Tetracycline Studies. Part 5.† New Syntheses of Anthracenes and Anthraquinones through Benzophenone Carbanions

By **Michael J. Broadhurst, Cedric H. Hassall,*** and **Gareth J. Thomas,** Roche Products Limited, Welwyn Garden City, Hertfordshire AL7 3AY

The synthesis of anthracenes and anthraquinones by a novel method involving the cyclisation of carbanions derived from substituted benzophenones is described. The procedure gives good yields and is of wide applicability. Regiospecificity has been achieved by preferential displacement of chloride ion. In certain circumstances treatment of 2-cyanomethylbenzophenones with trifluoroacetic anhydride gives derivatives of isoquinolin-3-one.

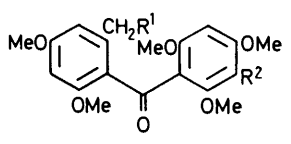
THE synthesis of highly substituted anthraquinones by chemical methods, such as the condensation of phthalic acid derivatives with phenols or phenol ethers [1] and the Lewis-acid-catalysed cyclisation of *o*-benzoylbenzoic acids, often gives poor yields.[2] Such methods are further complicated by problems associated with the control of substituent orientation which can lead to the formation of isomer mixtures that are difficult to separate

† Part 4, ref. 4.

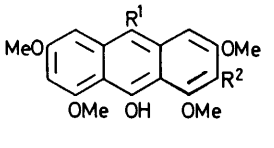
[1] (*a*) R. Eder and C. Widmer, *Helv. Chim. Acta*, 1922, **5**, 3; (*b*) R. Eder and C. Widmer, *ibid.*, 1923, **6**, 419; (*c*) M. V. Sargent, D. O'N. Smith, J. A. Elix, and P. Roffey, *J. Chem. Soc.* (*C*), 1969, 2763.

[2] (*a*) J. C. Lavie and R. H. Thomson, *J. Chem. Soc.*, 1961, 485; (*b*) T. F. Low, R. J. Park, M. D. Sutherland, and I. Vessey, *Austral. J. Chem.*, 1965, **18**, 182.

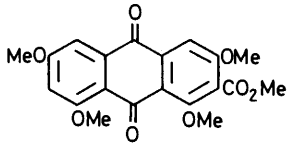
and identify unequivocally.[3] Recently we reported a new synthesis of anthraquinones which overcomes these problems.[4] This involves the base-catalysed cyclisation of appropriately substituted 2-cyanomethyl-2′-methoxybenzophenones; for example the conversion of the benzophenone (1) into the anthraquinone (6) through the anthracene derivative (4). The method has found application in the synthesis of natural products such as emodin, physcion,[4] nor-D-6-methylpretetramid,[5] a derivative of ptilometric acid,[6] and acid-sensitive anthraquinones such as (±)-*O*-methylaversin.[7] In what follows,



(1) R^1 = CN, R^2 = CO_2Me
(2) R^1 = CO_2Et, R^2 = CO_2Me
(3) R^1 = CO_2Me, R^2 = CN



(4) R^1 = CN, R^2 = CO_2Me
(5) R^1 = CO_2Me, R^2 = CN



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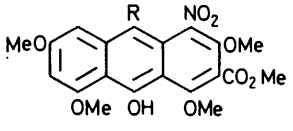

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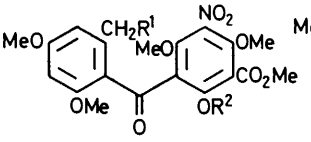
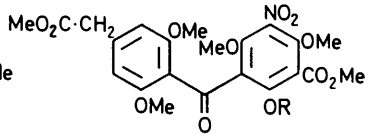
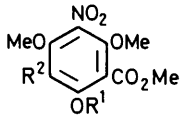


(8) R^1 = CN, R^2 = Me
(9) R^1 = CO_2Me, R^2 = Me
(10) R^1 = CO_2Me, R^2 = Et



(11) R = Me
(12) R = Et



(13) R^1 = Me, R^2 = CHO
(14) R^1 = Me, R^2 = CO_2H
(15) R^1 = Me, R^2 = COCl
(16) R^1 = Et, R^2 = CHO
(17) R^1 = Et, R^2 = CO_2H
(18) R^1 = Et, R^2 = COCl

we shall describe modifications which enable the preparation of a wider range of polysubstituted anthraquinones.

