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THE STRUCTURE OF ISOPHYLLOCLADENE

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Abstract—8β-Carboxy-13-oxopodocarpane (VIa) has been prepared from isophyllocladene and its rotatory dispersion curve examined. Isophyllocladene has also been converted to 13-oxopodocarp-8(14)-ene (XIII), identical with a sample prepared from manool. Thus the structure of isophyllocladene is established as I.

THE structure I was first proposed for isophyllocladene by Brandt,[1] on the evidence of a series of oxidations and dehydrogenations. The nature of ring D was further confirmed[2] by the demonstration that the *nor*-ketone derived from phyllocladene was present in a five-membered ring and that there was only one —CH_2-grouping adjacent to the carbonyl. No evidence has been presented to confirm the gem-dimethyl grouping at C_4 or the angular methyl at C_{10}, though it seems probable that these are placed as shown. Steric factors require ring D to be attached in a *cis* manner to ring C but nothing further is proven about the stereochemistry of the molecule.

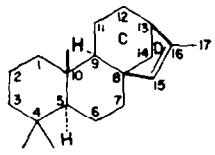
It appeared to us that the rotatory dispersion curve of the *bisnor*-keto-acid VIa (first obtained by Brandt) might cast some light on this problem and this paper describes the degradation of isophyllocladene to this compound and other products.

Treatment of isophyllocladene with osmium tetroxide gave rise to the known diol II. This was oxidized with either chromium trioxide in pyridine or 8 N chromic acid/sulphuric acid, when a mixture of products resulted. The α-ketol (VII) was formed in very small yield, the major product being an α,β-unsaturated ketone (VIII) obviously derived from the intramolecular cyclization of the keto-aldehyde (III). This had I.R. absorption in CS_2 at 1677 cm^{-1} indicative of a carbonyl group in a six-membered ring, and U.V. adsorption at 241 mμ $\varepsilon = 7800$. Wolff–Kishner reduction gave rise to a hydrocarbon most plausibly represented by IX, which, on hydrogenation, produced D-homo-dihydrophyllocladene, a new tetracyclic system.

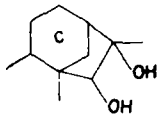
In view of the very low yield of α-ketol (VII), splitting of the diol (II) with lead tetracetate was attempted. The resulting keto-aldehyde (III) was readily obtained; as expected, treatment with sodium hydroxide, silver oxide or even chromatography on alumina caused its cyclization to VIII. Oxidation of III with chromium trioxide in acetic acid yielded a mixture of products. The acidic fraction was treated with hydrochloric acid in methanol in order to ensure complete epimerization at C_{13}. The major product was the known keto-acid (IV), together with a small amount of the *bisnor*-keto-acid (VIa). The neutral material was separated, subjected to further oxidation and the process repeated. Finally, chromatography of the residual neutral fraction gave the epimeric keto-aldehyde (XI).

[1] C. W. Brandt, *N. Z. J. Sci. Technol.* **34B**, 46 (1952).
[2] W. Bottomley, A. R. H. Cole and D. E. White, *J. Chem. Soc.* 2624 (1955).

This structure was confirmed by warming XI with sodium hydroxide when the unsaturated ketone (VIII) was produced. It should be noted that XI could be chromatographed on alumina while its epimer (III) was partially cyclized under these conditions.



I



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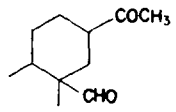

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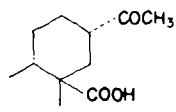
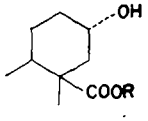
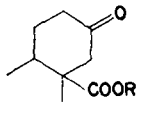


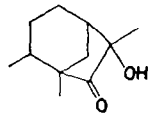
IV



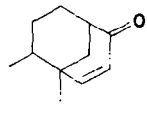
V a. R=H
b. R=Me



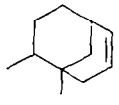
VI a. R=H
b. R=Me



VII



VIII



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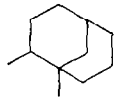

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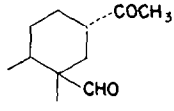
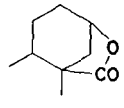


XI



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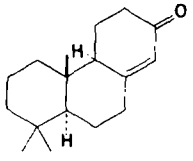
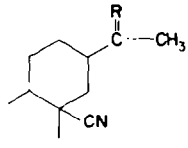
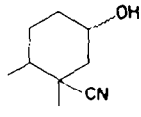


