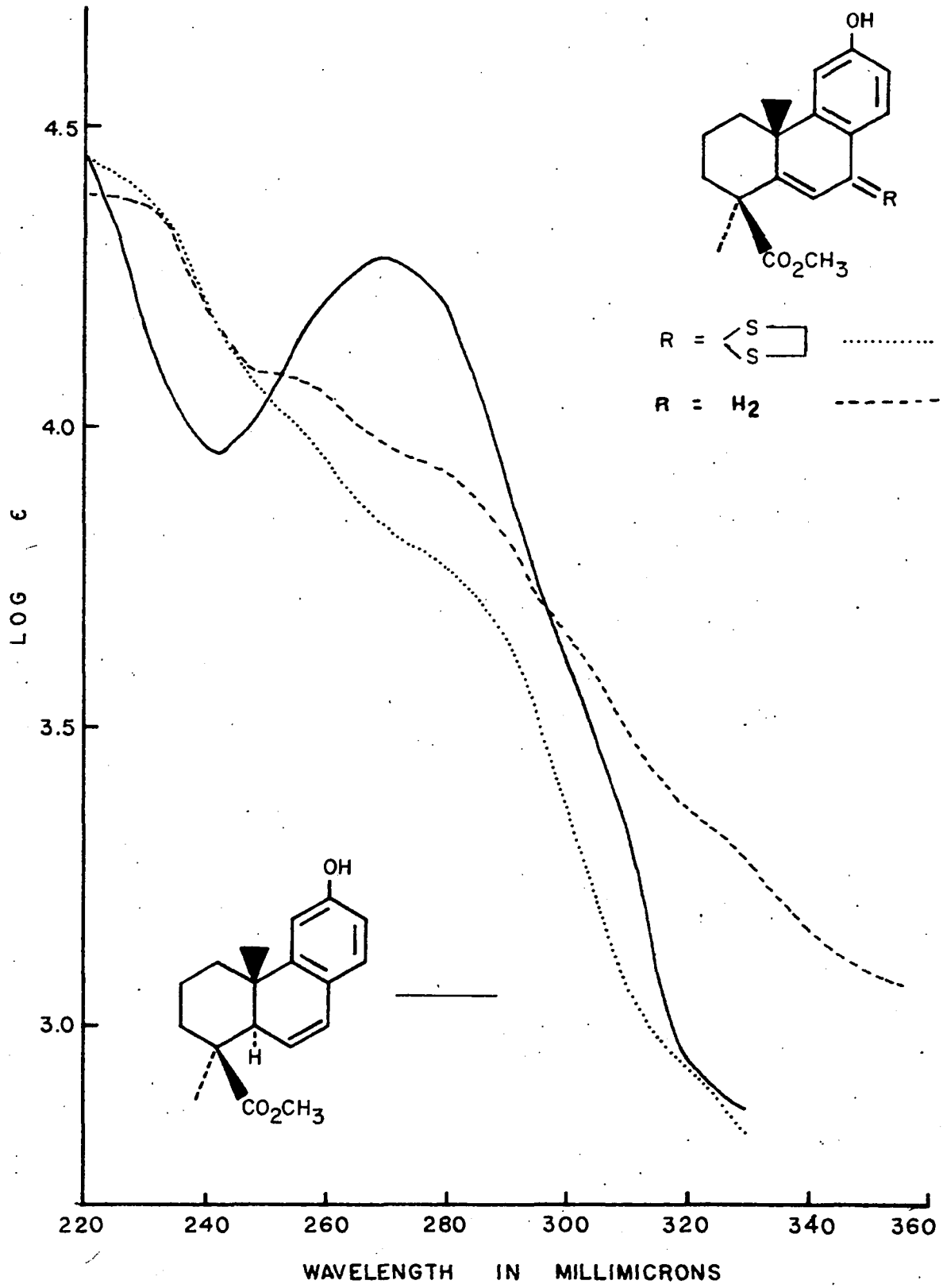
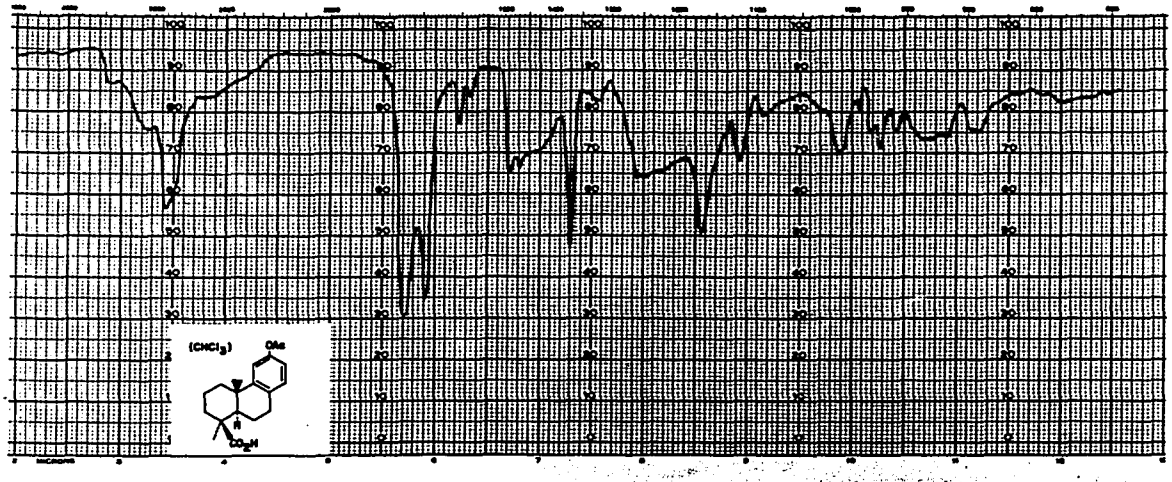
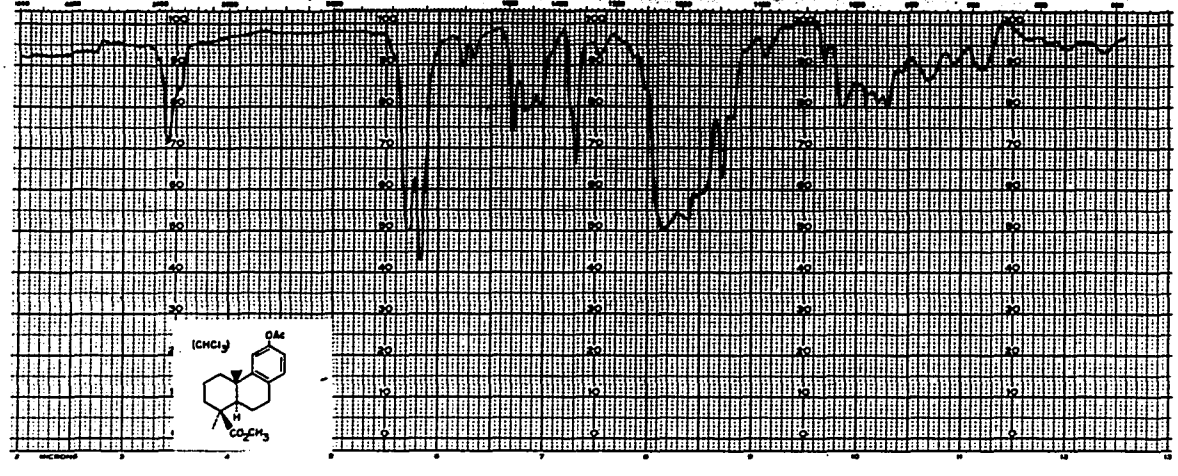

OH
R
CO2CH3
R = S S
R = H2
4.5
4.0
3.5
3.0
LOG ε
OH
H
CO2CH3
220
240
260
280
300
320
340
360
WAVELENGTH IN MILLIMICRONS

Figure 12. Infrared spectra


(CHCl3)
OAc
H
CO2H


(CHCl3)
OAc
H
CO2CH3

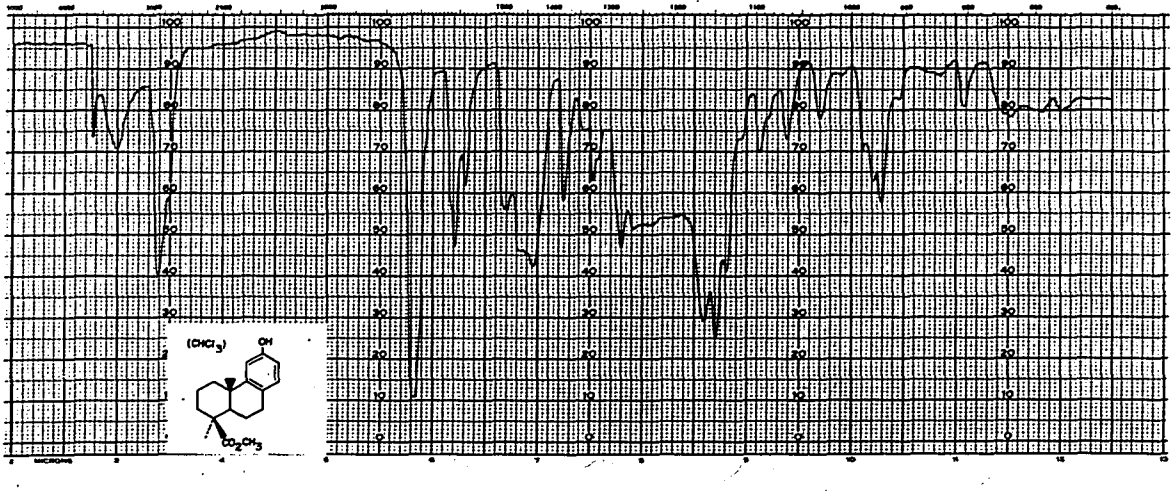
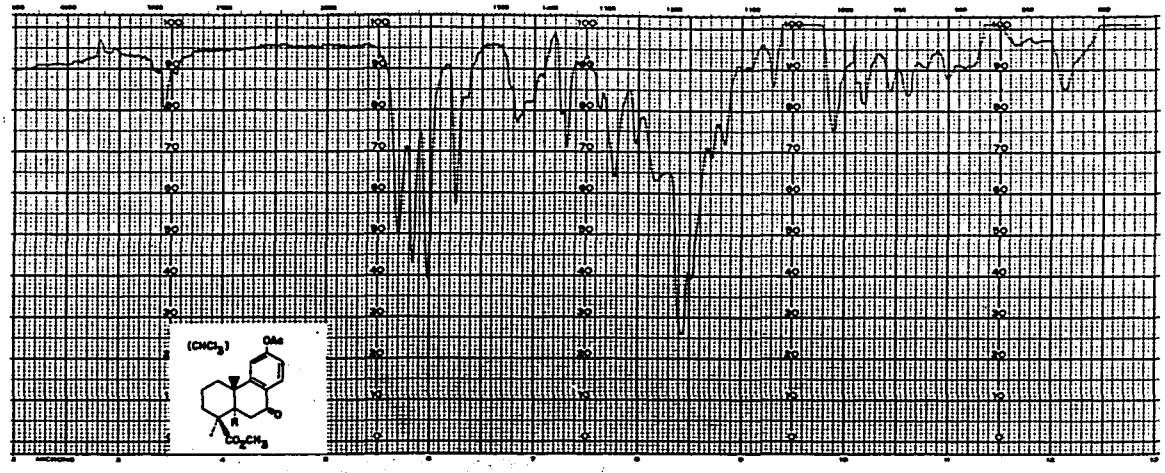
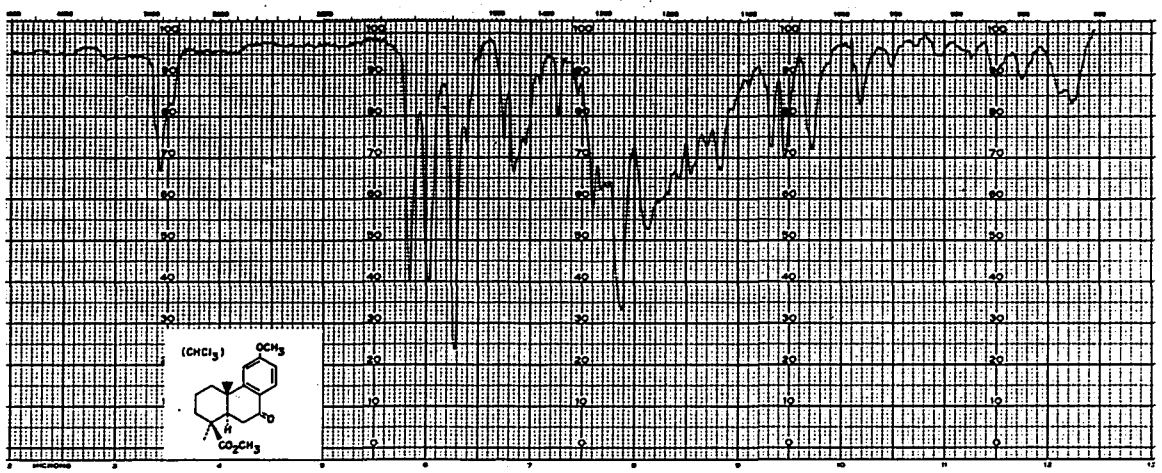

