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EXTRACTIVES FROM GUTTIFERAE—VI*

THE SIGNIFICANCE OF MACLURIN IN XANTHONE BIOSYNTHESIS

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Abstract—Maclurin, 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthones co-exist in *Symphonia globulifera* L. from Buganda. The biogenetic significance of this observation is discussed.

It has been previously suggested[1,2] that maclurin (I; R = OH) is the biogenetic precursor of the 1,3,5,6- and 1,3,6,7-tetraoxygenated xanthones (e.g. II and III; R = OH) which occur in higher plant families such as Guttiferae[2] and Moraceae.[1] Thus cyclization of the benzophenone (I; R = H or OH) by oxidative coupling involving the OH group at C-2 with the aromatic nucleus at either C-2′ or C-6′ can yield xanthones (II and III; R = H or OH). We now report the isolation of maclurin (I; R = OH), 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthone (II and III; R = OH) in considerable quantities from an acetone extract of the heartwood of *Symphonia globulifera* L. (Guttiferae).[3] Hitherto these metabolites have not been found together.[1,2] However, 1,3,6,7-tetrahydroxyxanthone (III; R = OH) is present as an impurity in commercial maclurin[2a] (I; R = OH) and this benzophenone also cyclizes *in vitro* to the xanthone (III; R = OH) by chemical or photochemical oxidation.[2a,2b]

The significance of these observations follows from a statistical analysis of natural xanthones found in higher plants (Table I). The oxygenation patterns suggest that one benzene ring of the xanthone nucleus is derived from a shikimate unit which after modification condenses with a polyacetate unit[1,4,5] to give a benzophenone precursor such as maclurin (I; R = OH). By oxidative coupling (according to scheme 1), 5- or 7-oxygenated xanthones (II and III; R = H or OH) can be expected. An inspection of Table 1 supports this prediction especially since oxygen functions are not often found in the same molecule at both C-5 and C-7 positions of the xanthone nucleus.[2b]

Celebixanthone (VI)[6] and other 2,3,4-oxygenated xanthones[7] (equivalent to

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[*] Part V: B. Jackson, H. D. Locksley and F. Scheinmann, *J. Chem. Soc.* (C), in the press, 1967.

[1] M. L. Wolfrom, F. Komitsky, G. Fraenkel, J. H. Looker, E. E. Dickey, P. McWain, A. Thompson, P. M. Mundell and O. M. Windrath, *J. Am. Chem. Soc.* 29, 692 (1964).

[2a] A. Jefferson and F. Scheinmann, *Nature, Lond.* 207, 1193 (1965); [b] A. Jefferson and F. Scheinmann, *J. Chem. Soc.* (C), 175 (1966); [c] H. D. Locksley, I. Moore and F. Scheinmann, *Ibid.* (C), 430 (1966); [d] H. D. Locksley, I. Moore and F. Scheinmann, *Ibid.* (C), 2186, (1966); 2265, (1966).

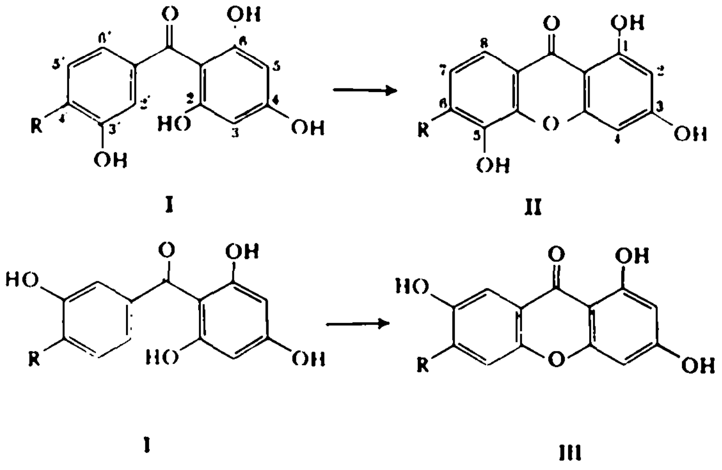
[3] We have previously isolated eight xanthones from *Symphonia globulifera* L., from extractions with chloroform or benzene which did not yield maclurin. See Refs. 2*c* and 2*d*.

