871. *The Synthesis of* 8-*Isopropylpodocarpane*-6,7-*diol* (6-*Hydroxytotarol*) *and of* 7,8-*Dimethoxypodocarpane.*

By N. F. Elmore and T. J. King.

Maytenone, $C_{40}H_{60}O_4$ (previous paper), decomposes on melting to give *inter al.* two phenolic materials. The synthesis of 8-isopropylpodocarpane-6,7-diol (6-hydroxytotarol) (I; R = $CHMe_2$) and of 7,8-dimethoxypodocarpane has shown that one of the phenols is 8-isopropylpodocarpane-6,7-diol and that the other is not identical, although it is isomeric, with podocarpane-7,8-diol (II).

The bisditerpene maytenone[1] characteristically decomposes on melting at *ca.* 195° to give propene and a mixture which consists substantially of two catechols both of which appear to be related to diterpenes. One of these was readily purified as the sparingly

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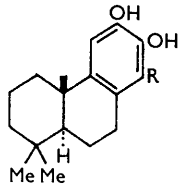
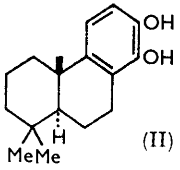
[1] Johnson, King, and Martin, preceding paper.

soluble dibenzoate and the other as the di-*p*-nitrobenzoate. Analysis and other considerations suggested that the crystalline dibenzoate was a derivative of a C_{20} catechol and a possible structure was that of 8-isopropylpodocarpane-6,7-diol (I; R = $CHMe_2$).



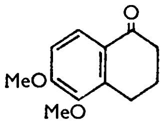
(I)



(II)

A quantity of totarol was available to us from the collection of the late Dr. W. F. Short through the kindness of Mrs. Short, and the 6-hydroxy-group was introduced into the molecule through 6-nitro- and 6-amino-totarol. The nitration was carried out following the method of Hodges and Raphael [2] for the nitration of 6-hydroxypodocarpane. The nitro-compound, characterised as its acetate, was readily reduced catalytically to aminototarol, previously prepared [3] by reduction of an azo-totarol. The aminophenol was diazotised in acetic acid solution and the resulting diazonium salt decomposed in boiling dilute sulphuric acid to give a moderate yield of a catechol which readily afforded a crystalline benzoate. A comparison of this benzoate with that derived from maytenone established their identity.

The second phenolic component of the pyrolysis of maytenone appears to be a C_{17} compound and the two most probable structures for this are 6,7- (I; R = H) and 7,8-dihydroxypodocarpane (II). We have synthesised the dimethyl ether of (II) by conventional means, following closely on Rao and Raman's synthesis of ferruginol.[4]



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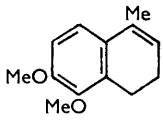

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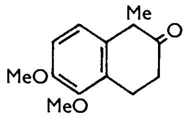

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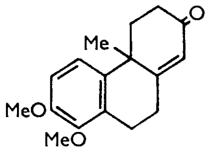


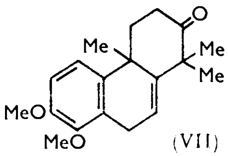
(VI)

Methylation [5] of *o*-vanillin gave *o*-veratraldehyde which was treated with malonic acid and then reduced with sodium amalgam.[6] The β-(2,3-dimethoxyphenyl)propionic acid so obtained was homologated in excellent yield by the Arndt–Eistert method and the derived butyric acid or its methyl ester was cyclised with concentrated sulphuric acid to the tetralone (III) in 70% yield. Polyphosphoric acid as a cyclising agent gave consistently lower yields. The crystalline " styrene " (IV) was obtained in nearly quantitative yield by the action of methylmagnesium iodide in cold benzene on the ketone and was converted into the 2-tetralone (V) by reaction with lead tetra-acetate in acetic acid followed by acid isomerisation. Ring extension by the Robinson–Mannich procedure afforded the ketone (VI) in 37% yield, and this was then dimethylated, the derived ketone (VII) being purified through the semicarbazone.

