Tetracycline Studies. Part IV.[1] Some Novel Cyclisations through Benzophenone Carbanions, including a New Synthesis of Anthraquinones

By **Cedric H. Hassall** *† and **Barry A. Morgan,** Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP

A tricyclic amide (2) related to 6-methylpretetramid (1), and several anthraquinones, including the natural products emodin (18) and physcion (19), have been synthesised in excellent yield through a base-catalysed ring closure reaction employing appropriately substituted 2-cyanomethyl-2'-methoxybenzophenones. This is a procedure of wide applicability for the synthesis of anthraquinones.

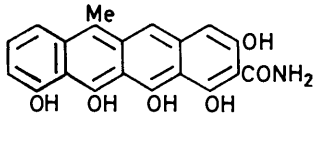
Our investigations of biosynthetic precursors of tetracyclines have led us to study methods of ring closure that might facilitate the synthesis of 6-methylpretetramid (1) and corresponding tricyclic compounds, which are closely related to anthraquinones. The majority of polyhydroxyanthraquinone syntheses which have been described employ either the action of concentrated sulphuric acid on the appropriate hydroxylated benzoic acid (the rufigallol reaction [2]) or the condensation of a

* *Present address:* Roche Products Ltd., Welwyn Garden City, Herts.

[1] Part III, C. H. Hassall and G. J. Thomas, *J. Chem. Soc.* (*C*), 1970, 636.

[2] Von Robiquet, *Annalen*, 1836, **19**, 204.

phthalic acid derivative with a phenol, or a phenol ether. These procedures may be reasonably satisfactory for some cases, particularly for anthraquinones with one unsubstituted ring. However, for many polyhydroxyanthraquinones, especially 1,3,8-trihydroxyanthraquinones, the yields are extremely low. In various cases, these low yields have been ascribed to difficulties in the cyclisation of the intermediate benzoylbenzoic acid.[3] Some investigations of other procedures, such as those based on the Diels–Alder reaction,[4] have not resulted in a generally applicable alternative method.



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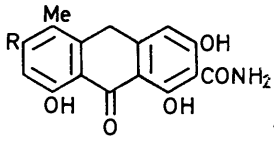

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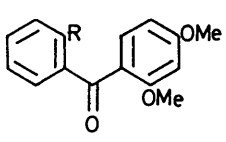

(4) R = CH_2CN
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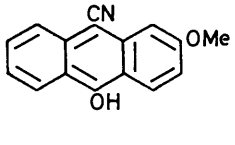

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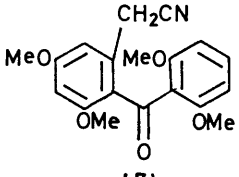

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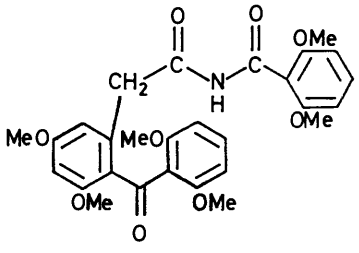

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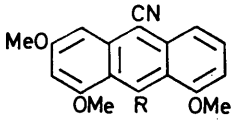

(9) R = OH
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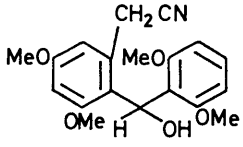

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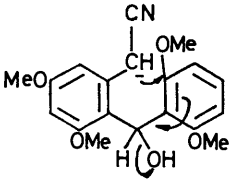

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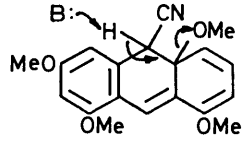

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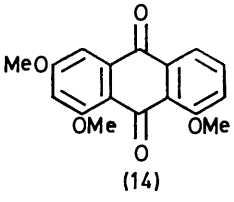


(14)

We established in an earlier study [5] that treatment of 2-cyanomethyl-2′,4′-dimethoxybenzophenone (4) with sodium methoxide in hot dimethyl sulphoxide (DMSO), followed by acidification, gave a quantitative yield of 9-cyano-2-methoxyanthracen-10-ol (6). Holmwood and Roberts [6] have followed a related procedure for the preparation of acid-sensitive anthraquinones. The present investigation is concerned with extending our earlier procedure to enable the synthesis, conveniently, of polyhydroxyanthraquinones, including a tricyclic analogue (2) of 6-methylpretetramid.

In the earlier study, the intermediate (4) was prepared from the corresponding 2-carboxybenzophenone (5) in six stages. This procedure was relatively tedious and had the disadvantage of limiting the nature of substituents. Various attempts to prepare the intermediate benzophenone more conveniently have led to the choice of condensation of a substituted 2-methoxybenzoic acid with a benzyl cyanide derivative, by means of trifluoroacetic anhydride. In a typical reaction, 3,5-dimethoxybenzyl cyanide was condensed with 2,6-dimethoxybenzoic acid at −15°, for 15 min, to give a 75% yield of the corresponding benzophenone (7). At higher temperatures and longer reaction times, a substantial amount of another product was formed. This was shown, largely by ^1H n.m.r. and mass spectrometry, to have the structure (8). There is a precedent for such an addition.[7]

The cyclisation of 2-cyanomethyl-2′,4,6,6′-tetramethoxybenzophenone was investigated using sodium hydride or sodium methoxide in dimethylformamide (DMF) or DMSO. In the case of sodium hydride–DMF, two products, the cyanoanthrol (9) and the cyanoanthracene (10) were formed in approximately equal proportions. As the cyanoanthrol (9) was not affected by sodium hydride–DMF, it appears likely that the cyanoanthracene (10) was formed through the alcohol (11) in a two-stage, base catalysed elimination involving the intermediates (12) and (13). Reduction of benzophenone to benzhydrol under similar conditions has been reported by Hauser.[8] Quantitative yields of

[3] (*a*) T. F. Low, R. J. Park, M. D. Sutherland, and I. Vessey, *Austral. J. Chem.*, 1965, **18**, 182; (*b*) G. D. Graves and R. Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2439; (*c*) R. A. Jacobsen and R. Adams, *ibid.*, 1924, **46**, 1312; (*d*) M. V. Sargent, D. O'N. Smith, J. A. Elix, and P. Roffey, *J. Chem. Soc.* (*C*), 1969, 2763.

[4] (*a*) L. F. Fieser and J. T. Dunn, *J. Amer. Chem. Soc.*, 1937, **59**, 1016; (*b*) M. M. Shemyakin, M. N. Kolosov, Y. A. Arbuzov, M. G. Karapetyan, E. S. Chaman, and A. A. Onishchenko, *Zhur. obshchei Khim.*, 1959, **29**, 1831; (*c*) H. H. Inhoffen, H. Muxfeldt, H. Schaefer, and H. Kramer, *Croat. Chem. Acta*, 1957, **29**, 329.

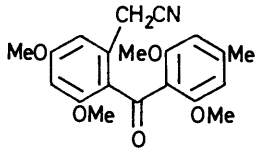
[5] J. S. Davies, V. H. Davies, and C. H. Hassall, *J. Chem. Soc.* (*C*), 1969, 1873.

[6] G. M. Holmwood and J. C. Roberts, *J. Chem. Soc.* (*C*), 1971, 3899.

[7] J. F. Wolfe and Chung-Ling Mao, *J. Org. Chem.*, 1966, **31**, 3069.

