A Synthesis of Bikaverin (7,12-Dihydro-6,11-dihydroxy-3,8-dimethoxy-1-methyl-10*H*-benzo[*b*]xanthene-7,10,12-trione) and some Related Benzoxanthones and Quinones

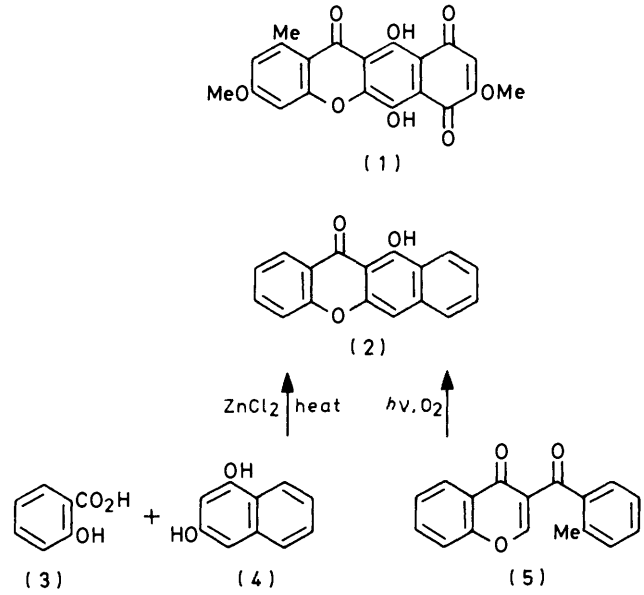
Dana Kjær, Anders Kjær,* and Elisabeth Risbjerg
Department of Organic Chemistry, The Technical University of Denmark, 2800 Lyngby, Denmark

Bikaverin, a biologically interesting fungal pigment with the highly oxidised benzoxanthone structure (1), has been synthesized in two steps from 2-hydroxy-4-methoxy-6-methylacetophenone (6f) and dimethyl 3,5-dimethoxyhomophthalate (7f). The synthesis involves a base-catalysed reaction between these substrates to give the substituted 11-hydroxybenzoxanthone (8f) in about 25% yield, followed by oxidation of the latter with trifluoroperacetic acid under controlled conditions directly to bikaverin in about 35% yield. The operational simplicity, together with the easy accessibility of the starting materials, make this synthesis compare favourably with two, previously reported syntheses of bikaverin. The preparation of five additional 11-hydroxybenzoxanthones, and the oxidative conversions of four of these, are also described.

Bikaverin (1) [1-3] is a structurally unique, red biochrome, produced in several species of the fungal genera *Fusarium*,[1] *Gibberella*,[3] and *Mycogone*.[4] The pigment possesses a number of interesting biological properties such as a vacuolation-inducing effect in fungi [1] and *in vitro* growth-inhibiting activity towards the protozoan *Leishmania brasiliensis* [5] and various tumour cell types,[6,7] the latter effected through uncoupling of the oxidative phosphorylation process.[8] These properties, a cumbersome *in vivo* production, and a certain structural similarity with the tetracycline and anthracycline antibiotics together explain the notable attention accorded to bikaverin as a target of synthesis. The independent syntheses of Barton *et al.*[9] and Kato and his co-workers,[10] starting from common chemicals such as orcinol, orsellinic acid, and vanillin, proceed through a dozen individual steps or more. A shorter approach, based on oxidative phenolic coupling, was explored but found to be without avail in the case of bikaverin.[11]

From the onset of our preparative endeavours several years ago our efforts were aimed at a synthesis proceeding in a few steps from readily available starting materials and possessing sufficient versatility to permit the preparation of structural analogues needed for structure–activity studies. Anticipating partial ring-oxidation to be a feasible, late step in the synthetic approach, we first focussed on an efficient synthesis of 11-hydroxy-12*H*-benzo[*b*]xanthen-12-one (2). A Nencki-type reaction, involving salicylic acid (3) and 1,3-dihydroxynaphthalene (4), had previously been reported to afford (2) in a yield of about 1%; [12] the compound was later produced much more efficiently by photo-induced, oxidative cyclisation of 3-(*o*-toluoyl)chromone (5), an interesting reaction, though of unexplored utility for more highly substituted substrates.[13]

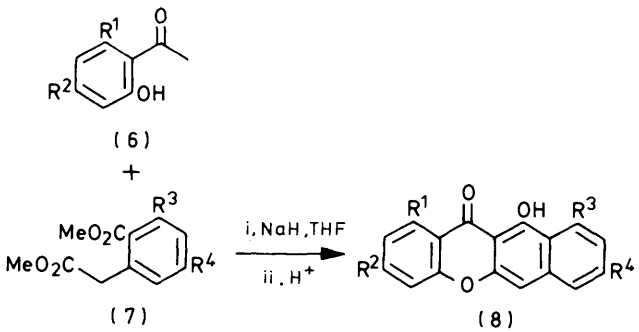
Retrosynthetic analysis suggested to us that an operationally simple one-step, double acylation of the methyl group of *o*-hydroxyacetophenones (6), accomplished *via* their dianions and with the carbonyl groups of dimethyl homophthalates (7) functioning as electrophiles, might lead to linearly annelated 11-hydroxybenzoxanthones (8). This proved indeed to be the case.[14] Comparable acidities of *o*-acetylphenolates and dimethyl homophthalates, supposedly resulting in complex enolate populations, make product distribution and yields in reactions between them highly sensitive to changes in substitution pattern and experimental conditions, notably the nature and quantities of base and solvent. By proper choice of conditions (see Experimental section), however, the six 11-hydroxybenzoxanthones (8a—f) were obtained in yields varying from 25 to 70% in this operationally simple one-step



