872. *The Synthesis of Podocarpane-6,7-diol, a Degradation Product of Maytenone.*

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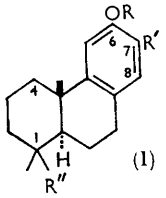
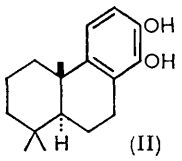
Podocarpane-6,7-diol has been synthesised from podocarpan-6-ol and shown to be identical with one of the phenolic pyrolysis products of maytenone.

The bis-diterpene maytenone [1] has been shown to decompose, when heated, into propene, 8-isopropylpodocarpane-6,7-diol (6-hydroxytotarol [2]), and a phenol, $C_{17}H_{24}O_2$, the probable structure of which was podocarpane-6,7- (I; R = H, R′ = OH, R″ = Me) or -7,8-diol (II). The latter (II) was synthesised [2] in the racemic form and shown not to be identical with the degradation product. The former has now been prepared from podocarpic acid and is identical with the degradation product.



(I)



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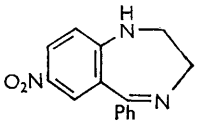
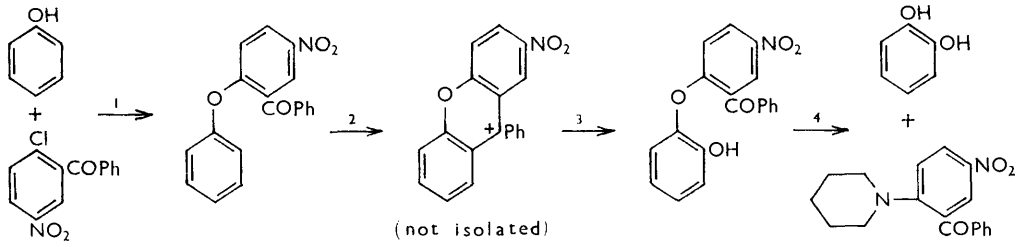


(III)

Initial attempts to synthesise (±)-podocarpane-6,7-diol by a method derived from Rao and Raman's route [3] to ferruginol and used for the preparation of the corresponding 7,8-dihydroxy-isomer [2] proved troublesome and were abandoned when a plentiful supply of podocarpic acid was made available to us through the courtesy of Dr. P. K. Grant of the Dominion Laboratory, Wellington. Podocarpic acid is readily converted into podocarpan-6-ol (I; R = R′ = H, R″ = Me) through the corresponding methoxy-alcohol and aldehyde,[4] and provides an obvious starting point for the synthesis.

Previous attempts to hydroxylate podocarpan-6-ol had been made by Martin [5] by conventional routes, namely, (*a*) oxidation by potassium nitrosodisulphonate, followed by reduction of the expected quinone, (*b*) oxidation of the 7-acetyl derivative with hydrogen peroxide, and (*c*) oxidation of the 7-acetate methyl ether with peracetic acid, but these were unsuccessful. We have also tried to introduce the second hydroxyl group *via*



Reagents: 1, KOH–EtOH; 2, H_2SO_4; 3, H_2O_2; 4, piperidine.

7-aminopodocarpan-6-ol,[4a] both by diazotisation (a method successful in the preparation of 6-hydroxytotarol [2]) and by oxidation to the *o*-quinone followed by reduction, but again without success. We finally turned to the method originated by Loudon and his

[1] Johnson, King, and Martin, *J.*, 1961, 4420.
[2] Elmore and King, *J.*, 1961, preceding paper.
[3] Rao and Raman, *Tetrahedron*, 1958, **4**, 294.
[4] (*a*) Hodges and Raphael, *J.*, 1960, 50; (*b*) Bible, jun., *Tetrahedron*, 1960, **11**, 22.
[5] Martin, unpublished work, University of Nottingham.

co-workers [6] for the specific *ortho*-hydroxylation of simple phenols and modified by Fishman, Tomasz, and Lehman [7] for use with more complex compounds. The essential features of the method are set out in the chart.

The possibility of carrying out these reactions with podocarpan-6-ol was first tested with the more readily available methyl podocarpate, which reacted with 2-chloro-5-nitrobenzophenone in alcoholic potassium hydroxide to give the crystalline ether (I; R = 2-benzoyl-4-nitrophenyl, R′ = H, R″ = CO_2Me) which was readily cyclised and oxidised to the hydroxy-ether (I; R = 2-benzoyl-4-nitrophenyl, R′ = OH, R″ = CO_2Me). The infrared absorption at 1666 cm.$^{-1}$ of the carbonyl group in the hydroxy-compound (1681 cm.$^{-1}$ before hydroxylation) indicated considerable hydrogen bonding and confirmed the presence of the hydroxyl group.

