Total Synthesis of Bikaverin (6,11-Dihydroxy-3,8-dimethoxy-1-methylbenzo[*b*]xanthen-7,10,12-trione) †

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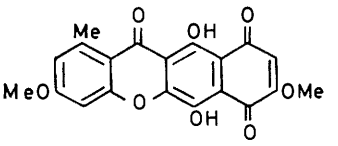
The total synthesis of the antibiotic bikaverin (1) is described, from orcinol and 3-(2,4,5-trimethoxyphenyl)-propiononitrile. The intermediate 6-hydroxy-3,7,8,10-tetramethoxy-1-methylbenzo[*b*]xanthen-12-one is oxidised to the 6,11-quinone (20), which is demethylated, preferably with iodide ion, to give bikaverin (1).

BIKAVERIN (1) is a wine-red pigment with specific anti-protozoal activity. It has been isolated from cultures of *Gibberella fujikuroi*,[1-3] *Fusarium oxysporum*, *Fusarium f. sp. bycopersici*,[4] and (recently) *Mycogone jaapai*.[5] Its determination of structure by Kjaer *et al.*[1] and simultaneously by Cornforth *et al.*[6] was confirmed by *X*-ray studies.[7] The benzo[*b*]xanthen-12-one system (2) has not been previously encountered amongst natural products, although we [8] and others [9] have synthesised this type of compound. We describe here a convenient synthesis of bikaverin.

Orcinol was converted into its dimethyl ether and monodemethylated with sodium thioethanoate in dimethylformamide to give the phenol (3).[10] Compound (3) reacted with methyl acrylate containing Triton B to give the ester (4). Saponification of this ester, followed by treatment of the resulting acid with polyphosphoric acid, gave the chromone (5). The overall yield from orcinol was 30—35%; consequently a modified synthesis of (5) was examined. Compound (3) was treated with acrylonitrile containing a catalytic amount of Triton B to give the nitrile (6). The nitrile (6) was converted *via* an intramolecular Houben–Hoesch reaction [11] into the chromone (5) in an overall yield of 82%. The chromone (5) was condensed with *o*-phthalaldehyde in ethanol–triethylamine to give the three-ring aldehyde (7). The aldehyde (7) was converted into its ethylene acetal (8) with ethylene glycol in benzene at reflux and a catalytic amount of toluene-*p*-sulphonic acid. Irradiation of the acetal (8) in dry benzene containing *o*-dichlorobenzoic acid (2 equiv.) gave, initially, the *cis*-tetracyclic compound (9), which on work-up was converted into the more stable *trans*-isomer (10).[8] Attempts to extend this model system to a compound appropriately substituted, namely (11), were not realised. Consequently, this approach was abandoned and a new synthesis based on that outlined in the Scheme was attempted.

In preliminary experiments (Scheme; $R^1 = R^2 = R^3 = H$), 3-phenylpropiononitrile (13; $R^3 = H$) was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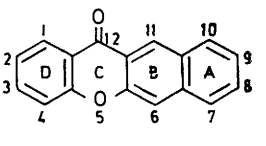
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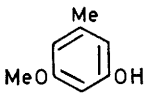
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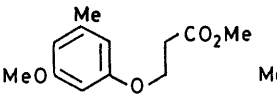
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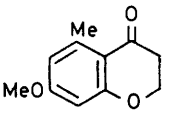
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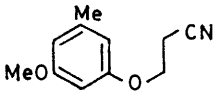
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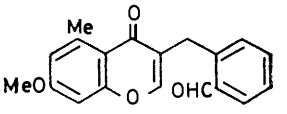
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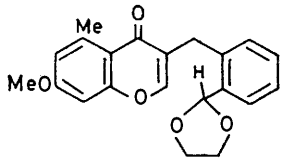
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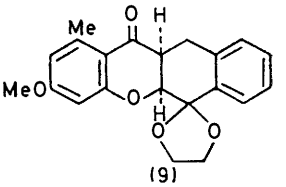
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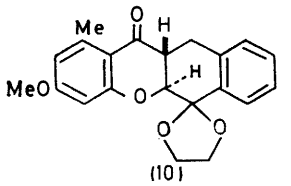
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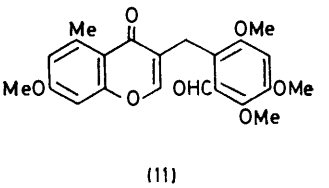
(11)

condensed with orcinol (12; $R^1 = R^2 = H$), in nitrobenzene containing zinc chloride–hydrogen chloride to give the dihydrochalcone (14; $R^1 = R^2 = R^3 = H$)[12]

† Preliminary report, D. H. R. Barton, L. Cottier, K. Freund, F. Luini, P. D. Magnus, and I. Salazar, *J.C.S. Chem. Comm.*, 1975, 646.

