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Structure studies in the diterpene series

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STRUCTURE STUDIES IN THE DITERPENE SERIES

by

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Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

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Of Science and Technology
Ames, Iowa

1961

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INTRODUCTION

The tools particularly suited to the structure determination of non-expendable or unavailable materials are, on the one hand, physical methods and, on the other, synthesis.

These two approaches are used in the attempted solution of structural and stereochemical problems in the diterpene hydrocarbons, oxides and phenols.

HISTORICAL

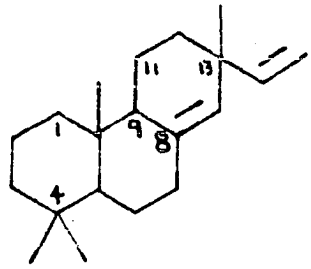
The conifers of New Zealand have been an abundant source of diterpenic compounds. The genus Dacrydium has yielded rimuene[1,2,3](I), phyllocladene[2,4,5,6,7](II), manoyl oxide[8,9](III) and ketomanoyl oxide[8,10,11](IV) in addition to other diterpenes. Phyllocladene appears to be particularly widely distributed as it appears in Phyllocladus[12,13,14,15,16], Araucaria[13] and Podocarpus[17]. Moreover, Podocarpus also yields rimuene[18] and totarol[19,20](V). A compound designated as hydroxytotarol[21] has been found in Podocarpus.

Genera not indigenous to New Zealand have yielded phyllocladene[22] and totarolone[23](VI).

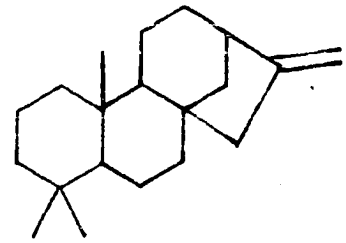
Isolation and Structure Determination of Rimuene

The first isolation of rimuene was reported in 1925 by McDowall and Finlay[24] who obtained a crystalline solid of $C_{20}H_{32}$ constitution from Dacrydium cupressinum. Carrie,[25] working in part with the compound isolated by the previous investigators, determined that rimuene possessed two double bonds, one of which was terminated in a methylene group. Beath[18] gleaned rimuene from Podocarpus totara, implying that the non-crystalline hydrocarbon totarane which Aitken[26] had previously isolated from this source was, in fact, impure rimuene. An interesting observation was made by Beath that rimuene on heating with formic acid yielded isophyllocladene

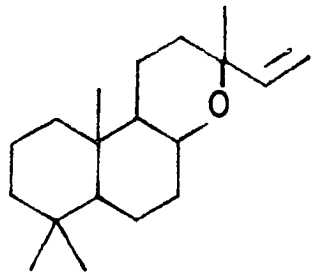
Plate 1. Diagram



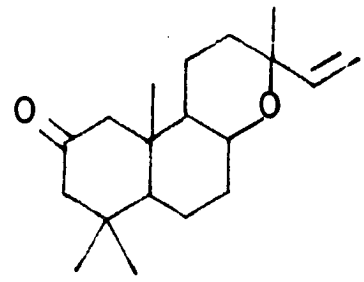
I



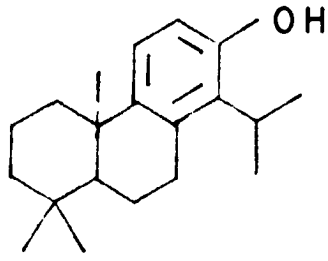
II



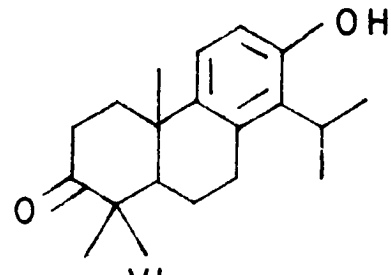
III



IV



V



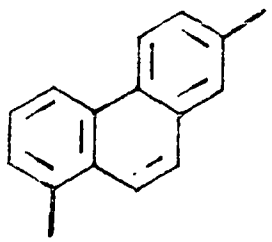
VI

(vide infra). Brandt[27] obtained pimanthrene (VII) upon selenium-induced dehydrogenation of rimuene and thereupon proposed VIII as the structure for rimuene.

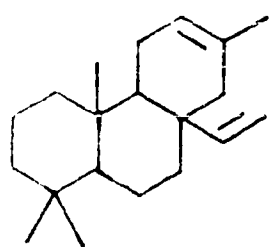
Wenkert[28] has pointed out that by analogy with the known pimaric acids (vide infra) rimuene should have structure I. Briggs et al.[1] have provided chemical confirmation for this proposal with their isolation of 1,2-dimethyl-2-ethyl-1,2,3,4-tetrahydrophenanthrene(IX) upon partial dehydrogenation of rimuene and of 1,2,7-trimethylphenanthrene(X) upon dehydrogenation of the product obtained from the reaction of dihydrorimuene epoxide with methyl magnesium iodide.

Briggs et al.[2,3] envision the stereochemistry of rimuene as shown in XI on the basis of the diterpene's acid-catalyzed conversion into isophyllocladene(XII) and an abietadiene XIII both of which are of known stereochemistry (vide infra). This argument assumed that the mechanistic pathway of this reaction is that of the suggested[28] and recently proven[29] biogenesis for a similar system. Further confirmation for the stereochemistry of rimuene as XI was provided by the reported conversion of sandaracopimaric acid[30](XIV) into rimuene by Galik et al.[31] Surprisingly, Ireland and Schiess,[32] in confutation of the Czech work, recently reported a conversion of sandaracopimaric acid into sandaracopimaradiene(XI) which was not identical with rimuene. Furthermore, the Ann Arbor workers also have converted pimaric(XV) and isopimaric(XVI)

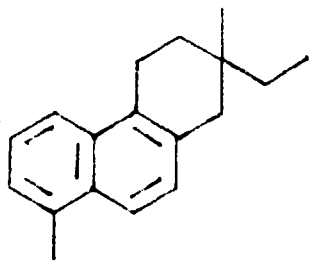
Plate 2. Diagram



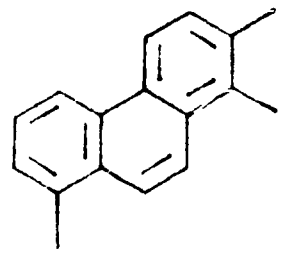
VII



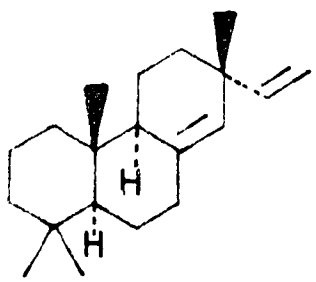
VIII



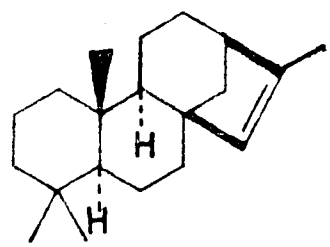
IX



X



XI



XII

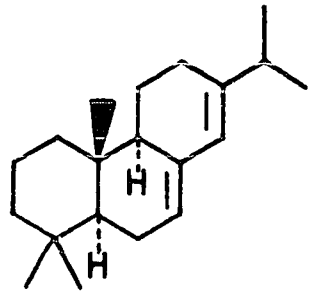
acids, the stereochemistry of which has been agreed upon by a number of workers[33,34,35,36] into the corresponding dienes(XVII and XVIII, respectively) neither of which was identical with rimuene.

Isolation and Structure Determination of Phyllocladene

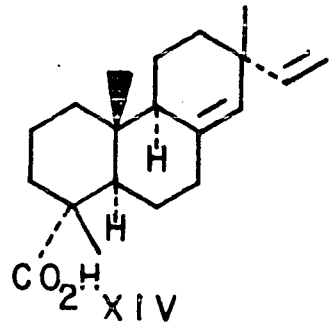
In 1910 Baker and Smith[12] reported the isolation of phyllocladene from Phyllocladus rhonboidalis. The same compound, erroneously named dacrene, was found in Dacrydium biforme[15,37,38] and Dacrydium colenso[16]. Sciadopitene isolated from Sciadoptys verticillata[22] is also identical with phyllocladene. Briggs[13] has reported obtaining phyllocladene from Phyllocladus alpinus and Araucaria excelsa. Moreover this author notes an unreported isolation of this diterpene from Dacrydium cupressinum. Briggs and Loe[18] have isolated phyllocladene from Podocarpus spicatus and Briggs and Sutherland[14] found this widely distributed compound along with isophyllocladene (vide infra) in Phyllocladus trichomanoides.

The early workers established that phyllocladene had a constitution of $C_{20}H_{32}$,[15] contained one double bond,[15,39] yielded two compounds upon hydrogenation[13] and led to isophyllocladene upon treatment with acid.[22,38] Uota's oxidation experiments[40] clarified the relationship of phyllocladene to isophyllocladene by establishing the existence of an exocyclic methlene group in the former and an endocyclic double

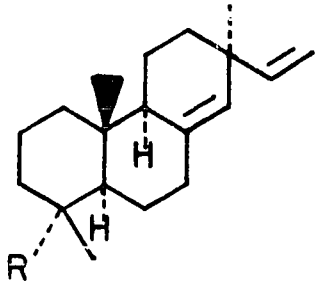
Plate 3. Diagram



XIII

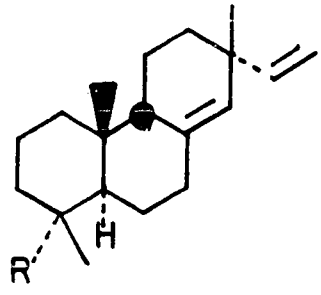


XIV



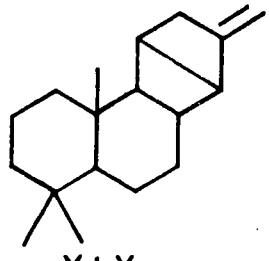
XV, R=CO_2H

XVII, R=CH_3

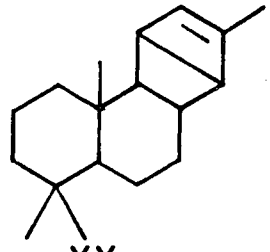


XVI, R=CO_2H

XVIII, R=CH_3



XIX



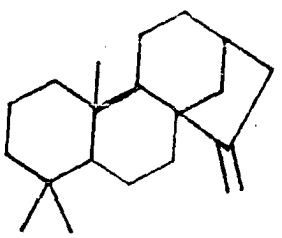
XX

bond in the latter. Uota proposed XIX and XX as the structures for phyllocladene and isophyllocaldene, respectively.

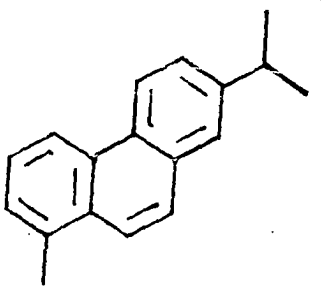
Brandt[27] obtained pimanthrene upon dehydrogenation of phyllocladene with selenium and proposed XXI and II as possible structures for phyllocladene. Proposal II was later preferred by Brandt[41] as he obtained retene(XXII) in further dehydrogenation experiments with the tetracyclic diterpene. Brandt followed an oxidation sequence similar to Uota's[39] and verified the latter's conclusions. In the course of these experiments the norketone XXIII and the keto-ester XXIV were characterized. Isophyllocladene was then established to be XXV. These structural assignments were later supported by Bottomley et al.[42] on infra-red evidence. Briggs et al.[43] have confirmed the relationship of isophyllocladene and phyllocladene with the conversion of the former into the latter, by means of an allylic oxidation and Wolff-Kishner reduction.

The first proposal as to the stereochemistry of phyllocladene was tendered by Djerassi et al.,[44] on the basis of the correspondence of the optical rotatory dispersion curve of XXIII with that of a similar derivative XXVI of cafestol (XXVII). These investigators considered phyllocladene to have either an A/B cis or antipodal trans configuration. By use of the octant rule Djerassi et al.[45] were able to establish that the keto-ester XXIV has a C_8 β carbomethoxy group, and

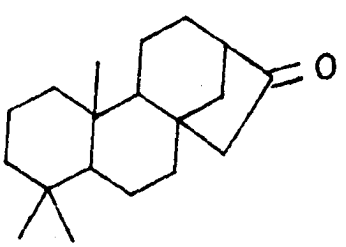
Plate 4. Diagram



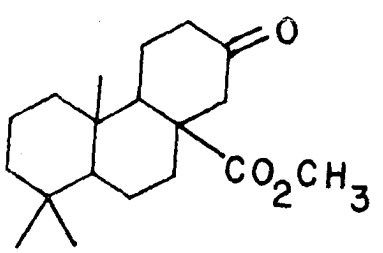
XXI



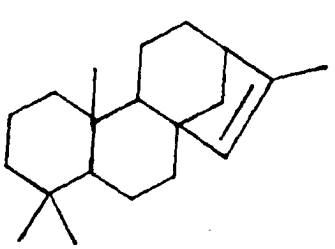
XXII



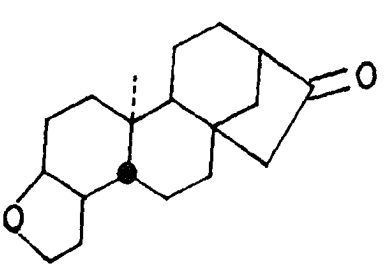
XXIII



XXIV



XXV

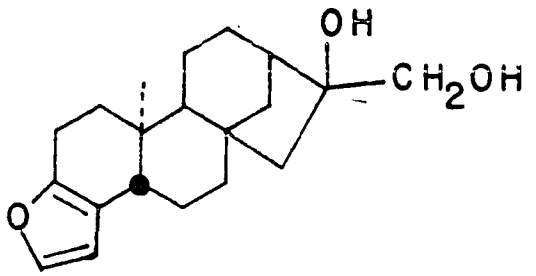


XXVI

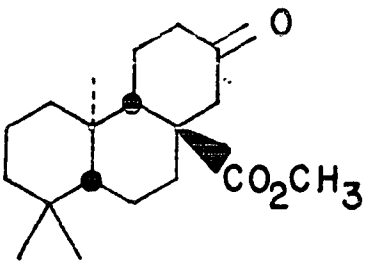
accordingly the keto ester was tentatively assigned the configuration XXVIII. The subsequent experiments of Briggs and co-workers[2,3] in which rimuene(I) yielded isophyllocladene(XII) and an abietadiene XIII, the latter having been derived from abietic acid of known stereochemistry,[46] established that phyllocladene possesses the normal A/B trans ring juncture. Further confirmation on this point was presented by Grant and Hodges[5] who converted isophyllocladene(XXV) into the known degradation product[47] XXIX of manool (vide infra). Hence the keto ester XXIV is correctly represented by XXX the nor-ketone XXIII by XXI, phyllocladene by XXXII and isophyllocladene by XII.

Church et al.[6] have confirmed these assignments by the total synthesis of the racemic keto-ester XXX. The aldol condensation of m-methoxy benzaldehyde and isopropyl methyl ketone yielded the unsaturated ketone XXXIII. This ketone condensed with 1-diethylamino-3-pentanone methiodide in the usual Robinson reaction to lead to the dieneone XXXIV, which could be reduced to the corresponding saturated alcohol XXXV in two steps. Cyclization of this alcohol was effected by polyphosphoric acid to the crystalline tricyclic ether XXXVI. Reduction of this compound with lithium and alcohol in liquid ammonia yielded the α,β-unsaturated ketone XXXVII previously obtained by Barltrop and Rogers[20] by a different route (vide infra). The eneone XXXVII was reduced

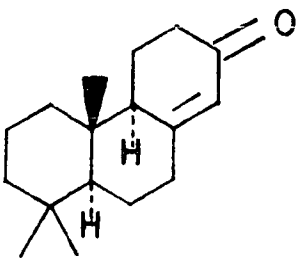
Plate 5. Diagram



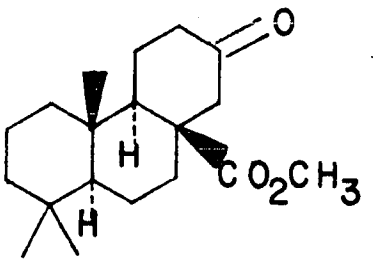
XXVII



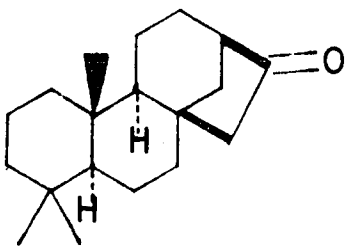
XXVIII



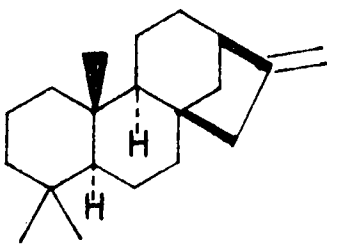
XXIX



XXX



XXXI

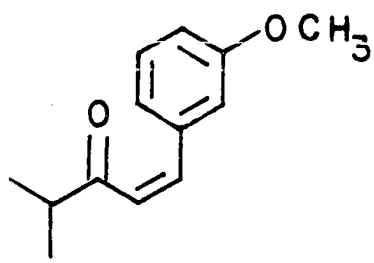


XXXII

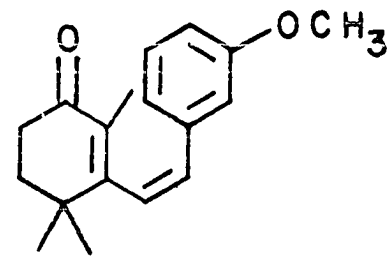
to the two epimeric alcohols which were readily separable. The quasi-equitorial alcohol XXXVIII was converted to the corresponding vinyl ether XXXIX and pyrolyzed according to the conditions of Burgstahler.[48] This furnished the aldehyde XL. The latter was oxidized in two steps to the corresponding triacid which was converted to the anhydride-ester XLI. XLI upon treatment with sodium methoxide underwent Dieckmann cyclization to a keto ester which could be hydrolized, decarboxylated and esterified to racemic XXX.

