Extractives from Guttiferae. Part XXV.[1] Synthesis of the Natural 1,5-Dioxygenated Xanthones, Dehydrocycloguanandin, Guanandin, Isoguanandin, and 5-Hydroxy-1-methoxyxanthone*

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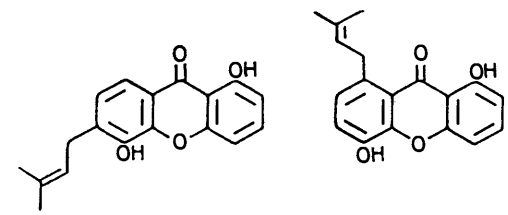
Total syntheses of the natural metabolites dehydrocycloguanandin, guanandin, isoguanandin, and 5-hydroxy-1-methoxyxanthone are described. These involved a modified synthesis of 1,5-dihydroxyxanthone from 2-hydroxy-2',3,6'-trimethoxybenzophenone and appropriate methylation, isoprenylation, and Claisen rearrangements.

THE isoprenyl and annulated 1,5-dioxygenated xanthones guanandin (1), isoguanandin (2), and dehydrocycloguanandin (3) have all been isolated from the heartwood of *Calophyllum brasiliense* Camb. (family Guttiferae).[2] In addition, guanandin (1) which has also been named Calophyllin B,[3] also occurs in *Calophyllum inophyllum* L.[3] and *C. scriblitifolium* Henderson and Wyatt-Smith.[4] We now describe total syntheses of these metabolites from 1,5-dihydroxyxanthone (4), involving *C*-isoprenylation studies for the synthesis of guanandin (1) and Claisen rearrangements for the formation of isoguanandin (2) and dehydrocycloguanandin (3). As part of these studies we have also prepared 5-hydroxy-1-methoxyxanthone (5) first isolated from *Mammea africana* G. Don and more recently from *Ochrocarpos odoratus* (Rafin) Merrill (both Guttiferae).[5b]

Two syntheses of 1,5-dihydroxyxanthone (4) have previously been reported.[6,7] In one,[7] 2,2',3,6'-tetramethoxybenzophenone (12) was cyclised to 1,5-dihydroxyxanthone (4) with hydrobromic acid. A better cyclisation method involves selective demethylation of the tetramethoxybenzophenone (12) with boron trichloride [8] to give 2-hydroxy-2',3,6'-trimethoxybenzophenone (13), followed by alkaline cyclisation with aqueous sodium hydroxide [9] or tetramethylammonium hydroxide [10] to give 1,5-dimethoxyxanthone (6). Demethylation of 1,5-dimethoxyxanthone (6) with hydrogen bromide in glacial acetic acid gives either 1,5-dihydroxyxanthone or 1-hydroxy-5-methoxyxanthone (7) according to the reaction conditions: the latter (7) was also available from selective demethylation of 1,5-dimethoxyxanthone (6) with boron trichloride. The yields for the cyclisation and demethylation reactions were virtually quantitative.

The structure of 2-hydroxy-2',3,6'-trimethoxybenzophenone (13) follows from spectral analysis and confirms the expectation that the most sterically hindered and therefore electronegative methoxy-group situated *ortho*



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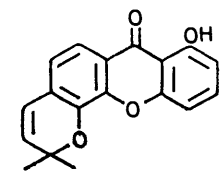
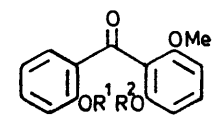


(3)



(12) $R^1 = R^2 = Me$
(13) $R^1 = H$, $R^2 = Me$
(14) $R^1 = Me$, $R^2 = H$

(4) $R^1 = R^2 = H$
(5) $R^1 = Me$, $R^2 = H$
(6) $R^1 = R^2 = Me$
(7) $R^1 = H$, $R^2 = Me$
(8) $R^1 = H$, $R^2 = CH_2Ph$
(9) $R^1 = Me$, $R^2 = CH_2Ph$
(10) $R^1 = H$, $R^2 = CH_2$·CH:CMe_2
(11) $R^1 = R^2 = CH_2CH$:CMe_2

to the benzophenone carbonyl group undergoes selective demethylation. This is confirmed by comparison of the n.m.r. spectrum of compound (13) with reference data.[11] In deuteriochloroform the alternative structure (14) would be expected to show a single methoxy-resonance at relatively high field [7,11] owing to the orientation of the methyl group in the shielding region of the adjacent benzene ring, whereas in the product (13) the highest observed signal is at τ 6·3 and represents two methoxy-

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[5] (*a*) I. Carpenter, H. D. Locksley, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1969, 2421; (*b*) A. J. Quillinan and F. Scheinmann, forthcoming publication.

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[7] H. D. Locksley and I. G. Murray, *J. Chem. Soc.* (*C*), 1970, 392.

