Synthesis of Bikaverin [1]

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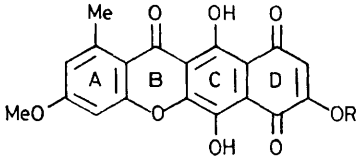
The total synthesis of bikaverin (1b) is described, from everninic acid (5) and 3,5-dihydrobenzoic acid (6). Dieckmann condensation of methyl 2-acetyl-3,5-bis(benzyloxy)phenylacetate (14), synthesised from (6), followed by treatment with protected everninic acid chloride (9) gave 1,3-bisbenzyloxy-6,8-bis(2-benzyloxy-4-methoxy-6-methylbenzoyloxy)naphthalene (16). Photoinduced Fries rearrangement of (16) afforded 1,3-bis(benzyloxy)-7-(2-benzyloxy-4-methoxy-6-methylbenzoyl)-6-(2-benzyloxy-4-methoxy-6-methylbenzoyloxy)-8-hydroxynaphthalene (23). Ring closure of (23) with tetramethylammonium hydroxide in pyridine gave the angular benzoxanthene, 1,3-bis(benzyloxy-6-hydroxy)-10-methoxy-8-methylbenzo[*c*]xanthen-7-one (25), which was oxidized with potassium dichromate to give the orthoquinone, 1,3-bis(benzyloxy)-10-methoxy-8-methylbenzo[*c*]xanthen-5,6,7-trione (28). By a novel type of rearrangement, (28) was transformed into the linear benzoxanthen, 8,10-bis(benzyloxy)-3-methoxy-1-methylbenzo[*b*]xanthen-6,11,12-trione (29) by treatment with silica gel. Oxidation and debenzylation of (29) with manganese dioxide in concentrated H_2SO_4 gave norbikaverin (1a).

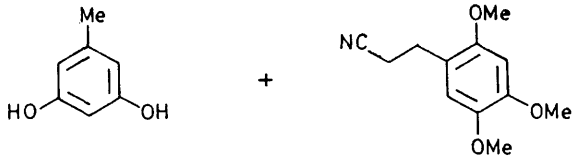
BIKAVERIN (1b), a red pigment having high vacuolation,[2] specific antiprotozoal,[3] and antitumour [4] activities, is isolated from cultures of *F. oxysporum*,[2,5] *F. oxysporum* f. sp. *lycopersici*,[2] *Gibberella fujikuroi*,[3,6,7] and *Mycogone jaapii*.[8] The structural assignment was made by *X*-ray structure analysis,[9] and several references have been reported concerning its chemical reactions.[3,10,11] Barton *et al.*[12] reported a total synthesis of bikaverin (1b) using the dihydrochalcone (4) as an intermediate, which was prepared from orcinol (2) and 3-(2,4,5-trimethoxyphenyl)propiononitrile (3). The synthesis of the benzo[*b*]xanthen skeleton, directed towards bikaverin, was also reported by Tanaka and co-workers.[13] The present paper reports on another synthetic route using everninic acid (5) and 3,5-dihydrobenzoic acid (6).



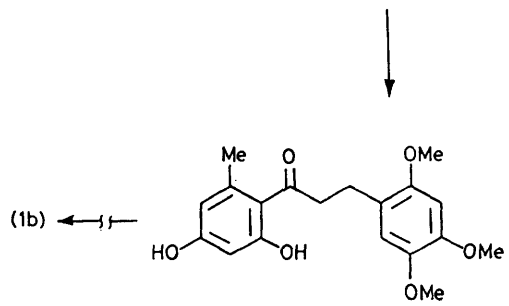
(1)

a; R = H (norbikaverin)

b; R = Me (bikaverin)



(2) (3)

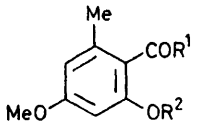


(4)

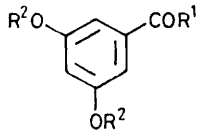
RESULTS AND DISCUSSION

Everninic acid (5) was prepared by the methylation, followed by the hydrolysis, of ethyl orsellinate (prepared from ethyl acetoacetate and diketen according to the procedure reported in a previous paper.[14] Reaction of the acid (5) with benzyl bromide in acetone in the presence of potassium carbonate gave the benzyl ester (7), which was hydrolysed with ethanolic potassium hydroxide to give the acid (8). Treatment of the acid (8) with thionyl chloride gave the acid chloride (9).

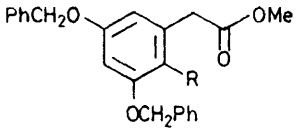
The CD ring moiety was prepared applying the procedure of the synthesis of flaviolin (10) reported by Roberts and Bycroft;[15] thus 3,5-dihydroxybenzoic acid (6) was treated with benzyl bromide to give benzyl 3,5-bis(benzyloxy)benzoate, which was hydrolysed to the acid (11). Chlorination with thionyl chloride, followed by diazotization with diazomethane, gave 3,5-bis(benzyloxy)diazoacetophenone (12). Arndt–Eistert reaction of the diazoacetophenone (12) in methanol afforded methyl 3,5-bis(benzyloxy)phenylacetate (13), which was acetylated with acetic anhydride to give methyl 2-acetyl-3,5-bis(benzyloxy)phenylacetate (14). From Dieckmann condensation of compound (14) with sodium hydride in tetrahydrofuran (THF) under a nitrogen atmosphere, the dihydroxynaphthalene (15) was obtained, which, without purification, was allowed to react with the acid chloride (9) to give the diacylated (16) and monoacylated compound (17) in 45 and 4% yields, respectively. Compound (15) was comparatively unstable, and when Dieckmann condensation was carried out without a nitrogen atmosphere, the unstable product (15) was readily oxidized to 5,7-di-*O*-benzylflaviolin (18).



