**870.** *Maytenone. Part I. Isolation and Structural Studies.*

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Maytenone is shown to be a bisditerpene, probably formed by the oxidation of a phenolic diterpene, such as ferruginol or totarol, to the corresponding α-hydroxycyclohexadienone, which then dimerises by a Diels–Alder mechanism. Several reactions of maytenone are described including the pyrolytic decomposition to propene and a mixture of a $C_{20}$ and a $C_{17}$ catechol. The former has been identified as 8-isopropylpodocarpane-6,7-diol (6-hydroxytotarol) and the latter as podocarpane-6,7-diol.

THE yellow outer root bark of the tree *Maytenus dispermus* is a source of the pigment, pristimerin,[1] which is obtained by counter-current distribution of the light-petroleum extract. Also obtained from this separation is a colourless crystalline material, in about 0·03% overall yield, which we have named maytenone. Analysis established the empirical formula as $C_{10}H_{15}O$ and molecular-weight determinations gave values of 266 (Rast), $2360/n$ (X-ray), and $624 \pm 25$ (thermistor-drop technique;[2] this determination was carried out in the University Chemical Laboratory, Cambridge, by Mr. G. Purdy, whose help we gratefully acknowledge). It is now known for reasons which will subsequently become apparent that the Rast method will give a false result, and the reactions of maytenone are best interpreted in terms of a molecular formula of $C_{40}H_{60}O_4$ (molecular weight 604·6). The significant ultraviolet absorption of maytenone occurs at 251 mμ (log ε 3·91) and there are, *inter al.*, weak absorption maxima in the infrared spectrum at 3478 and 3640, and strong absorption at 1710 and 1680 cm.⁻¹. These data are compatible with maytenone's containing two hydroxyl groups, one saturated ketonic grouping, and one αβ-unsaturated ketonic group, and these account for all the oxygen atoms of the

[1] Grant and Johnson, *J.*, 1957, 4079, 4669; Grant, Johnson, Juby, and King, *J.*, 1960, 549.
[2] Iyengar, *Rec. Trav. Chim.*, 1954, **73**, 789.

molecule. Finally, two strong bands of almost equal intensity at 1370 and 1390 cm.$^{-1}$ suggest the presence of at least one *gem*-dimethyl grouping ($>CMe_2$).

Maytenone is stable to quite vigorous treatment with alkali or aqueous or alcoholic mineral acid, fails to react with periodate, ozone, chromic acid, and the usual ketonic reagents, and is inert to catalytic hydrogenation. Its stability to chromic oxidation suggests that both hydroxyl groups are tertiary, a postulate supported by our inability to acetylate or benzoylate the compound. The presence of one of the ketone groups in maytenone was confirmed when lithium aluminium hydride reduction of an ethereal solution afforded an alcohol, maytenol, $C_{40}H_{62}O_4$, the spectral properties of which were consistent with the reduction of the saturated ketone group. Maytenol was readily acetylated and could be re-oxidised to maytenone. It is assumed that, because of steric reasons, the αβ-unsaturated ketone system is stable in the presence of lithium aluminium hydride under these conditions; other examples of this phenomenon have been reported, *e.g.*, 3-chloro-5,5-dimethylcyclohex-2-enone.[3] More vigorous reduction with lithium aluminium hydride reduced the αβ-unsaturated ketone function as well but the reaction was not always reproducible. The only crystalline compound obtained from the reaction still contained a carbonyl group and the reduction appeared to involve only the conjugated double bond. A similar reduction of the αβ-unsaturated ketone system of 6-oxocativic acid has been reported.[4]

During the attempted acetylation of maytenone with acetic anhydride and perchloric acid, a new compound was obtained, the ultraviolet absorption curve of which was similar to that of maytenone. The positions of the carbonyl bands in the infrared spectrum also corresponded to those of maytenone, but the hydroxyl bands were missing in the spectrum of the new product. This change is best interpreted as a dehydration involving both hydroxyl groups of maytenone to give an ether, anhydromaytenone, $C_{40}H_{58}O_3$, and this view was supported by analysis and by the appearance of a new band in the infrared spectrum at 1050 cm.$^{-1}$, which could be attributed to the presence of the ether grouping. Subsequently the same product was obtained from maytenone by the action of other acidic dehydrating agents, *e.g.*, formic acid and acetic anhydride–toluene-*p*-sulphonic acid. Anhydromaytenone was unaffected by the action of chromic acid or ozone or catalytic hydrogenation.