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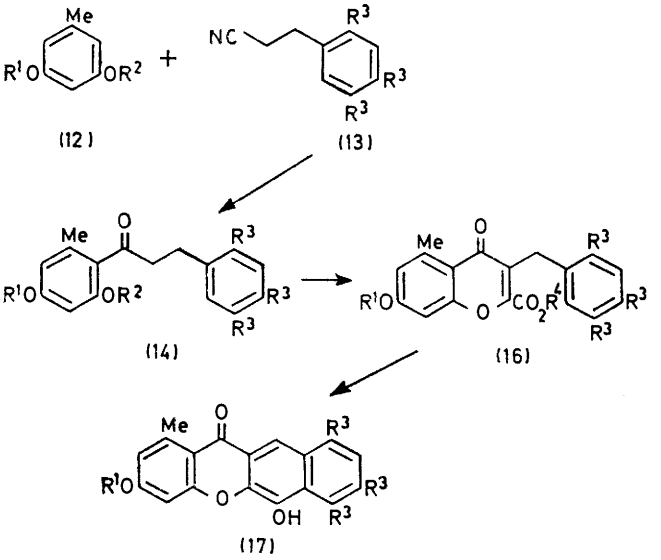
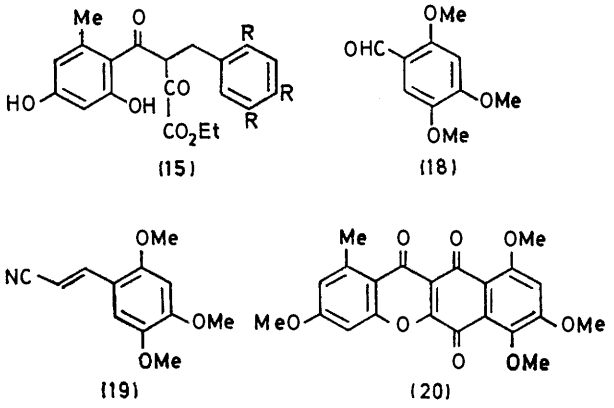
(65%). This dihydrochalcone in tetrahydrofuran was treated with dry sodium ethoxide followed by diethyl oxalate; work-up gave the intermediate ester (15; R = H), which was immediately dehydrated (*p*-TsOH–PhH at reflux) to give the chromone (16; $R^1 = R^3 =$ H, $R^4 =$ Et) (42%). This chromone was methylated (Me_2SO_4–K_2CO_3–Me_2CO) to yield the ether (16; $R^1 =$ Me, $R^3 =$ H, $R^4 =$ Et), which was hydrolysed (KOH in aq. EtOH) to the acid (16; $R^1 =$ Me, $R^3 = R^4 =$ H). The acid was converted into its acid chloride with thionyl chloride in benzene containing dimethylformamide. The crude acid chloride was treated with tin tetrachloride in dichloromethane at 0 °C, then at room temperature overnight, to give the benzo[*b*]xanthen-12-one (17; $R^1 =$ Me, $R^3 =$ H) (30%).

Since we now had a method of synthesising the benzo[*b*]xanthen-12-one system with the correct substituents in ring D, the remaining problem was to construct a suitable ring A unit. 2,4,5-Trimethoxybenzaldehyde (18) [13] was condensed with acetonitrile in benzene (reflux) containing Triton B to give the nitrile (19) (80%) (95% *trans*), which on hydrogenation gave the required ring A unit (13; $R^3 =$ OMe) (90%). Condensation of this nitrile (13; $R^3 =$ OMe) with orcinol (12; $R^1 = R^2 =$ H) in nitrobenzene containing anhydrous zinc chloride (hydrogen chloride passing through the mixture) for 4 days at room temperature gave the dihydrochalcone (14; $R^1 = R^2 =$ H, $R^3 =$ OMe) (70%). Treatment of this with diethyl oxalate in tetrahydrofuran containing