Huang-Minlon reduction of the pure semicarbazone removed the carbonyl oxygen and also caused migration of the double bond into conjugation with the benzene ring.

[2] Hodges and Raphael, *J.*, 1960, 50.
[3] Short and Wang, *J.*, 1951, 2979.
[4] Rao and Raman, *Tetrahedron*, 1958, **4**, 294.
[5] Cf. Barger and Silberschmidt, *J.*, 1928, 2924.
[6] Haworth, *J.*, 1927, 2282.

Although the product (VIII) was presumed to be a mixture of the *cis* and *trans* ring-fused compounds,[7] the final hydrogenation gave crystalline ether (IX). Subsequently the unsaturated ketone (VII) regenerated from the semicarbazone was reduced catalytically before removal of the carbonyl function but, as would be expected, reduction was much slower than with (VIII). This product presumably had a *trans* ring fusion. Huang-Minlon reduction of the ketone afforded the same crystalline ether as obtained previously. A comparison of the infrared absorption spectra of this ether and of that derived from the pyrolysis product of maytenone established their non-identity, and moreover, a small amount of the derived catechol, prepared from the ether with hydriodic acid, failed to give a crystalline di-*p*-nitrobenzoate.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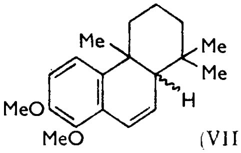
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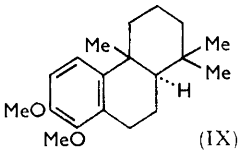
(IX)

EXPERIMENTAL

All melting points were determined on a Kofler block.

6-*Nitrototarol*.—Cupric nitrate trihydrate (2·3 g.) was added to a solution of totarol (5 g.) in acetic anhydride (40 c.c.) with shaking, and the resulting green mixture was left overnight at room temperature. Water (200 c.c.) was added and when the acetic anhydride had reacted the solution was extracted with ether. The extract was washed (water, sodium hydrogen carbonate solution, water), dried, and evaporated to give a brown oil which was taken up in ethanol (50 c.c.). After this solution had been kept for several days in the refrigerator, 6-*nitrototarol* separated and crystallised from ethanol as long yellow needles (1·8 g.), m. p. 73—74·5° (Found: C, 72·7; H, 8·7; N, 4·6. $C_{20}H_{29}NO_3$ requires C, 72·45; H, 8·8; N, 4·25%). The *acetate* (acetic anhydride–sulphuric acid) crystallised from ethanol as plates, m. p. 134—135° (Found: C, 70·7; H, 8·0; N, 4·0. $C_{22}H_{31}NO_4$ requires C, 70·75; H, 8·35; N, 3·75%).

6-*Aminototarol*.—6-Nitrototarol (650 mg.) in methanol (20 c.c.) was hydrogenated over Adams catalyst at atmospheric temperature and pressure. The calculated amount of hydrogen was absorbed in 30 min. and reduction then stopped. The residue, after catalyst and solvent had been removed, crystallised from light petroleum (b. p. 60—80°) as plates, m. p. 165—166° (lit.,[3] 166—167°).

6-*Isopropylpodocarpane*-6,7-*diol* (6-*Hydroxytotarol*) *Dibenzoate*.—6-Aminototarol (1·2 g.) in glacial acetic acid (40 c.c.) containing sulphuric acid (10 c.c. of 10%) was treated at −5° with aqueous sodium nitrite (1 c.c. containing 350 mg. of nitrite). After 1 hr. at 0°, urea was added to decompose excess of nitrous acid, and the solution was added gradually to refluxing sulphuric acid (20%; 90 c.c.) containing sodium sulphate (3 g.). When addition was complete the solution was cooled, diluted, and extracted with ether. The residue after evaporation of the ether, distilled at 160—180° (bath)/0·1 mm. to give a red resin having a green ferric reaction. The distillate (150 mg.) was dissolved in benzoyl chloride (1 c.c.) and shaken with aqueous sodium hydroxide during 5 min. The resulting *benzoate* was collected and crystallised from chloroform–ethanol, forming plates, m. p. 226—228° undepressed on mixture with a sample derived from maytenone (Found: C, 79·8; H, 7·1. $C_{34}H_{38}O_4$ requires C, 80·0; H, 7·5%). The infrared absorption curves of the two benzoate samples were identical.

