A New Regiospecific Synthesis of 1,4-Dihydroxyxanthones

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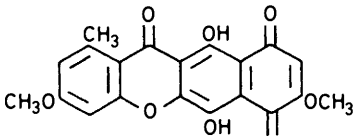
Several methyl salicylates have been found to substitute halogenated benzoquinones regiospecifically in the presence of anhydrous potassium fluoride. The resultant phenoxybenzoquinones were reduced and cyclized to highly functionalized xanthones of unambiguous structure. A number of natural substances, including three which had not been obtained previously by synthesis, were prepared by application of this method, which also established that the structure proposed earlier for the naturally occurring product '1,4-dihydroxy-2,3,7-trimethoxyxanthone' is indeed incorrect.

Recently the 1,4-dihydroxydibenzo-γ-pyrone structure has attracted considerable attention. This pattern is encountered in naturally occurring products[1-3] and constitutes a major part of the antitumour antibiotic bikaverin[4] (**1**). As a structural feature, it and related ones also have been incorporated into synthetic analogues such as the xanthocyclines.[5]

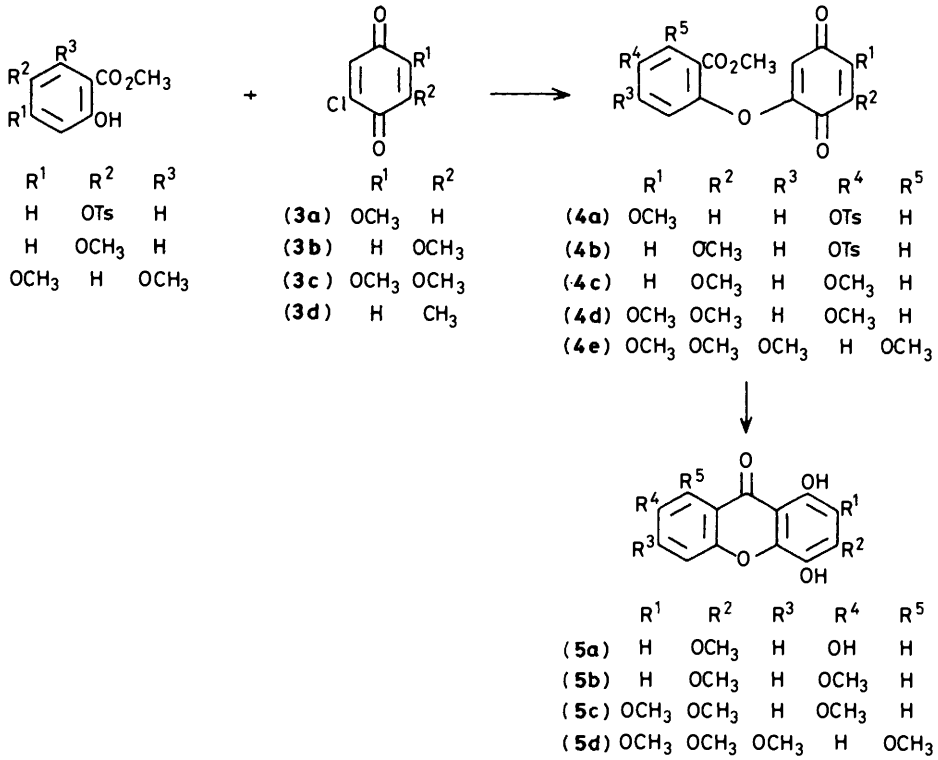


(**1**)

Simple 1,4-dihydroxyxanthones have been obtained conveniently by nucleophilic addition of phenols to alkoxycarbonylbenzoquinones, followed by methylation, hydrolysis, and finally cyclization[6] or by the oxidative ring-closure of *o*-hydroxybenzoylhydroquinones.[7] However, the regiochemical outcome is not always unequivocal in these instances and the availability of the required substrates remains problematic in the case of the most desirable examples.

In contrast, the substitution of halogenoquinones by *o*-hydroxybenzoates followed by reduction and cyclization would in principle resolve any problem due to the accessibility of highly substituted starting materials (since they or their immediate precursors are in general commercial products). This approach would also dispose of any regiochemical ambiguity providing it can be established that *O*-substitution occurs cleanly and is not complicated by *C*-arylation and addition reactions. The literature is not very explicit on this point since only fairly obvious circumstances seem to have been examined.[8]

Several substituted methyl salicylates (**2a—c**) have now been found to react smoothly with a number of halogenated benzoquinones (**3a—c**) giving exclusively the desired phenyl ether (the n.m.r. spectra in particular indicate that the substitution pattern is not changed at this stage). In some cases, the reaction is induced by hydrogen carbonate in acetone but is catalysed most efficiently by anhydrous potassium fluoride in dimethylformamide (DMF) (61—88%). Of the halogenated substrates examined only 2-chloro-6-methylbenzoquinone (**3d**) behaves erratically and gives a large number of unidentified products (Scheme).