[4] J. R. Lewis and R. H. Warrington, *J. Chem. Soc.* 5074 (1964).

[5] K. R. Markham, *Tetrahedron* 21, 3687 (1965).

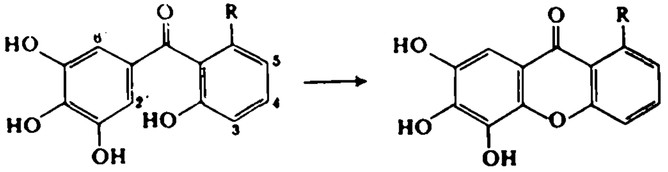
[6] G. H. Stout, V. F. Stout and M. J. Welsh, *Tetrahedron* 19, 667 (1963).

[7] O. R. Gottlieb, M. Taveira Magalhães, M. Camey, A. A. Lins Mesquita and D. de Barros Correa, *Tetrahedron* 22, 1777 (1966).

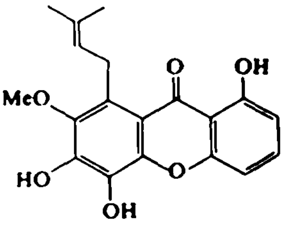


Scheme I

5,6,7-oxygenated xanthones) appear as exceptions but the oxygenation pattern can be understood if it is recognised that the benzophenone precursor (IV) contains one ring derived from gallic acid. In such a case, C-2′ and C-6′ in the benzophenone (IV) are equivalent and oxidative coupling can only lead to a 5,6,7-oxygenated xanthone (V).



R=H or OH



VI

Since the xanthones from *Gentiana bellidifolia* (Gentianaceae) have oxygen functions at either the 5,8- or the 7,8- positions it has been suggested[8] that an alternative mode of cyclization of a benzophenone precursor (VII) can account for both oxygenation patterns. Thus elimination of the elements of water (probably as pyrophosphate) from the OH groups at either C-2 and C-2′ or C-2 and C-6′ can lead to either 5,8- or 7,8-oxygenated xanthones (VIII) and IX (Scheme 2). Some xanthones from Guttiferae may also be formed in this way (see Table I).

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[8] See Ref. 5 and previous papers of that series.

TABLE 1. SUBSTITUTION PATTERN OF NATURAL XANTHONES IN HIGHER PLANTS

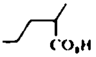
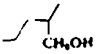
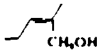
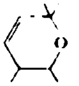
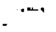
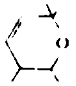
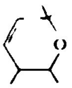
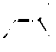
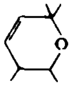
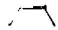
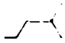
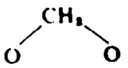
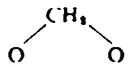
	Plant Family	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Ref.
2-Hydroxyxanthone*	*a*							OH		11
2-Methoxyxanthone*	*a*							OMe		12, 13
4-Hydroxyxanthone*	*a*					OH				28
Euxanthone	*a*	OH						OH		2*c*, 14
1,5-Dihydroxyanthone	*a*	OH				OH				28, 16
Scriblitifolic acid	*a*	OH				OMe				16
6-(4-Hydroxy-3-methylbutanyl)1-5-dihydroxyxanthone	*a*	OH				OH				16
6-(4-Hydroxy-3-methylbut-2-enyl)1-5-dihydroxyxanthone	*a*	OH				OH				16
6-(3,3-Dimethylallyl) 1,5-dihydroxyxanthone	*a*	OH				OH				16
1,5,6-Trihydroxyxanthone	*a*	OH				OH	OH			2*c*
Mbarraxanthone	*a*	OH		OH				OH		2*d*
2-(3,3-Dimethylallyl) 1,3,7-trihydroxyxanthone	*a*	OH		OH				OH		16
Osajaxanthone	*a*, *b*	OH						OH		16, 17
Gentisin	*c*	OH		OMe				OH		22
Isogentisin	*c*	OH		OH				OMe		22
2-(3,3-Dimethylallyl) 1,3,5-trihydroxyxanthone	*a*	OH		OH		OH				16
6-Desoxyjacareubin	*a*	OH				OH				16
1,3,5,6-Tetrahydroxyxanthone	*a*	OH		OH		OH	OH			16 2*c*, 2*d*
5-Hydroxy-1,3-dimethoxyxanthone	*a*	OMe		OMe		OH				7
1,5-Dihydroxy-3-methoxyxanthone	*a*	OH		OMe		OH				7
1,3,6,7-Tetrahydroxyxanthone	*a*, *b*	OH		OH			OH	OH		2*c*, 18
Jacareubin	*a*	OH				OH	OH			15, 16, 19
2-(3,3-Dimethylallyl) 1,3,5,6-tetrahydroxyxanthone	*a*	OH		OH		OH	OH			15