We have undertaken the synthesis of the anthracene derivative (7) in connection with our interest in analogues of tetracyclines. After unsuccessful attempts to prepare the benzophenone nitrile (8), synthesis of the corresponding ester (9) was investigated. It was obtained in 50% yield, together with 2% of the isomer (11), when the acid chloride (15) was condensed with methyl 3,5-dimethoxyphenylacetate in the presence of titanium tetrachloride. Although an earlier study had shown that the benzophenone ester (19) did not cyclise to the anthracene derivative (20),[8] this procedure was more successful with benzophenones substituted with electron-withdrawing groups. Treatment of the benzophenones (2) and (22) with potassium t-butoxide in dimethylformamide (DMF) at 90 °C and oxidation of the product with alkaline hydrogen peroxide gave moderate yields of the anthraquinones (6) and (32), respectively. The anthracene (5) was obtained in good yield by cyclisation of the benzophenone (3).

The benzophenone ester (9) was cyclised with potassium t-butoxide in DMF at room temperature to a mixture of compounds which were separated by chromatography into two fractions. The first consisted of the anthracenes (40) and (41), and the second of the related methoxycarbonyl derivatives (43) and (44). They were identified by comparison with the analogous products obtained from the cyclisation of the related benzophenone ester (10). In this case separation of all four products (41), (42), (44), and (45) was achieved.

It became clear from the experiments involving the benzophenones (9) and (10) that similar attempts to synthesise the nitroanthracene (46), an intermediate related to the tetracycline series, would yield an unduly complex mixture. Consequently, specificity of cyclisation was sought through displacement of chloride. Cyclisation of the nitrile (47) gave the cyanoanthrol (50) in 46% yield, but using the methoxycarbonylbenzophenone (48) no cyclic product was formed. This failure can be attributed to the absence of electron-withdrawing groups on the benzophenone, as in the case of (19).

The acid chloride (59) was condensed with methyl 3,5-dimethoxyphenylacetate to give the benzophenone (60), which cyclised to give a 75% yield of the required nitroanthrone (43). There was no indication of any products arising from the alternative mode of cyclisation or anthrols lacking the 10-methoxycarbonyl group.

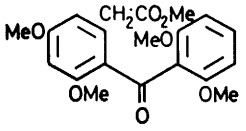
The different course of reaction leading to the elimination of the ester group when methoxide is the leaving group cannot be explained with certainty. Possibly it is the result of intramolecular attack by the displaced nucleophile on the ester group (Scheme). On this basis, the failure of chloride, as a leaving group, to participate in such a reaction leading to loss of the ester group may be attributed to lesser nucleophilicity.

In applying our earlier procedure [4] we encountered some cases in which the yield of the required product was much reduced by a side reaction arising from the cyclisation of *o*-cyanomethylbenzophenones with trifluoroacetic anhydride. It has now been established for three

[3] (*a*) L. J. Briggs, J. C. Dacre, and G. A. Nicholls, *J. Chem. Soc.*, 1948, 990; (*b*) E. Noah, *Ber.*, 1886, **19**, 332.
[4] C. H. Hassall and B. A. Morgan, *J.C.S. Perkin I*, 1973, 2853.
[5] C. H. Hassall and M. J. Broadhurst, unpublished results.
[6] J. K. K. Lam and M. V. Sargent, *J.C.S. Perkin I*, 1974, 1417.
[7] G. M. Holmwood and J. C. Roberts, *J. Chem. Soc.* (*C*), 1971, 3899.
[8] B. A. Morgan, Ph.D. Thesis, University of Wales, 1971.

related cases that the products of this reaction are derivatives of isoquinolin-3-ones, a class of compounds [9] which is relatively inaccessible by other means.

Under certain conditions the action of trifluoroacetic anhydride on 2,4,6-trimethoxy-3-methoxycarbonylbenzoic acid and 3-benzyloxy-5-methoxy-2-methylphenylacetonitrile (28) gave the isoquinolin-3-one (61) in



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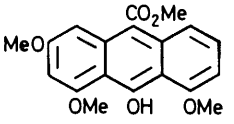

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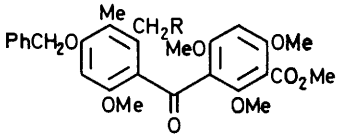
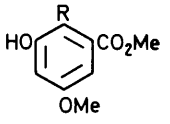
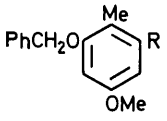


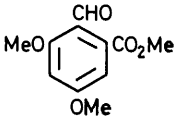
(21) R = CN
(22) R = CO_2Me



(23) R = CHO
(24) R = Me



(25) R = CO_2Me
(26) R = CH_2OH
(27) R = CH_2Br
(28) R = CH_2CN
(29) R = CH_2CO_2H
(30) R = CH_2CO_2Me



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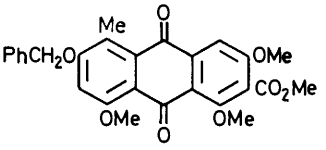