A relation of maytenone to the diterpenes was indicated by the isolation of a single crystalline product, 8-methyl-2-phenanthrol (I) from dehydrogenation of maytenone with selenium at 320—360°. Distillation of the phenol with zinc gave 1-methylphenanthrene. Dehydrogenation of totarol [5] (II; R = H, R' = CHMe$_2$) had previously given 8-methyl-2-phenanthrol, and we are indebted to Dr. Wang for an authentic specimen of this compound which was identified with our product. If pristimerin can be regarded as a modified triterpene, then this is one of the rare occasions where di- and tri-terpenes are found in co-existence.[cf. 6]
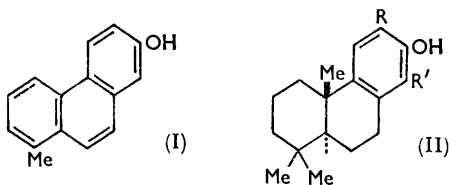


Perhaps the most striking reaction of maytenone is its decomposition on melting. This occurs with the evolution of gas and the formation of a pale yellow resin which distils under reduced pressure without further decomposition. The gas has been shown (vapour-phase chromatography and infrared spectrum) to be very pure propene. This highly

[3] Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.
[4] Halsall and Moyle, *J.*, 1960, 1324.
[5] Short and Stromberg, *J.*, 1937, 516; Short and Wang, *J.*, 1951, 2979.
[6] Cocker, Halsall, and Bowers, *J.*, 1956, 4259.

specific elimination of propene must have structural significance, especially as the pyrolytic decomposition of maytenol required a higher temperature, *ca.* 270°, and produced propene in smaller yield and accompanied by other gaseous products, *e.g.*, hydrogen, propane, ethylene, and water. Moreover, unlike the decomposition of maytenone, the pyrolysis of maytenol was acid-catalysed, phenols being produced readily at 190° in presence of potassium hydrogen sulphate and even by boiling formic acid. The resin from the pyrolysis of maytenone was phenolic (ultraviolet absorption) and in fact a catechol (green ferric reaction, reduction of pH of boric acid solutions, retardation on borate-treated paper, easy aerial oxidation of an alkaline solution), a conclusion confirmed by silver oxide oxidation of the phenol to an unstable coloured compound which gave a crystalline quinoxaline with *o*-phenylenediamine. Later work showed that the phenolic pyrolysis product was a mixture of two catechols, one of which gave a readily purified crystalline benzoate, the analysis of which indicated that it was derived from a $C_{20}$ dihydric phenol. In view of the production of the methylphenanthrol (I) by dehydrogenation, it seemed that a possible structure for the $C_{20}$ catechol was 8-isopropylpodocarpan-6,7-diol (6-hydroxytotarol) (II; R = OH, R' = CHMe$_2$). When this compound was synthesised from totarol by nitration, reduction, and diazotisation (following paper) it proved to be identical with the pyrolysis product of maytenone. A quantitative study of the pyrolysis showed that each molecule of maytenone gave only one of propene and suggested that the decomposition was taking the course, $C_{40} \longrightarrow C_{20} + C_3 + C_{17}$; this was confirmed by the yield of the $C_{20}$ dibenzoate. The mother liquors from which the crystalline dibenzoate had separated afforded, after removal of the benzoyl groups with lithium aluminium hydride, another catechol, $C_{17}H_{24}O_2$, which gave an oily dibenzoate but a crystalline di-*p*-nitrobenzoate. It was probable that this catechol was either (II; R = OH, R' = H) or (II; R = H, R' = OH) with the former structure favoured because the crude pyrolysis product gave a negative Gibbs test.[7] The catechol (II; R = H, R' = OH) was first synthesised (following paper) but did not give a crystalline di-*p*-nitrobenzoate. The catechol (II; R = OH, R' = H) has recently been synthesised (forthcoming publication) and its identity with the pyrolysis product from maytenone has been established.

