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KETONES DERIVED FROM PHYLLOCLADENE

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Abstract—Phyllocladene has been converted into some 15- and 16-oxo derivatives. The rotatory dispersion curves of these indicate that XV is the most likely structure for mirene.

SINCE the structure of phyllocladene has been established,[1] it was thought desirable to prepare a related series of compounds containing keto groups at C_{15} and C_{16} for rotatory dispersion studies. Throughout this paper a systematic nomenclature will be used, based on the parent hydrocarbon phyllocladane (I). In phylloclad-15-ene the double bond is much more hindered from the β-face, so it is probable that I corresponds to "α-dihydrophyllocladene", the sole product of catalytic hydrogenation.

Accordingly, phylloclad-15-ene was hydrated with diborane, giving an alcohol which was not characterized, but oxidized to the ketone II. It would be expected that the hydration should take place in a *cis* manner[2] from the α-face of the molecule, and hence II should have the 17-methyl group in the more congested β-configuration. This was confirmed by epimerization to the corresponding 17α-ketone (IIIa), which was also prepared by the action of boron trifluoride on 15,16-oxidophyllocladane (IVa).

In view of the nature of the Cotton effects of these ketones it was decided to prepare 15-oxo-17-norphyllocladane (IIIb). Hence, 16-oxonorphyllocladane (Va) was reduced with sodium borohydride to an alcohol which would be expected to have the structure VIa. This was converted into its tosylate which was not purified; on being heated under reflux in quinoline it underwent smooth elimination to produce the olefin VIIa. Hydrogenation of VIIa gave the parent hydrocarbon, 17-norphyllocladane (VIb).

Conversion of VIIa to the epoxide IVb followed by hydrogenolysis with lithium in ethylamine gave a mixture of alcohols which were readily separated by chromatography. That the more polar of these was the expected 16α-hydroxy-17-norphyllocladane (IXa) was shown by oxidation to Va, establishing that no skeletal rearrangements had taken place during this sequence of reactions. The other alcohol must therefore be 15α-hydroxy-17-norphyllocladane (VIIIa). Oxidation of this gave the desired ketone (IIIb).

Prior to this work other routes to IIIb were explored, but abandoned because of unsatisfactory yields. Since some of the intermediates may be of interest, these will be described.

Oxidation of phylloclad-15-ene with selenium dioxide produced an unsaturated aldehyde (VIIb) having I.R. absorption in CCl_4 at 2798, 2701 and 1679·5 cm^{-1} and U.V. absorption in MeOH at 256 mμ, ε 10,500. This high λ_{max} is not inconsistent with the proposed structure as ketones in strained 5-membered rings are known[3] to

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[1] P. K. Grant and R. Hodges, *Tetrahedron* **8**, 261 (1960).

[2] H. C. Brown and G. Zweifer, *J. Amer. Chem. Soc.* **81**, 247 (1959).

[3] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron* **9**, 254 (1960).

absorb at high wavelengths. It should be pointed out that the ketone XI[1] is also abnormal (λ_{max} 241 mμ, ϵ 7800) while XII[4] absorbs at the expected wavelength (λ_{max} 230 mμ). This difference is most probably due to the strain introduced into ring D by the proximity of the methyl group at C_{10}.

The aldehyde (VIIb) was reduced to the allylic alcohol (VIIc) which could be readily oxidized back to VIIb with manganese dioxide. Epoxidation of VIIc followed by reduction with lithium in ethylamine gave a mixture of diols, one of which was isolated as its monoacetate and shown to be identical with the product (IXb) obtained from acetylation of the known[5] 16,17-dihydroxyphyllocladane. The other diol is probably 15α,17-dihydroxy-16-epiphyllocladane (VIIIb), which should be convertable to IIIb. In view of the low yield of VIIIb, this has not been attempted.

Rearrangement of the epoxide (IVd) with boron trifluoride produced a mixture of at least three compounds, from which a substance was isolated (m.p. 108°) whose analysis would be consistent with either that of IIIc or X. However, this had I.R. absorption in CCl_4 at 1713·5 and 1747 cm^{-1} and no bands in the 2700–2800 region, which would make both these structures seem unlikely. This substance has not been further investigated.

In connexion with other work, the ketone (Vb) was prepared by alkylation of 16-oxo-norphyllocladane with propargyl chloride. The propargyl group must have an α-configuration since the β-epimer would appear, from models, to be sterically unlikely.

