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A BENZOPHENONE AND XANTHONE WITH UNUSUAL HYDROXYLATION PATTERNS FROM THE HEARTWOOD OF *GARCINIA PEDUNCULATA**

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Key Word Index—*Garcinia pedunculata*; Guttiferae; 2,4,6,3',5'-pentahydroxybenzophenone; 1,3,5,7-tetrahydroxyxanthone; biogenesis.

Abstract—From the heartwood of *Garcinia pedunculata*,2,4,6,3',5'-pentahydroxybenzophenone and 1,3,5,7-tetrahydroxyxanthone have been isolated. Their occurrence as natural products is of special interest, because they have an unusual hydroxylation pattern in one ring. Possible biosynthetic routes are discussed. The co-occurrence of the benzophenone and the corresponding xanthone supports the view that xanthones are formed by oxidative coupling of the hydroxybenzophenones. This heartwood also contains biflavanone GB-1a, talbotaflavone and 1,3,6,7-tetrahydroxyxanthone.

WHEN an acetone extract of the heartwood of *Garcinia pedunculata*[1] was chromatographed on silica gel, the first fractions mainly contained the biflavanone GB-1a, originally isolated by Jackson *et al.*[2] from *G. buchananii* and subsequently detected in several other *Garcinia* species. From the later fractions a phenolic ketone was isolated and identified as 2,4,6,3',5'-pentahydroxybenzophenone (**1**), a new natural product. The pentamethyl ether, m.p. 135°, was first characterized by its NMR spectrum in $CDCl_3$ (chemical shifts on the τ scale): 5 OMe at 6·17–6·34; 5 aromatic H at 3·8 (singlet for 2H), 2·95 (2H, *d*, *J* 2 Hz) and 3·34 (1H, *t*). Its identity was confirmed by comparison with the synthetic product from the Friedel–Crafts reaction between phloroglucinol trimethyl ether and 3,5-dimethoxybenzoyl chloride;[3] under the conditions used by us a mixture of the pentamethyl ether and 2-hydroxy-4,6,3',5'-tetramethoxybenzophenone was obtained in almost equal quantities.

The MS fragmentation of (**1**) is interesting; the base peak is at M-1, the next most intense peak is at M-2 and other major fragments are at *m/e* 153, 137, 125 and 109.

Karrer[4] records seven benzophenones as plant products: 4-hydroxybenzophenone, three methyl ethers of 2,4,6-trihydroxybenzophenone, maclurin (2,4,6,3',4'-pentahydroxybenzophenone) and two of its ethers. The three parent phenolics (4-hydroxy-, 2,4,6-trihydroxy- and 2,4,6,3',4'-pentahydroxybenzophenones) are presumably formed from acetate and shikimate derived moieties. Six benzophenones subsequently isolated are all derived from the same three parent phenolics.[1,4b] The new benzophenone (**1**) is of special interest, because 3,5-dihydroxybenzoic acid (**2**) is not a known or normal metabolite of shikimic

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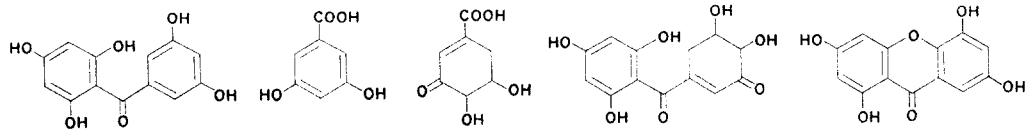
[1] *The Wealth of India (Raw Materials)* (1956) Vol. IV, p. 107, Council of Scientific and Industrial Research, New Delhi.

[2] JACKSON, B., LOCKSLEY, H. D., SCHEINMANN, F. and WOLSTENHOLME, W. A. (1967) *Tetrahedron Letters* 787.

[3] MAUTHNER, F. (1913) *J. prakt. Chem.* **87**, 409.