Turner and Shaw[7] have synthesized totally the keto-ester XXX in optically active form. The tricyclic eneone XLII was methylated, reduced and cleaved to the phenol XLIII. Reduction of XLIII to the saturated alcohol and oxidation yielded the racemic ketone XLIVa. Treatment of XLIVa with lithium aluminum hydride furnished an alcohol XLV which was resolved into its optically active forms. Oxidation of the (-)alcohol gave the optically active ketone XLVIVb. The furfurylidene derivative of XLIVb was alkylated with allyl bromide to provide XLVI. Oxidative ozonolysis of XLVI followed by esterification yielded triester XLVII which an exposure to cyclization, hydrolysis, decarboxylation and esterification gave (-)XXX.

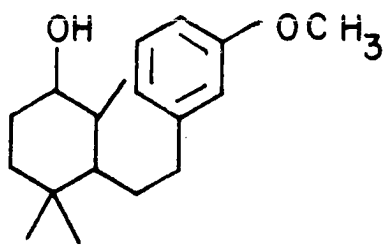
Plate 6. Diagram



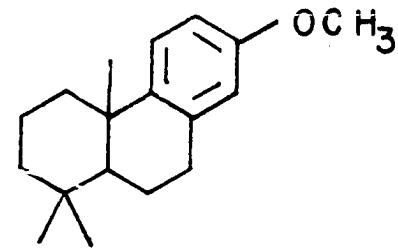
XXXIII



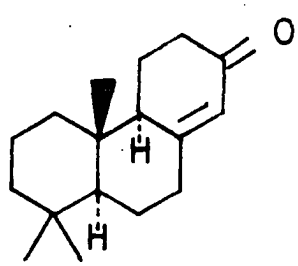
XXXIV



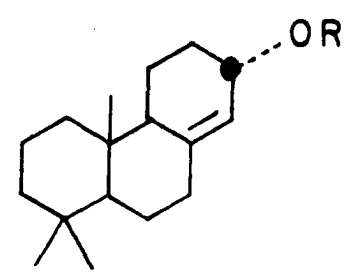
XXXV



XXXVI



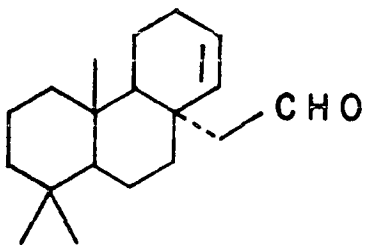
XXVII, (±)



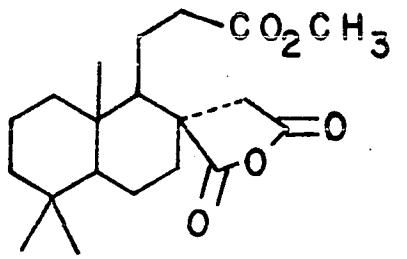
XXXVIII, R = H

XXXIX, R=CH=CH$_2$

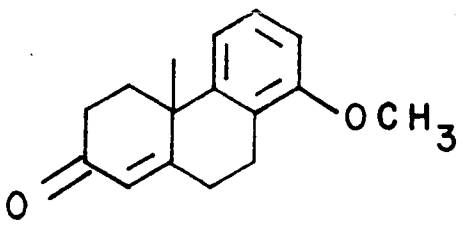
Plate 7. Diagram



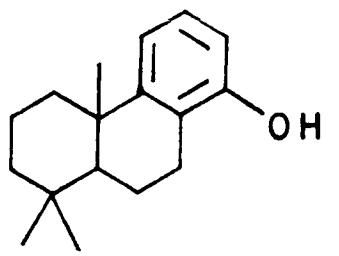
XL



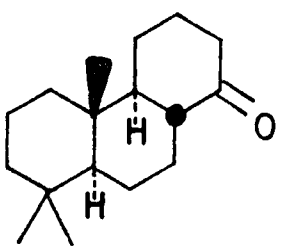
XLI



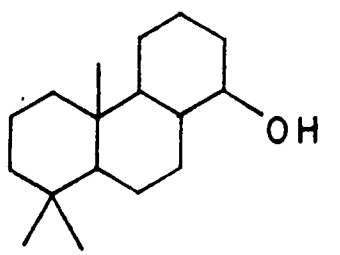
XLII



XLIII



XLIVa,b



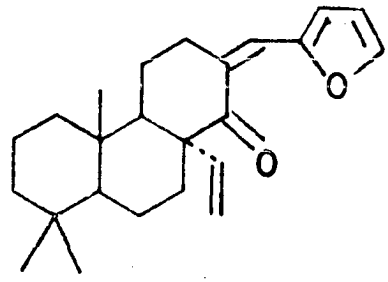
XLV

Isolation and Structure Determination of Manoyl Oxide and Ketomanoyl Oxide

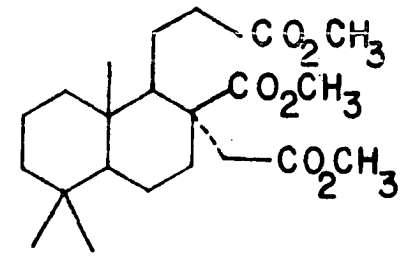
Manoyl oxide was first reported by Hosking and Brandt[49] who isolated the diterpene of constitution $C_{20}H_{34}O$ from Dacrydium colensoi. The presence of a terminal methylene group was established by reductive and oxidative means.[50] The inertness of the oxygen function to all but acidic reagents indicated to Hosking and Brandt[50] the presence of a ditertiary ether linkage in a five or six membered ring, with preference given to the former. Selenium dehydrogenation experiments on manoyl oxide which yielded 1,2,5-trimethylnapthalene(XLVIII) and 1,2,8-trimethylphenanthrene(XLIX) indicated that manoyl oxide was a napthalene derivative which could cyclize under the dehydrogenation conditions. The structural similarity of manoyl oxide, manool[8,51,52](L), and sclareol[52,53](LI) was indicated by the fact that these compounds and their dihydro derivatives gave identical trihydrochloro and dihydrochloro derivatives, respectively. Hence with the elucidation of the position of the exocyclic methylene group in manool Hosking[8] correctly formulated manoyl oxide as III.

Ohloff[54] obtained a compound from the treatment of sclareol with acetic anhydride to which he assigned the manoyl oxide structure. The discrepancies of melting points and optical rotations were explained on the basis of the assumed

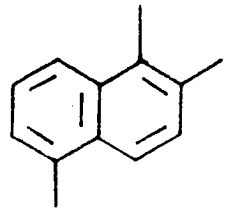
Plate 8. Diagram



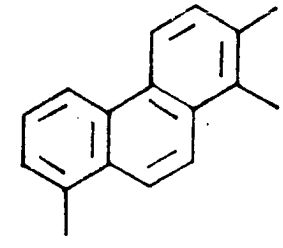
XLVI



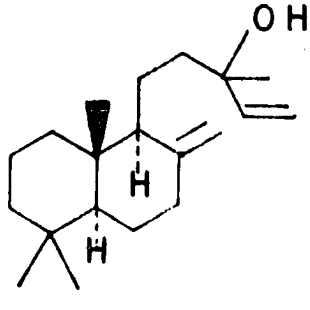
XLVII



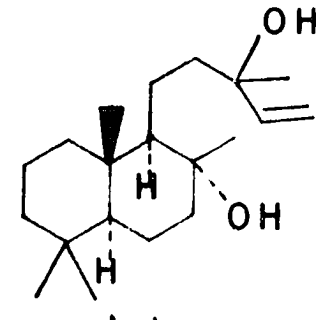
XLVIII



XLIX



L



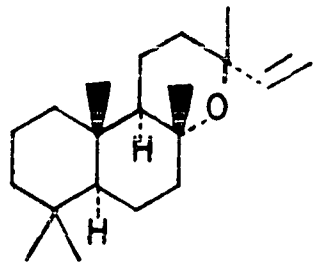
LI

impurity of natural manoyl oxide or the possibility that the synthetic compound was a C_8 or C_9 epimer of the natural product. Hodges and Reed[9] depict the stereochemistry of manoyl oxide as shown in LII. LII was observed to undergo hydrogenolysis to yield LIII. Moreover Ohloff's compound upon hydrogenolysis yielded LIII establishing it to be LIV, the C_{13} epimer of natural manoyl oxide. Accordingly Ohloff's compound was designated epimanoyl oxide. Tenuous chemical and physical evidence indicated that manoyl oxide possessed a α C-13 vinyl group. The configuration at this center was established by a comparison of the mass spectra of manoyl oxide and epimanoyl oxide and their acetylene derivatives.

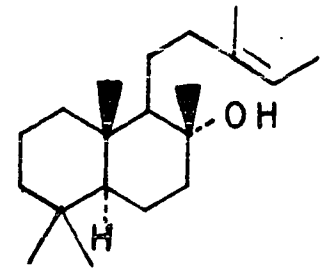
Ketomanoyl oxide was isolated from Dacrydium colensoi by Hosking and Brandt.[49] Since reduction of the keto group yielded manoyl oxide,[55] elucidation of the structure required merely establishment of the location of the carbonyl group. This was achieved by the reaction of ketomanoyl oxide with methyl magnesium iodide followed by catalytic hydrogenation, treatment with hydrochloric acid, aniline and selenium to yield 1,2,5,7-tetramethylnapthalene(LV) and 1,2,5,7-tetramethylphenanthrene(LVI). Ketomanoyl oxide was shown further to have a methylene group adjacent to the ketone by virtue of its ready formylation. Thus Hosking[8] suggested 2-ketomanoyl oxide(IV) as the structure of this diterpene.

Hosking and Brandt[56] have noted the low toxicity of

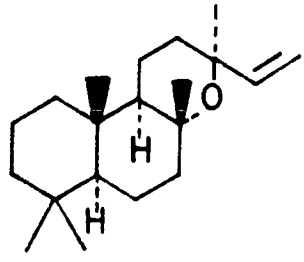
Plate 9. Diagram



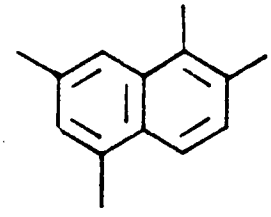
LII



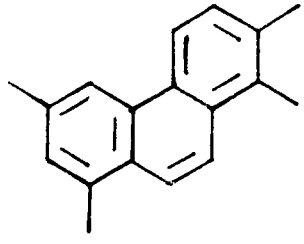
LIII



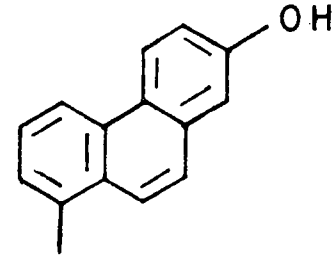
LIV



LV



LVI



LVII

2-ketomanoyl oxide and manoyl oxide.

After questioning Hosking's assignment Grant[57] has demonstrated that the ketone cannot be in the 3-position in ketomanoyl oxide in view of the failure of the alcohols derived from this ketone to undergo a retro-pinacol rearrangement expected[58] for such a system. Grant and Hodges[10] found support for the C_2 ketone position by demonstrating that dihydroketomanoyl oxide is capable of exchanging four protons in basic medium. This fact has been corroborated by Enzell[11] who further confirms the assignment by nuclear magnetic resonance and optical rotatory dispersion studies.

Isolation and Structure Determination of Totarol

Totarol was isolated by Easterfield and McDowell[59] in 1911 from Podocarpus totara. The constitution of this diterpene was established as $C_{20}H_{30}O$. Short and Stromberg[60] established that totarol contained three double bonds and yielded 1-methyl-7-hydroxyphenanthrene[61](LVII) upon dehydrogenation. Brandt and Thomas[62] established that totarol was cryptophenolic. This was confirmed by Short and Wang[20] who also found that 1-methyl-8-isopropylphenanthrene[63](LVIII) was obtained upon dehydrogenation of totarol. These investigators proposed structure V for totarol.

This structure has been verified by total synthesis of the racemic compound by Barltrop and Rogers.[21] The ethynyl

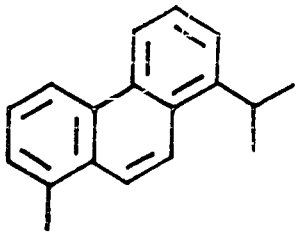
carbinol LIX was reduced and cyclized to yield the ether XXXVI. Reduction of XXXVI with lithium and alcohol in liquid ammonium gave a mixture of separable eneones(XXXVII and LX). The α,β -unsaturated ketone XXXVII was found to be the racemic form of XXIX. Both XXXVII and LX were alkylated with isopropyl iodide and aromatized by a bromination-dehydrobromication sequence to (±) totarol(V).

Chow and Erdtman[23] have verified the stereochemistry for the A/B ring juncture in totarol by the latter's oxidation to the known diacid[64] LXI.

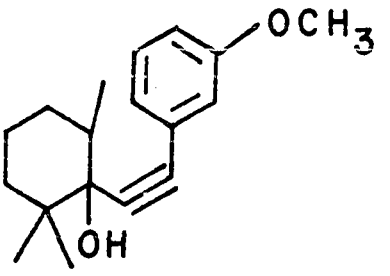
Isolation and Structure Determination of Totarolone

Chow and Erdtman[23] reported the isolation of totarolone from Tetraclinic articulata (Vahl, Masters) in 1960. These workers also elucidated the structure of totarolone as VI. Reduction of totarolone under Clemensen conditions yielded totarol(V). The position of the ketone was established as being adjacent to the gem-dimethyl group since treatment of the alcohol, obtained on sodium borohydride reduction of VI, with phosphorous pentachloride resulted in a retro-pinacol rearrangement.[58] The stereochemistry of totarolone was established by its relationship to totarol and its optical rotatory dispersion curve to be as shown in LXII. Chow and Erdtman also noted the occurrence of totarolenone LXIII along with totarolone.

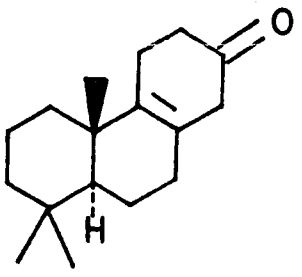
Plate 10. Diagram



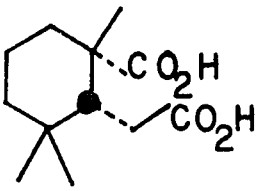
LVIII



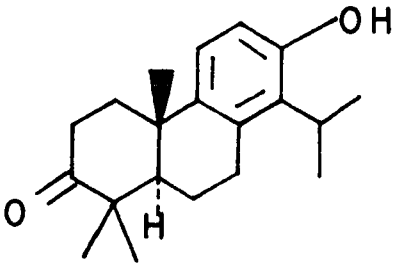
LIX



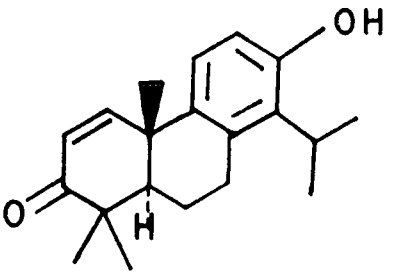
LX



LXI



LXII



LXIII

Isolation of Hydroxytotarol

A compound designated as hydroxytotarol was reported by Brandt and Thomas[22] as having been isolated from Podocarpus totara. No structure has yet been assigned to this compound.

DISCUSSION

The Attempted Syntheses of Rimuene and Phyllocladene

In view of the interest in rimuene as a possible central compound in the biogenesis of tetracarbocyclic diterpenes,[28] it was desirable to confirm the reported structure of this tricyclic diterpene(XI) by synthesis. An inviting aspect of this synthesis derives from the established conversions of rimuene to isophyllocladene and of the latter to phyllocladene (vide supra), hence a synthesis of rimuene also would be a synthesis of phyllocladene.

The recent total synthesis of optically active podocarpic acid[65](LXIV), which possesses the same A/B stereochemistry as XI, established this compound as an appropriate starting material for the synthesis of rimuene. Accordingly LXIV was converted to O-methylpodocarpol[66](LXV) in two steps. Oxidation of this alcohol with chromic acid-pyridine reagent[67] to the aldehyde LXVI followed by reduction by a modified Wolff-Kishner procedure[68] furnished O-methylpodocarpane(LXVII) in high yield. The modified reduction conditions were employed to preclude the cleavage of the ether which has been reported[69] to occur under the usual Wolff-Kishner conditions. This oxidation-reduction sequence somewhat parallels that used by King et al.[70] in a similar system. Analogous reactions have been reported also by Bible.[71]

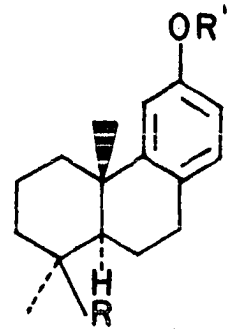
O-Methylpodocarpane also was prepared in low yield by tosylation of the alcohol LXV and treatment of the resulting oil with lithium aluminum hydride under forcing conditions. Ansell and Gadsby[72] have isolated the intermediate tosylate. However these workers were unable to realize the reduction.