SCHEME

sodium ethoxide, as in the model experiment, gave the intermediate ester (15; R = OMe), which was azeotroped in benzene (*p*-TsOH) to give the chromone (16; $R^1 =$ H, $R^3 =$ OMe, $R^4 =$ Et) (40%). Methylation of this chromone with dimethyl sulphate in acetone containing potassium carbonate gave the chromone (16; $R^1 =$ Me, $R^3 =$ OMe, $R^4 =$ Et) (90%). Hydrolysis of this compound with N-potassium hydroxide in ethanol gave the acid (16; $R^1 =$ Me, $R^3 =$ OMe, $R^4 =$ H) (90%), which was converted into its acid chloride ($SOCl_2$ in benzene–dimethylformamide) and cyclised to the tetracyclic



phenol (17; $R^1 =$ Me, $R^3 =$ OMe) (77%) with boron trifluoride–ether in dichloromethane. Oxidation of the phenol (17; $R^1 =$ Me, $R^3 =$ OMe) with potassium dichromate in glacial acetic acid gave the quinone (20), identical with the product* described in the literature.[1] Fremy's salt did not oxidise the phenol (17; $R^1 =$ Me, $R^3 =$ OMe) to the quinone (20). Demethylation of the quinone (20) with lithium iodide in methyl t-butyl ketone at reflux gave bikaverin (1) (80%), identical with the natural material.* Alternatively, aluminium trichloride in nitrobenzene at room temperature reacted with the quinone (20) to give bikaverin (1) (70%). This route to bikaverin provides a useful way of preparing substantial quantities of material for biological testing and should be readily adaptable for preparing analogues.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Unless otherwise stated, u.v. spectra were measured for solutions in ethanol, and i.r. spectra for Nujol mulls. N.m.r. spectra were run in deuteriochloroform with tetramethylsilane as internal standard. Solvents were purified by the usual techniques. Light petroleum refers to the fraction b.p. 40—60°. 3,5-Dimethoxytoluene and 3-hydroxy-5-methoxytoluene were prepared by literature methods.[10]

Methyl 3-(3-*Methoxy-5-methylphenoxy*)*propionate* (4).—3-Hydroxy-5-methoxytoluene (3) (10 g) in methyl acrylate (50 ml) containing an aqueous solution of Triton B (2 ml) was heated at reflux for 48 h. Work-up gave the *ester* (4) (55%), b.p. 118° at 0.1 mmHg, $\nu_{max.}$ 1 745 and 1 600 cm^{-1}, $\lambda_{max.}$ 223m, 273, and 279 nm (ε 9 140, 2 120, and 2 120), τ 3.58 (3 H, s), 5.76 (2 H, t, *J* 7 Hz), 6.26 (6 H), 7.23 (2 H, t, *J* 7 Hz), and 7.73 (3 H, s) (Found: C, 64.3; H, 7.3. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%).

3-(3-*Methoxy-5-methylphenoxy*)*propionic Acid*.—The ester (4) (10 g) in methanol (5 ml) and 6N-hydrochloric acid (100 ml) was heated at reflux for 24 h. The solution was cooled and the product filtered off. The crystals obtained were dissolved in aqueous 10% sodium carbonate and filtered.

* Professor and Mrs. Kjaer are thanked for making these comparisons, and for the information that bikaverin is also being synthesised in their laboratories.

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Acidification with concentrated hydrochloric acid gave the *acid* (89%), m.p. 81°, $\nu_{max.}$ 1 708, 1 605, and 1 164 cm^{-1}, $\lambda_{max.}$ 271 and 278 nm (ε 2 230 and 2 340), τ 3.68 (3 H, s), 5.74 (2 H, t, *J* Hz), 6.25 (3 H, s), 7.22 (2 H, t, *J* 7 Hz), and 7.76 (3 H, s) (Found: C, 62.8; H, 6.6. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%).

5-Methyl-7-methoxychroman-4-one (5).—The phenoxypropionic acid (4) (5 g) and phosphorus pentaoxide (10 g) in dry benzene (100 ml) were heated at reflux for 1 h. The mixture was cooled and more phosphorus pentaoxide (10 g) was added. The mixture was heated at reflux for a further 24 h. The benzene solution was decanted and the solid residues extracted with boiling benzene. The extracts were washed with aqueous 5% sodium hydroxide and water, dried (Na_2SO_4), and evaporated to give the *chromanone* (5) (72%), m.p. 68° (from benzene–light petroleum), $\nu_{max.}$ 1 665 and 1 618 cm^{-1}, $\lambda_{max.}$ 309 and 273 nm (ε 4 990 and 14 970), τ 3.67 (2 H, s), 5.55 (2 H, t, *J* 7 Hz), 6.21 (3 H, s), 7.29 (2 H, t, *J* 7 Hz), and 7.39 (3 H, s) (Found: C, 68.7; H, 6.3. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