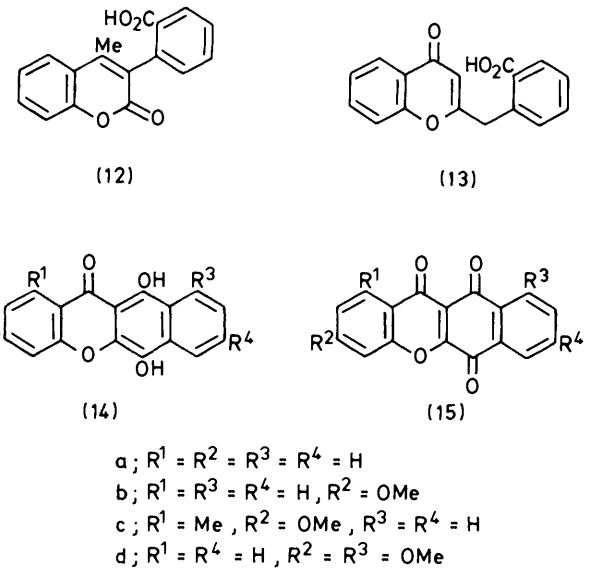
reaction. For further characterisation some of the corresponding *O*-acetates were prepared.

The structural formulation of compound (8a) follows from its identity with a specimen produced, as described,[12] from salicylic acid and 1,3-dihydroxynaphthalene which, in its turn, had been established as identical with the product arising from photo-induced cyclisation of (5); [13] the latter synthesis precludes the formation of angularly annelated isomers such as 6-hydroxy-7*H*-benzo[*c*]xanthen-7-one (9), not easily distinguishable from (8a) by spectroscopic means. The tetra-substituted product (8f) derives structural support from its conversion into bikaverin (1), as described below, whereas the formulations of the compounds (8b—e) rest on analogy and spectroscopic comparison with (8a) and (8f).

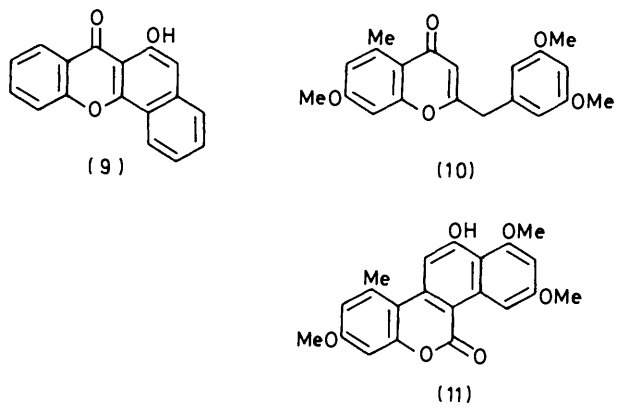
A few minor constituents were identified in the reaction mixtures. Thus, the benzylchromone (10), identified by its spectroscopic characteristics, was isolated as a minor product from the reaction of (6f) with (7f); the simple ester cleavage followed by decarboxylation is surprising in view of the known recalcitrance of the aromatic ester grouping in dialkyl homophthalates to hydrolyse. Another minor product, arising from the same reaction, was identified as 12-hydroxy-1,3,8-trimethoxy-10-methyl-5*H*-benzo[*b*]naphtho[2,1-*d*]pyran-5-one



a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = R^3 = R^4 = H, R^2 = OMe$
c; $R^1 = Me, R^2 = OMe, R^3 = R^4 = H$
d; $R^1 = R^4 = H, R^2 = R^3 = OMe$
e; $R^1 = Me, R^2 = R^3 = OMe, R^4 = H$
f; $R^1 = Me, R^2 = R^3 = R^4 = OMe$



a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = R^3 = R^4 = H, R^2 = OMe$
c; $R^1 = Me, R^2 = OMe, R^3 = R^4 = H$
d; $R^1 = R^4 = H, R^2 = R^3 = OMe$



(11) on the basis of its spectroscopic data. Obviously, its production signals the operation of an alternative, though minor, pathway, with the phenone grouping acting as the electrophile and the phenylacetate-derived enolate as the nucleophile. A similar course of events was encountered on heating methyl *o*-carboxyphenylacetate with *o*-hydroxyacetophenone in xylene in the presence of sodium; here the coumarin (12) was isolated as the sole product. In contrast, the same reaction, performed with sodium hydride in tetrahydrofuran (THF), afforded the isomeric chromone (13),[14] another illustration of the operation of the aromatic ketone and the ester in reversed roles depending on conditions.

The starting materials for the syntheses of (8a—f) were commercially available [(6a) and (7a)], or easily prepared in high yields. Thus, 2-hydroxy-4-methoxyacetophenone (6b) was produced by methylation of commercially available 2,4-dihydroxyacetophenone.[15] Similarly, methylation of 2,4-dihydroxy-6-methylacetophenone,[16] efficiently produced from orcinol by Hoesch synthesis,[17] afforded 2-hydroxy-4-methoxy-6-methylacetophenone (6c). Dimethyl-3-methoxyhomophthalate (7d) resulted from exhaustive methylation of 3-hydroxyhomophthalic acid, easily accessible from phenol and 3-chloropropionic acid as described previously.[18,19] Finally, dimethyl 3,5-dimethoxyhomophthalate (7f) was prepared either by *O*-methylation of dimethyl 3,5-dihydroxyhomophthalate, in its turn produced from dimethyl 3-oxoglutarate and sodium,[20] or, more efficiently, by carbonisation of the dianion of di-*O*-methylorsellinic acid,[21] followed by Fischer esterification.

With an efficient synthesis of the molecular skeleton of bikaverin (1) on hand, the outstanding synthetic modifications of (8f) included (i) selective demethylation of the *peri*-methoxy group, (ii) introduction of hydroxy groups at carbon atoms C-6 and C-7, and (iii) oxidation to the naphthazarin system. Controlled oxidation of the simplest 11-hydroxybenzoxanthone (8a), studied as a model, proved difficult and capricious; thus several of the commonly employed oxidation reagents (Fremy's salt, potassium persulphate, thallium triacetate, potassium dichromate, silver carbonate, and others) either were inefficient or gave complex product mixtures. One reagent, *viz.* trifluoroperacetic acid in chloroform, however, proved exceptional, converting (8a) surprisingly cleanly into 6,11-dihydroxy-12*H*-benzo[*b*]xanthen-12-one (14a), characterised as the di-*O*-acetate. A low temperature, as well as control of reaction time and molecular excess of oxidant, was essential in minimising side-reactions such as Baeyer–Villiger oxidation. By the same token, compounds (8b—d), were converted into the corresponding hydroquinones (14b—d), the first two of which were characterised as their di-*O*-acetates.

