348. *Diterpenes. Part V.*[1] *Phyllocladene.*

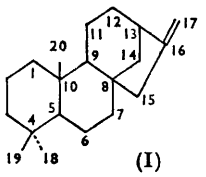
By Lindsay H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis.

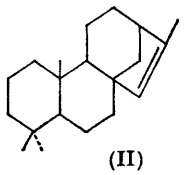
Evidence supporting the structure and determining the absolute configuration of phyllocladene has been obtained by study of the products of permanganate oxidation of phyllocladene and isophyllocladene. The latter has the unusual property of coupling with diazotised 2,4-dinitroaniline.

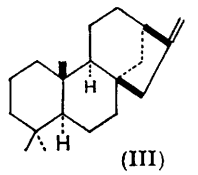
Structures (I) and (II) * were first suggested for phyllocladene and isophyllocladene, respectively, by Brandt [2] and were supported by spectral investigations.[3] In preliminary communications these structures were supported,[4] evidence for their absolute configuration,

* *Nomenclature.*—In these papers we have adopted the principle that the diterpenes biosynthetically related to the steroids and triterpenes should be numbered, as far as possible, in like manner. The numbering, therefore, follows the steroid (" Handbook for Chemical Society Authors," Chemical Society, London, 1961, p. 132) and triterpene systems (Guider, Halsall, and Jones, *J.*, 1953, 3024) and replaces the earlier system put forward by Klyne (*J.*, 1953, 3072). It is also in accordance with the practice adopted elsewhere, cf. cafestol (Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1959, **81**, 2386) and phyllocladene (Grant and Hodges, *Tetrahedron*, 1960, **8**, 261). The new numbering is illustrated in the diagrams at their first appearance in the text.

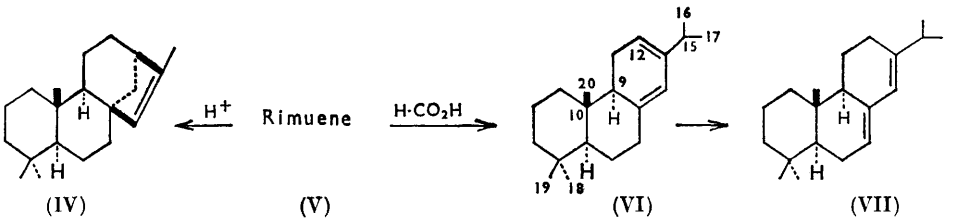
[1] Part IV, *J.*, 1950, 958.
[2] Brandt, *New Zealand J. Sci. Technol.*, (*a*) 1938, **20**, 8; (*b*) 1952, **34**, 46.
[3] Bottomley, Cole, and White, *J.*, 1955, 2624.
[4] Briggs, Cain, Davis, and Wilmshurst, *Tetrahedron Letters*, 1959, No. 8, 8.


(I)


(II)

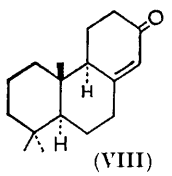

(III)

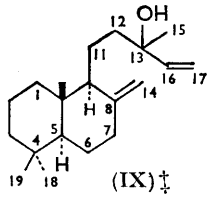
(III) and (IV) respectively, was adduced [5] and confirmed by the inter-relationships of rimuene (V) * to both isophyllocladene (IV) and abieta-7,13-diene (VII).[6] The structure of isophyllocladene has also been confirmed [7] by transformation into podocarp-8(14)-en-

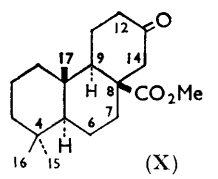


(IV) (V) (VI) (VII)

13-one (VIII) derived from manool (IX) of known configuration [8] and also more recently by synthesis of the derived keto-ester (X).[9] This paper presents details of our evidence [4,5] supporting the structure and configuration of phyllocladene.†


(VIII)


(IX)‡



(X)

The previous chemistry of phyllocladene and isophyllocladene has been adequately reviewed.[10] Uota [11] and Brandt [2b] oxidised phyllocladene with permanganate to the diol (XI; R = R′ = H) and the nor-ketone (XII).

We have characterised the diol as the diacetyl derivative (XI; R = R′ = Ac) by acetylation with acetic anhydride and fused sodium acetate or pyridine,[2b,11] but treatment with warm acetic anhydride in the absence of a catalyst or with glacial acetic acid at 100° gave the monoacetate (XI; R = H, R′ = Ac) of almost identical melting point, a structure supported by its infrared spectrum. Further acetylation with acetic anhydride–pyridine gave the diacetyl compound from which the diol could be recovered by hydrolysis.

Benzoylation of the diol with benzoyl chloride–pyridine at 100° for 4 hours yielded the dibenzoate (XI; R = R′ = Bz), but boiling benzoyl chloride–pyridine during 6½ hours brought about simultaneous dehydration and benzoylation to (XIII).

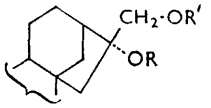
* From Church and Ireland's recent work (*Tetrahedron Letters*, 1961, No. 14, 493) it appears that the previously reported structures of rimuene (Briggs, Cain, and Wilmshurst, *Chem. and Ind.*, 1958, 599; Wenkert and Beak, *J. Amer. Chem. Soc.*, 1961, **83**, 998) are wrong.

† [*Added in proof.*] The total synthesis of phyllocladene has now been achieved by Turner and Gänshirst (*Tetrahedron Letters*, 1961, No. 7, 231).

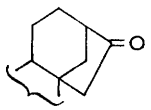
‡ See Hodges and Reed, *Tetrahedron Letters*, 1960, No. 10, 71.

[5] Briggs, Cain, Davis, and Wilmshurst, *Tetrahedron Letters*, 1959, No. 8, 13.
[6] Briggs, Cain, and Cambie, *Tetrahedron Letters*, 1959, No. 8, 17.
[7] Grant and Hodges, *Tetrahedron*, 1960, **8**, 261.
[8] Klyne, *J.*, 1953, 3072.
[9] Church, Ireland, and Marshall, *Tetrahedron Letters*, 1960, No. 17, 1; Turner and Shaw, *ibid.*, 1960, No. 18, 24.
[10] Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 334; Barton, *Quart. Rev.*, 1949, **3**, 36.
[11] Uota, *J. Dept. Agric. Kyushu Imp. Univ.*, 1937, **5** (3), 118.