[8] F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 2647.

the cyanoanthrol, alone, were obtained with sodium methoxide in either DMF or DMSO. The cyanoanthrol



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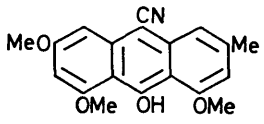

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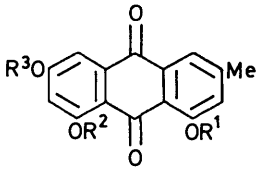
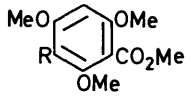
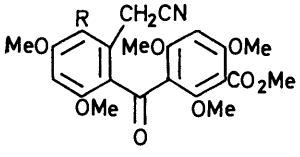


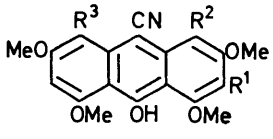
(17) $R^1=R^2=R^3=Me$
(18) $R^1=R^2=R^3=H$
(19) $R^1=R^2=H, R^3=Me$
(20) $R^1=H, R^2=R^3=Me$
(21) $R^2=Me, R^1=R^3=H$



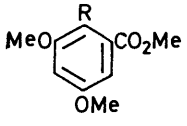
(22) R = CHO
(23) $R=CO_2H$
(24) R = H



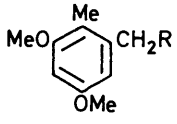
(25) R = H
(26) R = Me



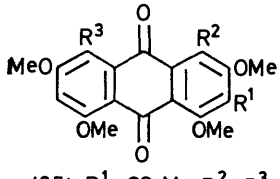
(27) $R^1=CO_2Me, R^2=R^3=H$
(28) $R^1=R^3=H, R^2=CO_2Me$
(29) $R^1=CO_2Me, R^2=H, R^3=Me$



(30) R = CHO
(31) R = Me



(32) R = OH
(33) R = Br
(34) R = CN



(35) $R^1=CO_2Me, R^2=R^3=H$
(36) $R^1=CO_2Me, R^2=H, R^3=Me$
(37) $R^1=R^3=H, R^2=CO_2Me$
(38) $R^1=H, R^2=CO_2Me, R^3=Me$
(39) $R^1=CONH_2, R^2=H, R^3=Me$
(40) $R^1=CO_2H, R^2=H, R^3=Me$

was converted into the corresponding anthraquinone (14), quantitatively, by hydrogen peroxide in alkali.

A similar reaction sequence has been applied to synthesise emodin (18); this anthraquinone has been prepared by other procedures [9] which are, however, relatively low yielding and less convenient. The benzophenone (15) was cyclised to the cyanoanthracene (16) which was converted in excellent yield by alkaline hydrogen peroxide, followed by demethylation with pyridine hydrochloride, into the anthraquinone (18). Specific demethylation of tri-*O*-methylemodin to physcion (19) and 1,3-dimethylemodin (20) was achieved using hydrobromic acid–acetic acid and boron tribromide–dichloromethane, respectively. The structure assigned to the compound (20) was in accord with the conversion to physcion, and the ^1H n.m.r. spectroscopic data. The specificity of the boron tribromide cleavage has been utilised for the synthesis of questin (21).[10]

Having established the applicability of this new procedure for anthraquinone synthesis, it has been applied to the preparation of a tricyclic analogue of 6-methylpretetramid, a biosynthetic precursor of the tetracyclines. One such compound, nor-D-6-methylpretetramid (3), has been prepared by a conventional route but the synthesis was laborious and low-yielding.[11]

As a preliminary experiment, we investigated the cyclisation of the benzophenone (25), prepared by the action of trifluoroacetic anhydride on 3,5-dimethoxybenzyl cyanide and 2,4,6-trimethoxy-3-methoxycarbonylbenzoic acid. The formation of the less hindered cyanoanthrol (27), rather than (28), was anticipated from the consideration of molecular models. The structure of the product was established as (27) by ^1H n.m.r. spectroscopy. The observed values of the chemical shifts of aromatic protons of the product were in good agreement with those deduced for (27), but not (28), from consideration of related 10-cyanoanthracen-9-ols (Table).

The anthraquinone (36) has been synthesised through the cyano-5-methylanthrol (29) as for the previous case. Again, the ^1H n.m.r. spectrum, in particular the signal at τ 2·80 for 4-H, established the orientation of the intermediate cyanoanthrol. Further support for the structures (27) and (29) came from the ^1H n.m.r. spectra of the anthraquinones (35) and (36) formed by oxidation. The chemical shifts of the ring protons of these anthraquinones were calculated using the substituent shielding values of Ballantine and Pillinger.[12] There was agreement of the observed with the calculated values for the structures (35) and (36), but not for the alternatives (37) and (38). The carbamoylanthraquinone (39) has been synthesised from the related ester (36) by conventional stages. The product was readily reduced with hydriodic acid to the nor-D-6-methylpretetramid derivative (2).

[9] (*a*) A. V. Rama Rao, I. N. Shaikh, and K. Venkataraman, *Indian J. Chem.*, 1969, **7**, 188; (*b*) T. Posternak, J. P. Jacob, and H. Ruelius, *Rev. Farm. Buenos Aires*, 1942, **84**, 264; (*c*) H. Mühlemann, *Pharm. Acta Helv.*, 1951, **26**, 195; (*d*) R. Eder and C. Widmer, *Helv. Chim. Acta*, 1923, **6**, 966; (*e*) H. Brockmann, F. Kluge and H. Muxfeldt, *Chem. Ber.*, 1957, **90**, 2302; (*f*) N. R. Ayyangar, D. S. Bapat and B. S. Joshi, *J. Sci. Ind. Res., India*, 1961, **20***B*, 493.

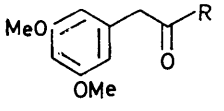
[10] R. F. Curtis, C. H. Hassall, and D. R. Parry, *J. Chem. Soc.* (*C*), 1972, 1971.

[11] C. H. Hassall and G. Wootton, *J. Chem. Soc.* (*C*), 1969, 2805.

[12] J. A. Ballantine and C. T. Pillinger, *Tetrahedron*, 1967, **23**, 1691.

U.v. and ^{1}H n.m.r. spectra supported the formulation of this compound.

The carbanions derived from two other benzophenones have been investigated for the ring closure reaction. The methyl ketone (43) was produced by condensation of the phenylpropanone (41) with 2,6-dimethoxybenzoic acid in trifluoroacetic anhydride. Treatment of this ketone with base under various conditions gave varying yields of the naphthol (45). It was formed, quantitatively, by refluxing with sodium ethoxide in ethanol.



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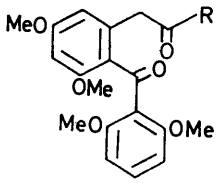
(42) R = Ph



(43) R = Me
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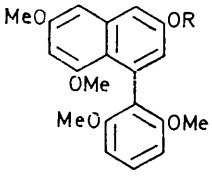
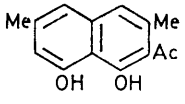


(45) R = H
(46) R = Ac



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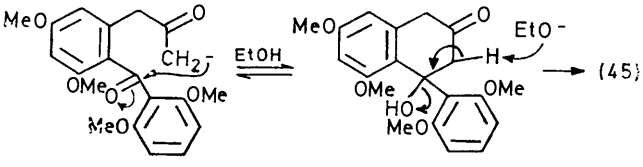

(47) (48)

Spectroscopic studies of the naphthol and its acetate (46) established the structure. Evidently, the cyclisation had proceeded through a carbanion such as (47), to be followed by base-catalysed elimination of the product (48). There is some similarity in this process to the mechanism proposed [13] for the intermolecular condensation of heptane-2,4,6-trione to give the 1,8-dihydroxynaphthalene (49). When the ketone (44) was treated with base, a deep red colouration was produced, indicating the formation of carbanion. However, on acidification, starting material, alone, was recovered. Steric hindrance may have inhibited cyclisation in this case.

