The Osmylation of Abietic Acid

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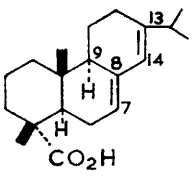
Osmylation of abietic acid, unlike hydroboration, leads to preferential attack on the 13,14-double bond to give the diol (IIa) accompanied by a small amount of the tetrol (V). Some reactions of the diol (IIa) are described.

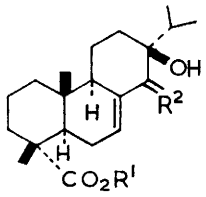
In connexion with work on bacterial transformations [1] of abietic acid (I) we required a number of hydroxy-abietic acid derivatives and the preparation of some of these compounds has been described.[2] This paper reports further work in this field.

Reaction of abietic acid with osmium tetroxide (1 mol.) in pyridine gave a product shown by t.l.c. to be a complex mixture. Purification afforded a diol, m.p. 154—155°,† as the main product and a small amount of a tetrol (V) of unknown stereochemistry at positions 7, 8, 13, and 14.

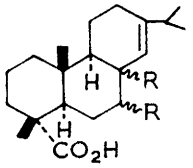
In the n.m.r. spectrum of the diol the C*H*·OH signal appeared as a doublet at τ 5·81 (J 2·5 c./sec.). This is incompatible with the 7,8-diol structures (IIIa) but is consistent with structure (IIa) in which the pseudo-axial 14α-proton is allylically coupled [4] to the 7-proton; a pseudo-equatorial 14β-proton would be expected to show only slight allylic coupling.[4] Furthermore the C-7 proton resonance in the diol appears at very low field (τ 3·73) as would be expected if it is deshielded by a



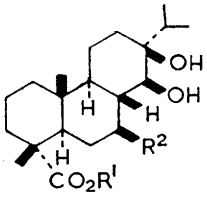
(I)



	R¹	R²
(II) a;	H	α-H, β-OH
b;	Me	α-H, β-OH
c;	Me	α-H, β-OAc
d;	H	O



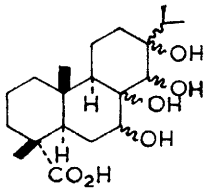
	R
(III) a;	OH
b;	H



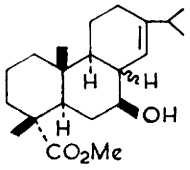
	R¹	R²
(IV) a;	H	H
b;	Me	OH

group in the same plane,[5] *i.e.* by a 14β- but not by a 14α-hydroxy-group. In agreement with structure (IIa), oxidation [6] of the diol gave an αβ-unsaturated ketone ($\lambda_{max.}$ 252 mμ, ε 10,100) formulated as (IId). Structure (IIa) for the diol was confirmed by hydrogenation to the known [2] saturated diol (IVa). The stereochemistry previously assigned [2] to the diol (IVa), *viz.* 13α,14α-dihydroxy-13β-isopropyl-8α-podocarpanoic acid, was based upon the 8α-configuration reported [7] for the 13,14-ene (IIIb) from which it was originally prepared. However, recent revision [8,9] of the stereochemistry of the 13,14-ene (IIIb) has shown it to be an 8β-compound and consequently the stereochemistry of the derived diol must be as shown in structure (IVa). These results show that, in contrast to hydroboration,[2] osmylation of abietic acid leads to preferential attack on the 13,14-double bond with reaction occurring on the β-face of the molecule.

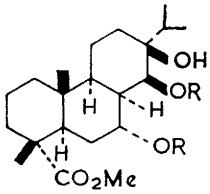
Some reactions of the methyl ester of the diol (IIa) were investigated as part of an unsuccessful attempt to confirm the structure of the bacterial transformation product (VI),[1] by partial synthesis from abietic acid. Hydroboration–oxidation of the ester (IIb) gave a product shown by t.l.c. to be a mixture of two compounds presumed to be the trihydroxy-esters (IVb) and (VIIa). Treatment of the mixture with acetone–



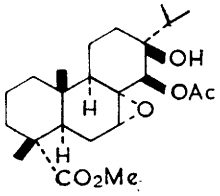
(V)



(VI)



	R
(VII) a;	H
b;	Ac



(VIII)

anhydrous copper sulphate, followed by chromatography of the product, gave the pure triol (VIIa) and a gum which ran as one spot on t.l.c. Acetic acid hydrolysis of the gum afforded a further quantity of the triol (VIIa) and another gum believed to be the isopropylidene derivative of the triol (IVb). Attempts to recover

† This diol may be the same as that, m.p. 153—154°, obtained [3] by oxidation of abietic acid with potassium permanganate.