[4] KARRER, W. (1958) *Konstitution und Vorkommen der organischen Pflanzenstoffe*, pp. 187–188, Birkhauser, Basel.

acid, although it could be produced from 5-dehydroshikimic acid (**3**) by dehydration. Alternatively, such dehydration leading directly to (**1**) could take place after the ketone (**4**) is formed by the condensation of (**3**) with phloroglucinol.[5] A third possibility is indicated by the observation that dehydroxylation of pyrogallol and of tea polyphenols to resorcinol has been observed, but only in rats and humans.[6] Total derivation of (**1**) from



(1) (2) (3) (4) (5)

acetate has also to be considered as a remote possibility. One of the products from orsellinic acid in the soil organism *Epicoccum nigrum* is 3,5-dihydroxybenzoic acid.[7,8] It is relevant that the structurally related 5,6,3′,5′-tetrahydroxyflavone has been isolated from *Casimiroa edulis*,[9] since the shikimate origin of the B-ring in flavonoids has extensive experimental support.[10]

Lewis[11] was the first to suggest the biosynthesis of xanthones by oxidative coupling of *o*-hydroxybenzophenones, subsequently supported by a statistical analysis of xanthones found in higher plants, based in particular on the significance of maclurin in xanthone biosynthesis.[12] Lewis *et al.*[13] looked for the presence of 2,4,6,3′-tetrahydroxybenzophenone in *Gentiana lutea*, because it contained 1,3,7-trihydroxyxanthone and its ethers. They succeeded in isolating the benzophenone and in establishing the rapid assimilation of sodium acetate-2-^{14}C by the plant under tissue culture conditions to form both labelled benzophenone and xanthone. However, no attempt was made to determine if the *m*-hydroxybenzoyl part came from acetate or shikimate. Locksley and Murray[14b] isolated the 4,6-dimethyl ether of the Lewis benzophenone from the heartwood of *Allanblackia floribunda*.

Isolation of the unusual benzophenone (**1**) led us to make a search for the corresponding xanthone (**5**) in the heartwood of *G. pedunculata*. The fractions containing the biflavanone GB-1a (**6**) displayed at least two minor constituents on paper chromatograms, but PLC or column chromatography on silica gel and other adsorbents proved inadequate for complete separation. The mixture was methylated and the ethers separated on silica gel to give five products A–E.

Compound A, $C_{17}H_{16}O_6$, had m.p. 228°; M^+ 316; λ_{max}^{EtOH} 256, 295, 350 nm, log ε 4·6, 4·2, 3·8 (tetraoxygenated xanthone); ν_{max} 1650 cm^{-1} (C=O); τ 6·0–6·07 (4 OMe); 2·61, 3·2, 3·38, 3·63 (aromatic H, four *m*-coupled doublets) and is thus the tetramethyl ether of the xanthone (**5**). This is the first natural xanthone to have the 1,3,5,7-orientation of hydroxyl

[5] Cf. GOTTLIEB, O. R. (1968) *Phytochemistry* **7**, 411.
[6] For references, see DEEDS, F. in *Comprehensive Biochemistry* (FLORKIN, M. and STOTZ, E. H., eds.). Vol. 20, p. 143. Elsevier, New Jersey.
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[12] LOCKSLEY, H. D., MOORE, I. and SCHEINMANN, F. (1967) *Tetrahedron* **23**, 2229.
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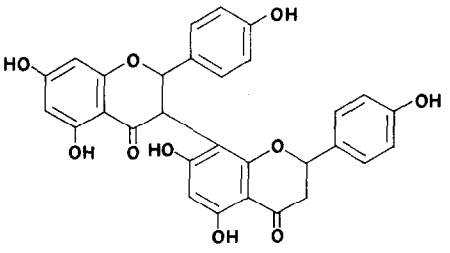
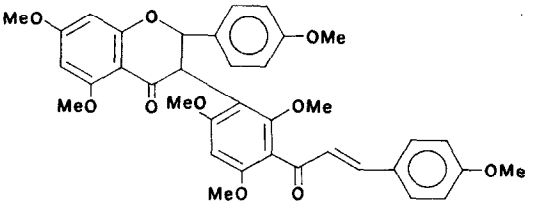
[14] (a) CARPENTER, I., LOCKSLEY, H. D. and SCHEINMANN, F. (1969) *Phytochemistry* **8**, 2013; (b) LOCKSLEY, H. D. and MURRAY, I. G. (1973) *J. Chem. Soc.* **C**, 1332.