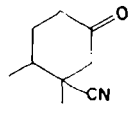
XIII



XIV a R=NOAc
b R=NOH
c R=O



XV



XVI

When the keto-acid (IV), the major product of the previous oxidation, was further oxidized with pertrifluoroacetic acid and the product hydrolysed, the trans-hydroxy acid (Va) was formed. This was readily oxidized to the required *bisnor*-keto-acid (VIa). The methyl ester (Vb) was not obtained crystalline, but a qualitative comparison of its rate of hydrolysis with that of VIb, confirmed the placing of the carbonyl group γ- to the carboxyl.[3]

The rotatory dispersion curve of VIb was determined and found to be identical with that of the keto-acid prepared independently by Briggs *et. al.*[4] A full discussion of the stereochemical possibilities for phyllocladene, based on the positive Cotton effect of VIb has now been published.[5]

[3] C. Djerassi and A. E. Lippman, *J. Amer. Chem. Soc.* **77**, 1825 (1955).
[4] L. H. Briggs, Personal communication.
[5] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).

Unequivocal proof of the structure of phyllocladene must ultimately rest on the establishment of relationship to a substance of known absolute stereochemistry. The most likely compound for this comparison would seem to be unsaturated ketone XIII derived from manool. With this in mind the silver salt of V was subjected to a Hunsdiecker degradation, but the only product isolated was the lactone XII. This substance was also formed as a sole product by treatment of VIa with sodium borohydride, when the carboxylate anion must control the stereochemistry of the reduction. It was thought likely that pyrolysis of the acetate of V would lead to elimination of acetic acid, possibly followed by decarboxylation, but the lactone XII was again produced by this procedure in high yield.

This correlation has been established by the following sequence of reactions. The dioxime of the keto-aldehyde (III), on treatment with acetic anhydride yielded XIVa, which deacetylated during chromatography on alumina giving XIVb. The parent keto-nitrile (XIVc) was regenerated and subjected to the action of pertrifluoroacetic acid. After hydrolysis, the β-hydroxy-nitrile XV was produced. This did not melt sharply and was almost certainly a mixture of 13-hydroxy isomers, epimerization taking place during the preceding reactions. Oxidation of the mixture gave 8β-cyano-13-oxopodocarpane (XVI) as sole product. When this substance was distilled under vacuum from powdered potassium hydroxide, hydrogen cyanide was eliminated, giving 13-oxopodocarp-8(14)-ene (XIII), identical with a sample prepared from manool.[6]

Hence isophyllocladene must possess the "normal" *trans* A/B ring junction, since the reactions described above do not permit the possibility of inversion at these centres. As Djerassi[5] has already pointed out that only one structure possessing this ring fusion is permitted by rotatory dispersion evidence, isophyllocladene must be represented by I.

EXPERIMENTAL

Rotations were measured in chloroform at room temp unless otherwise stated. M.p's were taken on a Kofler block and are corrected. The alumina used for chromatography had activity II. Light petroleum refers to the fraction with b.p. 60–80°.

Dihydro-15, 16-*dihydroxyphyllocladene* (II). Isophyllocladene (480 mg) was allowed to react with osmium tetroxide (460 mg) in ether (50 ml) and pyridine (5 ml) for 24 hr at 0°. The solution was then saturated with hydrogen sulphide, filtered, and the product crystallized from benzene as flat needles (420 mg) of dihydro-15,16-dihydroxyphyllocladene, m.p. 234–235°, with sublimation (lit,[1] m.p. 235°), $[\alpha]_D$ +7° (*c*, 0·6). (Found: C, 78·1; H, 11·0. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%.)

Chromic acid oxidation of dihydro-15,16-*dihydroxyphllocladene.* II (320 mg) in acetone (100 ml) was oxidized with 8N chromic acid/sulphuric acid in the usual way.[7] The product was adsorbed from light petroleum–benzene (1 : 1) on alumina (50 g). Elution with benzene gave the unsaturated D-homo-*ketone* (VIII) as needles from aqueous methanol, m.p. 115–115·5° $[\alpha]_D$ −152° (*c*, 1·2). (Found: C, 83·85; H, 10·6. $C_{20}H_{30}O$ requires: C, 83·85; H, 10·55%). Further elution with ether gave *dihydro*-16-*hydroxy*-15-*oxophyllocladene* (VII) as needles (40 mg) from aqueous methanol, m.p. 144–146°. (Found: C, 76·6; H, 10·15. $C_{20}H_{32}O_2 \cdot \frac{1}{2}CH_3OH$ requires: C, 76·8; H, 10·7%.) Infra-red absorption in CCl_4 at 1734 cm^{-1}.