Chemical shifts (τ) of aromatic protons of 10-cyanoanthracen-9-ols

Compound	Position 1	2	3	4	5	6	7	8
(9)	OMe	3·64	OMe	2·96	2·20	(H)	3·34	OMe
(16)	OMe	3·64	OMe	3·05	2·52	(Me)	3·59	OMe
(29)	OMe		OMe	2·80		(OMe)	3·76	OMe
Observed for product of cyclisation of (25)				2·90	3·10		3·77	
Estimated for (27)	OMe		OMe	2·90	3·10	(OMe)	3·7	OMe
Estimated for (28)	OMe	3·6	OMe		3·10	(OMe)	3·7	OMe

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer for KBr discs unless otherwise stated. U.v. and visible spectra were recorded for ethanolic solutions with a Unicam SP 800 spectrophotometer; log ε values have an accuracy of $\pm 5\%$. ^{1}H N.m.r. spectra were recorded on a Varian HA 100 instrument, for deuteriochloroform solutions unless otherwise stated, with tetramethylsilane as internal reference. An A.E.I. MS9 mass spectrometer, with a direct insertion probe was used to record mass spectra. Accurate mass measurements were relative to fragmentations from heptacosafluorotri-*N*-butylamine at a resolving power of $1{\cdot}5 \times 10^4$. Microanalyses were carried out by Mr. O. D. Hughes at Swansea. Organic solutions were dried (Na_2SO_4) and evaporated under reduced pressure. Petrol refers to light petroleum, b.p. 60—80°. Silica gel (220—300 mesh; Koch–Light) was used for column chromatography. Both thin layer and preparative plates were prepared from Kieselgel G (Merck). Solvent systems used for the development of chromatography plates were I, benzene–ether (5 : 1), II chloroform–ethyl acetate (1 : 1), and III benzene–methanol–acetic acid (10 : 2 : 1). All developed chromatograms were dried and examined under u.v. illumination (2537 Å; Hanovia). The plates were then sprayed with a 1% solution of ceric ammonium sulphate in 2N-sulphuric acid and heated in an oven at 130° for 30 min. Alternatively, the plates were visualised in a chromatography tank containing iodine vapour.

2-Cyanomethyl-2′,4,6,6′-tetramethoxybenzophenone (7) *and* N-(2,6-*Dimethoxybenzoyl*)-[3,5-*dimethoxy*-2-(2,6-*dimethoxybenzoyl*)*phenyl*]*acetamide* (8).—3,5-Dimethoxybenzyl cyanide [14] (880 mg, 5 mmol) was added to a stirred solution of 2,6-dimethoxybenzoic acid (910 mg, 5 mmol) in trifluoroacetic anhydride (2·5 g) and the mixture stirred at 20° for 10 min. The deep red solution was then poured into 5% aqueous sodium hydrogen carbonate (100 ml) and the red suspension extracted with chloroform (2 × 50 ml). The combined chloroform extracts were washed with water (100 ml), dried, and evaporated to yield a red gum (*ca.* 1·5 g) which was found to be a mixture of 3,5-dimethoxybenzyl cyanide and two new compounds. Column chromatography (silica; solvent II) gave the less polar *constituent* (7) as prisms (170 mg), m.p. (from ethyl acetate) 174·5° (Found: C, 66·85; H, 5·5; N, 4·05. $C_{19}H_{19}O_5N$ requires C, 66·85; H, 5·6; N, 4·1%), *M* (mass spectrometry) 341, $\lambda_{max.}$ 223, 238sh, 277, and 305sh nm (log ε 4·12, 4·07, 3·94, and 3·85), $\nu_{max.}$ 2250 (C≡N), 1665 (benzophenone

[13] (*a*) J. N. Collis, *J. Chem. Soc.*, 1893, **63**, 122, 329; (*b*) A. J. Birch, D. W. Cameron, and R. W. Rickards, *J. Chem. Soc.*, 1960, 4395; (*c*) J. R. Bethell and P. Maitland, *ibid.*, 1962, 3751.

[14] A. Bhati, *Tetrahedron*, 1962, **18**, 1519.

C=O), 1612, and 1598 cm^{-1} (aryl C=C), τ 2·82 (1H, t, *J* 8 Hz, ArH), 3·32 (1H, d, *J* 2 Hz, ArH), 3·53 (2H, d, *J* 8 Hz, 2ArH), 3·73 (1H, d, *J* 2 Hz, ArH), 6·04 (2H, s, ArCH_2C≡N), 6·21 (3H, s, OMe), 6·36 (6H, s, 2OMe), and 6·58 (3H, s, OMe). The more polar *constituent* (8) was recrystallised from ethyl acetate as needles (220 mg), m.p. 132—134° (Found: C, 64·5; H, 5·4; N, 2·7. $C_{28}H_{29}O_9N$ requires C, 64·25; H, 5·6; N, 2·7%), *M* (mass spectrometry) 523, $\nu_{max.}$ 3250br (NH), 1740 and 1690 (imide C=O), 1655 (benzophenone C=O), and 1595 cm^{-1} (aryl C=C), τ 2·79 (1H, dd, *J* 9 and 8 Hz, ArH), 2·81 (1H, dd, *J* 9 and 8 Hz, ArH), 3·46 (1H, d, *J* 2 Hz, ArH), 3·54 (4H, d, *J* 8·5 Hz, 4ArH), 3·76 (1H, d, *J* 2 Hz, ArH), 6·24 (3H, s, OMe), 6·30 (2H, s, ArCH_2C=O), 6·36 (6H, s, 2OMe), 6·41 (6H, s, 2OMe), 6·50 (3H, s, OMe), and −0·18br (1H, s, exchanged by D_2O, CONHCO).

An improved procedure for the benzophenone (7) is as follows. 3,5-Dimethoxybenzyl cyanide (2·65 g, 15 mmol) was added to a solution of 2,6-dimethoxybenzoic acid (2·7 g, 15 mmol) in trifluoroacetic anhydride (5 ml). The solution was immediately cooled to −15° and stirred at this temperature for 15 min. The dark red solution was then poured into 5% aqueous sodium hydrogen carbonate (250 ml) and the suspension extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water (100 ml), dried, and evaporated to give a red crystalline mass which was purified by column chromatography [silica (20 g); solvent II] to give the benzophenone (7) (65—75% yield) as prisms, m.p. 175°.

Reaction of the Benzophenone (7) *with Base;* 10-*Cyano*-1,3,8-*trimethoxyanthracen*-9-*ol* (9) *and* 10-*Cyano*-1,3,8-*trimethoxyanthracene* (10).—(a) *Sodium hydride–DMSO.* Sodium hydride (120 mg of a 50% dispersion in mineral oil; 2·5 mmol) was added to a stirred solution of the benzophenone (7) (340 mg, 1 mmol) in dry DMSO (20 ml). The resulting deep red solution was heated to 140° under nitrogen and stirred at that temperature for 100 min. The solution, which by this time had faded to a fluorescent light red, was cooled, poured into ice-cold 1M-HCl (200 ml) and extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water (6 × 200 ml), dried, and the solvent removed to give a yellow crystalline residue. Recrystallisation from ethyl acetate gave the *anthrol* (9) (240 mg, 80%) as yellow needles, m.p. 252° (Found: C, 69·9; H, 4·9; N, 4·6. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9; N, 4·55%), *M* (mass spectrometry) 309, $\nu_{max.}$ 3295br (OH), 2190 (C≡N), 1620, 1590, and 1570 cm^{-1} (aryl C=C), $\lambda_{max.}$ 228, 272, 308, 349, 368, 392sh, 413, 435, and 461 nm (log ε 4·26, 4·80, 4·21, 3·59, 3·82, 3·60, 3·81, 3·87, and 3·80), τ −1·48 (1H, s, exchanged with D_2O, ArO*H*), 2·20 (1H, d, *J* 8 Hz, ArH), 2·56 (1H, t, *J* 8 Hz, ArH), 2·96 (1H, d, *J* 2 Hz, ArH), 3·34 (1H, d, *J* 8 Hz, ArH), 3·64 (1H, d, *J* 2 Hz, ArH), 5·96 (3H, s, OMe), 6·00 (3H, s, OMe), and 6·05 (3H, s, OMe).

(b) *Sodium methoxide–DMSO.* Sodium methoxide (75 mg, 1·8 mmol) was added under nitrogen to a stirred solution of the benzophenone (7) (340 mg, 1 mmol) in dry DMSO (20 ml). The resulting red solution was heated to 140° and maintained at that temperature for 100 min. The solution was cooled and worked up as in (a) to give a yellow residue which was recrystallised from ethyl acetate to give the anthrol (9) (280 mg, 94%).

(c) *Sodium methoxide–DMF.* The procedure was the same as in (b) except that DMF (20 ml) was used as solvent. A 95% yield of the anthrol (9) was obtained.