	R^1	R^2	R^3
(**2a**)	H	OTs	H
(**2b**)	H	OCH_3	H
(**2c**)	OCH_3	H	OCH_3

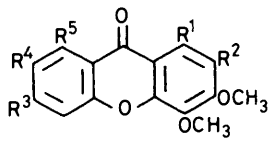
	R^1	R^2
(**3a**)	OCH_3	H
(**3b**)	H	OCH_3
(**3c**)	OCH_3	OCH_3
(**3d**)	H	CH_3

	R^1	R^2	R^3	R^4	R^5
(**4a**)	OCH_3	H	H	OTs	H
(**4b**)	H	OCH_3	H	OTs	H
(**4c**)	H	OCH_3	H	OCH_3	H
(**4d**)	OCH_3	OCH_3	H	OCH_3	H
(**4e**)	OCH_3	OCH_3	OCH_3	H	OCH_3

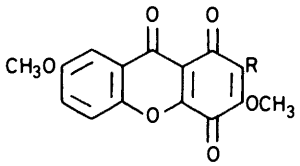
	R^1	R^2	R^3	R^4	R^5
(**5a**)	H	OCH_3	H	OH	H
(**5b**)	H	OCH_3	H	OCH_3	H
(**5c**)	OCH_3	OCH_3	H	OCH_3	H
(**5d**)	OCH_3	OCH_3	OCH_3	H	OCH_3

Scheme.

Reduction of the phenoxybenzoquinones (**4b—e**) with dithionite and cyclization of the crude hydroquinones in concentrated H_2SO_4 affords the corresponding xanthones (**5a—d**) (45—77%) which moreover can be converted into the corresponding quinones (**7**). The usefulness of the method is illustrated by the ready synthesis of seven naturally occurring compounds (**5a**), (**6a—d**), (**6f**), and (**6g**), either directly or by a subsequent regioselective conversion of the original product. For two of these compounds (**6a**) and (**6c**), direct comparison with authentic samples was possible and excellent agreement of spectral data with published values confirmed the identity of the other synthetic substances. The cyclization step failed in only one instance [(**4a**)] owing to prohibitive electronic effects (it would not in any event have led to a natural arrangement).



	R^1	R^2	R^3	R^4	R^5
(**6a**)	OH	H	H	OCH_3	H
(**6b**)	OCH_3	H	H	OCH_3	H
(**6c**)	OH	OCH_3	H	OCH_3	H
(**6d**)	OCH_3	OCH_3	H	OCH_3	H
(**6e**)	OH	OCH_3	OCH_3	H	OCH_3
(**6f**)	OCH_3	OCH_3	OCH_3	H	OCH_3
(**6g**)	OH	OCH_3	OCH_3	H	OH



	R
(**7a**)	H
(**7b**)	OCH_3

This approach allowed three natural products (**5a**), (**6f**) and (**6g**) to be obtained for the first time by synthesis and showed that the structure proposed for another is indeed incorrect. The method gave 1,4-dihydroxy-2,3,7-trimethoxyxanthone (**5c**) in a rigorously unambiguous way. The substance had physical and spectral characteristics at complete variance with those of the described product;[2] its 4-*O*-methyl (**6c**) and 1,4-di-*O*-methyl ethers (**6d**) however were obviously identical with the natural materials, indicating that the positions of the oxygen atoms at least are correct. But as the 1,2-, 1,4-, and 1,7-dihydroxylated species are now known, and considering the particular chemistry of this system, it is quite probable that the substance isolated previously is in fact the 1,3-dihydroxy-2,4,7-trimethoxy isomer.

Since this method has facilitated access to various 1,4-dihydroxyxanthones it became possible to extend to the corresponding acetates certain diagnostic criteria previously associated with 5,8-diacetoxyflavones.[9] In both cases the n.m.r. spectra reveal that the two types of esters resonate at lower fields (δ 2.47—2.57) than those in other positions. However, the natural compound described as the 1,4-dihydroxy-2,3,7-trimethoxyxanthone remains unavailable and it has not been possible to apply this test to its acetate.

Experimental

All m.p.s were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The u.v. spectra were determined on a Hewlett-Packard 8450A spectrophotometer, the i.r. spectra on a Beckman model IR-4250 instrument and calibrated with a film of polystyrene. N.m.r. spectra were recorded with a Bruker HX-90 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Woelm silica gel, activity III, and Merck silica gel $60F_{254}$, both for dry column chromatography, were used throughout in a product-to-adsorbent ratio of 1:50—100. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ether refers to diethyl ether.