(5) $R^1 = OH$, $R^2 = H$
(7) $R^1 = OCH_2Ph$, $R^2 = CH_2Ph$
(8) $R^1 = OH$, $R^2 = CH_2Ph$
(9) $R^1 = Cl$, $R^2 = CH_2Ph$



(6) $R^1 = OH$, $R^2 = H$
(11) $R^1 = OH$, $R^2 = CH_2Ph$
(12) $R^1 = CHN_2$ $R^2 = CH_2Ph$



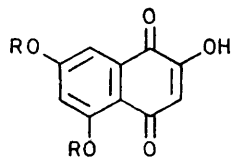
(13) R = H
(14) R = COMe

The acylated position of compound (17) was determined by the chemical shift of the acyl ring methyl group; the ring methyl signals of the diacylated derivative (16) in the n.m.r. spectrum appeared at δ 2.44 and 2.25. The signal at higher field (δ 2.25) can be assigned to the 8-acyloxy-ring methyl influenced by the 1-benzyloxy-group. The ring methyl signal of the monoacyl derivative (17) appeared at δ 2.48 as a singlet; therefore, compound (17) was assigned the 6-acyloxy-structure.

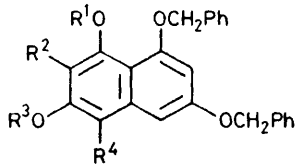
In order to further confirm the structure of compound (17), the following reactions were carried out. Acetylation of the monoacyl derivative (17) with acetic anhyride in anhydrous pyridine afforded the acetate (19). Hydrolysis of the diacyl derivative (16) afforded the monoacyl derivative (20), whose n.m.r. spectrum indicated the absence of the ring methyl signal due to the 6-acyloxy-moiety, and the presence of the 8-acyloxy-ring methyl signal at δ 2.18. The obtained monoacyl derivative (20) was treated with acetic anhydride in anhydrous pyridine to give the acetate (21).

To compare the chemical shifts of the 1- and 3-acetoxy-methyl groups, the diacetate (22) was also prepared by treatment of compound (15) with acetyl chloride.

The Table summarizes the chemical shifts of the acetyl methyl and acyloxy-ring methyl signals of the products. Acyloxy-ring methyl signals appear at δ *ca.* 2.4 for the 3- or 6-acyloxy-derivatives, while signals for the 1- or 8-substituted compounds appear at δ *ca.* 2.2. On the other hand, 1-acetoxy-methyl signals appear at δ 1.60 and 3-acetoxy-methyl signals appear at δ 2.30. These data can be explained by the ring-current effect of the benzene ring of the 1- or 8-benzyloxy-group.[16]



(10) R = H (flaviolin)
(18) $R = CH_2Ph$



(15) $R^1 = R^2 = R^3 = R^4 = H$
(16) $R^1 = R^3 = X$, $R^2 = R^4 = H$
(17) $R^1 = R^2 = R^4 = H$, $R^3 = X$
(19) $R^1 = COMe$, $R^2 = R^4 = H$, $R^3 = X$
(20) $R^1 = X$, $R^2 = R^3 = R^4 = H$
(21) $R^1 = X$, $R^2 = R^4 = H$, $R^3 = COMe$
(22) $R^1 = R^3 = COMe$, $R^2 = R^4 = H$
(23) $R^1 = R^4 = H$, $R^2 = R^3 = X$
(24) $R^1 = R^4 = X$, $R^2 = R^3 = H$

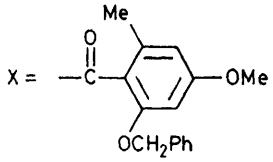
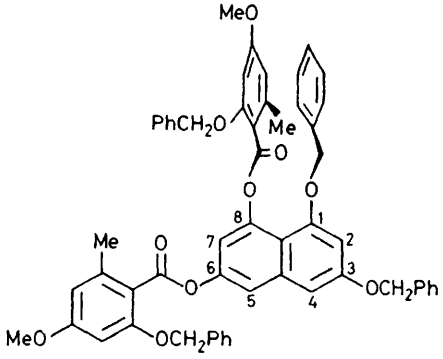


Photo-induced Fries rearrangement [17-19] of the diacyl derivative (16) afforded the phenolic products (23) and (24) in 27 and 19% yields, respectively. A similar



(16)

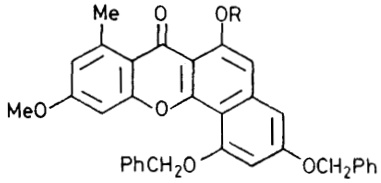
Chemical shifts (δ) of acyloxy ring methyl and acetoxy methyl protons *

Compound	1- or 8-acyloxy-Me	3- or 6-acyloxy-Me	1-acetoxy-Me	3-acetoxy-Me
(16)	2.25	2.44		
(17)		2.48		
(19)		2.48	1.60	
(20)	2.18			
(21)	2.21			2.30
(22)			1.58	2.29

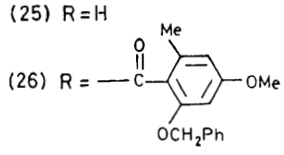
* Spectra were obtained in $CDCl_3$; chemical shifts are relative to tetramethylsilane.

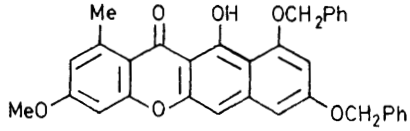
reaction of the monoacyl derivative (17) gave a complicated mixture.