(CHCl3)
OH
CO2CH3

Figure 13. Infrared spectra


(CHCl3)
OAc
H
CO2CH3


(CHCl3)
OCH3
H
CO2CH3

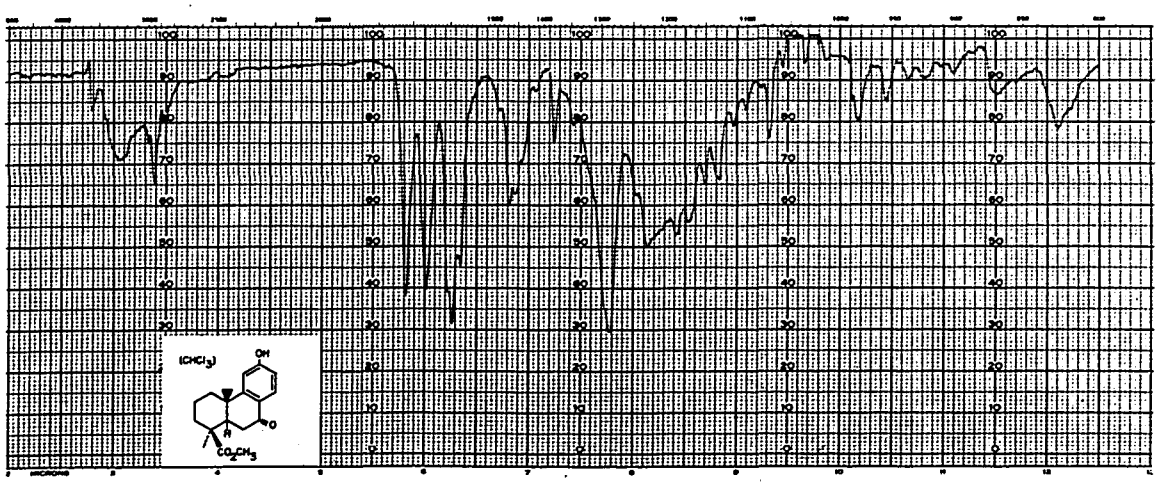
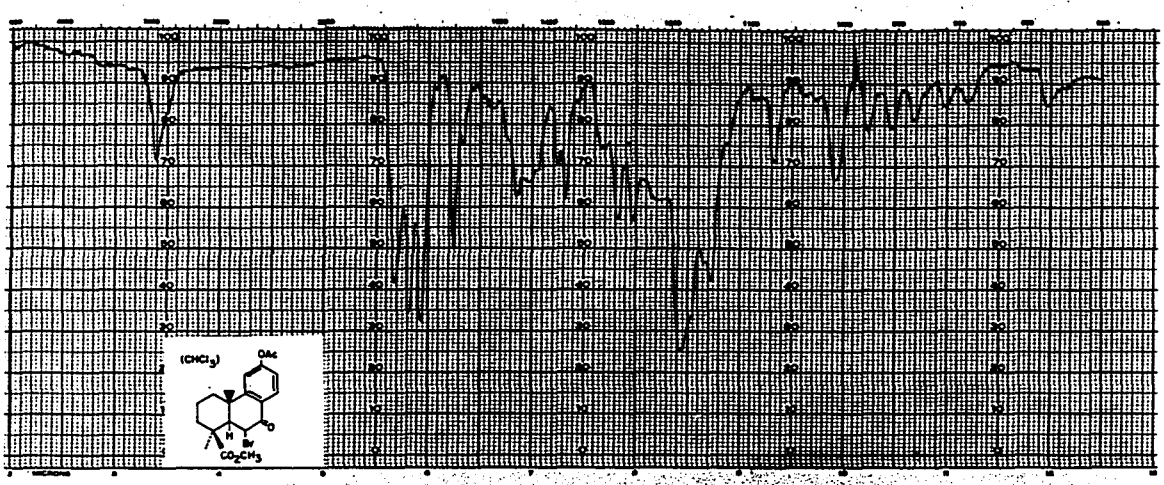
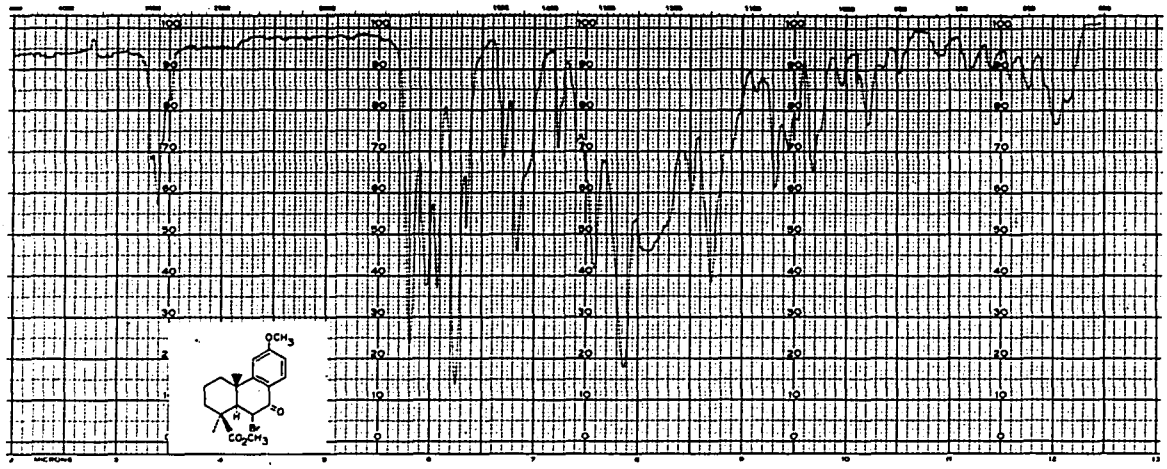