Preparation of Methyl Salicylates (**2a—b**).—*Methyl 2-hydroxy-5-(p-tolylsulphonyloxy)benzoate* (**2a**). The monotosylate (**2a**) was prepared from methyl gentisate (methyl 2,5-dihydroxybenzoate) (3.0 g, 18.0 mmol) in the usual way [*p*-TsCl (18.3 mmol)–$KHCO_3$ (54.0 mmol)–$(CH_3)_2CO$, 22 h] then washed with 10% aqueous Na_2CO_3, extracted with 1% NaOH, and precipitated by concentrated HCl (43% yield); m.p. 106.0—106.5 °C (from aqueous methanol), $\nu_{max.}$(KBr) 1 680, 1 620, 1 600, and 1 375 cm^{-1}; $\lambda_{max.}$(EtOH) 228 and 311 nm (log ε 4.40 and 3.64); δ($CDCl_3$) 2.49 (3 H, s, 4′-CH_3), 3.98 (3 H, s, CO_2CH_3), 6.88 (1 H, d, *J* 9.0 Hz, 3-H), 7.03 (1 H, dd, *J* 2.5, 9.0 Hz, 4-H), 7.39 (2 H, d, *J* 8.5 Hz, 3′- and 5′-H), 7.63 (1 H, d, *J* 2.5 Hz, 6-H), 7.77 (2 H, d, *J* 8.5 Hz, 2′- and 6′-H), and 10.78 (1 H, s, OH); *m/z* 322 (M^+).

Methyl 2-hydroxy-5-methoxybenzoate (**2b**). The monoether (**2b**) was obtained from methyl 2,5-dihydroxybenzoate (30.6 g, 0.18 mol) in the usual way [$(CH_3)_2SO_4$ (0.22 mol)–K_2CO_3 (0.36 mol)–$(CH_3)_2CO$, 10 h] and purified as in the preceding paragraph (70% yield); b.p. 90—92 °C/0.3 mmHg (lit.,[10] b.p. 235—240 °C); δ($CDCl_3$) 3.78 and 3.94 (2 × 3 H, 2 s, CO_2CH_3 and OCH_3), 6.90 (1 H, d, *J* 9.0 Hz, 3-H), 7.09 (1 H, dd, *J* 3.0, 9.0 Hz, 4-H), 7.28 (1 H, d, *J* 3.0 Hz, 6-H), and 10.38 (1 H, s, OH).

Preparation of (o-*Methoxycarbonylphenoxy*)*benzoquinones* (**4a—e**).*—*General method.* To a fine suspension of anhydrous KF (348 mg, 6.00 mmol) in dry DMF (30 ml) containing the methyl salicylate (**2a—c**) (2.20 mmol) was added (10 min) a solution of a chlorobenzoquinone (**3a—c**) (2.00 mmol) in the same solvent (20 ml). The reaction mixture was kept at 75 °C for 4 h [at 100—110 °C for 1 h in the case of (**3c**)], poured into water, and extracted with ether. Purification of the crude product was carried out by dry-column chromatography on silica gel. Thus obtained were the following compounds.

2-*Methoxy*-5-[2-*methoxycarbonyl*-4-(p-*tolylsulphonyloxy*)-*phenoxy*]*benzoquinone* (**4a**). A reaction between salicylate (**2a**) and quinone (**3a**),[11] after chromatography [benzene–ethyl acetate (5:1)], gave the *phenoxybenzoquinone* (**4a**) (83%), m.p. 165.5—166.0 °C (from ethanol); $\nu_{max.}$(KBr) 1 730, 1 715, 1 670, 1 600, and 1 370 cm^{-1}; $\lambda_{max.}$(EtOH) 227, 283, and 312 (sh) nm (log ε 4.35, 4.30, and 3.57); δ($CDCl_3$) 2.49 (3 H, s, 4″-CH_3), 3.83 and 3.91 (2 × 3 H, 2 s, CO_2CH_3 and OCH_3), 5.47 (1 H, s, 6-H), 6.02 (1 H, s, 3-H), 7.14 (1 H, d, *J* 9.5 Hz, 6′-H), 7.34 (1 H, dd, *J* 2.5, 9.5 Hz, 5′-H), 7.42 (2 H, d, *J* 8.5 Hz, 3″- and 5″-H), 7.76 (1 H, d, *J* 2.5 Hz, 3′-H), and 7.79 (2 H, d, *J* 8.5 Hz, 2″- and 6″-H); *m/z* 458 (M^+) (Found: C, 57.8; H, 4.0; S, 7.1. $C_{22}H_{18}O_9S$ requires C, 57.64; H, 3.96; S, 6.99%).