Wolff–Kishner reduction of VIII. The D-*homo*-ketone (VIII, 60 mg) was heated under reflux with diethylene glycol (20 ml) and hydrazine (1 ml, 95%) for 1 hr. Potassium hydroxide (2 g) was then added and the temp of the solution raised to 205° by distillation. The reaction was maintained at this temp for 12 hr, the product extracted with light petroleum and crystallized from methanol as needles

[6] J. R. Hosking, *Ber. Dtsch. Chem. Ges.* **69**, 780 (1936).
[7] A Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2543 (1953).

(45 mg) of IX, m.p. 92–93·5°, $[\alpha]_D$ −14·5° (*c*, 1·2). (Found: C, 88·5; H, 11·5. $C_{20}H_{32}$ requires: C, 88·15; H, 11·85%.) D-homo-*dihydrophyllocladene* (X). IX (12·1 mg) was hydrogenated using Adams' catalyst in acetic acid. The product crystallized as needles (11 mg) of X from methanol, m.p. 118–119°, $[\alpha]_D$ +4° (*c*, 0·9). (Found: C, 87·7; H, 12·2. $C_{20}H_{34}$ requires: C, 87·5; H, 12·5%).

13*β*-*Acetyl*-8*β*-*aldehydopodocarpane* (III). The diol II (308 mg) was heated under reflux with lead tetracetate (750 mg) in benzene (100 ml) for 1 hr. The mixture was then poured into water, the product extracted with benzene and crystallized from light petroleum as long plates (195 mg) of 13*β*-*acetyl*-8*β*-*aldehydopodocarpane*, m.p. 138–140°, $[\alpha]_D$ −39° (*c*, 0·9). (Found: C, 79·15; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.) Infra-red absorption in CCl_4 at 1713 (C=O), 2847 and 2869 cm^{-1} (C—H).

Chromic acid oxidation of III. III (709 mg) in acetic acid (70 ml) was allowed to react with chromium trioxide (185 mg) for 12 hr. The acidic product (210 mg) was separated and the neutral material (480 mg) treated as before with chromium trioxide. This process of oxidation was repeated (usually 3 times in all) until the acid being formed was no longer crystalline. The combined acidic fractions were dissolved in methanol containing 10% of hydrochloric acid and heated under reflux for 3 hr. The product was adsorbed from benzene on silica gel (100 g) and eluted with benzene–chloroform (2 : 3) as plates (340 mg) of 13α-acetyl-8*β*-carboxypodocarpane (IV) from light petroleum–chloroform, m.p. 174·5–175° (lit,[1] m.p. 176°), $[\alpha]_D$ −26° (*c*, 1·3). (Found: C, 75·25; H, 10·15. $C_{20}H_{32}O_3$ requires: C, 74·95; H, 10·05%.) Further elution with chloroform–methanol (19 : 1) gave another acid (20 mg) from light petroleum, m.p. 185–186°, undepressed on admixture with an authentic specimen of VIa.

The residual neutral material from the oxidation was adsorbed from light petroleum on alumina. Elution with benzene gave 13α-*acetyl*-8*β*-*aldehydopodocarpane* (XI) as plates (12 mg) from aqueous methanol, m.p. 84·5–86°, $[\alpha]_D$ −14° (*c*, 0·8). Found: C, 78·55; H, 11·0. $C_{20}H_{30}O_2$ requires C, 78·9; H, 10·6%.)

Cyclization of the keto-aldehydes (III) *and* (XI). Chromatography of III on alumina brought about partial formation of the unsaturated ketone VIII. Complete cyclization was accomplished by treatment with methanolic potassium hydroxide (5%) for 3 hr at room temp. XI required to be heated under reflux for 1 hr with methanolic potassium hydroxide (10%) to affect cyclization.