(d) *Sodium hydride–DMF.* Sodium hydride (120 mg of a 50% dispersion in mineral oil; 2·5 mmol) was added under nitrogen to a solution of the benzophenone (7) (340 mg, 1 mmol). The red solution was heated at 140° for 100 min, cooled and worked up as in (a) to give a yellow residue which was found to be a mixture of two compounds, the more polar of which was identified as the anthrol (9). The less polar component was isolated by thick layer chromatography and recrystallised from ethyl acetate to give the *anthracene* (10) (125 mg, 40%) as yellow prisms, m.p. 212·5° (Found: C, 73·15; H, 5·0; N, 4·65. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·15; N, 4·8%), *M* (mass spectrometry) 293, $\nu_{max.}$ 2210 (C≡N), 1640, 1630, and 1580 cm^{-1} (aryl C=C), τ 0·74 (1H, s, ArH), 2·17 (1H, d, *J* 9 Hz, ArH), 2·49 (1H, t, *J* 8 Hz, ArH), 2·96 (1H, d, *J* 2 Hz, ArH), 3·31 (1H, d, *J* 7 Hz, ArH), 3·62 (1H, d, *J* 2 Hz, ArH), 5·98 (3H, s, OMe), 6·01 (3H, s, OMe), and 6·03 (3H, s, OMe).

1,3,8-*Trimethoxyanthraquinone* (14).—A solution of hydrogen peroxide (100 vol; 6 ml) and sodium hydroxide (100 mg, 2·5 mmol) in water (10 ml) was added dropwise to a solution of the anthrol (9) (310 mg, 1 mmol) in warm ethanol (100 ml). After 6 h more hydrogen peroxide (100 vol; 5 ml) was added. After a further 12 h the precipitate of golden yellow plates was collected, washed with water and recrystallised from ethanol to give the anthraquinone (14) (273 mg, 91%) as yellow plates, m.p. 200° (lit.,[15] 196°) (Found: C, 69·0; H, 4·85. Calc. for $C_{17}H_{14}O_5$: C, 68·45; H, 4·75%), *M* (mass spectrometry) 298, $\lambda_{max.}$ 225, 276, and 397 nm (log ε 4·44, 4·34, and 3·81), $\nu_{max.}$ 1660 (quinone C=O), 1600, and 1565 cm^{-1} (aryl C=C), τ 2·19 (1H, dd, *J* 6·5 and 1·5 Hz, ArH), 2·44 (1H, t, *J* 7 Hz, ArH), 2·71—2·74 (2H, m, 2ArH), 3·37 (1H, d, *J* 2 Hz, ArH), 6·03 (3H, s, OMe), 6·06 (3H, s, OMe), and 6·08 (3H, s, OMe).

2-*Cyanomethyl*-2′,4,6,6′-*tetramethoxy*-4′-*methylbenzophenone* (15).—3,5-Dimethoxybenzyl cyanide (1·77 g, 10 mmol) was added to a solution of 2,6-dimethoxy-4-methylbenzoic acid [16] (1·96 g, 10 mmol) in trifluoroacetic anhydride (5 ml). The solution was immediately cooled to −5° and stirred at that temperature for 10 min. The resulting suspension was poured into 5% aqueous sodium hydrogen carbonate (100 ml) and extracted with chloroform (3 × 75 ml). The combined chloroform extracts were washed with water (150 ml), dried, and the solvent evaporated to leave a mass of reddish crystals. Purification by chromatography [silica (20 g); solvent II] and recrystallisation from ethyl acetate–chloroform gave the *benzophenone* (15) (2·6 g, 70%) as prisms, m.p. 181·5° (Found: C, 67·9; H, 6·3; N, 3·75. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·95; N, 3·95%), *M* (mass spectrometry) 355, $\lambda_{max.}$ 226, 277, and 299 nm (log ε 4·14, 3·93, and 3·88), $\nu_{max.}$ 2245 (C≡N), 1665 (benzophenone C=O), 1610, and 1590 cm^{-1} (aryl C=C), τ 3·32 (1H, d, *J* 2 Hz, ArH), 3·70 (2H, s, 2ArH), 3·73 (1H, d, *J* 2 Hz, ArH), 6·08 (2H, s, ArCH_2CN), 6·20 (3H, s, OMe), 6·36 (6H, s, 2OMe), 6·54 (3H, s, OMe), and 7·70 (3H, s, Ar*Me*).

10-*Cyano*-1,3,8-*trimethoxy*-6-*methylanthracen*-9-*ol* (16).—Sodium methoxide (250 mg, 6 mmol) was added to a solution of the benzophenone (15) (1·07 g, 3 mmol) in DMSO (30 ml) and the solution stirred under nitrogen at 130° for 100 min. The solution was cooled, poured into 1M-HCl (200 ml), and extracted with chloroform (3 × 150 ml). The combined chloroform extracts were washed with

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[16] A. Robertson and R. Robinson, *J. Chem. Soc.*, 1927, 2196.

water (6 × 150 ml), dried, and the solvent evaporated to give a yellow residue. Recrystallisation from ethyl acetate gave the *anthrol* (16) (910 mg, 90%) as yellow prisms, m.p. 236° (Found: C, 70·6; H, 5·1; N, 4·3. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%), *M* (mass spectrometry) 323, $\lambda_{max.}$ 235, 275, 301, 350, 368, 392sh, 411, 433, and 456sh nm (log ε 4·14, 4·79, 4·31, 3·52, 3·69, 3·60, 3·78, 3·82, and 3·60), $\nu_{max.}$ 3260 (OH), 2200 (C≡N), 1630, and 1580 cm^{-1} (aryl C=C), τ −1·20 (1H, s, exchanged by D_2O, ArO*H*), 2·53br (1H, d, *J* 2 Hz, ArH), 3·05 (1H, d, *J* 2 Hz, ArH), 3·58br (1H, d, *J* 2 Hz, ArH), 3·74 (1H, d, *J* 2 Hz, ArH), 6·01 (3H, s, OMe), 6·04 (3H, s, OMe), 6·08 (3H, s, OMe), and 7·56 (3H, s, Ar*Me*).

1,3,8-*Trimethoxy*-6-*methylanthraquinone* (17).—A solution of hydrogen peroxide (100 vol; 6 ml) and sodium hydroxide (100 mg, 2·5 mmol) in water (100 ml) was added dropwise to a stirred solution of the anthrol (16) (325 mg, 1 mmol) in hot ethanol (100 ml). After 3 h more hydrogen peroxide (100 vol; 6 ml) was added. After a further 12 h the solution was diluted with water (100 ml) and the yellow precipitate was collected, dried, and recrystallised from ethyl acetate to give the anthraquinone (17) (281 mg, 93%) as yellow needles, m.p. 163° (lit.,[17] 163°) (Found: C, 69·3; H, 5·0. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·15%), *M* (mass spectrometry) 312, $\lambda_{max.}$ 225, 278, and 403 nm (log ε 4·45, 4·38, and 3·61), $\nu_{max.}$ 1670 (quinone C=O), 1600, and 1565 cm^{-1} (aryl C=C), τ 2·40br (1H, s, ArH), 2·73 (1H, d, *J* 2 Hz, ArH), 2·95br (1H, s, ArH), 3·29 (1H, d, *J* 2 Hz, ArH), 6·06 (3H, s, OMe), 6·08 (3H, s, OMe), 6·10 (3H, s, OMe), and 7·58 (3H, s, Ar*Me*).

1,3,8-*Trihydroxy*-6-*methylanthraquinone* (*Emodin*) (18).—1,3,8-Trimethoxy-6-methylanthraquinone (17) (300 mg) was heated with pyridinium chloride (5·0 g) at 160° until a homogeneous melt was obtained. The temperature was then raised to 175—180° for 6 h and the resulting mass cooled and digested with water (100 ml). The precipitate was collected and dissolved in 5% aqueous sodium carbonate (100 ml). The filtered solution was acidified and the bright yellow precipitate filtered off, washed with water, and recrystallised from aqueous pyridine to give the anthraquinone (18) (241 mg, 93%) as golden yellow needles, m.p. 256° (lit.,[18] 256—257°).