(CHCl3)
OH
H
CO2CH3

Figure 14. Infrared spectra


(CHCl3)
OAc
H
Br
CO2CH3


OCH3
H
Br
CO2CH3

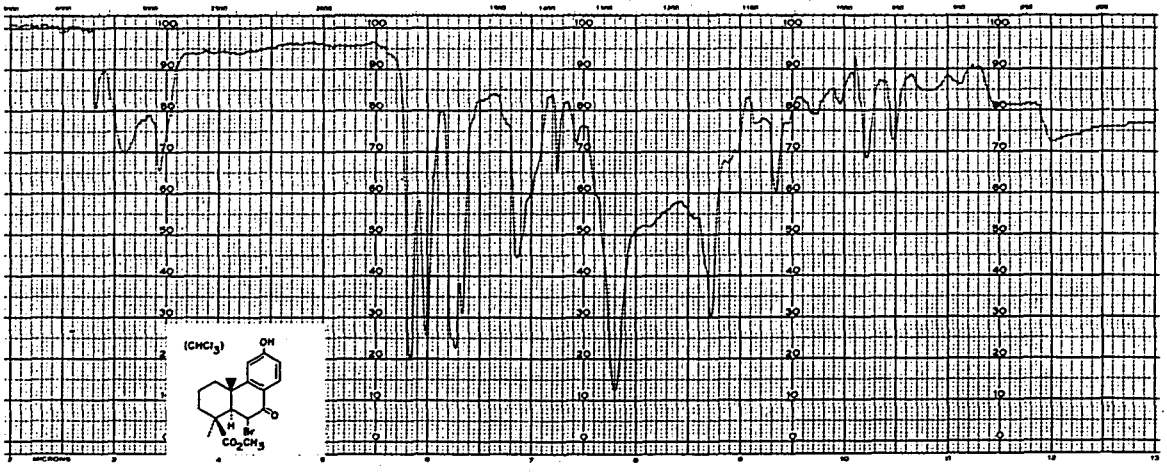
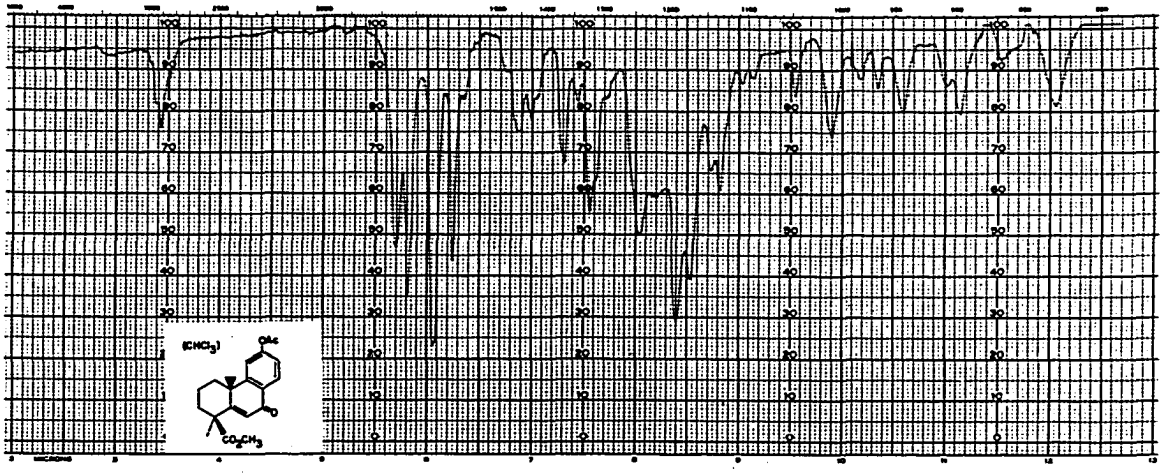
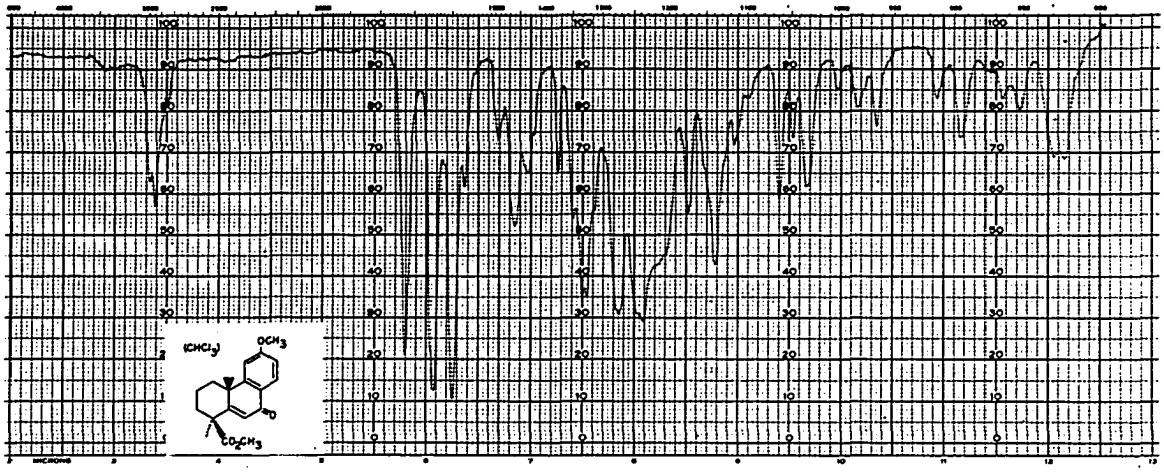

(CHCl3)
OH
H
Br
CO2CH3

Figure 15. Infrared spectra


(CHCl3)
OAc
CO2CH3


(CHCl3)
OCH3
CO2CH3

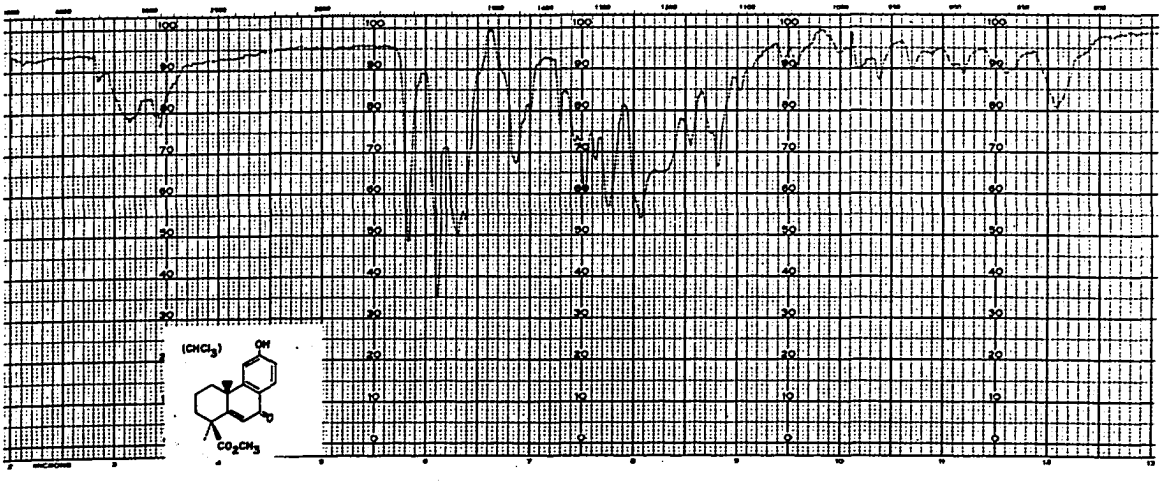
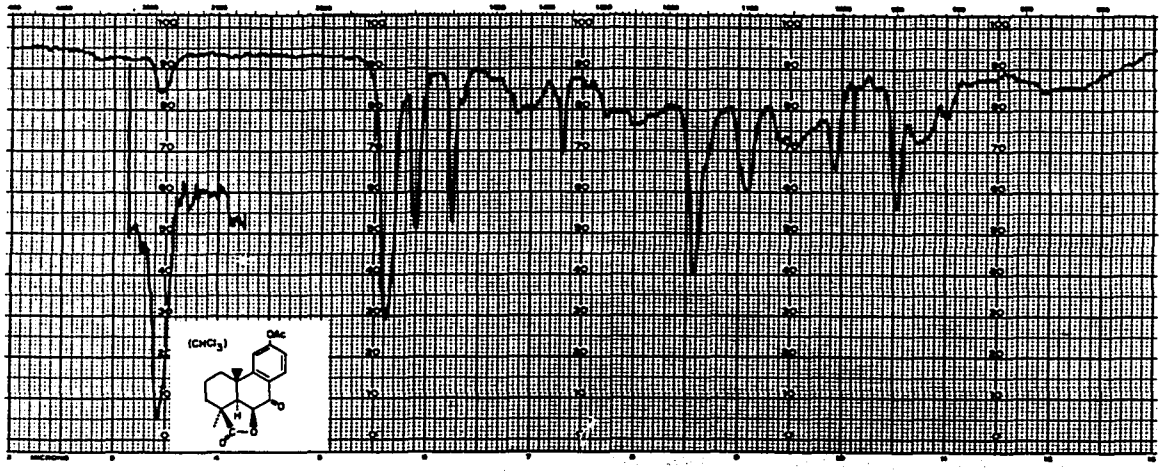
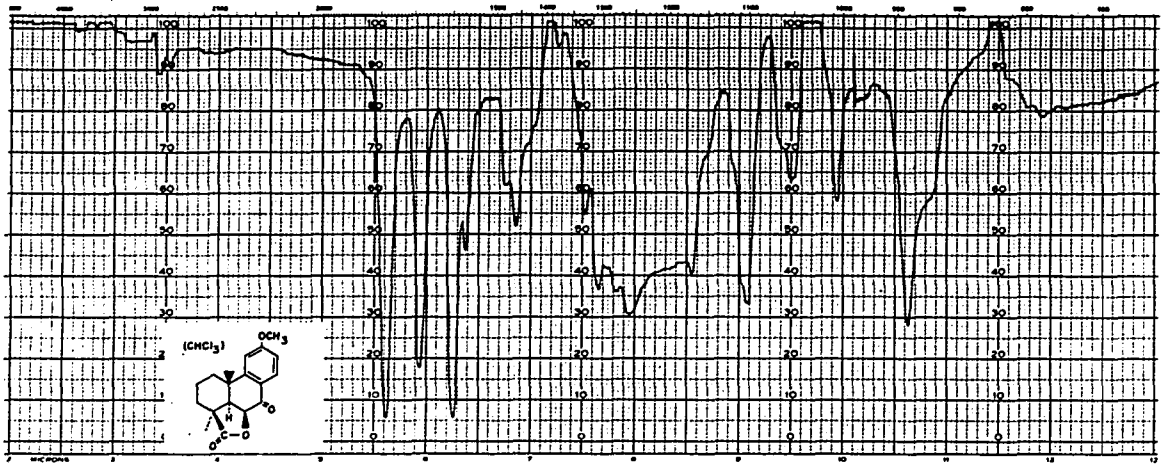