[1] B. E. Cross and P. L. Myers, *Biochem. J.*, 1968, **108**, 303.
[2] B. E. Cross and P. L. Myers, *J. Chem. Soc.* (*C*), 1968, 471.
[3] L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, 1938, **21**, 565; 1940, **23**, 341.
[4] N. S. Bhacca and D. H. Williams, ' Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 108.
[5] Ref. 4, p. 189.
[6] R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 1953, 457.
[7] J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, 1966, **31**, 4128.
[8] J. W. Huffman, personal communication.
[9] A. W. Burgstahler, personal communication.

the triol from the latter by treatment with mineral acid gave a mixture of products. The stereochemistry of the triol (VIIa) at positions 7 and 8 was deduced from its n.m.r. spectrum in deuteriochloroform. The 14-proton resonance appeared as a doublet at τ 6·23 with a coupling constant of 4·5 c./sec., thus excluding structure (IVb) in which the protons at both positions 8 and 14 are axial. Hence the triol must have the stereochemistry depicted in (VIIa) and this was confirmed by the n.m.r. spectrum of its diacetate (VIIb) in which the C-17 methyl resonance occurred at τ 8·81 (in carbon tetrachloride) indicating that rings B/C are *cis*-fused.[6] Ring C in the triol (VIIa) may be distorted (*cf.* 8α,14α-dihydroxy-13α-isopropyl-8α-podocarpanoic acid [2]) to relieve the interaction between the 14β-hydroxy-group and the 17-methyl group. Furthermore, the half-band widths of the 7-H signals in both the triol and its diacetate vary with the solvent and are considerably greater than have been previously observed (6 c./sec.) [2] for 7α-substituted 8α-podocarpanes. Thus for the triol (VIIa), the 7-H resonance is found as a multiplet at τ 5·55 ($W_{\frac{1}{2}}$ = *ca.* 15 c./sec.) in deuteriochloroform, but in pyridine it forms a rough quartet ($W_{\frac{1}{2}}$ *ca.* 10 c./sec.). These results may indicate that ring B is conformationally distorted.

Reaction of the 7-ene (IIc) with *m*-chloroperbenzoic acid gave only one epoxide, which is tentatively assigned structure (VIII), since a Dreiding model of the 7-ene shows that the β-face is the more hindered. An attempt to rearrange the epoxide to a 7-ketone with boron trifluoride was unsuccessful.

EXPERIMENTAL

Chromatographic materials and general experimental methods have been previously described.[2]

Osmylation of Abietic Acid.—Abietic acid (1·15 g.) in pyridine (10 ml.) was treated with osmium tetroxide (1 g.) for 36 hr. Water (30 ml.), pyridine (25 ml.), and sodium metabisulphite (2 g.) were added and the solution was shaken for 3 hr. The product was recovered in ethyl acetate and chromatographed on silica gel. Elution with ethyl acetate–light petroleum (2 : 3) yielded 13β,14β-*dihydroxy*-13α-*isopropylpodocarp*-7-*en*-15-*oic acid* (IIa) which crystallised from ethyl acetate–light petroleum as solvated prisms; these when dried at 100° *in vacuo* for 12 hr. gave the solvent-free acid (541 mg.), m.p. 154—155° (Found: C, 71·0; H, 9·85. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ 3400, 2640, and 1690 cm.$^{-1}$, τ 9·02 (s; 17-Me), 8·97 and 8·88 (2d, *J* 7 c./sec. Pr^i), 8·53 (s, 16-Me), 5·81 (1H, d, *J* 2·5 c./sec., CH·OH), 3·73 (1H, m, $W_{\frac{1}{2}}$ 7 c./sec., 7-H).

The *methyl ester* (IIb), prepared with ethereal diazomethane, crystallised from ether–light petroleum as needles, m.p. 110—113° (Found: C, 71·55; H, 9·8. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%), $\nu_{max.}$ 3460 and 1720 cm.$^{-1}$, τ ($CDCl_3$) 9·14 (s, 17-Me), 9·1 and 9·06 (2d, *J* 6·5 c./sec.; Pr^i), 8·74 (s, 16-Me), 6·37 (3H, s, CO_2Me), 6·05br (1H, CH·OH), 4·14br (1H, 7-H).