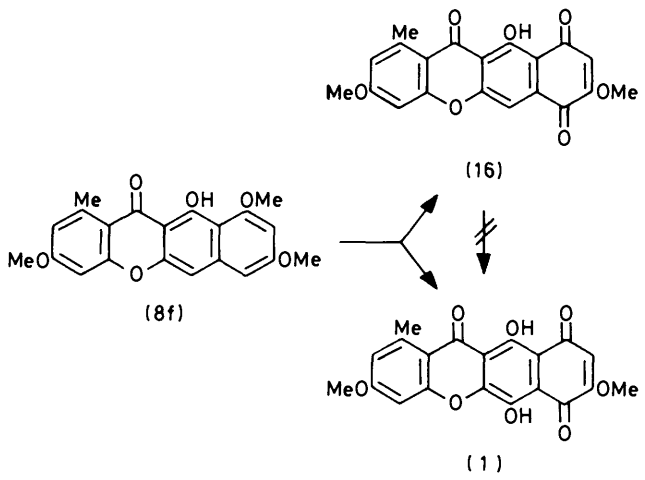
Further oxidation of the hydroquinones (14a—d) to the level of quinones was conveniently accomplished with silver carbonate on Celite (Fétizon's reagent),[22] yielding the quinones (15a—d) in virtually quantitative yield. The presence of methoxy groups in the terminal naphthalene ring renders oxidation with trifluoroperacetic acid easier but, at the same time, more demanding with regard to control of conditions.

It was both surprising and gratifying therefore that conditions could be established (see Experimental section) for *a one-step conversion* of the 11-hydroxybenzoxanthone (8f) into a mixture, essentially consisting of the yellow 6-deoxybikaverin (16) and bikaverin (1) in a ratio of about 1 : 1.

After separation of the two products by careful chromatography on silica gel, bikaverin (1) was consistently obtained in yields of 35—40% from several runs. The synthetic material proved indistinguishable from authentic bikaverin[3] on critical comparison.

The sequence of events leading from (8f) to (1) and (16) has not been established in detail. Suffice it to note that (16) and (1) are produced competitively rather than consecutively since excess of oxidant leaves (16) unaffected under the reaction conditions employed.

In summary, the synthesis of bikaverin (1), as outlined



above, proceeds in two steps, with yields of 25 and 40%, from 2-hydroxy-4-methoxy-6-methylacetophenone (6f) and dimethyl 3,5-dimethoxyhomophthalate (7f). In view of this, and the ready accessibility of the starting materials, we believe the present synthesis to possess practical advantages over the two bikaverin syntheses previously reported.[9,10]

The various tetracyclic products reported in the present paper are being subjected to biological studies, the results of which will be published elsewhere.

Experimental

I.r. spectra were recorded in KBr on a Perkin-Elmer 421 grating instrument; ^{1}H n.m.r. spectra on a Bruker HXE-90 or a HX-270 spectrometer; and mass spectra on a VG Micromass 7070 F operating at 70 eV and equipped with a VG 2035 data system. Microanalyses were performed by Mr. G. Cornali and his staff. All m.p.s are uncorrected and were determined in an electrically heated block. Preparative layer chromatography (p.l.c.) was performed on silica gel 40 × 20 cm plates which were used without prior activation. Light petroleum refers to that fraction boiling in the range 40—60 °C.

Dimethyl 3-*Methoxyhomophthalate* (7d).—A solution of 3-hydroxyhomophthalic acid (5.0 g, 25.5 mmol) (prepared from phenol and 3-chloropropionic acid as described [18,19]) in acetone containing silver oxide [prepared from silver nitrate (12 g)] and methyl iodide (25 ml, 400 mmol) was stirred at room temperature for 48 h. Filtration, followed by evaporation and distillation, b.p. 140—142 °C/1.7 mmHg, gave the ester (7d) (5.4 g, 89%) as an oil possessing ^{1}H n.m.r. data identical with those reported for a specimen prepared by a different route.[23]

Dimethyl 3,5-*Dimethoxyhomophthalate* (7f).—Two alternative methods were used for preparing this ester. (A) An acetone solution of dimethyl 3,5-dihydroxyhomophthalate (1.4 g, 5.8 mmol) (produced by a two-step reaction, in an overall yield of *ca.* 15%, from dimethyl 3-oxoglutarate [20,24]), containing silver oxide [prepared from silver nitrate (4 g)] and methyl iodide (15 ml, 240 mmol), was stirred at room temperature for 72 h. After filtration and evaporation, the residual oil was purified by flash chromatography on silica gel, with chloroform as eluant, to give the ester (7f) (1.3 g, 84%), as a chromatographically homogeneous oil.

(B) To a solution of 3,5-dimethoxyhomophthalic acid (1.9 g, 7.8 mmol) (prepared in three steps, from ethyl orsellinate,[2] in an overall yield of 55%) in methanol (10 ml) was added methanol (10 ml), saturated at 0 °C with hydrogen chloride, and the mixture was refluxed for 2 h. Evaporation afforded the ester (7f) as an oil (2.0 g, 95%) which crystallised overnight in the refrigerator to afford crystals, m.p. 40—41 °C.

The esters made according to procedures A and B both possessed ^{1}H n.m.r. characteristics in agreement with those reported for an oily specimen produced by methylation of dimethyl 3,5-dihydroxyhomophthalate with dimethyl sulphate and potassium carbonate in refluxing acetone.[25] In our hands, the latter procedure proved less efficient for complete methylation.