The model experiments having proved successful, similar transformations were easily carried out with podocarpan-6-ol. Difficulty was, however, experienced in isolating the dihydric phenol after the final reaction (fission of the ether with piperidine) because of the low solubility of the catechol in aqueous alkali and its ready aerial oxidation in that medium (5-nitro-2-piperidinobenzophenone is not soluble in acid), and the use of light petroleum and Claisen's alkali in the working-up was also unsatisfactory. However, when ethylenediamine was substituted for piperidine as the reagent, the fission was more complete (this was first tested with the nitrobenzophenone ether of α-naphthol) and the derived benzophenone was readily extracted from a benzene solution of the products with dilute acid, leaving the catechol. After one distillation this product, which was a gum giving an intense green ferric reaction, had an infrared spectrum virtually indistinguishable from that of the decomposition product from maytenone. The identity was confirmed (mixed m. p., infrared absorption) by the preparation of its crystalline di-*p*-nitrobenzoate.

Aminolysis of the ether derived from methyl podocarpate similarly afforded 7-hydroxypodocarpic acid (I; R = R′ = OH, R″ = CO_2H), hydrolysis of the ester occurring during the reaction.

The acidic extracts from the aminolysis mixtures presumably contained 2-2′-aminoethylamino-5-nitrobenzophenone as the hydrochloride. When this was basified, the product obtained was no longer readily soluble in acid and showed no infrared carbonyl absorption, having instead absorption at 1620 cm.$^{-1}$ suggesting the presence of an azomethine linkage. It appears that cyclisation had occurred and that the compound must be formulated as 2,3-dihydro-7-nitro-5-phenyl-1*H*-benzo[*f*][1,4]diazepine (III). Direct reaction of 2-chloro-5-nitrobenzophenone with ethylenediamine also produced this derivative.

Experimental

M. p.s were determined on a Kofler block; alumina was Spence's grade H; infrared measurements refer to solutions in carbon tetrachloride.

Methyl O-(2-*Benzoyl*-4-*nitrophenyl*)*podocarpate*.—A mixture of methyl podocarpate (10·4 g.), 2-chloro-5-nitrobenzophenone [6] (8·3 g.), and potassium hydroxide (1·94 g.) was heated under reflux in 95% ethanol (320 c.c.) for 48 hr. Most of the solvent was then evaporated and the cooled mixture was diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated and the residue was transferred to an alumina (300 g.) column from which benzene eluted the *ether* (11·65 g., 72%). Further elution with chloroform and then methanol afforded methyl podocarpate (3·0 g.). Crystallisation from chloroform–ethanol without chromatography gave the product (41%) which separated from chloroform–ethanol as prisms, m. p. 152—154° (Found: C, 72·8; H, 6·0. $C_{31}H_{31}NO_6$ requires C, 72·5; H, 6·1%).

Methyl O-(2-*Benzoyl*-4-*nitrophenyl*)-7-*hydroxypodocarpate*.—The above ether (1 g.) in acetic acid (24 c.c.) was treated dropwise with cooling and shaking with ice-cold concentrated sulphuric

[6] Loudon, Robertson, Watson, and Aiton, *J.*, 1950, 55; Loudon and Scott, *J.*, 1953, 265.
[7] Fishman, Tomasz, and Lehman, *J. Org. Chem.*, 1960, **25**, 585.

acid (32 c.c.). After 30 min., the deep red solution was diluted with acetic acid (40 c.c.), and 30% hydrogen peroxide (100 c.c.) was added slowly. After 30 min., the now colourless solution was poured into water and the precipitate (0·94 g.) was collected and crystallised from chloroform–methanol. The analytical sample formed pale yellow prisms, m. p. 180—181° (Found: C, 70·5; H, 5·9. $C_{31}H_{31}NO_7$ requires C, 70·3; H, 5·9%).

6-(2-*Benzoyl*-4-*nitrophenoxy*)*podocarpane*.—A mixture of podocarpan-6-ol [4] (2 g.), 2-chloro-5-nitrobenzophenone (1·85 g.), and potassium hydroxide (0·43 g.) was heated under reflux in 95% ethanol (70 c.c.) for 48 hr. Most of the solvent was then evaporated and after the addition of water and acidification of the residue, the product was collected with ether. The brown gum which remained when the ether was evaporated was purified by elution from alumina with benzene–light petroleum (b. p. 60—80°) (1 : 1) to give the *ether* (1·2 g., 36%), which crystallised from ether–hexane as prisms, m. p. 109—117°, unchanged by further crystallisation (Found: C, 77·2; H, 6·5; N, 2·8. $C_{30}H_{31}NO_4$ requires C, 76·7; H, 6·65; N, 3·0%), $\nu_{max.}$ (in CCl_4) 1681 cm.$^{-1}$.