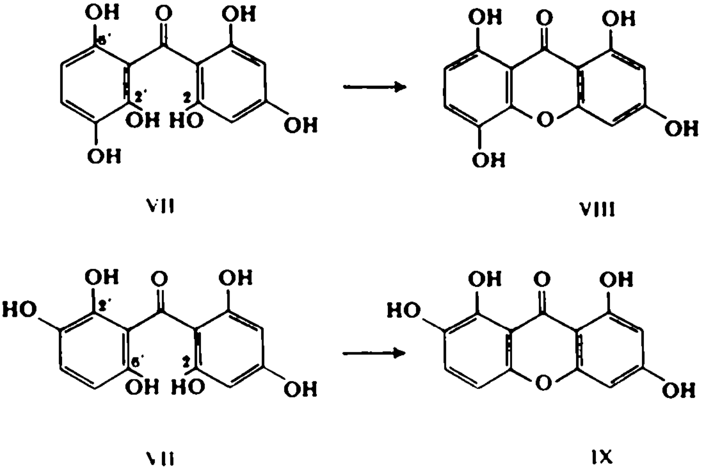
TABLE 1 (Cont'd).

	Plant Family	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Ref.
Ugaxanthone	*a*	OH		OH		OH	OH			2*d*
3,5,6-Trihydroxy-1-methoxyxanthone	*a*	OMe		OH		OH	OH			15
Alvaxanthone	*a*	OH		OH		OH	OH			23
Macluraxanthone	*b*	OH				OH	OH			1
Symphoxanthone	*a*	OH	OH			OH	OH			2*d*
Globuxanthone	*a*	OH	OH			OH				2*d*
Mangostin	*a*	OH		OH			OH	OMe		21
Mangiferin	*d*	OH	C-gluc	OH			OH	OH		24
Celibixanthone	*a*	OH				OH	OH	OMe		6
3,4-Dihydroxy-2-methoxyxanthone*	*a*					OH	OH	OMe		7
4-Methoxy-2,3-methylenedioxyxanthone*	*a*					OMe				7
4-Hydroxy-2,3-methylenedioxyxanthone*	*a*					OH				7
2,3-Dimethoxy-4-hydroxy xanthone*	*a*					OH	OMe	OMe		7
Bellidifolin	*c*	OH		OMe		OH			OH	8
Isobellidifolin	*c*	OH		OH		OMe			OH	8
Desmethylbellidifolin	*c*	OH		OH		OH			OH	8
Methylbellidifolin (Swerchirin)	*c*	OH		OMe		OMe			OH	8
Corymbiferin	*c*	OH		OH	OMe	OMe			OH	8
Swertianol	*c*	OH		OH		OMe			OH?	22
Decussatin	*c*	OMe		OMe				OMe	OH	22
Swertinin	*c*	OMe		OMe				OH	OH	22
4,7-Di-O-methylbellidin	*c*	OH		OH	OMe			OMe	OH	8
2,8-Dihydroxy-1-methoxyxanthone*	*a*	OH						OH	OMe	20
1-Hydroxy-7,8-dimethoxyxanthone	*a*	OH						OMe	OMe	20

a = Guttiferae *b* = Moraceae *c* = Gentianaceae *d* = Anacardiaceae

* For convenience in constructing the table the equivalent positions C-1 = C-8, C-2 = C-7, C-3 = C-6 and C-4 = C-5 have been used.