[8] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

[9] D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1958, 1767.

[10] G. H. Stout, E. N. Christensen, W. J. Balkenhol, and K. L. Stephens, *Tetrahedron*, 1968, **25**, 1961; G. H. Stout and W. J. Balkenhol, *ibid.*, 1969, **25**, 1947.

[11] H. D. Locksley and I. G. Murray, *J. Chem. Soc.* (*C*), 1971, 1332.

functions. Furthermore, comparison of the n.m.r. spectra of compound (13) in deuteriochloroform and in hexadeuteriobenzene (Table 3) shows that all three methoxy-group resonances are shifted upfield by about 0·5 p.p.m. in the aromatic solvent,[12,13] giving clear supporting evidence for structure (13).* Mass spectrometry, however, does not differentiate between the isomers (13) and (14), since both structures have one phenyl ring substituted with one hydroxy- and one methoxy-group, and the other ring with two methoxy-functions. Ketone fragmentation is generally capable of resolving such questions of isomerism, even in the absence of other data, for benzophenones which have an unequal number of oxygen functions on each ring. This feature has proved invaluable in related studies.[5b,14]

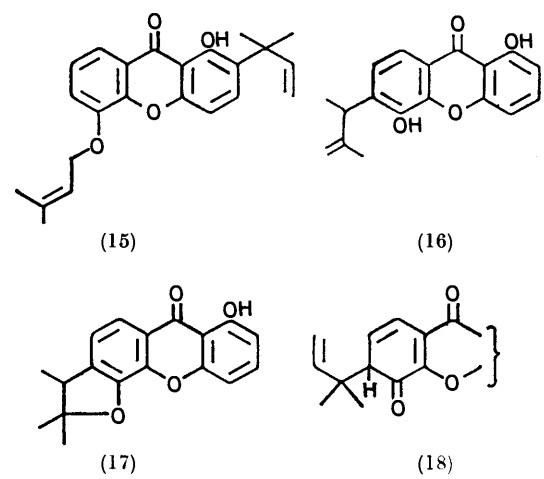
Preparation of 5-hydroxy-1-methoxyxanthone (5) involves the protection of the more reactive 5-hydroxy-group in 1,5-dihydroxyxanthone (4) prior to methylation. Thus, treatment of 1,5-dihydroxyxanthone (4) with benzyl chloride gave the 5-benzyl ether (8) which on methylation with dimethyl sulphate gave 5-benzyloxy-1-methoxyxanthone (9). Reductive cleavage of the benzyl group with hydrogen in the presence of platinum gave 5-hydroxy-1-methoxyxanthone (5), identical with the metabolite from *Mammea africana* G. Don [5a] and *Ochrocarpos odoratus* (Rafin) Merrill.[5b]

The isoprenylation of 1,5-dihydroxyxanthone (4) with 3-methylbut-2-enyl bromide in the presence of sodium methoxide was investigated as a possible route to either guanandin (1) or isoguanandin (2). The reaction was continued in the presence of a large excess of these reagents until 5-etherification was complete, as judged by t.l.c., and the complex mixture of products formed was partly separated by chromatography. Three fractions were obtained.

At lowest R_F value and in greatest abundance was 1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (10), identical with an authentic sample prepared by the reaction of the dihydroxyxanthone (4) with 3-methylbut-2-enyl bromide in the presence of potassium carbonate and acetone.

The second fraction, intermediate in R_F value and abundance, was shown to be 2-(1,1-dimethylallyl)-1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (15), largely by its n.m.r. spectrum. The third fraction was a complex mixture of 1-hydroxyxanthone 5-ethers, as shown by its t.l.c. properties. De-etherification with aqueous morpholine [15] assisted separation and enabled the isolation of guanandin (1), which showed clear spectroscopic (Tables 1 and 2) and physical identity with the natural product from *Calophyllum scriblitifolium* Henderson and Wyatt-Smith.[4] Attempts to identify isoguanandin (2) were not pursued because an efficient synthesis of this compound was available from the Claisen rearrangement of 1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (10). The structure of 2-(1,1-dimethylallyl)-1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (15) follows largely from its n.m.r. spectrum (Table 2). Thus the 1,1-dimethylallyl group [16] attached to C-2 gives a singlet for the six methyl protons (τ 8·5), and for the olefinic protons there is a quartet (1H, *J* 18 and 10 Hz) at τ 3·8 and a complex signal (2H) at τ 5·05. The *O*-3-methylbut-2-enyl group is indicated by a methylene doublet (2H, *J* 7 Hz) at τ 5·43, a triplet (1H, *J* 7 Hz) at τ 4·55, and a singlet for the two methyl groups at τ 8·28 (6H). The rest of the spectrum shows a hydrogen-bonded 1-hydroxy-group at τ −3·35 and the expected signals for the aromatic protons at C-3, C-4, C-6, C-7, and C-8. The signal at τ 3·18 (d, *J* 9 Hz) is particularly decisive in indicating the presence of a hydrogen atom at C-4, and this provides confirmation that the 1,1-dimethylallyl group is at C-2 (*cf.* Table 2; measurements at 100 MHz). In addition, a spot test confirms that the side-chain is at C-2: treatment of the xanthone (15) with hydrobromic acid showed, on t.l.c. examination, a new white fluorescence at R_F 0·6 in benzene–ethyl acetate (4 : 1) typical of a 1-alkoxy-5-hydroxyxanthone [as seen with 5-hydroxy-1-methoxyxanthone (5)].