γ-(2,3-*Dimethoxyphenyl*)*butyric Acid*.—β-(2,3-Dimethoxyphenyl)propionyl chloride (b. p. 106—107°/2 mm.; 47·5 g.), prepared from the acid[6] (52 g.) with thionyl chloride, in dry ether (200 c.c.) at 0°, was added slowly with stirring to a cold solution of diazomethane (from 90 g. of methylnitrosourea) in dry ether (1 l.). Evolution of nitrogen stopped after 1 hr., and after

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[7] Wenkert and Stevens, *J. Amer. Chem. Soc.*, 1956, **78**, 2318, 5627.

a further 30 min. at room temperature the solvent was removed (vacuum) to afford the diazoketone as an orange-yellow viscous oil. This was dissolved in dry methanol (500 c.c.), and to the solution was added 2 c.c. of a 10% solution of silver benzoate in triethylamine.[8] The evolution of nitrogen was brisk and was maintained at a steady rate by further addition of the catalyst until it stopped abruptly. The solution was then boiled for 30 min., filtered and evaporated. The residue was distilled to give *methyl γ-(2,3-dimethoxyphenyl)butyrate* (42·7 g., 72·5%), b. p. 112°/2 mm., n_D^{12} 1·5080 (Found: C, 65·5; H, 7·65. $C_{13}H_{18}O_4$ requires C, 65·55; H, 7·6%).

When the Wolff rearrangement was carried out in aqueous dioxan with a silver oxide–sodium thiosulphate catalyst,[9] *γ-(2,3-dimethoxyphenyl)butyric acid* was obtained directly. However, the yields were variable and the method described above is considered preferable. The acid obtained in this way or by hydrolysis of the ester crystallised from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 58·5—60° (Found: C, 63·9; H, 6·95. $C_{12}H_{16}O_4$ requires C, 64·25; H, 7·2%).

5,6-*Dimethoxy*-1-*tetralone* (III).—The above methyl ester (5 g.) was heated at 85—90° for 15 min. with sulphuric acid (85%; 50 c.c.). The resulting dark red solution was poured on ice and the precipitate was collected and crystallised from cyclohexane (charcoal) to give the *tetralone* in 70—75% yield as plates, m. p. 104—105°, $\lambda_{max.}$ 232 (log ε 4·26) and 281 mμ (log ε 4·12) (Found: C, 69·8; H, 6·5. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·85%). The 2,4-*dinitrophenylhydrazone* crystallised from chloroform–methanol as deep red plates, m. p. 255—257°, $\lambda_{max.}$ 304 (log ε 4·01) and 401 mμ (log ε 4·43) (Found: C, 55·7; H, 4·9; N, 14·3. $C_{18}H_{18}N_4O_6$ requires C, 55·95; H, 4·7; N, 14·5%).

Similar yields of ketone were obtained by cyclising the acid under the same conditions.