2-*Methoxy*-6-[2-*methoxycarbonyl*-4-(p-*tolylsulphonyloxy*)-*phenoxy*]*benzoquinone* (**4b**). A substitution reaction of the benzoquinone (**3b**)[11] with salicylate (**2a**), after chromatography [benzene–ethyl acetate (5:1)], afforded the *phenoxybenzoquinone* (**4b**) (61%) [10% of the starting material (**3b**) was

* In the n.m.r. assignments of compounds (**4a—e**), primed and double primed numbers refer to the phenoxy and tolylsulphonyloxy substituents respectively.

recovered], m.p. 165.0—165.5 °C (from ethanol); $\nu_{max.}$(KBr) 1 730, 1 700, 1 645, 1 600, and 1 370 cm^{-1}; $\lambda_{max.}$(EtOH) 226, 282, and 378 nm (log ε 4.54, 4.21, and 2.95); δ($CDCl_3$) 2.49 (3 H, s, 4″-CH_3), 3.83 and 3.91 (2 × 3 H, 2 s, CO_2CH_3 and OCH_3), 5.48 (1 H, d, *J* 2.0 Hz, 5-H), 5.92 (1 H, d, *J* 2.0 Hz, 3-H), 7.12 (1 H, d, *J* 9.5, 6′-H), 7.32 (1 H, dd, *J* 3.0, 9.5 Hz, 5′-H), 7.40 (2 H, d, *J* 8.5 Hz, 3″- and 5″-H), 7.73 (1 H, d, *J* 3.0 Hz, 3′-H), and 7.78 (2 H, d, *J* 8.5 Hz, 2″- and 6″-H); *m/z* 458 (M^+) (Found: C, 57.6; H, 4.1; S, 7.1. $C_{22}H_{18}O_9S$ requires C, 57.64; H, 3.96; S, 6.99%)

2-*Methoxy*-6-(4-*methoxy*-2-*methoxycarbonylphenoxy*)-*benzoquinone* (**4c**). A similar reaction between quinone (**3b**) and salicylate (**2b**) provided the *phenoxybenzoquinone* (**4c**) (70%) [14% of the starting material (**3b**) was recovered], m.p. 128.5—129.0 °C (from carbon tetrachloride); $\nu_{max.}$(KBr) 1 730, 1 715, 1 695, 1 650, 1 645, 1 625, 1 610, and 1 595 cm^{-1}; $\lambda_{max.}$(MeOH) 231 and 283 nm (log ε 4.10 and 4.23); δ($CDCl_3$) 3.84 and 3.89 (3 H and 6 H, 2 s, CO_2CH_3 and OCH_3), 5.52 (1 H, d, *J* 2.5 Hz, 5-H), 5.89 (1 H, d, *J* 2.5 Hz, 3-H), 7.02—7.29 (2 H, m, 5′- and 6′-H), and 7.58 (1 H, d, *J* 2.5 Hz, 3′-H); *m/z* 318 (M^+) (Found: C, 60.1; H, 4.6. $C_{16}H_{14}O_7$ requires C, 60.38; H, 4.43%).

2,3-*Dimethoxy*-5-(4-*methoxy*-2-*methoxycarbonylphenoxy*)-*benzoquinone* (**4d**). The crude product obtained from quinone (**3c**)[12] and salicylate (**2b**) was purified by chromatography [benzene–ethyl acetate (20:1)] and afforded the *phenoxybenzoquinone* (**4d**) (87%), m.p. 103.5—104.0 °C (from carbon tetrachloride); $\nu_{max.}$(KBr) 1 730, 1 670, 1 660, 1 605, and 1 585 cm^{-1}; $\lambda_{max.}$(EtOH) 228 (sh) and 287 nm (log ε 4.25 and 4.31); δ($CDCl_3$) 3.87 and 3.91 (2 × 3 H, 2 s, CO_2CH_3 and 4′-OCH_3), 4.07 and 4.13 (2 × 3 H, 2 s, 2- and 3-OCH_3), 5.41 (1 H, s, 6-H), 7.04—7.27 (2 H, m, 5′- and 6′-H), and 7.59 (1 H, d, *J* 2.5 Hz, 3′-H); *m/z* 348 (M^+) (Found: C, 58.5; H, 4.6. $C_{17}H_{16}O_8$ requires C, 58.62; H, 4.63%).