The Claisen rearrangement of 1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (10) was examined as a possible route to isoguanandin (2). Reaction at 200° in boiling *NN*-dimethylaniline gave rise to an abnormal Claisen rearrangement, and 6-(1,2-dimethylallyl)-1,5-dihydroxyxanthone (16) was isolated as the main product. The



trimethylfuroxanthone (17) and 1,5-dihydroxyxanthone (4) were also isolated, as minor constituents.

The structure of the 1,2-dimethylallylxanthone (16)

* A Refereree has suggested that chemical evidence for structure (13) can be provided by vigorous oxidation to give 2,6-dimethoxybenzoic acid.

[12] P. J. Garratt, F. Scheinmann, and F. Sondheimer, *Tetrahedron*, 1967, **23**, 2413.

[13] J. Ronayne and D. H. Williams, *J. Chem. Soc.* (*B*), 1967, 540 and references cited therein.

[14] J. A. Ballantine and C. T. Pillinger, *Org. Mass Spectrometry*, 1968, **1**, 425.

[15] A. Jefferson, A. J. Quillinan, F. Scheinmann, and K. Y. Sim, *Austral. J. Chem.*, 1970, **23**, 2539.

[16] H. D. Locksley, A. J. Quillinan, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1971, 3804.

follows from its n.m.r. spectrum (Table 2) and its conversion into the trimethylfuroxanthone (17) on boiling with hydrobromic acid. Diagnostic for the side chain are the methyl singlet and doublet (J 7 Hz) resonances at τ 8·55 and 8·32, respectively, a methine quartet (J 7 Hz) at τ 5·98, and a sharp peak at τ 4·98 corresponding to two olefinic protons.

The tendency of the rearrangement to go only as far as C-6 implies a ready enolisation of the dienone intermediate [17] (18) in the Claisen rearrangement, under these conditions. In an attempt to reduce the degree of enolisation at this stage the rearrangement was effected in decalin. The result was particularly significant. The main product under these conditions was the desired natural product isoguanandin, previously obtained from *Calophyllum brasiliense* Camb.[2] The other products that were identified from the Claisen rearrangement are 1,5-dihydroxyxanthone (4), the abnormal Claisen product (16), and the furoxanthone (17).

The interaction of 1,5-dihydroxyxanthone (4) and

[17] A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22**, 391, and references cited therein.

TABLE 1

U.v. spectra of 1,5-dioxygenated xanthones

	$\lambda_{max.}$/nm ($\varepsilon \times 10^{-3}$)					
(7) [a]			251 (41·4)		311 (7·78)	375 (4·97)
(6) [a]			248 (48·1)		303 (9·08)	349 (6·54)
(4) [b]	235 (23·6)		248 (36·5)		313 (6·83)	370 (3·79)
(16) [b]	208 (12·9)		251 (50·9)		313 (12·9)	368 (5·15)
(2) [b]	208 (14·6)		251 (41·9)		316 (11·1)	367 (4·57)
(17) [b]	210 (9·56)	235sh (25·0)	251 (43·3)	272sh (5·69)	321 (10·3)	369 (3·87)
(15) [b]	209 (6·60)	239sh (28·2)	254 (33·1)		313 (6·36)	378 (4·48)
(8) [a]			250 (41·9)		311 (7·73)	370 (6·12)
(9) [a]			247 (45·5)		302 (10·6)	349 (8·30)
(5) [a]			247 (43·3)		303 (11·8)	349 (6·49)
(2) [b]	210 (22·2)	235sh (29·6)	252 (40·7)		320 (9·62)	374 (5·18)
(3) [b]	211 (19·6)	234 (27·6)	263 (26·1)		305sh (5·88)	343 (16·7)

[a] In chloroform. [b] In methanol.