O-Methylpodocarpane has been prepared in optically active form by Hodges and Raphael[73] and in both the optically active and racemic forms by Fetizon and Delobelle.[74] The racemic form also has been reported by Raman and Rao[75] and Ansell and Gadsby,[72] and as a mixture with the cis compound by King et al.[76]

Reduction of the aromatic ring in O-methylpodocarpane was accomplished by the use of lithium and alcohol in liquid ammonia under vigorous conditions[77] to furnish, after acid-catalyzed hydrolysis, the α,β-unsaturated ketone LXVIII as the main isolable product. The assignment of structure to the eneone was based on its infrared and ultraviolet spectral properties. The stereochemistry of the C_8 proton in LXVIII was indicated to be β by the non-isomerizability of the compound with dilute sodium methoxide. This designation was verified by the correspondence of the portion of optical rotatory dispersion curve of LXVIII observed with that of Δ 4-cholestene-3-one.[78]

The saturated ketone LXIX was a minor product of the lithium-alcohol reduction. The structure was assigned on the

Plate 11. Diagram

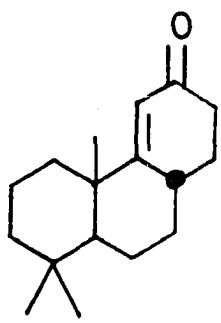


LXIV, $R = CO_2H$, $R' = H$

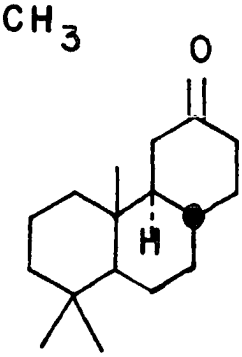
LXV, $R = CH_2OH$, $R' = CH_3$

LXVI, $R = CHO$, $R' = CH_3$

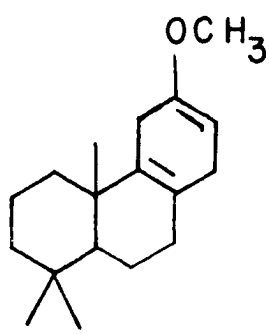
LXVII, $R = R' = CH_3$



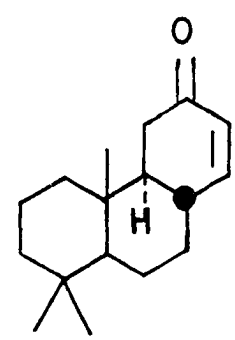
LXVIII



LXIX



LXX



LXXI

basis of spectral data and the fact that LXIX was the product of the reduction of the α,β-unsaturated ketone LXVIII with lithium in liquid ammonia. Furthermore, with the assumption of axial protonation[79] in the latter reaction, the stereochemistry of the ring junctures of LXIX is established as trans-antitrans. Confirmation for this stereochemistry, as well as for the absolute configuration indicated, was found in the correspondence of the optical rotatory dispersion curve of LXIX with that of cholestan-2-one.[80] It should be noted that a recent publication by Sondheimer and Gibson[81] in an unavailable source may involve a similar synthesis of LXIX. Bible and Burtner[82] have recently reported an analogous reduction sequence involving O-methypodocarpol.

Although the α,β-unsaturated ketone LXVIII almost certainly originated from the enol ether LXX, the origin of the saturated ketone LXIX is less clear. A reasonable explanation for its occurrence is that under the forcing conditions of the reduction the intermediate resembling the enol ether LXX undergoes rearrangement to a conjugated diene which then is capable of further reduction.[83]

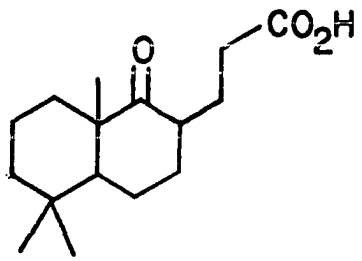
Catalytic hydrogenation of the unsaturated ketone LXVIII led to an oily mixture of saturated ketones from which a forty-four percent yield of crude LXIX could be isolated by fractional crystallization. The remainder of this oil might be the trans-syn-cis ketone although it was not characterized

further.

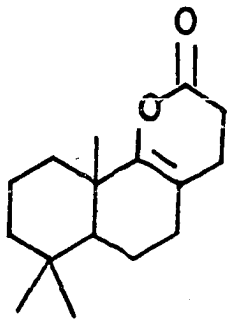
The conversion of the saturated ketone LXIX to rimuene XI was envisioned as proceeding by a bromination-dehydrobromination sequence to yield the α,β-unsaturated ketone LXXI. The latter could then be subjected to the appropriate alkylation and reduction procedures required to furnish XI. At this juncture, due to the work of Ireland and Schiess,[32] it became apparent that the reports establishing the stereochemistry of rimuene as XI were not as reliable as had been claimed (vide supra). Consequently efforts on the synthesis of XI were abandoned temporarily until the stereochemistry of rimuene was determined.

Although the synthesis of phyllocladene via rimuene thus was blocked, it seemed still feasible to synthesize phyllocladene by utilization of intermediates at hand. Accordingly the eneone LXVIII was ozonized and treated with hydrogen peroxide[84] to produce trans-2-(β-carboxyethyl)-5,5,9-trimethyl-1-decalone (LXXII). Upon exposure to acetyl chloride and acetic anhydride LXXII was readily converted to the enol lactone LXXIII. Neither the keto acid LXXII nor its methyl or t-butyl esters could be induced to undergo base-catalyzed condensation with methyl vinyl or methyl β-chloroethyl ketone to yield the tricyclic keto-acid LXXIV (R=H) or keto-ester LXXIV (R-methyl,t-butyl), key intermediates needed for further synthesis. Attempts to condense LXXII

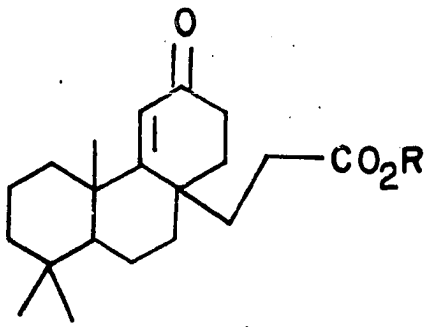
Plate 12. Diagram



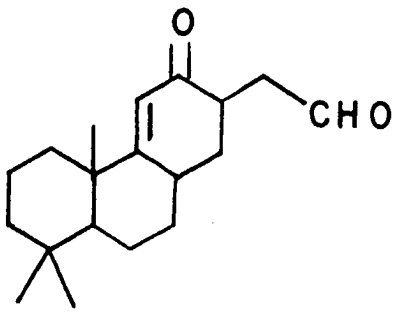
LXXII



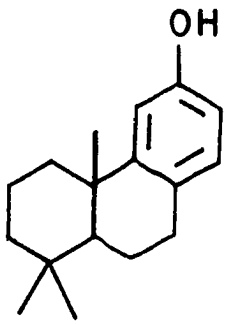
LXXIII



LXXIV



LXXV



LXXVI

and the corresponding methyl ester with methyl ethinyl ketone also proved unsuccessful.

In view of the failure to obtain a quaternary center at C_8 by intermolecular reactions an approach involving intramolecular condensations was designed. The tricyclic C_{13} substituted system LXXV was envisioned as being capable of undergoing intramolecular cyclization at C_8 and a synthesis in this direction was initiated.

Experience dictated that the introduction of the C_{13} substituent would be most readily accomplished in the aromatic precursor of the reduced system.

The first attempt to introduce a two-carbon side chain involved the alkylation of the phenol[69] LXXVI, obtained by cleavage of the ether LXVII with pyridine-hydrochloride,[85] with ethyl bromoacetate.[86] The product isolated from the crude reaction mixture was distilled and shown to be approximately a one:four mixture of two compounds by vapor phase chromatography. Presumably this represents a mixture of C- and O-alkylated materials. The uncertainty of the identity of the major product made this route unattractive.

Since the introduction of substituents at C_{13} in analogous systems[87] had been accomplished readily by the Friedel-Crafts reaction, this approach was investigated. When O-methylpodocarpane (LXVII) was reacted with ethoxalyl chloride[88] in the presence of aluminum chloride 13-ethoxalyl-

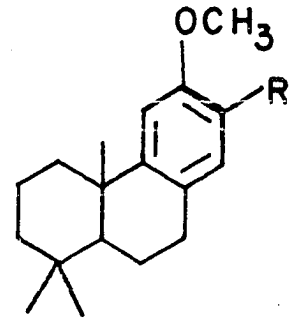
O-methylpodocarpane could be isolated. Ketalization of the crude ester with ethanedithiol followed by reduction with Raney nickel furnished the ether ester LXXVII in fair yield. Unfortunately LXXVII could not be induced to undergo reduction with lithium and alcohol in liquid ammonia.

In an attempt to activate the aromatic ring for reduction 13-acetyl-O-methylpodocarpane (LXXVIII) was prepared by the Friedel-Crafts procedure and converted to the crude ether-acid LXXIX by a bromoform reaction. The reduction of the aromatic ring of LXXIX by the use of lithium and alcohol in liquid ammonia could not be realized.

The Stereochemistry of Rimuene

The conflicting reports on the stereochemistry of rimuene (*vide supra*) made it apparent that elucidation of the correct stereoformula was necessary before rational synthetic work could proceed. Evaluation of the relevant literature indicated that the work of Ireland and Schiess[32] and of Briggs *et al.*[1] was the most reliable data on the structure of rimuene. Hence a most attractive assumption for the stereochemistry of this diterpene was LXXX which incorporated a previously unknown system in ring C, but had the normal A/B configuration. An additionally felicitous feature of this assumption was the fact that with the use of appropriate model compounds this proposal could be tested by means of the two recently developed powerful physical methods of optical

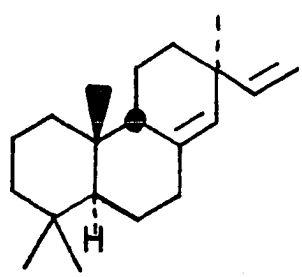
Plate 13. Diagram



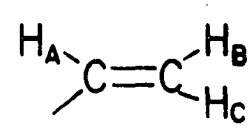
LXXVII, $R=CH_2CO_2C_2H_5$

LXXVIII, $R=COCH_3$

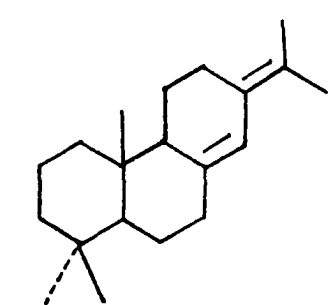
LXXIX, $R=CO_2H$



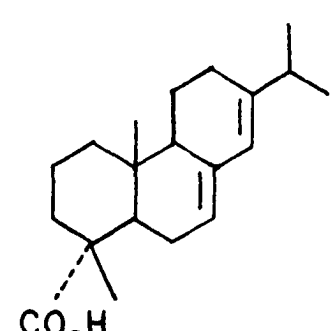
LXXX



LXXXI



LXXXII



LXXXIII

rotatory dispersion and nuclear magnetic resonance.

Accordingly the optical rotatory dispersion curve of rimuene was compared with those of pimaric(XV), isopimaric(XVI) and sandaracopimaric(XIV) acids (Figure 1). The shapes of the curves obtained for the acids corresponded to those recorded by Bose.[36] A comparison of the curves of the pimaric acids which differ only at C_{13} offered a clear illustration of the control of the sign of the curve by the configuration of the vinyl group. The curve of sandaracopimaric acid was plain and negative; whereas that of pimaric acid was plain and positive. Isopimaric acid, which is known to have the same C_{13} configuration as sandaracopimaric acid, had a plain and very slightly negative curve. Rimuene revealed a plain and positive optical rotatory dispersion curve.

Since the models indicated that the configuration at C_{13} controls the sign of the optical rotatory dispersion curve and since pimaric acid and rimuene revealed curves of the same sign, the conclusion that these two diterpenes have the same configuration of their vinyl group, necessarily followed. This was a partial confirmation of structure LXXX for rimuene.

Verification of the presence of a C_{13}-β-vinyl group as well as evidence for a C_9-β-porton in rimuene was obtained from a study of the nuclear magnetic resonance spectrum of rimuene, using the methyl esters of pimaric, isopimaric and sandacacopimaric acids as model compounds.

The region of the spectra most relevant to the problem at hand was the olefinic region, where absorptions due to both the vinyl group and the C_{14} proton appear. The spectra of this region are presented in Figure 2. Absorptions of the vinyl group protons were recognized by their characteristic twelve or fourteen line pattern. The C_{14} proton was expected to show only secondary coupling and gave a single, albeit sometimes broadened, peak. The chemical shifts of these protons expressed as δ^{89} and the experimentally measured coupling constants are gathered in Table 1.

Table 1. Chemical shifts (in δ parts per million) and coupling constants (in cycles per second)

	$C_{14}H$	H_A	H_B	H_C	J_{AB}	J_{BC}	J_{AC}
Methyl isopimarate	5.26	5.76	4.78	4.82	9.5	17.0	1.4
Methyl sandaracopimarate	5.17	5.72	4.68	4.84	10.5	17.4	1.7
Methyl pimarate	5.11	5.69	4.90	4.85	10.1	17.1	1.9
Rimuene	5.36	5.72	4.90	4.79	9.0	15.5	1.4

The vinyl group was considered an ABC system LXXXI.[90, p. 131, p. 238; 91, p. 91; 92, p. 106] In the cases of methyl isopimarate and methyl sandaracopimarate the four line system expected for the A proton in a vinyl group[90] was observed. The corresponding proton in the spectrum of methyl pimarate

and rimuene, however, exhibited six lines. This result, while theoretically possible,[90] was at first surprising in view of the apparent lack of analogies. However during the course of this work Schafer and Schneider[93] reported that a six line spectrum may be observed for the A proton in vinyl bromide in the presence of specific amounts of benzene. These authors attributed the appearance of this type of spectrum to an increase in the electronic screening of the vinyl protons by benzene. In the cases of methyl pimarate and rimuene molecular models that a C_{13} β -vinyl group might have a conformation such that it could be electronically shielded by the Δ 8(14) double bond. In any event, the identical configurations of the vinyl groups in methyl pimarate and rimuene was verified by these observations.

The proposal that rimuene possesses a C_9 β -proton was consistent with the nuclear magnetic resonance spectra. Neoabietic acid (LXXXII),[44] methyl pimarate and methyl isopimarate, compounds with a C_9 α -proton, exhibited a single peak for the C_{14} olefinic proton with half-widths (the width at one-half the height of the peak) of 4.1, 3.4, and 3.7 cycles per second (c.p.s.), respectively. The latter two compounds revealed allylic proton peaks at 2.2 parts per million (p.p.m.). In methyl isopimarate the C_{14} proton peak was split and had a half-width of 7.6 c.p.s. Moreover the allylic proton peaks were shifted upfield and masked by other

absorptions. Chien has commented on the nature of these allylic absorptions in the pimaric and isopimaric systems.[94]

In the nuclear magnetic resonance spectrum of rimuene the C_{14} proton was split such that its half-width was 6.9 c.p.s. and allylic proton absorptions were shifted upfield. Hence the correspondence of methyl isopimarate and rimuene at C_9 was indicated.

The stereochemistry for rimuene as XI as proposed by the earlier workers (vide supra) then was clearly not in accord with the compound's optical rotatory dispersion and nuclear magnetic resonance characteristics. The only stereoformula which was consistent with these properties and most of the reported chemical data was LXXX.