3-(3-Methyl-5-methoxyphenoxy)propionitrile (6).—3-Hydroxy-5-methoxytoluene (3) (10 g) in acrylonitrile (50 ml) containing aqueous Triton B (2 ml) was heated at reflux for 48 h. The cooled solution was extracted with ether, and the extract washed with water and 6N-hydrochloric acid, and dried (Na_2SO_4). Evaporation gave the *nitrile* (6) (92%), m.p. 73—74° (from benzene–light petroleum), $\nu_{max.}$ 2 260, 1 595, and 1 155 cm^{-1}, τ 3.69 (3 H, s), 5.88 (2 H, t, *J* 7 Hz), 6.27 (3 H, s), 7.26 (2 H, t, *J* 7 Hz), and 7.72 (3 H, s) (Found: C, 69.2; H, 6.8; N, 7.3. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.8; N, 7.3%).

5-Methyl-7-methoxychroman-4-one (5).—The nitrile (6) (5.0 g) in anhydrous ether (50 ml) at 0 °C containing anhydrous zinc chloride (7.0 g) was treated with hydrogen chloride gas for 2 h. The precipitate was filtered off and dissolved in boiling water (100 ml). The mixture was heated at reflux for 2 h, then cooled, and the chromanone (5) (95%) was filtered off.

3-(2-Formylbenzyl)-5-methyl-7-methoxychromone (7).—Phthalaldehyde (0.5 g) and the chromanone (5) (0.6 g) in absolute ethanol (10 ml) containing triethylamine (10 ml) were heated at reflux for 18 h. A slow stream of nitrogen was passed through the flask to remove water. The mixture was heated in an oil-bath (150—160 °C) and further portions of ethanol–triethylamine (1 : 1) were added. After 6 h the mixture was cooled, dissolved in benzene, and chromatographed over alumina (G3) to give the aldehyde (7) (75%), m.p. 159—161° (from benzene), characterised as its acetal (8).

3-[2-(1,3-Dioxolan-2-yl)benzyl]-5-methyl-7-methoxychromone (8).—The aldehyde (7) (0.5 g) in benzene (180 ml) containing ethylene glycol (1.5 ml) and toluene-*p*-sulphonic acid (20 mg) was heated at reflux for 5 h, the vapour being allowed to pass through a calcium hydride Soxhlet thimble. The cooled solution was added to aqueous 10% sodium carbonate (200 ml) and the benzene layer was separated and dried (Na_2SO_4). Evaporation gave the *acetal* (8) (81%), m.p. 116—118° (from benzene–light petroleum), $\nu_{max.}$ 1 655 and 1 190 cm^{-1}, $\lambda_{max.}$ 222, 238, 246, 271, 283, and 299 nm (ε 17 990, 18 870, 16 330, 7 720, 5 960, and 6 060), τ 2.35—3.60 (6 H, m), 4.04 (1 H, s), 5.99 (2 H, s), 6.04 (4 H, t, *J* 4 Hz), 6.16 (3 H, s), and 7.13 (3 H, s) (Found: C, 71.5; H, 5.7. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%).

trans-5a,11a,6-*Ethylenedioxy*-5a,6,11,11a-*tetrahydro*-1-*methyl*-3-*methoxybenzo*[b]*xanthen*-12-*one* (10).—The acetal (8) (40 mg) was irradiated (tungsten lamp, 750 W) in dry benzene (10 ml) containing *o*-dichlorobenzoic acid (0.2 g). After 6 h the solvent was evaporated off and the residue chromatographed on alumina (G3), with ethyl acetate–light petroleum (2 : 1) as eluant. Before chromatography, t.l.c. had indicated that two new compounds were present [(9) and (10)].[8] Evaporation of the eluate gave the *tetrahydrobenzoxanthone* (10) (50%), m.p. 121—123° (from benzene–light petroleum), $\nu_{max.}$ 1 695 and 1 610 cm^{-1}, $\lambda_{max.}$ 241, 248, and 282 nm (ε 4 930, 4 670, and 1 970), τ 2.15—3.20 (6 H, m), 5.62 (1 H, d), 5.95 (4 H, m), 6.12 (3 H, s), 6.96 (2 H, m), 7.11 (3 H, s), and 7.30 (1 H, m) (Found: C, 71.8; H, 5.7. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%).