TABLE 2

^{1}H N.m.r. absorptions of substituted 1,5-dioxygenated xanthones (60 MHz; τ values; solutions in deuteriochloroform; Me_4Si as internal reference)

Compd.	H-2	H-3	H-4	OMe	H-7 or H-6 and H-7	H-8	OH	CH_2	Ph	CH=	Me	CH–	=CH_2
(7)	3·15(d)	2·31(t)	2·92(d)	5·93(s)	2·70(m)	2·11(q)	−2·79(s)						
(6)	3·17(d)	2·35(t)	2·81(d)	6·00(s)	2·75(m)	2·06(q)							
(8)	3·21(d)	*ca.* 2·4	3·00(d)		*ca.* 2·70	2·13(q)	−2·70	4·77(s)	2·55br(s)				
(9)	3·20(d)	*ca.* 2·4	2·82(d)	6·01(s)	*ca.* 2·75(m)	2·06(q)		4·72(s)	2·510(s)				
(15) [a]		2·55(d)	3·18(d)		2·95(m)	2·34(t)	−3·35(s)	5·43(d)		3·80(q)	8·28(s)		5·05(q)
										4·55(t)	8·50(s)		
(10)	3·15(d)	2·35(t)	2·91(d)		2·66(m)	2·11(q)	−2·73(s)	5·24(d)		4·37(t)	8·20(s)		
(16)	3·15(d)	2·35(t)	3·00(d)		2·77(d)	2·16(d)	−2·71(s)				8·32(s)	5·98(q)	4·98(s)
											8·55(d)		
(2) [b]	3·21(q)	2·30(t)	2·95(q)		2·85(d)		−2·92(s)	6·00(d)		4·56(t)	8·28(s)		
					2·65(d)								
(1) [b]	3·23(q)	2·31(t)	2·96(q)		2·79(d)	2·34(d)	−2·74(s)	6·49(d)		4·61(t)	8·27br(s)		
(17) [a,c]	3·35(d)	2·58(t)	3·11(d)		3·00(d)	2·32(d)					8·48(s)	6·75(q)	
											8·65(s)		
											8·78(d)		
(3) [a,c]	3·35(d)	2·58(t)	3·12(d)		3·10(d)	2·40(d)	−2·59(s)			3·70(d)	8·49(s)		
										4·30(d)			
(7) [a]	3·35(d)	2·53(t)	3·12(d)	6·12(s)	2·90(t)	2·31(q)	−2·47(s)						

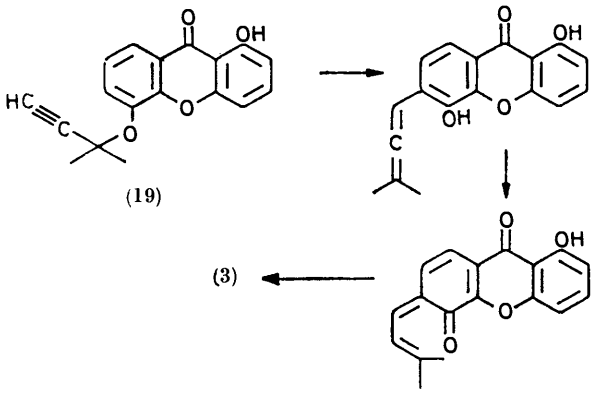
[a] 100 MHz spectrum. [b] In $(CD_3)_2CO$. [c] Xanthone numbering referred to.

TABLE 3

N.m.r. data (τ values) for the benzophenone (13) in deuteriochloroform and in hexadeuteriobenzene; Me_4Si as internal reference

Solvent	OH	H-4′	H-4	H-5	H-6	H-3′	H-5′	MeO	MeO	MeO
$CDCl_3$	−2·50(s)	2·60(q)		2·80—3·20(m)		3·35(d)	3·35(d)	6·10(s)	6·30(s)	6·30(s)
C_6D_6	−3·18(s)	2·65—3·00(m)		3·10—3·53(m)		3·68(d)	3·68(d)	6·58(s)	6·80(s)	6·80(s)
$\Delta(C_6D_6 - CDCl_3)$	−0·68					+0·33	+0·33	0·48	0·50	0·50

either 3-methylcrotonaldehyde or 4-methyl-4-hydroxybutyraldehyde dimethyl acetal in pyridine [18] was examined as a possible route to dehydrocycloguanandin (3). However, only unchanged xanthone (4) was recovered from the reaction mixture. This method of chromen synthesis from phenols is most successful for phloroglucinol and resorcinol systems and less favoured for the catechol grouping. Our attention was therefore



SCHEME

turned to the Claisen rearrangement of 5-(1,1-dimethylprop-2-ynyloxy)-1-hydroxyxanthone (Scheme).[19] Reaction of 1,5-dihydroxyxanthone (4) with 3-bromo-3-methylbut-1-yne in acetone in the presence of potassium carbonate caused concurrent etherification and Claisen rearrangement to give the pyranoxanthone dehydrocycloguanandin (3), with properties identical (Tables 1 and 2) to those reported [2] for the natural product.