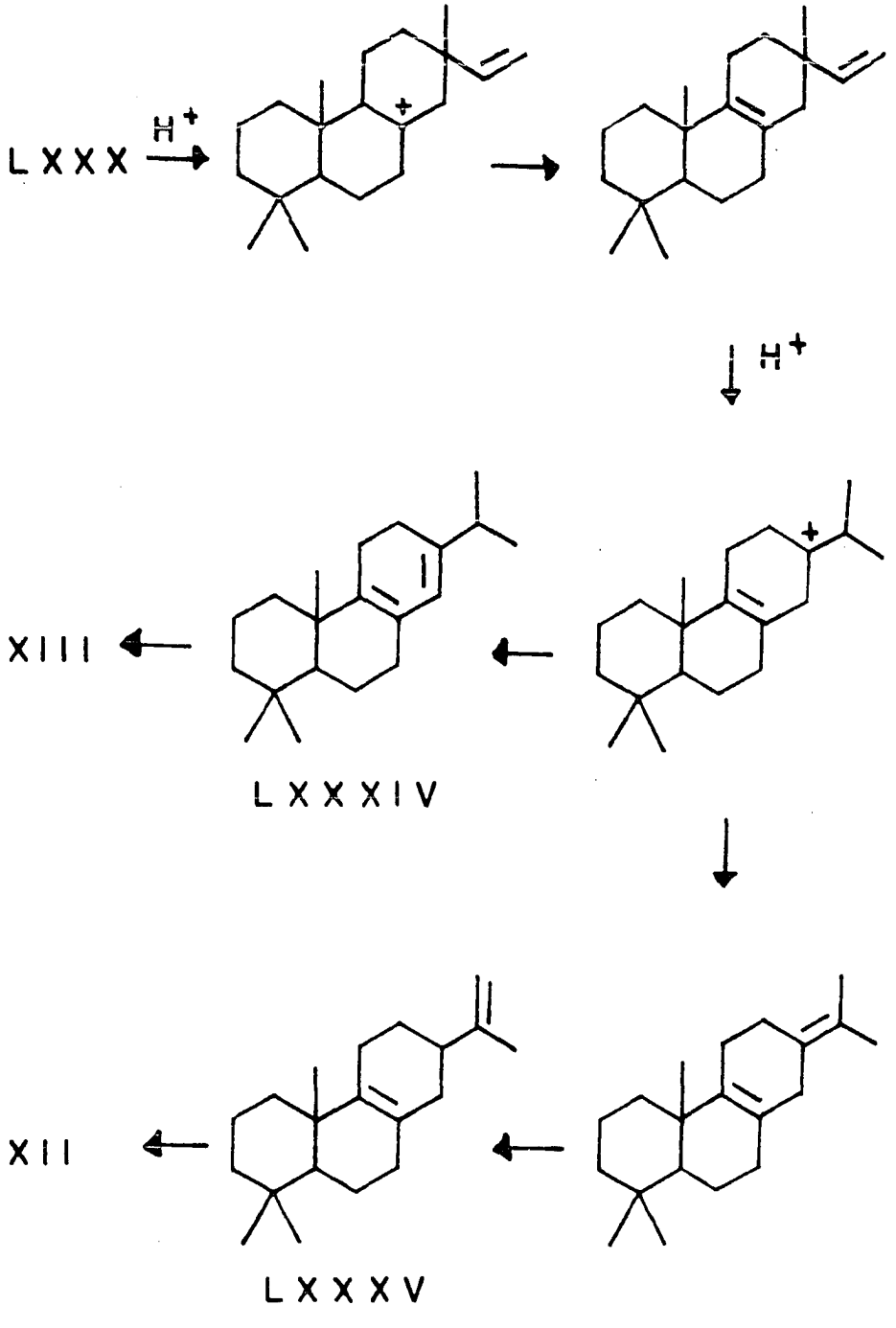
Ireland and Schiess[32] have implied that rimuene might possess a diene system different from those found in the pimaric acids. It should be noted that this suggestion would be inconsistent with the degradation work[1] unless double bond migration is claimed to have occurred during this work. While this hypothesis could not be completely ruled out, it would seem that the alternative structures which these authors might suggest would possess a methylene group adjacent to the olefinic proton, such that the olefinic proton's nuclear magnetic resonance absorption would be expected to be broadened or even split by the resultant spin-spin coupling interactions to a value larger than the 6.9 c.p.s. observed. The fact

that the C_7 proton in abietic acid[46] (LXXXIII) has a half-width of 8 c.p.s. weakens this argument, although the trend is still in the direction consistent with LXXX as the correct structure for rimuene.

In view of the proposal of LXXX as the correct structure for rimuene the reported conversion of sandaracopimaric acid (XIV) into rimuene by Galik et al.[31] is inexplicable. The Czech workers were in fact not able to compare physically their synthetic diene with the natural product and therefore may have been misled by a coincidental correspondence of physical properties. However the fact that the physical properties of the diene obtained by Galik et al. were different from those reported by Ireland and Schiess[32] is unexpected. The possibility that the Czech and Canadian[30] workers might have worked with different natural products was eliminated by a comparison of the physical and spectral properties of the acids from the separate laboratories which showed these acids to be identical.

The other support for structure XI for rimuene had come from the work of Briggs and coworkers.[2,3] The rationale for this stereochemistry was based on the conversion of rimuene with formic acid into isophyllocladene(XII) and an abietadiene XIII (vide supra). The explanation offered for this conversion was that it was mechanistically analogous to a suggested[28] biosynthetic pathway. Thus a C_{13} α-vinyl group

Plate 14. Diagram


LXXX
H+
H+
XIII
LXXXIV
XII
LXXXV

would be required for rimuene to yield isophyllocladene. In view of the proposal of LXXX as the correct stereoformula for rimuene it must be held that the methyl migration and carbon carbon double bond rearrangements lead to a mixture of abietadienes (e.g. LXXXIV and LXXXV) from which XII and XIII can arise (vide infra). If a mechanistic pathway such as this was followed the stereochemical integrity at C_{13} would be destroyed and any structural assignments based on the assumption of the maintenance of stereochemistry would be invalid.

A New Method for the Assignment of Stereochemistry at C_{13} in the Diterpene Oxides the Stereochemistry of Colensone Oxide

The nuclear magnetic resonance absorptions of the protons of the vinyl group in rimuene had proven to be important in the assignment of stereochemical configuration to this group. Accordingly it was desirable to examine the absorption characteristics of vinyl groups in other diterpenes in order to determine the limitation of this method and to provide solutions for other structural problems.

In both of these regards the diterpene oxide systems offered appropriate compounds for further study. The nuclear magnetic resonance spectra of manoyl oxide(LII), epimanoyl oxide(LIV), 2-ketomanoyl oxide(LXXXVI), a ketomanoyl oxide

of unknown constitution* and colensone oxide** (LXXXVII) were obtained. The chemical shifts of the absorptions of the relevant protons and methyl groups in p.p.m. along with the experimentally determined coupling constants for the vinyl groups are gathered in Table 2.

The spectrum of manoyl oxide(LII) exhibited the twelve line pattern expected for a vinyl group of the ABC(LXXXI) type.[90, p. 131, p. 238] The vinyl group absorption is reproduced in Figure 3. The center group of the three in the BC region of the spectrum contained four lines. The two methyl groups situated at C_8 and C_{13} were expected to undergo a paramagnetic shift relative to the other methyl groups in the molecule due to the deshielding of these methyls by substituents. If the deshielding effects were additive then a further paramagnetic shift of the C_{13} methyl group relative to the C_8 methyl group of approximately 0.1 p.p.m. would be expected.[91, p. 53] In fact the two methyl groups which absorbed at lowest field in manoyl oxide were not actually separated from one another. However, the half-width of .08

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*Dr. John Morgan, Department of Scientific and Industrial Research, Forest Products Research Laboratory, Princess Risborough, Aylesbury, Bucks, England. A ketomanoyl oxide. Private communication. (1961)

**Dr. P. K. Grant and Mr. R. M. Carmen, Department of Scientific and Industrial Research, Dominion Laboratories, Wellington, New Zealand. Colensone oxide. Private communication. (1961)

Table 2. Chemical shifts in δ and coupling constants in c.p.s.

	H_A	H_B	H_C	J_{AB}	J_{AC}	J_{BC}	C_{13}-CH_3 C_8-CH_3	C_{10}-CH_3 C_4-CH_3's
Manoyl oxide	5.90	4.88	5.09	10.1	17.3	1.7	1.27 1.27	.85,.78 .78
Epimanoyl oxide	6.04	4.89	4.96	10.9	18.5	1.4	1.17 1.08	.81,.74 .68
2-Ketomanoyl oxide	5.91	4.89	5.10	10.0	17.5	1.8	1.28 1.28	1.06,.89 .83
Morgan ketomanoyl oxide	5.95	4.91	5.14	10.2	17.4	1.7	1.32 1.27	1.08,1.02 .91
Colensone oxide	5.92	4.90	5.11	9.9	17.3	1.8	1.32 1.29	.99,.97 .82

p.p.m. of the peak assigned to these methyl groups indicated that some separation of absorptions was achieved.

The epimeric relationship of manoyl oxide and epimanoyl oxide (LIV) at C_{13} was confirmed by the nuclear magnetic resonance spectrum of the latter. The vinyl group absorption of LIV is illustrated in Figure 3. The spectrum of epimanoyl oxide revealed the usual twelve line pattern for its vinyl group. The chemical shifts of the A and C protons (LXXXI) and the C_8 and C_{13} methyl groups (Table 2), and the pattern of lines in the BC region of the spectrum, where the quartet was a group of peaks at highest field, served to differentiate the spectrum of epimanoyl oxide from that of manoyl oxide. If epimanoyl oxide is accepted to have structure LIV then the upfield shift of the C_8 methyl group might be explained by the long range diamagnetic shielding of the vinyl function [9, p. 129] which is in 1,3-diaxial non-bonded interaction with the methyl group. The observed shift might also be due to a change in bond angles in the ring itself due to the alteration in the interactions of the axial groups. This interpretation would imply that the well-known interactions of 1,3-diaxial substituents on a six membered ring would be reflected in the chemical shifts of the interacting groups. Such an effect has been noted previously by Rosen et al.[95] for 1,3-diaxial methyl groups.

The fact that a 4 line pattern was found for the A

proton in epimanoyl oxide, which presumably has a C_{13} β -vinyl group, supports the suggestion that the six-line pattern observed for this proton in the nuclear magnetic resonance spectrum of rimuene (LXXX) and the methyl ester of pimaric acid (XV) was due to the presence of the $\Delta 8(14)$ carbon-carbon double bond in the latter compounds.

Clearly the nuclear magnetic resonance spectra of manoyl oxide and epimanoyl oxide had exhibited differences which confirmed the epimeric relationship of these oxides at C_{13}. Moreover, since the only difference in the two diterpene oxides was their configuration at C_{13} (vide supra), it was assumed that these spectral characteristics could be utilized for the assignment of the stereochemistry at C_{13} in similarly constituted systems.

Confirmation of this hypothesis was provided by the spectra of 2-ketomanoyl oxide and the Morgan ketomanoyl oxide. Both of these compounds had been converted to manoyl oxide (vide supra) and therefore were known to contain the normal C_{13} configuration. The nuclear magnetic resonance spectra of the two ketones were quite similar.

The coincidence of the stereochemistry at C_{13} in the ketomanoyl oxides and manoyl oxide was indicated by the virtual identity of their vinyl group absorptions and the similarity of their C_8 and C_{13} methyl group absorptions (Table 2). Hence, these spectra established that the pro-

tons in the proximity of C_{13} are sufficiently insensitive to changes in distant parts of the molecule to allow the postulated spectral and stereochemical correlation to be maintained.

The nuclear magnetic resonance spectra of these compounds were utilized to provide support for or information about the location of the ketone groups in the keto-oxides.

Enzell[11] has utilized the nuclear magnetic resonance spectrum of 2-ketomanoyl oxide to confirm the presence of four protons adjacent to a ketone, but has not commented on the type of absorptions found. The spectrum of LXXXVI had a single somewhat broad 3.8 proton peak at 2.22 p.p.m., which was presumed to be due to the two central unresolved peaks of the quartet expected for the AB[90, p. 119] systems of the four protons located at C_1 and C_3. Evidence for the correctness of this assignment was obtained from the location of a low-intensity peak 14.3 c.p.s. towards lower field from the doublet and in the correct position for the lowest field peak of the quartet. The closeness of the two central peaks and the low intensity of the outer peak indicated that the sp^2 carbon atom between the C_1 and C_3 methylene protons tended to remove the conformational distinction between these protons with the result that the expected AB system approached an A_2 system. The fact that the methylene protons were not further coupled indicated that these protons were adjacent

to quaternary carbon atoms and provided further support for the C_2 ketone position in this diterpene.

The nuclear magnetic resonance spectrum of the Morgan ketomanoyl oxide provided information on the location of the ketone group in this diterpene. A complex multiplet, which was found at 2.49 p.p.m., represented two protons adjacent to the ketone. The complexity of these peaks indicated that these protons, presumably a methylene group, were probably adjacent to another methylene group. This information restricted the ketone to C_1, C_3, C_7 or C_{12}. The fact that the C_8 and C_{13} methyl groups in ketomanoyl oxide had chemical shifts very similar to that in manoyl oxide eliminated C_7 and C_{12} from further consideration. A definite distinction as to whether the ketone group was located at C_1 or C_3 could not be made from the nuclear magnetic resonance spectrum. However, since two of the methyl groups in ring A of ketomanoyl oxide were observed to have undergone a paramagnetic shift relative to the corresponding methyl groups in manoyl oxide, an assignment of the ketone group to C_3 was preferred. Ketomanoyl oxide was tentatively assigned structure LXXXVIII.

An opportunity to establish the C_{13} stereochemistry in a diterpene oxide system by means of nuclear magnetic resonance spectral correlation (*vide supra*) appeared in the case of colensone oxide (LXXXVII). Although the gross structural features of colensone oxide had been elucidated and the nature

of the A/B ring juncture had been postulated as A/B antipodal cis the stereochemistry at C_8 and C_{13} had not been elucidated.* It should be noted that the location of the carbonyl group in colensone oxide at C_1 rather than at C_2 was based upon negative evidence and must be regarded as insecure. If, in fact, the ketone were located at C_2 the optical rotatory dispersion results reported by Grant and Carman** would be correlated best by an A/B trans normal configuration for this ring A nor-diterpene.[96,97]

The nuclear magnetic resonance spectrum of colensone oxide has been interpreted by Grant to provide evidence for the presence of a vinyl group, a methylene group adjacent to a ketone and five methyl groups in the molecule. Since it seemed reasonable that additional correlations could be made, the nuclear magnetic resonance spectrum of colensone oxide was re-examined. The absorptions of the vinyl protons and the two lowest field methyl groups clearly demonstrated that colensone oxide was identical with manoyl oxide at C_{13} and probably also at C_8. Model studies showed that the stereochemistry at C_9 does not necessarily affect the conformations at C_8 and C_{13}.

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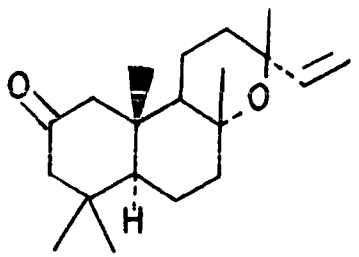
*Dr. P. K. Grant and Mr. R. M. Carman, Department of Scientific and Industrial Research, Dominion Laboratories, Wellington, New Zealand. Colensone oxide. Private communication. (1961)

**Ibid.

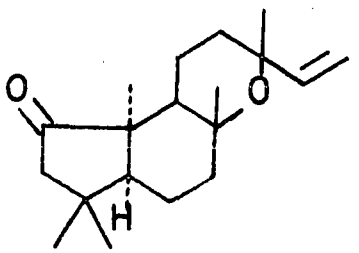
The spectrum of colensone oxide exhibited three peaks of a two proton AB quartet centered at 2.04 p.p.m. with a coupling constant of 15.8 c.p.s. which was assigned to a methylene located between a ketone and a quaternary carbon atom. In the absence of any definite knowledge as to the effect of a carbonyl group on the chemical shift of the protons of an adjacent gem-dimethyl group in a rigid system, the spectrum could not be used to determine the position of the keto group in colensone oxide. However, on the basis of the factors noted for the Morgan ketomanoyl oxide (vide supra) C_3 might be preferred. Colensone oxide was assigned the structure portrayed in LXXXIX.

A reasonable biosynthetic pathway leading to colensone oxide might involve ring contraction of a C_1, C_2, or a C_2, C_3 dioxygenated precursor, followed by oxidative removal of the newly exo-cyclic carbon atom. The first step of this process finds analogy in the biosynthetic elaboration of ring B of gibberelic acid.[29] If the biosynthetic precursor to colensone oxide were either of the ketomanoyl oxides mentioned above then colensone oxide would be expected to possess the normal trans A/B configuration.

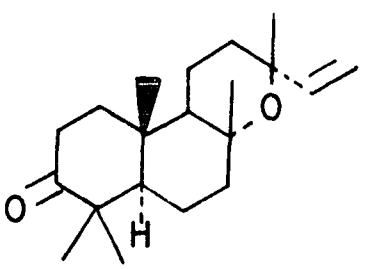
Plate 15. Diagram



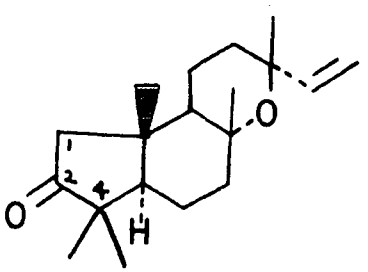
LXXXVI



LXXXVII



LXXXVIII



LXXXIX

A New Method for the Assignment of Stereochemistry of C_4-Substituents in the A/B Trans Diterpenes The Structure of Hydroxytotarol

The empirical nuclear magnetic resonance spectral correlations used to establish the C_{13} vinyl group configurations in rimuene and colensone oxide indicated that a similar method might be leveled at other sterochemical problems in the diterpene field.

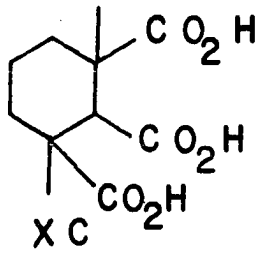
A pattern of C_4 carboxy substitution with an A/B trans normal ring juncture is found in both the bicyclic and the tricyclic diterpene systems. The elucidation of the configuration of substituents at this position has sometimes involved drastic oxidations which yielded the C_{11} acid XC whose optical activity was utilized to assign the stereochemistry at C_4.[98] More routinely the differences between the chemical reactivity of an axial and equatorial carboxy group towards basic[70] or reductive[99] hydrolysis have been used in this connection.

Rosen *et al.*[95] and Slomp and McGarvey[100] have observed different chemical shifts in nuclear magnetic resonance spectra of steroids for axial and equatorial methyl groups on a six-membered carbocyclic ring. It therefore seemed reasonable that if the axial and equatorial carboxy groups at C_4 in the diterpenes could be suitably modified, differences of chemical shift associated with the dissimilar steric environments of the resultant groups would be observed.