Barton and Scott [20] reported that 2-alkoxy-2′-hydroxybenzophenone, on treatment with base, was transformed into xanthone. Applying this method, compound (23) was treated with tetramethylammonium hydroxide in pyridine to give the tetracyclic compounds (25) and (26) in 59 and 17% yields, respectively. Compound (26), on treatment with ethanolic potassium hydroxide, was hydrolysed to give compound (25) in quantitative yield. Treatment of compound (23) with aqueous potassium hydroxide afforded the angular tetracyclic compound (25) and the linear compound (27) in 32 and 9% yields, respectively. On the other hand, compound (24) with tetramethylammonium hydroxide gave the benzo[*a*]xanthen, 8,10-bis(benzyloxy)-3-methoxy-1-methylbenzo[*a*]xanthen-12-one.[21] Oxidation of compound (25) with potassium dichromate gave the *ortho*-quinone (28), whose mass spectrum indicated the $[M + 2]^+$ ion peak due to the *ortho*-quinone structure.[22] Similar oxidation of compound (27) gave the *para*-quinone (29). Furthermore, the para-quinone (29) was quantitatively obtained from the *ortho*-quinone (28) by treatment with silica gel in chloroform and methanol. The mechanism of the conversion of the angular compound (28) to the linear tetracyclic compound (29) would be illustrated as shown in the Scheme; *i.e.*, acid hydrolysis of (28) results in ring fission of the pyrone ring *via* the dihydroxy-intermediate A. The intermediate B would be transformed to the thermodynamically more stable *para*-quinone intermediate C, which recyclises giving the linear tetracyclic compound (29). In this reaction, the silica gel would act as a solid acid as well as an adsorbent. However, this reaction did not proceed successfully in the presence of a protic acid such as acetic acid.



(25) R = H

(26) R = 



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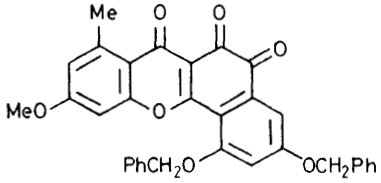

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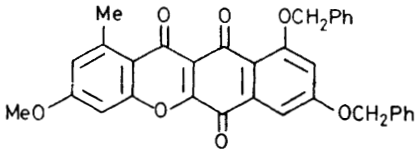
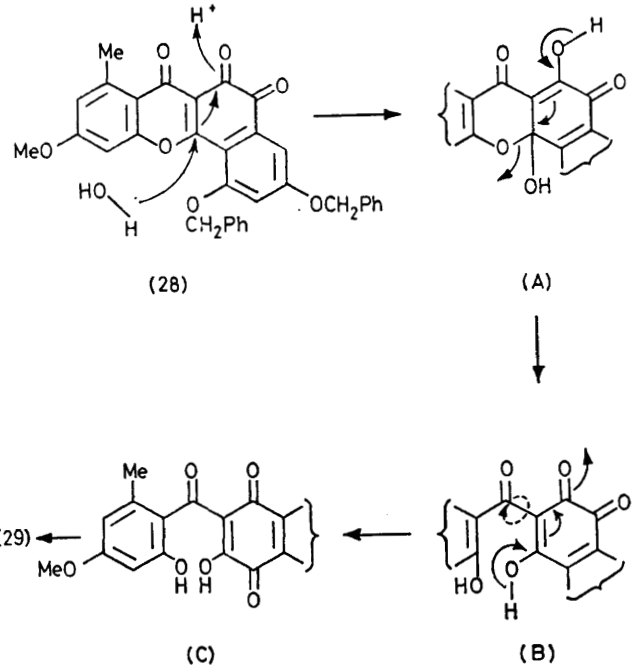


(29)



Applying the procedure reported by Brockmann and Müller,[23] the bisbenzyloxy-derivative (29) was treated with manganese oxide in concentrated sulphuric acid to give norbikaverin (1a), m.p. 310 °C (decomp.), whose i.r. spectrum was identical in every respect with that of the natural product obtained previously.[11] The retention time of compound (1a) on high performance liquid chromatography (h.p.l.c.) also coincides with that of the natural product.[11] Treatment of (1a) with methyl iodide in the presence of silver oxide gave bikaverin (1b), whose i.r. spectrum was identical in every respect with that

of an authentic sample provided by Cornforth and Ryback.

EXPERIMENTAL

M.p.s were determined on a Yanaco model MP; i.r. spectra were recorded on a JASCO model LR-S spectrometer; n.m.r. spectra were recorded using tetramethylsilane as internal standard on Hitachi model R-20A and JEOL model PS-100 spectrometers at 60 and 100 MHz, respectively. Mass spectra were recorded on a Hitachi model M-52, and high-resolution mass spectra on a Hitachi model M-80 + M-003 system. U.v. spectra were recorded on a Hitachi model 124 spectrophotometer. The irradiation source used for photo-Fries rearrangement was Rayonet photochemical reactor lamp (cat. No. RPR-3000 Å). Merck Kieselgel 60F 254 was employed for t.l.c.

Benzyl 2-Benzyloxy-4-methoxy-6-methylbenzoate (7).—A mixture of everninic acid (5) [14] (4 g), benzyl bromide (9 g), and potassium carbonate (13 g) in acetone (70 ml) was refluxed for 48 h. The reaction mixture was then evaporated to dryness under reduced pressure and the residue was extracted with ether. The ether solution was washed with water, dried over sodium sulphate, and the solvent evaporated. The resulting residue was purified by recrystallization from light petroleum (b.p. 45—50 °C) to give the product (7) (7.6 g, 95%) as colourless *prisms*, m.p. 63 °C (Found: C, 76.35; H, 6.1. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%); $\nu_{max.}$ (KBr) 1 730, 1 615, and 1 595 cm^{-1}.

2-Benzyloxy-4-methoxy-6-methylbenzoic Acid (8).—To a solution of the ester (7) (4 g) in ethanol (25 ml), was added a solution of 20% potassium hydroxide in ethanol (25 ml). After being refluxed for 2 h, the reaction mixture was neutralized with concentrated hydrochloric acid with ice-cooling, and the mixture was then evaporated under reduced pressure. The residue was extracted with ether, and the ether solution was washed with water, dried over sodium sulphate, and evaporated. The crystalline residue was recrystallized from benzene–light petroleum (1 : 1) to give the product (8) (2.7 g, 90%) as colourless *columns*, m.p. 98 °C (Found: C, 70.3; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.55; H, 5.9%); $\nu_{max.}$ (KBr) 3 400—3 200, 1 695, 1 610, and 1 590 cm^{-1}.