EXPERIMENTAL

Microanalyses were performed by Drs. Weiler and Strauss, Oxford, and Mr. J. Jordan, Salford. U.v. spectra were measured for solutions in methanol with a Unicam SP 800 recording spectrophotometer, and i.r. spectra for Nujol mulls with a Perkin-Elmer 257 grating spectrophotometer; n.m.r. spectra were measured with Varian A-60 and HA-100 instruments. Analytical and preparative t.l.c. was carried out on silica G (Merck nach Stahl) with thicknesses of 0·3 and 1·0 mm, respectively; column chromatography was on silica gel MFC (Hopkin and Williams). Mass spectra were obtained with an A.E.I. MS12 (single-focusing) or an MS 9 (double-focusing) instrument operated at 70 eV.

Selective Demethylation of 2,2′,3,6′-Tetramethoxybenzophenone (12).—2,2′,3,6′-Tetramethoxybenzophenone [7] (5·5 g) in dichloromethane (50 ml) containing boron trichloride (20 ml ≡ 5 g BCl_3 in CH_2Cl_2) was stirred for 0·5 h. The red complex was poured into water (400 ml), further dichloromethane (70 ml) was added, and the mixture was stirred for 3 h. The pale yellow organic layer was collected, dried ($MgSO_4$), and evaporated to a yellow oil which formed needles from methanol. *2-Hydroxy-2′,3,6′-trimethoxybenzophenone* (13) (4·6 g) had m.p. 146—148°, $\nu_{max.}$ 1645, 1620, 1600, 1260, 1120, 785, and 750 cm^{-1}; n.m.r. Table 3 (Found: C, 66·5; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Further fractions of the same compound (0·5 g) were obtained on removal of the methanol.

1,5-Dimethoxyxanthone (6).—(*a*) A solution of 2-hydroxy-2′,3,6′-trimethoxybenzophenone (2 g) in methanol (12 ml) containing water (12 ml) and sodium hydroxide (2·7 g) was refluxed overnight. The mixture, on cooling, deposited white needles, which were collected, washed with water, and dried to give 1,5-dimethoxyxanthone (1·35 g), m.p. 206—208° (lit.,[5a] 194—196°); u.v. Table 1; n.m.r., Table 2; $\nu_{max.}$ 1667, 1605, 1571, 1495, 1275, 1110, and 787 cm^{-1}.

(*b*) A solution of 2-hydroxy-2′,3,6′-trimethoxybenzophenone (4 g) in pyridine (25 ml) containing water (16 ml) and tetramethylammonium hydroxide (25% w/v solution in water; 6 ml) was refluxed for 5 h. The cooled mixture was poured into an excess of 4N-hydrochloric acid (500 ml) and extracted with dichloromethane (3 × 100 ml). Evaporation of the dried ($MgSO_4$) extracts gave a granular solid (3·9 g) which crystallised as needles from ethanol to give pure 1,5-dimethoxyxanthone (3 g), identical with a sample prepared by the previous method. T.l.c. showed that no trace of either 1-hydroxy-5-methoxyxanthone or 1-methoxy-5-hydroxyxanthone had been formed.

1-Hydroxy-5-methoxyxanthone (7).—1,5-Dimethoxyxanthone (2·5 g) in dichloromethane (35 ml) containing boron trichloride (20 ml ≡ 5 g BCl_3 in CH_2Cl_2) was stirred for 0·5 h. The red complex was poured into water (250 ml) containing dichloromethane (50 ml) and the mixture was stirred until a pale yellow clear solution was obtained (2 h). Evaporation of the dried ($MgSO_4$) organic layer gave a pale yellow oil which solidified (2·3 g). 1-Hydroxy-5-methoxyxanthone formed lustrous yellow needles (from ethanol), m.p. 217—219° (lit.,[5a] 214—215°); u.v. Table 1; n.m.r., Table 2; $\nu_{max.}$ 1655, 1630, 1615, 1590, 1095, 971, and 791 cm^{-1} (Found: C, 69·4; H, 4·3. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%).

1,5-Dihydroxyxanthone (4).—1,5-Dimethoxyxanthone (5·32 g) in hydrobromic acid solution (45% w/v; 90 ml) was refluxed for 8 h. After 1·25 h, a sample (10 ml) was withdrawn for subsequent examination. Further hydrobromic acid solution (3 × 20 ml) was added to the reaction mixture after 2·4 and 6 h. After 8 h the solution was evaporated at atmospheric pressure and the residue (80 ml) was allowed to cool. 1,5-Dihydroxyxanthone, m.p. 286° (decomp.), separated as yellow needles (3·1 g). The filtrate was poured into water (300 ml). More 1,5-dihydroxyxanthone (0·85 g) appeared as a pale yellow solid. Both fractions were dried and recrystallised from ethyl acetate–light petroleum (b.p. 100—120°), giving the pure compound, m.p. 286° (decomp.), identical with an authentic sample.