11-*Hydroxy*-12H-*benzo*[b]*xanthen*-12-*one* (8a) ≡ (2).—To an argon-covered suspension of sodium hydride (2.4 g of a 40% suspension in oil, *i.e.* 40 mmol) in anhydrous THF (15 ml), containing *o*-hydroxyacetophenone (6a) (1.4 g, 10 mmol) was added a solution of dimethyl homophthalate (7a) (2.2 g, 11 mmol) in THF (15 ml) during 5 min. The stirred suspension was refluxed for 5 h. After the mixture had cooled, excess of 6M hydrochloric acid was cautiously added and, after being kept overnight, the precipitate was filtered off and dissolved in diethyl ether. After being washed successively with aqueous sodium hydrogencarbonate and water, the solution was dried and evaporated to dryness. The residue was extracted with methylene dichloride, a small quantity of insoluble red material (*ca.* 15 mg) was removed by filtration, and the filtrate was taken to dryness to give orange 11-hydroxy-12*H*-benzo[*b*]-xanthen-12-one (8a) (1.8 g, 70%), m.p. 203—205 °C (from diethyl ether) (lit.,[12] 198—203 °C; [13] 205—209 °C); $\nu_{max.}$ 2 920w (chelate OH), 1 640, 1 620 (chelate carbonyl), and 1 600 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.18 (1 H, br s, 6-H), 7.32 (1 H, dt, *J* 8 and 1.5 Hz, 2-H), 7.39 (1 H, dd, *J* 9 and 1.5 Hz, 4-H), 7.41 (1 H, dt, *J* 9 and 1.5 Hz, 9-H), 7.60 (1 H, dt, *J* 9 and 1.5 Hz, 8-H), 7.71 (1 H, dt, *J* 8 and 1.5 Hz, 3-H), 7.73 (1 H, dt, *J* 9 and 1.5 Hz, 7-H), 8.24 (1 H, dd, *J* 8.5 and 1.5 Hz, 1-H), 8.39 (1 H, br d, *J* 9 Hz, 10-H), and 13.3 (1 H, s, OH); *m/z* 262 (M^+, 100%), 205 (10), and 176 (9). The product proved indistinguishable (i.r. and mixed m.p.) from a specimen, m.p. 205 °C (from aqueous EtOH), prepared from salicylic acid and 1,3-dihydroxynaphthalene as previously reported.[12]

The O-*acetate* was produced by acetylation of (8a) with acetic anhydride in pyridine (12 h; 20 °C) and was purified by p.l.c. on silica gel with chloroform as eluant; yellow needles (from ethyl acetate–light petroleum), m.p. 182—183 °C (Found: C, 74.6; H, 3.9. $C_{19}H_{12}O_4$ requires C, 74.98; H, 3.98%); δ_H (270 MHz; $CDCl_3$) 2.69 (3 H, s, OAc), 7.32 (1 H, dt, *J* 8 and 1.5 Hz, 2-H), 7.42 (1 H, dd, *J* 9 and 1.5 Hz, 4-H), 7.50 (1 H, dq, *J* 8 and 1.5 Hz, 9-H), 7.62 (1 H, dq, *J* 9 and 1.5 Hz, 8-H), 7.69 (1 H, dq, *J* 8 and 1.5 Hz, 3-H), 7.79 (1 H, br s, 6-H), 7.87 (1 H, br d, *J* 9 Hz, 7-H), 8.11 (1 H, dd, *J* 8 and 1.5 Hz, 10-H), and 8.26 (1 H, dd, *J* 8 and 1.5 Hz, 1-H); *m/z* 304 (M^+, 4%), 263 (50), and 262 (100).

6,11-*Dihydroxy*-12H-*benzo*[b]*xanthen*-12-*one* (14a).—A solution of the phenol (8a) (262 mg, 1 mmol), trifluoroacetic acid (0.8 ml, 1.1 mmol), and 40% hydrogen peroxide (1.1 ml, *ca.* 13 mmol) in chloroform (15 ml) was stirred for 6 h at 0 °C, during which time the red product gradually separated out. It was filtered off, freed of traces of starting material by washing with chloroform, and recrystallised twice from hot chloroform to give red needles of the hydroquinone (14a) (152 mg, 55%), m.p. 273—275 °C (decomp.); *m/z* 279 (18%), 278 (M^+, 100), and 277 (26). Difficulties in obtaining reliable combustion analyses for this and other hydroquinones as well as low solubility in ordinary n.m.r. solvents rendered preparation and characterisation of the di-*O*-acetate desirable.

The *di*-O-*acetate*, prepared in 80% yield from (14a) (acetic

anhydride–pyridine; 12 h; 20 °C), was obtained as yellow needles from diethyl ether, m.p. 256—258 °C (decomp.) (Found: C, 69.4; H, 3.95. $C_{21}H_{14}O_6$ requires C, 69.60; H, 3.89%); δ_H (270 MHz; $CDCl_3$) 2.61 (3 H, s, 6- or 11-OAc), 2.67 (3 H, s, 11- or 6-OAc), 7.34 (1 H, dt, *J* 8 and 1.5 Hz, 2-H), 7.41 (1 H, dd, *J* 9 and 1.5 Hz, 4-H), 7.55 (1 H, dq, *J* 8 and 1.5 Hz, 9-H), *ca.* 7.70 (2 H, m, 3- and 8-H), 7.93 (1 H, br d, *J* 9 Hz, 7-H), 8.16 (1 H, dd, *J* 8 and 1.5 Hz, 10-H), and 8.25 (1 H, dd, *J* 8 and 1.5 Hz, 1-H); *m/z* 362 (M^+, 2%) 320 (31), 279 (31), 278 (100), and 277 (37).