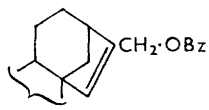
Reduction of the nor-ketone (XII) with sodium borohydride or lithium aluminium hydride produced the nor-alcohol (XIV).



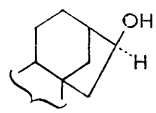
(XI)



(XII)



(XIII)

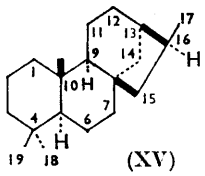


(XIV)

Reduction of the nor-ketone with hydrides would be expected to give the β-alcohol as a consequence of approach of the reducing agent from the less-hindered side.[12] For this reason the stereochemistry shown in (XIV) is preferred. For the same reason [13] it is suggested that α-dihydrophyllocladene [14] produced as the major isomer by catalytic hydrogenation has the stereochemistry as in (XV), which will be referred to as phyllocladane, while the β-isomer,[14] epimeric at C_{16}, will be referred to as epiphyllocladene.

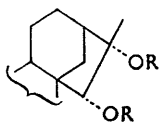
As a model for projected rearrangements in this series the *m*-nitrobenzenesulphonate and toluenesulphonate of the nor-alcohol (XIV) were treated with anhydrous potassium acetate and glacial acetic acid.[15] No rearrangement occurred but the derivatives were unexpectedly oxidised to the nor-ketone (XII).

Brandt [2b] showed that oxidation of isophyllocladene with permanganate gave the diol (XVI; R = H) and the keto-acids (XVII) and (XVIII; R = H). Uota [11] also prepared the keto-acid (XVII) by the same method while Grant and Hodges [7] have prepared all three compounds by different methods.



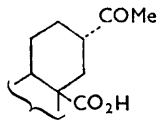
(XV)

; (II) ⟶



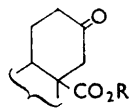
(XVI)

+



(XVII)

+



(XVIII)

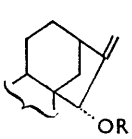
Much of Brandt's work has been repeated, and the oxidation shown to proceed by different pathways depending on the reaction conditions. When isophyllocladene was oxidised with permanganate in acetone–water (10 : 1), an equivalent of 3 atoms of oxygen being used, the diol (XVI; R = H) and the keto-acid (XVII) were the chief products.

In contrast to the 16,17-diol, the 15,16-diol was not acetylated by boiling glacial acetic acid while acetylation with acetic anhydride–pyridine at 100° or under reflux afforded the diacetate (XVI; R = Ac), which smoothly reverted to the diol on alkaline hydrolysis. On benzoylation, however, with benzoyl chloride and pyridine at reflux temperature simultaneous benzoylation and dehydration occurred to give an unsaturated benzoate, formulated as (XIX; R = Bz) from its mode of formation and infrared spectrum. Debenzoylation gave the unsaturated alcohol (XIX; R = H) which, although not obtained pure, had infrared bands consistent with the formula (bands at 3448, *ca.* 1300 and 1096 cm.$^{-1}$ assignable to a secondary alcohol and a strong band at 901 cm.$^{-1}$ corresponding to the grouping C:CH_2).

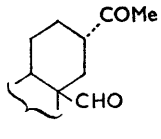
The *cis*-glycol,[16] on further oxidation with sodium periodate, chromium trioxide–pyridine, or lead tetra-acetate yielded the keto-aldehyde (XX), also prepared by Grant and Hodges [7] by the last reaction, while Oppenauer oxidation of the glycol afforded the α-ketol (XXI), also obtained as a minor product together with the D-homo-ketone (XXII) [7] from oxidation with chromium trioxide. As oxidation of a double bond by permanganate

[12] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579; Umland and Jefraim, *ibid.*, p. 2788.
[13] Cf. Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[14] Briggs, *J.*, 1937, 79.
[15] Kent and Wallis, *J. Org. Chem.*, 1959, **24**, 1235; Moriarty and Wallis, *ibid.*, p. 1274.
[16] Cf. Wiberg and Saegebarth, *J. Amer. Chem. Soc.*, 1957, **79**, 2822.

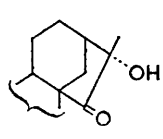
is a *cis*-process and would be expected to occur on the less-hindered α-face of isophyllocladene, the stereochemistry of the diol (XVI; R = H) and the related ketol (XXI) shown is preferred. Periodate oxidation of the α-ketol gave the keto-acid (XVII), identical with Brandt's compound, and prepared also by Grant and Hodges.[7] It gave iodoform with alkaline hypoiodite but did not react with Girard's reagent. It was stable to acid



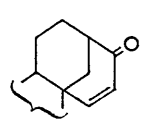
(XIX)



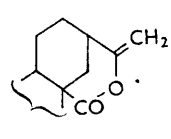
(XX)



(XXI)



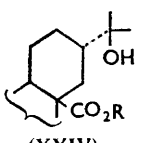
(XXII)



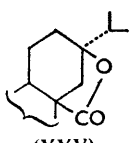
(XXIII)

and base and is thus assigned the equatorial 13α-configuration, epimerisation apparently occurring during its formation. Under forcing conditions, however, with benzoyl chloride in refluxing pyridine the enol lactone (XXIII) was produced wherein both oxygenated carbon atoms must have axial conformations.

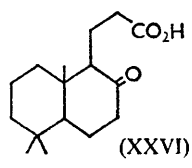
In initial experiments designed to convert phyllocladene into abietane derivatives the keto-acid (XVII) was treated with excess of methylmagnesium iodide to give the hydroxy-acid (XXIV; R = H). In attempted dehydration, treatment of the hydroxy-acid with iodine in boiling toluene afforded a lactone which, from its infrared spectrum (strong band at 1760 cm.$^{-1}$), is formulated as (XXV), probably formed by addition of the carboxyl group to the double bond of an initially formed γδ-unsaturated acid.