The fraction withdrawn after 1·25 h (10 ml) was poured into water (75 ml); the fine precipitate was extracted with chloroform (2 × 20 ml) and the extract was dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from ethanol gave pure 1-hydroxy-5-methoxyxanthone (0·47 g) as pale yellow needles, m.p. 217—219°, identical (n.m.r. and i.r. spectra, m.p., and mixed m.p.) with an authentic sample, $\nu_{max.}$ 1655, 1630, 1615, 1095, 971, and 791 cm^{-1}.

[18] L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 368, 894; W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *ibid.*, 1969, 58; *J. Chem. Soc.* (*C*), 1971, 811.

[19] J. Hlubucek, E. Ritchie, and W. C. Taylor, *Tetrahedron Letters*, 1969, 1369; *Chem. and Ind.*, 1969, **49**, 1780.

Demethylation and Cyclisation of 2,2′,3,6′-*Tetramethoxybenzophenone* (12).—A solution of 2,2′,3,6′-tetramethoxybenzophenone (2·5 g) in glacial acetic acid (30 ml) containing aqueous hydrobromic acid (40% w/v; 30 ml) was refluxed for 2 h and allowed to cool overnight. The crystalline precipitate (0·67 g) was removed and recrystallised from methanol. 2-Hydroxy-2′,3,6′-trimethoxybenzophenone (0·42 g) formed bright yellow needles, m.p. 146—148°, $\nu_{max.}$ 1650, 1620, 1600, 790, and 750 cm^{-1}, identical (m.p., mixed m.p., i.r., and n.m.r. spectra) with the sample obtained previously.

The filtrate was evaporated under reduced pressure; a solution of the resulting brown oil in hydrobromic acid in glacial acetic acid (45% w/v; 38 ml) was refluxed for 9 h. Further hydrobromic acid (10 ml) was added at intervals of 2 h. The mixture was distilled at atmospheric pressure, and the residue (30 ml) poured into water (180 ml). After 12 h the precipitate was removed, dried, and recrystallised from ethyl acetate–light petroleum (b.p. 100—120°). 1,5-Dihydroxyxanthone appeared as a yellow microcrystalline powder (0·53 g), m.p. 286° (decomp.), identical (m.p., mixed m.p., and i.r. spectra) with a sample from *Mammea africana* G. Don.[5]

5-*Benzyloxy*-1-*hydroxyxanthone* (8).—1,5-Dihydroxyxanthone (2·1 g) in acetone (110 ml) containing excess of anhydrous potassium carbonate (6·5 g) and excess of benzyl chloride (5 g) was refluxed briefly until all the xanthone starting material had reacted [t.l.c., benzene–ethyl acetate (17 : 3) as eluant] (75 min). The mixture was immediately cooled, filtered, and evaporated to dryness *in vacuo*. Extraction with chloroform, filtration, and evaporation of the filtrate gave a solid free from traces of inorganic salts. Recrystallisation from ethanol gave 1-*hydroxy*-5-*benzyloxyxanthone* (1·7 g) as yellow needles, m.p. 172—173°, $\nu_{max.}$ 1647, 1612, 1575, 1275, 1077, 788, and 723 cm^{-1}; n.m.r. Table 2 (Found: C, 75·4; H, 4·7. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

5-*Benzyloxy*-1-*methoxyxanthone* (9).—5-Benzyloxy-1-hydroxyxanthone (0·8 g) in acetone (60 ml) containing potassium carbonate (2·3 g, anhydrous) and dimethyl sulphate (2·1 g) was refluxed overnight. Evaporation of the filtered solution gave an oil which was decomposed with water (12 ml). The granular precipitate was recrystallised from methanol to give 5-*benzyloxy*-1-*methoxyxanthone* (0·53 g) as white needles, m.p. 196—198°, $\nu_{max.}$ 1662, 1603, 1485, 1280, 780, 725, and 702 cm^{-1}; n.m.r. Table 2 (Found: C, 75·9; H, 4·9. $C_{21}H_{16}O_4$ requires C, 75·9; H, 4·8%).

5-*Hydroxy*-1-*methoxyxanthone* (5).—5-Benzyloxy-1-methoxyxanthone (400 mg) in ethanol (110 ml) containing Adams platinum oxide (67 mg) was shaken under hydrogen overnight. Evaporation of the filtered solution gave 5-hydroxy-1-methoxyxanthone as white needles (175 mg), m.p. 250—252° [from ethyl acetate–light petroleum (b.p. 100—120°)]. The synthetic compound and the natural product isolated from *Mammea africana* G. Don were identical (Found: C, 69·2; H, 4·2. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·1%).