(CHCl3)
OH
CO2CH3

Figure 16. Infrared spectra


(CHCl3)
OAc


(CHCl3)
OCH3

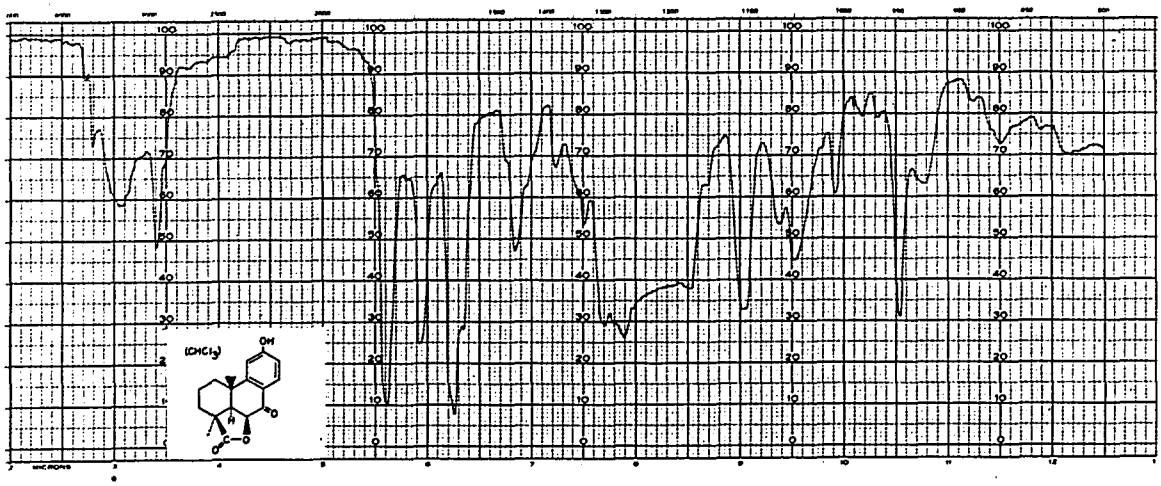
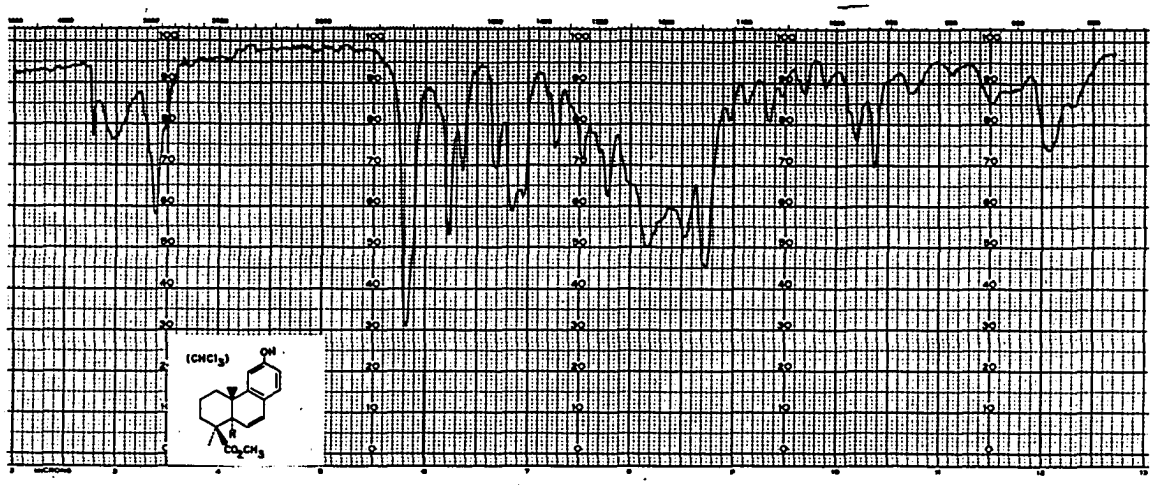
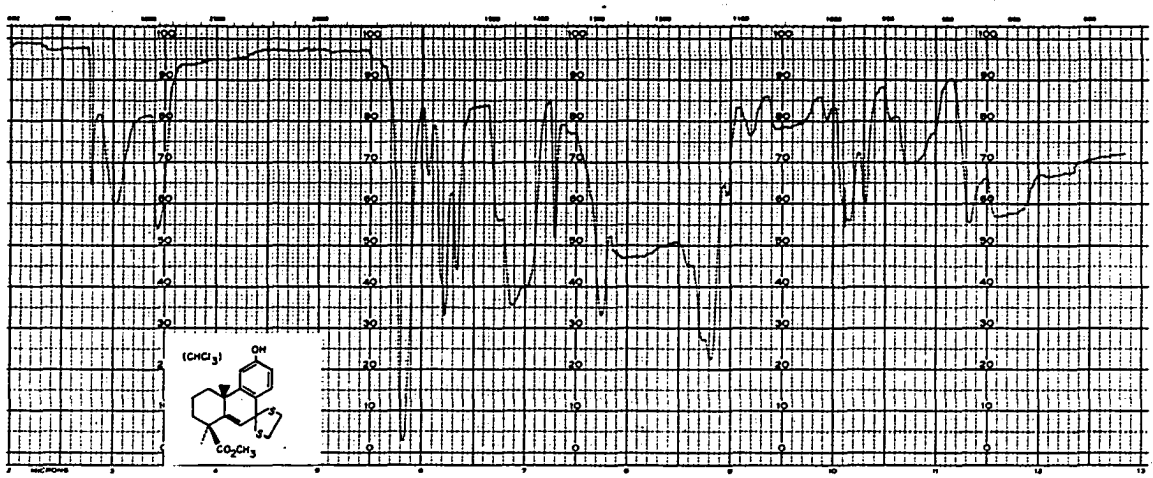

(CHCl3)
OH

Figure 17. Infrared spectra


(CHCl3)
OH
CO2CH3


(CHCl3)
OH
CO2CH3

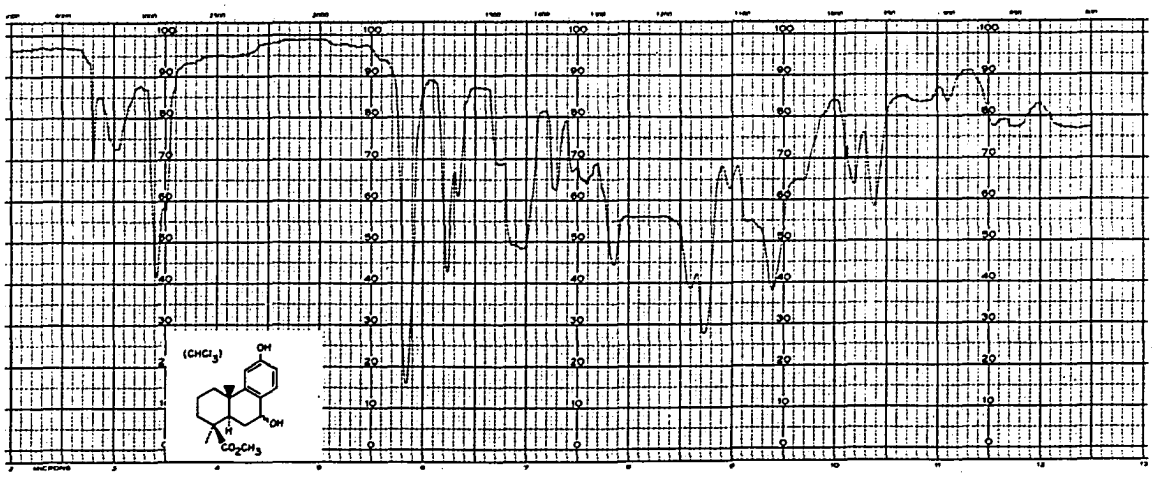
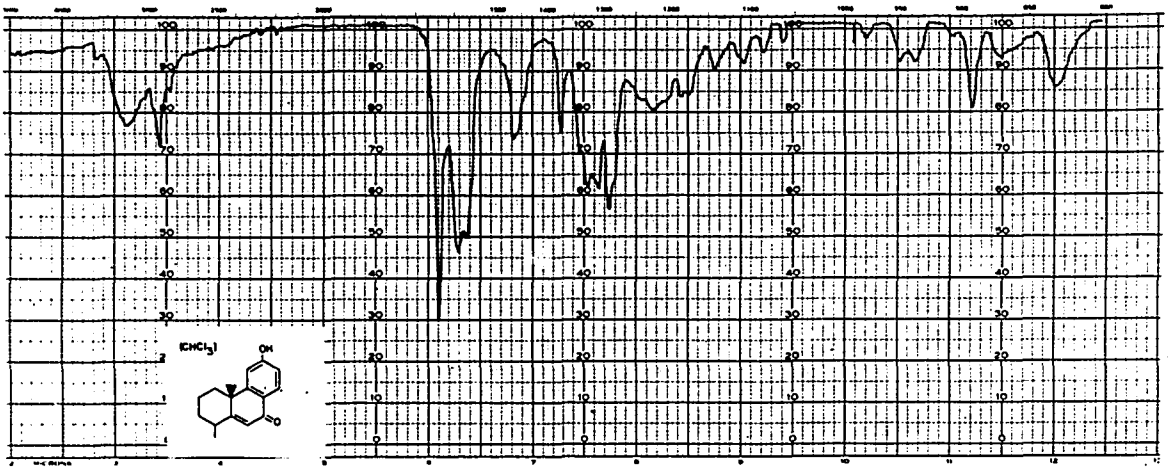
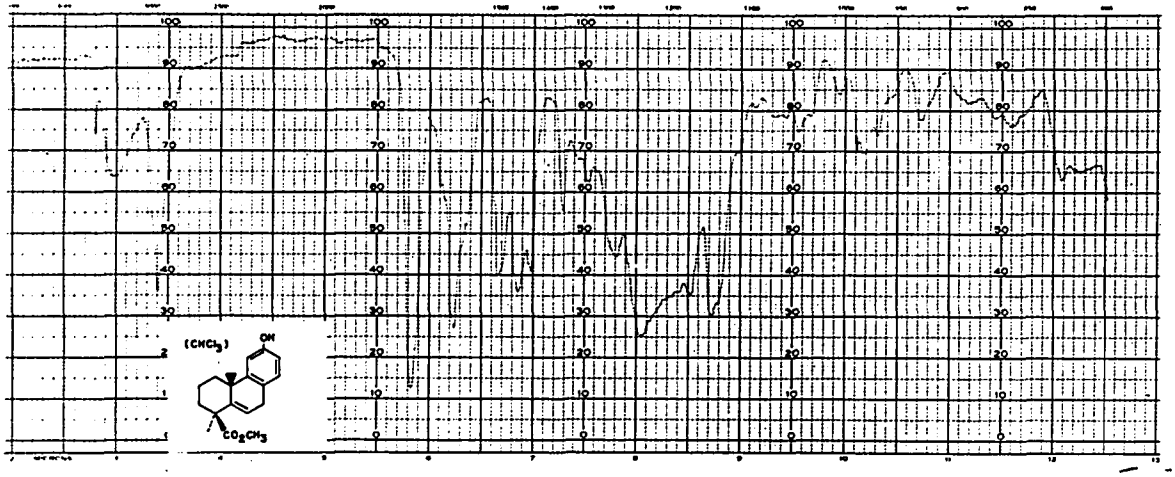
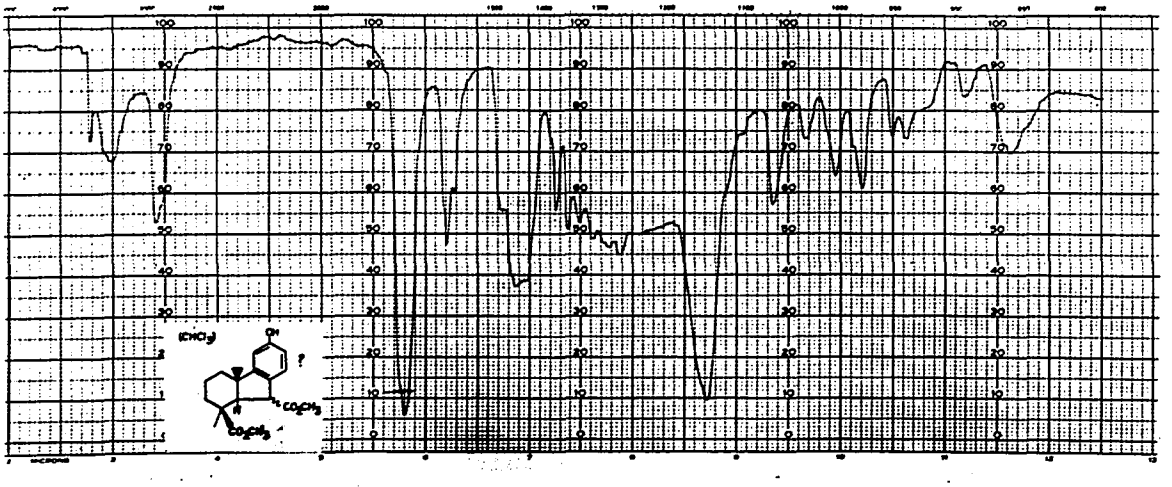

(CHCl3)
OH
OH
CO2CH3

Figure 18. Infrared spectra


(CHCl3)
OH
O


(CHCl3)
OH
CO2CH3


(CHCl3)
OH
?
CO2CH3
CO2CH3

EXPERIMENTAL

Procedure Notes

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

Chromatography was carried out on two adsorbents, alumina and Bentonite-Celite. The alumina was prepared by refluxing commercially available alumina in water containing concentrated hydrochloric acid (in the ratio of 1 kg. : 2.7 l. : 7 ml., respectively) for 4 hours. The alumina was then washed with warm water until a negative silver nitrate test was observed, and dried in an oven for 24 hours. The Bentonite-Celite adsorbent was prepared by mechanically mixing 4 gm. of Bentonite (USP, powder) for each gram of Celite used.