6,12-*Dihydro*-11H-*benzo*[b]*xanthene*-6,11,12-*trione* (15a).—A suspension of the red hydroquinone (14a) (278 mg, 1 mmol) and silver carbonate on Celite [22] (2.8 g) in methylene dichloride (140 ml) was stirred at ambient temperature for 5 min, during which time the colour changed from red to orange. After filtration and evaporation, the *quinone* (15a) was obtained in virtually homogeneous form (270 mg, 98%), m.p. 276—278 °C (decomp.) (from chloroform–light petroleum) (Found: C, 73.9; H, 2.95. $C_{17}H_8O_4$ requires C, 73.92; H, 2.92%); δ_H (90 MHz; $CDCl_3$) *ca.* 7.5 (1 H, m), *ca.* 7.8 (4 H, m), and *ca.* 8.2 (3 H, m, 1-, 7-, and 10-H); *m/z* 278 (29%), 277 (25), 276 (M^+, 100), 248 (29), 220 (22), 163 (16), 104 (32), and 76 (31).

11-*Hydroxy*-3-*methoxy*-12H-*benzo*[b]*xanthen*-12-*one* (8b).—The reaction between 2-hydroxy-4-methoxyacetophenone (6b) (1.7 g, 10 mmol) and dimethyl homophthalate (7a) (2.3 g, 11 mmol) in THF (35 ml) containing sodium hydride (2.4 g; 40% suspension; *ca.* 40 mmol) was performed as described above for (8a), giving the yellow *hydroxybenzoxanthone* (8b) (1.8 g, 63%), m.p. 183—184 °C (from methylene dichloride) (Found: 73.75; H, 4.2. $C_{18}H_{12}O_4$ requires C, 73.97; H, 4.13%); δ_H (270 MHz; $CDCl_3$) 6.74 (1 H, s, 4-H), 6.82 (1 H, dd, *J* 9 and 2 Hz, 2-H), 7.10 (1 H, br s, 6-H), 7.39 (1 H, dt, *J* 8 and 1.5 Hz, 9-H), 7.57 (1 H, dt, *J* 8 and 1.5 Hz, 8-H), 7.70 (1 H, br d, *J* 9 Hz, 7-H), 8.09 (1 H, d, *J* 9 Hz, 1-H), and 8.33 (1 H, br d, *J* 9 Hz, 10-H); *m/z* 292 (M^+, 100%) and 249 (12).

The O-*acetate* was prepared in the usual way (93% yield), m.p. 222—224 °C (from ethyl acetate) (Found: C, 71.75; H, 4.15. $C_{20}H_{14}O_5$ requires C, 71.85; H, 4.22%); *m/z* 334 (M^+, 1%) and 292 (100).

6,11-*Dihydroxy*-3-*methoxy*-12H-*benzo*[b]*xanthen*-12-*one* (14b).—The 11-hydroxybenzoxanthone (8b) was oxidised to the hydroquinone (52% yield) as described above for the analogue (8a); the product (14b) had m.p. 239—241 °C (decomp.) (from chloroform; *m/z* 308 (M^+, 100%), 307 (32), and 306 (70). The dark orange product was characterised as the pale yellow O-*diacetate*, prepared in the usual way (93% yield), m.p. 243—245 °C (decomp.) (from chloroform–light petroleum) (Found: C, 67.45; H, 4.15. $C_{22}H_{16}O_7$ requires C, 67.35; H, 4.11%); *m/z* 392 (M^+, <0.1%), 350 (19), and 308 (100).

6,12-*Dihydro*-3-*methoxy*-11H-*benzo*[b]*xanthene*-6,11,12-*trione* (15b).—Oxidation of (14b) with Fétizon's reagent, as described above, yielded the yellow *quinone* (15b) (84% yield), m.p. 285—287 °C (decomp.) (from chloroform–light petroleum) (Found: C, 70.4; H, 3.35. $C_{18}H_{10}O_5$ requires C, 70.59; H, 3.29%); δ_H (90 MHz; $CDCl_3$) 3.93 (3 H, s, MeO), *ca.* 7.0 (2 H, m, 2- and 4-H), *ca.* 7.8 (2 H, m, 8- and 9-H), and *ca.* 8.2 (3 H, m, 1-, 7-, and 10-H); *m/z* 306 (M^+, 100%), 278 (32), 263 (19), and 235 (15).

11-*Hydroxy*-3-*methoxy*-1-*methyl*-12H-*benzo*[b]*xanthen*-12-*one* (8c).—Condensation of 2-hydroxy-4-methoxy-6-methylacetophenone (6c) with dimethyl homophthalate (7a), as outlined above for the non-substituted *o*-hydroxyacetophenone, yielded the light orange 11-*hydroxybenzoxanthone* (8c) in 52% yield, m.p. 209—211 °C (from chloroform–light petroleum) (Found: C, 74.45; H, 4.65. $C_{19}H_{14}O_4$ requires C, 74.50; H, 4.60%); δ_H (270 MHz; $CDCl_3$) 2.87 (3 H, s, 1-Me), 3.91 (3 H, s, OMe), 6.60 (1 H, m, 2-H), 6.67 (1 H, d, *J* 2 Hz, 4-H), 7.09 (1 H, s, 6-H), 7.40 (1 H, dq, *J* 8 and 1.5 Hz, 9-H), 7.57 (1 H, dq, *J* 8 and 1.5 Hz, 8-H), 7.71 (1 H, br d, *J* 8 Hz, 7-H), 8.37 (1 H, dd, *J* 8 and 1.5 Hz, 10-H), and 12.1 (1 H, s, OH); *m/z* 306 (M^+, 100%).

The O-*acetate* was prepared in the usual way (96% yield), m.p. 223—225 °C (from methylene dichloride) (Found: C, 72.35; H, 4.7. $C_{21}H_{16}O_5$ requires C, 72.41; H, 4.62%); *m/z* 348 (M^+, <0.1%) and 306 (100).