The diol (IIa) (2·05 g.) in acetic anhydride (10 ml.) and pyridine (20 ml.) was left for 24 hr. Recovery in ethyl acetate and chromatography on silica gel gave, on elution with ethyl acetate–light petroleum (3 : 7), the acetate. Methylation with ethereal diazomethane then afforded *methyl* 14β-*acetoxy*-13β-*hydroxy*-13α-*isopropylpodocarp*-7-*en*-15-*oate* (IIc) as needles, m.p. 137—140° (Found: C, 70·25; H, 9·35. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%), $\nu_{max.}$ 1740 and 1720 cm.$^{-1}$, τ 9·09, 8·89, and 8·86 (methyls), 8·72 (s, 16-Me), 7·96 (s, OAc), 6·44 (3H, s, CO_2Me), 5·28br (1H, CH·OAc), 4·47br (7-H), (in CCl_4) 9·24 and 9·04 (2s, halves of Pr^i doublets), 9·13 (s, overlapping halves of Pr^i doublets and 17-Me), 8·77 (s, 16-Me), 7·90 (3H, s, OAc), 6·38 (3H, s, CO_2Me).

Elution with ethanol–ethyl acetate (1 : 1) gave 7ξ,8ξ,13ξ,14ξ-*tetrahydroxy*-13ξ-*isopropylpodocarpan*-15-*oic acid* (V) which crystallised from ethanol–ethyl acetate as needles (69 mg.), m.p. 229—232° (Found: C, 64·35; H, 9·15. $C_{20}H_{34}O_6$ requires C, 64·8; H, 9·25%), $\nu_{max.}$ 3520, 1700sh, and 1680 cm.$^{-1}$, τ 8·84 (d, *J* 6·5 c./sec., Pr^i), 8·79 (s, 17-Me), 8·47 (s, 16-Me), 6·83 (1H, t, J_{AX+BX} 17 c./sec., 9-H), 5·75 (1H, s, 14-H), 5·01 (1H, t, J_{AX+BX} 15 c./sec., 7-H).

Oxidation of the Diol (IIa).—The diol (150 mg.) in acetone (50 ml.) was treated at 0° with the 8N-chromium trioxide reagent [6] (0·25 ml.) for 3 min. The product, isolated in the usual manner,[2] was chromatographed on silica gel. Elution with ethyl acetate–light petroleum (3 : 7) gave 13β-*hydroxy*-13α-*isopropyl*-14-*oxopodocarp*-7-*en*-15-*oic acid* (IId) which crystallised as needles (66 mg.), m.p. 189—190°, from ether–light petroleum (Found: C, 71·55; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%), $\nu_{max.}$ ($CHBr_3$) 3510 (OH), 2660 and 1696 (CO_2H), 1690sh. (C = O), and 1614 (C=C) cm.$^{-1}$, $\lambda_{max.}$ 252 mμ (ε 10,100), τ (in $CDCl_3$) 9·23 (s, 17-Me), 9·10 (d, *J* 6 c./sec., Pr^i), 8·75 (3H, s, 16-Me), 2·99 (1H, m, $W_{\frac{1}{2}}$ 7 c./sec., 7-H).

Hydrogenation of the Dihydroxy-acid (IIa).—The acid (350 mg.) in glacial acetic acid (50 ml.) was hydrogenated in the presence of pre-reduced Adams catalyst (300 mg.) until uptake ceased (1·1 mol. in 90 min.). The solution was filtered, diluted with water, and extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution and water and then dried. Recovery, followed by chromatography on silica gel in ethyl acetate–light petroleum (1 : 1) gave the dihydroxy-acid (IVa) as needles, m.p. 186—188°, identical (i.r. and n.m.r. spectra) with a sample prepared [2] from the 13,14-ene (IIIb; 8β-epimer) and with samples kindly supplied by Professors A. W. Burgstahler and J. W. Huffman.