Rotatory dispersion curves of the five ketones, II, IIIa, IIIb, Va and Vb, were compared. The first three of these all had negative Cotton effects with only slight differences in amplitude; that of IIIa being less than II, in agreement with the assigned configurations of their 17-methyl groups. In addition Va and Vb both showed positive Cotton effects. It is clear that alkyl substitution at a carbon adjacent to a carbonyl group at C_{15} or C_{16} makes very little contribution to the Cotton effect. This confirms the observations of Bourn and Klyne[6] that the sign of the Cotton effect of ketones in rigid 5 membered rings is largely determined by the asymmetry of the ring containing the carbonyl group and that the substituents have only minor effects. Thus the structure XIII which has been proposed[7] for oxo-normirene would be anomalous if it showed a Cotton effect of different sign from that of Va. Since oxonormirene does in fact have a negative effect, we would suggest that it does not have the proposed structure.

Any formula for mirene must contain a methylene group, exocyclic to a 5 membered ring and must account the nature of the rotatory dispersion curve of its derived norketone and for its acid catalysed rearrangement to phylloclad-15-ene. It was thought possible that XIV might be capable of rearrangement to phylloclad-15-ene, the driving force being the high degree of steric interaction between the substituents at C_{10} and C_{16}. However, the ketone (IIIb), while having a rotatory dispersion curve of the same type, is not identical with oxonormirene.

The structure XV should satisfy the first two requirements for mirene, although an unusual path must be invoked for its rearrangement to phylloclad-15-ene. Work aimed at preparing structures of this type is now in progress.

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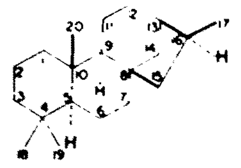
[4] W. Parker. Personal communication.

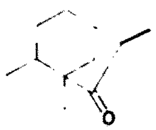
[5] C. W. Brandt, *N.Z. J. Sci. Technol.* **34B**, 46 (1952).

[6] P. M. Bourn and W. Klyne, *J. Chem. Soc.* 2044 (1960).

[7] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters* No. 8, 13 (1959).



I



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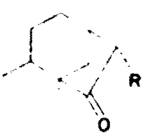
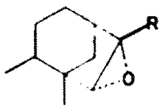
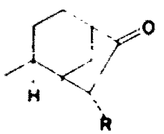


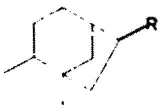
III a, R = Me
b, R = H
c, R = CH_2OAc



IV a, R = Me
b, R = H
c, R = CH_2OH
d, R = CH_2OAc

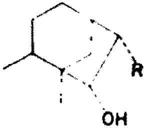


V a, R = H
b, R = $CH_2{\cdot}C{\equiv}CH$



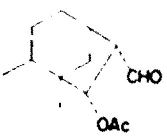
VI a, R = OH
b, R = H

VII a, R = H
b, R = CHO
c, R = CH_2OH
d, R = CH_2OAc



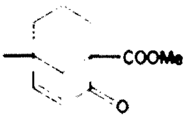
VIII a, R = H
b, R = CH_2OH

IX a, R = H
b, R = CH_2OAc



X

XI



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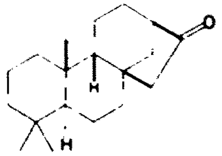
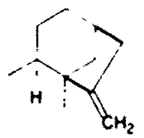
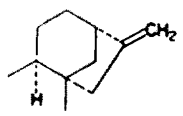


XIII



XIV



XV

EXPERIMENTAL

Rotations were measured in chloroform at 20°. M.p.'s were taken on a Kofler block and are corrected. Alumina used for chromatography had activity II. Light petroleum refers to the fraction b.p. 60–80°.

15-Oxophyllocladane (II). Lithium aluminium hydride (610 mg) in ether (25 ml) was added slowly to a solution of phylloclad-15-ene (415 mg) and boron trifluoride etherate (3·5 g) in ether (100 ml) under nitrogen. After 1 hr the product was isolated, dissolved in tetrahydrofuran (20 ml) and treated with hydrogen peroxide (5 ml, 30%) and methanolic sodium hydroxide. After a further hour the product was adsorbed from benzene on alumina and eluted with benzene ether (1 : 1) as a colourless gum which could not be crystallized. Oxidation of this material, in acetone with chromic acid/sulphuric acid gave 15-*oxophyllocladane* (125 mg) as plates from methanol, m.p. 101–102°, $[\alpha]_D$ −62° (*c*, 0·8). (Found: C, 82·95; H, 11·2. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