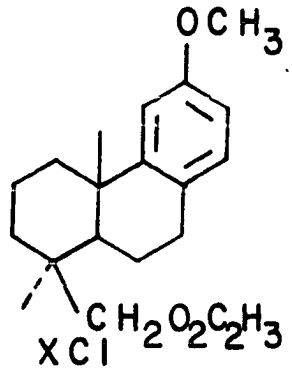
Reduction of the carboxy group to a hydroxymethyl group seemed to be the most propitious modification when the factors of ease of chemical operation, applicability to other naturally-occurring systems and the possession of a chemical shift and splitting pattern which would minimize interferences from other absorptions and maximize ease of location in a spectrum, were considered. Moreover, since in the model cases the nuclear magnetic resonance spectrum of the parent ester could be compared with that of the alcohol, an unambiguous assignment of peaks to the hydroxymethyl protons should be possible. A further verification of absorption assignments could be obtained by the acetylation of the alcohol, since the acetylated compound would be expected to show a paramagnetic shift of approximately 0.5 p.p.m.[92, p. 55] for the methylene protons of the hydroxymethyl group. It was of interest to note that with the acetylation of a secondary alcohol a paramagnetic shift of about 1.0 p.p.m.[92, p. 55] is observed for the proton adjacent to the oxygen. Hence in case of interference of these absorptions in a compound, separation of peaks might be obtained by acetylation.

The nuclear magnetic resonance spectra of O-methylpodocarpol(LXV), O-methylpodocarpyl acetate(XCI), vouacapenol[70] (XCII), dehydroabietol[101](XCIII), dehydroabietyl acetate (XCIV) and vinhaticol[70](XCV) were obtained and compared. The alcohols were obtained by reduction of the corresponding

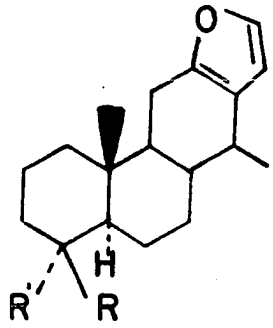
Plate 16. Diagram



XC

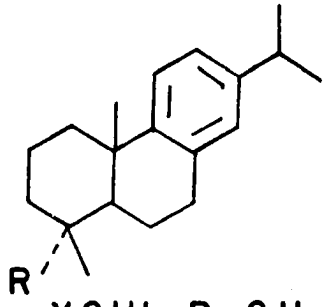


XCI



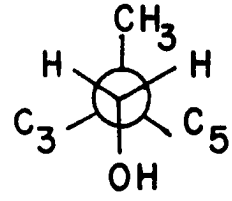
XCII, R=CH_2OH, R'=CH_3

XCV, R=CH_3, R'=CH_2OH



XCIII, R=CH_2OH

XCIV, R=$CH_2O_2C_2H_3$



XCVI

methyl esters with lithium aluminum hydride. The chemical shifts gathered in Table 3 manifestly demonstrate that in the trans A/B diterpenes containing a C_{10} methyl group, the chemical shift of the methylene protons of a C_4 hydroxymethyl group is indicative of the conformation and configuration of that group. The peak assignments were confirmed by the change in chemical shifts observed for the acetates of LXV and XCIII and by comparison of the spectra of the alcohols with their parent esters.

Table 3.

	Conformation of CH_2OR	Chemical shift
O-Methylpodocarpol	axial	3.69
O-Methylpodocarpyl acetate	axial	4.16
Vouacapenol	axial	3.60
Dehydroabietol	equatorial	3.28
Dehydroabietyl acetate	equatorial	3.84
Vinhaticol	equatorial	3.25

The peaks assigned to the nuclear magnetic resonance absorptions of the methylene protons were in every case observed to be a relatively symmetrical quartet of the AB type. The chemical shifts recorded were taken at the center of the quartet. The non-equivalence of the two methylene

protons in question was postulated to arise from a degree of restricted rotation imposed on the system by the buttressing of the alcoholic oxygen and C_4 methyl group. In the case of dehydroabietol, for example, the energetically favored conformation portrayed in XCVI places the methylene protons in magnetically different environments by virtue of the dissimilarity between C_3 and C_5. The spectrum of dehydroabietol was used to compare the observed and calculated intensity ratio of the inner to outer lines in the AB system. The parameters of 10.8 c.p.s. for the separation of the inner and outer peaks and of 7.4 c.p.s. for the separation of the inner peaks were substituted into the equations derived on a theoretical basis by Pople et al.[90, p. 119] The theoretical ratio of intensities was .29 ± .04 and the observed value was .35 ± .02. This relatively close agreement further corroborates the peak designations.

In an effort to test the hypothesis that equatorial and axial hydroxymethyl groups will possess the chemical shifts indicated by the model compounds the nuclear magnetic resonance spectrum of erythrodiol[102](XCVII) and iresine[103](XCVIII) were obtained.

The hydroxymethyl group in erythrodiol is located on a cis ring juncture and therefore is axial to ring D and equatorial to ring E. The effect of this dual conformation is reflected in the chemical shift of this group of 3.36 p.p.m.,

a value intermediate to that found for the purely axial and equatorial cases. A broad peak due to the absorption of the C_3 proton, which did not interfere with the assignment, was observed under the high field high intensity peak of the AB quartet. The chemical shift obtained indicated that the spectral correlations in such a case were not totally reliable for configurational assignment. In such cases reductive hydrolysis[99] remains the method of choice.

The nuclear magnetic resonance spectrum of iresine illustrated that the location of the peaks due to the methylene protons of the hydroxy methyl group might not be possible in the presence of interfering absorptions. The absorptions of the C_3,C_{11} and hydroxymethyl protons were found to overlap in the spectrum of this sesquiterpene. Another problem in this system might be the induction of a paramagnetic shift in the methylene protons of interest by the C_3 oxygen. This effect has been observed with methyl groups in a similar system.[104] In view of the above results, assignments of configuration to hydroxymethyl groups based on nuclear magnetic resonance should be restricted to systems which closely approximate the stereochemical situation in the model compounds.

Such a situation is found in the case of hydroxytotarol. In view of the very limited amount of this diterpene which was available a structure proof based entirely on physical

methods was undertaken.

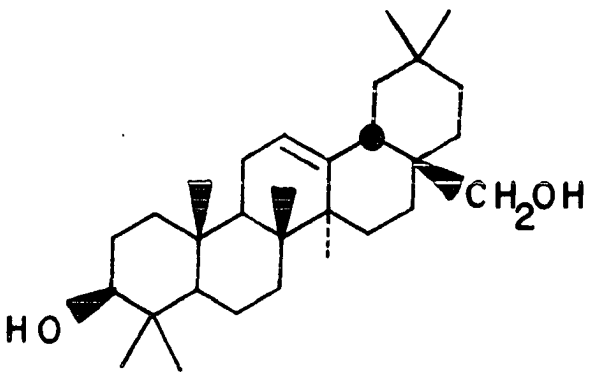
Brandt and Thomas[21] have established the constitution and alcoholic nature of hydroxytotarol.

The close correspondence of hydroxytotarol and totarol(V) was indicated by the virtual identity of the ultraviolet absorption spectra of the two compounds. Both the solution and nujol infrared spectrum of totarol and hydroxytotarol were strikingly similar. All of the strong and medium intensity peaks and all but one of the low intensity peaks which appear in the spectrum of the former were observed in that of the latter. Hydroxytotarol exhibited a strong absorption at 9.9 μ and a medium peak at 10.8 μ which did not appear in the spectrum of totarol. The peak at 9.9 μ was assigned to the O-H deformation vibration of a primary alcohol.[105] It is of interest to note that both compounds show similar absorptions in the 6.9 μ region. The spectra of the cis and trans 10-methyl-2-decalols[106] show significant differences in this region. However this indication that totarol and hydroxytotarol possess the same A/B stereochemistry must be regarded as tenuous.

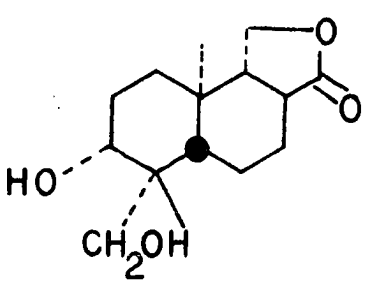
The nuclear magnetic resonance spectra of totarol and hydroxytotarol served not only to confirm the structural similarity of these two compounds but also to define the structure and stereochemistry of the latter.

The spectrum of totarol exhibited an AB quartet

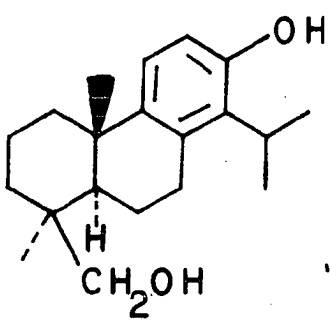
Plate 17. Diagram



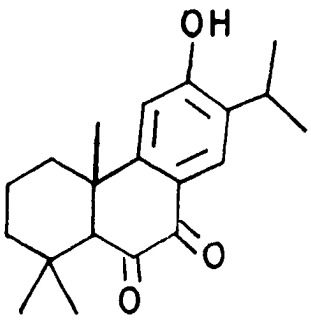
XCVII



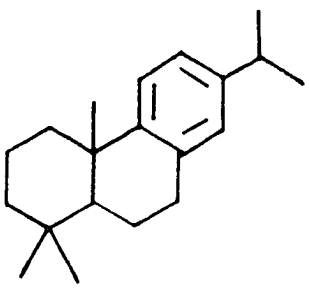
XCVIII



XCIX



C



CI

assigned to the aromatic protons at 6.7 p.p.m. with a coupling constant of 8.9 c.p.s. A broad low peak at 4.35 p.p.m. was assigned to the phenolic proton. Five of the expected seven peaks ascribed to the isopropyl proton were centered at 3.07 p.p.m. with a coupling constant of 7.2 c.p.s. A complex multiplet at 2.78 p.p.m. was assigned to the C_7 protons. The methyl group protons in totarol have chemical shifts of 1.35, 1.23, 1.12, .94, and .92 p.p.m. The coupling constant of 7.2 c.p.s. expected for the isopropyl methyl groups required a chemical shift difference of 0.12 p.p.m. Hence no rigorous assignment was made other than to assign the benzylic methyl groups to the three lowest field and the gem-dimethyl group to the two highest field absorptions.

The nuclear magnetic resonance spectrum of hydroxytotarol was of somewhat disappointing quality due to slight impurities in the small amount of available sample. It was found that a purer specimen could not be obtained in sufficient quantity to improve the results. The spectrum was quite similar to that of totarol with few exceptions. In the methyl group region one of the highest field methyl groups was absent and the other had undergone a 0.1 p.p.m. paramagnetic shift. The low field methyl group absorptions were found at about the same chemical shift as in totarol. A most significant feature of the spectrum was the presence of a two proton AB quartet at 3.66 p.p.m. with a coupling constant of 10.9 c.p.s.

The change in the methyl group absorptions from totarol to hydroxytotarol was interpreted as indicating that the latter compound possessed a C_4 hydroxymethyl group. The chemical shift of the methylene protons of the hydroxymethyl group established that this group was axial. Furthermore the chemical shifts of the ring A methyl groups in hydroxytotarol coincide with those observed in podocarpol (vide infra).

On the basis of these results structure XCIX can be assigned to hydroxytotarol.

The Chemical Shifts of the Ring A Methyl Groups in the Diterpene Series

Previous assignments of chemical shifts to methyl groups located in ring A of diterpenic systems made by Chien[94] and by Bredenberg and Shoolery[107] provided a frame of reference for similar assignments in the compounds studied. In view of the limited knowledge about the factors affecting the chemical shifts in rigid systems, many of the assignments both herein and by previous workers[94,107] must be considered tentative. Indeed the assignment of the highest field absorption in the nuclear magnetic resonance spectrum of xanthoperol[107](C) to the C_{10} methyl group by Bredenberg and Shoolery ignored the magnetic moments caused by the aromatic ring currents of the adjacent benzene ring.[90, p. 80] This

effect has been established by Chien[94] to cause a paramagnetic shift of about 0.3 p.p.m. of the C_{10} methyl relative to a system in which ring C is hydroaromatic. Hence in the case of xanthoperol a reassignment of peaks should be made. The nuclear magnetic resonance spectra obtained in the previous work seemed suitable for the study of chemical shifts of ring A methyl groups.

Assignments of peaks to specific methyl groups were made in an attempt to correlate changes in the chemical shifts of these groups with the changes in chemical structure at C_4. The tentative assignments are listed in Table 4. The nuclear magnetic resonance spectra of O-methylpodocarpane and dehydrobietane(I) are included in this table.

Table 4. δ in p.p.m.

	C_4-CH_3	C_{10}-CH_3
O-methyl podocarpane	0.95,0.95	1.19
O-methyl podocarpol	1.03	1.16
O-methyl podocarpy acetate	1.06	1.20
Methyl O-methyl podocarpate	1.24	1.02
Dehydroabietane	0.92,0.92	1.16
Dehydroabietol	0.87	1.18
Dehydroabietyl acetate	0.93	1.21
Methyl dehydroabietate	1.20	1.28
Methyl vouacapenate	1.21	0.72
Vouacapenol	0.97	0.72
Methyl vinhaticoate	1.19	0.91
Vinhatical	0.92	0.81

On the basis of these models some tentative correlations which might be applicable to rigid six membered carbocyclic rings were noted. A methyl group in 1,3-diaxial interaction with a carbomethoxy group underwent a diamagnetic shift of .12 ± .04 p.p.m. relative to the same interaction with a methyl or hydroxymethyl group. Models indicated that a C_4 axial carbomethoxy group may be oriented in a manner that would put the C_{10} methyl group in the conical region associated with positive shielding above the plane of the carbomethoxy double bond.[91, p. 122] It was surprising to find that the magnitude of this diamagnetic shift seemed to be independent of the nature of ring C. In the ring C aromatic case the change in buttressing interactions of the C_{10} methyl group might be expected to change its location in the field induced by ring C and consequently change its chemical shift.

A methyl group on the same carbon atom as a hydroxy methyl group was observed to undergo a paramagnetic shift of .26 ± .06 p.p.m. when the hydroxymethyl group was transformed into a carboxymethyl group. The fact that groups relatively distant in the molecule can affect the chemical shift is illustrated by the 0.1 p.p.m. paramagnetic shift of C_{10} methyl groups when an equatorial hydroxymethyl group at C_4 is changed to a carbomethoxy group.

In the cases studied an axial methyl group adjacent to a hydroxymethyl group had an absorption at higher fields than

did the corresponding equatorial cases. This effect is in the opposite direction of that expected on the basis of the work of Slomp and McGarvery.[100] The fact that the C_4 methyl groups in dehydroabietane appeared at slightly lower field than did the C_4 methyl group in dehydroabietol was also unexpected.

These results indicated that some of the factors determining the chemical shifts of the methyl groups in these systems were quite subtle. Hence work with appropriately deuterated compounds and special solvent systems[108] may need to precede further assignments.

SPECTRA

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

Ultraviolet spectra were measured in 95% ethanol solution with a Cary Model 14 spectrophotometer.

The nuclear magnetic resonance spectra were obtained with either ca. 20% deuterochloroform or saturated deuterochloroform solutions on a Varian Model HR60 spectrometer at 60 mc/sec. with tetramethylsilane acting as an internal standard. The position of the major peaks was determined by the audio-frequency side band technique while that of minor peaks was determined by interpolation. Peak positions were expressed in δ^{89}.