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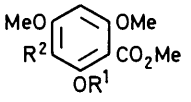
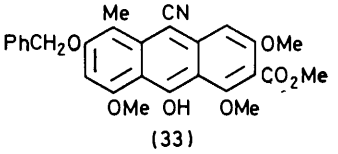


(34) R^1 = Me, R^2 = CH:NOH
(35) R^1 = Me, R^2 = CN
(36) R^1 = R^2 = H
(37) R^1 = H, R^2 = CHO
(38) R^1 = Et, R^2 = CHO



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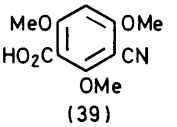
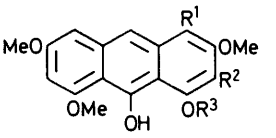


(39)

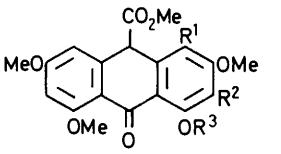
addition to the benzophenone (21). Compound (61) was also formed, together with products arising from debenzylation, when a solution of the benzophenone (21) was treated with the same reagent. The analogues (62) and (63) have also been prepared from the corresponding benzophenones. In each case, the structure of the product was established by spectroscopic evidence.

The absence of i.r. absorption characteristic of the $O_2C{\cdot}CF_3$ group and the presence of a long-wavelength band (*ca.* 500 nm) in the visible spectrum are incompatible with the isomeric structure (65).

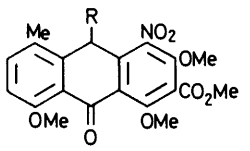
Selective removal of the trifluoroacetyl group from (62) was achieved with dilute ammonium hydroxide. The structure of the yellow product, which gave a red-brown colouration with iron(III) chloride,[10] was established as (66) by spectroscopy. The u.v. and n.m.r. data indicated that the lactam tautomer predominates.[11] In ethanol the spectrum showed a single long-wavelength band ($\lambda_{max.}$ 404 nm) but there was a small bathochromic shift (10 nm) when the solvent was changed to chloroform. 2-Methylisoquinolin-3-one showed a correspond-



(40) R^1 = NO_2, R^2 = CO_2Me, R^3 = Me
(41) R^1 = CO_2Me, R^2 = NO_2, R^3 = Me
(42) R^1 = NO_2, R^2 = CO_2Me, R^3 = Et



(43) R^1 = NO_2, R^2 = CO_2Me, R^3 = Me
(44) R^1 = CO_2Me, R^2 = NO_2, R^3 = Me
(45) R^1 = NO_2, R^2 = CO_2Me, R^3 = Et



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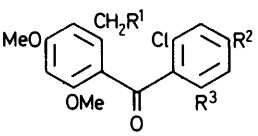
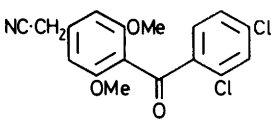


(47) R^1 = CN, R^2 = Cl, R^3 = H
(48) R^1 = CO_2Me, R^2 = H, R^3 = OMe



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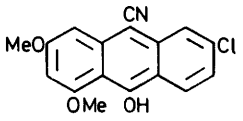

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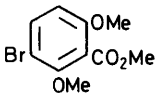

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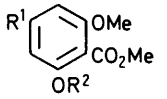
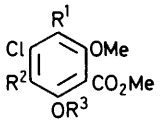
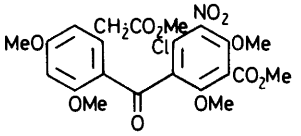


(52) R^1 = NH_2, R^2 = Me
(53) R^1 = Cl, R^2 = Me
(54) R^1 = Cl, R^2 = H



(55) R^1 = R^3 = H, R^2 = CHO
(56) R^1 = NO_2, R^2 = CHO, R^3 = H
(57) R^1 = NO_2, R^2 = CHO, R^3 = Me
(58) R^1 = NO_2, R^2 = CO_2H, R^3 = Me
(59) R^1 = NO_2, R^2 = COCl, R^3 = Me



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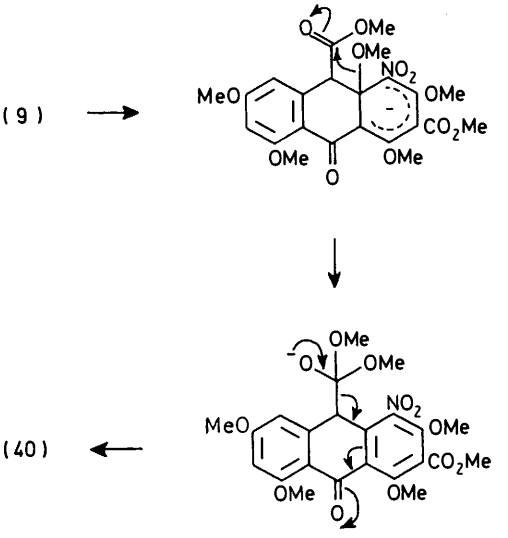
[9] M. A. Ainscough and A. F. Temple, *J.C.S. Chem. Comm.*, 1976, 695.