All infrared spectra were taken on a Perkin-Elmer model 21 infrared spectrophotometer, except those denoted by the term "Infracord" which refers to spectra recorded on a Perkin-

Elmer model "Infracord" infrared spectrophotometer.

Ultraviolet spectra were run in 95% ethanol on a Cary model 12 recording spectrophotometer.

Special Reagents

The Raney nickel catalyst was prepared by the method of Mozingo (99) and was refrigerated thereafter.

Commercially available collidine was purified by allowing it to stand 3 or 4 days over barium oxide and distilling it under reduced pressure.

Acetylation of Podocarpic Acid

To 10 gm. (36.5 mmoles) of podocarpic acid was added 100 ml. of acetic anhydride and 2.4 gm. of sodium acetate and refluxed for 3.5 hours. The excess acetic anhydride was removed by vacuum distillation. To the oily residue was added 100 ml. of water, and the entire mixture was extracted three times with chloroform. The combined extracts were washed once with water and dried over anhydrous sodium sulfate. Crystallization from ethanol-water (cooling not generally required) afforded 11.25 gm. (98%) of O-acetylpodocarpic acid (CLXXII), m.p. 160-175°. The analytical sample was recrystallized five times from ethanol-water, m.p. 178-183°. [Lit. value, m.p. 173-176° (100).]

Analysis

Calculated for $C_{19}H_{24}O_4 \cdot H_2O$: C,68.29; H,7.79. Found: C,68.61; H,8.05.

Infrared spectrum

See figure 12.

Methylation of O-Acetylpodocarpic Acid (CLXXII)

A cold ether solution of diazomethane was prepared by reacting 14 gm. (136 mmoles) of N-methyl-N-nitrosourea with 35 ml. of 50% potassium hydroxide solution with 400 ml. ether as solvent. The diazomethane solution was slowly poured into a cold ether solution of 11.2 gm. (35.5 mmoles) of O-acetylpodocarpic acid and allowed to stir at room temperature overnight. The ether was then evaporated, leaving an oil which crystallized on standing (11.7 gm., 99%), m.p. 110-126°. Recrystallization five times from methanol-water afforded methyl O-acetylpodocarpate (CLXXIII), m.p. 123.5-125.0°. [Lit. value, m.p. 125.0-125.5° (101).]

Infrared spectrum

See figure 12.

Ultraviolet spectrum

See figure 9.

Optical rotation

$[\alpha]_D^{22^\circ}$ +113°

Chromic Acid Oxidation of
Methyl O-Acetylpodocarpate (CLXXIII)

Twelve grams (0.035 mole) of the crude diester CLXXIII was dissolved with heating in 160 ml. of glacial acetic acid. Fourteen grams (0.14 moles) of chromium trioxide in 50 ml. of glacial acetic acid and 14 ml. of water was added dropwise over a period of 20 minutes with stirring, care being taken to maintain the temperature below 18° C. Cooling of the reaction was continued for another hour and then allowed to warm to room temperature for 12 hours. The reaction mixture was poured into 600 ml. of saturated salt solution and extracted three times with chloroform. The combined extracts were washed successively with cold 5% sodium hydroxide, dilute hydrochloric

acid, and saturated salt solution. The solution was dried over anhydrous sodium sulfate and, after evaporation of the solvent, chromatographed rapidly (total time: 40 min.) over alumina. The chromatographic column was prepared with benzene, and the oxidation product eluted with benzene. The yield of crude material was 12.94 gm. The analytical sample was recrystallized from methanol-water, once from benzene-petroleum ether, and again from methanol-water giving methyl 0-acetyl-7-ketopodocarpate (CLXXIV), m.p. 132-136°.

Analysis

Calculated for $C_{20}H_{24}O_5$: C,69.75; H,7.02. Found: C,69.39; H,6.97.

Infrared spectrum

See figure 13.

Ultraviolet spectrum

See figure 6.

Optical rotation

$$[\alpha]_D^{25^\circ} +70.0^\circ$$

Bromination of Methyl 0-Acetyl-7-ketopodocarpate (CLXXIV)

Two grams (5.8 mmoles) of the keto diester was dissolved with heating in 10 ml. of glacial acetic acid. Two drops of 15% hydrobromic acid were added, and then 1 ml. of bromine (2.9 gm., 36 mmoles) in 10 ml. of glacial acetic acid was introduced dropwise, with stirring, at room temperature over a period of 5-10 minutes. Stirring was continued for another 10 minutes, whereupon all volatile material was evaporated *in vacuo*. The remaining oil was taken up in methanol and crystallized. Total weight of product, m.p. 119-127°, was 1.97 gm. (79%). The analytical sample was recrystallized five times from methanol giving methyl 0-acetyl-6-bromo-7-ketopodocarpate (CLXXV), m.p. 128-130°.

Analysis

Calculated for $C_{20}H_{26}O_4Br$: C,56.80; H,5.44; Br,18.88. Found: C,57.11; H,5.67; Br,18.65.

Infrared spectrum

See figure 14.

Ultraviolet spectrum

See figure 7.

Optical rotation

$[\alpha]_D^{25^\circ}$ +59.1°

Sodium Methoxide Treatment of
Methyl O-Acetyl-6-bromo-7-ketopodocarpate (CLXXV)

To 10 ml. of anhydrous methanol was added 375 mg. (16.3 mmoles) of sodium. After the sodium had reacted completely, 3 gm. (7.1 mmoles) of the diester CLXXV was introduced. The solution was refluxed under anhydrous conditions for 5.5 hours. The reaction mixture was worked up by the addition of 30 ml. of saturated salt solution containing 1.5 ml. of conc. hydrochloric acid (giving a pH of 2) and extraction of the resulting solution three times with chloroform. The combined extracts were washed once with saturated salt solution and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* leaving an oil which was crystallized from methanol-water giving 1.90 gm. (89%) of methyl $\Delta^{5,6}$-7-ketopodocarpate (CLXXVI), m.p. 205-230°. The analytical sample was recrystallized five times from a methanol-water mixture, then sublimed *in vacuo*, m.p. 217-220°.

Analysis

Calculated for $C_{18}H_{20}O_4$: C,71.59; H,6.67. Found: C,72.00; H,6.67.

Infrared spectrum

See figure 15.

Ultraviolet spectrum

See figure 8.

Optical rotation

$$[\alpha]_D^{25^\circ} +143^\circ$$

Collidine Treatment of Methyl
O-Acetyl-6-bromo-7-ketopodocarpate (CLXXV)

To 396 mg. (0.94 mmoles) of the diester CLXXV was added 3.0 ml. of anhydrous collidine and the solution was refluxed under anhydrous conditions for 2 hours. During this time the reaction developed a dark color. After cooling, 14 ml. of water was added and conc. hydrochloric acid introduced dropwise until pH 2 was reached. The aqueous solution was

extracted four times with chloroform, and the combined extracts were washed three times with saturated salt solution containing dil. hydrochloric acid to remove residual traces of collidine. After a final washing with saturated salt solution the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left an oil (383 mg.) with the faint odor of collidine, whose infrared spectrum showed bands characteristic of a mixture of the lactone of 6-hydroxy-7-keto-O-acetylpodocarpic acid (CLXXVII) and the enone acetate CLXXVIII. The crude mixture was chromatographed on a Bentonite-Celite column.

Preparation of the Bentonite-Celite column

To a chromatographic column 2.7 cm. in diameter was added a cotton plug, 1 cm. of sand, and 50-100 ml. of carbon tetrachloride, in that order. Approximately 6 gm. of the adsorbent mixture was slurried in 20-30 ml. of carbon tetrachloride, care being taken to break up all the lumps, and added in several portions to the column. Solvent was allowed to drip slowly from the column as the adsorbent settled. The settling material on the column was stirred at frequent intervals. The total time allowed for settling was about 1 hour. When the solvent was allowed to drip too rapidly, the column packed tightly and the flow rate was too slow. Although the column

was only 3-4 cm. high, moderate to good separations could be effected.

The chromatography of the product from the reaction of the diester CLXXV with collidine is summarized in the following chart.

No. of Fractions	Eluent	Wt. of Eluate (mg.)	Products Found
4	CCl_4	169	I, II[a,b]
2	CCl_4:C_6H_6 10:1		I, II[b]
2	CCl_4:C_6H_6 10:2		I, II[b]
2	CCl_4:C_6H_6 2:1		I, II[b]
2	CCl_4:C_6H_6 1:1		I, II[b]
2	C_6H_6		II, III[a,b]
1	C_6H_6:$CHCl_3$ 10:1	131	II, III[b]
5	C_6H_6:$CHCl_3$ 10:2		III[b]
2	C_6H_6:$CHCl_3$ 2:1		III[b]
9	$CHCl_3$		III[b]

[a] I - starting diester CLXXV
II - enone acetate CLXXVIII
III - lactone acetate CLXXVII

[b] based on the position and intensity of the carbonyl peaks in the infrared.

The fractions through benzene were combined (169 mg.). The infrared spectrum of this material showed peaks at 5.70,

5.79, and 6.04μ, which proved to be identical with the spectrum of authentic CLXXVIII. The crude material was crystallized three times from methanol-water, m.p. 141-145°; mixed m.p. with authentic enone acetate, 140-145°. The ultraviolet spectrum of this compound was similar to the spectrum of authentic CLXXVIII.

The remaining fractions (131 mg.) were combined. The infrared spectrum showed peaks at 5.60 (broad) and 5.89μ. The crude product was crystallized from methanol-water, m.p. 137-166°. The analytical sample was recrystallized three times from the same solvent mixture giving long needles of the lactone acetate CLXXVII, m.p. 161-164°. These two compounds accounted for utilization of 98% of the starting material.

Analysis

Calculated for $C_{19}H_{20}O_5$: C,69.51; H,6.10. Found: C,69.63; H,6.50.

Infrared spectrum

See figure 16.