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

Figure 1. Optical rotatory dispersion curves

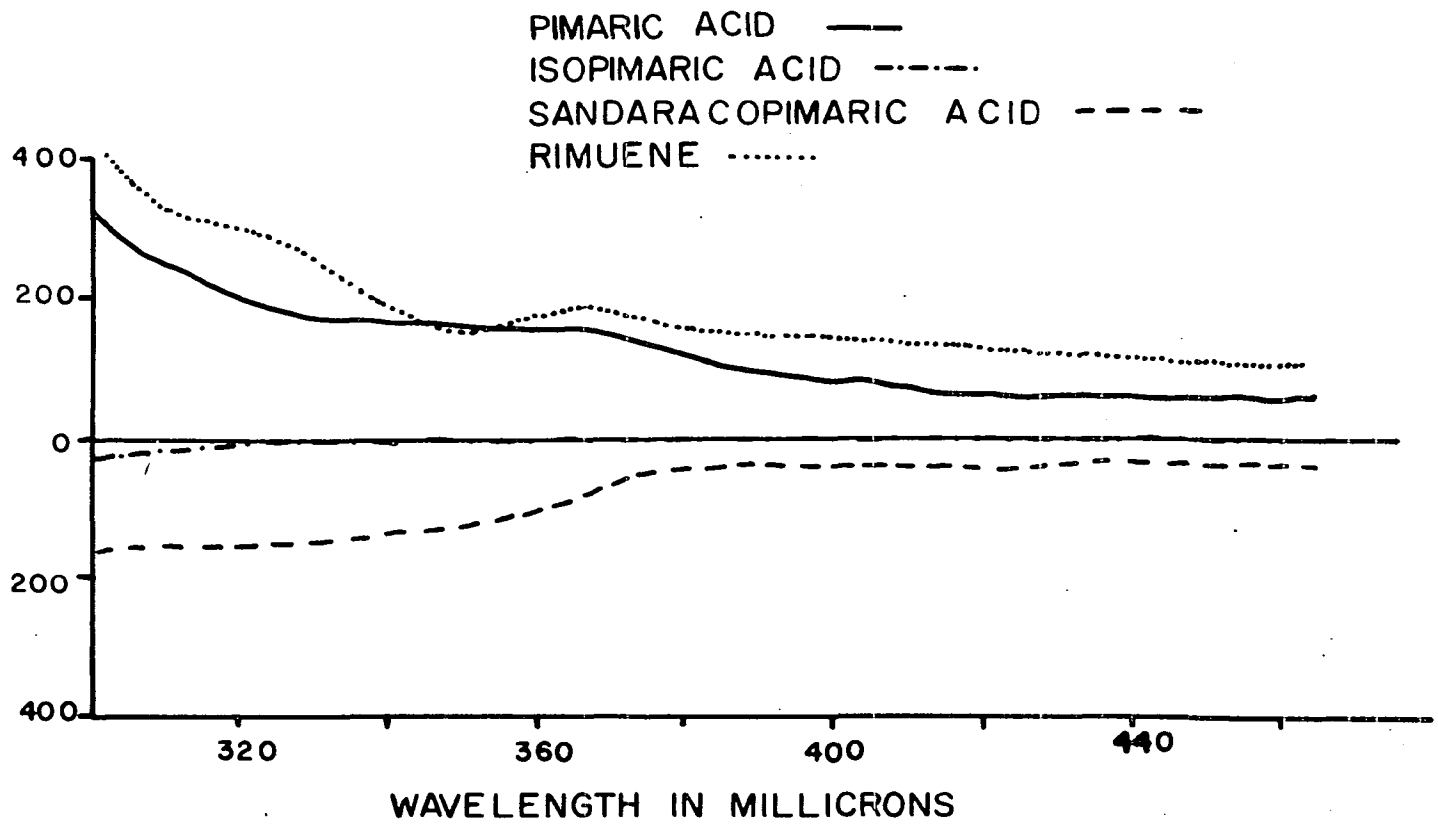

PIMARIC ACID
ISOPIMARIC ACID
SANDARACOPIMARIC ACID
RIMUENE
400
200
0
200
400
320
360
400
440
WAVELENGTH IN MILLICRONS

Figure 2. Nuclear magnetic resonance spectra

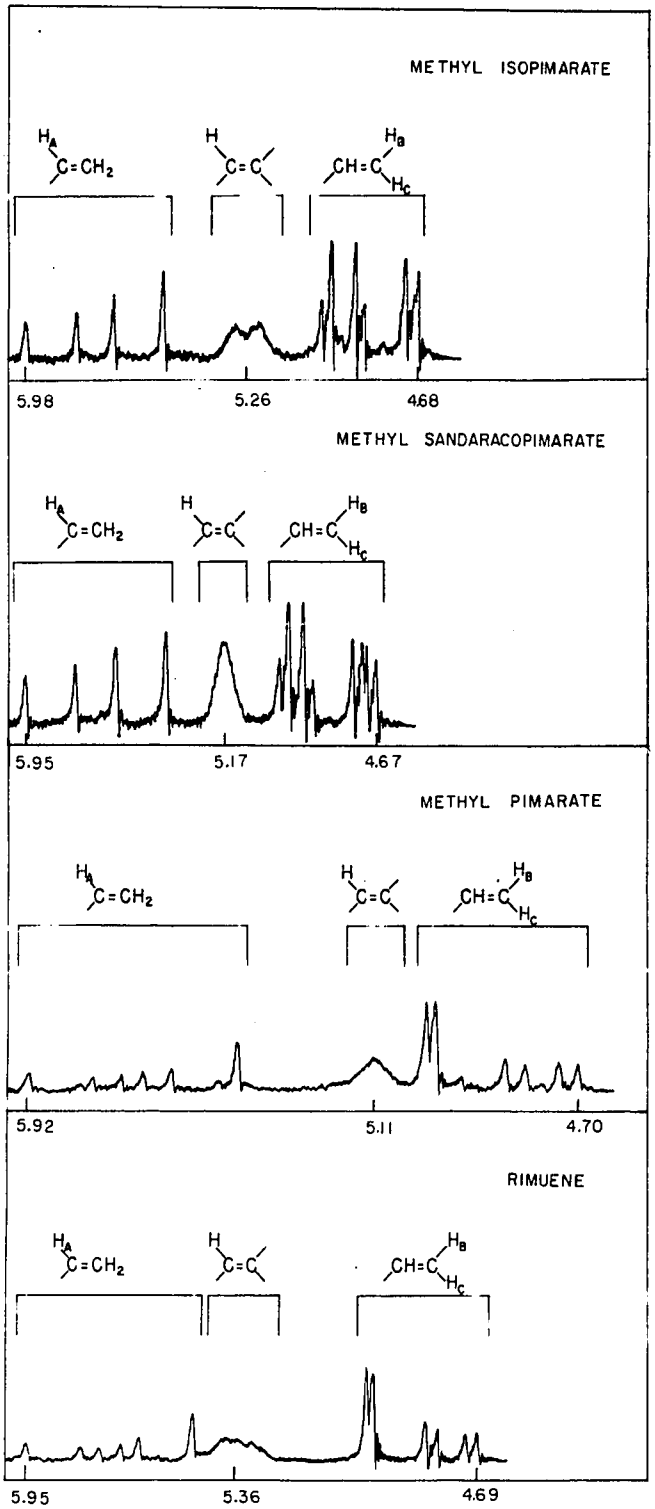

METHYL ISOPIMARATE
5.98
5.26
4.68
METHYL SANDARACOPIMARATE
5.95
5.17
4.67
METHYL PIMARATE
5.92
5.11
4.70
RIMUENE
5.95
5.36
4.69

Figure 3. Nuclear magnetic resonance spectra

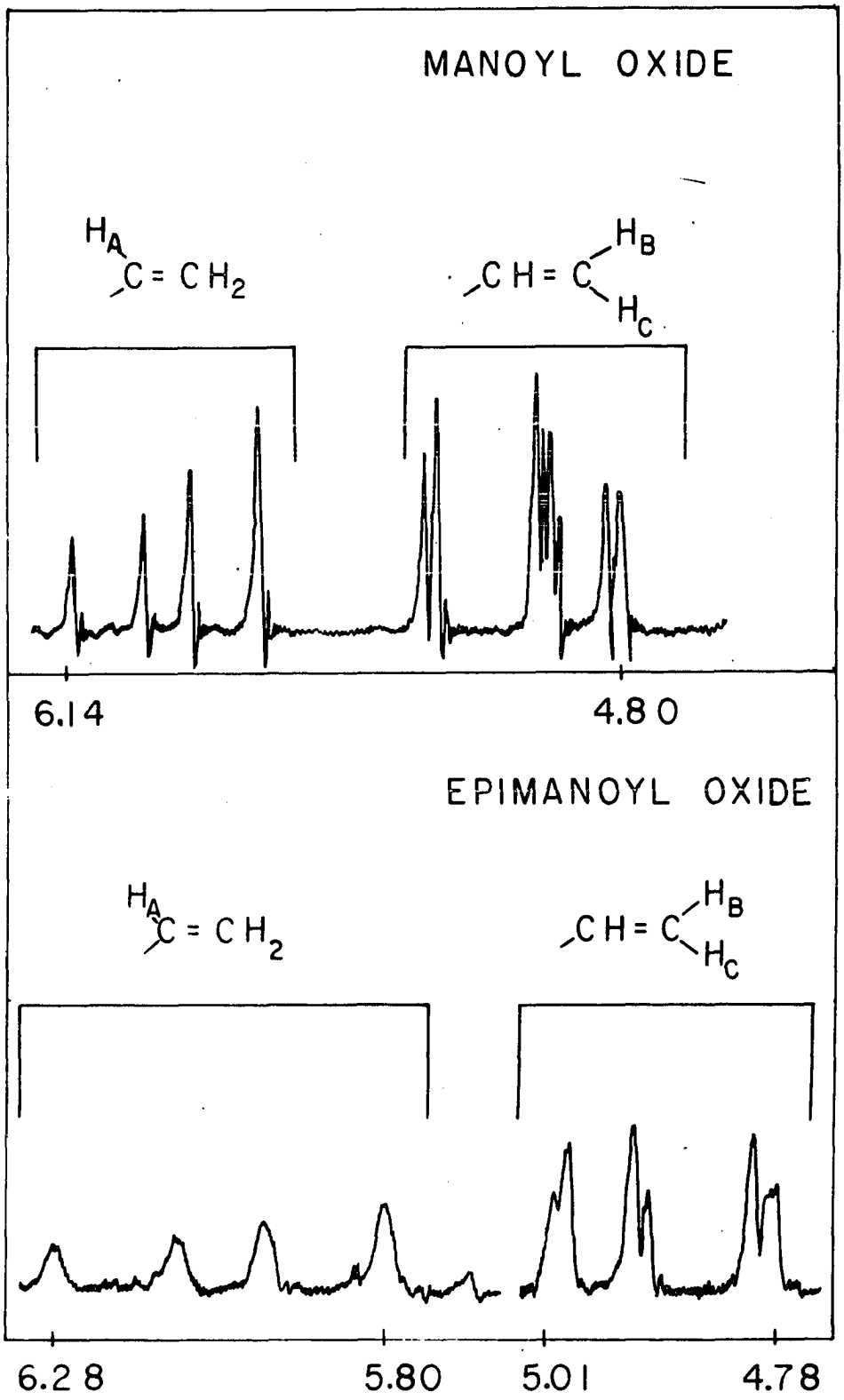

MANOYL OXIDE
H_A
C = CH_2
CH = C
H_B
H_C
6.14
4.80
EPIMANOYL OXIDE
H_A
C = CH_2
CH = C
H_B
H_C
6.28
5.80
5.01
4.78

Figure 4. Ultraviolet spectra

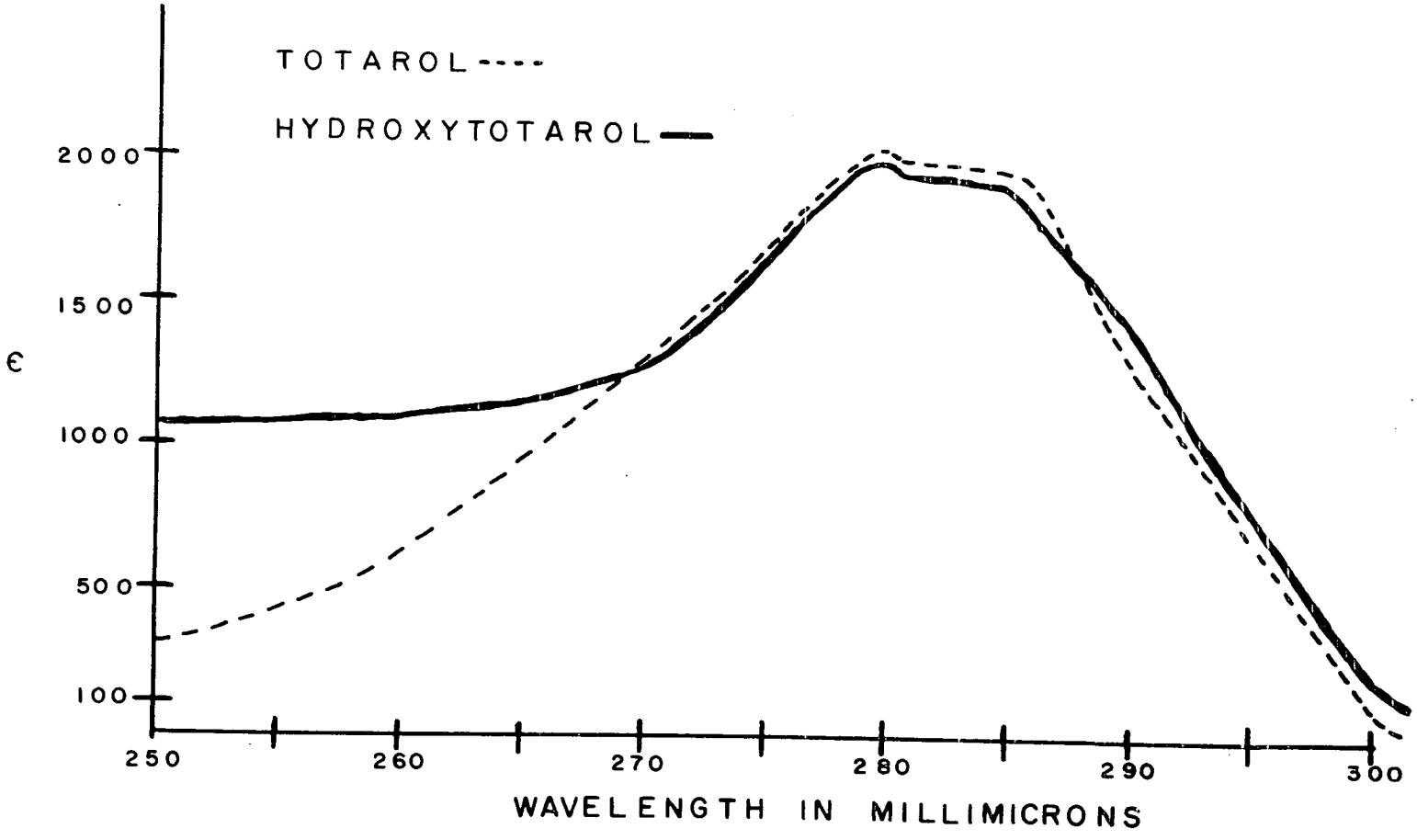
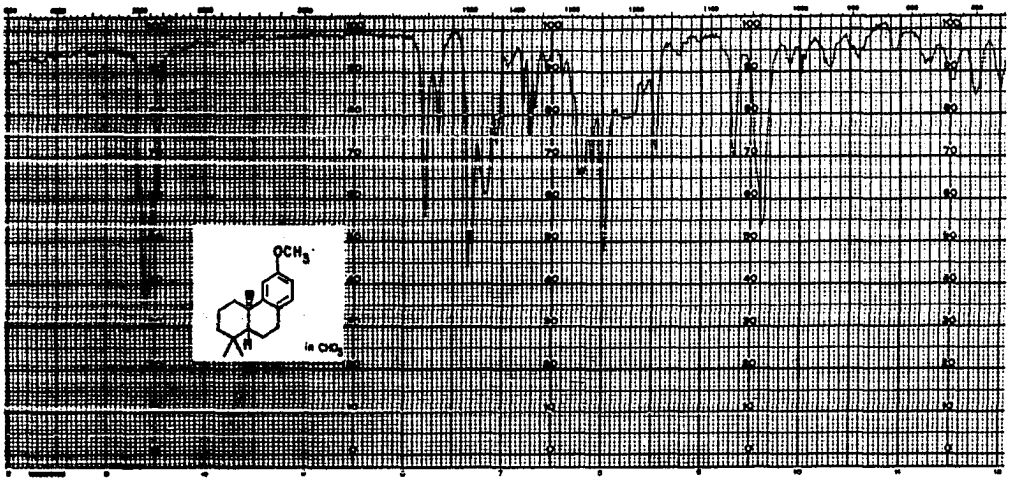
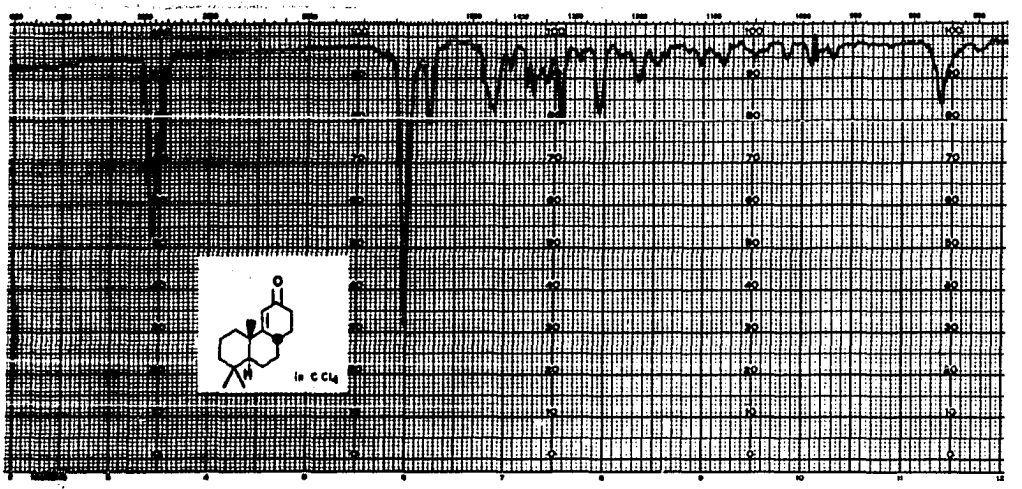