Compounds biogenetically derived from xanthones such as gambogic acid,[28] morellin[29] and aphloiol[27] have not been included in the table.



Scheme 2

Xanthones from mould metabolites and lichens appear to have a different biogenetic origin.[4,9] Thus the ergochromes which have a reduced xanthone skeleton and co-occur with anthraquinone derivatives, appear to be formed by transformation of an acetate derived anthracene intermediate.[10]

Note added in proof.—After this paper had been accepted for publication, T. R. Govindachari, B. R. Pai, P. S. Subramaniam, U. R. Rao and N. Muthukumaraswamy, *Tetrahedron* **23**, 243 (1967), reported the isolation of 1,7-dihydroxyxanthone (euxanthone), 1,5-dihydroxy-3-methoxyxanthone and 1,5,6-trihydroxyxanthone from the heartwood of *Mesua ferrea* L. (Guttiferae), and thus provide further evidence for our conclusions.

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[10a] B. Franck, F. Hüper, D. Gröger and D. Erger. *Angew Chem. Int.* 728 (1966); [b] D. Gröger, B. Franck and F. Hüper, *The Chemistry of Natural Products—IUPAC Symposium.* Stockholm, June (1966).

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[19] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 3932 (1953); 563 (1957).

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[22] J. C. Roberts, *Chem. Revs.* **61**, 591, 1961, and Refs quoted therein.

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EXPERIMENTAL

M.ps were uncorrected. IR spectra in nujol were measured on a Perkin-Elmer Infracord 137. Analytical TLC was on silica gel G by Stahl (Merck). The natural products and their derivatives were detected by TLC, and identified by m.m.p. and identity of IR spectra.[3a,3b,3c]

A section of the heartwood of *Symphonia globulifera* L., supplied by the Tropical Products Institute, London, from the Buto-Buvuma forest in West Mengo, Buganda, Uganda, was ground to a powder in an Apex cutter mill. The wood powder (2 kg) was extracted with hot benzene for 60 hr in a soxhlet extractor and on removal of the solvent, the extract yielded a dark brown tar (18 g). The benzene extracted wood was then further extracted with hot acetone for 60 hr and evaporation of the solvent gave a pale brown solid (100 g).

The crude acetone extract (40 g) was chromatographed on silica gel (600 g). Elution with chloroform (fractions 1–5) and with Chf–EtOAc (fractions 6–50) gave fifty fractions (each 500 ml) whose composition was investigated by TLC. Fractions 1–3 yielded euxanthone (100 mg) m.p. 237–240°, identical with a synthetic sample.[3c] Fractions 4–10 yielded 1,5,6-trihydroxyxanthone (2 g) m.p. 281° (decomp.), identical with a synthetic sample.[3c] Fractions 11–50 yielded a mixture of tetrahydroxyxanthones (4·2 g) m.p. 300° (decomp.) and maclurin (11·6 g) m.p. 218–222°.

Maclurin, which preferentially crystallized out from fractions 11–50, was collected and recrystallized from benzene–EtOAc (5:1) to give yellow needles (11·2 g) m.p. 221–222°. The product was identical with maclurin purchased from the Aldrich Chemical Company.[3a] The filtrate from fractions 11–50 was concentrated to precipitate a mixture of 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthones which was recrystallized from a solution of Chf–EtOAc.

Methylation of the tetrahydroxyxanthones (1 g) with dimethyl sulphate (2 ml) and an excess of anhydrous potassium carbonate (2 g) confirmed the presence of both 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthone as their tetramethyl ethers.[3a,3b,3c]

We thank the D.S.I.R., for a grant to purchase equipment, the Tropical Products Institute, London, for supplies of wood, and the Governors of the Royal College of Advanced Technology for a Demonstratorship (to I. M.).