2,3-*Dimethoxy*-5-(3,5-*dimethoxy*-2-*methoxycarbonylphenoxy*)*benzoquinone* (**4e**). Chromatography [benzene–ethyl acetate (10:1)] of the reaction mixture obtained from quinone (**3c**) and salicylate (**2c**)[13] gave the *phenoxybenzoquinone* (**4e**) (88%), m.p. 114.0—114.5 °C (from carbon tetrachloride); $\nu_{max.}$(KBr) 1 735, 1 665, 1 655, 1 620, 1 600, and 1 580 cm^{-1}; $\lambda_{max.}$(MeOH) 273 and 283 (sh) nm (log ε 4.24 and 4.22); δ($CDCl_3$) 3.80, 3.82, and 3.87 (3 × 3 H, 3 s, CO_2CH_3 and 3′- and 5′-OCH_3), 4.02 and 4.10 (2 × 3 H, 2 s, 2- and 3-OCH_3), 5.64 (1 H, s, 6-H), 6.23 (1 H, d, *J* 2.5 Hz, 4′-H), and 6.44 (1 H, d, *J* 2.5 Hz, 6′-H); *m/z* 378 (M^+) (Found: C. 57.3; H, 4.8. $C_{18}H_{18}O_9$ requires C, 57.14; H, 4.80%).

Preparation of 1,4-*Dihydroxyxanthones* (**5a—d**).—*General method.* A phenoxybenzoquinone (**4b—e**) (400 mg) was dissolved in CH_2Cl_2 (50 ml) and shaken with an aqueous solution (50 ml) of $Na_2S_2O_4$ (1.6 g) until the mixture became colourless. The organic extract and washings, after being dried, were evaporated and the residue stirred with concentrated H_2SO_4 (4 ml) for 5 min at room temperature, then at 60 °C for 15—20 min. Ice and water (50 ml) were added to the cooled reaction mixture which was diluted to 200 ml and filtered. The following compounds were thus prepared.

1,4,7-*Trihydroxy*-3-*methoxyxanthone* (**5a**). The phenoxybenzoquinone (**4b**) was converted by this method into the xanthone (**5a**) (69%), m.p. 283 °C (decomp.) (from methanol) [lit.,[14] 273—277 °C (decomp.)]; $\nu_{max.}$(KBr) 3 260br, 1 655, 1 625, 1 610, 1 585, and 1 575 cm^{-1}; $\lambda_{max.}$(MeOH) 233, 270, 321, and 402 nm (log ε 4.39, 4.50, 3.85, and 3.71); δ[$(CD_3)_2SO$] 3.97 (3 H, s, OCH_3), 6.58 (1 H, s, 2-H), 7.34 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.48 (1 H, d, *J* 3.0 Hz, 8-H), and 7.57 (1 H, d, *J* 9.0 Hz, 5-H); *m/z* 274 (M^+) (Found: C, 61.4; H, 3.7. Calc. for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68%). Acetylation (Ac_2O–H_2SO_4) of the foregoing substance (**5a**) gave the corresponding triacetate, m.p. 199.5—200.5 °C (from ethanol); δ($CDCl_3$)[15] 2.33, 2.47, and 2.51 (3 × 3 H, 3 s, 3 $OCOCH_3$), 3.98 (3 H, s, OCH_3), 6.73 (1 H, s, 2-H), 7.46 (2 H, d, J_{obs} = 0.5, $J_{AB} + J_{AC}$ = 1.7 Hz, 5- and 6-H), and 7.95 (1 H, t, J_{AB} 3.5 Hz, J_{AC} *ca.* 0 Hz, 8-H).

1,3,4,7-*Tetramethoxyxanthone* (**6b**). Methylation [$(CH_3)_2SO_4$–K_2CO_3–$(CH_3)_2CO$, 9.5 h] of the trihydroxylated xanthone (**5a**) gave the tetramethoxy compound (**6b**) (94%), m.p. 186.0—186.5 °C (from ethanol) (lit.,[16] 187.0—188.5 °C); $\nu_{max.}$(KBr) 1 655, 1 615, 1 595, and 1 575 cm^{-1}; $\lambda_{max.}$(EtOH) 234, 258, 300 (sh), 310, and 371 nm (log ε 4.48, 4.67, 4.03, 4.08, and 3.95); δ($CDCl_3$) 3.94, 3.99, and 4.06 (3 H, 3 H, and 6 H, 3 s, 4 OCH_3), 6.46 (1 H, s, 2-H), 7.29 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.51 (1 H, d, *J* 9. 0 Hz, 5-H), and 7.76 (1 H, d, *J* 3.0 Hz, 8-H); *m/z* 316 (M^+) (Found: C, 64.6; H, 5.2. Calc. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10%)