Further elution with the same solvents yielded another substance as a gum (0·27 g.) which crystallised on addition of ether. After recrystallisation from ether–hexane it was obtained as faintly yellow prisms, m. p. 114—115°, and identified as 2-*ethoxy*-5-*nitrobenzophenone* (Found: C, 66·6; H, 5·0. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8%), $\lambda_{max.}$ 281 and 329 mμ (log ε 4·17 and 4·05). This compound was also formed by reaction of 2-chloro-5-nitrobenzophenone with alcoholic potassium hydroxide. Elution of the chromatogram with benzene gave unchanged podocarpan-6-ol (1·06 g.).

In another experiment the yield of the required podocarpane ether was *ca.* 80% and 2-ethoxy-5-nitrobenzophenone was not obtained.

6-(2-*Benzoyl*-4-*nitrophenoxy*)*podocarpan*-6-*ol*.—The preceding ether (1 g.) was oxidised as described above. The *hydroxy-ether* (0·83 g.) so obtained crystallised from methanol as pale yellow needles, m. p. 169—170° (Found: C, 74·5; H, 6·2. $C_{30}H_{31}NO_5$ requires C, 74·2; H, 6·4%), $\nu_{max.}$ (in CCl_4) 1662 cm.$^{-1}$.

Podocarpane-6,7-*diol*.—The above hydroxy-ether (0·4 g.) and 98% ethylenediamine (8 c.c.) were heated under reflux for 4 hr. The cooled solution was diluted, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with dilute hydrochloric acid and water, and then by distillation afforded *podocarpane*-6,7-*diol* (0·185 g., 86%), b. p. 170—180° (bath)/0·1 mm., as a pale yellow glass (Found: C, 78·3; H, 8·9. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%), that gave a dark green ferric reaction and afforded (in pyridine) a *di*-p-*nitrobenzoate*, colourless needles (from chloroform–methanol), m. p. 188—190°, undepressed on admixture with the di-*p*-nitrobenzoate of the C_{17} catechol obtained on pyrolysis of maytenone (Found: C, 66·6; H, 5·6; N, 5·0. $C_{31}H_{30}N_2O_8$ requires C, 66·65; H, 5·4; N, 5·0%).

7-*Hydroxypodocarpic Acid*.—The corresponding nitrobenzophenone ether (above) (0·7 g.) was treated as in the previous experiment. The *acid* (0·32 g.) was isolated without distillation as a solid which crystallised from methanol as colourless needles, m. p. 237—239°, with a green ferric reaction (Found: C, 70·0; H, 7·8. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). The benzoate was not obtained crystalline, but dimethyl sulphate in acetone in the presence of potassium carbonate yielded *methyl* 7-*methoxy*-O-*methylpodocarpate*, b. p. 160—170° (bath temp.)/0·1 mm. (from a bulb tube) (Found: C, 71·9; H, 8·3. $C_{20}H_{28}O_4$ requires C, 72·25; H, 8·5%).

1-(2-*Benzoyl*-4-*nitrophenoxy*)*naphthalene*.—α-Naphthol (1·75 g.) was treated with 2-chloro-5-nitrobenzophenone (2·75 g.) as described above for methyl podocarpate and, after chromatography on alumina and elution with benzene–light petroleum (7 : 3), the *product* (1 g.) was obtained as a yellow gum (Found: C, 74·7; H, 4·2. $C_{23}H_{15}NO_4$ requires C, 74·8; H, 4·1%), $\lambda_{max.}$ 220, 256, and 286 mμ (log ε 4·84, 4·25, and 4·16 respectively).

Treatment of this nitrobenzophenone ether with 98% ethylenediamine as described above caused scission and the formation of α-naphthol (60%), m. p. 91—93°, and after basification of the acidic fraction there was obtained a dark yellow solid which formed yellow needles, m. p. 206—211°, on crystallisation from chloroform–methanol. The latter proved to be 2,3-dihydro-7-nitro-5-phenyl-1*H*-benzo[*f*][1,4]diazepine, identical with the product synthesised in the following experiment.

2,3-*Dihydro*-7-*nitro*-5-*phenyl*-1H-*benzo*[f][1,4]*diazepine*.—2-Chloro-5-nitrobenzophenone (1 g.) was heated under reflux in 98% ethylenediamine for 4 hr. The cooled solution was diluted and made alkaline with aqueous sodium hydroxide. The *product* was collected into chloroform and purified by chromatography on alumina, from which it was eluted by chloroform. It

separated from chloroform–methanol as yellow needles, m. p. 210—211° (Found: C, 67·3; H, 4·9; N, 15·2. $C_{15}H_{13}N_3O_2$ requires C, 67·4; H, 4·9; N, 15·7%).

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