63. *Some Derivatives of Totarol.*

By E. A. Adegoke, P. Ojechi, and D. A. H. Taylor.

An investigation has been made of the lead tetra-acetate oxidation of 14-isopropylpodocarpa-8,11,13-triene-6α,13-diol. It was hoped to obtain a compound in which one of the angular methyl groups was oxidised to a carboxyl. Although a cyclic ether was formed this did not oxidise further, and ring opened derivatives were not obtained.

It has been shown by Wettstein and his colleagues [1] that the reaction of 4-hydroxy-steroids with lead tetra-acetate and iodine is a convenient way of oxidising the A/B angular methyl group, which appears in the product as a lactone.

It was of interest to see whether a totarol derivative could be oxidised in a similar way to convert one of the angular 4-methyl groups into carboxyl, and so obtain compounds related to the totaroloic acid recently described.[2]

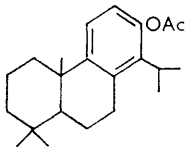
In the case of a diterpene there are three angular methyl groups attached to ring A which might be oxidised in this way instead of the one present in a steroid, but if the oxidation is carried out on 14-isopropylpodocarpa-8,11,13-triene-6α,13-diol (6α-hydroxy-totarol) it should be the 4α-methyl group which would be oxidised, giving a compound epimeric at C-4 with the natural acid.

Totarol acetate was oxidised with chromic acid to the 7-oxo-derivative,[3] and this was reduced with lithium aluminium hydride to give a poorly crystalline substance, presumably a stereoisomeric mixture of isopropylpodocarpatriene-7,13-diols (7-hydroxytotarols).[4] This dehydrated readily on treatment with sulphuric acid to give 6-dehydrototarol, isolated as its acetate (III). Oxidation of the dehydro-compound with perbenzoic acid gave a single crystalline oxide. Presumably this is the α-oxide as the β-side of the molecule is hindered by two axial methyl groups.

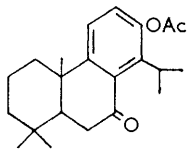
Hydrogenation of this oxide over Adams catalyst gave 6α-hydroxytotaryl acetate, the benzylic C–O linkage being the one which is split. That hydrogenation had occurred in this way was shown by oxidation of the alcohol to 6-oxototaryl acetate, which was different from the original 7-oxototaryl ester. This ketone was stereochemically stable to hydrolysis, giving the corresponding phenol from which it was recovered by acetylation. This shows that in this series the A/B *trans* configuration is the more stable, as would be expected.

[1] Heusler, Kalvoda, Wieland, Anner, and Wettstein, *Helv. Chim. Acta*, 1962, **45**, 2575.
[2] Taylor, *J.*, 1963, 1553.
[3] Chow and Erdtman, *Acta Chem. Scand.*, 1960, **14**, 1852.
[4] Hodges, *J.*, 1961, 4247.

6α-Hydroxytotaryl 13-acetate was oxidised with lead tetra-acetate and iodine, as described for 4-hydroxy-steroids. Unfortunately, the product showed infrared absorption for only one carbonyl group, identified as the original phenolic acetate, and on analysis was found to differ from the original by the loss of only two hydrogen atoms. As its infrared spectrum no longer showed a band corresponding to hydroxyl, the compound group is considered to be a cyclic ether. The n.m.r. spectrum, kindly determined by



(I)



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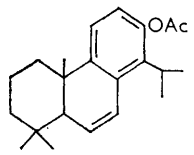

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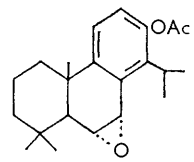

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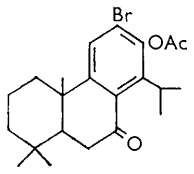

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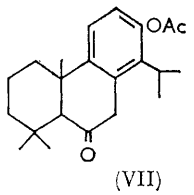

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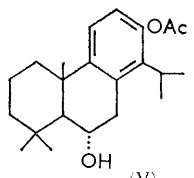

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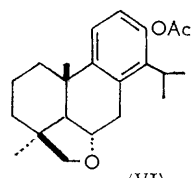

(VI)

Dr. A. Melera, of Varian Associates, Zurich, agrees with structure (VI) in which the ether linkage is 6α,16, involving the axial methyl group at C-4, but not with the isomeric structure in which C-17 is oxidised. Comparison of the spectra of compounds (V) and (VI) show that the two bands at 0·95 and 0·92 p.p.m. corresponding to the two axial methyl groups in (V) are both absent from the spectrum of (VI), being replaced by one new band at 1·20. Examination of a model shows that a 6α,15-epoxy-bridge is impossible, while a 6α,16 bridge can only be formed if ring A goes into a boat conformation, in which case C-15 is no longer axial to ring A. This would seem to be the likely explanation of the spectral data. Why a 6α,16 bridge with ring A in the boat form should be formed in preference to a 6α,17 bridge, in which ring A could retain the chair conformation is not known.

The oxide was boiled with acetic anhydride and toluene-*p*-sulphonic acid in the hope of obtaining a 16-acetate which could be converted into totaroloic acid, but no crystalline product was obtained.

An investigation was also made of the bromination of 7-oxototaryl acetate. In methylene chloride or acetic acid this gave the aromatic bromo-compound 12-bromo-7-oxototaryl acetate (VIII). Alkaline hydrolysis of this gave the corresponding phenol, from which the acetate was recovered on acetylation. When this bromo-compound was dissolved in acetic acid together with one molecular proportion of bromine and left for 48 hr. at room temperature, no change occurred, the bromo-compound being recovered.