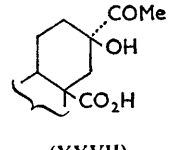
(XXIV)



(XXV)



(XXVI)



(XXVII)

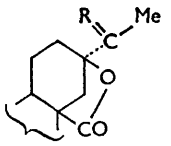
Oxidation of isophyllocladene in dry acetone followed a different pathway, allylic oxidation being at least one phase. Fractionation of the acidic products gave the keto-acids (XVII) and (XVIII; R = H), and a hydroxy-keto-acid identical with material assigned the structure (XXVI) by Brandt.[2b]

The hydroxy-keto-acid exhibited infrared bands at 3414 (OH), 2703 (carboxyl OH), 1739 and 1718 cm.$^{-1}$ (C:O) and gave an iodoform reaction. That it was an α-ketol was shown by oxidation with sodium bismuthate to the keto-acid (XVIII; R = H). The compound is thus (XXVII). It yielded a 2,4-dinitrophenylhydrazone and a semicarbazone with loss of the elements of water. These derivatives had infrared bands at *ca.* 1760 cm.$^{-1}$ indicative of γ-lactones and are thus represented as (XXVIIIb) and (XXVIIIc). The parent γ-lactone (XXVIIIa) (infrared bands at 1761 and 1706 cm.$^{-1}$) was isolated by chromatography of the neutral fraction in one oxidation experiment. It gave derivatives identical with those described above; its lactonic nature was confirmed by direct titration. The free hydroxy-keto-acid (XXVII), with a tertiary hydroxyl group, failed to react with chromium trioxide–pyridine, while the 2,4-dinitrophenylhydrazone had $\lambda_{max.}$ 355 mμ, characteristic of an α-ketol derivative.[17]

That the stereochemistry of the acid (XXVII) is as shown was further suggested by treatment of this compound with acetic anhydride and a trace of perchloric acid. A lactone enol acetate (XXIX) was formed (infrared bands at 1757 and 1656 cm.$^{-1}$) which on hydrolysis regenerated (XXVII). From the absolute configuration of phyllocladene (see later), the carboxyl group must be axial to ring C—the hydroxyl group at $C_{(13)}$ must

[17] Reich and Samuels, *J. Org. Chem.*, 1956, **21**, 68.

also be axial and the acetyl group equatorial. Since the acetyl group is derived from the bridge ring where its $C_{(8)}$ and $C_{(13)}$ bonds must also have been axial, structure (XXVII) must arise from epimerisation at some stage. However, by direct crystallisation of the material obtained from one oxidation of isophyllocladene with permanganate in dry

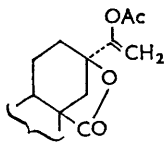


(XXVIII)

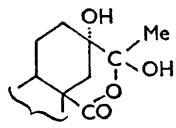
(a) R = O

(b) R = N·NH·$C_6H_3(NO_2)_2$

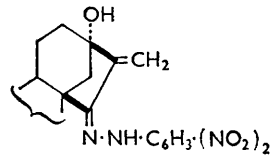
(c) R = N·NH·CO·NH_2



(XXIX)



(XXX)



(XXXI)

acetone, a compound was obtained in which the positions of the hydroxyl and potential acetyl groups are reversed. The product, with infrared bands at 3610 (OH) and 1745 $cm.^{-1}$ (δ-lactone), failed to react with 2,4-dinitrophenylhydrazine in the cold, but in the warm (XXVIIIb) was smoothly produced. The lactonol structure (XXX) is suggested for this compound.

The isolation of this material suggests that hydroxylation is allylic and occurs before fission of the bridge ring. Confirmation of this view was sought by examining the neutral products from permanganate oxidation in dry acetone. Treatment of the crude neutral fraction with Girard's reagent furnished a ketone which was characterised as its 2,4-dinitrophenylhydrazone. Analysis favoured a formula, $C_{20}H_{30}O\}$=N·NH·$C_6H_3(NO_2)_2$, while the ultraviolet spectrum ($\lambda_{max.}$ 378 mμ) indicated an αβ-unsaturated ketone derivative. It is formulated as (XXXI) and presumably arises from a keto-diol on dehydration with Girard's or Brady's reagent.[17]

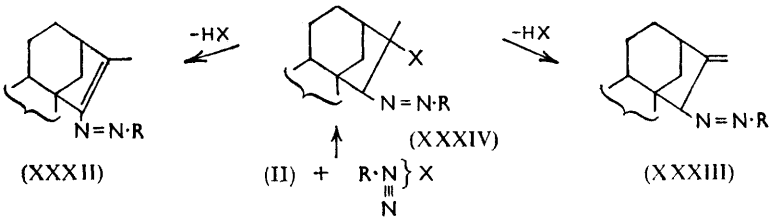
It thus appears that, in dry acetone, allylic attack by a hydroxyl radical or ion is a primary reaction path. A radical mechanism is favoured since decomposition of isophyllocladene ozonide also gives the hydroxy-keto-acid (XXVII).

The rotatory dispersion of the ester (XVIII; R = Me) has a positive Cotton effect, the rotation of the initial peak ($[\alpha]_{320}$ +925°) being almost the same as that of cholestanone ($[\alpha]_{307}$ +959°).[18] The significance of the rotatory dispersion of the isomeric keto-esters of this structure has been discussed [19,20] in connexion with the constitution of cafestol.

Since rimuene can be isomerised to isophyllocladene and also to abieta-7,13-diene [6] of known configuration [8] phyllocladene must possess a *trans*-A/B ring junction. Four isomers of the corresponding keto-ester (XVIII; R = Me) are then possible. By application of the octant rule [21] it was predicted [20] that three isomers would have a negative Cotton effect while one, (X), would have a positive effect. It follows, therefore, from the rotatory dispersion evidence, that (III) represents the absolute configuration of phyllocladene.

During investigations on the chemistry of the bicyclo[3,2,1]octane system, isophyllocladene was found to couple with diazotised 2,4-dinitroaniline to give two isomeric products whose infrared and ultraviolet spectra suggest that they are not geometrical but structural isomers. Formulæ (XXXII) and (XXXIII) are suggested for these isomers arising from the precursor (XXXIV). Further investigation on the scope of this reaction is in progress.

