198. *Some Potential Intermediates for the Synthesis of Diterpenes.*

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Syntheses of derivatives of the *gem*-di(hydroxymethyl)cyclohexene (IVb; R′ = H), the *gem*-di(hydroxymethyl)cyclohexanol (IIIb; R′ = R″ = H), and related compound are described.

THE diol (I) is a potential intermediate in the stereospecific synthesis of podocarpic acid, for it has been shown that the equatorial 1-hydroxymethyl group in vinhaticol can be converted into methyl by reduction of the toluenesulphonate ester whereas the corresponding axial group in vouacapenol cannot.[1] This paper describes the synthesis of several compounds containing the protected *gem*-di(hydroxymethyl) group, which, it was hoped, would cyclise to derivatives of the diol (I).

The tri(hydroxymethyl) ketone (II; R = $CH_2{\cdot}OH$, R′ = R″ = H) was formed from 2-methylcyclohexanone by an aldol condensation with formaldehyde. It was obtained as a viscous, water-soluble oil and was characterised as its triacetate. The benzylidene derivative (II; R = $CH_2{\cdot}OH$, R′ + R″ = $C_6H_5{\cdot}CH{<}$) could not be isolated on reaction of the triol with benzaldehyde and hydrogen chloride, but treatment of the product with alkaline hydrogen peroxide afforded the ketone (II; R = H, R′ + R″ = $C_6H_5{\cdot}CH{<}$). This crystalline compound melted sharply and gave a single peak on gas–liquid chromatography; it was therefore considered not to be a mixture of the two possible geometric isomers. The ketone (II; R = H, R′ + R″ = $C_6H_5{\cdot}CH{<}$) condensed readily with lithium *p*-methoxyphenylacetylide to give the acetylenic carbinol (IIIa; R′ + R″ = $C_6H_5{\cdot}CH{<}$)

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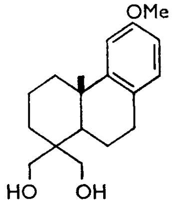
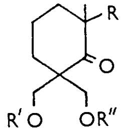
[1] King, King, and Godson, *J.*, 1955, 1117.

in which the hydroxyl (at $C_{(1)}$) and hydrogen (at $C_{(6)}$) appeared to be in *trans*-relationship since the alcohol readily lost water in addition to benzaldehyde on acid-hydrolysis, yielding the acetylenic diol (IVa; $R' = H$). This compound and its diacetate (IVa; $R' = Ac$) and ditoluene-*p*-sulphonate were reduced with hydrogen in the presence of palladised strontium carbonate to the respective cyclohexenes (IVb); the reductions proceeded stepwise and in the cases of the diol and the ditoluene-*p*-sulphonate the dienes (IVc) were isolated. The *cis*-ethylenic linkages in these products prevented coplanarity of the cyclohexene rings and their styryl substituents and their ultraviolet spectra resembled that of styrene.


(I)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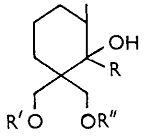
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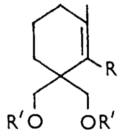
(IV)

a : $R = \cdot C{:}C\cdot C_6H_4\cdot OMe$

b : $R = \cdot CH_2\cdot CH_2\cdot C_6H_4\cdot OMe$

c : $R = \cdot CH{:}CH\cdot C_6H_4\cdot OMe$

Reduction of the acetylenic carbinol (IIIa; $R' + R'' = C_6H_5\cdot CH\langle$) with an aged sample of palladium black gave the cyclohexanol (IIIb; $R' + R'' = C_6H_5\cdot CH\langle$), whilst reduction with freshly prepared catalyst, under slightly acidic conditions, yielded the triol (IIIb; $R' = R'' = H$) characterised as its diacetate. An attempt to convert this triol into its dibenzyl ether was not successful.