6,11-*Dihydroxy*-3-*methoxy*-1-*methyl*-12H-*benzo*[b]*xanthen*-12-*one* (14c).—Oxidation of (8c) in the usual fashion afforded the hydroquinone (14c), but only in moderate yield (31%), as dark orange needles, m.p. 265—268 °C (decomp.) (from chloroform); *m/z* 322 (M^+, 49%), 321 (29), 320 (100), and 306 (32).

The O-*diacetate*, prepared in 93% yield, formed pale yellow needles, m.p. 257—259 °C (decomp.) (from chloroform–light petroleum) (Found: C, 67.75; H, 4.55. $C_{23}H_{18}O_7$ requires C, 67.98; H, 4.46%); *m/z* 406 (M^+, <0.1%), 364 (18), and 322 (100).

6,12-*Dihydro*-3-*methoxy*-1-*methyl*-11H-*benzo*[b]*xanthene*-6,11,12-*trione* (15c).—Oxidation of (14c) with Fétizon's reagent afforded the *quinone* (15c) in 91% yield as yellow needles, m.p. 272—275 °C (decomp.) (from methylene dichloride–light petroleum) (Found: C, 71.0; H, 3.95. $C_{19}H_{12}O_5$ requires C, 71.25; H, 3.78%); δ_H (90 MHz; $CDCl_3$) 2.82 (3 H, s, Me), 3.89 (3 H, s, MeO), 6.73 (1 H, d, *J* 1.5 Hz, 2- or 4-H), 6.93 (1 H, d, *J* 1.5 Hz, 4- or 2-H), 7.6—7.9 (2 H, m, 8- and 9-H), and 8.1—8.3 (2 H, m, 7- and 10-H); *m/z* 320 (M^+, 100%).

11-*Hydroxy*-3,10-*dimethoxy*-12H-*benzo*[b]*xanthen*-12-*one* (8d).—Upon condensation of 2-hydroxy-4-methoxyacetophenone (6b) and dimethyl 3-methoxyhomophthalate (7d), the 11-hydroxybenzoxanthone derivative (8d) was obtained in 38% yield as orange needles, m.p. 245—247 °C (decomp.) (from methylene dichloride) (Found: C, 70.4; H, 4.35. $C_{19}H_{14}O_5$ requires C, 70.80; H, 4.37%); δ_H (270 MHz; $CDCl_3$) 3.94 (3 H, s, MeO), 4.05 (3 H, s, MeO), 6.75 (1 H, br d, *J* 8 Hz, 9-H), 6.81 (1 H, d, *J* 2 Hz, 4-H), 6.88 (1 H, dd, *J* 8 and 2 Hz, 2-H), 7.09 (1 H, s, 6-H), 7.29 (1 H, br d, *J* 8 Hz, 7-H), 7.47 (1 H, br t, *J* 8 Hz, 8-H), and 8.19 (1 H, d, *J* 8 Hz, 1-H); *m/z* 322 (M^+, 100%).

6,12-*Dihydro*-3,10-*dimethoxy*-11H-*benzo*[b]*xanthene*-6,11,12-*trione* (15d).—Oxidation of the 11-hydroxybenzoxanthone (8d) with trifluoroperacetic acid in the usual way proceeded to give the dark orange 6,11-dihydroxy-3,10-dimethoxy-12*H*-benzo[*b*]xanthen-12-one (14d) in 37% yield, m.p. 202—204 °C (decomp.) (from methylene dichloride); δ_H (90 MHz; $CDCl_3$) 3.89 (3 H, s, MeO), 3.98 (3 H, s, MeO), 5.9 (1 H, br s, 6-OH), 6.6—7.3 (5 H, m, ArH), 8.07 (1 H, d, *J* 9 Hz, 1-H), and 10.0 (1 H, s, chelate OH); *m/z* 338 (M^+, 100%), 323 (65), 320 (35), and 295 (40). Further oxidation with Fétizon's reagent gave a 90% yield of the orange quinone (15d), m.p. 320—322 °C (decomp.) (from methylene dichloride) (Found: C, 67.45; H, 3.65. $C_{19}H_{12}O_6$ requires C, 67.86; H, 3.59%); δ_H (90 MHz; $CDCl_3$) 3.91 (3 H, s, MeO), 4.00 (3 H, s, MeO), *ca.* 7.0 (2 H, m, 2- and 9-H), 7.4—7.9 (3 H, m, 4-, 7-, and 8-H), and 8.2 (1 H, dd, *J* 8 and 0.5 Hz, 1-H); *m/z* 336 (M^+, 100%), 320 (22), and 317 (31).

11-*Hydroxy*-3,10-*dimethoxy*-1-*methyl*-12H-*benzo*[b]*xanthen*-12-*one* (8e).—The reaction between 2-hydroxy-4-methoxy-6-methylacetophenone (6c) and dimethyl 3-methoxyhomophthalate (7d) was performed in the usual manner, though with a reflux time of 8 h. After purification by flash chromatography with hexane–benzene–ethyl acetate–formic acid (8 : 8 : 2 : 1) as eluant, the 11-hydroxybenzoxanthone (8e) was obtained as orange needles (42%), m.p. 252—254 °C (decomp.) (from methylene dichloride) (Found: C, 70.95; H, 4.7. $C_{20}H_{16}O_5$ requires C, 71.42; H, 4.79); δ_H (90 MHz; $CDCl_3$) 2.73 (3 H, s, Me), 3.87 (3 H, s, MeO), 3.96 (3 H, s, MeO), 6.4—6.7 (3 H, m, 2-, 4-, and 9-H), 6.96 (1 H, s, 6-H), and 7.1—7.5 (2 H, m, 7- and 8-H); *m/z* 336 (M^+, 100%), 318 (50), and 307 (38).