TOTAROL----
HYDROXYTOTAROL
2000
1500
1000
500
100
ε
250
260
270
280
290
300
WAVELENGTH IN MILLIMICRONS

Figure 5. Infrared spectra


OCH3
in CHCl3


O
in CCl4

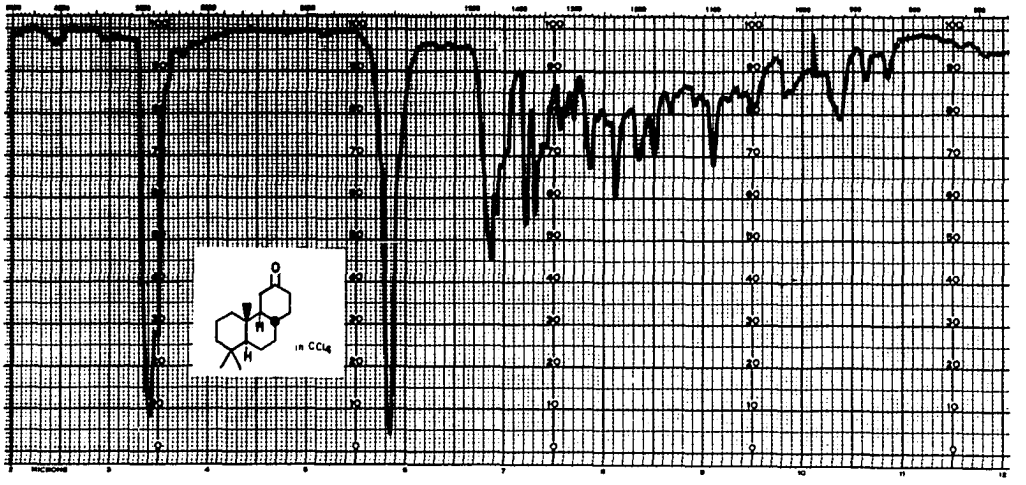
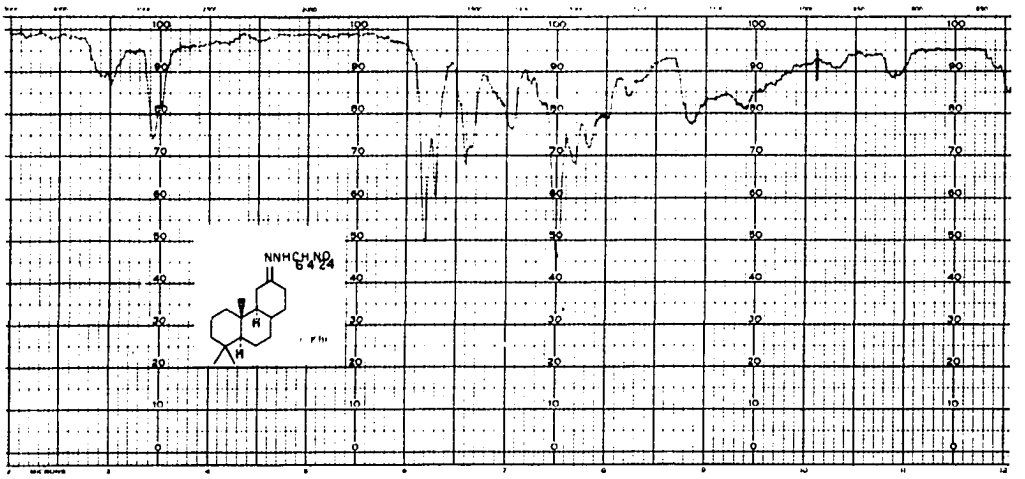
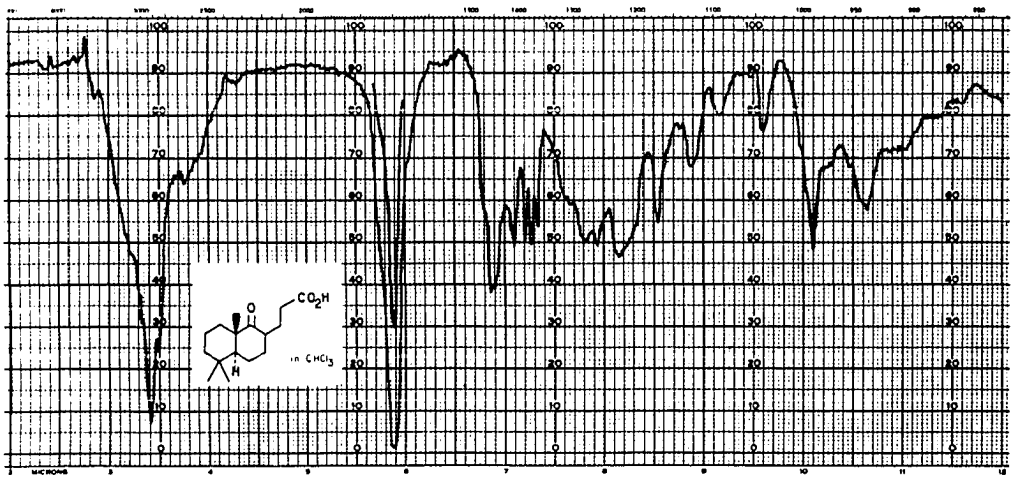

O
in CCl4

Figure 6. Infrared spectra


NNHC6H4NO2
H
H


O
CO2H
H
MICRONS

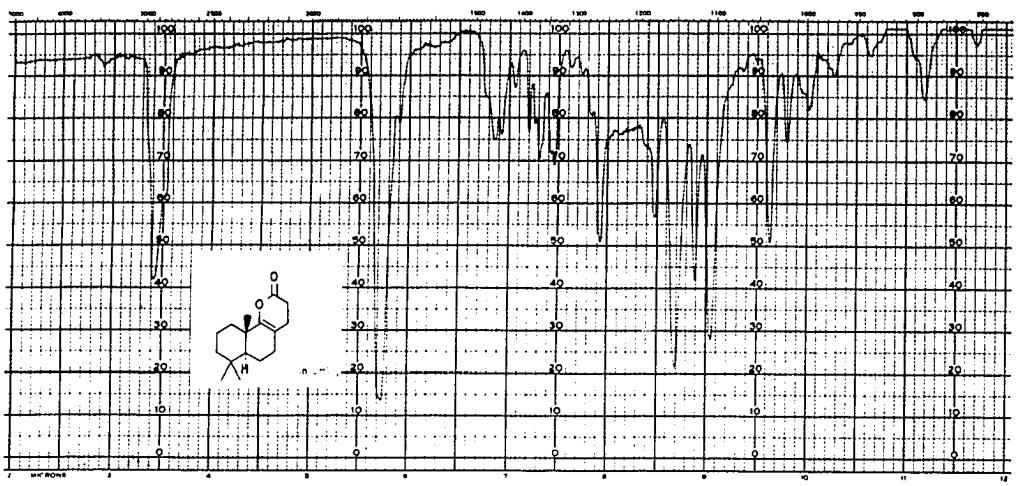
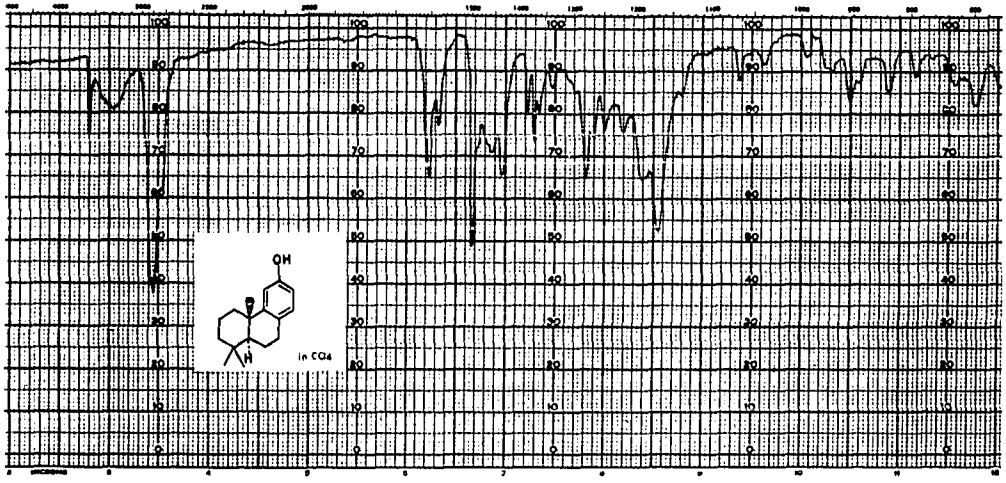
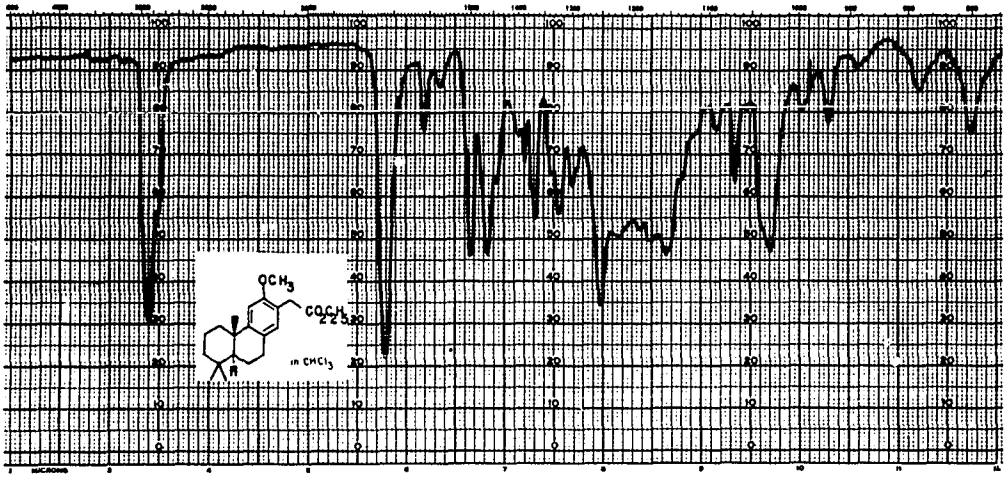

O
O
H

Figure 7. Infrared spectra


OH
in CCl_4


OCH_3
$COCH_3$
in $CHCl_3$

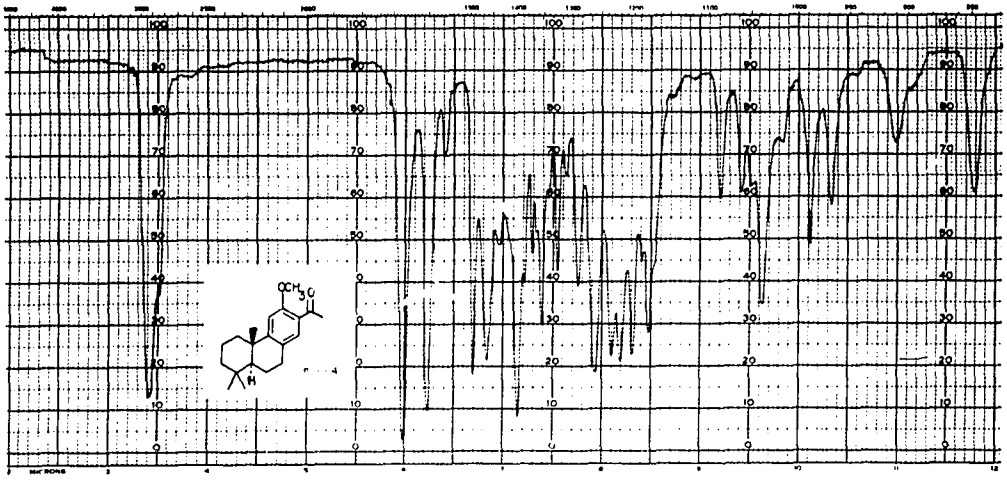
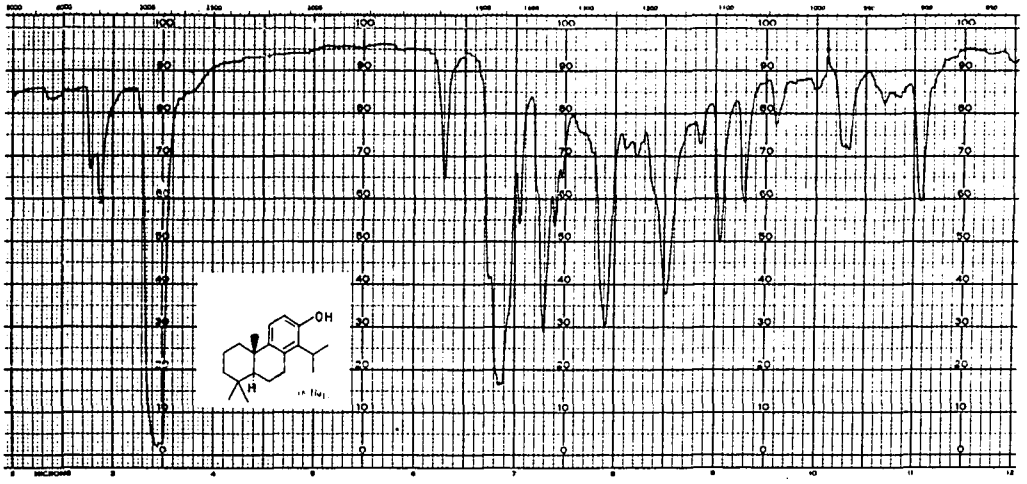
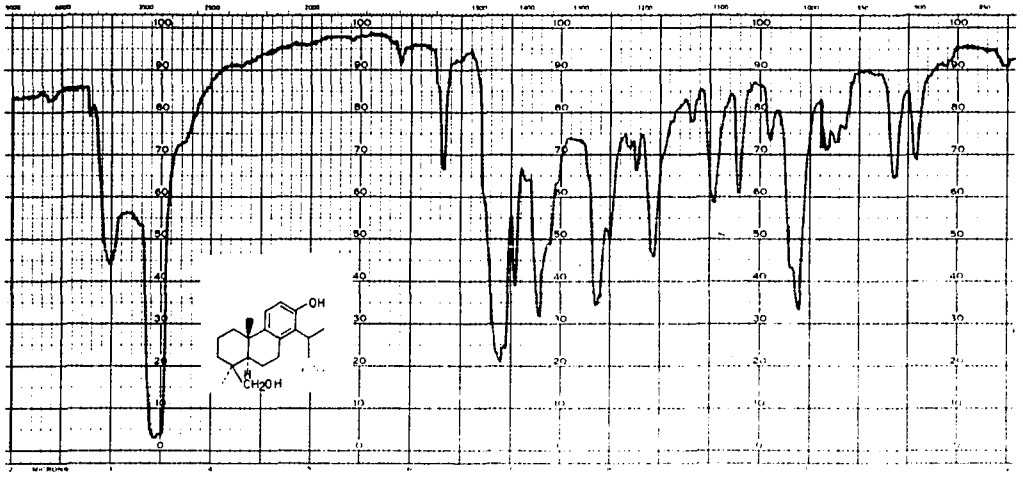

OCH_3

Figure 8. Infrared spectra


OH
H


OH
H
CH2OH

EXPERIMENTAL

The microanalyses were performed by Midwest Microlab, Indianapolis, Indiana; Alfred Bernhardt of the Max Plank Institute, Mulheim(Ruhr), Germany; and Mr. L. Dorfman of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Absorbents for Chromatography

Activated alumina, 80-200 mesh, was allowed to stand under ethyl acetate for 48 hours, then washed with water and methanol and dried at 120° for 48 hours.

Physical Measurements

All melting and boiling points are uncorrected. The optical rotations were taken in chloroform solution unless otherwise noted on an O. C. Rudolf polarimeter.

O-Methylpodocarpol(LXV)

O-Methylpodocarpol, m.p. 92-94°, was prepared by standard methods.[66]

O-Methylpodocarpal(LXVI)

A solution of 8.3 g. of LXV in 40 ml. of anhydrous pyridine was added to a mixture of 11.9 g. of chromic acid in 120 ml. of anhydrous pyridine.[67] After standing one hour at room temperature the mixture was poured into ice water and

extracted with ether. The extract was washed with 5% hydrochloric acid and 2N sodium hydroxide, dried over sodium sulfate and evaporated. Crystallization of the crude neutral product, 6.25 g. (76%), from aqueous ethanol gave LXVI, m.p. 130-133.[69]

The alkaline extracts were acidified and extracted with ether. The organic extract was dried over sodium sulfate and evaporated, yielding 0.97 g. (11%) of crude acid. Crystallization of this compound from aqueous methanol gave O-methylpodocarpic acid, m.p. 158-160°.[116]

O-Methylpodocarpane(LXVII)

(a) A solution of 7.67 g. of LXVI and 85 ml. of 95% hydrazine in 350 ml. of anhydrous diethylene glycol was heated at 110-120° for 90 minutes. After cooling for 15 minutes 40.6 g. of potassium hydroxide pellets was added and the mixture refluxed at 155-165° for 7 hours.[68] The solution was poured into 2 liters of ice water, made strongly acid with hydrochloric acid and extracted with ether. The extract was dried over sodium sulfate, evaporated and chromatographed on 100 g. of alumina. Elution with petroleum ether (b.p. 65°) gave 5.86 g. (81%) of an oil which crystallized on standing. Crystallization of O-methylpodocarpane from aqueous ethanol yielded needles, m.p. 31-32°.[73]

Analysis

Calculated for C H O: C, 83.66; H, 10.14. Found: C, 84.0; H, 10.4.

Infrared spectrum

See Figure 5.