Ultraviolet spectrum

See figure 10.

Optical rotation

$$[\alpha]_D^{22^\circ} +84^\circ$$

Hydrolysis of Methyl
O-Acetyl-6-bromo-7-ketopodocarpate (CLXXV)

Dry hydrogen chloride was bubbled into 5 ml. of absolute ethanol, and 200 mg. (0.047 mmoles) of the diester was added and refluxed under anhydrous conditions for 2 hours. The solvent was evaporated under reduced pressure leaving a solid. The residue was recrystallized from methanol-water, giving a phenol (by infrared analysis), m.p. 193-200° (dec.). A total of 158 mg. (88%) was collected. The analytical sample was recrystallized four times from methanol giving methyl 6-bromo-7-ketopodocarpate (CLXXIX), m.p. 199-204° (dec.).

Analysis

Calculated for $C_{18}H_{21}O_4Br$: C,56.71; H,5.51. Found: C,56.46; H,5.72.

Infrared spectrum

See figure 14.

Ultraviolet spectrum

See figure 7.

Optical rotation

$$[\alpha]_D^{25^\circ} +60.5^\circ$$

Sulfuric Acid Hydrolysis of the Diester CLXXV

To 10 ml. of conc. sulfuric acid in a 100 ml. beaker was added 435 mg. (1.03 mmoles) of the diester CLXXV, and the solution was allowed to react at room temperature for 4 hours. The diester dissolved readily upon addition to the sulfuric acid, giving an amber cast to the solution which became darker as the reaction proceeded. The work-up was accomplished by adding ice (40-50 gm.) with concomitant stirring, then water to a total volume of 90 ml. The aqueous solution was extracted three times with chloroform. The combined extracts were washed once with saturated salt solution and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure the remaining solid residue (380 mg., 97%) was crystallized from methanol-water, m.p. 193-199° (dec.). The analytical sample was recrystallized five times from the same solvent mixture, m.p. 200-202° (dec.). Mixed m.p. with

authentic CLXXIX, 200-204° (dec.).

Infrared spectrum

The spectrum (Infracord) was identical with that of pure CLXXIX.

Ultraviolet spectrum

Maxima: 232 ($\log\epsilon$; 4.212) and 298mμ (4.076). Minima: 218 (4.128) and 261 (3.828).(cf. figure 7).

Base Hydrolysis of the Diester CLXXV

To 500 mg. (1.18 mmoles) of the diester CLXXV in 5 ml. of absolute methanol was added a solution of 35 mg. (1.52 mmoles) of sodium in 5 ml. of absolute methanol, and the mixture was allowed to react for approximately one minute. The reaction was immediately quenched with a saturated salt solution containing dil. hydrochloric acid. The solution was extracted twice with chloroform. The combined extracts were washed with saturated salt solution and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo the residual oil (513 mg.) was crystallized from methanol-water, giving 265 mg. (59%) of a phenol, m.p. 187-194° (dec.). Recrystallization three times from this solvent mixture gave m.p. 197-202°

(dec.). Mixed m.p. with authentic methyl 6-bromo-7-ketopodocarpate (CLXXIX) was 195-201° (dec.).

Infrared spectrum

Peaks at 5.78 and 5.95μ (cf. figure 14).

Ultraviolet spectrum

Maxima: 299 mμ (logϵ; 4.042) and 232 (4.127). Minima: 258 (3.729 and 218 (4.028).(cf. figure 7).

Chromic Acid Oxidation of Methyl O-Methylpodocarpate (CCVII)

To 1 gm. of methyl O-methylpodocarpate (3.4 mmoles) [prepared by treating podocarpic acid with dimethyl sulfate (100)], m.p. 120-130°, dissolved in 10 ml. glacial acetic acid was added slowly with stirring 700 mg. (7.0 mmoles) chromium trioxide in 1.7 ml. of 80% acetic acid. The temperature was maintained at 15-18° throughout the addition. The entire mixture was placed in the refrigerator for 3.5 days and then allowed to stand at room temperature for one day. Ten ml. of water was introduced and the solution then extracted three times with chloroform. The combined extracts were washed three times with 10% sodium hydroxide, three times with water,

and dried over sodium sulfate. After removing the solvent at reduced pressure, the remaining oil (1.1 gm.) was crystallized from ethanol-water giving needles of methyl 7-keto-0-methyl-podocarpate (CCVIII), m.p. 117-23°. A total of 906 mg. of 7-keto compound was isolated (84%). The analytical sample was recrystallized five times from ethanol-water, m.p. 121.0-122.5°. A crystalline form change occurs at 108-110°.

Analysis

Calculated for $C_{19}H_{24}O_4$: C,72.15; H,7.60. Found: C,72.36; H,7.60.

Infrared spectrum

See figure 13.

Ultraviolet spectrum

See figure 6.

Optical rotation

$$[\alpha]_D^{25^\circ} +78.6^\circ$$

Bromination of the Ketone CCVIII

To 732 mg. (2.32 mmoles) of CCVIII in 15 ml. of anhydrous carbon tetrachloride was added 420 mg. (4.26 mmoles) of N-bromosuccinimide. The solution was heated until most of the N-bromo compound had dissolved and then allowed to stand at room temperature for 26 hours (approximately 13 hours in sunlight). The solids which precipitated (mostly succinimide) were filtered off, and the solvent was removed under reduced pressure leaving an oil (1.09 gm.). The residue was crystallized from methanol-water, yielding 861 mg. (74%) of cubic crystals, m.p. 118-122°. The analytical sample was recrystallized five times from methanol-water, m.p. 123-126°. [Lit. value, 142-144.5° (81).] The analytical sample gave unsatisfactory values.

Infrared spectrum

See figure 14.

Ultraviolet spectrum

See figure 7.

Optical rotation

$$[\alpha]_D^{20^\circ} +86.8^\circ$$

Base Treatment of Methyl O-Methyl-6-bromo-7-ketopodocarpate (CCIX)

To 261 mg. (0.66 mmoles) of the O-methyl ether CCVIII in absolute methanol was added a solution of 20 mg. (0.87 mmoles) of sodium in 5 ml. of absolute methanol and refluxed under dry conditions for 4 hours. After cooling, saturated salt solution containing dil. hydrochloric acid was added until the reaction mixture was at ca. pH of 2. Then 15 ml. more of salt solution was added. The products were extracted with chloroform, the combined extracts were washed three times with saturated salt solution, and the solution was then dried over anhydrous sodium sulfate. Removal of the solvent left an oil (260 mg.) which, upon crystallization from methanol-water, gave 175 mg. (84%) of methyl O-methyl- $\Delta^{5,6}$-7-ketopodocarpate (CCX), m.p. 170-178°. The analytical sample was recrystallized five times from methanol-water, m.p. 173-175°.

Analysis

Calculated for $C_{19}H_{22}O_4$: C,72.62; H,7.01. Found: C, 72.20; H,7.23.

Infrared spectrum

See figure 15.

Ultraviolet spectrum

See figure 8.

Optical rotation

$$[\alpha]_D^{20^\circ} +152.5^\circ$$

The mother liquors were dried over anhydrous sodium sulfate, and the solvent removed in vacuo leaving an oil (25 mg.) which was added to a Bentonite-Celite column in several drops of chloroform. The progress of the chromatography was followed by infrared analysis. Elution through benzene:chloroform (2:1) gave a solid residue (21 mg.) with carbonyl peaks identical with those of the enone CCX. Elution with chloroform gave ca. 7 mg. of a mixture of enone and lactone CCXI, the former being predominant. The amount of lactone that had formed did not exceed 2 mg., on the basis of the infrared results.

Collidine Treatment of Methyl 0-Methyl-6-bromo-7-ketopodocarpate (CCIX)

To 310 mg. (0.79 mmoles) of CCIX was added 3.0 ml. of anhydrous collidine and refluxed under dry conditions for 2 hours. Then 14 ml. of water was introduced and conc. hydro-

chloric acid was added until a pH 2 was reached. The aqueous mixture was extracted three times with chloroform. The combined extracts were washed three times with saturated salt solution containing dil. hydrochloric acid and once with saturated salt solution alone. After drying of the extract over anhydrous sodium sulfate the solvent was evaporated. Infrared examination of the remaining oil showed peaks which indicated the presence of a mixture of a lactone and an unsaturated ketone. The crude oil was added to a Bentonite-Celite column in a minimal amount of chloroform and chromatographed. The following chart shows the results of this chromatography.

No. of fractions	Eluent	Wt. of eluate (mg.)	Products found
10	CCl_4	99.5	I[a,b]
5	$CHCl_3$	50.5	I,II[a,b]
10	$CHCl_3$	70.5	II[b]

[a] I - enone ether CCX

II - lactone ether CCXI

[b] determined by the position of the carbonyl peaks in the infrared spectrum.

The combined fractions from carbon tetrachloride elution gave infrared peaks at 6.05 and 5.79μ, in agreement with those of authentic enone CCX. The material was crystallized

three times from methanol-water, m.p. 166-170° (m.p. of authentic CCX, 171-173°).

The first fractions eluted with chloroform were judged to be mixtures of *ca.* an 80:20 ratio of lactone to enone. One crystallization from methanol-water gave m.p. 135-160° (*vide supra*).

The later chloroform fractions contained nearly pure lactone CCXI. The combined fractions were crystallized from methanol-water, m.p. 193-198°. The analytical sample was recrystallized four times from the same solvent mixture, m.p. 195-197.5° [Lit. value, 198-200.5° (81)]. About 91% of the starting material was accounted for by the products isolated.

Analysis

Calculated for $C_{18}H_{20}O_4$: C,72.00; H,6.67. Found: C,72.15; H,6.66.

Infrared spectrum

See figure 16.

Ultraviolet spectrum

See figure 10.

Optical rotation

$$[\alpha]_D^{20^\circ} +89^\circ$$

Collidine Treatment of the Bromophenol CLXXIX

To 265 mg. (0.70 mmoles) of CLXXIX was added 3.0 ml. of anhydrous collidine. The solution was refluxed under dry conditions for 2 hours. After cooling, 14 ml. of water was introduced and conc. hydrochloric acid was added dropwise until pH 2 was reached. The aqueous solution was extracted three times with chloroform. The combined extracts were washed three times with saturated salt solution containing dil. hydrochloric acid and once with water. After drying the chloroform solution over anhydrous sodium sulfate, the solvent was removed under reduced pressure leaving an oil (297 mg.) whose infrared spectrum made it appear to be a mixture of the enone CLXXVI and predominantly a lactone. The oil was added to a Bentonite-Celite column (2.5 x 3.5 cm. in height) in a small amount of chloroform and chromatographed over a period of 125 hours. A summary of the chromatography is given in the following chart.