2′,4′-Dihydroxy-6′-methyl-3-phenylpropiophenone (14; $R^1 = R^2 = R^3 = H$).—3-Phenylpropiononitrile (13; $R^3 = H$) [14] (3.5 g), and orcinol (12; $R^1 = R^2 = H$) (4.0 g) in dry nitrobenzene (10 ml) were treated with dry hydrogen chloride gas in the presence of freshly fused zinc chloride (1.5 g) at room temperature for 4 days. The mixture was poured into 4N-sulphuric acid (150 ml), and the aqueous solution was decanted, washed with ether (2 × 75 ml), and set aside at 0 °C for 4 days. The precipitate was filtered off, washed with cold ether (3 × 50 ml), and hydrolysed in boiling water (200 ml) for 1 h. The resulting mixture was extracted with chloroform (5 × 60 ml), and the extract washed with water and dried (Na_2SO_4). Evaporation gave the dihydrochalcone (14; $R^1 = R^2 = R^3 = H$) (65%), m.p. 118° (lit.,[12] 118.5°), $\nu_{max.}$ 3 300, 1 620, and 1 580 cm^{-1}, $\lambda_{max.}$ 308, 282, and 214 nm (ε 5 400, 8 800, and 11 700).

3-Benzyl-2-ethoxycarbonyl-7-hydroxy-5-methylchromone (16; $R^1 = R^3 = H$, $R^4 = Et$).—The dihydrochalcone (14; $R^1 = R^2 = R^3 = H$) (0.5 g) in tetrahydrofuran (10 ml) was added, under nitrogen, to dry sodium ethoxide [from sodium (0.27 g)] in tetrahydrofuran (10 ml) at 0 °C, followed by diethyl oxalate (2 g). The mixture was stirred at room temperature for 5 h, neutralised with 6N-hydrochloric acid, and evaporated. The residue was extracted with chloroform (6 × 50 ml). The dried (Na_2SO_4) extracts were evaporated to give the crude product (15; R = H) (0.420 g), m.p. 200° (from ethanol). The ester (15; R = H) (0.4 g) in benzene (25 ml) was treated with toluene-*p*-sulphonic acid (0.4 g) and the mixture was heated at reflux for 2 h with provision (Dean–Stark) for the removal of water. The product crystallised as the reaction proceeded. The crude product was chromatographed over silica gel [elution with dichloromethane–ethyl acetate (9 : 1)] to give the *chromone* (16; $R^1 = R^3 = H$, $R^4 = Et$) (42%), m.p. 203° (from methanol), $\nu_{max.}$ 3 240, 1 730, 1 720, 1 630, 1 620, and 1 600 cm^{-1}, $\lambda_{max.}$ 311, 265, 258, 236, and 226 nm (ε 9 850, 10 300, 12 600, 18 300, and 21 500), τ [$(CD_3)_2SO$] 8.78 (3 H, t, *J* 7 Hz), 7.4 (3 H, s), 6.8 (1 H, m), 5.98 (2 H, s), 5.73 (2 H, q, *J* 7 Hz), 3.4 (2 H, s), 2.88 (5 H, s) (Found: C, 70.9; H, 5.4. $C_{20}H_{18}O_5$ requires C, 71.0; H, 5.4%).

3-Benzyl-2-ethoxycarbonyl-7-methoxy-5-methylchromone (16; R^1 = Me, $R^3 = H$, $R^4 = Et$).—The hydroxychromone (16; $R^1 = R^3 = H$, $R^4 = Et$) (0.15 g) in acetone (10 ml) containing potassium carbonate (0.12 g) and dimethyl sulphate (0.99 g) was heated at reflux for 2 h. Evaporation and chromatography of the residue on silica [elution with dichloromethane–ethyl acetate (95 : 5)] gave the *chromone* (16; R^1 = Me, $R^3 = H$, $R^4 = Et$) (90%), m.p. 130° (from methanol), $\nu_{max.}$ 1 735, 1 650, 1 620, and 1 580 cm^{-1}, $\lambda_{max.}$ 306, 262, 254, 237, and 227 nm (ε 10 200, 10 400, 12 400, 18 600, and 25 200), τ [$(CD_3)_2SO$] 8.75 (3 H, t, *J* 7 Hz), 7.36 (3 H, s),

[14] V. Brec, *Bull. Soc. chim. belges*, 1948, **57**, 71.

6.18 (3 H, s), 5.94 (2 H, s), 5.68 (2 H, q, *J* 7 Hz), 3.24 (1 H, m), 3.14 (1 H, d, *J* 2 Hz), and 2.84 (5 H, m) (Found: C, 71.4; H, 5.6. $C_{21}H_{20}O_5$ requires C, 71.6; H, 5.7%).