Optical rotation

$[\alpha]_D^{25^\circ}$ + 71.7°

Ultraviolet spectrum

λ max. 279 mμ (ϵ 2380) and shoulder 284 mμ (ϵ 2100)

(b) A solution of 525 mg. of O-methylpodocarpol and 290 mg. of p-toluenesulfonyl chloride in 5 ml. of pyridine was allowed to stand at 0° for 50 hours. The mixture was poured into ice water and extracted with chloroform. The extract was washed with 5% hydrochloric acid and 2N sodium hydroxide, dried over sodium sulfate and evaporated. A solution of the resulting gum and 1.6 g. of lithium aluminum hydride was refluxed for 68 hours. The suspension was diluted with 150 ml. of ether and the excess hydride decomposed with a sodium sulfate slurry saturated with water. After filtration, the solution was dried over anhydrous sodium sulfate and evaporated. The resulting gum was chromatographed on 20 g. of alumina. Elution with petroleum ether gave 59 mg. (12%) of

oily O-methylpodocarpane. Elution with chloroform led to 458 mg. (87%) of crude starting alcohol, m.p. 65-88°. Both substances were identified by comparison of their infrared spectra with those of authentic samples.

ℓ 4,4,10-trimethyl-1,2,3,4,5α,6,7,8β, 10,12,13,14 Dodecahydro-12 Phenanthrone(LXVIII) and
d_ 4,4,10-Trimethyl-trans-anti-trans-perhydro-12-phenanthrone(LXIX)

A mixture of 2.00 g. of LXVII, 170 ml. of anhydrous ethanol, 30 ml. of tetrahydroforan and 350 ml. of anhydrous ammonia was cooled in a Dry Ice-acetone bath and stirred vigorously while 20 g. of lithium was added over an 80 minute period. Toward the end of this period a henna color appeared at the top of the otherwise deep blue mixture.[77] Stirring was continued until the blue color had faded whereupon the ammonia was allowed to evaporate. The residue was taken up in 2 liters of ice water and extracted with ether. The extracts were washed with 5% hydrochloric acid and evaporated in vacuo. The remaining oil was dissolved in 320 ml. of 95% ethanol, mixed with 3.4 ml. of concentrated hydrochloric acid and heated at 70°C for one hour. The solution was poured into ice and water and extracted with ether. The extract was dried over sodium sulfate and evaporated.

The residue was chromatographed on 100 g. of alumina. Elution with petroleum ether gave 78 mg. (4%) of starting material (LXVII), 49:1 petroleum ether-benzene saturated

ketone, 24:1 petroleum ether-benzene a mixture of saturated and unsaturated ketones, 7:3 petroleum ether-benzene unsaturated ketone and chloroform 40 mg. of unidentified oil. The eluates containing mixtures of ketones were rechromatographed. Similar fractions from the two chromatograms were combined.

Repetition of the ethanolic hydrochloric acid treatment with the saturated ketone, whose yield was 80 mg. (4%), and infrared analysis of the products ("Infracord") revealed it to contain a maximum of 5-10% of material equilibratable with the conjugated ketone. After micro-distillation (oil bath at 196°/5 mm.) the ketone solidified. Four crystallizations from aqueous ethanol gave crystalline ketone LXIX, m.p. 48-49°.

Analysis

Calculated for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.17; H, 11.40.

Infrared spectrum

See Figure 5.

Optical rotation

$[\alpha]_D^{25^\circ}$ + 33.8

Optical rotatory dispersion curve

R.D. (C.108); $[\alpha]_{589}$+2.8, $[\alpha]_{400}$+111, $[\alpha]_{350}$+297, $[\alpha]_{325}$+984, $[\alpha]_{317}$+1277, $[\alpha]_{310}$+1120, $[\alpha]_{38}$+703

The 2,4 dinitrophenylhydrazone of LXIX was prepared and found to be identical with the derivatives of the saturated ketone obtained by two different reductions of ketone LXVIII (vide infra).

The unsaturated ketone LXVIII whose yield was 905 mg. (47%), solidified on rechromatography. Five crystallizations from aqueous dimethylformamide gave crystalline ketone LXVIII, m.p. 56-57°.

Analysis

Calculated for $C_{17}H_{26}O$: C, 82-87; H, 10.64. Found: C, 83.07; H, 10.61.

Infrared spectrum

See Figure 5.

Optical rotation

$[\alpha]_D^{24^\circ}$ - 14.30

Optical rotatory dispersion curve

R.D. (c,0,104); $[\alpha]_{589}$-1.3, $[\alpha]_{48}$-12.2, $[\alpha]_{350}$-40.3 (signal lost at 330 mm. due to strong absorption)

Ultraviolet spectrum

$\lambda_{max.}$ 240 mμ (ε 19,400)

A solution of 43 mg. of LXVIII in methanol containing 24 mg. of sodium was stirred under nitrogen for 24 hours. The solution was poured into water and extracted with ether. The ether extract was dried over sodium sulfate and evaporated to yield 31 mg. (75%) of crude ketone, m.p. 43-53°. The melting point was undepressed upon mixture with an authentic sample of LXVIII. The infrared spectrum of the crude ketone ("Infracord") in both Nujol and solution was identical with that of LXVIII.

Ketone LXIX by reduction of ketone LXVIII

(a) A mixture of 200 mg. of LXIX and 30 mg. of 10% palladium-charcoal in 5 ml. of ethyl acetate was hydrogenated at atmospheric pressure. When after 2 hours one equivalent of hydrogen had been taken up, the catalyst was filtered and the solvent evaporated. The oily product was dissolved in benzene and passed through a column of 2 g. of alumina. Evaporation of the filtrates yielded 163 mg. of oil whose infrared spectrum exhibited only a 5.84 carbonyl peak ("Infracord"). The oil gave only one peak when subjected to gas phase chromatography at 200° on apiezon and silicone columns. When 30 mg. of the oil was seeded with a crystal of ketone LXIX, obtained from the Birch reduction of LXVIII

(vide supra), slow crystallization occurred. The resulting oily solid was dried on a porous plate for several hours, leading to 13 mg. of needles, m.p. 35-46°, whose Nujol infrared spectrum ("Infracord") was the same as that of LXIX (vide supra). Four crystallizations of its 2,4-dinitrophenylhydrazone from aqueous ethanolic ethyl acetate yielded yellow needles, m.p. 160-162°.

Analysis

Calculated for $C_{23}H_{32}O_4N_2$: C, 64.46; H, 7.53; N, 13.08. Found: C, 64.49; H, 7.58; N, 13.21.

Infrared spectrum

See Figure 6.

(b) A solution of 77 mg. of LXVIII in 10 ml. of anhydrous tetrahydroforan was added to a stirred solution of 80 ml. of ammonia, containing 80 mg. of dissolved lithium and being cooled in a Dry Ice-acetone bath, and the stirring continued for 10 minutes. Solid ammonium chloride was added until the blue color was discharged and the mixture was allowed to evaporate. The residue was taken up in water and extracted with ether. The extract was washed with 5% hydrochloric acid, dried over sodium sulfate and evaporated. The residue was chromatographed on 5 g. of alumina. Elution with 40:1 petroleum ether-benzene gave 42 mg. (54%) of the desired

saturated ketone while elution with 24:1 petroleum ether-benzene yielded 5 mg. of starting ketone. Three crystallizations of the product from aqueous ethanol afforded needles of ketone LXIX, m.p. 46-49°, identical in all respects with the saturated ketone obtained from the Birch reduction of LXVII. Its 2,4-dinitrophenylhydrazone, m.p. 158-160°, also corresponded to that of the latter.

d Trans-2-(β-carboxyethyl-) 5,5,9-trimethyl-1-decalone(LXXII)

Two equivalents of ozone were passed through a solution of 122 mg. of the enone LXVIII in 6 ml. of 1:1 ethyl acetate-glacial acetic acid. The solution was treated with 1 ml. of water and 0.1 ml. of 30% hydrogen peroxide and allowed to stand for 24 hours.[84] After the addition of 45 ml. of 2N sodium hydroxide to the solution, cooled in an ice-bath, it was extracted with ether and the extracts discarded. The aqueous solution was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated. Four crystallizations of the crude acid, 119 mg. (90%), gave the ketoacid LXXII, m.p. 88.5-90°.

Analysis

Calculated for $C_{16}H_{26}O_3$: C, 77.14; H, 9.84. Found: C, 77.04; H, 9.65.

Infrared spectrum

See Figure 6.

Optical rotation

$[\alpha]_D^{25^\circ}$ - 10.4°

Enol Lactone of LXXIII

A solution of 50 mg. of the keto acid LXXII in 2 ml. of freshly distilled acetyl chloride was refluxed for 40 hours. The excess acetyl chloride was removed in vacuo and the residue taken up in ether. The organic solution was washed with 5% sodium bicarbonate, dried over sodium sulfate and evaporated. Two sublimations of the crude product, 31 mg. (67%), gave pure enol lactone LXXIII, m.p. 93-94° after sintering at 91°.

Analysis

Calculated for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.71; H, 10.02.

Infrared spectrum

See Figure 6.

Podocarpane

Pyridine hydrochloride was prepared by dropwise addition of 90% of the calculated amount of pyridine to a 25% mixture of hydrochloric acid and ice. The water was stripped in vacuo and the resulting solid azeotroped dry by means of several strippings with benzene.

The ether LXVII, 3.26 g., was treated with 120 g. of pyridine hydrochloride at 240-260° for 45 minutes. After cooling water was added and the resulting precipitate was collected by filtration. The crude phenol, 2.75 g., was dissolved in hot petroleum-ether, decolorized with Norite and allowed to crystallize. One additional crystallization provided 1.84 g. (60%) of off-white material, m.p. 137-140°. Three crystallizations from petroleum ether gave pure LXXVVI, m.p. 140-141° after sintering at 139°.

Infrared spectrum

See Figure 7.

Optical rotation

$[\alpha]_D^{25^\circ}$ + 75.4°

Ultraviolet spectrum

$\lambda_{max.}$ 281 mμ(ϵ 2.39x10^3)

Alkylation of Podocarpane

The solution prepared by the addition of 1.06 g. of LXXVI to 12 ml. of .38N methanolic sodium methoxide was stripped to dryness *in vacuo*. Dry benzene was distilled from the residue two times. The dry salt was mixed with 20 ml. of ethyl bromoacetate and the mixture refluxed under nitrogen at 180-190° for four hours. The excess ethyl bromoacetate was removed *in vacuo*, and the residue taken up in petroleum ether. The petroleum ether was washed with water dried over sodium sulfate and evaporated to yield a slightly yellow oil.

The oil was chromatographed on 30 g. of alumina. Elution with petroleum ether gave 1.1 g. of a clear oil whose infrared spectrum ("Infracord") had a broad absorption at 5.70 . Elution with methanol gave 60 mg. of an unidentified oil.

The oil from the petroleum ether fraction was distilled (oil bath at 180° 1 mm.) and 845 mg. of oil material collected. The distillate was shown to be composed of two major substances in a 1:4 ratio by gas phase chromatography at 260° on a silicone rubber gum column.

Ethoxalylchloride

Ethoxalyl chloride, b.p. 125-131°C., was prepared by the method of Kindler *et al*.[88]

13-Carboethoxymethyl-O-methylpodocarpane(LXXVII)

A solution of 2.0 g. of anhydrous aluminum chloride, 1.53 g. of ethoxalyl chloride and 35 ml. of nitrobenzene was stirred 5 minutes at room temperature and a solution of 2.4 g. of O-methylpodocarpane in 15 ml. of nitrobenzene was added. The dark brown reaction mixture was stirred 8 hours. Dilution with ether was followed by cautious addition of ice and water. After decomposition of the aluminum chloride, the etheral solution was washed with water, saturated sodium bicarbonate solution, 5% hydrochloric acid, and water a second time. The ether was evaporated and the residue steam distilled until the removal of the nitrobenzene was complete. The aqueous solution was cooled and extracted with ether. The organic extract was washed with water and dried over sodium sulfate. Evaporation of the ether gave 2.0 g. (60%) of a brown oil. The infrared spectrum ("Infracord") of this oil showed strong absorptions at 5.78 and 6.03 .

A solution of 530 mg. of the crude oxalyl ester, .53 ml. of freshly distilled boron trifluoride etherate, .53 ml. of freshly distilled ethanedithiol and 5 ml. of glacial acetic acid was allowed to stand 5 days at room temperature. After the addition of 5 ml. of water to the solution a precipitate slowly formed. The resultant solid was filtered from the mixture and dissolved in ether. The ether was washed with water, dried over sodium sulfate and stripped to give a brown

solid. To a solution of this solid in 5 ml. of absolute ethanol 2 g. of W-2 Raney nickel was added and the mixture was stirred and refluxed for 12 hours. The catalyst was filtered off and washed once with absolute ethanol. Upon evaporation of the filtrate 400 mg. (78%) of a brown solid, m.p. 88-102°, remained. Decolorization of the crude product with Norit, followed by five crystallizations from absolute ethanol gave pure LXXVII, m.p. 100-102°.

Analysis

Calculated for $C_{21}H_{32}O_3$: C, 75.88; H, 9.70. Found: C, 76.3; H, 9.7 (analysis done on .7 mg.).

Infrared spectrum

See Figure 7.

Optical rotation

$[\alpha]_D^{25^\circ}$ + 81.5°

Ultraviolet spectrum

$\lambda_{max.}$ 283 mμ (ε 3190)

13-Acetyl-O-methylpodocarpane(LXXVIII)

A solution of .9 g. of anhydrous aluminum chloride, .7 g. of freshly distilled acetyl chloride and 20 ml. of nitro-

benzene was stirred for 5 minutes at room temperature and a solution of 1.0 g. of O-methylpodocarpane in 10 ml. of nitrobenzene was added. After stirring 20 hours, the reaction was poured into ether and pieces of ice were slowly added. After decomposition of the aluminum chloride the etheral solution was washed with water, saturated sodium bicarbonate solution, 5% hydrochloric acid, and water a second time. The ether was evaporated and the residue steam-distilled until removal of the nitrobenzene was complete. The cooled aqueous solution was extracted with ether, and the organic extracts were washed with water and dried over sodium sulfate. Evaporation of the ether yielded 800 mg. of crude oily product which was chromatographed on 50 g. of alumina. Elution with 1:1 petroleum ether-benzene yielded 600 mg. (50%) of crude LXXVIII, m.p. 67-72°. Five crystallizations from acetone-water followed by two crystallizations from methanol gave pure LXXVIII, m.p. 76-78° with sintering at 75°.

Analysis

Calculated for $C_{20}H_{28}O_2$: C, 79.95; H, 9.14. Found: C; 80.22; H, 9.02.

Infrared spectrum

See Figure 7.

Optical rotation

$[\alpha]_D^{25^\circ}$ + 79.1°

Ultraviolet spectrum

$\lambda_{max.}$ 258 mμ (ε 12200), $\lambda_{max.}$ 319 mμ (ε 5290)

Vouacapenol, Vinhaticol, Dehydroabietol and Erythrodiol

The alcohols were prepared by reduction of the corresponding methyl esters with lithium aluminum hydride by standard methods.[66]

O-Methylpodocarpyl Acetate and Dehydroabietyl Acetate

A solution of ca. 100 mg. of alcohol in 5 ml. pyridine was added to a solution of 2 molar equivalents of acetic anhydride in 5 ml. of pyridine. After the solution was heated one hour on a steam bath 5 ml. of water was added and the solution allowed to cool. After the addition of a large excess of dilute hydrochloric acid, the solution was extracted with ether. The organic extracts were washed with 2N sodium hydroxide and water and dried over sodium sulfate. Evaporation of the ether gave the crude acetates as gums. An attempt was made to determine the purity of the acetates by gas phase

chromatography. However decomposition of the compounds on the column was indicated by the fact that both compounds gave two peaks the relative areas of which were dependent upon the column temperature. A comparison of the areas of the methyl group absorptions in the nuclear magnetic resonance spectra of the compounds indicated that they were at least 95% homogeneous.

Infrared spectra ("Infracord")

Both XCL and XCIV had strong peaks at 5.78μ.

Comparison of the Sandaracopimacic Acids of Edwards and Petru

The samples were supplied by the two main authors.[30,31]

Melting points

Edwards' acid sintered at 155° and melted at 163-168°. Petru's acid sintered at 157° and melted at 167-171°. A 1:1 mixture of the two acids sintered at 160° and melted at 165-170°.

Infrared spectra

The Nujol spectra of the two acids were identical.

Nuclear magnetic resonance spectra

The methyl esters of the two acids had identical spectra.

Hydroxytotarol XCIX

This sample was supplied by Dr. B. Thomas.[21] The compound was a white solid, m.p. 230-231°.

Analysis

Calculated for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.06; H, 10.08.

Infrared spectrum

See Figure 8.

Optical rotation

$[\alpha]_D^{25^\circ}$ (95% ethanol) + 29°

Ultraviolet spectrum

See Figure 4.

SUMMARY

The conversion of podocarpic acid to trans-2-(β-carboxyethyl-) 5,5,9-trimethyl-1-decalone has been achieved and the intermediates characterized. The utilization of these compounds for the synthesis of rimuene and phyllocladene has been made but has not proven successful.

The stereochemistry of rimuene has been elucidated by means of nuclear magnetic resonance and optical rotatory dispersion correlations with systems of known stereochemistry. An analogous approach has revealed that the vinyl group in colensone oxide has the same configuration as in manoyl oxide.

Nuclear magnetic resonance spectral correlations for the establishment of stereochemistry at C_4 in the trans A/B diterpenes have been presented. These correlations and other physical methods have been used to assign the structure and stereochemistry of hydroxytotarol.

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