1,4-*Dihydroxy*-3,7-*dimethoxyxanthone* (**5b**). Reduction and cyclization of the phenoxybenzoquinone (**4c**) according to the general method gave the xanthone (**5b**) (66%), m.p. 292 °C (decomp.) (from ethylene dichloride); $\nu_{max.}$(KBr) 3 310, 1 655, 1 610, and 1 595 cm^{-1}; $\lambda_{max.}$(MeOH) 233, 272, 313 (sh), 323, and 399 nm (log ε 4.38, 4.50, 3.85, 3.86, and 3.69); δ[$(CD_3)_2SO$] 3.89 and 3.95 (2 × 3 H, 2 s, 2 OCH_3), 6.62 (1 H, s, 2-H), and 7.53—7.66 (3 H, m, 5-, 6-, and 8-H); *m/z* 288 (M^+) (Found: C, 62.2; H, 4.4. $C_{15}H_{12}O_6$ requires C, 62.50; H, 4.20%). Acetylation (Ac_2O–H_2SO_4) of the preceding compound (**5b**) gave the diacetate, m.p. 205—206 °C (from ethanol); δ($CDCl_3$) 2.47 and 2.52 (2 × 3 H, 2 s, 2 $OCOCH_3$), 3.91 and 3.98 (2 × 3 H, 2 s, 2 OCH_3), 6.72 (1 H, s, 2-H), 7.28 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.42 (1 H, d, *J* 9.0 Hz, 5-H), and 7.65 (1 H, d, *J* 3.0 Hz, 8-H).

1-*Hydroxy*-3,4,7-*trimethoxyxanthone* (**6a**). Selective methylation of the dihydroxylated xanthone (**5b**) (0.26 mmol) [$(CH_3)_2SO_4$ (2.10 mmol)–K_2CO_3 (2.38 mmol)–$(CH_3)_2CO$, 2 h] gave a mixture of compounds from which the trimethoxy compound (**6a**) (75%) was separated by chromatography [benzene–ethyl acetate (20:1)], m.p. 184 °C (from methanol) (lit.,[17] 182—183 °C); $\nu_{max.}$(KBr) 1 650, 1 600, and 1 590 cm^{-1}; $\lambda_{max.}$(MeOH) 233, 264, 311, and 382 nm (log ε 4.30, 4.45, 3.88, and 3.68); δ($CDCl_3$) 3.95, 3.97, and 4.01 (3 × 3 H, 3 s, 3 OCH_3), 6.46 (1 H, s, 2-H), 7.36 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.55 (1 H, d, *J* 9.0 Hz, 5-H), 7.67 (1 H,d, *J* 3.0 Hz, 8-H), and 12.82 (1 H, s, OH); *m/z* 302 (M^+, 40%) and 287 (100) (Found: C, 63.8; H, 4.9. Calc. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67%). This compound was indistinguishable from an authentic sample (mixed m.p. and t.l.c. in four solvent systems). A slower moving zone [benzene–ethyl acetate (1:1)] consisted of the tetramethoxy compound (**6b**) (25%).

3,7-*Dimethoxyxanthene*-1,4,9-*trione* (**7a**). A mixture of the xanthone (**5b**) (50 mg, 0.17 mmol), silver(I) oxide (80 mg, 0.35 mmol), and anhydrous $MgSO_4$ (0.1 g) in tetrahydrofuran (THF) (15 ml) was stirred for 3 h and filtered. Evaporation of the filtrate gave the corresponding *quinone* (**7a**) in nearly quantitative yield, m.p. 245—246 °C (decomp) (from methanol); $\nu_{max.}$(KBr) 1 695, 1 680, 1 625, and 1 595 cm^{-1}; $\lambda_{max.}$(MeOH) 247 (sh), 277, 328, and 367 nm (log ε 4.29, 4.11, 3.61, and 3.57); δ($CDCl_3$) 3.91 and 3.94 (2 × 3 H, 2 s, 2 OCH_3), 6.09 (1 H, s, 2-H), 7.37 (1 H, dd, *J* 3.0, 9.5 Hz, 6-H), 7.65 (1 H, d, *J* 3.0 Hz, 8-H), and 7.66 (1 H, d, *J* 9.5 Hz, 5-H); *m/z* 286 (M^+) (Found: C, 62.95: H, 3.7. $C_{15}H_{10}O_6$ requires C, 62.94; H, 3.52%).