[10] H. R. Bentley, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 1952, 1763.

[11] D. W. Jones, *J. Chem. Soc.* (*C*), 1969, 1729.

ing band ($\lambda_{max.}$ 410 nm) but there were two long-wavelength bands in the spectrum of isoquinolin-3-ols; this indicated a mixture of lactam ($\lambda_{max.}$ 405 nm) and lactim ($\lambda_{max.}$ 344 nm) tautomers. The n.m.r. spectrum includes a signal, τ 3.45, due to H-4; *cf.* the signals at τ 3.45 and



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2.9 for the corresponding protons in 1,2-dimethylisoquinolin-3-one and 1-phenylisoquinolin-3-ol, respectively.[11]

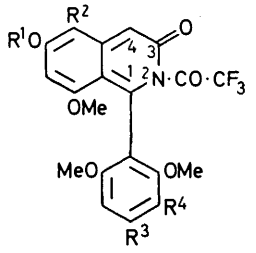
A red compound obtained by Lam and Sargent from the trifluoroacetic-anhydride-catalysed condensation of 3,5-dimethoxyphenylacetonitrile with 3-bromo-2,6-dimethoxy-4-propylbenzoic acid was assigned the benzophenone structure (67).[6] We suggest, rather, that this compound has the isoquinolinone structure (64); this is in accord with the limited spectral data given [6] and the similarity to compounds prepared in this investigation. In particular, the i.r. and u.v. spectra of the compounds we have prepared are incompatible with the benzophenone structure.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. Unless otherwise stated i.r. spectra were recorded with a Unicam SP 1000 spectrophotometer for Nujol mulls. U.v.–visible spectra were recorded for solutions in chloroform with a Unicam SP 8000 spectrophotometer and ^{1}H n.m.r. spectra with a Varian T60 or XL100 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference. Mass spectra were recorded with an A.E.I. MS902 spectrometer by direct insertion. Microanalyses were carried out by Mr. M. R. Cottrell. Organic solutions were dried ($MgSO_4$) and evaporated using a rotary evaporator. Silica gel used for column chromatography was Kieselgel 60 (70—230 mesh; Merck).

Methyl 3-Formyl-2,4,6-trimethoxy-5-nitrobenzoate (13).—Methyl 3-formyl-2,4,6-trimethoxybenzoate [4] (12.60 g, 50 mmol) was added to conc. H_2SO_4 (50 ml) and the solution was stirred vigorously at 0 °C. Potassium nitrate (6.00 g, 59 mmol) was added and the mixture was stirred for 1 h at 20 °C, then poured with stirring into ice–water (600 ml) to precipitate a bright yellow solid. The suspension was extracted with chloroform (2 × 200 ml) and the combined extracts were washed with water (2 × 200 ml), dried, and evaporated. The crude product was purified by column chromatography [silica (800 g); ether–light petroleum (b.p. 40—60 °C) (1 : 3; 3 l); ether–light petroleum (b.p. 40—60 °C) (1 : 1; 2.4 l); ether (2 l)] to yield the *nitro-aldehyde* (13) (6.26 g, 42%) as a white, crystalline solid, m.p. 105° (Found: C, 48.1; H, 4.4; N, 4.8. $C_{12}H_{13}NO_8$ requires C, 48.2; H, 4.4; N, 4.7%), M^+ 299, $\nu_{max.}$ 1 720, 1 685, 1 590, 1 565, and 1 540 cm^{-1}, τ −0.27 (1 H, s, CHO), 5.99, (3 H, s, OMe), and 6.00 (9 H, s, 3 OMe).