No. of fractions	Eluent	Wt. of eluate (mg.)	Products found
2	CCl_4	negligible	
2	CCl_4:C_6H_6 10:1	negligible	
2	CCl_4:C_6H_6 10:2	negligible	
9	CCl_4:C_6H_6 2:1	10	I[a,b]
19	CCl_4:C_6H_6 1:1	33	mainly I[b]
5	C_6H_6	2-5	90% I[b]
6	C_6H_6:$CHCl_3$ 10:1	34	95% I[b]
6	C_6H_6:$CHCl_3$ 10:2		
24	C_6H_6:$CHCl_3$ 2:1	142	II[a,b]
5	$CHCl_3$	8	mixed I, II[b]

[a] I - enone phenol CLXXVI

II - lactone phenol CCXII

[b] estimated from the position and intensity of the carbonyl peaks in the infrared.

The early fractions from the column contained a material (80 mg.) with an infrared absorption at 6.07 μ and appeared to be the enone CLXXVI. The ultraviolet and infrared spectra of this material were identical with those of authentic CLXXVI. Several of these fractions were combined and acetylated with acetic anhydride-sodium acetate. The infrared and ultraviolet spectra of the crude product were those of the enone acetate CLXXVIII.

The next material eluted (150 mg.) appeared to be a lactone on the basis of its infrared spectrum. Its spectral properties were consistent with the structure CCXII. However, it did not prove possible to crystallize the oil from any solvent or solvent combination that was tried. In order to prove its structure the material was acetylated with acetic anhydride-sodium acetate to give crystals of the lactone acetate CLXXVII, m.p. 161-164°. A mixed m.p. with authentic CLXXVII was 160-165°. The infrared and ultraviolet spectra of this acetate were identical with the spectra of pure CLXXVII.

Hydrolysis of the Lactone CLXXVII

To 32 mg. (0.10 mmoles) of CLXXVII dissolved in 5 ml. of absolute methanol was added a methanol solution of 5 mg. (2 molar quantity) of sodium. The solution immediately became yellow. The hydrolysis was allowed to run for 2 minutes and then quenched with 10 ml. of a saturated salt solution containing dil. hydrochloric acid. The aqueous solution was extracted twice with chloroform. The combined extracts were washed once with saturated salt solution and dried over anhydrous sodium sulfate. The oil which remained could not be made to crystallize from aqueous methanol. Its infrared spectrum showed clean peaks at 5.60 and 5.95 μ in agreement

with the absorptions expected for the hydrolyzed lactone acetate CCXII. The infrared and ultraviolet spectra of the oil were identical with those of the pure lactone obtained from treatment of the bromo-phenol CLXXIX with collidine.

Reacetylation of this oily product was carried out by adding 1.5 ml. of acetic anhydride containing 2 drops of anhydrous pyridine and heating the mixture on a steam plate for 2 hours. The reaction mixture was poured into water and extracted twice with chloroform. The extracts were washed twice with dil. hydrochloric acid and once with saturated salt solution. After drying over anhydrous sodium sulfate the solvent was removed leaving an oil which contained no phenol absorptions in the infrared. The oil crystallized from methanol-water to give needles of the lactone acetate CLXXVII, m.p. 161-165°. Mixed m.p. with authentic CLXXVII, 161-166°.

Infrared spectrum

The infrared spectrum was identical with that of pure CLXXVII.

Ultraviolet spectrum

The ultraviolet spectrum showed maxima and extinction coefficients identical with those of the spectrum of authentic CLXXVII.

Methylation of Methyl $\Delta^{5,6}$-7-Ketopodocarpate (CLXXVI)

To 153 mg. (0.51 mmoles) of the ester CLXXVI in a three-necked flask fitted with a condenser was added 52 mg. (1.25 mmoles) of sodium hydroxide in 3 ml. of 1:1 ethanol:water and 0.1 ml. (1.06 mmoles) of dimethyl sulfate at room temperature. The mixture was heated with stirring to approximately 120° for 20 minutes and then allowed to cool. As the measured pH was only 8, 50 mg. of sodium hydroxide was added, followed by a large excess of water (ca. 10 ml.). The resulting solution was extracted three times with ether, and the combined extracts were dried over magnesium sulfate. The ether was then evaporated. An infrared spectrum of the residue gave no evidence for the presence of a free phenol and peaks attributable to an aryl ether were present. The yield was 89 mg. (56%). The methyl ether was crystallized from petroleum ether-benzene, m.p. 169-174°. The analytical sample was prepared by three recrystallizations from the same solvent mixture and two sublimations, m.p. 171-174°.

Analysis

Calculated for $C_{19}H_{22}O_4$: C,72.50; H,7.01. Found: C,72.63; H,7.11.

Infrared spectrum

See figure 15.

Ultraviolet spectrum

See figure 8.

Optical rotation

$[\alpha]_D^{20^\circ}$ +152.5°

Acetylation of Methyl $\Delta^{5,6}$-7-Ketopodocarpate (CLXXVI)

To 200 mg. (0.585 mmoles) of the phenol CLXXVI was added 100 mg. (1.22 mmoles) of sodium acetate and 5 ml. of acetic anhydride and the mixture was refluxed for 3 hours. The excess acetic anhydride was evaporated under reduced pressure, 10 ml. of water was added, and the mixture was extracted twice with chloroform. After washing the combined extracts once with water and drying the organic layer over anhydrous sodium sulfate, the solvent was evaporated, leaving an oil (415 mg.) which crystallized upon standing. Recrystallization from methanol-water gave 211 mg. (84%) of the acetate, m.p. 143-146°. The analytical sample was recrystallized five times from methanol-water, m.p. 143-146°.

Analysis

Calculated for $C_{20}H_{22}O_5$: C,70.20; H,6.44. Found: C,70.22; H,6.52.

Infrared spectrum

See figure 15.

Ultraviolet spectrum

See figure 8.

Optical rotation

$$[\alpha]_D^{25^\circ} +147^\circ$$

Hydrolysis of Methyl O-Acetyl-7-ketopodocarpate (CLXXIV)

To 100 mg. (0.29 mmoles) of the diester CLXXIV was added 10 ml. of 5% sodium hydroxide and 1 ml. of ethanol. The solution was stirred for 3 hours at room temperature. Ten ml. of saturated salt solution was introduced and conc. hydrochloric acid added to pH 2. The solution was extracted four times with chloroform. The combined extracts were washed with saturated salt solution and dried over magnesium sulfate. After evaporation of the solvent the remaining oil (96 mg.)

was crystallized from methanol-water, m.p. 220-238° (75 mg., 85% yield). The analytical sample was recrystallized five times from the same solvent mixture to give methyl 7-keto-podocarpate (CLXXXII), m.p. 235-240°.

Analysis

Calculated for $C_{18}H_{22}O_4$: C,71.52; H,7.28. Found: C,71.23; H,7.20.

Infrared spectrum

See figure 13.

Ultraviolet spectrum

See figure 6.

Optical rotation

$$[\alpha]_D^{25^\circ} +52.7^\circ$$

Acid Treatment of the Enone Phenol CLXXVI

To 100 mg. (0.33 mmoles) of enone, m.p. 215-218.5° was added 2.0 ml. of glacial acetic acid and 3 mg. of p-toluene-

sulfonic acid, and the mixture was heated at 85-90° for 15 hours. The acetic acid was removed in vacuo, and the oily residue was crystallized from methanol-water giving 82 mg. (82%) of the starting material, m.p. 216-218.5°. Mixed m.p. with starting material gave 219-221.5°. The mother liquors (4 mg.) were chromatographed on an alumina column, but only an insignificant residue was eluted even through methanol.

Thioketal Formation of Methyl $\Delta^{5,6}$-7-Ketopodocarpate (CLXXVI)

To 300 mg. (1 mmole) of CLXXVI dissolved in 6 ml. of glacial acetic acid (with heating) was added 0.3 ml. of ethanedithiol and 0.6 ml. of boron trifluoride etherate (freshly distilled, b.p. 123.5-125.5° (1 atm.)) and allowed to stand at room temperature for 48 hours with occasional shaking. A deep red color gradually developed which proved difficult to remove during purification. Water was introduced dropwise, with cooling, until the thioketal precipitated. There was collected 272 mg. (70%) of methyl $\Delta^{5,6}$-7-ketopodocarpate thioketal (CCXIII), m.p. 234-239°. An analytical sample was prepared by recrystallizing six times from aqueous methanol giving white platelets, m.p. 237-241° (dec.).

Analysis

Calculated for $C_{20}H_{24}O_3S_2$: C,63.80; H,6.38. Found: C,63.39; H,6.34.

Infrared spectrum

See figure 17.

Ultraviolet spectrum

See figure 11.

Optical rotation

$$[\alpha]_D^{20^\circ} +128.5^\circ$$

Desulfurization of the Thioketal CCXIII with Raney Nickel

W-2 Raney nickel in absolute ethanol

To 19 mg. (0.05 mmoles) of the thioketal in 4 ml. of absolute ethanol was added a tenfold quantity of Raney nickel and refluxed for 6 hours. The ethanol was then evaporated *in vacuo*, the residue was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate. The chloroform was evaporated, and the remaining solid was recrystal-

lized twice from methanol-water, giving methyl podocarpate, m.p. 203-209°, mixed m.p. with authentic methyl podocarpate, 200-209°. The infrared spectrum was identical with authentic CCXVI (Infracord).

W-2 Raney nickel in acetone

To 59 mg. of thioketal in 10 ml. of acetone was added a tenfold quantity of Raney nickel and the mixture was refluxed for 2 hours. The catalyst was filtered (Celite), and the acetone removed under reduced pressure. The residual oil (64 mg.) was light yellow, and changed to a deep red color when exposed to air. This oil resisted all attempts at recrystallization. Attempted chromatography on a Bentonite-Celite column gave only a deep red oil. However, some solid material was formed on high vacuum sublimation although its melting point did not indicate very high purity.

Infrared spectrum

See figure 18.

Ultraviolet spectrum

See figure 11.

Optical rotation

$$[\alpha]_D^{25^\circ} +108^\circ$$

Hydrogenation of Methyl $\Delta^{5,6}$-Podocarpate (CCXIV)

To 64 mg. (0.22 mmoles) of the crude desoxy compound in 5 ml. ethyl acetate in a micro-hydrogenation flask was added 10 mg. palladium-carbon catalyst (10%) and two drops of conc. sulfuric acid. The catalyst was pre-equilibrated and the sample was hydrogenated for 3.5 hours. Most of the hydrogen uptake occurred during the first hour. The yellow color disappeared. The catalyst was removed by filtration (Celite). The ethyl acetate solution was washed once with 5% sodium bicarbonate and once with saturated salt solution. After drying over anhydrous sodium sulfate the solvent was evaporated leaving crystals of methyl podocarpate (40 mg., 90% yield based on the amount of thioketal used). Recrystallization from methanol-water gave m.p. 197-204°. A mixed m.p. with authentic CCXVI was 197-206.5°. Infrared (Infracord) and ultraviolet spectra were identical with those of authentic CCXVI.