Oxidation of 13α-*Acetyl*-8*β*-*carboxypodocarpane* (IV). IV (149 mg) in methylene chloride (1 ml) was added dropwise to a stirred solution of pertrifluoroacetic acid, prepared from trifluoroacetic anhydride (0·145 ml) and hydrogen peroxide (0·02 ml) in methylene chloride (3 ml) at 0°. The mixture was maintained at 0° for 10 min and then heated under reflux for 30 min. The product, after hydrolysis with methanolic potassium hydroxide (10%, 1 hr under reflux) was adsorbed from benzene–chloroform (1 : 1) on silica gel (20 g) and eluted with chloroform–methanol (19 : 1). Crystallization from light petroleum–ethanol gave needles (80 mg) of 8*β*-*carboxy*-13α-*hydroxypodocarpane* (Va), m.p. 280–282° with sublimation, $[\alpha]_D$ −26° (*c*, 0·6 in MeOH). (Found: C, 73·75; H, 9·85. $C_{18}H_{30}O_3$ requires: C, 73·45; H, 10·25%.)

Methylation of the above acid with ethereal diazomethane gave the corresponding methyl ester Vb as an uncrystallizable oil.

8*β*-*Carbomethoxy*-13-*oxopodocarpane* (VIb). The methyl ester Vb (30 mg) in acetone (10 ml) was oxidized with 8 N chromic acid/sulphuric acid. The product crystallized from chloroform–light petroleum as prisms (25 mg) of VIb, m.p. 159–161°, $[\alpha]_D$ −15° (*c*, 1·4). (Found: C, 74·7; H, 9·8. $C_{19}H_{30}O_3$ requires: C, 74·45; H, 9·85%.)

8*β*-*Carboxy*-13-*oxopodocarpane* (VIa). The methyl ester VIb (11·8 mg) was heated under reflux with 20% aqueous methanol (7 ml) containing sodium hydroxide (2%) for 14 hr. After this time approx 80% of the ester had been hydrolysed. (Under identical hydrolysis conditions the methyl ester Vb was recovered unchanged.) The acidic product was crystallized from light petroleum–chloroform as needles (8 mg) of VIa, m.p. 185–186° with sublimation (lit[1] m.p. 182–183°), $[\alpha]_D$ −23° (*c*, 0·5). (Found: C, 73·7; H, 9·4. $C_{18}H_{28}O_3$ requires: C, 73·95; H, 9·65%.) This same acid was also prepared by oxidation of Va with chromic acid.

Hunsdiecker reaction on silver salt of (Va). The silver salt (236 mg) of the hydroxy-acid Va was suspended in dry carbon tetrachloride (100 ml) maintained under reflux. Bromine (0·033 ml) in CCl_4 was added and the heating continued for 5 min till the bromine colour had disappeared. The neutral product was sublimed and crystallized as needles (85 mg) of the *lactone* XII from methanol, m.p. 151–152°, $[\alpha]_D$ +1° (*c*, 0·7). (Found: C, 78·15; H, 10·1. $C_{18}H_{28}O_2$ requires: C, 78·2; H, 10·2%.)

Infra-red absorption in $CHCl_3$ at 1778 cm^{-1}. From the acidic fraction, Va (78 mg) was recovered.

Pyrolysis of the acetate of (Va). The hydroxy-acid Va (28 mg), acetic anhydride (0·2 ml) and pyridine (0·4 ml) were allowed to react at room temp for 18 hr. The solvents were removed under vacuum at 40°, the product dissolved in benzene and adsorbed on silica gel (20 g). Elution with benzene–chloroform (1 : 3) gave the acetate of Va as an oil which could not be crystallized. This oil was heated, under nitrogen, with copper bronze (50 mg) for 15 min at 250–260°. On cooling, the mixture solidified. Sublimation gave the lactone XII (21 mg).

Reduction of the 8β-carboxy-13-oxopodocarpane (VIa). VIa (45 mg) in 50% aqueous methanol (15 ml) was allowed to react with sodium borohydride (70 mg) for 12 hr. After acidification the neutral product (21 mg) crystallized as needles from aqueous methanol, m.p. 151–152° undepressed on admixture with the lactone XII. Chromatography of the acidic fraction on silica gel gave unchanged VIa (20 mg).