15-Oxo-16-epiphyllocladane. II (30 mg) was heated under reflux with methanolic sodium hydroxide (5 ml, 2%) for 8 hr. Repeated crystallization of the product from aqueous methanol yielded 15-*oxo-16-epiphyllocladane* (IIIa), m.p. 127·5–129°, $[\alpha]_D$ −50° (*c*, 0·5). (Found: C, 83·4; H, 11·35. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

15,16-*Oxidophyllocladane* (IVa). Phylloclad-15-ene (620 mg) was reacted with an excess of monoperphthalic acid in ether for 15 hr at 0°. Crystallization from methanol gave the epoxide (490 mg), m.p. 92–93°, $[\alpha]_D$ −30° (*c*, 0·9). (Found: C, 82·95; H, 10·9. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.)

Treatment of IVa (450 mg) in benzene (30 ml) with boron trifluoride etherate (0·5 ml) for 15 min at 20° gave a mixture of ketones (440 mg, m.p. 112–118°) which after repeated crystallization from methanol yielded 15-oxo-16-epiphyllocladane.

16β-*Hydroxy*-17-*norphyllocladane* (VIa). 16-Oxonorphyllocladane (V) (1·20 g) was treated with sodium borohydride (400 mg) in aqueous methanol (50 ml, 90%) for 12 hr at 20°. The product crystallized as needles (1·11 mg) of VIa from light petroleum, m.p. 150–151·5°, $[\alpha]_D$ +17° (*c*, 0·9). (Found: C, 82·45; H, 11·85. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

17-*Norphylloclad*-15-*ene* (VIIa). VIa (1·10 mg) was reacted with *p*-toluenesulphonyl chloride (1 g) in pyridine (15 ml) for 8 hr at 20°. The resulting tosylate was heated under reflux in quinoline (5 ml) and the product, in light petroleum was filtered through alumina. Crystallization from aqueous ethanol gave VIIa (940 mg) as plates, m.p. 72·5–73°, $[\alpha]_D$ −7° (*c*, 0·7). (Found: C, 88·1; H, 11·65. $C_{19}H_{30}$ requires: C, 88·3; H, 11·7%.)

17-*Norphyllocladane* (VIb). Hydrogenation of VIIa in ethyl acetate using Adams' catalyst gave VIb as plates from aqueous ethanol, m.p. 85–86°, $[\alpha]_D$ +3° (*c*, 0·9). (Found: C, 87·4; H, 12·4. $C_{19}H_{32}$ requires: C, 87·6; H, 12·4%.)

15α,16-*Oxido*-17-*norphyllocladane* (IVb). VIIa (830 mg) was allowed to react with an excess of monoperphthalic acid in ether for 24 hr at 0°. Crystallization from methanol gave IVb as plates (580 mg), m.p. 84·5–86°, $[\alpha]_D$ +16° (*c*, 0·9). (Found: C, 83·15; H, 10·65. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·0%).

Reduction of the epoxide (IVb). IVb (550 mg) in ethylamine (30 ml) was treated with lithium and allowed to react for 1 hr after a permanent blue colour had appeared. The product was adsorbed on alumina from light petroleum and eluted with benzene ether (4 : 1) as needles (180 mg from aqueous methanol) of 15α-*hydroxy*-17-*norphyllocladane* (VIIIa), m.p. 125–126° (with melting and resolidification at 116–118°), $[\alpha]_D$ +4° (*c*, 0·8). (Found: C, 82·8; H, 11·85. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

Further elution with ether gave 16α-*hydroxy*-17-*norphyllocladane* (IXa) as needles (190 mg from light petroleum), m.p. 156–157°, $[\alpha]_D$ −7° (*c*, 0·8). (Found: C, 82·9; H, 11·95. $C_{19}H_{32}O$ requires: C, 82·55; H, 11·65%.)

15-*Oxo*-17-*norphyllocladane* (IIIb). Oxidation of VIIIa (47 mg) in acetone (5 ml) with chromic acid/sulphuric acid gave the ketone IIIb as needles (39 mg from light petroleum), m.p. 132–133°, $[\alpha]_D$ 33° (*c*, 1·0). (Found: C, 82·95; H, 10·8. $C_{19}H_{30}O$ requires: C, 83·15; H, 11·0%.)

Oxidation of IXa yielded 16-oxonorphyllocladane identical with an authentic sample, $[\alpha]_D$ +71° (*c*, 0·8).