The thermal decomposition of maytenone, which is not catalysed by acid or alkali, suggests that the reaction might be of the reverse Diels–Alder type, in which case the two units making up the maytenone molecule would probably be of the α-hydroxycyclohexa-dienone type. Such compounds are oxidation products of phenols [8] and are known to be dimerised easily by the Diels–Alder reaction. Thus Adler *et al.*[9] have shown that the 2-hydroxycyclohexadienone derived from 2,4-dimethylphenol cannot be isolated because it dimerises almost spontaneously, and the spectral properties of the dimer (III), as reported by Adler *et al.*, closely resemble those of maytenone. Further, as with maytenone, periodate fails to react with the dimer (III), and the latter does not exhibit any normal ketonic properties.

However, the dimer (III) is more susceptible to catalytic hydrogenation than is maytenone, although the latter's stability may well be the consequence of steric factors.

The pyrolytic decomposition of maytenone does not reverse the mode of formation and, as has been outlined above, it involves the elimination of propene from one of the units. Although the precise structure of maytenone has not yet been determined, many of the observed reactions can be interpreted on the assumption that the biogenesis of maytenone involves an oxidation of ferruginol (IV) to the corresponding hydroxycyclo-hexadienone (V) which then dimerises to a structure (VI) which we now use to illustrate the reactions of maytenone. Because the gas produced from the pyrolysis of maytenol is impure propene it is assumed that the propene is derived from the unit (B) containing the saturated carbonyl group. The $C_{17}$ catechol has not been detected in the pyrolysis

[7] King, King, and Manning, *J.*, 1957, 563.
[8] Review: Wessely, *J. Roy. Inst. Chem.*, 1959, 424.
[9] Adler, Junghahn, Lindberg, Berggren, and Westin, *Acta. Chem. Scand.*, 1960, **14**, 1261.

products from maytenol, which reaction may well proceed by a fundamentally different mechanism. In the case of the other unit (A) of maytenone which gives rise to the isopropylpodocarpanediol (hydroxytotarol) in the pyrolysis it would be necessary to



(III)          (IV)          (V)
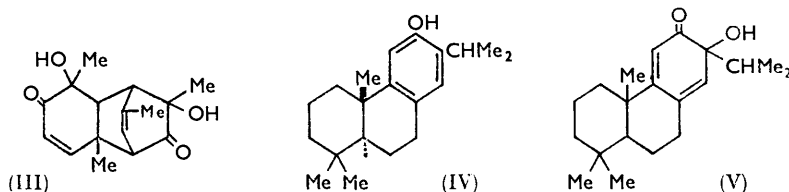
postulate a migration of the isopropyl grouping, on the basis of structure (VII). Such a rearrangement could well occur in the biogenesis of totarol which does not obey the isoprene rule.



(VI) ; X = OH, Y = CHMe₂

(VII)
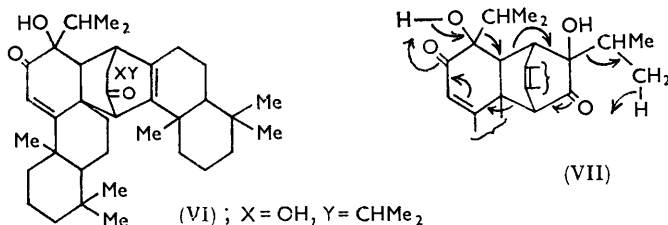
The final formulation of maytenone may well depend on a possible synthesis by oxidation of ferruginol or totarol or a mixture of the two diterpenes. These experiments are now in progress in our laboratories.