2-Benzyloxy-4-methoxy-6-methylbenzyl Chloride (9).—A solution of compound (8) (270 mg, 1 mmol) in thionyl chloride (3 ml) was refluxed for 2 h. Removal of excess of thionyl chloride followed by co-evaporation with dry benzene gave the product (9), which, without purification, was used for the preparation of compounds (16) and (17).

3,5-Bis(benzyloxy)benzoic Acid (11).—To a solution of 3,5-dihydroxybenzoic acid (6) (5 g) in acetone (100 ml), was added potassium carbonate (25 g) and benzyl bromide (17 g). The reaction mixture was refluxed with stirring for 72 h, and solvent evaporated under reduced pressure. The residue was extracted with ether, and the ether solution was washed with water, dried over sodium sulphate, and evaporated. The resulting residue was refluxed in 10% ethanolic sodium hydroxide (150 ml) for 1.5 h. The mixture was neutralized with concentrated hydrochloric acid (pH 3—4) and then solvent evaporated under reduced pressure. The residue was extracted with ether, and the ether solution was washed with water, dried, and evaporated to give the *product* (11) (8.7 g, 80%) as colourless needles, m.p. 214—216 °C (Found: C, 75.75; H, 5.45. $C_{21}H_{18}O_4$ requires C, 75.45; H, 5.45); $\nu_{max.}$ (KBr) 3 200—2 800, 1 690, and 1 600.

3,5-Bis(benzyloxy)diazoacetophenone (12).—A solution of compound (11) (9.9 g, 0.03 mol) and thionyl chloride (20 g) in pure dry benzene (10 ml) was refluxed for 1 h. Removal of excess of thionyl chloride and benzene from the reaction mixture afforded an oily residue, which was kept in a vacuum desiccator. After 30 min, the residue was dissolved in dry ether (20 ml). The ether solution was added dropwise with ice-cooling to a solution of diazomethane (2.1 g, 0.05 mol) and triethylamine (3 g, 0.03 mol) in dry ether (100 ml, dried over sodium hydroxide pellets). The reaction mixture was stirred for 4 h, and evaporated under reduced pressure. The residue was submitted to silica gel column chromatography (Wako-gel C-200) using benzene as eluant to give a yellowish oily substance, which was kept in a refrigerator to give pale yellow needles (6.2 g, 60%), m.p. 37—38 °C; $\nu_{max.}$ (KBr) 2 120 and 1 595 cm^{-1}; $\delta(CDCl_3)$ 5.00 (4 H, s, 2 × OCH_2Ph), 5.72 (1 H, s, $COCHN_2$), 6.71 (1 H, t, *J* 2.5 Hz, 4-H), 6.94 (2 H, d, *J* 2.5 Hz, 2-, 6-H), and 7.33 (10 H, s, 2 × Ph).

Methyl 3,5-Bis(benzyloxy)phenylacetate (13).—To a solution of compound (12) (6.2 g, 0.017 mol) in pure dry methanol (100 ml), was added dropwise a solution of silver benzoate (6 g) in triethylamine (25 ml). Addition was continued until evolution of nitrogen ceased. The reaction mixture was refluxed for 1 h, and then evaporated *in vacuo* to give a residue, which was extracted with ether. The ether solution was washed with 10% sodium hydrogencarbonate, dried, and evaporated. The residue was purified by silica gel column chromatography (Wako-gel C-200) using benzene as eluant to give the product (13) (5.4 g, 86%) as colourless *needles* (from benzene), m.p. 62 °C (Found: C, 76.45; H, 6.15. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%); $\nu_{max.}$ (KBr) 1 730, 1 610, and 1 600 cm^{-1}; $\delta(CDCl_3)$ 3.70 (2 H, s, CH_2CO), 3.82 (3 H, s, CO_2Me), 5.25 (4 H, s, 2 × OCH_2Ph), 6.86 (3 H, s, 2-, 4-, 6-H), and 7.73 (10 H, s, 2 × Ph).

Methyl 2-Acetyl-3,5-bis(benzyloxy)phenylacetate (14).—To a solution of compound (13) (5.4 g, 0.015 mol) in a mixture of acetic anhydride (3.2 g, 0.03 mol) and acetic acid (6.4 g) was added perchloric acid (3 drops). The mixture was stirred for 15 min at room temperature, then poured into ice–water (30 ml). The mixture was extracted with ether, and the ether solution was washed with 10% sodium hydrogencarbonate (3 × 10 ml). The ether solution was dried and condensed, and the residue was chromatographed on a silica gel column (Wako-gel C-200). Benzene elution gave the product (15) (3.3 g, 55%) as colourless *prisms* (from benzene), m.p. 80 °C (Found: C, 74.05; H, 6.1. $C_{25}H_{24}O_5$ requires C, 74.25; H, 6.0%); $\nu_{max.}$ (KBr) 1 740, 1 660, 1 610, and 1 590 cm^{-1}; $\delta(CDCl_3)$ 2.50 (3 H, s, COMe), 3.70 (3 H, s, CO_2Me), 3.72 (2 H, s, CH_2CO), 5.09 (4 H, s, 2 × OCH_2Ph), 6.49 (1 H, d, *J* 2.5 Hz), 6.58 (1 H, d, *J* 2.5 Hz), and 7.40 (10 H, s, 2 × Ph); *m/e* 404 (M^+), 389, 362, and 314.

