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NUBIGENOL: AN α-HYDROXYDIHYDROCHALCONE FROM *PODOCARPUS NUBIGENA*

DEWAN BHAKUNI, MAGALIS BITTNER and MARIO SILVA
Laboratorio de Quimica de Productos Naturales, Universidad de Concepcion, Chile

and

PETER G. SAMMES
Chemistry Department, Imperial College, London SW7 2AY

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Abstract—The structure of nubigenol, a new chalcone from *Podocarpus nubigena*, has been identified as α,2,4,6,4′-pentahydroxydihydrochalcone (I).

INTRODUCTION

THE PRELIMINARY screening of the members of the Podocarpaceae indigenous to Chile has entailed a phytochemical study of *Podocarpus andina*,[1] *P. saligna*[2] and *P. nubigena*.[3] During a further examination of the latter plant, originally aimed at the isolation of the minor diterpenes related to nagilactone C[4] and nubilactone,[3] a new compound was isolated, provisionally called nubigenol.

RESULTS

Examination of the ethyl acetate extract from the leaves and stems of the dried plant afforded, by column chromatography and PLC, nubigenol (I), analysed as $C_{15}H_{14}O_6$. The IR spectrum showed the presence of a carbonyl group, ν_{max} 1622 cm^{-1}. The remaining 5 oxygen atoms were all hydroxylic since acetylation afforded a pentaacetate (II). The NMR spectrum of nubigenol (d_5-pyridine) showed the presence of the part structure (a) as an *ABMX* system. The hydroxyl group was separate from the phenolic hydroxyl groups and occurred as a doublet at τ 5·02 (J_{MX} 7·5 Hz). The adjacent proton occurred as an eight-line signal at τ 5·60 (J_{MX} 7·5, J_{AM} 5·0, J_{BM} 8·0 Hz), whilst the remaining two benzylic protons were detected as a pair of double doublets at τ 6·55 (J_{AB} 14, J_{AM} 5·0 Hz) and 6·85 (J_{AB} 14, J_{BM} 8·0 Hz). Addition of D_2O to the solution caused collapse of the hydroxyl signal by exchange, and simplification of the signal at 5·60. The low frequency of the carbonyl absorption in the IR spectrum, coupled with a positive Tollen's test indicated the presence of an α-hydroxy ketone.[5] The 100 MHz NMR spectrum on the pentaacetate (II) clearly showed the presence of the acetylated system (b) as well as the presence of the six aromatic

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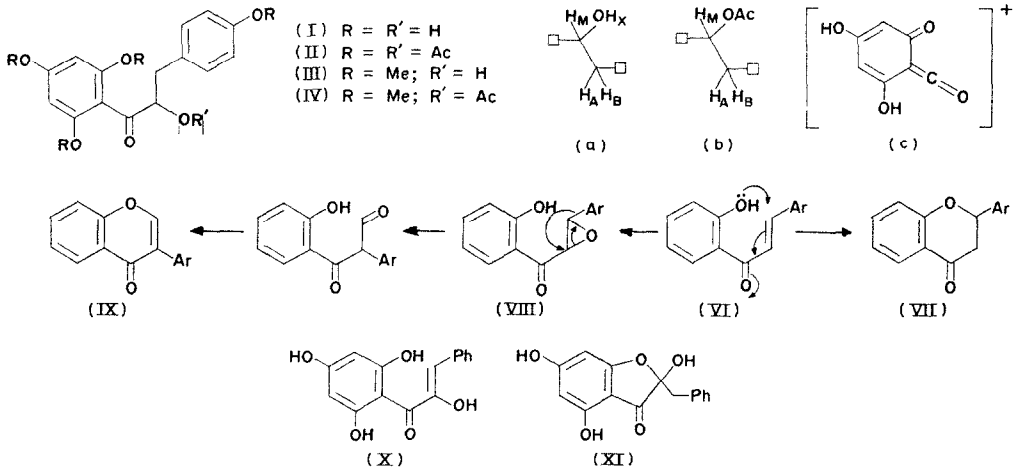
protons occurring as a multiplet at 2·5–3·0. The MS of the alcohol (I) did not show a molecular ion, loss of water being too efficient and giving rise to the ion at *m/e* 272; fragmentation to the ion (c) at 152 was also observed. The acetate (II) gave a related fragmentation pattern. These results suggested that the natural product was an α-hydroxydihydrochalcone of the type (I).

The exact substitution pattern of the aromatic rings in nubigenol was confirmed by preparation of its tetramethyl ether (III) and its corresponding monoacetate (IV). In the NMR spectrum of the latter the aromatic protons were clearly separated into two groups, one typical of an *AA'BB'* system and the other as two *meta*-substituted protons (*J* 1·5 Hz). Biosynthetic evidence precludes the possibility of other isomers.[6]

The isolation of nubigenol is of biosynthetic interest. Whilst the pathway to the flavanoid skeleton is well established, the details of many of the steps remain hidden.[7,8] The main route to the flavanoids involves the intermediacy of a chalcone (e.g. VI) and its further elaboration. For example, cyclization can occur to give the flavanone (VII), whilst prior epoxidation, to (VIII), followed by cyclization with rearrangement, is proposed as the principal route to the isoflavones (IX). Recently,[9] the isolation of *cis*- and *trans*-derivatives of α-hydroxychalcones (X) from certain heartwoods has been reported and it was proposed that these are the probable precursors to the 2-hydroxy-2-benzylcoumaranones (XI).[10] Nubigenol (I) may either represent an artefact from chalcones of the type (X) or, more likely, it may be intimately involved in further transformations into cyclic derivatives, for example to isoflavanones (e.g. XII), see Scheme 1. *In vitro* studies on the chemistry of nubigenol are in progress.