Methyl Hydrogen 2,4,6-Trimethoxy-5-nitroisophthalate (14).—The nitro-aldehyde (13) (20.45 g, 68 mmol) was stirred in acetone (375 ml) and water (375 ml). Potassium permanganate (20.6 g, 130 mmol) was added and the mixture stirred at 20 °C for 1 h. Sulphur dioxide was bubbled through to give a clear solution which was then adjusted to pH 1 (conc. HCl) and extracted with chloroform (2 × 400 ml). The combined extracts were washed with aqueous 5% sodium hydrogen carbonate (2 × 500 ml) and discarded. The combined aqueous washings were acidified and extracted with chloroform (2 × 400 ml). The combined extracts were dried and evaporated to give the *acid* (14) as a pale yellow crystalline solid (16.07 g, 75%), m.p. 110—111° (from ether–light petroleum) (Found: C, 45.75;

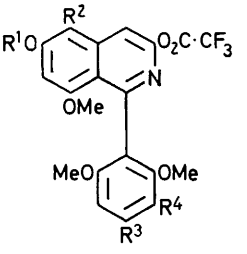


(61) R^1 = CH_2Ph, R^2 = Me, R^3 = OMe, R^4 = CO_2Me

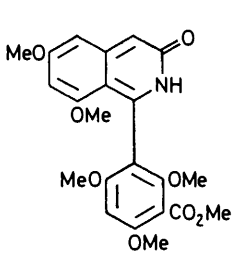
(62) R^1 = Me, R^2 = H, R^3 = OMe, R^4 = CO_2Me

(63) R^1 = Me, R^2 = R^4 = H, R^3 = Me

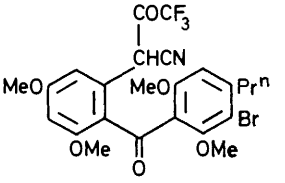
(64) R^1 = Me, R^2 = H, R^3 = Pr^n, R^4 = Br



(65)



(66)



(67)

H, 3.95; N, 4.3. $C_{12}H_{13}NO_9$ requires C, 45.7; H, 4.2; N, 4.45%), M^+ 315, $\nu_{max.}$ 3 400—2 400, 1 740, 1 710, 1 600, 1 580, and 1 550 cm^{-1}, τ 1.73br (1 H, s, exch. D_2O, CO_2H), and 6.00, 6.03, and 6.05 (total 12 H, 4 OMe).

Methyl 3-Chloroformyl-2,4,6-trimethoxy-5-nitrobenzoate (15).—The nitro-acid (14) (9.45 g, 30 mmol) was suspended in benzene (60 ml) and oxalyl chloride (5.7 g, 45 mmol) was added. The mixture was stirred at 20 °C for 3 h to give a clear solution. This was evaporated to yield a white crystalline solid, which was redissolved in benzene and the

solution evaporated. This process was repeated twice and the acid chloride was then used without further purification for subsequent reactions.

Methyl 3,5-Dimethoxy-2-(2,4,6-trimethoxy-3-methoxycarbonyl-5-nitrobenzoyl)phenylacetate (9).—A solution of the acid chloride (12) (10.0 g, 30 mmol) and methyl 3,5-dimethoxyphenylacetate [12] (2.10 g, 10 mmol) in nitromethane (40 ml) was stirred at 0 °C and a solution of titanium tetrachloride (6.3 g, 33 mmol) in nitromethane (60 ml) was added to give an immediate dark red colour. The mixture was stirred at 0 °C for 30 min and then poured into 5% sodium hydrogen carbonate solution (1 l). The solution was extracted with ether (2 × 500 ml). The aqueous solution was acidified, extracted with ether (2 × 500 ml), and discarded. The combined extracts were washed with water (2 × 1 l), dried, and evaporated to yield the nitro-acid (14) (7.51 g). The ethereal extracts containing non-acidic material were combined, washed with water (2 × 1 l), dried, and evaporated to yield an orange gum (4.00 g.). Column chromatography [silica (150 g); ether–light petroleum (b.p. 40—60 °C) (1 : 1; 2.625 l); ether–light petroleum (b.p. 40—60 °C) (3 : 1; 1.875 l)] gave unchanged methyl 3,5-dimethoxyphenylacetate (0.47 g, 22%) and the *phenylacetate* (9) (2.55 g, 50%) as a gum (Found: C, 54.0; H, 5.0; N, 3.1. $C_{23}H_{25}NO_{12}$ requires C, 54.5; H, 5.0; N, 2.8%), M^+ 507, $\nu_{max.}$ (film) 1 735, 1 650, 1 600, 1 575, and 1 540 cm^{-1}, τ 3.47 (1 H, d, *J* 2 Hz, ArH), 3.60 (1 H, d, *J* 2 Hz, ArH), 6.07 (6 H, s, 2 OMe), 6.13 (5 H, s, OMe, ArCH_2·CO_2R), 6.25 (3 H, s, OMe), 6.27 (3 H, s, OMe), 6.37 (3 H, s, OMe), and 6.40 (3 H, s, OMe).