1,8-*Dihydroxy*-3-*methoxy*-6-*methylanthraquinone* (*Physcion*) (19).—The anthraquinone (17) (100 mg) was dissolved in a solution of hydrobromic acid in acetic acid (constant boiling solution; 10 ml) and the solution heated under reflux for 30 min. The cooled solution was diluted with water (100 ml) and extracted with chloroform (2 × 75 ml). The combined chloroform extracts were washed with water (3 × 100 ml) and 5% aqueous sodium hydrogen carbonate (2 × 100 ml), dried, and the solvent removed to give an orange residue. Purification by chromatography gave the anthraquinone (19) as yellow needles, m.p. 207° (lit.,[19] 207°) (Found: C, 67·2; H, 4·5. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%), $\nu_{max.}$ 3200br (OH), 1675, and 1630 cm^{-1} (quinone C=O), τ −2·20 (1H, s, exchanged by D_2O, ArO*H*), −2·00 (1H, s, exchanged by D_2O, ArO*H*), 2·44br (1H, s, ArH), 2·71 (1H, d, *J* 2 Hz, ArH), 2·98br (1H, s, ArH), 3·38 (1H, d, *J* 2 Hz, ArH), 6·10 (3H, s, OMe), and 7·59 (3H, s, Ar*Me*).

1,3-*Dimethoxy*-8-*hydroxy*-6-*methylanthraquinone* (20).—A solution of the anthraquinone (17) (100 mg) in dichloromethane (10 ml) was cooled to −70°. Boron tribromide (*ca.* 500 mg) in dichloromethane (10 ml) was added to give a blood-red solution which was allowed to attain room temperature (*ca.* 30 min) and then poured into 1M-HCl (50 ml). The product was extracted with dichloromethane (2 × 50 ml) and the combined extracts washed with aqueous sodium hydrogen carbonate (100 ml) and water (100 ml), dried, and the solvent removed to give an orange residue (90 mg). Purification by chromatography gave the anthraquinone (20) (85 mg) which was recrystallised from chloroform–ethyl acetate to give orange needles, m.p. 210° (lit.,[20] 210°), *M* (mass spectrometry) 298, $\nu_{max.}$ 3600, 3300 (OH), 1670, and 1630 cm^{-1} (anthraquinone C=O), τ −1·99 (1H, s, exchanged with D_2O, OH), 2·51br (1H, s, ArH), 2·64 (1H, d, *J* 2 Hz, ArH), 2·99br (1H, s, ArH), 3·31 (1H, d, *J* 2 Hz, Ar*H*), 6·04 (3H, s, OMe), 6·08 (3H, s, OMe), and 7·62 (3H, s, Ar*Me*), τ [$(CD_3)_2SO$] 2·71br (1H, s, 5-H), 2·88 (1H, s, 4-H), 3·00br (1H, s, 7-H), and 3·14 (1H, s, 2-H), τ [$(CD_3)_2SO$–NaOD] 3·02 (1H, s, 4-H), 3·24 (1H, s, 2-H), 3·41br (1H, s, 5-H), and 3·56br (1H, s, 7-H). The resonances of 5- and 7-H were identified as broadened singlets due to coupling with the adjacent methyl group. The large upfield shifts of the signals due to these protons in the anion indicate that they are either *ortho* or *para* to a phenolic hydroxy-group.[21] These spectroscopic data established the structure (20) of this compound.

Methyl 2,4,6-*Trimethoxybenzoate* (24).—2,4,6-Trimethoxybenzoic acid (68 g, 0·4 mol), anhydrous potassium carbonate (280 g, 2 mol), and dimethyl sulphate (250 g, 2 mol) were added to dry acetone (1·5 l) and the mixture vigorously stirred for 24 h at room temperature. The suspension was then filtered and the filtrate evaporated to give an oil which was crystallised from ether–petrol to give the methyl ester (24) as large prisms (81·4 g, 90%), m.p. 143° (lit.,[22] 143°).

Methyl 3-*Formyl*-2,4,6-*trimethoxybenzoate* (22).—Phosphoryl chloride (30·6 g, 18·3 ml, 0·2 mol) was carefully added to ice-cold DMF (29·2 g, 31 ml, 0·4 mol). Methyl 2,4,6-trimethoxybenzoate (22·6 g, 0·1 mol) was added and the deep-red mixture heated on a water-bath for 2 h. The dark-red viscous solution was then poured into ice–water (1 l) and left at 0° for 12 h. The crystalline product was then filtered, washed with water, and dried to give the *benzoate* (22) (21·6 g, 87%) as tan needles, m.p. 113—114° (Found: C, 56·5; H, 5·9. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%), $\nu_{max.}$ 1735 (ester C=O), 1680 (aldehyde C=O), and 1600 cm^{-1} (aryl C=C).

2,4,6-*Trimethoxy*-3-*methoxycarbonylbenzoic Acid* (23).—The benzoate (22) (12·5 g) was suspended in a stirred solution of potassium permanganate (12·5 g) in water (500 ml). After 1 h sulphur dioxide was bubbled through the muddy-brown suspension to dissolve the precipitated manganese dioxide and the resulting clear, colourless solution extracted with chloroform (2 × 300 ml). The chloroform extracts were combined, washed with water (2 × 300 ml), dried, and evaporated to give the *acid* (23) (9·1 g, 70%) as crystals, m.p. 135—137° (Found: C, 53·4; H, 5·15. $C_{12}H_{14}O_7$ requires C, 53·35; H, 5·2%), $\nu_{max.}$ 3250 (OH), 1730 (ester C=O), and 1700 cm^{-1} (acid C=O), τ 0·45

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(1H, s, exchanged with D_2O, $ArCO_2H$), 3·78 (1H, s, ArH), and 6·1—6·2 (12H, m, 4OMe).

2′-Cyanomethyl-2,4,4′,6,6′-pentamethoxy-3-methoxycarbonylbenzophenone (25).—3,5-Dimethoxybenzyl cyanide (1·8 g, 10 mmol) was added to a solution of the acid (23) (2·70 g, 10 mmol) in trifluoroacetic anhydride (15 g). The pink solution was immediately cooled to −20°, stirred at this temperature for 40 min, and then poured into 5% aqueous sodium hydrogen carbonate (500 ml). The aqueous suspension was extracted with chloroform (2 × 300 ml), the chloroform extracts combined, washed with water (2 × 300 ml), dried, and the solvent removed to give a deep-pink gum (*ca.* 3 g). Purification by column chromatography [silica (50 g); solvent II] gave the *benzophenone* (25) (2·4 g, 70%) as prisms, m.p. (from ethyl acetate) 153·5° (Found: C, 61·5; H, 5·3; N, 3·4. $C_{22}H_{23}O_8N$ requires C, 61·55; H, 5·4; N, 3·25%), *M* (mass spectrometry) 429, $\nu_{max.}$ 2220 (C≡N), 1720 (ester C=O), and 1665 cm^{-1} (benzophenone C=O), τ 3·31 (1H, d, *J* 2 Hz, ArH), 3·71 (1H, d, *J* 2 Hz, ArH), 3·83 (1H, s, ArH), 6·06 (2H, s, $ArCH_2CN$), 6·16 (3H, s, OMe), 6·17 (6H, s, 2OMe), 6·33 (3H, s, OMe), 6·44 (3H, s, OMe), and 6·50 (3H, s, OMe).

10-Cyano-1,3,6,8-tetramethoxy-2-methoxycarbonylanthracen-9-ol (27).—The benzophenone (25) (430 mg, 1 mmol) was dissolved in dry DMF (10 ml) and treated, under nitrogen, with sodium methoxide (150 mg, 3 mmol). The resulting deep-purple solution was stirred at 100° for 45 min, cooled, poured into 1M-HCl (200 ml), and extracted with chloroform (2 × 200 ml). The chloroform extracts were combined, washed with water (6 × 200 ml), and the solvent removed to leave an orange residue which was recrystallised from ethyl acetate to give the *anthrol* (27) (380 mg, 95%) as fine orange-yellow needles, m.p. 247—250° (Found: C, 63·9; H, 5·0; N, 3·35. $C_{21}H_{19}O_7N$ requires C, 63·45; H, 4·8; N, 3·55%), *M* (mass spectrometry) 397, $\nu_{max.}$ 3270 (OH), 2205 (C≡N), and 1740 cm^{-1} (ester C=O), τ −0·92 (1H, s, exchanged with D_2O, $ArOH$), 2·91 (1H, s, ArH), 3·09 (1H, d, *J* 2·5 Hz, ArH), 3·77 (1H, d, *J* 2 Hz, ArH), 5·97 (3H, s, OMe), and 6·02—6·08 (12H, m, 4OMe).