(6) GB-1a



(7)

groups. The structures of (**5**) and the tetramethyl ether were confirmed by comparison with the products, obtained in very poor yield, of the ferricyanide oxidation[11] of the ketone (**1**) and its tetramethyl ether respectively. Further, the occurrence of (**5**) as the tetrahydric phenol, and not an ether, was confirmed by the identical R_f values (on paper and silica gel TLC) of (**5**) obtained by oxidation of (**1**) and of one of the constituents of the crude heartwood extract. Demethylation of the ether also yielded (**5**), which was ultimately isolated in minute quantity by chromatographing the acetone extract of the heartwood on a cellulose column and eluting with 10% HOAc.

Product B, m.p. 206–208° (M^+ 316), was identified as the tetramethyl ether of 1,3,6,7-tetrahydroxyxanthone, isolated earlier from *Chlorophora*,[15] *Maclura*,[16] *Mammea*, *Allanblackia*,[14] *Athyrium*, *Calophyllum* and *Symphonia*[17] species.

Products D and C proved respectively to be the hexamethyl ether of GB-1a (**6**) and the ether (**7**) formed by ring opening during methylation of the flavanone moiety not substituted in the 3-position. Compound E, m.p. 272–274° (M^+ 624), gave colour reactions for a flavanone. The IR spectrum showed two C=O bands at 1670 and 1648 cm^{-1}, characteristic of flavanone and flavone carbonyls respectively. From the NMR and MS data, it was characterized as the hexamethyl ether of talbotaflavone (volkensiflavone) isolated earlier from other *Garcinia* species.[18,19]

EXPERIMENTAL

Isolation of 2,4,6,3′,5′-*pentahydroxybenzophenone* (**1**). The powdered heartwood (1 kg) was extracted in a Soxhlet with Me_2CO. The residue (19 g) after removal of the solvent showed 2 major spots in TLC (silica gel; MeOH–$CHCl_3$, 1:9). The mixture (5 g) was chromatographed on a column of silica gel (100 g) using the same solvent; 50 ml fractions were collected and monitored by TLC. The first few fractions contained mostly GB-1a. The last fractions were pooled, solvent removed and the residue crystallized from $CHCl_3$–MeOH. The bright yellow needles (0·8 g) had m.p. 258–260° (Found: C, 59·5; H, 4·3; M^+ 262. $C_{13}H_{10}O_6$ requires: C, 59·5; H, 3·8%; M 262). The pentamethyl ether (DMS–K_2CO_3 method) crystallized from EtOAc–C_6H_6 in colourless needles, m.p. 135° (lit.[3] m.p. 132–133°) (Found: C, 64·9; H, 6·1; M^+ 332. $C_{18}H_{20}O_6$ requires: C, 65·2; H, 6·0%; M 332). 2,4,6,3′,5′-Pentaacetoxybenzophenone, colourless needles from MeOH, had m.p. 125°.

Synthesis of 2-*hydroxy*-4,6,3′,5′-*tetramethoxy*- *and* 2,4,6,3′,5′-*pentamethoxybenzophenones*. A mixture of phloroglucinol trimethyl ether (1 g), 3,5-dimethoxybenzoyl chloride (1 g) and anhyd. $AlCl_3$ (2 g) in dry Et_2O (80 ml) was left at 25° for 48 hr. The product was chromatographed on a silica gel column using C_6H_6 for elution. The faster moving compound was characterized as 2-hydroxy-4,6,3′,5′-tetramethoxybenzophenone (0·3 g; pale yellow needles, m.p. 118° from MeOH). The slower moving compound was 2,4,6,3′,5′-pentamethoxybenzophenone (0·35 g), m.p. and m.m.p. with the methyl ether of the natural benzophenone (**1**), 135°.

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[18] JOSHI, B. S., KAMAT, V. N. and VISWANATHAN, N. (1970) *Phytochemistry* **9**, 881.
[19] HERBIN, G. A., JACKSON, B., LOCKSLEY, H. D., SCHEINMANN, F. and WOLSTENHOLME, W. A. (1970) *Phytochemistry* **9**, 221.