The diol (IVb; $R' = H$), its diacetate and ditoluene-*p*-sulphonate, and the benzylidene compound (IIIb; $R' + R'' = C_6H_5\cdot CH\langle$) were subjected to a variety of cyclisation conditions. In no case was the desired derivative of the octahydrophenanthrene diol (I) obtained. The principal products appeared to be either polymers or monomers in which one or both protecting groups had been lost and water eliminated in accompanying Wagner–Meerwein rearrangements.

EXPERIMENTAL

The light petroleum used had b. p. 60—80°. Ultraviolet absorption spectra were determined in ethanol unless otherwise stated, on a Unicam S.P. 500 spectrophotometer.

2,2,6-*Tri*(*hydroxymethyl*)-6-*methylcyclohexanone*.—A 10% solution of formaldehyde (270 ml.) was added during 2 hr. to a stirred suspension of calcium hydroxide (15 g.) in a solution of 2-methylcyclohexanone (33·6 g.), dioxan (250 ml.), and water (900 ml.) at 0°. After a further 2 hr., the solution was filtered through a coarse filter paper, acidified with formic acid, and evaporated under reduced pressure at 45°, to give the crude product and calcium formate. The viscous mass was triturated with methanol (150 ml.) and filtered. Evaporation of the filtrate gave the crude triol (II; $R = CH_2\cdot OH$, $R' = R'' = H$) as a clear viscous involatile oil, soluble in all common solvents with the exception of benzene and light petroleum. Acetic anhydride–pyridine at 100° gave the *triacetate* (II; $R = CH_2\cdot OAc$, $R' = R'' = Ac$), b. p. 144—150° (bath)/0·3 mm. (Found: C, 58·8; H, 7·3; Ac, 36·6. $C_{16}H_{24}O_7$ requires C, 58·5; H, 7·4; Ac, 39·3%).

OO-*Benzylidene Derivative of* 2,2-*Di*(*hydroxymethylene*)-6-*methylcyclohexanone*.—Hydrogen chloride was bubbled through a solution of the crude triol (56 g.) in benzaldehyde (50 g.) maintained at −5°, until turbidity persisted. The reactants were shaken for 30 min. at room temperature, cooled to −5°, rapidly rendered alkaline to phenolphthalein by addition of a 5% ethanolic solution of sodium ethoxide (*ca.* 150 ml.), and diluted with water (400 ml.). The crude product obtained was extracted into ether, washed with 20% sodium hydrogen sulphite solution, sodium hydrogen carbonate solution, and water, and transferred to ethanol (180 ml.). 100-Vol. hydrogen peroxide (75 ml.) was added to this solution at 0° with stirring, followed by chilled 30% ethanolic potassium hydroxide solution (150 ml.), during 15 min. Further 100-vol. hydrogen peroxide (25 ml.) was added after 5 hr. and the solution allowed to attain room temperature overnight, efficient stirring being maintained. The resulting solution was diluted with water (800 ml.) and adjusted to about pH 8 with 6N-hydrochloric acid. Distillation of the product, isolated by ether-extraction, gave the crude *benzylidene ketone* (II; R = H, R′ + R″ = $C_6H_5{\cdot}CH\langle$), b. p. 125—170°/0·08 mm. Crystallisations from ethanol afforded prisms, m. p. 102—103° (Found: C, 73·9; H, 7·5. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·8%). The yield was 18·2% based on 2-methylcyclohexanone. The ketone gave an *oxime*, needles (from aqueous methanol), m. p. 170—171° (Found: C, 70·4; H, 7·6; N, 5·05. $C_{16}H_{21}NO_3$ requires C, 69·9; H, 7·6; N, 5·1%), and a *semicarbazone*, prisms (from methanol), m. p. 215—216° (Found: C, 64·4; H, 7·4. $C_{17}H_{23}N_3O_3$ requires C, 64·3; H, 7·3%).