1,4-*Dihydroxy*-2,3,7-*trimethoxyxanthone* (**5c**). Application of the usual method of cyclization to phenoxybenzoquinone (**4d**) yielded the *xanthone* (**5c**) (45%), m.p. 248—250 °C (from methanol); $\nu_{max.}$(KBr) 3 370, 1 655, 1 610, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 234, 277, 306 (sh), and 4.00 nm (log ε 4.45, 4.53, 3.95, and 3.68); δ[$(CD_3)_2SO$] 3.88, 3.92, and 4.03 (3 × 3 H, 3 s, 3 OCH_3) and 7.50—7.76 (3 H, m, 3 H); *m/z* 318 (M^+, 80%) and 303 (100) (Found: C, 60.5; H, 4.4. $C_{16}H_{14}O_7$ requires C, 60.38; H, 4.43%). Acetylation of the foregoing compound (**5c**) (Ac_2O–H_2SO_4) gave the corresponding diacetate, m.p. 166.0—166.5 °C (from ethanol); δ($CDCl_3$) 2.51 and 2.57 (2 × 3 H, 2 s, 2

$OCOCH_3$), 3.92, 3.94, and 4.10 (3 × 3 H, 3 s, 3 OCH_3), 7.32—7.47 (2 H, m, 5- and 6-H), and 7.64 (1 H, d, *J* 2.5 Hz, 8-H).

1-*Hydroxy*-2,3,4,7-*tetramethoxyxanthone* (**6c**). Partial methylation of substance (**5c**) [$(CH_3)_2SO_4$–K_2CO_3–$(CH_3)_2CO$, 45 min] followed by chromatography of the crude product [benzene–ethyl acetate (20:1)] gave the tetramethoxy compound (**6c**) (79%), m.p. 116.0—116.5 °C (from methanol) (lit.,[16] 118—119 °C;[2] 116—117 °C); $\nu_{max.}$(KBr) 1 650, 1 605, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 235, 270, 303, and 390 nm (log ε 4.46, 4.55, 4.05, and 3.76); δ($CDCl_3$) 3.96, 4.02, and 4.21 (3 H, 6 H, and 3 H, 3 s, 4 OCH_3), 7.38 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.56 (1 H, d, *J* 9.0 Hz, 5-H), 7.66 (1 H, d, *J* 3.0 Hz, 8-H), and 12.74 (1 H, s, OH); *m/z* 332 (M^+, 65%) and 317 (100) (Found: C, 61.3; H, 4.9. Calc. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85%). The compound was identical with an authentic sample (mixed m.p. and t.l.c. in four solvent systems). A slower moving band consisted of the permethylated substance (**6d**) (9%).

1,2,3,4,7-*Pentamethoxyxanthone* (*Polygalaxanthone B*) (**6d**). Prolonged methylation of (**5c**) (10.5 h) as in the preceding case gave polygalaxanthone B (**6d**) (85%), m.p. 120.5 °C (from methanol) (lit.,[18] 120—121 °C;[17] 118—119 °C;[16] 123—125 °C); $\nu_{max.}$(KBr) 1 660, 1 615, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 240, 261, 287, 309 (sh), and 368 nm (log ε 4.51, 4.63, 4.00, 3.83, and 3.85); δ($CDCl_3$) 3.94, 3.98, 4.03, 4.05, and 4.17 (5 × 3 H, 5 s, 5 OCH_3), 7.33 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.52 (1 H, d, *J* 9.0 Hz, 5-H), and 7.73 (1 H, d, *J* 3.0 Hz, 8-H); *m/z* 346 (M^+, 45%) and 331 (100) (Found: C, 62.6; H, 5.3. Calc. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24%).

2,3,7-*Trimethoxyxanthene*-1,4,9-*trione* (**7b**). Oxidation of the xanthone (**5c**) was carried out as for the preparation of (**7a**) and gave a nearly quantitative yield of quinone (**7b**), m.p. 221—222 °C (from methanol); $\nu_{max.}$(KBr) 1 700, 1 670, 1 650, 1 630, 1 605, and 1 575 cm^{-1}; $\lambda_{max.}$(MeOH) 246, 266, 332 (sh), and 380 nm (log ε 4.24, 4.31, 3.54, and 3.77); δ($CDCl_3$) 3.96, 4.09, and 4.22 (3 × 3 H, 3 s, 3 OCH_3), 7.39 (1 H, dd, *J* 3.0, 9.0 Hz, 6-H), 7.67 (1 H, d, *J* 3.0 Hz, 8-H), and 7.68 (1 H, d, *J* 9.0 Hz, 5-H); *m/z* 316 (M^+) (Found: C, 60.8; H, 4.1. $C_{16}H_{12}O_7$ requires C, 60.76; H. 3.82%).