3,4-*Dihydro*-5,6-*dimethoxy*-1-*methylnaphthalene* (IV).—The above tetralone (24 g.) in dry benzene (100 c.c.) was added during 1 hr. to a solution of methylmagnesium iodide (from 8·2 g. of magnesium) in benzene (200 c.c.) with stirring and cooling in ice. After 2 hr. at 0° a test sample gave no precipitate with cold methanolic dinitrophenylhydrazine sulphate. Next day the mixture was decomposed with ice-cold dilute sulphuric acid, and the benzene layer was separated, washed with aqueous sodium hydroxide, and evaporated. Methanol (40 c.c.) was added to the residue and after cooling overnight in the refrigerator the crystalline precipitate (21·2 g.) was collected. The 3,4-*dihydro*-5,6-*dimethoxy*-1-*methylnaphthalene* crystallised from methanol in plates, m. p. 69—70°, $\lambda_{max.}$ 216 (log ε 4·27) and 268 mμ (log ε 4·10) (Found: C, 76·1; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·45; H, 7·9%).

5,6-*Dimethoxy*-1-*methyl*-2-*tetralone* (V).—Lead tetra-acetate (9·4 g.) was added gradually to an ice-cold solution of the above dihydronaphthalene (4·0 g.) in glacial acetic acid (50 c.c.), and the solution was allowed to warm to room temperature. After 45 min. the solution was poured into water and extracted with ether. The extract was washed and evaporated and the residue was boiled for 2 hr. with ethanol containing sulphuric acid (18%; 15 c.c.). The red solution so obtained was diluted with water (200 c.c.) and its ether extract was dried and distilled. The 2-*tetralone* (2·7 g., 70%) came over at 115—116°/0·2 mm. as a yellow oil which solidified after several weeks (Found: C, 70·6; H, 6·75. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). The 2,4-*dinitrophenylhydrazone* was obtained as yellow needles (from chloroform–methanol), m. p. 190—192°, $\lambda_{max.}$ 234 (log ε 4·29) and 366 mμ (log ε 4·35) (Found: C, 56·8; H, 5·0; N, 13·9; OMe, 14·7. $C_{19}H_{20}N_4O_6$ requires C, 57·0; H, 5·05; N, 14·0; 2OMe, 15·5%).

2,3,4,4a,9,10-*Hexahydro*-7,8-*dimethoxy*-4a-*methyl*-2-*oxophenanthrene* (VI).—A solution of potassium ethoxide (from 2·15 g. of potassium and 60 c.c. of ethanol) was added at 0° with swirling to a mixture of the 2-tetralone (8 g.) and diethylaminobutan-2-one methiodide (from 5·2 g. of ketone and 5·2 g. of methyl iodide) in dry benzene (60 c.c.) under nitrogen. The mixture was stirred during 15 min. and left at 0° for 1½ hr. The pale yellow solution was then boiled for 30 min., cooled, and decomposed with dilute sulphuric acid. The organic layer was separated and the aqueous layer extracted with ether. The combined organic solutions were washed, dried, and evaporated and the residue was distilled to give a resin, b. p. 140—160°/0·05 mm., which crystallised from cold ether (solid carbon dioxide) to give 2,3,4,4a,9,10-*hexahydro*-7,8-*dimethoxy*-4a-*methyl*-2-*oxophenanthrene* (3·65 g., 36·9%). The analytical sample crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 107—108·5°, $\lambda_{max.}$ 233 mμ (log ε 4·38),

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[8] Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

[9] Bachmann and Struve, " Organic Reactions," Volume I, John Wiley and Sons, New York, 1942, p. 38.

$\nu_{max.}$ (in carbon tetrachloride) 1681 cm.$^{-1}$ (Found: C, 74·7; H, 7·3. $C_{17}H_{20}O_3$ requires C, 74·95; H, 7·4%). The *semicarbazone* formed needles (from ethanol), m. p. 198—199°, $\lambda_{max.}$ 228 (log ε 4·15) and 270 mμ (log ε 4·52) (Found: C, 65·4; H, 6·95. $C_{18}H_{23}N_3O_3$ requires C, 65·65; H, 7·05%).