The more polar isomer *methyl 3,5-dimethoxy-4-(2,4,6-trimethoxy-3-methoxycarbonyl-5-nitrobenzoyl)phenylacetate* (11) was obtained as a gum (0.10 g, 2%), M^+ 507, $\nu_{max.}$ ($CHCl_3$) 1 740, 1 675, 1 600, 1 585, and 1 545 cm^{-1}, τ 3.50 (2 H, s, 2 ArH), 6.04 (3 H, s, OMe), 6.06 (3 H, s, OMe), 6.19 (5 H, s, OMe, ArCH_2·CO_2R), 6.26 and 6.28 (9 H, 3 OMe), and 6.40 (3 H, s, OMe).

Ethyl 3,5-Dimethoxy-2-(2,4,6-trimethoxy-3-methoxycarbonylbenzoyl)phenylacetate (2).—Trifluoroacetic anhydride (5 g, 24 mmol) was added to a suspension of 1-methyl hydrogen 2,4,6-trimethoxyisophthalate (5.4 g, 20 mmol) in nitromethane (20 ml) at −10 °C. After stirring at this temperature for 10 min ethyl 3,5-dimethoxyphenylacetate (2.24 g, 10 mmol) was added and the mixture stirred at −10 °C for a further 50 min. The resulting solution was added with stirring to 5% potassium hydrogen carbonate solution (100 ml) and extracted with chloroform (2 × 100 ml). The extracts were combined, washed with water, dried, and evaporated to give a red-brown syrup (*ca.* 5.0 g). Column chromatography [silica (70 g); ethyl acetate–chloroform (1 : 1)] gave the *phenylacetate* (2) (4.4 g, 95%) as prisms, m.p. 112—113° (from ethyl acetate–ether) (Found: C, 60.25; H, 6.1. $C_{24}H_{28}O_{10}$ requires C, 60.5; H, 5.9%), M^+ 462, $\nu_{max.}$ 1 740, 1 735, and 1 650 cm^{-1}, τ 3.48 (1 H, d, *J* 2.5 Hz, ArH), 3.64 (1 H, d, *J* 2.5 Hz, ArH), 3.76 (1 H, s, ArH), 5.82 (2 H, q, *J* 7 Hz, OCH_2·CH_3), 6.15 (8 H, m, 2 OMe and ArCH_2·CO_2Et), 6.26 (3 H, s, OMe), 6.33 (3 H, s, OMe), 6.38 (3 H, s, OMe), 6.47 (3 H, s, OMe), and 8.75 (3 H, t, *J* 7 Hz, OCH_2·CH_3).

1,3,6,8-Tetramethoxy-2-methoxycarbonylanthraquinone (6).—The benzophenone (2) (460 mg, 1 mmol) in dry dimethylformamide (10 ml) under nitrogen was treated with potassium t-butoxide (280 mg, 2.5 mmol). The resulting deep red solution was stirred at 90 °C for 35 min, cooled, poured into M-HCl (200 ml), and extracted with dichloromethane (2 × 200 ml). The extracts were combined and evaporated to leave an orange mixture which was dissolved in ethanol (75 ml). A solution of hydrogen peroxide (100 vol; 10 ml) and sodium hydroxide (200 mg, 50 mmol) in water (20 ml) was added and the solution heated at 70 °C for 45 min. After cooling, more hydrogen peroxide (100 vol; 12 ml) was added and the solution stirred for 14 h at room temperature, poured into water (100 ml), and extracted with ethyl acetate (3 × 50 ml). The extracts were combined, washed with water (3 × 100 ml), dried, and evaporated. Crystallisation of the residue from ethyl acetate gave 1,3,6,8-tetramethyl-2-methoxycarbonylanthraquinone (6) (190 mg, 49%) as yellow needles, m.p. 209—210° (lit.,[4] 210°), M^+ 386, identical (mixed m.p., t.l.c., and n.m.r. and i.r. spectra) with a sample prepared by oxidation of 10-cyano-1,3,6,8-tetramethoxy-2-methoxycarbonylanthracen-9-ol.[4]