OO-*Benzylidene Derivative of* 2,2-*Di*(*hydroxymethyl*)-1-p-*methoxyphenylethynyl*-6-*methylcyclohexanol*.—The above ketone (6·2 g.) was added under nitrogen, batchwise during 15 min., to a stirred solution of lithium *p*-methoxyphenylacetylide in ether, prepared by adding *p*-methoxyphenylacetylene [2] (3·4 g.) in dry ether (10 ml.) to n-butyl-lithium [3] (1·5 g.) in dry ether (360 ml.) and refluxing the mixture for 2 hr. The solution was refluxed for 1·5 hr., then poured into chilled water. The crude product, obtained as a glass from the ethereal layer and ether-extracts of the aqueous phase, crystallised from light petroleum. Purification on an alumina column gave the *alcohol* (IIIa; R′ + R″ = $C_6H_5{\cdot}CH\langle$) (7·3 g.) as prisms, m. p. 129—130° (Found: C, 76·5; H, 7·1. $C_{25}H_{28}O_4$ requires C, 76·5; H, 7·2%), $\lambda_{max.}$ 204 (log ε 4·82) and 253 mμ (log ε 4·44).

3,3-*Di*(*hydroxymethyl*)-2-p-*methoxyphenylethynyl*-1-*methylcyclohexene*.—A solution of the above alcohol (IIIa) (2 g.) in ethanol (200 ml.), containing concentrated sulphuric acid (2 ml.), was refluxed for 15 min., cooled, neutralised with solid sodium hydrogen carbonate, diluted with water, and extracted with ether. From the ether extract (150 ml.), washed with 10% sodium hydrogen sulphite solution (3 × 25 ml.) to remove benzaldehyde, was obtained the acetylenic *diol* (IVa; R′ = H) (1·3 g.), elongated prisms (from aqueous methanol), m. p. 98—99·5° (Found: C, 75·1; H, 7·7. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%), $\lambda_{max.}$ 285 (log ε 4·40) and 301 mμ (log ε 4·27). The *diacetate*, prepared with acetic anhydride in pyridine at 100°, crystallised as needles (from aqueous methanol), m. p. 112—113° (Found: C, 71·3; H, 7·1. $C_{22}H_{26}O_5$ requires C, 71·3; H, 7·1%). The *ditoluene*-p-*sulphonate* was obtained, by treatment with toluene-*p*-sulphonyl chloride in pyridine at room temperature for 14 hr., as prisms (from ethanol), m. p. 123—124° (decomp.) or 136—137° (decomp.) on rapid heating (Found: C, 64·5; H, 5·6; S, 10·1. $C_{32}H_{34}O_7S_2$ requires C, 64·6; H, 5·8; S, 10·8%).

Reductions of 3,3-*Di*(*hydroxymethyl*)-2-p-*methoxyphenylethynyl*-1-*methylcyclohexene and its Derivatives*.—The acetylenic diol (IVa; R′ = H) (3·0 g.) was reduced in ethanol with hydrogen and 5% palladised strontium carbonate. Reduction ceased after an uptake of 2·1 mol. of hydrogen, and the diol (IVb; R′ = H) was obtained as an oil. Treatment with acetic anhydride–pyridine afforded 3,3-*di*(*acetoxymethyl*)-2-p-*methoxyphenethyl*-1-*methylcyclohexene* (IVb; R′ = Ac) (2·5 g.) as elongated prisms (from light petroleum), m. p. 63·5—64° (Found: C, 70·4; H, 8·1; Ac, 26·9. $C_{22}H_{30}O_5$ requires C, 70·6; H, 8·1; Ac, 27·3%).

By stopping a similar reduction when the hydrogen uptake had reached 1·2 mol., 3,3-*di*(*hydroxymethyl*)-2-2′-p-*methoxyphenylvinyl*-1-*methylcyclohexene* (IVc; R′ = H) was obtained as flat elongated prisms (from light petroleum), m. p. 106—107° (Found: C, 74·8; H, 8·8. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·4%), $\lambda_{max.}$ 205 (log ε 4·36) and 268 mμ (log ε 4·19).