1,3-Bis(benzyloxy)-6,8-bis-(2-benzyloxy-4-methoxy-6-methylbenzoyloxy)naphthalene (16) *and 1,3-Bis(benzyloxy)-6-(2-benzyloxy-4-methoxy-6-methylbenzoyloxy)-8-hydroxynaphthalene* (17).—To a suspension of sodium hydride (60 mg, 2.5 mmol) in pure dry THF (10 ml) was added dropwise a solution of compound (14) (0.2 g, 0.05 mmol) in pure dry THF (5 ml) with stirring at room temperature, and the mixture was stirred for 2 h, during which time the apparatus was swept with a dry nitrogen stream. Stirring was continued until the starting ester (14) was consumed (t.l.c.). To this mixture was added dropwise a solution of 2-benzyl-

oxy-4-methoxy-6-methylbenzoyl chloride (9) (0.29 g, 1 mmol) in pure dry THF (5 ml) with stirring and ice-cooling, and stirring was continued for 30 min. To the reaction mixture was added a small amount of water to destroy any excess of sodium hydride, and the mixture was neutralized with concentrated hydrochloric acid. After removal of solvent from the reaction mixture, the residue was extracted with benzene. The benzene solution was dried and condensed *in vacuo*, and the residual oil was submitted to chromatography (Wako-gel C-200). Benzene elution gave the *monoacyl derivative* (17) (13 mg, 4%) as colourless prisms (from ethanol), m.p. 130 °C (Found: C, 75.85; H, 5.5. $C_{40}H_{34}O_7 \cdot 0.5H_2O$ requires C, 75.6; H, 5.5%); $\nu_{max.}$ (KBr) 3 400—3 200, 1 740, and 1 610 cm^{-1}; $\delta(CDCl_3)$ 2.48 (3 H, s, ring Me), 3.81 (3 H, s, OMe), 5.16 (2 H, s, OCH_2Ph), 5.17 (2 H, s, OCH_2Ph), 5.23 (2 H, s, OCH_2Ph), 6.43 (2 H, s, ring H), 6.58 (1 H, d, *J* 2.5 Hz, ring H), 6.62 (1 H, d, *J* 2.5 Hz, ring H), 6.70 (1 H, d, *J* 2.5 Hz, ring H), 6.91 (1 H, d, *J* 2.5 Hz, ring H), 7.44 (15 H, s, 3 × Ph), and 9.29 (1 H, s, OH); *m/e* 626 (M^+) and 535.

Elution was continued with benzene to give the *diacyl derivative* (16) (0.2 g, 45%) as colourless prisms (from ethanol), m.p. 118 °C (Found: C, 75.75; H, 5.55. $C_{56}H_{48}O_{10} \cdot 0.5H_2O$ requires C, 75.6; H, 5.5%); $\nu_{max.}$ (KBr) 1 730, 1 600, and 1 590 cm^{-1}; $\delta(CDCl_3)$ 2.25 (3 H, s, ring Me), 2.44 (3 H, s, ring Me), 3.79 (3 H, s, OMe), 3.83 (3 H, s, OMe), 4.99 (4 H, s, 2 × OCH_2Ph), 5.14 (4 H, s, 2 × OCH_2Ph), 6.15 (1 H, d, *J* 2.5 Hz, ring H), 6.28 (1 H, d, *J* 2.5 Hz, ring H), 6.45 (2 H, s, ring H), 6.59 (1 H, d, *J* 2.5 Hz, ring H), 6.74 (1 H, d, *J* 2.5 Hz, ring H), 6.90 (1 H, d, *J* 2.5 Hz, ring H), 7.06 (2 H, s, ring H), and 7.13—7.60 (20 H, m, 4 × Ph); *m/e* 880 (M^+).

5,7-*Di*-O-*benzylflaviolin* (18).—Following the same procedure described in the above run, the ester (14) (0.2 g) was treated with sodium hydride (60 mg) in pure dry THF (10 ml) under a dry nitrogen atmosphere at room temperature, and the mixture was stirred for 2 h. Dry oxygen gas was then bubbled through for 1 h, a small amount of water was added, and the solvent was removed by vacuum distillation. The residue was extracted with chloroform, and the chloroform solution was dried and evaporated to give a residue, which was recrystallized from benzene to give yellowish *needles* (105 mg, 55%), m.p. 191—192 °C (Found: C, 74.35; H, 4.75. $C_{24}H_{18}O_5$ requires C, 74.6; H, 4.7%); $\nu_{max.}$ (KBr) 3 500—3 100, 1 660, 1 625, and 1 600; $\delta(CDCl_3)$ 5.16 (2 H, s, OCH_2Ph), 5.20 (2 H, s, OCH_2Ph), 6.20 (1 H, s, 3-H), 6.88 (1 H, d, *J* 2.5 Hz, 6-H), 6.99 (1 H, br s, OH), and 7.49 (1 H, d, *J* 2.5 Hz, 8-H); *m/e* 386 (M^+) and 295.

1-*Acetoxy*-6,8-*bis*(*benzyloxy*)-3-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyloxy*)*naphthalene* (19.)—A mixture of the monoacyl derivative (17) (50 mg) and acetic anhydride (2 ml) in anhydrous pyridine (10 ml) was stirred at room temperature for 2 h. After removal of the solvent *in vacuo*, the residue was submitted to silica gel column chromatography (Wako-gel C-200). Benzene elution gave a pale yellow oily substance, which was crystallized from benzene–light petroleum (4 : 1) to give a quantitative yield of the product (19) as a colourless *powder*, m.p. 137—138 °C (Found: C, 75.2; H, 5.4. $C_{42}H_{36}O_8$ requires C, 75.45; H, 5.45%); $\nu_{max.}$ (KBr) 1 710 and 1 590 cm^{-1}; $\delta(CDCl_3)$ 1.60 (3 H, s, OCOMe), 2.48 (3 H, s, ring Me), 3.85 (3 H, s, OMe), 5.07 (2 H, s, OCH_2Ph), 5.16 (4 H, s, 2 × OCH_2Ph), 6.45 (2 H, br s, ring H), 6.69 (4 H, br s, ring H), and 7.35—7.60 (15 H, br s, 3 × Ph); *m/e* 668 (M^+) and 626.