3-Benzyl-2-carboxy-7-methoxy-5-methylchromone (16; R^1 = Me, R^3 = R^4 = H).—The chromone (16; R^1 = R^3 = H, R^4 = Et) (0.44 g) in ethanol (10 ml) and N-potassium hydroxide (25 ml) was stirred at room temperature for 24 h. Evaporation and acidification of the residue with 6N-hydrochloric acid gave the *carboxychromone* (16; R^1 = Me, R^3 = R^4 = H) (90%), m.p. 209° (from methanol), $\nu_{max.}$ 1 740, 1 640, 1 600, and 1 595 cm^{-1}, $\lambda_{max.}$ 302, 263, 253, 238, 226, and 218 nm (ε 8 800, 8 800, 12 200, 17 300, 19 700, and 21 600), τ [$(CD_3)_2SO$] 7.38 (3 H, s), 6.2 (3 H, s), 5.9 (2 H, s), 4.8 (1 H, m), 3.28 (1 H, m), 3.14 (1 H, d, *J* 2 Hz), and 2.84 (5 H, m) (Found: C, 70.7; H, 5.1. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%).

6-Hydroxy-3-methoxy-1-methylbenzo[b]*xanthen-12-one* (17; R^1 = Me, R^3 = H).—The acid (16; R^1 = Me, R^3 = R^4 = H) (0.15 g) in benzene (3 ml) was treated with thionyl chloride (0.8 g) and dimethylformamide (1 drop). The mixture was heated at reflux for 2 h and then evaporated. The residue was dissolved in dichloromethane (5 ml) and tin tetrachloride (0.1 ml) was added. The mixture was left at 0 °C for 0.5 h, then at room temperature for 1 h, heated at reflux for 5 h, then set aside at room temperature overnight. The reaction was quenched with aqueous ammonium chloride solution (10 ml) and extracted with chloroform (5 × 10 ml); the extracts were dried (Na_2SO_4) and evaporated to give the *benzo*[b]*xanthen-12-one* (17; R^1 = Me, R^3 = H) (40 mg), m.p. 275° (from ethanol), $\nu_{max.}$ 3 500, 1 670, 1 650, 1 610, and 1 675 cm^{-1}, $\lambda_{max.}$ 405, 332, 313, 287, 264, 236, 232, and 207 nm (ε 2 800, 5 100, 8 300, 20 100, 39 000, 12 500, 13 300, and 18 200), τ [$(CD_3)_2SO$] 7.32 (3 H, s), 6.4 (1 H, m), 6.14 (3 H, s), 3.28 (1 H, m), 3.1 (1 H, d, *J* 2 Hz), 2.5 (2 H, m), and 1.85 (3 H, m) (Found: C, 74.6; H, 4.8. $C_{19}H_{14}O_4$ requires C, 74.5; H, 4.6%).

2,4,5-Trimethoxycinnamonitrile (19).—2,4,5-Trimethoxybenzaldehyde (18) (16.4 g) in benzene (150 ml) and acetonitrile (50 ml) was treated with aqueous Triton B (2.5 ml). The mixture was heated under reflux under a Dean–Stark head for 2 h, cooled, poured into water (100 ml), and extracted with benzene (4 × 100 ml). The extracts were dried ($MgSO_4$) and evaporated and the residue (20 g) was chromatographed on silica [elution with dichloromethane (94%)–ethyl acetate (6%)] to give the *cinnamonitrile* (19) (15 g), m.p. 84° (from ethanol–light petroleum), $\nu_{max.}$ 3 000 and 2 210 cm^{-1}, $\lambda_{max.}$ 350, 289, and 240 nm (ε 14 900, 14 000, and 13 000), τ 6.25 (3 H, s), 6.15 (6 H, s), 4.1 (1 H, d, *J* 17 Hz), 3.5 (1 H, s), 3.05 (1 H, s), and 2.5 (1 H, d, *J* 17 Hz) (Found: C, 65.6; H, 6.0; N, 6.8. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%).

3-(2,4,5-Trimethoxyphenyl)propiononitrile (13; R^3 = OMe).—2,4,5-Trimethoxycinnamonitrile (19) (8.5 g) in ethanol (125 ml) was hydrogenated over 10% palladium–carbon (2 g) at room temperature and atmospheric pressure. The solution was filtered through Celite 545 and evaporated to give the *nitrile* (13; R^3 = OMe) (8 g), m.p. 64° (from light petroleum), $\nu_{max.}$ 2 290 cm^{-1}, $\lambda_{max.}$ 290, 232, and 209 nm (ε 4 980, 8 750, and 12 800), τ 7.3 (4 H, m), 6.2 (9 H, m), 3.5 (1 H, s), and 3.3 (1 H, s) (Found: C, 65.4; H, 6.9; N, 6.2. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%).