1,3,6,8-Tetramethoxy-2-methoxycarbonylanthraquinone (35).—A solution of hydrogen peroxide (100 vol, 6 ml) and sodium hydroxide (100 mg, 2·5 mmol) in water (10 ml) was added dropwise to a stirred solution of the anthrol (27) (400 mg, 1 mmol) in hot ethanol (75 ml). After 3 h more hydrogen peroxide (100 vol, 6 ml) was added and the solution stirred for a further 12 h before diluting with water (100 ml). The precipitated solid was collected, washed, dried, and recrystallised from ethyl acetate to give the anthraquinone (35) (368 mg, 97%) as fine yellow needles, m.p. 210° (lit.,[23] 209—210°) (Found: C, 62·0; H, 4·5. Calc. for $C_{20}H_{18}O_8$: C, 62·15; H, 4·7%), *M* (mass spectrometry) 386, $\nu_{max.}$ 1745 (ester C=O) and 1660 cm^{-1} (anthraquinone (C=O), τ 2·50 (1H, s, ArH), 2·72 (1H, d, *J* 2·5 Hz, ArH), 3·72 (1H, d, *J* 2·5 Hz, ArH), 6·02 (6H, s, 2OMe), 6·04 (3H, s, OMe), and 6·06 (6H, s, 2OMe).

Methyl 2-Formyl-3,5-dimethoxybenzoate (30).—(i) Phosphoryl chloride (15·3 g, 0·1 mol) was carefully added to ice-cold DMF (15 g, 0·2 mol). Methyl 3,5-dimethoxybenzoate (10·0 g, 0·05 mol) was added and the mixture heated at 85—90° for 90 min. The dark viscous mixture was then poured into ice-cold water (1 l) and stirred vigorously for 5 min to coagulate any precipitate which was filtered off (20—60% of the starting material was recovered at this stage) and the clear filtrate left at 0° for 12 h. The crystalline precipitate was then collected, washed with water, dried, and recrystallised from methanol to give the *benzoate* (30) (10—40%) as needles, m.p. 108° (Found: C, 59·1; H, 5·6. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%), $\nu_{max.}$ 1730 (ester C=O), 1667 (aldehyde C=O), and 1605 and 1580 cm^{-1} (aryl C=C), τ −0·27 (1H, s, $ArCHO$), 3·53 (2H, ABq, ΔAB 2 Hz, *J*— 3 Hz, 2ArH), 6·15 (3H, s, OMe), 6·17 (3H, s, OMe), and 6·19 (3H, s, OMe).

(ii) Titanium tetrachloride (11·0 ml, 0·1 mol) was added to a solution of methyl 3,5-dimethoxybenzoate (10 g, 0·05 mol) in dry dichloromethane (200 ml) and the mixture cooled to 0° to give a deep-red suspension. Dichloromethyl methyl ether [24] (6·0 ml, 0·065 mol) was added, the cooling bath removed, and the mixture stirred for 15 min to give a clear deep-red solution. 1M-HCl (500 ml) was added carefully and the mixture shaken vigorously in a separating funnel until clear of any milkiness. The organic phase was then separated, washed with water (2 × 200 ml), dried, and the solvent removed to give the benzoate (30) (11·4 g, 99%) as a mass of needles, m.p. (from methanol) 108°.

Methyl 3,5-Dimethoxy-2-methylbenzoate (31).—The aldehyde (30) (2·24 g, 10 mmol) in ethyl acetate (50 ml) was shaken with palladium on carbon (100 mg; 10%) in a hydrogen atmosphere. Uptake of hydrogen ceased after approximately 2 equiv. (450 ml) had been absorbed. The catalyst was removed by filtration through Celite and the filtrate evaporated to give the chromatographically homogeneous *benzoate* (31) (2·0 g, 95%) as a liquid [Found: *M* (mass spectrometry) 210. $C_{11}H_{14}O_4$ requires *M*, 210], $\nu_{max.}$ (film) 1720 (ester C=O) and 1610 cm^{-1} (aryl C=C), τ 3·10 (1H, d, *J* 2·5 Hz, ArH), 3·44 (1H, d, *J* 2·5 Hz, ArH), 6·12 (3H, s, OMe), 6·18 (6H, s, 2OMe), and 7·65 (3H, s, $ArMe$).

3,5-Dimethoxy-2-methylbenzyl Cyanide (34).—The ester (31) (10·5 g, 50 mmol) in dry ether (150 ml) was added to a stirred suspension of lithium aluminium hydride (1·5 g) in dry ether (100 ml) at a rate sufficient to maintain vigorous reflux. After addition was complete the mixture was heated under reflux for 1 h, cooled, and excess of hydride was consumed by dropwise addition of ethyl acetate in ether. Water (20 ml) was then cautiously added followed by 4M-sulphuric acid (300 ml). The ether layer was separated, washed with water (2 × 200 ml) and evaporated to give 3,5-dimethoxy-2-methylbenzyl alcohol (32) as a chromatographically homogeneous crystalline mass, m.p. 50°, $\nu_{max.}$ 3250 cm^{-1} (OH). The product was used directly for the next stage. The alcohol (32) was dissolved in dry ether (200 ml) and treated with freshly distilled phosphorus tribromide (6·0 g, *ca.* 30% excess) in dry ether (50 ml). The mixture was heated under reflux for 1 h, cooled, and decanted into ice-cold water (300 ml). The syrupy residue of phosphoric acid was washed with ether (50 ml) and the washings added to the main fraction. The ether layer was separated, washed with water (2 × 200 ml), dried, and the solvent removed to yield 3,5-dimethoxy-2-methylbenzyl bromide (33) as a chromatographically homogeneous crystalline mass, m.p. 90°, $\nu_{max.}$ 1610 and 1585 cm^{-1} (aryl C=C). The product was used directly for the next stage. The benzyl bromide (33) and potassium cyanide (10 g) were added to a mixture of ethanol (160 ml) and water (40 ml) and the mixture heated under reflux for 3 h. The solution was then cooled, poured into ice–water (300 ml), and left to

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crystallise. After 12 h the product was collected, washed well with water, dried, and recrystallised from ethanol–water to give the *cyanide* (34) [6·9 g, 72% from the ester (30)] as fine needles, m.p. 59° (Found: C, 69·0; H, 6·4; N, 7·05. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85; N, 7·35%), $\nu_{max.}$ 2220 (C≡N) and 1610 and 1595 cm^{-1} (aryl C=C), τ 3·53 (1H, d, *J* 2·5 Hz, ArH), 3·64 (1H, d, *J* 2·5 Hz, ArH), 6·24 (6H, s, 2OMe), 6·43 (2H, s, $ArCH_2CN$), and 7·93 (3H, s, Ar*Me*).

2′-Cyanomethyl-2,4,4′,6,6′-pentamethoxy-3-methoxycarbonyl-3′-methylbenzophenone (26).—The nitrile (34) (1·9 g, 10 mmol) was added to a solution of 2,4,6-trimethoxy-3-methoxycarbonylbenzoic acid (23) (2·7 g, 10 mmol) in trifluoroacetic anhydride (15 g) and the mixture immediately cooled to −20° and stirred at this temperature for 1 h. The resulting solution was added dropwise to 5% sodium hydrogen carbonate solution (200 ml) and extracted with chloroform (2 × 150 ml). The chloroform extracts were combined, washed with water (2 × 150 ml), dried, and the solvent removed to give a deep red syrup (*ca.* 3·5 g). Purification by column chromatography [silica (50 g); solvent II] gave the *benzophenone* (26) (3·08 g, 71%) as prisms, m.p. (from ethyl acetate) 180·5° (Found: C, 62·4; H, 5·6; N, 3·1. $C_{23}H_{25}O_8N$ requires C, 62·3; H, 5·7; N, 3·15%), *M* (mass spectrometry) 443, $\nu_{max.}$ 2225 (C≡N), 1725 (ester C=O), and 1670 cm^{-1} (benzophenone C=O), τ 3·69 (1H, s, ArH), 3·84 (1H, s, ArH), 6·15—6·18 (11H, m, 3OMe + $ArCH_2CN$), 6·32 (3H, s, OMe), 6·34 (3H, s, OMe), 6·48 (3H, s, OMe), and 7·77 (3H, s, Ar*Me*).