Methyl 2-Formyl-3-hydroxy-5-methoxybenzoate (23).—Boron trichloride (20 g, 0.16 mol) in dichloromethane (100 ml) was added during 15 min to a stirred solution of methyl 2-formyl-3,5-dimethoxybenzoate (31) [4] (22.4 g, 0.1 mol) in dichloromethane (200 ml) cooled to −70 °C. The resulting solution was allowed to return to room temperature, stirred at this temperature for 3 h, and then poured with stirring into ice-cold M-HCl (500 ml). The dichloromethane layer was separated, washed with water (4 × 300 ml) and saturated aqueous sodium chloride (300 ml), dried, and evaporated to give a white crystalline residue. Recrystallisation from ethanol gave the benzoate (23) (18.5 g, 88%) as needles, m.p. 86—86.5° (Found: C, 56.8; H, 4.8. $C_{10}H_{10}O_5$ requires C, 57.1; H, 4.8%), M^+ 210, $\nu_{max.}$ 3 000—2 500, 1 720, and 1 660 cm^{-1}, τ −2.72 (1 H, s, exch. D_2O, ArOH), −0.42 (1 H, s, CHO), 3.04 (1 H, d, *J* 3 Hz, ArH), 3.51 (1 H, d, *J* 3 Hz, ArH), 6.08 (3 H, s, OMe), and 6.15 (3 H, s, OMe).

Methyl 3-Benzyloxy-5-methoxy-2-methylbenzoate (25).—The aldehyde (23) (5.2 g, 20 mmol) suspended in ethanol (75 ml) was shaken with palladium–carbon (500 mg; 10%) in hydrogen. Uptake ceased after *ca.* 2 equiv. (900 ml) had been absorbed. The catalyst was removed by filtration through Celite and the filtrate evaporated to give *methyl 3-hydroxy-5-methoxy-2-methylbenzoate* (24) (4.7 g, 95%) as a chromatographically homogeneous white crystalline mass, M^+ 196, $\nu_{max.}$ 3 330 and 1 690 cm^{-1}, τ 3.10 (1 H, d, *J* 3 Hz, ArH), 3.50 (1 H, d, *J* 3 Hz, ArH), 4.2br (1 H, s, exch. D_2O, ArOH), 6.14 (3 H, s, OMe), 6.28 (3 H, s, OMe), and 7.66 (3 H, s, $ArCH_3$), used directly for the next stage. The benzoate (24) was dissolved in dry DMF (50 ml), benzyl chloride (4.5 ml, 33 mmol) and anhydrous potassium carbonate (10 g) were added, and the mixture was stirred at 75 °C under nitrogen for 4 h. The suspension was cooled, poured into water (250 ml), and extracted with ether (3 × 150 ml). The extracts were combined, washed with water (3 × 150 ml), dried, and evaporated. Crystallisation of the residue from ethanol gave the benzoate (25) (6.0 g, 87.5%), m.p. 67—67.5° (Found: C, 70.9; H, 6.2. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%), M^+ 286, $\nu_{max.}$ 1 715 and 1 610 cm^{-1}, τ 2.5—2.8 (5 H, m, ArH), 3.10 (1 H, d, *J* 2 Hz, ArH), 3.41 (1 H, d, *J* 2 Hz, ArH), 5.01 (2 H, s, OCH_2Ar), 6.14 (3 H, s, OMe), 6.25 (3 H, s, OMe), and 7.61 (3 H, s, ArMe).

3-Benzyloxy-5-methoxy-2-methylphenylacetonitrile (28).—The ester (25) (5.7 g, 20 mmol) in dry ether (50 ml) was added to a stirred suspension of lithium aluminium hydride (1.0 g) in dry ether (100 ml) at a rate sufficient to maintain vigorous reflux. The mixture was then heated under reflux

[12] A. J. Birch, B. Moore, and R. W. Richards, *J. Chem. Soc.*, 1962, 220.

for 1 h and cooled to 0 °C and the excess of hydride consumed by dropwise addition of water (1 ml), aqueous 15% sodium hydroxide (1 ml), and water (3 ml) while maintaining vigorous stirring. Filtration and evaporation left *3-benzyloxy-5-methoxy-2-methylbenzyl alcohol* (26) as a chromatographically homogeneous crystalline mass, m.p. 75—77°, $\nu_{max.}$ 3 400—3 200 cm^{-1}, used directly for the next stage. The alcohol (26) was dissolved in dry ether (150 ml) at 0 °C and treated with phosphorus tribromide (1.4 g) in ether (25 ml). After being stirred at 0 °C for 3 h the solution was poured into water (200 ml). The ether layer was separated, washed with aqueous 5% potassium hydrogen carbonate (200 ml) and water (200 ml), dried, and evaporated to yield *3-benzyloxy-5-methoxy-2-methylbenzyl bromide* (27) as a crystalline mass, m.p. 65°, $\nu_{max.}$ 1 615 and 1 590 cm^{-1}, used directly for the next stage. The benzyl bromide (27) and potassium cyanide (6 g) were added to ethanol (160 ml) and water (40 ml). The mixture was heated under reflux for 3 h, was then cooled, poured into ice–water (300 ml), and left to crystallise. After 12 h the product was collected, washed with water, dried, and recrystallised from ethanol–water to give the *nitrile* (28) (4.05 g, 81%) as needles, m.p. 86—87° (Found: C, 76.2; H, 6.5; N, 5.5. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%), M^+ 267, $\nu_{max.}$ 2 230 cm^{-1}, τ 2.5—2.8 (5 H, m, ArH), 3.53 (2 H, ABq, *J* 2.5 Hz, ArH), 5.01 (2 H, s, OCH_2Ar), 6.25 (3 H, s, OMe), 6.42 (2 H, s, $ArCH_2CN$), and 7.85 (3 H, s, ArMe).