## Experimental

M. p.s are uncorrected. Ultraviolet absorption spectra were measured on ethanolic solutions and optical rotations were measured for the D line in chloroform except where otherwise stated.

*Isolation of Maytenone.*—The yellow outer root bark (1 kg.) of *Maytenus dispermus* was extracted by the method used in the isolation of pristimerin.[1] More maytenone was obtained by Soxhlet extraction of the " spent " bark with ether. The compound was finally crystallised from ether–light petroleum (b. p. 60—80°) as colourless needles (average 0·3 g. per batch), m. p. 197° (decomp.), $[\alpha]_D^{18}$ +115° (Found: C, 79·4; H, 9·85. Calc. for $C_{40}H_{60}O_4$: C, 79·4; H, 10·0%); $\lambda_{max.}$ 212 and 252 m$\mu$ (log $\varepsilon$ 3·93 and 3·91); $\nu_{max.}$ (carbon tetrachloride solution) 858, 885, 911, 1025, 1046, 1120, 1140, 1157, 1175, 1240, 1275, 1310, 1370, 1390, 1430, 1460, 1600, 1680, 1710, 2920, 3478, and 3610 cm.$^{-1}$. A counter-current distribution of maytenone over 100 tubes in methanol–light petroleum (b. p. 60—80°) was followed by light-absorption measurements on the contents of each tube; the plot showed only a single peak.

*Maytenol.*—Maytenone (1 g.) was dissolved in dry ether (50 c.c.), and the solution added dropwise to a stirred suspension of lithium aluminium hydride (1 g.) in dry ether (50 c.c.). The mixture was stirred at room temperature for 10 hr. and then the excess of reagent was destroyed by addition of water (20 c.c.) followed by dilute hydrochloric acid. The product, *maytenol*, was extracted from the mixture with ether, and crystallised from aqueous ethanol as prisms (0·9 g.), m. p. 265—266° (decomp.), $[\alpha]_D^{20}$ +114° [Found, on a sample sublimed at 190°/5·5 × 10$^{-4}$ mm.: C, 79·5; H, 10·4%; $M$ (Rast), 574. $C_{40}H_{62}O_4$ requires C, 79·2; H, 10·3%; $M$, 607]; $\lambda_{max.}$ 204 and 255 m$\mu$ (log $\varepsilon$ 3·89 and 3·78, respectively); $\nu_{max.}$ (potassium bromide disc) showed max. at 842, 857, 884, 1019, 1066, 1150, 1166, 1212, 1256, 1311, 1373, 1462, 1649, 1671, 2947, and 3442 cm.$^{-1}$; $\nu$ (in carbon tetrachloride solution) 3410, 3500, and 3610 cm.$^{-1}$ (OH). The corresponding *acetate* (acetic anhydride–pyridine) had m. p. 144—146° after crystallisation from aqueous ethanol (Found: C, 77·3; H, 10·0. $C_{42}H_{64}O_5$ requires C, 77·7; H, 9·95%).

Oxidation of maytenol with chromic acid, either in pyridine or glacial acetic acid solution, re-formed maytenone.

*Dihydromaytenol.*—Maytenone (1 g.) was dissolved in dry tetrahydrofuran (60 c.c.), lithium aluminium hydride (1 g.) was added, and the mixture was heated under reflux for $1\frac{1}{2}$ hr. and then cooled. The excess of reagent was destroyed by the successive addition of water and dilute hydrochloric acid and the product, *dihydromaytenol*, was isolated by ether extraction and crystallised from aqueous methanol; it then formed prisms (0·4 g.), m. p. 239—240° (decomp.), $[\alpha]_D^{20}$ +41·0° (Found: C, 78·6; H, 10·5. $C_{40}H_{64}O_4$ requires C, 78·9; H, 10·6%). No maxima were present in the ultraviolet absorption curve between 200 and 400 mμ; $\nu_{max.}$ (in carbon tetrachloride) 879, 1016, 1031, 1079, 1114, 1143, 1157, 1178, 1216, 1248, 1268, 1366, 1377, 1388, 1467, 1662, 1707, 2843, 2933, and 3406 cm.$^{-1}$.