10-Cyano-1,3,6,8-tetramethoxy-2-methoxycarbonyl-5-methylanthracen-9-ol (29).—The benzophenone (26) (220 mg, 0·5 mmol) in dry DMF (10 ml) under nitrogen was treated with sodium methoxide (50 mg, 1 mmol) and the resulting deep red solution stirred at 90° for 1 h. The solution was then cooled, poured into 1M-HCl (100 ml) and extracted with chloroform (2 × 100 ml). The chloroform extracts were combined, washed with water (6 × 100 ml), dried, and the solvent removed to give a yellow residue which was recrystallised from ethyl acetate to give the *anthrol* (29) (195 mg, 95%) as fine yellow needles, m.p. 225·5° (Found: C, 64·6; H, 4·9; N, 3·4. $C_{22}H_{21}O_7N$ requires C, 64·2; H, 5·15; N, 3·4%), *M* (mass spectrometry) 411, $\nu_{max.}$ 3200 (OH), 2195 (C≡N), and 1725 cm^{-1} (ester C=O), τ −1·50 (1H, s, exchanged with D_2O, ArOH), 2·80 (1H, s, ArH), 3·76 (1H, s, ArH), 6·00 (3H, s, OMe), 6·03 (6H, s, 2OMe), 6·13 (3H, s, OMe), 6·21 (3H, s, OMe), and 7·34 (3H, s, Ar*Me*).

1,3,6,8-Tetramethoxy-2-methoxycarbonyl-5-methylanthraquinone (36).—A solution of hydrogen peroxide (100 vol, 5 ml) and sodium hydroxide (100 mg, 2·5 mmol) in water (5 ml) was added dropwise to a solution of the anthrol (29) (205 mg, 0·5 mmol) in hot ethanol (50 ml). After 3 h, more hydrogen peroxide (100 vol, 5 ml) was added and the mixture left for a further 12 h before diluting with water (100 ml). The yellow precipitate was collected, washed with water, and dried to give the *anthraquinone* (36) (192 mg, 96%) as fine yellow needles, m.p. (from ethyl acetate) 227·5° (Found: C, 62·9; H, 5·1. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·05%), *M* (mass spectrometry) 400, $\nu_{max.}$ 1732 (ester C=O) and 1660 cm^{-1} (anthraquinone C=O), τ 2·63 (1H, s, ArH), 3·31 (1H, s, ArH), 6·02—6·10 (15H, m, 5OMe), and 7·52 (3H, s, Ar*Me*).

2-Carboxy-1,3,6,8-tetramethoxy-5-methylanthraquinone (40).—The ester (36) (2·0 g, 5 mmol) was added to a solution of potassium hydroxide (5 g) in methanol–water (2 : 1; 100 ml) and the mixture heated under reflux for 18 h. The resulting deep red solution was cooled, concentrated to *ca.* 25 ml under reduced pressure, diluted with water (250 ml), and acidified (pH *ca.* 2) with HCl. The yellow precipitate was collected, washed with water, and dried to give the *anthraquinone* (40) (1·94 g, 100%) as minute yellow needles, m.p. 225—227° (Found: C, 62·1; H, 4·7. $C_{20}H_{18}O_8$ requires C, 62·15; H, 4·7%), *M* (mass spectrometry) 386, $\nu_{max.}$ 3300—2800 (acid OH), 1750 (acid C=O), and 1645 cm^{-1} (anthraquinone C=O), τ [$(CDCl_3$–$(CD_3)_2SO$] 2·64 (1H, s, ArH), 3·26 (1H, s, ArH), 6·0—6·2 (12H, m, 4OMe), and 7·53 (3H, s, Ar*Me*).

2-Carbamoyl-1,3,6,8-tetramethoxy-5-methylanthraquinone (39).—The acid (40) (1·00 g) was treated with oxalyl chloride (5·0 g). After the initial vigorous reaction was over (*ca.* 30 min) the mixture was diluted with dry benzene (15 ml) and heated under reflux for 3 h. The resulting clear solution was cooled and excess of oxalyl chloride and solvent removed under reduced pressure. The yellow residue was dissolved in dry benzene (250 ml) and treated with dry ammonia for 30 min. The yellow precipitate was collected, washed with water, and dried to give the *anthraquinone* (39) (940 mg, 93%) as a microcrystalline orange-yellow powder, m.p. >320° (Found: C, 62·0; H, 4·6; N, 3·6. $C_{20}H_{19}O_7N$ requires C, 62·35; H, 4·95; N, 3·65%) [Found: *M* (mass spectrometry) 385·1161 ± 16. $C_{20}H_{19}O_7N$ requires *M*, 385·11614], $\nu_{max.}$ 3420, 3320 and 3190 (amide NH), and 1670 cm^{-1} (C=O), τ [$(CD_3)_2SO$] 2·3br (2H, s, exchanged slowly with D_2O, $ArCONH_2$), 2·70 (1H, s, ArH), 3·07 (1H, s, ArH), 6·06 (3H, s, OMe), 6·09 (6H, s, 2OMe), 6·18 (3H, s, OMe), and 7·59 (integral obscured by solvent resonance, s, Ar*Me*).

2-Carbamoyl-1,3,6,8-tetrahydroxy-5-methylanthracen-9(10H)-one (2).—The anthraquinone (39) (100 mg) was treated with hydriodic acid (55%, 4 g) and phenol (4 g) and the mixture heated under reflux for 2·5 h. The dark solution was then cooled, diluted with water (200 ml), and the precipitate collected, washed with water, and then acetone to give the *anthracen-9(10H)-one* (2) (65 mg, 78%) as a microcrystalline light-yellow solid, m.p. >320°, $\lambda_{max.}$ 228, 235, 272, 314, and 372 nm, $\nu_{max.}$ 3460 and 3350 (amide NH), 3300—2500 (H bonded OH), and 1655sh and 1604 cm^{-1} (amide and anthrone C=O), τ [$(CD_3)_2SO$; 84°] −4·85br (1H, s, exchanged with D_2O, OH), −2·90br (2H, s, exchanged with D_2O, 2OH), 2·0br (2H, s, exchanged slowly with D_2O, $ArCONH_2$), 2·60 (1H, s, ArH), 2·76 (1H, s, ArH), 5·98 (2H, s, CH_2), and 8·02 (3H, s, Ar*Me*).

3,5-Dimethoxyphenylacetyl Chloride.—Oxalyl chloride (6·3 g, 50 mmol) was added to a solution of 3,5-dimethoxyphenylacetic acid (5·0 g, 25 mmol) in dry benzene (100 ml) and the mixture was stirred for 24 h. Removal of excess of oxalyl chloride and solvent gave a quantitative yield of 3,5-dimethoxyphenylacetyl chloride as a light-yellow oil, $\nu_{max.}$ (film) 1795 cm^{-1}, which was used without further purification.

1-(3,5-Dimethoxyphenyl)propan-2-one (41).—A mixture of diethyl malonate (8 g), dry ethanol (2·90 g), and dry benzene (10 ml) was slowly added to a stirred suspension of magnesium (1·2 g) in dry benzene (6 ml). The mixture was then heated under reflux for 3 h before the excess of ethanol was removed by distillation as a benzene–ethanol azeotrope (*ca.* 5 ml). 3,5-Dimethoxyphenylacetyl chloride (from 5·0 g of the acid) in benzene (20 ml) was added and the mixture heated under reflux for 1 h. The mixture was then cooled, the magnesium complex decomposed with ice-cold

4N-sulphuric acid (150 ml), and the solution extracted with benzene (2 × 100 ml). The combined benzene extracts were washed with water (200 ml), dried, and evaporated to give a syrup which was heated under reflux with a mixture of acetic acid (15 ml), sulphuric acid (2 ml), and water (10 ml) until evolution of carbon dioxide ceased (*ca.* 3 h). The cooled mixture was then made alkaline with 2M-sodium hydroxide and extracted with ether (2 × 75 ml). The combined ether extracts were washed with water (2 × 150 ml), dried, and evaporated to give the *propanone* (41) (3·0 g, 65% from 3,5-dimethoxyphenylacetic acid) as a chromatographically homogenous light-brown oil [Found: *M* (mass spectrometry), 194. $C_{11}H_{14}O_3$ requires *M*, 194], $\nu_{max.}$ (film) 1705 (C=O) and 1600 cm^{-1} (aryl C=C), τ 3·69 (3H, s, 3ArH), 6·37 (6H, s, 2OMe), 6·45 (2H, s, ArCH_2COMe), and 7·90 (3H, s, CH_2CO*Me*).