Experimental

6-*Dehydrototaryl Acetate* (III).—A solution of 7-oxototaryl acetate (II) (17 g.) in ether was added to lithium aluminium hydride (3 g.) in ether. The product, isolated in the usual way, was a gum which partly crystallised. It was dissolved in methanol (100 ml.), and a mixture of sulphuric acid (10 ml.) and water (50 ml.) added. The solution was refluxed for 1 hr., and the product was isolated with ether and then acetylated with pyridine–acetic anhydride. Crystallisation from methylene chloride–methanol gave 6-dehydrototaryl acetate (III) (16·5 g.) as prisms, m. p. 136—139° (Found: C, 80·5; H, 8·8. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%); $\lambda_{max.}$ (hexane) 226 and 270 mμ (ε 3·2 × 10^4 and 1·4 × 10^4), $[\alpha]_D^{28}$ ($CHCl_3$) −100°.

6α,7α-*Epoxytotaryl Acetate* (IV).—The dehydro-acetate (III) (13·3 g.) was dissolved in ether (100 ml.) and treated with perbenzoic acid in ether (0·3M; 140 ml.). After being kept overnight, the solution was washed with aqueous sodium hydroxide and with water and evaporated. The residue was crystallised from methylene chloride–methanol, giving 6α,7α-*epoxytotaryl acetate* (IV) (10·6 g.) as prisms, m. p. 138—139° (Found: C, 77·5; H, 8·5. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%); $[\alpha]_D^{25}$ ($CHCl_3$) −19°.

6α-*Hydroxytotaryl* 13-*Acetate* (V).—The oxide (IV) (10 g.) in tetrahydrofuran (50 ml.) and methanol (50 ml.) was hydrogenated over Adams catalyst (100 mg.), the calculated amount was absorbed in 9 hr. After filtration from catalyst the solution was evaporated and the residue crystallised from hexane–methylene chloride, giving 6α-*hydroxytotaryl* 13-*acetate* (V) (6·4 g.) as rhombs, m. p. 116—118° (Found: C, 76·8; H, 8·8. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%), $[\alpha]_D^{25}$ ($CHCl_3$) +16°. Hydrolysis with alcoholic potassium hydroxide gave 14-*isopropyl-podocarpa*-8,11,13-*triene*-6α,13-*diol* (6α-hydroxytotarol), which crystallised from benzene–hexane in needles, m. p. 186—187° (Found: C, 79·1; H, 9·4. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). The diacetate did not crystallise.

6-*Oxototaryl Acetate* (VII).—The hydroxy-acetate (V) (1 g.) dissolved in acetone, was oxidised with a slight excess of chromic acid. The product, isolated in the usual way, crystallised from methanol to give 6-*oxototaryl acetate* (VII) as very pale yellow needles, m. p. 156—158° (Found: C, 76·6; H, 8·4. $C_{22}H_{30}O_3$ requires C, 77·1; H, 8·8%); $\nu_{max.}$ (Nujol) 1720 $cm.^{-1}$, $[\alpha]_D^{25}$ ($CHCl_3$) +67°. Hydrolysis with alcoholic potassium hydroxide gave 6-*oxotarol* as needles, m. p. 143°, from which the acetate was obtained, on re-acetylation, as needles, m. p. and mixed m. p. as the original specimen.

6α,16-*Epoxytotaryl Acetate* (VI).—Lead tetra-acetate (15·0 g.), calcium carbonate (5 g.), and cyclohexane (500 ml.) were warmed to 80° with stirring, then cooled, and 6α-hydroxytotaryl 13-acetate (V) (2·5 g.) and iodine (2·5 g.) were added. The mixture was stirred for 1 hr. whilst being irradiated by a 100w lamp. The colourless solution was then filtered, washed with water and sodium thiosulphate solution, and evaporated. The residue, in acetone (100 ml.), was treated with silver acetate (4 g.) and stored overnight. Chromic acid solution (8N; 4 ml.) was added at 0°, and after 1 hr. at this temperature the solution was diluted with water and ether, and the ether layer evaporated. The residue crystallised from methanol–methylene chloride to give a product, probably 6α,16-*epoxytotaryl acetate* (VI) (1·25 g.), as prisms m. p. 146—148° (Found: C, 76·7; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%), $[\alpha]_D^{25}$ ($CHCl_3$) +57°. The infrared spectrum did not show a hydroxyl band.

12-*Bromo*-7-*oxototaryl Acetate* (VIII).—7-Oxototaryl acetate (II) (25 g.) was dissolved in methylene chloride (100 ml.) and acetic acid (100 ml.) and treated with bromine (4 ml.) dissolved in a little acetic acid. The final solution was diluted with water, the organic layer washed and evaporated, and the residue crystallised from methanol–methylene chloride. 12-*Bromo*-7-*oxototaryl acetate* (17·5 g.) crystallised in prisms, m. p. 176—178° (Found: C, 62·3; H, 6·6. $C_{22}H_{29}O_3Br$ requires C, 62·7; H, 6·9%), $[\alpha]_D^{25}$ −22·5°. Hydrolysis with alcoholic alkali gave the corresponding phenol, m. p. 225° (Found: C, 63·05; H, 7·4. $C_{20}H_{27}O_2Br$ requires C, 63·3; H, 7·1%). The acetate was obtained on reacetylation.

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