[18] Djerassi, Closson, and Lippman, *J. Amer. Chem. Soc.*, 1956, **78**, 3163.
[19] Davis, Thesis, University of New Zealand, 1957.
[20] Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1959, **81**, 2386; Finnegan and Djerassi, *ibid.*, 1960, **82**, 4342.
[21] Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, Chap. 13.



Experimental

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infrared spectra were measured for potassium bromide discs with a Beckman IR2 instrument and ultraviolet spectra for ethanol solutions with a Beckman DU instrument. Light petroleum was of b. p. 50—60°.

High-pressure Hydrogenation of Phyllocladene: Phyllocladane (XV) *and Epiphyllocladane.*—Phyllocladene (1 g.) in cyclohexane (25 c.c.) was shaken with hydrogen at 2000 lb./sq. in. at 200° for 4 hr. in the presence of Raney nickel. Fractional crystallisation from ethanol gave phyllocladane (α-dihydrophyllocladene) (900 mg.), m. p. 73—74° (recorded [11,14] m. p. 73—74°), and epiphyllocladane (β-dihydrophyllocladene) (80 mg.), m. p. 53—54° (recorded [14] m. p. 55°).

Ozonolysis of Phyllocladene: 17-*Norphyllocladan*-16-*one* (XII).—Phyllocladene was ozonised in chloroform solution according to Uota.[11] The product crystallised when a saturated chloroform solution was poured into methanol, and after recrystallisation from chloroform—methanol it had m. p. 197·8—198°. A satisfactory analysis, however, could not be obtained. The ozonide was very stable but was cleaved by boiling acetic acid containing a little water and zinc dust during 4 hr. The product was chromatographed on alumina and eluted with light petroleum and benzene. The product eluted with benzene contained the nor-ketone (XII), which crystallised from methanol or ethanol in plates, m. p. 101—102° (recorded [11,2b] m. p. 101—102°).

The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in yellow needles, m. p. 193—195° (Found: C, 65·7; H, 7·4. $C_{25}H_{34}N_4O_4$ requires C, 66·05; H, 7·5%).

17-*Norphyllocladan*-16β-*ol* (XIV).—Sodium borohydride (50 mg.) was added to an ethanolic solution of 17-norphyllocladan-16-one (300 mg.) cooled in solid carbon dioxide and the mixture kept in the cold for ½ hr. and then at room temperature for 24 hr. After removal of the solvent *in vacuo* the residue was crystallised twice from ethanol, giving 17-*norphyllocladan*-16β-*ol* (230 mg.) in irregular plates, m. p. 141—142°. The same product was also obtained by reduction with lithium aluminium hydride in refluxing dry ether for 4 hr. (Found: C, 82·5; H, 11·6. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%), $\nu_{max.}$ 3333 cm.$^{-1}$ (OH).

The m-*nitrobenzenesulphonate* was prepared by treating a dry pyridine solution of the nor-alcohol (100 mg.) cooled in solid carbon dioxide with *m*-nitrobenzenesulphonyl chloride (162 mg.) during ½ hr. After the mixture had been kept cold for a further hour and at room temperature for 24 hr. the product, after repeated crystallisations from aqueous ethanol, formed microcrystalline needles, m. p. 110—111° (141 mg.) (Found: C, 65·55; H, 7·7; N, 2·9. $C_{25}H_{35}NO_5S$ requires C, 65·05; H, 7·6; N, 3·0%).

The *toluene*-p-*sulphonate*, similarly prepared, crystallised from aqueous ethanol in microcrystalline needles, m. p. 107—108° (Found: C, 72·1; H, 8·6. $C_{26}H_{38}O_3S$ requires C, 72·5; H, 8·9%).

Attempted Acetolysis of 17-*Norphyllocladan*-16β-*yl* m-*Nitrobenzenesulphonate and Toluene*-p-*sulphonate.*—A solution of the *m*-nitrobenzenesulphonate (140 mg.) and anhydrous potassium acetate (230 mg.) in glacial acetic acid (8 c.c.) was heated at 100° for 10 hr. Most of the solvent was removed *in vacuo* and potassium acetate removed from the cooled solution. The filtrate was poured into water and yielded to ether a gummy residue which crystallised from aqueous ethanol in plates, m. p. and mixed m. p. with 17-norphyllocladan-16-one, 97—98° (identical 2,4-dinitrophenylhydrazone and infrared spectrum).

The same product (20 mg.) was similarly obtained from the toluene-*p*-sulphonate (80 mg.).

Acetylation of Phyllocladane-16,17-*diol.*—(*a*) Acetylation of the diol [11,2b] with acetic anhydride–pyridine or acetic anhydride–fused sodium acetate gave the diacetate, m. p. and mixed m. p. 134—135°.[11,2b]

(*b*) The diol (150 mg.) was heated with glacial acetic acid (5 c.c.) at 100° for 4 hr. After removal of the solvent *in vacuo* the residue was repeatedly crystallised from ethanol, giving plates of phyllocladane-16,17-diol 17-acetate (120 mg.), m. p. 136—137°, depressed in melting point on admixture with the diacetate (Found: C, 75·3; H, 10·55. Calc. for $C_{22}H_{36}O_3$: C, 75·8; H, 10·4%), $\nu_{max.}$ 3448 (OH), 1718 cm.$^{-1}$ (OAc). The recorded [22] m. p. is 142—143·5°.

The same monoacetate was obtained by acetylation of the diol with acetic anhydride alone at 100° for 1 hr. Further acetylation of the monoacetate with acetic anhydride (100°; 2 hr.) gave the diacetate, having no hydroxyl absorption band in the infrared spectrum. Hydrolysis of the diacetate by boiling 2N-methanolic potassium hydroxide afforded the original diol, m. p. and mixed m. p. 174—175°.

Benzoylation of Phyllocladane-16,17-diol.—(*a*) The diol (135 mg.) was heated with benzoyl chloride (1 c.c.) and pyridine (0·5 c.c.) at 100° for 4 hr., and the cooled solution poured on crushed ice. Trituration of the oil so obtained with sodium hydrogen carbonate solution followed by four crystallisations from ligroin gave *phyllocladane-16,17-diol dibenzoate* (205 mg.) as needles, m. p. 157—158° (Found: C, 78·75; H, 7·7. $C_{34}H_{42}O_4$ requires C, 79·3; H, 8·2%).