Hydroboration-oxidation of the Diol (IIb).—The diol (1·96 g.) in tetrahydrofuran (50 ml.) was treated at 0° with a ten-fold excess of diborane in tetrahydrofuran (10 ml.) for 18 hr. under nitrogen. Water (5 ml.) and 5N-sodium hydroxide (15 ml.) were added, followed by 40% hydrogen peroxide (15 ml.; dropwise). The solution was stirred for 30 min. at 60° and then for a further 2 hr. at room temperature. Recovery in ethyl acetate gave a gum (2·1 g.) which appeared, from t.l.c. in acetic acid–di-isopropyl ether (1 : 9) and acetic acid–ethyl acetate (1 : 99), to be a 1 : 1 mixture of two compounds. The gum, in acetone (100 ml.), was shaken with anhydrous copper sulphate (20 g.) for 16 hr. and the resultant product was chromatographed in alumina (Grade V). Elution with ethyl acetate–light petroleum (1 : 9) gave a gum (A) (1·06 g.) which ran as one spot on t.l.c. Elution with ethyl acetate gave *methyl* 7α,13β,14β-*trihydroxy*-13α-*isopropyl*-8α-*podocarpan*-15-*oate* (VIIa) (463 mg.) which crystallised from ether–light petroleum as needles, m.p. 144—145° (Found: C, 68·1; H, 10·0. $C_{21}H_{36}O_5$ requires C, 68·4;

H, 9·85%), $\nu_{max.}$ 3530, 3475, and 1717, (in $CHCl_3$) 3580, 3430, and 1714 cm.$^{-1}$, τ 8·97 (d, J 6·5 c./sec., Pr^i), 8·86 (s, 17-Me), 8·69 (s, 16-Me), 6·35 (3H, s, CO_2Me), 5·93 (1H, d, J 4 c./sec.; 14-H), 5·34 (1H, q, $W_{\frac{1}{2}}$ *ca.* 10 c./sec., 7-H), (in $CDCl_3$) 9·18 and 9·14 (Pr^i), 9·03 (s, 17-Me and Pr^i), 8·77 (s, 16-Me), 6·33 (s, CO_2Me), 6·23 (d, J 4·5 c./sec., 14-H), 5·55 (m, $W_{\frac{1}{2}}$ *ca.* 15 c./sec., 7-H).

The diacetate (VIIb), prepared by treating the triol (VIIa) with acetic anhydride in pyridine for 3 days followed by chromatography on alumina, was a gum, $\nu_{max.}$ (in $CHBr_3$) 3570 (OH) and 1722 (C=O) cm.$^{-1}$, τ (in CCl_4) 9·16 and 9·13 (2d, J 6·5 c./sec., Pr^i), 8·81 (s, 17-Me), 8·03 and 7·90 (6H, 2s, 2 OAc), 7·38 (m, 9-H), 6·36 (3H, s, CO_2Me), *ca.* 5·28 (1H, m, $W_{\frac{1}{2}}$ *ca.* 12 c./sec., 7-H), 5·02 (1H, d, J 3·5 c./sec., 14-H).

The gum (A) was treated with 70% acetic acid (50 ml.) at 70° for 4 hr., the solution was adjusted to pH 8 and extracted with ethyl acetate to give a gum (963 mg.) which was chromatographed on alumina (Grade V). Elution with ethyl acetate–light petroleum (1 : 9) afforded a gum believed to be the isopropylidene derivative of (IVb). Elution with ethyl acetate gave the triol (VIIa) (216 mg.) identified by its i.r. spectrum.

Epoxidation of the 7-*Ene* (IIc).—*m*-Chloroperbenzoic acid (200 mg.) in chloroform (20 ml.) was added, with stirring, to the 7-ene (200 mg.) in chloroform (40 ml.). After 2 hr. the solution was washed with dilute sodium hydroxide solution and water and then dried. Recovery gave *methyl* 14β-*acetoxy*-13β-*hydroxy*-13α-*isopropyl*-7α,8α-*oxidopodocarpan*-15-*oate* (VIII) which crystallised from ether–light petroleum (b.p. 40—60°) as prisms (170 mg.), m.p. 172—173° (Found: C, 67·75; H, 9·15. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%), $\nu_{max.}$ 3640, 1735, 1720, and 835 cm.$^{-1}$, τ 9·04 and 8·91 (2d, J 7 c./sec., Pr^i) 9·02 (s, 17-Me), 8·79 (s, 16-Me), 8·06 (s, OAc), 6·87 (1H, d, J 5 c./sec., 7-H), 6·4 (3H, s, CO_2Me), 6·62 (1H, s, 14-H).

Reaction of Epoxide (VIII) *with Boron Trifluoride*.—The epoxide (100 mg.) in dry benzene (20 ml.) was treated with freshly distilled boron trifluoride (0·1 ml.) for 3 min. The mixture was poured into sodium hydrogen carbonate solution and the product was recovered in ether as a gum which was chromatographed on alumina. Elution with ether–light petroleum (7 : 3) gave the major component which failed to react with 2,4-dinitrophenylhydrazine in methanol.

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