11-*Hydroxy*-3,8,10-*trimethoxy*-1-*methyl*-12H-*benzo*[b]*xanthen*-12-*one* (8f).—This 11-hydroxybenzoxanthone was obtained by condensation of 2-hydroxy-4-methoxy-6-methylacetophenone (6c) and dimethyl 3,5-dimethoxyhomophthalate (7f) essentially as described above for the non-substituted analogue. The reaction time was 15 h, and the crude reaction product was purified by p.l.c. with methylene dichloride containing 1% of acetic acid as eluant to give the 11-*hydroxybenzoxanthone* (8f) as dark yellow needles (20—25% yield in several runs), m.p. 260—262 °C (from methylene dichloride–light petroleum) (Found: C, 68.9; H, 4.95. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%); δ_H (90 MHz; $CDCl_3$) 2.82 (3 H, s, Me), 3.87 (3 H, s, MeO), 3.89 (3 H, s, MeO), 3.98 (3 H, s, MeO), 6.31 (1 H, d, *J* 1.5 Hz, 7- or 9-H), 6.50 (1 H, d, *J* 1.5 Hz, 9- or 7-H), 6.6 (2 H, m, 2- and 4-H), and 6.78 (1 H, s, 6-H); *m/z* 366 (M^+, 100%), 348 (36), and 337 (23).

A slower moving band from the chromatographic purification of the above reaction mixture afforded a colourless, crystalline compound (10%), assigned the structure 2-(3,5-*dimethoxybenzyl*)-7-*methoxy*-5-*methylbenzopyran*-4-*one* (10), m.p. 128—129 °C (from diethyl ether) (Found: C, 70.5; H, 5.9. $C_{20}H_{20}O_5$ requires C, 70.56; H, 5.92%); δ_H (90 MHz; $CDCl_3$) 2.76 (3 H, s, Me), 3.73 (9 H, br s, 3 × MeO), 3.82 (2 H, s, CH_2), 5.95 (1 H, s, C=C*H*), and 6.3—6.6 (5 H, m, ArH); *m/z* 340 (M^+, 81%) and 165 (100).

An additional, minor reaction product was recognized as a yellow band travelling faster than (8f) and exhibiting a strong blue fluorescence in u.v. light. It was isolated as pale yellow needles (*ca.* 200 mg from a synthesis on the 10 mmol scale), m.p. 264—266 °C (from methylene dichloride–light petroleum) (Found: C, 68.5; H, 5.05. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%), and was assigned the structure 12-hydroxy-1,3,8-trimethoxy-10-methyl-5*H*-benzo[*b*]naphtho[2,1-*d*]pyran-5-one (11); δ_H (90 MHz; $CDCl_3$) 2.87 (3 H, s, Me), 3.87 (3 H, s, MeO), 3.91 (3 H, s, MeO), 3.98 (3 H, s, MeO), 6.33 (1 H, d, *J* 1.5 Hz, 2-H), 6.53 (1 H, d, *J* 1.5 Hz, 4-H), and 6.6—6.8 (3 H, m, 7-, 9-, and 11-H); *m/z* 366 (M^+, 100%), 323 (13), 169 (15).

3-(2-*Carboxyphenyl*)-4-*methylcoumarin* (12).—To a suspension of methyl *o*-carboxyphenylacetate (10 mmol) and *o*-hydroxyacetophenone (5 mmol) in xylene (5 ml) was gradually added sodium sand (20 mmol). After the initial reaction had ceased the stirred mixture was heated to 100 °C for 1 h, after which time the sodium was consumed and the hydrogen evolution had ceased. Cautious addition of ice and water was followed by extraction with benzene. The acid fraction, obtained by extraction with aqueous hydrogen carbonate, was re-extracted into benzene after acidification. Evaporation left a yellow, crystalline *product* (20%), m.p. 248—249 °C (from benzene–light petroleum) to which structure (12) was assigned (Found: C, 72.65; H, 4.35. $C_{17}H_{12}O_4$ requires C, 72.83; H, 4.31%); $\lambda_{max.}$ (EtOH) 313, 290, and 281 nm (log ε 4.0, 4.1, and 4.0) [lit.,[26] (for 3-phenylcoumarin) 326, 294, and 289 nm (log ε 4.06, 4.11, and 4.10)]; $\nu_{max.}$ 1 718 and 1 668 cm^{-1} [lit.,[26] (for 3-phenylcoumarin) 1 706 cm^{-1}]; δ_H [60 MHz; $(CD_3)_2SO$] 2.20 (3 H, s, Me) and 7.3—8.3 (8 H, m, ArH); *m/z* 280 (M^+, 100%), 262 (100), and 235 (100).

2,2′-*Carboxybenzylbenzopyran*-4-*one* (13).—When the same reactants were allowed to react in an equimolar ratio in THF in the presence of sodium hydride as described,[14] the *chromone* (13) was obtained in 55% yield, m.p. 209 °C (from aqueous ethanol) (Found: C, 72.75; H, 4.35. $C_{17}H_{12}O_4$ requires C, 72.83; H, 4.31%); $\nu_{max.}$ 1 702 and 1 618 cm^{-1}; δ_H (90 MHz; $CDCl_3$ with a drop of CF_3CO_2H) 4.58 (2 H, s, CH_2), 6.49 (1 H, s, C=CH), 7.3—8.0 (6 H, m, ArH), and 8.20 (2 H, m, 3′- and 5-H); *m/z* 280 (M^+, 100%), 262 (16), and 235 (23).

7,12-*Dihydro*-11-*hydroxy*-3,8-*dimethoxy*-1-*methyl*-10H-*benzo*[b]*xanthene*-7,10,12-*trione* (6-*Deoxybikaverin*) (16) *and* 7,12-*Dihydro*-6,11-*dihydroxy*-3,8-*dimethoxy*-1-*methyl*-10H-*benzo*[b]*xanthene*-7,10,12-*trione* (*Bikaverin*) (1).—Two solutions were prepared at 0 °C: (a) 40% hydrogen peroxide (1.1 ml, 13 mmol) was suspended in chloroform (5 ml), and trifluoroacetic acid (1 ml, 13 mmol) was added; (b) the 11-hydroxybenzoxanthone (8f) (183 mg, 0.5 mmol) was dissolved in chloroform (30 ml). After 15 min, solution (b) was added to (a), and the mixture was stirred at 0 °C for 6 h, and was then poured into aqueous hydrogen carbonate and extracted with chloroform. The dried extract was evaporated to give a crystalline residue which, according to t.l.c., consisted essentially of a yellow and a red compound.