1,2,3,4,4a,9-*Hexahydro*-7,8-*dimethoxy*-1,1,4a-*trimethyl*-2-*oxophenanthrene* (VII).—The above ketone (3·65 g.) was added at 30° under nitrogen to a solution of potassium (1·9 g.) in t-butyl alcohol (50 c.c.). The red solution was then cooled in ice, and methyl iodide (5 c.c.) was added in one portion. The contents of the flask were left at room temperature for 2 hr., and then boiled for 30 min. The oil obtained after dilution with water was collected in ether and isolated by evaporation as a gum whose infrared spectrum showed that it contained about 75% of a non-conjugated ketone. The crude ketone was converted into the *semicarbazone* which after crystallisation from ethanol had m. p. 208·5—211°, $\lambda_{max.}$ 226 mμ (log ε 4·26) (Found: N, 11·9. $C_{20}H_{27}N_3O_3$ requires N, 11·8%). The *hexahydrophenanthrone* was recovered by heating the semicarbazone with an acetic acid solution of pyruvic acid and sodium acetate and after isolation in the usual way distilled at 168—172° (bath)/0·15 mm. The distillate solidified in the receiver; its infrared absorption showed it to contain little if any αβ-unsaturated ketone, $\lambda_{max.}$ 274 mμ (log ε 3·20) (Found: C, 75·7; H, 8·25. $C_{19}H_{24}O_3$ requires C, 75·95; H, 8·05%).

1,2,3,4,4a,10a-*Hexahydro*-7,8-*dimethoxy*-1,1,4a-*trimethylphenanthrene* (VIII).—The above semicarbazone was heated in diethylene glycol (50 c.c.) containing hydrazine hydrate (100%; 3 c.c.) and potassium hydroxide (4 g.) at 150° for 1 hr. and then at 190° for 5 hr. The oil extracted by ether from the diluted and acidified solution gave a green ferric reaction and was methylated (acetone–methyl sulphate–potassium carbonate) to give the *product*, which distilled at 110—120° (bath)/0·01 mm.; this did not display hydroxyl group absorption in the infrared spectrum; $\lambda_{max.}$ 227 (log ε 4·37) and 268 mμ (log ε 3·91) (Found: C, 79·5; H, 9·25. $C_{19}H_{26}O_2$ requires C, 79·9; H, 9·15%).

trans-1,2,3,4,4a,9,10,10a-*Octahydro*-7,8-*dimethoxy*-1,1,4a-*trimethyl*-2-*oxophenanthrene*.—The above hexahydrophenanthrone (regenerated from the semicarbazone; 1·5 g.) was hydrogenated in acetic acid over 10% palladised charcoal, the theoretical uptake of hydrogen being achieved after 48 hr. The *product*, isolated in the usual manner, distilled at 190—195° (bath)/0·3 mm. and slowly crystallised (Found: C, 75·1; H, 8·5. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%).

trans-1,2,3,4,4a,9,10,10a-*Octahydro*-7,8-*dimethoxy*-1,1,4a-*trimethylphenanthrene* (IX).—(*a*) The above saturated ketone was reduced in the same way as described for its unsaturated derivative. Remethylation and distillation of the product afforded 6,7-*dimethoxypodocarpane* as an oil, b. p. 135—145° (bath)/0·01 mm., which crystallised as plates, m. p. 48—52° (Found: C, 79·4; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

(*b*) 1,2,3,4,4a,10a-Hexahydro-7,8-dimethoxy-1,1,4a-trimethylphenanthrene (128 mg.) was hydrogenated in acetic acid at room temperature and pressure over 5% palladised charcoal. Hydrogen uptake was complete in 10 hr. The product (75 mg.), isolated in the usual way, had b. p. 180—184° (bath)/0·15 mm., and solidified as plates, m. p. 52—53° undepressed by the material prepared by route (*a*), $\lambda_{max.}$ 277 mμ (log ε 3·12) (Found: C, 79·5; H, 9·9%).

The infrared absorption curves of this material and the dimethyl ether prepared from the phenol derived from maytenone showed many points of dissimilarity.

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