5-Hydroxy-1-methoxyxanthone (65 mg) was methylated with dimethyl sulphate to give 1,5-dimethoxyxanthone (38 mg), m.p. 206—208°, identical with an authentic sample.

C-*Isoprenylation of* 1,5-*Dihydroxyxanthone*.—A solution of 1,5-Dihydroxyxanthone (0·86 g) in methanol (100 ml) containing sodium methoxide [from sodium (2 g)] and 3-methylbut-2-enyl bromide (8·5 g) was refluxed 3 h. Further sodium methoxide [from sodium (3 g)] and 3-methylbut-2-enyl bromide (14 g) were added gradually during each of the second and third hours. The yellow solution was filtered and the white crystalline precipitate rejected. Evaporation of filtrate, neutralisation (2N-HCl), and extraction with chloroform gave, on evaporation of the filtered solution, a yellow oil.

Chromatography on silica gel, with benzene–ethyl acetate (9 : 1) as eluant gave three fractions, A, B, and C in order of decreasing polarity. Fraction C (greatest abundance) crystallised from light petroleum as needles to give 1-hydroxy-5-(3-methylbut-2-enyloxy)xanthone (10) (0·41 g), m.p. 138—140°, identical with an authentic sample (m.p., i.r., and n.m.r. spectra). Fraction B (next greatest abundance) was a pale yellow oil (0·18 g), and was almost pure. Preparative t.l.c. on silica gel [with benzene–ethyl acetate (17 : 3)] furnished an analytical sample of 2-(1,1-*dimethylallyl*)-1-*hydroxy*-5-(3-*methylbut*-2-*enyloxy*)*xanthone* (15), $\lambda_{max.}$ Table 1; n.m.r. Table 2 [Found: C, 75·8; H, 6·5%; *M* (mass spectrum), 364. $C_{23}H_{24}O_4$ requires C, 75·8; H, 6·6%; *M*, 364]. Fraction A (least abundance) was a mixture (0·13 g) which partly crystallised. The entire fraction, dissolved in morpholine (10 ml) containing water (10 ml), was refluxed for 72 h. Acidification with 2N-hydrochloric acid, extraction into chloroform, and evaporation of the extract gave a brown oily solid.

Preparative t.l.c. on silica gel [with benzene–ethyl acetate (17 : 3)] gave a band, R_F *ca.* 0·85. Removal of this material and crystallisation from ethyl acetate–light petroleum gave 1,5-*dihydroxy*-6-(3-*methylbut*-2-*enyl*)*xanthone* (1) (21 mg), m.p. 217—220°, identical (i.r. and u.v. spectra, m.p., and mixed m.p.) with an authentic sample, $\nu_{max.}$ 3380, 1651, 1612, 1582, 1305, 1293, 1232, 1086, 1055, 903, 800, and 725 cm^{-1}, $\lambda_{max.}$ Table 1; n.m.r. Table 2 [Found: C, 73·1; H, 5·4%; *M* (mass spectrum), 296. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%; *M*, 296].

Claisen Rearrangements of 1-*Hydroxy*-5-(3-*methylbut*-2-*enyloxy*)*xanthone* (10).—(a) *In* NN-*dimethylaniline*. A solution of the xanthone (10) (1·6 g) in *NN*-dimethylaniline (25 ml) was refluxed for 5 h. The cooled mixture was poured into an excess of 4N-hydrochloric acid (500 ml) and the beige precipitate was collected. Recrystallisation twice from benzene afforded 6-(1,2-*dimethylallyl*)-1,5-*dihydroxyxanthone* as a bright yellow powder (0·97 g), m.p. 181—182°, $\lambda_{max.}$ Table 1; n.m.r. Table 2; $\nu_{max.}$ 3330, 1650, 1620, 1280, 1168, 800, and 691 cm^{-1} (Found: C, 73·1; H, 5·4. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). Evaporation of the combined liquors from the crystallisation, and preparative plate chromatography on silica gel [with benzene–ethyl acetate (9 : 1)] gave, in addition to the foregoing xanthone, 1,5-dihydroxyxanthone (78 mg), m.p. 277—280° (decomp.) [from ethyl acetate–light petroleum (b.p. 100—120°)], identical with an authentic sample (m.p., mixed m.p., and i.r. spectrum), and 2,3-dihydro-7-hydroxy-2,2,3-trimethylfuro[2,3-*c*]xanthen-6-one (17) (0·11 g), m.p. 122—123° [from light petroleum (b.p. 60—80°)], identical with a sample described later.