The two components were roughly separated on flash chromatography with chloroform, containing first 1%, later 2% acetic acid, as eluant. Further purification of each fraction was achieved by t.l.c. (0.5 mm plates; repeated development) with 0.5% of methanol in chloroform, containing a trace of acetic acid, as eluant.

The *yellow* compound (68 mg, 37%), m.p. 315—317 °C (decomp.) [from chloroform–methanol (2 : 1), with a drop of concentrated hydrochloric acid] (Found: C, 65.5; H, 4.05. $C_{20}H_{14}O_7$ requires C, 65.58; H, 3.85%) was formulated as 6-*deoxybikaverin* (16) on the basis of its spectroscopic characteristics: δ_H (270 MHz; $CDCl_3$) 2.88 (3 H, s, Me), 3.90 (3 H, s, MeO), 3.93 (3 H, s, MeO), 6.17 (1 H, s, 9-H), 6.77 (2 H, br s, 2- and 4-H), and 7.62 (1 H, s, 6-H) [the high-field value (δ 6.17) of the 9-H, together with the fact that irradiation at the frequency of the OMe signals causes intensity enhancement solely of the signal at δ 6.17 precludes an alternative structure with the quinone grouping situated in the penultimate ring; in this case, both 7- and 9-H would be affected]; *m/z* 366 (M^+, 100%), 351 (39), 323 (29), and 267 (15).

The *red* compound (72 mg, 38%) proved indistinguishable from authentic bikaverin [3] by comparison of i.r., n.m.r., and mass spectra, as well as by t.l.c. in several solvent systems.

The substrate (8f) for the above oxidation was recovered unchanged from a chloroform solution, containing trifluoroacetic acid (10% v/v), after 24 h at 20 °C, and attempts to oxidise 6-deoxybikaverin (16) to bikaverin by subjecting it to the oxidation conditions employed failed.

Acknowledgements

We are grateful to Drs. K. Bock, J. Ø. Madsen, and S. Refn for their kind assistance in the spectroscopic work, and to The Danish Natural Science Research Council for financial support to one of us (E. R.). The 270 MHz n.m.r. spectra were recorded on an instrument placed at our disposal by the same Research Council.

References

1 J. W. Cornforth, G. Ryback, P. M. Robinson, and D. Park, *J. Chem. Soc. C*, 1971, 2786.
2 J. J. de Boer, D. Bright, G. Dallinga, and T. G. Hewitt, *J. Chem. Soc. C*, 1971, 2788.
3 D. Kjær, A. Kjær, C. Pedersen, J. D. Bu'Lock, and J. R. Smith, *J. Chem. Soc. C*, 1971, 2792.
4 N. Terashima, M. Ishida, T. Hamasaki, and Y. Hatsuda, *Phytochemistry*, 1972, **11**, 2880.
5 J. Balan, J. Fuska, I. Kuhr, and V. Kuhrová, *Folia Microbiol. (Prague)*, 1970, **15**, 479.
6 J. Fuska, L. P. Ivanitskaya, L. V. Makukho, and L. Ya. Volkova, *Antibiotiki (Moscow)*, 1974, **19**, 890.
7 J. F. Henderson, M. L. Battell, G. Zombor, J. Fuska, and P. Nemec, *Biochem. Pharmacol.*, 1977, **26**, 1973.
8 L. Kováč, E. Böhmerová, and J. Fuska, *J. Antibiot.*, 1978, **31**, 616.
9 D. H. R. Barton, L. Cottier, K. Freund, F. Luini, P. D. Magnus, and I. Salazar, *J. Chem. Soc., Perkin Trans. 1*, 1976, 499.
10 N. Katagiri, J. Nakano, and T. Kato, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2710.
11 J. R. Lewis and J. G. Paul, *J. Chem. Soc., Perkin Trans. 1*, 1981, 770.
12 W. A. Henderson, Jr., and E. F. Ullman, *J. Am. Chem. Soc.*, 1965, **87**, 5424.
13 P. G. Sammes and T. W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1845.
14 Preliminary communication: A. Kjær and D. Kjær, *Acta Chem., Scand., Ser. B*, 1982, **36**, 417.
15 R. Adams, *J. Am. Chem. Soc.*, 1919, **41**, 247.
16 S. S. Pandit and S. Sethna, *J. Indian Chem. Soc.*, 1951, **28**, 357.
17 K. Hoesch, *Ber. Dtsch. Chem. Ges.*, 1915, **48**, 1122.
18 S. Wagatsuma, S. Higuchi, H. Ito, T. Nakano, Y. Naoi, K. Sakai, T. Matsui, Y. Takahashi, A. Nishi, and S. Sano, *Org. Prep. Proced. Int.*, 1973, **5**, 65.
19 S. Huneck and K. Schreiber, *Phytochemistry*, 1977, **16**, 543.
20 R. N. Hurd and D. H. Shah, *J. Med. Chem.*, 1973, **16**, 543.
21 F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1977, **42**, 4155.
22 V. Balogh, M. Fétizon, and M. Golfier, *J. Org. Chem.*, 1971, **36**, 1339.
23 Y. Arai, T. Kamikawa, T. Kubota, Y. Masuda, and R. Yamamoto, *Phytochemistry*, 1973, **12**, 2279.
24 R. H. Hurd and D. H. Shah, *J. Org. Chem.*, 1973, **38**, 610.
25 E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, 1966, **49**, 1283.
26 J. N. Chatterjea, N. Prasad, and K. D. Banerji, *J. Indian Chem. Soc.*, 1964, **41**, 93.

Received 19*th May* 1983; *Paper* 3/805