(*b*) Similar treatment of the diol (200 mg.) with benzoyl chloride (1 g.) in pyridine (2 g.) but under reflux for 6½ hr. afforded *phylloclad-15-en-17-yl benzoate* which, after chromatography on alumina in benzene solution and crystallisation from benzene–ethanol, formed needles, 161—163° (Found: C, 82·3, 82·3; H, 9·4, 9·0. $C_{27}H_{36}O_2$ requires C, 82·6; H, 9·2%), $\nu_{max.}$ 1709 (OBz), 853 cm.$^{-1}$ (C:CH).

Permanganate Oxidation of Isophyllocladene in Aqueous Acetone.—Isophyllocladene (18 g.) in acetone (1·5 l.) and water (25 c.c.) was treated with potassium permanganate (21 g.; 3 atoms of O), portionwise, with stirring at room temperature. When the solution had decolorised (1 hr.) the manganese dioxide was filtered off. The filtrate was treated with sodium dithionite and dilute hydrochloric acid and gave a solid. Acetone was removed from the filtrate and the two solid fractions combined. Partition between ether and aqueous alkali yielded two fractions: (*a*) Acidification of the alkaline solution gave an acid (10·94 g.). Repeated crystallisation from 50% aqueous ethanol gave irregular plates (7·14 g.) of the keto-acid (XVII), m. p. and mixed m. p. with Brandt's sample, 175—176·5°. (*b*) Removal of the ether from the neutral fraction and crystallisation from ethanol gave crystals (2·64 g.) which were further purified by treatment with boiling light petroleum. The insoluble fraction, on recrystallisation from ethanol–ethyl acetate, had m. p. and mixed m. p. with phyllocladane-15α,16-diol prepared by Brandt, 228—229° (1·88 g.).

In a similar experiment with isophyllocladene (4·63 g.) and potassium permanganate (3·58 g., 2 atoms of O) in 90% aqueous acetone (200 c.c.), the products obtained were isophyllocladene (818 mg.), phyllocladane-15α,16-diol (540 mg.), an acidic fraction (2·37 g.), and, by use of Girard's reagent, a neutral ketonic fraction.

Permanganate Oxidation of Isophyllocladene in Anhydrous Acetone.—(i) Isophyllocladene (16 g.) in dry acetone (2·5 l.; distilled from permanganate) was stirred at room temperature while potassium permanganate (19 g., 100 mesh) was added in small quantities as consumed. When the reaction was complete the solution was neutralised with 2N-sulphuric acid and most of the acetone distilled off. The product was dissolved in dry benzene, the solution partially evaporated to remove water, and the remainder chromatographed on alumina (Grade I). Unchanged isophyllocladene (83 mg.) was removed by elution with benzene. Elution with benzene–ether (20 : 1) gave a trace of oil while benzene–ether (1 : 1) gave a gel (1·34 g.) which could not be crystallised. Elution with benzene–acetone (20 : 1) afforded the *lactone* (XXVIIIa) of 13α-acetyl-13β-hydroxypodocarpane-8-carboxylic acid, crystallising from alcohol in lustrous plates (yield, 360 mg.), m. p. 175—176° (Found: C, 75·15; H, 9·9. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 1761 (γ-lactone), 1706 cm.$^{-1}$ (C:O). The *semicarbazone*, crystallised from ethanol, had m. p. 281° (Found: C, 67·7; H, 9·1; N, 11·3. $C_{21}H_{33}N_3O_3$ requires C, 67·2; H, 8·9; N, 11·2%), $\lambda_{max.}$ 230 mμ (log ε 4·92). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in yellow needles, m. p. 284—285° (Found: C, 62·4; H, 7·0; N, 11·2. $C_{26}H_{34}N_4O_6$ requires C, 62·6; H, 6·9; N, 11·2%), $\nu_{max.}$ 1761 cm.$^{-1}$ (γ-lactone).

Continued elution with benzene–methanol (10 : 1) gave *13α-acetyl-13β-hydroxypodocarpane-8-carboxylic acid* (XXVII) crystallising from light petroleum (b. p. 100—110°)–ethyl acetate in needles (7·97 g.), m. p. 212—213°. The acid decomposed when dried (P_2O_5) at 100° in a vacuum [Found on sample dried (P_2O_5) at room temperature in a vacuum: C, 69·25, 69·35;

[22] Henderson and Hodges, *Tetrahedron*, 1960, **11**, 226.

H, 9·6, 9·6. $C_{20}H_{32}O_4,\frac{1}{2}H_2O$ requires C, 69·5; H, 9·6. Found on sample dried (P_2O_5) at 40° under vacuum: C, 70·65; H, 9·8. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%], $\nu_{max.}$ 3571, 3378 (OH), 1739, 1709 cm.$^{-1}$ (C:O). The melting point was not depressed by a compound, m. p. 215°, reputed by Brandt [2b] to have formula (XXVI). The semicarbazone and 2,4-dinitrophenylhydrazone proved to be identical (mixed m. p. and infrared spectra) with the respective perivatives prepared from the lactone (XXVIIIa). Brandt,[2b] however, records m. p. 237—238° for the semicarbazone. Both the hydroxy-keto-acid and Brandt's acid, m. p. 215°, gave the iodoform test but the expected dicarboxylic acid could not be crystallised. Titrated in 75% ethanol with potassium hydroxide solution to a Phenol Red end-point it gave an equivalent weight of 326 ($C_{20}H_{32}O_4$ requires equiv., 336).

No further material could be eluted from the column.

(ii) Potassium permanganate (14·68 g., 3 atoms of O) was added in portions, as consumed, to a stirred solution of isophyllocladene (12·67 g.) in purified, dry acetone (1 l.) during 48 hr. Manganese dioxide was filtered off and washed with water. The aqueous filtrate on acidification gave mixed acids from which the hydroxy-keto-acid (XXVII), m. p. and mixed m. p. 213—214°, was obtained in needles [from light petroleum (b. p. 100—110°)–ethyl acetate].