2′,4′-Dihydroxy-6′-methyl-3-(2,4,5-trimethoxyphenyl)propiophenone (14; R^1 = R^2 = H, R^3 = OMe).—The nitrile (13; R^3 = OMe) (26 g) and anhydrous orcinol (25 g) in dry nitrobenzene (80 ml) were treated with dry hydrogen chloride gas in the presence of freshly fused zinc chloride (9 g) at room temperature for 4 days. The mixture was poured into cold water (200 ml) and the solid filtered off and washed with ice-cold ether (8 × 50 ml), dissolved in warm water (400 ml), and heated at reflux for 1 h. The cooled aqueous solution was extracted with chloroform (8 × 100 ml); the extracts were washed with water, dried ($MgSO_4$), and evaporated to give the *dihydrochalcone* (14; R^1 = R^2 = H, R^3 = OMe) (70%), m.p. 147° (from ethanol–light petroleum), $\nu_{max.}$ 3 400 and 1 600 cm^{-1}, $\lambda_{max.}$ 322, 288, 232, 223, and 208 nm (ε 3 800, 11 000, 14 900, 18 300, and 24 700), τ [$(CD_3)_2SO$] 8.14 (3 H, s), 7.45 (2 H, t, *J* 6 Hz), 7.18 (2 H, t, *J* 6 Hz), 6.88 (1 H, s), 6.56 (3 H, s), 6.46 (6 H, s), 4.10 (1 H, m), 4.02 (1 H, d, *J* 2 Hz), 3.58 (1 H, s), and 3.48 (1 H, s) (Found: C, 65.9; H, 6.2. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

2-Ethoxycarbonyl-7-hydroxy-5-methyl-3-(2,4,5-trimethoxybenzyl)chromone (16; R^1 = H, R^3 = OMe, R^4 = Et).—To a suspension of sodium ethoxide [from sodium (6.6 g)] in dry benzene (100 ml) was added the dihydrochalcone (14; R^1 = R^2 = H, R^3 = OMe) (16.6 g) in dry benzene (300 ml) and diethyl oxalate (40 ml). The suspension was stirred under nitrogen at room temperature for 4 h. Neutralisation with acetic acid, and washing the benzene layer with water (4 × 100 ml), followed by extraction (EtOAc), drying (Na_2SO_4), and evaporation gave the intermediate oxalate (15; R = OMe) (25%), m.p. 195° (from dichloromethane). This oxalate (5.5 g) in benzene (500 ml) containing toluene-*p*-sulphonic acid (1.2 g) was heated at reflux for 2 h. Evaporation and extraction of the residue with ethyl acetate, washing with water, drying (Na_2SO_4), and evaporation gave the *chromone* (16; R^1 = H, R^3 = OMe, R^4 = Et) (92%), m.p. 185° (from ethanol), $\nu_{max.}$ 3 300, 1 745, 1 635, 1 605, and 1 580 cm^{-1}, $\lambda_{max.}$ 300, 256, 228, 217, and 209 nm (ε 8 700, 10 100, 18 300, 21 800, and 21 600), τ[$(CD_3)_2SO$] 8.7 (3 H, t, *J* 7 Hz), 8.2 (1 H, m, exchanged by D_2O), 7.35 (3 H, s), 6.3 (3 H, s), 6.25 (6 H, s), 6.06 (2 H, s), 5.64 (2 H, q, *J* 7 Hz), 3.8 (1 H, s), and 3.3 (3 H, m) (Found: C, 64.9; H, 5.9. $C_{23}H_{24}O_8$ requires C, 64.7; H, 5.8%).

2-Ethoxycarbonyl-7-methoxy-5-methyl-3-(2,4,5-trimethoxybenzyl)chromone (16; R^1 = Me, R^3 = OMe, R^4 = Et).—Prepared from the hydroxychromone (16; R^1 = H, R^3 = OMe, R^4 = Et) by the method described for the model hydroxychromone (16; R^1 = H, R^3 = H, R^4 = Et), the *methoxychromone* (16; R^1 = Me, R^3 = OMe, R^4 = Et) had m.p. 131° (from methanol), $\nu_{max.}$ 1 750, 1 640, 1 620, 1 580, and 1 520 cm^{-1}, $\lambda_{max.}$ 295, 254, 227, 216, and 210 nm (ε 11 300, 12 200, 22 200, 25 000, and 24 200), τ [$(CD_3)_2SO$] 8.75 (3 H, t, *J* 7 Hz), 7.4 (3 H, s), 6.48 (3 H, s), 6.33 (3 H, s), 6.21 (3 H, s), 6.14 (2 H, s), 5.72 (2 H, q, *J* 7 Hz), 3.48 (1 H, s), 3.4 (1 H, s), 3.28 (1 H, s), and 3.2 (1 H, s) (Found: C, 66.6; H, 5.2. $C_{22}H_{20}O_7$ requires C, 66.7; H, 5.1%).