1-[2-(2,6-*Dimethoxybenzoyl*)-3,5-*dimethoxyphenyl*]*propan*-2-*one* (43).—The propanone (41) (1·94 g, 10 mmol) was added to a solution of 2,6-dimethoxybenzoic acid (1·8 g, 10 mmol) in trifluoroacetic anhydride (5·0 ml) and the mixture stirred at 0° for 1 h. The resulting red mixture was added dropwise to 5% aqueous sodium hydrogen carbonate (100 ml) and extracted with ethyl acetate (2 × 75 ml). The combined ethyl acetate extracts were washed with water (2 × 100 ml), dried, evaporated, and the residue recrystallised from ethyl acetate to give the *propanone* (43) (3·02 g, 70%) as fine needles, m.p. 146·5° (Found: C, 66·9; H, 6·4. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), *M* (mass spectrometry) 358, $\nu_{max.}$ 1720 (propanone C=O), 1658 (benzophenone C=O), and 1600 cm^{-1} (aryl C=C), τ 2·84 (1H, t, *J* 8·5 Hz, ArH), 3·54 (2H, d, *J* 8·5 Hz, 2ArH), 3·68 (1H, d, *J* 2 Hz, ArH), 3·75 (1H, d, *J* 2 Hz, ArH), 6·25 (3H, s, OMe), 6·28 (2H, s, ArCH_2COMe), 6·38 (6H, s, 2OMe), 6·59 (3H, s, OMe), and 7·79 (3H, s, CH_2CO*Me*).

5,7-*Dimethoxy*-4-(2,6-*dimethoxyphenyl*)-2-*naphthol* (45).—(i) The diketone (43) (180 mg, 0·5 mmol) was added to a solution of sodium (15 mg, 0·6 mg atom) in dry ethanol (10 ml) and the mixture heated under reflux for 24 h. The resulting yellow solution was poured into 1M-HCl (100 ml) and extracted with ether (2 × 75 ml). The combined ether extracts were washed with water (2 × 150 ml), dried, and evaporated to give the *naphthol* (45) as a chromatographically homogenous light yellow gum (154 mg, 95%) which could not be crystallised, *M* (mass spectrometry) 340, $\lambda_{max.}$ 235, 245, and 300 nm, $\nu_{max.}$ 3450 (OH) and 1625 and 1590 cm^{-1} (aryl C=C), τ 2·82 (1H, t, *J* 9 Hz, ArH), 3·24 (1H, d, *J* 3 Hz, ArH), 3·4—3·5 (3H, including d, *J* 9 Hz, 3Ar*H*), 3·53 (1H, d, *J* 2·5 Hz, ArH), 3·82 (1H, d, *J* 2·5 Hz, ArH), 5·0br (1H, s, exchanged with D_2O, ArO*H*), 6·22 (3H, s, OMe), 6·42 (6H, s, 2OMe), and 6·65 (3H, s, OMe).

(ii) The diketone (43) (180 mg, 0·5 mmol) was added to a suspension of sodium hydride (30 mg of a 50% dispersion in mineral oil; 0·6 mmol) in dry DMF (10 ml) and the mixture stirred at 20° for 24 h. The yellow solution was then poured into 1M-HCl (100 ml) and extracted with ether (2 × 75 ml). The combined ether extracts were washed with water (6 × 150 ml), dried, and evaporated to give the naphthol (45) (145 mg, 90%) as a pale yellow gum.

Acetate (46) *of Naphthol* (45).—The naphthol (45) (170 mg, 0·5 mmol) was dissolved in acetic anhydride (7 ml). Dry pyridine (0·2 ml) was added and the mixture heated on a water-bath for 2 h. The cooled solution was stirred with water (100 ml) for a short time and extracted with ethyl acetate (2 × 75 ml). The combined ethyl acetate extracts were washed with 1M-HCl (100 ml), 5% sodium carbonate (100 ml), and water (2 × 100 ml), dried, and evaporated to give the *acetate* (46) (186 mg, 100%) as pale yellow needles, m.p. 129° (Found: C, 69·1; H, 5·8. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%), *M* (mass spectrometry) 382, $\lambda_{max.}$ 245, 289, 300sh, 320sh, and 334 nm (log ε 4·72, 3·79, 3·76, 3·48, and 3·48), $\nu_{max.}$ 1758 (acetate C=O) and 1622, 1600, and 1587 cm^{-1} (aryl C=C), τ 2·59 (1H, d, *J* 2·5 Hz, ArH), 2·79 (1H, t, *J* 9 Hz, ArH), 3·19 (1H, d, *J* 2·5 Hz, ArH), 3·30 (1H, d, *J* 2·5 Hz, ArH), 3·43 (2H, d, *J* 9 Hz, 2ArH), 3·67 (1H, d, *J* 2·5 Hz, ArH), 6·15 (3H, s, OMe), 6·38 (6H, s, 2OMe), 6·60 (3H, s, OMe), and 7·72 (3H, s, OCOMe).

3,5-*Dimethoxybenzyl Phenyl Ketone* (42).—Freshly powdered aluminium chloride (4 g) was added to a solution of 3,5-dimethoxyphenylacetyl chloride (prepared from 2·0 g of the acid) in dry benzene (25 ml). The mixture was stirred at room temperature (20°) for 2 h and then poured into ice-cold 2M-HCl (100 ml) and extracted with ether (2 × 75 ml). The combined ether extracts were washed with water (2 × 150 ml), dried, and evaporated to give a yellow oil which was purified by column chromatography [silica (40 g)] to give the *ketone* (42) (2·50 g, 93%) as a chromatographically homogenous oil [Found: *M* (mass spectrometry), 256. $C_{16}H_{16}O_3$ requires *M*, 256], $\nu_{max.}$ (film) 1680 (C=O) and 1600 cm^{-1} (aryl C=C).

3,5-*Dimethoxy*-2-(2,6-*dimethoxybenzoyl*)*benzyl Phenyl Ketone* (44).—The ketone (42) (1·30 g, 5 mmol) was dissolved in trifluoroacetic anhydride (2·5 g) and added to a solution of 2,6-dimethoxybenzoic acid (910 mg, 5 mmol) in trifluoroacetic anhydride (1 ml) and the mixture stirred at 10° for 30 min. The deep-red solution was then poured into 5% aqueous sodium hydrogen carbonate (100 ml) and extracted with chloroform (2 × 75 ml). The chloroform extracts were combined, washed with water (2 × 100 ml), dried, and evaporated to give a yellow residue which was purified by chromatography to give the *ketone* (44) (1·51 g, 71%) as needles, m.p. 146·5° (Found: C, 71·4; H, 5·75. $C_{25}H_{24}O_6$ requires C, 71·6; H, 6·0%), *M* (mass spectrometry) 420, $\nu_{max.}$ 1682 (benzyl ketone C=O), 1668 (benzophenone C=O), and 1590 and 1580 cm^{-1} (aryl C=C), τ 2·0 (2H, m, 2ArH), 2·56—2·66 (3H, m, 3ArH), 2·89 (1H, t, *J* 8·5 Hz, ArH), 3·59 (2H, d, *J* 8·5 Hz, 2ArH), 3·64 (1H, d, partially obscured, ArH), 3·76 (1H, d, *J* 2·5 Hz, ArH), 5·63 (2H, s, ArCH_2COPh), 6·26 (3H, s, OMe), 6·39 (6H, s, 2OMe), and 6·58 (3H, s, OMe).

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