Acetone was removed from the original filtrate and the material distributed between ether and dilute sodium hydroxide solution. Acidification of the aqueous alkaline layer afforded acidic material (3·29 g.) which, when crystallised successively from ethyl acetate–ligroin and aqueous ethanol, gave the keto-acid (XVII), m. p. and mixed m. p. with Brandt's material, 173·5—175·5°.

The neutral ethereal solution was reduced to a pale yellow oil (5·87 g.). Treatment with Girard's reagent T in ethanol–acetic acid afforded carbonyl (3·69 g.) and non-carbonyl (1·84 g.) fractions. The carbonyl fraction contained a small amount (330 mg.) of material soluble in warm aqueous alcoholic alkali which was presumably lactonic. The neutral solution gave an oil which could not be crystallised but from which 13-*hydroxyphyllocladane*-16-*en*-15-*one* 2,4-*dinitrophenylhydrazone* (XXXI) could be obtained in red needles, m. p. 169—171° (from chloroform–methanol) (Found: C, 65·1; H, 6·7; N, 11·75. $C_{26}H_{34}N_4O_5$ requires C, 64·7; H, 7·1; N, 11·6%), $\lambda_{max.}$ 378 mμ (log ε 4·46), $\nu_{max.}$ 3509, 3356 (OH, NH), 920 cm.$^{-1}$ (C:CH_2).

The neutral non-carbonyl fraction was further purified by crystallisation from ethanol–ethyl acetate or by chromatography on alumina followed by crystallisation from methanol to give phyllocladane-15α,16-diol, m. p. and mixed m. p. 226·5—228·5°.

(iii) Isophyllocladene (5·44 g.) in dry acetone (400 c.c.) was treated with potassium permanganate (6 × 2·11 g.; each equivalent to 1 atom of O), the times between additions being 10, 15, 20, 225, and 400 min., severally. When worked up as described for oxidation in aqueous acetone, except that both fractions were treated with sodium dithionite and hydrochloric acid, the oxidation product amounted to 5·51 g.

One portion gave needles of the *dihydroxy-lactone* (XXX), m. p. 235—237° (from ethyl acetate–ethanol) (Found: C, 71·75; H, 9·7. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%).

The dihydroxylactone did not react with Brady's reagent in the cold but when heated it formed the 2,4-dinitrophenylhydrazone (XXVIIIb), m. p. and mixed m. p. 280—282°.

The remaining material was combined with the acidic products derived from other permanganate oxidations of phyllocladene (19 g. in all) and systematically fractionated. The material, dissolved in ethanol (250 c.c.) and acetic acid (25 c.c.), was treated with Girard's reagent T (19·65 g.) at 100° for 1½ hr. Water (500 c.c.) was added and the solution extracted with ether (3 × 200 c.c.). The ethereal fraction yielded to 2% sodium hydroxide solution, followed by acidification, amorphous acidic material (14·67 g.).

The aqueous fraction, warmed with hydrochloric acid for 1 hr., liberated ketonic material. Successive crystallisations from benzene, light petroleum–ethyl acetate, and aqueous ethanol gave the hydroxy-keto-acid (XXVII), m. p. 208—211°. Fractional crystallisation of the mother liquors from light petroleum–ethyl acetate afforded 13-oxopodocarpane-8-carboxylic acid (XVIII; R = H), m. p. 185—187°, mixed m. p. 184·5—185·5° with Brandt's material [2b] of m. p. 182—183°. The infrared spectrum was anomalous with different results in different media (Nujol, saturated and dilute carbon tetrachloride solutions) indicating, particularly in saturated carbon tetrachloride solution, that it occurs in part as the corresponding lactonol form.

The methyl ester, prepared with diazomethane, crystallised from aqueous methanol in plates, m. p. 153·5—155·5° (Found: C, 74·8; H, 9·8. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·9%), $\nu_{max.}$ 1721 cm.$^{-1}$ (C:O). Grant and Hodges [7] record m. p. 159—161°.

The amorphous acidic material, when again treated with Girard's reagent T, gave a further 360 mg. of material recovered from the aqueous layer. The residue, on crystallisation from aqueous ethanol and ethyl acetate–light petroleum, yielded the keto-acid (XVII), m. p. and mixed m. p. 173—175°.

Ozonolysis of Isophyllocladene.—Isophyllocladene was ozonised in carbon tetrachloride solution according to Uota.[11] The product was isolated by pouring a saturated carbon tetrachloride solution into 5 volumes of light petroleum (b. p. 40—75°) but could not be crystallised. It was purified by precipitation as above four times. Although a satisfactory analysis could not be obtained the analysis (Found: C, 67·40, 67·36; H, 9·04, 9·22%) did suggest a structure other than a simple ozonide (Calc. for $C_{20}H_{32}O_5$: C, 68·15; H, 9·15%).

It was decomposed by adding a carbon tetrachloride solution to a 5% solution of hydrogen peroxide in acetic acid at reflux temperature. When worked up in the usual way a tarry acid (630 mg.) was obtained which, when treated with 2,4-dinitrophenylhydrazine, gave (XXVIIIb), m. p. and mixed m. p. with that derived from the permanganate oxidation of isophyllocladene 283°.

Oxidation of Isophyllocladene with Peracetic Acid.—Isophyllocladene (330 mg.) was added to a solution of peracetic acid, prepared by warming glacial acetic acid (18 c.c.) with hydrogen peroxide (100 vol.; 6 c.c.) for 1 hr. The solution was warmed for 5 hr. and left at room temperature for 20 hr. The solvent was removed *in vacuo* at 100° and water added to the residue. The solid recovered after trituration with light petroleum formed cubes (from aqueous ethanol), m. p. and mixed m. p. with phyllocladane-15α,16-diol, 228—230°.

Acetylation of Phyllocladane-15α,16-diol (XVI; R = H).—The diol (210 mg.) was heated with acetic anhydride (2 c.c.) and pyridine (1 c.c.) at 100° for 7 hr. Chromatography of the product in benzene gave a fraction which, on crystallisation from ethanol–ligroin, gave *phyllocladane-15α,16-diol diacetate* as large prisms, m. p. 225—226° (Found: C, 73·8; H, 9·8. $C_{24}H_{38}O_4$ requires C, 73·8; H, 9·8%), also obtained by acetylation of the diol with the same reagents under reflux for 5 hr.