17-*Oxophylloclad*-15-*ene* (VIIb). Phylloclad-15-ene (1·69 g) and selenium dioxide (1·5 g) were heated together under reflux in acetic acid (20 ml) for 30 min. The product was adsorbed from light petroleum on alumina deactivated with 5% of 10% acetic acid and eluted with benzene as needles (1·49 g from light petroleum) of VIIb, m.p. 129–130°, $[\alpha]_D$ 71° (*c*, 1·0). (Found: C, 83·45; H, 10·55. $C_{20}H_{30}O$ requires: C, 83·85; H, 10·55%.)

17-*Hydroxyphylloclad*-15-*ene* (VIIc). Reduction of VIIb (1·30 g) with lithium aluminium hydride in ether produced VIIc as needles (1·21 g from light petroleum), m.p. 125·5–126·5, $[\alpha]_D$ +14° (*c*, 0·9). (Found: C, 83·15; H, 11·1. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%.) This alcohol was quantitatively oxidized back to the aldehyde (VIIb) by shaking for 12 hr with manganese dioxide in chloroform.

Acetylation of VIIc by heating under reflux with acetic anhydride and sodium acetate gave 17-*acetoxyphylloclad*-15-*ene* (VIId) as plates from aqueous methanol, m.p. 38–39°. (Found: C, 80·15, H, 10·65. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·35%.)

17-*Hydroxy*-15,16-*oxidophyllocladane* (IVc). Reaction of VIIc (350 mg) with an excess of monoperphthalic acid in ether for 2 days at 0° produced the epoxide as needles (270 mg from light petroleum), m.p. 149–151°, $[\alpha]_D$ +39° (*c*, 0·6). (Found: C, 78·95; H, 10·5. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.)

Similarly 17-*acetoxy*-15,16-*oxidophyllocladane* (IVd) formed needles from aqueous methanol, m.p. 86·5–87·5°, $[\alpha]_D$ +29° (*c*, 0·7). (Found: C, 76·0; H, 10·15%. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%.)

Reduction of the epoxide (IVc). IVc (170 mg) was reacted with lithium in ethylamine as before. The product was acetylated with acetic anhydride in pyridine for 12 hr at 20°. Adsorption from light petroleum on alumina deactivated with 5% of 10% acetic acid, followed by elution with light petroleum gave a crude diacetate which was not obtained crystalline. Further elution with benzene–chloroform (3 : 2) gave 17-acetoxy-16-hydroxyphyllocladane (IXb; 43 mg from light petroleum), m.p. 142–143·5°. (Found: C, 76·0; H, 10·5. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%.) This was identical with a specimen prepared by partial acetylation of 16,17-dihydroxyphyllocladane.

The crude diacetate from above was hydrolysed with methanolic sodium hydroxide, adsorbed from benzene on alumina and eluted with ether–methanol (19 : 1) as needles (65 mg from light petroleum–chloroform) of 15α,17-*dihydroxy*-16-*epiphyllocladane* (VIIIb) m.p. 192–193°, $[\alpha]_D$ +10° (*c*, 0·9). (Found: C, 78·75; H, 10·2. $C_{20}H_{34}O_2$ requires C, 78·4; H, 10·2%.)

Reaction of BF_3 on IVd. IVd (75 mg) in benzene was allowed to react with boron trifluoride etherate (0·2 ml) for 2 days at 0°. The product was adsorbed on deactivated alumina and eluted with benzene as needles (15 mg from aqueous methanol), m.p. 108–109·5°, $[\alpha]_D$ −2° (*c*, 0·7). (Found: C, 76·0; H, 10·15. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%.)

Further elution with chloroform gave an inseparable mixture of dihydroxyacetates (43 mg) crystallizing as plates from light petroleum–chloroform, m.p. 173–179°. (Found: C, 72·35; H, 10·35. $C_{22}H_{36}O_4$ requires: C, 72·5; H, 9·95%.)

16-*Oxo*-15α-*propargylnorphyllocladane* (Vb). 16-*Oxonorphyllocladane* (520 mg) and sodamide (250 mg) in xylene (50 ml) were heated together under reflux for 4 hr. After cooling, propargyl chloride (0·5 ml) was added and the mixture heated for a further 3 hr. The product was adsorbed from light petroleum on alumina and eluted with benzene as prisms of Vb (80 mg from methanol), m.p. 168–170°, $[\alpha]_D$ −66° (*c*, 0·5). (Found: C, 84·6; H, 10·15. $C_{22}H_{32}O$ requires: C, 84·55; H, 10·3%.)

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