1,3-*Bis*(*benzyloxy*)-8-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyloxy*)-6-*hydroxynaphthalene* (20).—A mixture of the diacyl derivative (16) (100 mg) in 10% ethanolic NaOH (50 ml) was refluxed for 1 h. The reaction mixture was neutralized with concentrated HCl with cooling. After removal of the solvent *in vacuo*, the residue was extracted with benzene. The benzene solution was washed with water, dried over sodium sulphate, and evaporated to give a residue which was purified by preparative t.l.c. (Merck Kieselgel 60F) using benzene as eluant to afford the product (20) (30 mg, 42%) as colourless prisms [from ethanol–hexane (1 : 2)], m.p. 66—67 °C; $\nu_{max.}$ (KBr) 3 350, 1 720, 1 630, and 1 600 cm^{-1}; $\delta(CDCl_3)$ 2.18 (3 H, s, ring Me), 3.77 (3 H, s, OMe), 4.99 (6 H, s, 3 × OCH_2Ph), 6.13 (1 H, d, *J* 2.5 Hz, ring H), 6.31 (1 H, d, *J* 2.5 Hz, ring H), 6.42 (2 H, s, ring H), 6.52 (1 H, d, *J* 2.5 Hz, ring H), 6.77 (1 H, d, *J* 2.5 Hz, ring H), and 7.02—7.56 (15 H, m, 3 × Ph); *m/e* 626 (M^+), 535, 371, and 255.

3-*Acetoxy*-6,8-*bis*(*benzyloxy*)-1-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyloxy*)*naphthalene* (21).—A solution of the monoacyl derivative (20) (30 mg) and acetic anhydride (1 ml) in anhydrous pyridine (5 ml) was stirred for 2 h at room temperature. The reaction mixture was poured into ice–water and extracted with ether; the ether solution was washed with water and dried over sodium sulphate. After removal of the solvent *in vacuo*, the residue was crystallized from ethanol to give a quantitative yield of the *product* (21) as colourless prisms, m.p. 139—140 °C (Found: C, 75.2; H, 5.6. $C_{42}H_{36}O_8$ requires C, 75.45; H, 5.45%); $\nu_{max.}$ (KBr) 1 760, 1 725, 1 630, and 1 600 cm^{-1}; $\delta(CDCl_3)$ 2.21 (3 H, s, ring Me), 2.30 (3 H, s, OCOMe), 3.77 (3 H, s, OMe), 5.01 (4 H, s, 2 × OCH_2Ph), 5.12 (2 H, s, OCH_2Ph), 6.12 (1 H, d, *J* 2.5 Hz, ring H), 6.31 (1 H, d, *J* 2.5 Hz, ring H), 6.59 (1 H, d, *J* 2.5 Hz, ring H), 6.71 (1 H, d, *J* 2.5 Hz, ring H), 6.80 (1 H, d, *J* 2.5 Hz, ring H), and 7.04—7.55 (16 H, m, ring H and 3 × Ph); *m/e* 668 (M^+), 626, and 255.

1,3-*Diacetoxy*-6,8-*bis*(*benzyloxy*)*naphthalene* (22).—Following the procedure given for (16) and (17), the ester (14) (0.2 g) was treated with sodium hydride (60 mg) in THF (10 ml) under a dry nitrogen atmosphere at room temperature. The mixture was stirred for 2 h. To this mixture was added dropwise a solution of an excess of acetyl chloride (0.15 g) with stirring and ice-cooling. Stirring was continued for 30 min. The reaction mixture was poured into crushed ice–water, and the mixture was neutralized with concentrated hydrochloric acid. The neutralized solution was extracted with benzene (50 ml × 2). The benzene solution was washed with water, dried, and evaporated *in vacuo*. The oily residue was submitted to column chromatography on silica gel (Wako-gel C-200), and benzene elution gave the *diacetate* (22) (150 mg, 65%), as colourless needles (from ethanol), m.p. 140—141 °C (Found: C, 73.55; H, 5.50. $C_{28}H_{24}O_6$ requires C, 73.65; H, 5.3%); $\nu_{max.}$ (KBr) 1 765, 1 630, 1 610, and 1 590 cm^{-1}; $\delta(CDCl_3)$ 1.58 (3 H, s, OCOMe), 2.29 (3 H, s, OCOMe), 5.03 (2 H, s, OCH_2Ph), 5.12 (2 H, s, OCH_2Ph), 6.64—6.72 (2 H, m, ring H), 6.79 (1 H, d, *J* 2.5 Hz, ring H), and 7.26—7.55 (11 H, m, ring H); *m/e* 456 (M^+), 414, 372, 323, and 281.

Photoreaction of the Diacyl Derivative (16).—A solution of compound (16) (700 mg) in ethanol (2.8 l) was irradiated with a mercury lamp (3 000 Å) for 1 h. The reaction mixture was evaporated *in vacuo*, and the oily residue was submitted to silica gel column chromatography (Wako-gel C-200). Benzene elution gave 1,3-bis(benzyloxy)-5-(2-benzyloxy-4-methoxy-6-methylbenzoyl)-8-(2-benzyloxy-4-methoxy-6-methylbenzoyloxy)-6-hydroxynaphthalene (24)

(133 mg, 19%) as a yellowish powder (from ethanol), m.p. 67—68 °C; $\nu_{max.}$ (KBr) 3 600—3 200, 1 740, 1 615, and 1 590 cm^{-1}; δ($CDCl_3$) 2.21 (3 H, s, ring Me), 2.29 (3 H, s, ring Me), 3.75 (3 H, s, OMe), 3.80 (3 H, s, OMe), 4.96 (4 H, s, 2 × OCH_2Ph), 5.06 (2 H, s, OCH_2Ph), 5.18 (2 H, s, OCH_2Ph), 6.13 (1 H, d, *J* 2.5 Hz, ring H), 6.29 (1 H, d, *J* 2.5 Hz, ring H), 6.41 (2 H, d, *J* 2.5 Hz, ring H), 6.72 (2 H, br s, 2 × ring H), 6.86—7.57 (21 H, m, ring H and 4 × Ph), and 14.12 (1 H, s, OH); *m/e* 880 (M^+).