Heating the diacetate under reflux with 2N-methanolic potassium hydroxide afforded the original diol, m. p. and mixed m. p. 232—235°.

Benzoylation of Phyllocladane-15α,16-diol.—The diol (120 mg.) was heated with benzoyl chloride (1 c.c.) and pyridine (0·5 c.c.) at 100° or at reflux temperature for 3 hr. Chromatography of the product in benzene and crystallisation from alcohol in both cases formed *phylloclad-16-en-15α-yl benzoate* (XIX; R = Bz) as large plates (140 mg.), m. p. 130—131° (Found: C, 82·6; H, 9·0. $C_{27}H_{36}O_2$ requires C, 82·6; H, 9·2%), $\nu_{max.}$ 1712 (OBz), 903 cm.$^{-1}$ (C:CH_2).

Hydrolysis of the unsaturated monobenzoate (135 mg.) with 2N-methanolic potassium hydroxide and crystallisation of the product from aqueous methanol gave large plates of phylloclad-16-en-15α-ol (96 mg.), m. p. 110—111°, $\nu_{max.}$ 3448 (OH), 901 cm.$^{-1}$ (C:CH_2). A satisfactory analysis, however, could not be obtained.

Oxidation of Phyllocladane-15α,16-diol (XVI; R = H).—(a) *With chromium trioxide–pyridine.* The diol (300 mg.) in pyridine (4 c.c.) was added to the yellow slurry prepared from chromium trioxide (360 mg.) and pyridine (3 c.c.), the mixture kept at room temperature for 12 hr., and saturated oxalic acid solution then added. The precipitate was crystallised from aqueous ethanol, giving 13α-acetyl-8-homopodocarpan-8-al (XX) (250 mg.) in large rectangular plates, m. p. 137—138° (recorded [7] m. p. 138—140°) (Found: C, 79·2; H, 10·5. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·6%).

The *bis-2,4-dinitrophenylhydrazone* crystallised from nitrobenzene–ethanol in yellow needles, m. p. 290—291° (Found: C, 57·1; H, 5·8; N, 16·0. $C_{32}H_{40}N_8O_8$ requires C, 57·8; H, 6·1; N, 16·9%).

Isophyllocladene D-*homoketone.* Cyclization of the keto-aldehyde at reflux temperature [7] afforded the D-homo-ketone (XXII), m. p. 113—114° (recorded [7] m. p. 115—115·5°) (Found: C, 84·2; H, 10·7. Calc. for $C_{20}H_{30}O$: C, 83·9; H, 10·6%), $\nu_{max.}$ 1681 and 1608 cm.$^{-1}$ (C:C·C:O).

Its *2,4-dinitrophenylhydrazone* crystallised from chloroform–methanol in orange needles, m. p. 183—184° (Found: C, 66·7; H, 7·1. $C_{26}H_{34}N_4O_4$ requires C, 66·9; H, 7·35%).

(b) *With chromium trioxide–sulphuric acid.* The diol (160 mg.) was oxidised by 8N-chromium trioxide–sulphuric acid as described by Grant and Hodges,[7] and the product isolated by pouring into water. Direct crystallisation of the flocculent precipitate from 80% aqueous methanol and recrystallisation from aqueous ethanol gave the keto-aldehyde (XX) (120 mg.),

m. p. and mixed m. p. 137—138°. The mother liquors were poured into water and the precipitate chromatographed in benzene solution. Fractions eluted with benzene afforded the D-homo-ketone (XXII) (15 mg.), which, after crystallisation from aqueous methanol, had m. p. and mixed m. p. 111—112°. The fractions eluted with benzene–ether (1 : 1) contained 16-hydroxyphyllocladan-15-one (XXI) (25 mg.), needles, m. p. 141—142°, from aqueous methanol (recorded [7] m. p. 144—146°) (Found: C, 78·5; H, 10·3. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·6%). The final fractions eluted with ether gave unchanged diol (40 mg.).

(c) *With periodate.* Sodium periodate solution (20 c.c.; 0·3M) was added to a solution of the diol (860 mg.) in ethanol (100 c.c.) at room temperature. A fine precipitate slowly appeared. After 3 days the material was crystallised repeatedly from 80% ethanol, giving the keto-aldehyde (XX) in large rectangular plates, m. p. 132—134° (yield 92%).

(d) *By the Oppenauer method.* A mixture of the diol (120 mg.) and aluminium isopropoxide (250 mg.) in purified acetone (30 c.c.) and " AnalaR " benzene (40 c.c.) was heated under reflux for 6 hr. with exclusion of moisture. Most of the solvent was removed, more benzene added, and the filtered solution washed with 10% sulphuric acid and then repeatedly with water. The gum recovered from the dried solution was chromatographed in benzene solution. Fractions eluted with ether contained the ketol (XXI) (98 mg.), which crystallised from aqueous methanol in needles, m. p. and mixed m. p. 142—143°.

Periodic Acid Oxidation of 16-Hydroxyphyllocladan-15-one.—The ketol (60 mg.) in ethanol (2 c.c.) was heated under reflux with 50% periodic acid (1 c.c.) for ½ hr. and the cooled solution then poured into water. Crystallisation from aqueous methanol gave the keto-acid (XVII) (40 mg.), m. p. and mixed m. p. 174—175·5°.

Enol Lactone (XXIII) *from 13α-Acetylpodocarpane-8-carboxylic acid.* The acid (190 mg.) was heated under reflux with benzoyl chloride (2 c.c.) and pyridine (6 c.c.) for 2½ hr. Contact with crushed ice and repeated trituration with water gave an oily solid which, after repeated crystallisation from ethanol, afforded the *enol lactone* (XXIII) in rods, m. p. 213—215° (Found: C, 79·1; H, 9·9. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%), $\nu_{max.}$ 1748 (δ-lactone), 1650, 907 cm.$^{-1}$ (C:CH_2).