SCHEME 1.

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EXPERIMENTAL

Extraction. The powdered, dried leaves and stems of *P. nubigena* (30 kg), collected from Puerto Montt in the Llanquihue province of Chile, were defatted by extraction with C_6H_6 and then to exhaustion with EtOH. The ethanolic extract (1·3 kg) was treated with H_2O and the insoluble material discarded. The aqueous filtrate was sequentially extracted with petrol, C_6H_6, EtOAc and *n*-BuOH. The EtOAc fraction (175 g) contained nubigenol.

Isolation of nubigenol. The EtOAc fraction (10 g) was chromatographed on silica gel (300 g) and the column eluted with C_6H_6–EtOAc mixtures. The eluate (EtOAc–C_6H_6, 1:4) (0·5 g) was further purified by PLC to give *nubigenol* (220 mg), m.p. 168–170° dec. (EtOAc), $[\alpha]_D$ 0° (*c* 1·0, $CHCl_3$) λ_{max}^{MeOH}: 210, 232, 280 nm, +$AlCl_3$ 287 nm, + MeONa 297, 424 nm, +NaOAc + H_3BO_3 283, 287 nm, ν_{max}: 3380, 3260, 1622, 1608, 1515, 1460, 1373, 1285, 1145 and 1030 cm^{-1}, τ (pyridine-d_5) 5·02 (1H, *d*, *J* 7·5 H2, OH), 5·60 (1H, *ddd*, *J* 5·0, 7·5, 8·0 Hz), 6·55 (1H, *dd*, *J* 5, 14 Hz), 6·85 (1H, *dd*, *J* 8·0, 14 Hz), *m/e* 290 (very weak), 272, 271, 167, 165, 163, 152, 139, 123 (Found: C, 61·60; H, 5·21, $C_{15}H_{14}O_6$ requires: C, 62·07; H, 4·82%).

Nubigenol pentaacetate (II). A sample of the free alcohol (100 mg) was acetylated in the normal manner to give the pentaacetate (110 mg) as an amorphous powder (ex PLC), m.p. 68–70°, $[\alpha]_D$ 0° (*c* 1·0, $CHCl_3$), λ_{max}^{MeOH}: 209, 237, 278 nm, ν_{max}: 1770–1750 (aromatic acetates), 1740 (aliphatic acetate), 1625, 1598, 1210, 1130 cm^{-1}, τ 2·6–2·8 (4H, aromatic), 3·35 (1H, aromatic, *d*, *J* 1·5 Hz), 3·45 (1H, aromatic, *d*, *J* 1·5 Hz), 4·90 (1H, *m*), 7·1 (2H, *m*), 7·80 (4 × AcO), 8·05 (1 × AcO) *m/e* 500 (M^+), 458, 440, 416, 398, 356, 314, 272, 194, 191, 163, 152, 139, 123, and 101 (Found: C, 60·03; H, 5·20. $C_{25}H_{24}O_{11}$ requires: C, 60·01; H, 4·84%).

Tetra-O-methylnubigenol (III). Nubigenol (50 mg) in MeOH (10 ml) was treated with an excess of ethereal CH_2N_2 at room temp. After 2 days the mixture was separated and purified by PLC to give the ether (III) (30 mg), m.p. 118–120° (MeOH), $[\alpha]_D$ 0° (*c* 1, $CHCl_3$), λ_{max}^{MeOH}: 209, 232, 278 nm ν_{max}: 3360, 2980, 1625, 1600, 1260, 1230 cm^{-1}, τ: 3·11–3·95 (6H, aromatic), 5·45 (1H, *d*, *J* 7·5 Hz, OH), 6·1–6·4 (4 × MeO), 5·90 (1H, *m*), 7·00 (1H, *dd*, *J* 5, 14 Hz), 7·50 (1H, *dd*, *J* 8, 14 Hz), *m/e* 346 (M^+), 332, 225, 195, 180, 167 (base peak), 151, 137, 135, 121, 109 (Found: C, 65·42, H, 6 50. $C_{19}H_{22}O_6$ requires: C, 65·89; H, 6·35%).

Tetra-O-methylnubigenol acetate (IV). The tetramethyl ether (III) (45 mg) was acetylated to give the acetate (IV), *m/e* 388·1520 (Calc. for $C_{21}H_{24}O_7$; 388·1520), and 346, 328, 313, 297, 180, 167, 149, 121, 113, τ 3·10 (4H, aromatic) 3·90 (1H, *d*, *J* 1·5 Hz, aromatic), 3·96 (1H, *d*, *J* 1,5 Hz, aromatic), 4·70 (1H, *dd*, *J* 5, 8 Hz), 6·18–6·30 (4 × MeO), 7·20 (2H, *m*), 8·10 (3H, *s*).

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