Elution was continued with the same solvent to give 1,3-*bis*(*benzyloxy*)-7-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyl*)-6-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyloxy*)-8-*hydroxynaphthalene* (23) (190 mg, 27%) as a yellowish powder (from ethanol), m.p. 68 °C (Found: M^+, 880.3197. $C_{56}H_{48}O_{10}$ requires *M*, 880.3244); $\nu_{max.}$ ($CHCl_3$) 3 600—3 200, 1 735, 1 620, 1 600, and 1 590 cm^{-1}; δ($CDCl_3$) 2.18 (3 H, s, ring Me), 2.27 (2 H, s, ring Me), 3.61 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.70 (2 H, s, OCH_2Ph), 4.98 (2 H, s, OCH_2Ph), 5.15 (2 H, s, OCH_2Ph), 5.26 (2 H, s, OCH_2Ph), 5.98 (2 H, s, OCH_2Ph), 6.30 (2 H, m, 2 × ring H), 6.60 (2 H, m, 2 × ring H), 6.85—7.75 (23 H, m, 3 × ring H and 4 × Ph), and 14.77 (1 H, s, OH); *m/e* 880 (M^+).

Ring Closure of Compound (23).—(*a*) A solution of compound (23) (0.1 g) and 10% tetramethylammonium hydroxide (1.5 ml) in pyridine (3 ml) was refluxed for 2.5 h. The reaction mixture was poured into ice–water, and the solution was neutralized with concentrated hydrochloric acid. The mixture was then evaporated under reduced pressure, and the resulting residue was extracted with chloroform (3 × 20 ml). The chloroform solution was washed with water, dried, and concentrated to give an oily product, which was purified by silica gel column chromatography (Wako-gel C-200) using benzene as eluant to give 1,3-*bis*(*benzyloxy*)-6-*hydroxy*-10-*methoxy*-8-*methylbenzo*[C]*xanthen*-7-*one* (25) (35 mg, 59%) as yellow needles (from benzene), m.p. 208 °C (Found: C, 75.85; H, 4.95. $C_{33}H_{26}O_6 \cdot 0.25H_2O$ requires C, 75.8; H, 5.05%); $\nu_{max.}$ (KBr) 3 700—3 300, 1 655, 1 605, and 1 560 cm^{-1}; $\lambda_{max.}$ (95% EtOH) 388, 339, 323, and 300 nm (log ε 3.53, 3.98, 3.97, and 4.40); δ($CDCl_3$) 2.83 (3 H, s, ring Me), 3.60 (3 H, s, OMe), 5.14 (2 H, s, OCH_2Ph), 5.17 (2 H, s, OCH_2Ph), 6.08 (1 H, d, *J* 2.5 Hz, ring H), 6.59 (2 H, s, 2 × ring H), 6.66 (1 H, d, *J* 2.5 Hz, ring H), and 6.79 (1 H, s, ring H); *m/e* 518 (M^+) and 428. Subsequent elution with benzene gave 1,3-*bis*(*benzyloxy*)-6-(2-*benzyloxy*-4-*methoxy*-6-*methylbenzoyloxy*)-10-*methoxy*-8-*methylbenzo*[c]-*xanthen*-7-*one* (26) (15 mg, 17%) as colourless prisms (from benzene), m.p. 208—209 °C (Found: C, 75.9; H, 5.15. $C_{49}H_{40}O_9$ requires C, 76.15; H, 5.2%); $\nu_{max.}$ (KBr) 1 740, 1 630, 1 605, and 1 565 cm^{-1}; δ($CDCl_3$) 2.73 (3 H, s, ring Me), 2.81 (3 H, s, ring Me), 3.60 (3 H, s, OMe), 3.88 (3 H, s, OMe), 5.17 (2 H, s, OCH_2Ph), 5.19 (4 H, s, 2 × OCH_2Ph), 6.11 (1 H, d, *J* 2.5 Hz, ring H), 6.48 (3 H, s, ring H), 6.57 (1 H, d, *J* 2.5 Hz, ring H), 6.75 (1 H, s, ring H), and 6.78 (1 H, d, *J* 2.5 Hz, ring H); *m/e* 772 (M^+), 682, and 518. Compound (26) (20 mg) was dissolved in a 10% solution of potassium hydroxide in ethanol (5 ml). The reaction mixture was refluxed for 3 h, and neutralized with concentrated hydrochloric acid. The solvent was removed from the reaction mixture, and the residue was extracted with benzene. The benzene extract gave compound (26) as yellowish needles in a quantitative yield.

(*b*) Compound (23) (200 mg) was dissolved in a mixture of dioxan (1 ml) and ethanol (9 ml), and to this solution was added 40% ethanolic potassium hydroxide (5 ml). The mixture was refluxed for 2.5 h, and neutralized with concentrated hydrochloric acid with ice-cooling. After removal of the solvent under reduced pressure, the residue was extracted with benzene. The benzene extract was purified by silica gel column chromatography (Wako-gel C-200) using benzene as eluant to give 8,10-*bis*(*benzyloxy*)-11-*hydroxy*-3-*methoxy*-1-*methylbenzo*[b]*xanthen*-12-*one* (27) (11 mg, 9%) as yellowish needles (from benzene), m.p. 234 °C (Found: M^+, 518.1702. $C_{33}H_{26}O_6$ requires *M*, 518.1727); $\nu_{max.}$ (KBr) 3 700—3 300, 1 655, 1 610, and 1 565 cm^{-1}; $\lambda_{max.}$ (95% EtOH) 420, 341, 326, 292, and 254 nm (log ε 3.96, 3.97, 4.00, 4.38, and 4.32); δ($CDCl_3$) 2.90 (3 H, s, ring Me), 3.93 (3 H, s, OMe), 5.19 (2 H, s, OCH_2Ph), 5.28 (2 H, s, OCH_2Ph), 6.55 (1 H, d, *J* 2.5 Hz, ring H), 6.60—6.74 (4 H, m, 4 × ring H), 6.92 (1 H, s, ring H), and 15.62 (1 H, s, OH); *m/e* 518 (M^+) and 428. Subsequent elution with benzene gave compound (25) (37 mg, 32%).