Borohydride Reduction of the Keto Diester CLXXIV

To 200 mg. (0.58 mmoles) of CLXXIV, dissolved in 5 ml. of 95% ethanol and 1 ml. of water, was added 200 mg. (5.3 mmoles) of sodium borohydride and 200 mg. of sodium carbonate. The mixture was stirred at room temperature for 2.5 hours. Conc. hydrochloric acid was added dropwise until bubbling ceased, whereupon more was added until pH 2 was reached. Approximately 5 ml. of water was introduced, and the solution was extracted twice with chloroform. The combined extracts were washed once with saturated salt solution and dried over anhydrous sodium sulfate. After evaporation of the solvent there remained a colorless oil (197 mg.) whose infrared spectrum gave indication that the product was methyl 7-hydroxypodocarpate (CCXV). Attempted purification by crystallization gave only oils. This material was employed for the subsequent reaction without further purification.

Infrared spectrum

See figure 17.

Ultraviolet spectrum

See figure 9.

Optical rotation

$$[\alpha]_D^{25^\circ} +64.9^\circ$$

Catalytic Hydrogenation of the Hydroxyphenol CCXV

A mixture of 88 mg. (0.29 mmoles) of the crude borohydride product, 3 mg. of pre-equilibrated palladium-carbon catalyst (10%), 2 drops of conc. sulfuric acid, and 3 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature. Approximately 75% of the total hydrogen uptake occurred in the first 5 minutes of reaction. After 2.5 hours the hydrogenation was stopped and the catalyst removed by filtration (Celite). After washing twice with water to remove the mineral acid, the solution was dried over anhydrous sodium sulfate. Removal of the solvent left a solid residue (62 mg.) which was crystallized from methanol giving needles of CCXVI, m.p. 207-211.5°. Mixed m.p. with authentic methyl podocarpate, 207-211.5°.

Infrared spectrum

The infrared spectrum (Infracord) was identical with that of authentic methyl podocarpate.

Ultraviolet spectrum

Identical with the ultraviolet spectrum of pure CCXVI.

Dehydration of Methyl 7-Hydroxypodocarpate (CCXV)

The crude 7-hydroxy compound (95 mg., 0.32 mmoles) was dissolved in 5 ml. of methanol. One ml. of conc. hydrochloric acid was added and the solution refluxed for 8 hours. The methanol was stripped in vacuo, and the remaining solids were washed with 0.5 ml. of water to remove the remaining hydrochloric acid. Crystallization from methanol-water gave colored solid material, m.p. 135-175°. Vacuum sublimation gave a crystalline solid, m.p. 172-176°.

Infrared spectrum

See figure 17.

Ultraviolet spectrum

See figure 11.

Optical rotation

$$[\alpha]_D^{20^\circ} -74.9^\circ$$

Hydrogenation of Methyl $\Delta^{6,7}$-Podocarpate (CCXVII)

To 14.4 mg. (0.05 mmoles) of CCXVII was added 4 ml. of ethyl acetate, 2 drops of conc. sulfuric acid, and 3-5 mg. of palladium-carbon catalyst (10%). After equilibration of the catalyst the compound was allowed to react for 14 hours. The major portion of hydrogen uptake occurred during the first 10 minutes of hydrogenation. The catalyst was removed by filtration (Celite) and, after successive washings with 5% sodium bicarbonate and water, the solution was dried over anhydrous sodium sulfate. Removal of the solvent at reduced pressure left a crystalline residue (15 mg., 100% yield). One crystallization from methanol-water gave m.p. 206-210°. Mixed m.p. with authentic methyl podocarpate, 206-211.5°.

Infrared spectrum

Identical with that of methyl podocarpate.

Ultraviolet spectrum

Identical with the ultraviolet spectrum of pure CCXVI.

Borohydride Reduction of the Ketophenol CLXXXII

To 63 mg. (0.21 mmoles) of CLXXXII dissolved in 2.5 ml. of 95% ethanol and 0.5 ml. of water was added 63 mg. (1.67

mmoles) of sodium borohydride and 63 mg. of anhydrous sodium carbonate. The solution bubbled vigorously upon addition of the borohydride and was stirred at room temperature for 1 hour. Conc. hydrochloric acid was added dropwise until pH 2 was reached. Then 10 ml. of water was introduced. After extracting the solution twice with chloroform, the combined extracts were washed once with water and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo an infrared spectrum was taken of the residual oil and showed a small peak at 6.05μ, which is present in the starting material (see figure 13). Reduction was continued using the same amount of reagents for another hour. After identical work-up an infrared analysis on the product (68 mg.) showed no absorption at 6.05μ.

Hydrogenation of the borohydride product

This reduction product was hydrogenated in 3 ml. of ethyl acetate with 3 mg. of palladium-carbon catalyst (10%) and 2 drops of conc. sulfuric acid at atmospheric pressure and room temperature. The catalyst was pre-equilibrated. Although the hydrogenation was continued for 1 hour, absorption of hydrogen stopped after 10 minutes. The catalyst was filtered (Celite), the filtrate was washed twice with water, and the solution was dried over anhydrous sodium sulfate. Evaporation of the solvent left a solid (42 mg., 70% based on CLXXXII),

which was crystallized from methanol, m.p. 205-209°. Mixed m.p. with authentic methyl podocarpate, 207-211°.

Infrared spectrum

Identical with that of pure methyl podocarpate.

Ultraviolet spectrum

Identical spectrum with that of pure CCXVI.

Attempted Reduction of the Enone Acetate CLXXVIII

To 100 mg. (0.29 mmoles) of the acetate CLXXVIII in 2.5 ml. of 95% ethanol and 0.5 ml. of water there was added 100 mg. (2.6 mmoles) of sodium borohydride and 100 mg. of sodium carbonate. The reaction was stirred at room temperature for 3 hours. Work-up was identical with that used in the reduction of the diester CLXXIV and gave a slightly yellow oil (93 mg.) which appeared to be the enone phenol CLXXVI from the infrared spectrum. Also, ultraviolet analysis showed maxima at 242 and 307 mμ and minima at 222 and 268 mμ (cf. figure 8). Attempted crystallization failed to produce any solid material.

The residue (89 mg.) was acetylated with 2 ml. of acetic anhydride containing 30 mg. of sodium acetate as catalyst.

After work-up there remained an oil (55 mg.) which was crystallized from methanol-water, m.p. 140-147°. Its infrared spectrum revealed it to be impure enone acetate CLXXVIII.

Base Hydrolysis of the Enone CLXXVI

To 790 mg. (2.63 mmoles) of CLXXVI was added approximately 7.0 ml. of distilled collidine and 2.8 gm. (20.3 mmoles) of lithium iodide, and the solution was refluxed under nitrogen for 10 hours. Evolution of a gas was noted during the first 10 minutes of refluxing. The gas appeared to be basic judging from its action on litmus paper. After cooling 15 ml. of water was added to the reaction mixture. Then conc. hydrochloric acid was introduced dropwise until pH 2 was reached. The aqueous solution was extracted four times with chloroform. The combined extracts were washed twice with saturated salt solution containing dil. hydrochloric acid and once with saturated salt solution alone. The solution was dried over magnesium sulfate. After removal of the solvent in vacuo there remained a dark colored residue which contained traces of collidine and was partly crystalline.

The dark colored residue could be recrystallized from methanol-water but, unfortunately, without loss of the dark color. The latter was removed finally by chromatography. A chloroform solution of the crude product was added to an

alumina column and eluted immediately with methanol. This gave slightly yellow crystalline material (ca. 200 mg., 31% yield) which gave an infrared spectrum that contained only one band in the carbonyl region. This peak was located at 6.07 . Again recrystallization from methanol-water gave slightly colored platelets, m.p. 232-236° (a crystal change to needles at 200°). Final purification of the analytical sample was accomplished by sublimation at 130-140° in high vacuum. This gave white platelets of 4-decarboxy- $\Delta^{5,6}$-7-ketopodocarpic acid (CCXVIII), m.p. 234-237°.

Analysis

Calculated for $C_{16}H_{18}O_2$: C,79.35; H,7.44. Found: C,79.01; H,7.96.

Infrared spectrum

See figure 18.

Ultraviolet spectrum

Maxima: 242 and 301 mμ. Minima: 220 and 267 mμ.

Optical rotation

$$[\alpha]_D^{25^\circ} +115^\circ$$

Acid Treatment of the Decarboxylated Ketone CCXVIII

To 2.5 mg. (0.009 mmoles) of CCXVIII was added 0.9 ml. of 5% hydrochloric acid and sufficient methanol to dissolve the compound. The solution was allowed to stand at room temperature for 42 hours. The methanol was removed by an air stream. The precipitate which remained was crystallized from methanol-water, m.p. 226-230° (crystals change to needles before melting).

Ultraviolet spectrum

Maxima: 241 and 302 mμ. Minima: 221 and 267 mμ. (cf. with the spectrum of CCXVIII, p. 139).

Selenium Dioxide Oxidation of Methyl O-Acetyl-7-Ketopodocarpate (CLXXIV)

To 200 mg. (0.58 mmoles) of diester was added 680 mg. (6.1 mmoles) of freshly sublimed selenium dioxide and 20 ml. of glacial acetic acid. The solution was refluxed for 5.5 hours, during which time a dark precipitate of selenium formed. The dark precipitate was filtered off (Celite), and the acetic acid was removed under reduced pressure. The residue was extracted three times with ether and dried over anhydrous sodium sulfate. After evaporation of the ether the

remaining oil was crystallized from methanol-water giving 130 mg. (62%) of the enone acetate CLXXVIII, m.p. 130-144°. Recrystallization three times from methanol-water afforded crystals of enone acetate, m.p. 143-145.5°. Mixed m.p. with authentic CLXXVIII gave a value of 142-146°.

Infrared spectrum

Identical with the spectrum of CLXXVIII.

Ultraviolet spectrum

Identical with that of pure CLXXVIII.

SUMMARY

1. Several selected α-haloketones in the podocarpic acid series were reacted with collidine. The products in each case were shown to be mixtures of the appropriate lactone and dehydrobrominated compound. Attempt was made to prove whether a "quasi-Favorskii" reaction occurs in the reaction of the bromoketone CLXXV with sodium methoxide. Some evidence is presented in favor of this reaction.

2. The catalytic hydrogenation of a $\Delta^{5,6}$ unsaturated derivative of podocarpic acid was shown to proceed stereospecifically to give the product predicted on the basis of previously reported investigations. A number of other podocarpic acid derivatives were hydrogenated catalytically and their products determined.

3. A new method for preparing the A-ring of podocarpic acid for modification by further chemical reactions is reported.

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