The same product was obtained from the reduction of maytenol under similar conditions.

*Anhydromaytenone.*—Maytenone (0·2 g.) was dissolved in acetic anhydride (20 c.c.) containing perchloric acid (1 drop), and the solution was kept at room temperature for 1 hr. The mixture was then poured into cold water and kept overnight. Next day the precipitate, *anhydromaytenone*, was crystallised from aqueous ethanol, forming prisms (0·15 g.), m. p. 232—233° $[\alpha]_D^{20}$ +98° [Found: C, 81·6; H, 9·85%; M (Rast), 601. $C_{40}H_{58}O_3$ requires C, 81·85; H, 9·95%; M, 587]; $\lambda_{max.}$ 222 and 246 mμ (log ε 3·85 and 3·94); $\nu_{max.}$ (carbon tetrachloride) 893, 939, 968, 1020, 1050, 1095, 1120, 1140, 1155, 1165, 1190, 1270, 1325, 1335, 1370, 1390, 1455, 1625, 1680, 1725, and 2900 cm.$^{-1}$. Anhydromaytenone gave negative reactions with Schiff's reagent and ammoniacal silver nitrate and it was not oxidised by chromic acid in pyridine.

The same product was obtained from maytenone by the action of boiling formic acid or boiling acetic acid, or acetic anhydride containing a trace of concentrated sulphuric acid or toluene-*p*-sulphonic acid.

*Dehydrogenation of Maytenone.*—Maytenone (3 g.) was intimately mixed with powdered selenium (7 g.) and heated under a long air condenser at 280—320° for 22 hr. The product was cooled and thoroughly triturated with ether in a mortar. The ethereal extract was clarified (charcoal) and the brown gum obtained after evaporation of the solvent was distilled at 0·6 mm.; a yellow resin (1 g.) was collected at 160—220°. This was dissolved in ether and then extracted with 5% aqueous sodium hydroxide in order to remove the phenols. This extract was acidified (dilute hydrochloric acid) and again extracted with ether, and the ethereal extract washed and dried. Removal of the solvent gave a yellow gum which, when treated with hot light petroleum (b. p. 60—80°) and cooled, yielded a slightly coloured crystalline product, m. p. 187—188°, which did not depress the m. p. of authentic 8-methyl-2-phenanthrol; $\lambda_{max.}$ 234, 260, 291, 326, 341, and 358 mμ (log ε 4·29, 4·77, 4·27, 3·91, 3·09, and 3·10, respectively). The corresponding acetate and methyl ether had m. p.s 134—135° and 133—134°, respectively, and did not depress the m. p.s of the corresponding authentic compounds.[11] The *s*-trinitrobenzene derivative had m. p. 186—187°, and distillation of the phenol with zinc gave 1-methylphenanthrene, m. p. 123° (lit.,[12] 123°).

*Pyrolysis of Maytenone.*—(i) 8-*Isopropylpodocarpane*-6,7-*diol* (*hydroxytotarol*). Maytenone (1 g.) was heated to 195—200° whereupon it rapidly decomposed with the evolution of a gas to give a yellow resin (0·903 g.). This product soon darkened in air and rapidly decomposed in alkaline solution to give a dark brown intractable gum. The product was purified by vacuum distillation [it distilled at 180—190° (bath temp.)/10$^{-2}$ mm.] and chromatography on alumina, but it still failed to crystallise. Light absorption: $\lambda_{max.}$ at 203 and 287 mμ (log ε, 4·28 and 3·56). The corresponding *dibenzoate* (modified Schotten–Baumann method by dissolving the catechol in benzoyl chloride and adding alkali with shaking) formed plates (0·82 g.), m. p. 227—228° (from ethanol) not depressed on admixture with an authentic specimen (following paper) (Found: C, 79·7; H, 7·4. $C_{34}H_{38}O_4$ requires C, 80·0; H, 7·5%); $\lambda_{max.}$ 231 mμ (log ε 4·52), with an inflection at 275 mμ (log ε 4·48). Hydrogenolysis (lithium aluminium hydride) of the dibenzoate gave the free catechol as a brown gum which was distilled from a bulb tube to yield 8-*isopropylpodocarpane*-6,7-*diol* (6-*hydroxytotarol*) as a yellow resin, b. p. (bath temp.) 190°/10$^{-2}$ mm. (Found: C, 79·2; H, 9·9. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%); $\lambda_{max.}$ 282 mμ (log ε 3·54). The *di-p-nitrobenzoate* (*p*-nitrobenzoyl chloride and pyridine at 100°) formed pale yellow prisms (methanol–chloroform), m. p. 210—212° (Found: C, 67·7; H, 6·0. $C_{34}H_{36}N_2O_8$ requires C, 68·0; H, 6·0%).