2-Carboxy-7-methoxy-5-methyl-3-(2,4,5-trimethoxybenzyl)chromone (16; R^1 = Me, R^3 = OMe, R^4 = H).—Prepared from the ester (16; R^1 = Me, R^3 = OMe, R^4 = Et) as in the model series (16; R^1 = Me, R^3 = H, R^4 = H), the *carboxychromone* (16; R^1 = Me, R^3 = OMe, R^4 = H) had m.p. 178° (from ethanol), $\nu_{max.}$ 1 730, 1 630, 1 600, 1 570, and 1 520 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 296, 286, and 244 nm (ε 38 300, 42 000, and 54 800), τ [$(CD_3)_2SO$] 7.39 (3 H, s), 6.48 (3 H, s), 6.32 (6 H, s), 6.21 (3 H, s), 6.1 (2 H, s), 5.6 (1 H, m), 3.46 (1 H, s), 3.4 (1 H, s), 3.28 (1 H, m), and 3.14 (1 H, d, *J* 2 Hz) (Found: C, 63.6; H, 5.6. $C_{22}H_{22}O_8$ requires C, 63.8; H, 5.4%).

6-Hydroxy-3,7,8,10-tetramethoxy-1-methylbenzo[b]*xanthen-*

12-*one* (17; R^1 = Me, R^3 = OMe).—The acid (16; R^1 = Me, R^3 = OMe, R^4 = H) (1.1 g) in dry benzene (25 ml) containing thionyl chloride (1 ml) and dry dimethylformamide (3 drops) was heated at reflux for 3 h. The mixture was evaporated to dryness and the residue dissolved in dichloromethane. To this solution boron trifluoride–ether complex (1 ml) in dichloromethane (5 ml) was added; the mixture was heated at reflux for 5 h, then stirred at room temperature overnight. Aqueous ammonium chloride (satd.) was then added and the dichloromethane layer was dried (Na_2SO_4) and passed through alumina (G3) (elution with chloroform) to give, after evaporation, the *xanthen*-12-*one* (17; R^1 = Me, R^3 = OMe) (77%), m.p. 243° (from chloroform–light petroleum), $\nu_{max.}$ 3 300, 1 650, 1 620, 1 610, 1 570, and 1 510 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 414, 340, 302, and 260 nm (ε 18 700, 18 000, 82 000, and 116 000), τ 7.16 (3 H, s), 6.18 (3 H, s), 6.08 (6 H, s), 6.02 (3 H, s), 3.56 (1 H, s), 3.42 (1 H, m), 3.2 (1 H, d, *J* 2 Hz), 1.4 (1 H, s), and 0.04 (1 H, s) (Found: C, 66.6; H, 5.2. $C_{22}H_{20}O_7$ requires C, 66.7; H, 5.1%).

Di-O-methylbikaverin (20).—The phenol (17; R^1 = Me, R^3 = OMe) (350 mg) in glacial acetic acid (50 ml) was treated with potassium dichromate (350 mg) at room temperature for 2.5 h. The mixture was extracted with chloroform, the dried extracts were evaporated, and the residue (300 mg) was chromatographed on silica [elution with dichloromethane–methanol (9.5 : 0.5)] to give di-*O*-methylbikaverin [1] (20) (55%), m.p. 263° (from chloroform–ether), identical with an authentic sample.

Bikaverin (1).—The crude di-*O*-methylbikaverin (20) (85 mg) in methyl t-butyl ketone (20 ml) containing lithium iodide (90 mg) was heated at reflux for 5 h. The mixture was evaporated and the residue treated with 6N-hydrochloric acid (15 ml) for 2.5 h. The mixture was extracted with chloroform and dried (Na_2SO_4). Evaporation and treatment of the residue with methanol and a few drops of concentrated hydrochloric acid gave pure crystalline bikaverin (1) [1] (80%), identical with an authentic sample.

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