Oxime of 13β-acetyl-8β-cyanopodocarpane (XIVb). 13β-Acetyl-8β-aldehydopodocarpane (1·14 g), hydroxylamine hydrochloride (2 g), pyridine (1·5 ml) and ethanol (20 ml) were heated together under reflux for 1 hr. The crude dioxime (850 mg), isolated by precipitation with water and crystallization from aqueous methanol, had m.p. 192–199°. This material was heated under reflux with acetic anhydride (15 ml) and sodium acetate (1 g) for 1 hr. Isolation, as above, gave a product which absorbed at 1730 cm^{-1}, indicating the presence of an acetate, XIVa. This substance was adsorbed from benzene on alumina (50 g) and eluted with ether–methanol (19 : 1) as prisms (505 mg from light petroleum–chloroform) of XIVb, m.p. 195–197° with sublimation, $[\alpha]_D$ −13° (*c*, 0·8). (Found: C, 75·75; H, 10·0; N, 9·15. $C_{20}H_{32}ON_2$ requires: C, 75·9; H, 10·2; N, 8·85%.)

13-Acetyl-8β-cyanopodocarpane (XIVc). A solution of sodium nitrite (460 mg) in water (1·5 ml) was added to XIVb (460 mg) in acetic acid (10 ml) and the mixture maintained at room temp for 4 hr. The crystalline product, isolated in the usual manner, appeared to be a mixture of the expected ketone and the nitrimine,[8] It was dissolved in dioxane–water (25 ml, 4 : 1) and heated on a steam bath for 2 hr. Dilution with water and extraction with ether gave a substance which was adsorbed on alumina (30 g) from light petroleum–benzene (1 : 1) and eluted with benzene–ether (9 : 1) as needles (175 mg from aqueous methanol) of *13-acetyl-8β-cyanopodocarpane*, m.p. 102–104° with softening at 96–100°. (Found: C, 79·9; H, 10·85; N, 4·45. $C_{20}H_{31}ON$ requires: C, 79·65; H, 10·35; N, 4·65%.)

8β-Cyano-13-hydroxypodocarpane (XV). 13-Acetyl-8β-cyanopodocarpane (158 mg) was oxidized with pertrifluoroacetic acid in the presence of anhydrous disodium hydrogen phosphate (400 mg) in the manner previously described. The product, after hydrolysis with methanolic potassium hydroxide (2%, 1 hr under reflux) was adsorbed from benzene on alumina (20 g). Elution with ether–methanol (9 : 1) gave XV as needles (85 mg) from light petroleum–chloroform, m.p. 95–115°. (Found: C, 78·8; H, 10·85. $C_{18}H_{29}ON$ requires: C, 78·5; H, 10·6%.)

8β-Cyano-13-oxopodocarpane (XVI). 8β-Cyano-13-hydroxypodocarpane (68 mg) in acetone (10 ml) was oxidized with 8N chromic acid/sulphuric acid. The product was adsorbed from benzene on alumina (10 g) and eluted with benzene–ether (4 : 1) as needles (42 mg from chloroform–light petroleum) of XVI, m.p. 160–161° with prior melting and resolidification at 153–154·5°, $[\alpha]_D$ +33° (*c*, 0·6). (Found: C, 78·85; H, 9·7. $C_{18}H_{27}ON$ requires: C, 79·05; H, 9·95%.)

13-Oxopodocarp-8(14)-ene (XIII). 8β-Cyano-13-oxopodocarpane (15 mg) was mixed with powdered potassium hydroxide (150 mg) and the mixture distilled at 120° (0·01 mm). The product was adsorbed on alumina (5 g) from light petroleum and eluted with benzene–ether (9 : 1) as prisms (6 mg from methanol) of XIII, m.p. 64–66°, $[\alpha]_D$ +45° (*c*, 0·4), λ_{max} (MeOH) 242·5 mμ, ε = 16,000. A specimen of the same material prepared from manool had m.p. 64–66° (undepressed on admixture with XIII), $[\alpha]_D$ +49° (*c*, 0·9), λ_{max} (MeOH) 242·5 mμ, ε = 16,400.

The infra-red spectra of the two samples in CCl_4 were identical.

Acknowledgements—We wish to thank Professor R. A. Raphael for his help and encouragement, and Professors C. Djerassi and L. H. Briggs for communicating the results of their experiments prior to publication. We are also indebted to Professor C. Djerassi for determining the rotatory dispersion curve of VIb.

[8] S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney and L. J. Wyman, *J. Chem. Soc.* 4614 (1958).