1,4-*Dihydroxy*-2,3,6,8-*tetramethoxyxanthone* (**5d**). The phenoxybenzoquinone (**4e**) was converted into the xanthone (**5d**) (77%) according to the general procedure; m.p. 192.0—192.5 °C (from ethylene dichloride); $\nu_{max.}$(KBr) 3 400, 3 160, 1 650, 1 615, and 1 580 cm^{-1}; $\lambda_{max.}$(MeOH) 242 (sh), 248, 272, 324, and 378 nm (log ε 4.23, 4.24, 4.26, 4.11, and 3.36); δ[$(CD_3)_2SO$] 3.84, 3.91, 3.93, and 3.98 (4 × 3 H, 4 s, 4 OCH_3), 6.60 (1 H, d, *J* 2.0 Hz, 7-H), and 6.77 (1 H, d, *J* 2.0 Hz, 5-H); *m/z* 348 (M^+, 79%) and 333 (100). Acetylation of (**5d**) in the usual way (Ac_2O–H_2SO_4) afforded the corresponding diacetate, m.p. 179—181 °C (from aqueous ethanol); δ($CDCl_3$) 2.48 and 2.52 (2 × 3 H, 2 s, 2 $OCOCH_3$), 3.89, 3.91, 3.96, and 4.04 (4 × 3 H, 4 s, 4 OCH_3), 6.36 (1 H, d, *J* 2.5 Hz, 7-H), and 6.42 (1 H, d, *J* 2.5 Hz, 5-H).

1-*Hydroxy*-2,3,4,6,8-*pentamethoxyxanthone* (**6e**). Partial methylation of the hydroquinone (**5d**) in the usual way (2.5 h) and separation of the crude product by chromatography [benzene–ethyl acetate (5:1)] gave the *pentamethoxy compound* (**6e**) (84%), m.p. 140.5 °C (from methanol); $\nu_{max.}$(KBr) 1 650, 1 620, 1 595, and 1 570 cm^{-1}; $\lambda_{max.}$(MeOH) 250, 260 (sh), 323, and 369 (sh) nm (log ε 4.42, 4.36, 4.28, and 3.56); δ($CDCl_3$) 3.95, 3.98, 3.99, 4.02, and 4.16 (5 × 3 H, 5 s, 5 OCH_3), 6.36 (1 H, d, *J* 2.5 Hz, 7-H), 6.58 (1 H, d, *J* 2.5 Hz, 5-H), and 13.22 (1 H, s, OH); *m/z* 362 (M^+, 64%) and 347 (100) (Found: C, 59.8; H, 5.1. $C_{18}H_{18}O_8$ requires C, 59.67; H, 5.01%).

A second band [benzene–ethyl acetate (1:1)] consisted of the hexamethoxy compound (**6f**) (5%), m.p. 140.5—141.5 °C [from light petroleum (b.p. 65—110 °C] (lit.,[19] 158—161 °C); $\nu_{max.}$(KBr) 1 670, 1 620, 1 595, and 1 570 cm^{-1}; $\lambda_{max.}$(MeOH) 250, 304, and 337 (sh) nm (log ε 4.60, 4.30, and 3.79); δ($CDCl_3$) 3.93, 3.94, 3.98, 4.02, and 4.12 (3 H, 3 H, 3 H, 6 H, and 3 H, 5 s, 6 OCH_3), 6.38 (1 H, d, *J* 2.5 Hz, 7-H), and 6.56 (1 H, d, *J* 2.5 Hz, 5-H); *m/z* 376 (M^+, 27%) and 361 (100) (Found: C, 60.8; H, 5.5. Calc. for $C_{19}H_{20}O_8$: C, 60.64; H, 5.36%).

1,8-*Dihydroxy*-2,3,4,6-*tetramethoxyxanthone* (**6g**). A mixture of the xanthone (**6e**) (50 mg, 0.14 mmol) and a *ca.* 41% solution of HBr in AcOH (4 ml) was heated at 100 °C for 15 min,[20] cooled, diluted with water, and extracted with ether. Chromatography [benzene–ethyl acetate (5:1)] of the crude product gave the dihydroxyxanthone (**6g**) (22 mg, 46%), m.p. 171.5—172.0 °C (from methanol) (lit.,[3] 168—169 °C); $\nu_{max.}$(KBr) 1 665, 1 630, 1 605, and 1 570 cm^{-1}; $\lambda_{max.}$(MeOH) 235, 260, 333, and 381 (sh) nm (log ε 4.33, 4.53, 4.35, and 3.63); δ($CDCl_3$) 3.90, 3.95, and 4.14 (3 H, 6 H, and 3 H, 3 s, 4 OCH_3), 6.36 (1 H, d, *J* 2.5 Hz, 7-H), 6.51 (1 H, d, *J* 2.5 Hz, 5-H), and 11.90 and 11.98 (2 × 1 H, 2 s, 2 OH); *m/z* 348 (M^+, 75%) and 333 (100) (Found: C, 58.8; H, 4.7. Calc. for $C_{17}H_{16}O_8$: C, 58.62; H, 4.63%). The natural and synthetic materials are indistinguishable by direct comparison of their spectra (i.r., u.v., n.m.r., and m.s.).

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