Reduction of the acetylenic diacetate (IVa; R′ = Ac) under the same conditions gave the diacetate (IVb; R′ = Ac), m. p. and mixed m. p. 63—64°.

Reduction of the acetylenic ditoluene-*p*-sulphonate (1 g.) in ethyl acetate with 5% palladised strontium carbonate afforded the *diester* (IVb; R′ = *p*-$C_{10}H_4Me{\cdot}SO_2$) (0·9 g.) as prisms (from acetone–light petroleum), m. p. 85—85·5° (decomp.) (Found: C, 63·9; H, 6·6; S, 10·3. $C_{32}H_{38}O_7S_2$ requires C, 64·2; H, 6·4; S, 10·7%).

A similar reduction was stopped after 1·1 mol. of hydrogen has been adsorbed and the *diene ditoluene*-p-*sulphonate* (IVc; R′ = $C_6H_4Me{\cdot}SO_2$) was obtained as elongated prisms (from aqueous alcohol), m. p. 83—83·5° (decomp.), depressed to 79—79·5° (decomp.) when mixed with

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[2] Bergmann and Bondi, *Ber.*, 1933, **66**, 278.

[3] Gilman, Bell, Brannen, Bullock, Dunn, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 1499.

the toluene-*p*-sulphonate (IVb; R′ = $C_6H_4Me{\cdot}SO_2$) (Found: C, 64·3; H, 6·2; S, 10·2. $C_{32}H_{36}O_7S_2$ requires C, 64·4; H, 6·1; S, 10·7%), $\lambda_{max.}$ (in CH_2Cl_2) 267 mμ (log ε 4·17).

Reductions of the OO-*Benzylidene Derivative of* 2,2-*Di*(*hydroxymethyl*)-1-p-*methoxyphenylethynyl*-6-*methylcyclohexanol.*—(*a*) The acetylenic carbinol (IIIa; R′ + R″ = $C_6H_5{\cdot}CH\!<$) (4 g.) was hydrogenated in ethanol (30 ml.) containing concentrated hydrochloric acid (1 drop) over freshly prepared palladium black. Reduction ceased after 4·1 mol. of hydrogen had been adsorbed and the triol (IIIb; R′ = R″ = H) (2·9 g.) was obtained as an oil on filtration and removal of the solvent and toluene under reduced pressure. Treatment with acetic anhydride–pyridine at 100° gave 2,2-*di*(*acetoxymethyl*)-1-2′-p-*methoxyphenylethyl*-6-*methylcyclohexanol* (IIIb; R′ = R″ = Ac), b. p. 210° (bath)/0·04 mm. (Found: C, 67·3; H, 8·1; Ac, 23·6. $C_{22}H_{32}O_6$ requires C, 67·3; H, 8·2; Ac, 21·9%).

The triol, when kept in dry acetone over potassium carbonate for 3 days, was converted into the *isopropylidene derivative* (1·15 g.), b. p. 180—184° (bath)/0·03 mm. (Found: C, 72·3; H, 9·0. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), which gave acetone on acid hydrolysis.

(*b*) The acetylenic carbinol (IIIa; R′ + R″ = $C_6H_5{\cdot}CH\!<$) (3 g.) in alcohol was reduced with an aged sample of palladium black. Reduction ceased after 1·8 mol. of hydrogen had been absorbed. Filtration and removal of the solvent gave the *benzylidene derivative* (IIIb; R′ + R″ = $C_6H_5{\cdot}CH\!<$) (2·5 g.) as an oil, b. p. 260° (bath)/0·01 mm. (Found: C, 76·1; H, 8·3. $C_{25}H_{32}O_4$ requires C, 75·7; H, 8·1%), which was hydrolysed with acid to give benzaldehyde.

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