1,3-*Bis*(*benzyloxy*)-10-*methoxy*-8-*methylbenzo*[c]*xanthene*-5,6,7-*trione* (28.)—To a solution of compound (25) (40 mg) in dioxan–acetic acid (1 : 1) (40 ml) was added potassium dichromate (80 mg). After stirring for 20 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was extracted with chloroform. The chloroform solution was washed with water, dried, evaporated *in vacuo*, and the residue obtained recrystallized from chloroform to give the product (28) (21 mg, 52%) as red *needles*, m.p. 250 °C (Found: C, 73.75; H, 4.6. $C_{33}H_{24}O_7 \cdot 0.33H_2O$ requires C, 73.6; H, 4.6%); $\nu_{max.}$ (KBr) 1 680, 1 620, 1 600, and 1 580 cm^{-1}; $\lambda_{max.}$ (95% EtOH) 460, 370, 306, 269, and 247 nm (log ε 3.32, 3.75, 4.20, 4.18, and 4.27); δ([$^2H_5$]pyridine) 2.89 (3 H, s, ring Me), 3.57 (3 H, s, OMe), 5.28 (2 H, s, OCH_2Ph), 5.33 (2 H, s, OCH_2Ph), 6.12 (1 H, d, *J* 2.5 Hz, ring H), 6.75 (1 H, d, *J* 2.5 Hz, ring H), 7.34 (1 H, d, *J* 2.5 Hz, ring H), and 7.40—7.90 (11 H, m, ring H and 2 × Ph); *m/e* 534 ($M^+ + 2$) and 443.

8,10-*Bisbenzyloxy*-3-*methoxy*-1-*methylbenzo*[b]*xanthen*-6,11,12-*trione* (29).—A mixture of compound (27) (15 mg) and potassium dichromate (30 mg) in dioxan–acetic acid (2 : 1) (30 ml) was stirred at room temperature for 5 h. The mixture was evaporated under reduced pressure, and the residue was extracted with chloroform. The chloroform solution was washed with water, dried, and concentrated to given an oily pale yellowish residue, which was purified by silica gel column chromatography (Wako-gel C-200). Elution with chloroform containing a trace of ethanol ($CHCl_3$: EtOH = 25 ml : 1 drop), gave the product (29), (10 mg, 65%) as yellowish *needles* [from chloroform–ethanol (1 : 5)], m.p. 250 °C (Found: M^+, 532.1491. $C_{33}H_{24}O_7$ requires *M*, 532.1520); $\nu_{max.}$ (KBr) 1 680, 1 620, and 1 595 cm^{-1}; $\lambda_{max.}$ (95% EtOH) 412, 343, and 273 nm (log ε 3.31, 3,51, and 4.30); δ($CDCl_3$) 2.87 (3 H, s, ring Me), 3.92 (3 H, s, OMe), 5.21 (2 H, s, OCH_2Ph), 5.24 (2 H, s, OCH_2Ph), 6.78 (1 H, br s, ring H), 6.95 (1 H, d, *J* 2.5 Hz, ring H), 6.98 (1 H, d, *J* 2.5 Hz, ring H), and 7.39—7.63 (11 H, m, ring H and 2 × Ph); *m/e* 532 (M^+) and 441.

Transformation of the Angular Benzoxanthen (28) *into the Linedr Benzoxanthen* (29).—To a solution of compound (28) (15 mg) in chloroform (20 ml) was added silica gel (Wako-gel C-200) (10 g) and ethanol (1 ml). After being allowed to stand at room temperature for 72 h, the mixture was filtered. After washing with chloroform, the filtrate was evaporated to give a crystalline product, which was recrystallized from chloroform–ethanol (1 : 5) to give a quantitative yield of the product (28), whose i.r. spectrum was identical in every respect with that of compound (29) obtained as above.

Norbikaverin (1a).—A mixture of the benzoxanthen (29) (20 mg), manganese dioxide (50 mg), and concentrated sulphuric acid (2 ml) was stirred for 30 min at 60 °C. The reaction mixture was poured into ice–water, and extracted with chloroform. The red chloroform extract was dried over sodium sulphate and evaporated. The resulting residue was purified by deactivated silica gel column chromatography [24] using chloroform as eluant to give norbikaverin (1a) [11] (4 mg, 28%), m.p. 310 °C (decomp.); $\nu_{max.}$ (KBr) 3 600—2 400, 1 650, and 1 610 cm^{-1}; $\delta(CF_3CO_2H)$ 3.02 (3 H, s, ring Me), 4.16 (3 H, s, OMe), 6.86 (1 H, s, ring H), and 7.25—7.35 (2 H, m, ring H); *m/e* 368 (M^+) and 340 ($M^+ - CO$); retention time (HPLC) 3.5 min (Waters Associates instrument (M 6000 pump: U6K injector), packing: μ-Bondapak C_{18}, column: 4 mm × 30 cm; solvent 5% AcOH in MeOH–H_2O (5 : 1); flow rate: 2 ml min^{-1}; detector, u.v. absorption at 280 nm).

Bikaverin (1b).—Applying the procedure reported by Kjaer *et al.*,[3] norbikaverin (1a) (5 mg) was treated with silver oxide (100 mg) and methyl iodide (100 mg) in dioxan (20 ml) for 1.5 h at room temperature to give bikaverin (1b), m.p. 320 °C (decomp.); $\nu_{max.}$ (KBr) 3 600—2 400, 1 655, 1 640 and 1 610 cm^{-1}; $\delta(CDCl_3)$ 2.84 (3 H, s, ring Me), 3.88 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.28 (1 H, s, ring H), 6.68—6.85 (2 H, m, ring H), 12.60 (1 H, s, OH), and 14.14 (1 H, s, OH); *m/e* 382 (M^+), 367 ($M^+ - Me$), and 339 ($M^+ - Me - CO$).

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