(b) *In decalin*. A solution of the xanthone (10) (0·72 g) in decalin (12 ml) was refluxed for 6 h. On cooling, the mixture deposited lustrous yellow plates (0·60 g). Recrystallisation from benzene gave pure 4,8-*dihydroxy*-1-(3-*methylbut*-2-*enyl*)*xanthone* (2) (0·47 g), m.p. 185—186° (lit.,[2] 175—176°) $\lambda_{max.}$ Table 1; n.m.r. Table 2; $\nu_{max.}$ 3330, 1650, 1612, 1600, 1590, 1289, 1071, 821, and 735 cm^{-1}

(Found: C, 72·8; H, 5·4. $C_{18}H_{16}O_4$ requires C, 72·95; H, 5·4%). Evaporation of most (8 ml) of the decalin gave a solid, and the liquors from the benzene recrystallisation gave a further solid. The solids were combined and recrystallised from benzene. Further isoguanandin (0·11 g) was obtained (m.p. 185—186°) as lustrous plates. The combined filtrates (benzene and decalin) were evaporated. The residue was examined by t.l.c. alongside appropriate standards. Components corresponding to 1,5-dihydroxyxanthone, 6-(1,2-dimethylallyl)-1,5-dihydroxyxanthone, and 2,3-dihydro-7-hydroxy-2,2,3-trimethylfuro[2,3-*c*]xanthen-6-one were observed in addition to the major component, which was isoguanandin (2).

Cyclisation of 6-(1,2-*Dimethylallyl*)-1,5-*dihydroxyxanthone* (16).—A solution of the xanthone (16) (210 mg) in hydrobromic acid (45% w/v in glacial acetic acid; 12 ml) was refluxed for 3 h. Removal of the hydrobromic acid *in vacuo* gave a brown oil, which was applied to four preparative silica plates (20 × 20 × 0·1 cm). The plates were developed in benzene–ethyl acetate (17 : 3) and the main band, R_F *ca.* 0·85, was removed and eluted with chloroform. Evaporation of the filtered solution gave 2,3-*dihydro*-7-*hydroxy*-2,2,3-*trimethylfuro*[2,3-c]*xanthen*-6-*one* (17) as a pale yellow solid which crystallised as needles [from light petroleum (b.p. 60—80°)] (120 mg), m.p. 122—123°; $\lambda_{max.}$ Table 1; n.m.r. Table 2 (Found: C, 72·9; H, 5·4. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

Approaches to and Synthesis of Dehydrocycloguanandin.—(*a*) A solution of pure crystalline 1,5-dihydroxyxanthone (0·75 g), pure (n.m.r.) redistilled 3-bromo-3-methylbut-1-yne (2·0 g), and anhydrous potassium carbonate (3·0 g) in dry acetone (100 ml) was refluxed for 24 h. After 12 h, further 3-bromo-3-methylbut-1-yne (2·0 g) and potassium carbonate (1·5 g) were added. After 24 h, very little reaction had taken place (t.l.c.). The mixture was therefore diluted with acetone (50 ml), and regular additions of 3-bromo-3-methylbut-1-yne (2 g) and potassium carbonate (3·5 g) were made every 12 h. After 140 h, the solution was filtered and evaporated to leave a red oil from which 1,5-dihydroxyxanthone precipitated. The chloroform-soluble portion was chromatographed on silica gel (with benzene–ethyl acetate). *Dehydrocycloguanandin* (8-*hydroxy*-2,2-*dimethylpyrano*[2,3-a]*xanthen*-7-*one*) (3) crystallised from ethyl acetate–light petroleum as a yellow solid (89 mg), m.p. 175—177° (lit.,[2] 167—169°); u.v. Table 1; n.m.r. Table 2 (Found: C, 73·4; H, 4·6. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

In another experiment, the chloroform-soluble fraction, after removal of 1,5-dihydroxyxanthone (0·11 g) was evaporated to dryness, and the residue was dissolved in *NN*-dimethylaniline (12 ml) and refluxed for 4 h. The dark brown mixture was poured into 4N-hydrochloric acid, and the precipitate was extracted with chloroform (100 ml). Evaporation of the dried ($MgSO_4$) extract gave an oil which was chromatographed as before.

Dehydrocycloguanandin (175 mg) appeared as a yellow solid, m.p. 175—177°, identical with the material from the previous preparation.

(*b*) A solution of 1,5-dihydroxyxanthone (2 g) in pyridine (50 ml) containing 3-methylcrotonaldehyde (4 g) was refluxed for 72 h. The cooled mixture was acidified (2N-HCl) and extracted with chloroform. T.l.c. showed that no dehydrocycloguanandin had been formed. 1,5-Dihydroxyxanthone (1·8 g) was recovered [m.p. 286° (decomp.)] as the only product.

The experiment was repeated with 4,4-diethoxy-2-methylbutan-2-ol (7·5 g) in place of 3-methylcrotonaldehyde. 1,5-Dihydroxyxanthone [m.p. 286° (decomp.)] was again recovered unchanged (1·9 g).

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