Reaction of 13α-Acetylpodocarpane-8-carboxylic Acid with Methylmagnesium Iodide.—A solution of the acid (1·25 g.) in dry ether (60 c.c.) was added to one of methylmagnesium iodide (15 moles) [prepared from methyl iodide (8·88 g.) and magnesium (1·59 g.) in dry ether (30 c.c.)]. The mixture was heated under reflux for 38 hr. and the excess of the reagent decomposed with dilute sulphuric acid. The hydroxy-acid (XXIV; R = H) was obtained in quantitative yield and formed plates, m. p. 184—185° (from aqueous ethanol) (Found: C, 75·1; H, 10·7. $C_{21}H_{36}O_3$ requires C, 75·0; H, 10·8%), $\nu_{max.}$ 3484, 3165 (OH), 1698 cm.$^{-1}$ (C:O).

Lactonisation of the Hydroxy-acid (XXIV; R = H).—The hydroxy-acid (40 mg.) was heated under reflux with toluene (5 c.c.) containing a little iodine for 5 hr. Treatment with sodium thiosulphate solution, removal of solvent, and crystallisation from ethanol yielded the lactone (XXV) (32 mg.) as needles, m. p. 190—191° (Found: C, 79·2; H, 10·7. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%), $\nu_{max.}$ 1761 cm.$^{-1}$ (γ-lactone).

Methyl 15-Hydroxyabietane-8-carboxylate * (XXIV; R = Me).—The hydroxy-acid (XXIV; R = H) (365 mg.) in ether (dried over sodium) was treated at 0° with excess of ethereal diazomethane and the mixture kept at room temperature for 12 hr. This viscous liquid obtained was purified by repeated distillation *in vacuo*. The *ester* (372 mg.) was obtained as a viscous liquid, b. p. 170—175°/0·1 mm. (Found: C, 75·2; H, 10·6. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%), $\nu_{max.}$ 3521, 1149 (tertiary OH), 1724 cm.$^{-1}$ (C:O).

Dehydrogenation of the Hydroxy-acid (XXIV; R = H).—The hydroxy-acid (770 mg.) was heated with 10% palladium–charcoal catalyst (750 mg.) at 320—350° for 4 hr. A light-petroleum solution of the reaction mixture was chromatographed on alumina. A band exhibiting strong purple fluorescence in ultraviolet light was eluted to give a colourless, crystalline solid (34 mg.). From this retene *s*-trinitrobenzoate was obtained, which, after repeated crystallisation from ethanol, formed needles, m. p. and mixed m. p. 138°.

Action of Acetic Anhydride–Perchloric Acid on the Hydroxy-keto-acid (XXVII).—Perchloric acid (60%; 1 drop) was added to a suspension of the acid (650 mg.) in acetic anhydride (4 c.c.), and the mixture warmed briefly and then kept at room temperature for 2 hr. Treatment with dilute sodium carbonate solution (20 hr.) gave a product (770 mg.) which yielded the *enol lactone acetate* (XXIX) in long needles, m. p. 221—222° (from methanol) (Found: C, 73·6;

* It is suggested that abietane be represented with the isopropyl group in the β-position.

H, 8·6. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·9%), $\lambda_{max.}$ 225·5 mμ (log ε 3·27), $\nu_{max.}$ 1757 (C:O), 1656, 887 cm.$^{-1}$ (C:CH_2).

Hydrolysis of the Enol Lactone Acetate (XXIX).—The enol lactone acetate (120 mg.) was heated under reflux with potassium hydroxide (100 mg.) in ethanol (20 c.c.) for 3½ hr. Neutralisation, removal of solvent, addition of water, and crystallisation from aqueous ethanol, yielded the hydroxy-keto-acid (XXVII) (quantitative yield) in pointed plates, m. p. 206·5—208·5°, undepressed on admixture with the original acid. The identity was confirmed by combustion, infrared spectrum, and preparation of the 2,4-dinitrophenylhydrazone.

Sodium Bismuthate Oxidation of the Hydroxy-keto-acid (XXVII).—The hydroxy-keto-acid (140 mg.), in glacial acetic acid (10 c.c.), was treated with 1 mole of sodium bismuthate (calc. as 85% pure) at 80° for 6 hr. The bismuth was precipitated with an equivalent amount of phosphoric acid, the filtrate evaporated, and the acid crystallised from aqueous alcohol. The keto-acid (XVIII; R = H) (yield 74 mg.) had m. p. and mixed m. p. 184° (Found: C, 74·05; H, 9·6. Calc. for $C_{18}H_{28}O_3$: C, 73·9; H, 9·65%). The semicarbazone, m. p. 232—233° (Found: C, 64·9; H, 8·5; N, 11·6. Calc. for $C_{19}H_{31}N_3O_3$: C, 65·3; H, 8·9; N, 12·0%), shows maximal absorption at 230 mμ (log ε 4·19). The 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate–ethanol in rectangular orange plates, m. p. 231° (Found: C, 61·25; H, 7·1; N, 12·1. $C_{24}H_{32}N_4O_6$ requires C, 61·0; H, 6·8; N, 11·9%).

Isomeric 2,4-*Dinitrophenylazophyllocladenes* (XXXII) *and* (XXXIII).—Isophyllocladene (1 g.) was treated with diazotised 2,4-dinitroaniline (5 g.) in glacial acetic acid. The red amorphous solid (1·26 g.) formed by pouring the mixture into water was chromatographed on alumina in benzene solution. The forerunnings gave α-2,4-*dinitrophenylazophyllocladene* in orange needles (25 mg.), m. p. 213—215° (from ligroin) (Found: C, 66·9; H, 7·7; N, 11·8. $C_{26}H_{34}N_4O_4$ requires C, 66·9; H, 7·4; N, 12·0%), $\lambda_{max.}$ 259 (log ε 4·12) and 373 mμ (log ε 4·46).

The later eluant from the chromatogram afforded β-2,4-*dinitrophenylazophyllocladene*, red plates (12 mg.), m. p. 225° (from ligroin) (Found: C, 67·3; H, 7·6; N, 12·1), $\lambda_{max.}$ 256, 260, and 383 mμ (log ε 4·262, 4·259, and 4·325 respectively).

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