Isolation of the minor constituents of the acetone extract as methyl ethers. The earlier fractions from the chromatography of the acetone extract of the heartwood were pooled and the solvent was removed. The residue (4 g), anhyd. K_2CO_3 (20 g), Me_2SO_4 (5 ml) and dry Me_2CO (100 ml) were refluxed for 12 hr. The product (4 g) was chromatographed on a column of silica gel (80 g), using Me_2CO–C_6H_6 (1:9) for elution. Fractions of 100 ml were collected. Fractions 1 and 2 contained 1,3,5,7-tetramethoxyxanthone (0·15 g) which crystallized from MeOH in colourless needles, m.p. 228° (Found: C, 65·0; H, 5·0; M^+ 316. $C_{17}H_{16}O_6$ requires: C, 64·5; H, 5·0%; M 316). Demethylation of 0·15 g with Ac_2O (3 ml) and HI (2 ml) and PLC of the product (silica gel; Me_2CO–C_6H_6) gave 1,3,5,7-tetrahydroxyxanthone, m.p. 320° (decomp). Fraction 3 gave 1,3,6,7-tetramethoxyxanthone (0·17 g), crystallizing from MeOH in colourless needles, m.p. 206–208° (lit.[15b] m.p. 207–208°) (Found: C, 64·5; H, 5·2; M^+ 316. $C_{17}H_{16}O_6$ requires: C, 64·5; H, 5·0%; M 316). Fractions 4–6 gave a product (1·8 g) which crystallized from MeOH in pale yellow needles, m.p. 226–228° (Found: C, 68·9; H, 5·6; M^+ 640. $C_{37}H_{36}O_{10}$ requires: C, 69·3; H, 5·6%; M, 640). From its NMR and MS it was identified as (**7**), although the m.p. cited earlier[20] is 135° upwards. A. D. Pendse (private communication) has isolated large amounts of GB-1a from *Garcinia xanthochymus* wood and its behaviour on methylation will be discussed elsewhere. Fractions 7–9 gave GB-1a hexamethyl ether (1 g), which crystallized from MeOH in colourless needles, m.p. 140° (Found: C, 68·9; H, 5·4; M^+ 626. $C_{36}H_{34}O_{10}$ requires: C, 69·0; H, 5·4%; M 626). The last fractions contained talbotaflavone hexamethyl ether (0·37 g) which crystallized from MeOH in colourless needles, m.p. 272–274° (lit.[18] m.p. 265°) (Found: C, 69·0; H, 4·7; M^+ 624. $C_{36}H_{32}O_{10}$ requires: C, 69·2; H, 5·1%; M 624).

Isolation of 1,3,5,7-tetrahydroxyxanthone. The acetone extract (5 g) of the heartwood was chromatographed on a column of cellulose using 10% aq. HOAc as the solvent. Earlier fractions contained mostly GB-1a. Later fractions which contained a new compound different in R_f value (on paper) from GB-1a and the pentahydroxybenzophenone (**1**) were pooled. The product was further purified by PLC (silica gel impregnated with 3% aq. oxalic acid; solvent Me_2CO–C_6H_6, 2:8). The major band yielded yellow needles from Me_2CO, m.p. and m.m.p. with the demethylation product described earlier, 320° (decomp); λ_{max}^{EtOH} (log ϵ) 237 (4·3), 254 (4·4), 268 (*sh*, 3·9), 312 (4·1) and 361 (3·9) nm (Found: C, 59·9; H, 3·5; M^+ 260. $C_{13}H_8O_6$ requires: C, 59·9; H, 3·8; M 260).

Oxidation of 2,4,6,3′,5′-pentahydroxybenzophenone to 1,3,5,7-tetrahydroxyxanthone. The benzophenone (0·2 g) in aq. NaOH (0·4 g in 10 ml H_2O) and pyridine (10 ml) was mixed with $K_3Fe(CN)_6$ (0·5 g in 10 ml H_2O) and left on a mechanical shaker for 6 hr. The soln was acidified and extracted with EtOAc (2 × 50 ml). The residue on PLC (silica gel; Me_2CO–C_6H_6, 3:7) and crystallization from Me_2CO gave yellow needles (0·02 g), m.p. and m.m.p. with the natural xanthone, 320° (decomp). Under similar conditions 2-hydroxy-4,6,3′,5′-tetramethoxybenzophenone (0·1 g) gave 1,3,5,7-tetramethoxyxanthone, m.p. 228° in similar low yield (0·01 g), but the starting material (0·05 g) was recovered.

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