[10] Conradi and McLaren, *J. Amer. Chem. Soc.*, 1960, **82**, 4745.
[11] Short and Wiles, *J.*, 1936, 319.
[12] Pschorr, *Ber.*, 1906, **39**, 3106.

In water-saturated n-butanol, the purified isopropylpodocarpanediol had $R_F$ 0·95 in an ascending chromatograph but only 0·83 on paper impregnated with 0·1N-aqueous sodium borate. Dehydrogenation of the purified isopropylpodocarpanediol with selenium by the method given for maytenone gave 8-methyl-2-phenanthrol, m. p. and mixed m. p. 181—183° (above).

(ii) *The* $C_{17}$ *catechol* (II; R = OH, R' = H). The mother liquors from the preparation of the isopropylpodocarpanediol dibenzoate (above) were evaporated, and the dried residue dissolved in ether. Lithium aluminium hydride (slight excess) was added and the solution heated under reflux for 1 hr. The reaction mixture was decomposed and, after extraction and removal of the solvent, the residue was distilled (bulb tube) to remove benzyl alcohol and then the higher boiling fraction was collected. It was dissolved in pyridine, treated with *p*-nitrobenzoyl chloride, and heated at 100° for 1 hr. The *di*-p-*nitrobenzoate* formed needles (methanol–chloroform), m. p. 186—188° (Found: C, 66·4; H, 5·6. $C_{31}H_{30}N_2O_8$ requires C, 66·65; H, 5·4%).

(iii) *Propene.* Pure dry maytenone (74 mg.) was placed in a tube connected to an evacuated gas cell, and the maytenone heated until decomposition was initiated. The evolved gas filled the cell at a calculated pressure of 20 mm.; the infrared spectrum of the gas showed the following maxima: 915, 995, 1036, 1447, 1478, 1642, 1667, 1818, 1840, 2951, 2977, 3076, and 3100 cm.$^{-1}$. This pattern is identical with that of authentic propene.

In another series of experiments, dry maytenone (26·5 mg.) was contained in a small tube connected to a vapour-phase chromatogram, oxygen-free nitrogen being used as the carrier gas in a 14-ft. column packed with Celite and a saturated solution of silver nitrate in ethylene glycol (20% by wt. of Celite). The gas evolved on pyrolysis of the maytenone was shown to be pure propene (78% for 1 mole per mole of maytenone), uncontaminated with water, ethylene, or paraffins.

Pyrolysis of maytenol at 270° in the same apparatus was shown to yield a mixture of gases including hydrogen, propane, ethylene, and water as well as propene.

*Action of Formic Acid on Maytenol.*—Maytenol (0·2 g.) was dissolved in formic acid (98%; 12 c.c.), and the solution heated under reflux for 1 hr. The mixture was cooled and poured into water, whereupon a precipitate was obtained which could not be crystallised but gave a green ferric test. Benzoylation (Schotten–Baumann) of this material gave a benzoate which crystallised from ethanol as plates, m. p. 224—225°, not depressed on admixture with 8-isopropylpodocarpane-6,7-diol dibenzoate (above).

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