3-Benzyloxy-5-methoxy-2-methylphenylacetic Acid (29).—The nitrile (28) (6.7 g, 25 mmol) was dissolved in ethanol (70 ml), 10M-sodium hydroxide (70 ml) was added. The mixture was heated under reflux with stirring for 24 h, then poured into water (500 ml), acidified with conc. HCl, and left to crystallise. After 12 h the product was collected, washed with water, dried, and recrystallised from ether–hexane to give the *acid* (29) (7.1 g, 99%), m.p. 121—121.5° (Found: C, 71.3; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%), M^+ 286, $\nu_{max.}$ 1 700 cm^{-1}, τ −0.67br (1 H, s, exch. D_2O, $ArCH_2CO_2H$), 2.43—2.63 (5 H, m, ArH), 3.53 (2 H, ABq, *J* 2.5 Hz, ArH), 4.95 (2 H, s, OCH_2Ar), 6.20 (3 H, s, OMe), 6.33 (2 H, s, $ArCH_2CO_2H$), and 7.80 (3 H, s, ArMe).

Methyl 3-Benzyloxy-5-methoxy-2-methylphenylacetate (30).—The acid (29) (5 g) was dissolved in warm methanol (100 ml) and cooled to 0 °C, and thionyl chloride (2.5 ml) was added dropwise with stirring. The solution was allowed to reach room temperature and stirred at this temperature for 4 h. The bulk of the solvent was evaporated off, the residue dissolved in ether (100 ml), and the solution washed with water (50 ml), aqueous 5% potassium hydrogen carbonate (50 ml), and water (50 ml), dried, and evaporated to yield a pale yellow residue. Crystallisation from methanol gave the *phenylacetate* (30) (5 g, 95%) as needles, m.p. 51—52° (Found: C, 71.9; H, 6.65. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%), M^+ 300, $\nu_{max.}$ 1 745, 1 610, and 1 600 cm^{-1}, τ 2.47—2.67 (5 H, m, ArH), 3.55 (2 H, ABq, *J* 2.5 Hz, ArH), 4.97 (2 H, s, OCH_2Ar), 6.25 (3 H, s, OMe), 6.30 (3 H, s, OMe), 6.40 (2 H, s, $ArCH_2CO_2Me$), and 7.83 (3 H, s, ArMe).

5-Benzyloxy-3-methoxy-2-(2,4,6-trimethoxy-3-methoxycarbonylbenzoyl)-6-methylphenylacetonitrile (21).—Trifluoroacetic anhydride (57 g, 0.27 mol) was added to a stirred suspension of methyl hydrogen 2,4,6-trimethoxyisophthalate (60 g, 0.22 mol) in nitromethane (100 ml) at −15 °C. After all the solid had dissolved the nitrile (28) (30 g, 0.11 mol) in nitromethane (70 ml) was added and the deep red solution stirred for 1.5 h with the temperature maintained at −12 °C. The solution was then poured with stirring into aqueous 10% potassium hydrogen carbonate (800 ml) and extracted with chloroform (4 × 400 ml). The extracts were combined, washed with water (800 ml), dried, and evaporated to give a deep red crystalline residue. Column chromatography [silica (1.0 kg); ethyl acetate–chloroform–hexane (1 : 1 : 1)] gave the *nitrile* (21) (34 g, 58%) as prisms, m.p. 169—170° (from ethyl acetate) (Found: C, 66.9; H, 5.9; N, 2.6. $C_{29}H_{29}NO_8$ requires C, 67.0; H, 5.6; N, 2.7%), M^+ 519, $\nu_{max.}$ 2 230, 1 730, and 1 670 cm^{-1}, τ 2.5—2.8 (5 H, m, ArH), 3.62 (1 H, s, ArH), 3.84 (1 H, s, ArH), 4.94 (2 H, s, OCH_2Ar), 6.14 (6 H, s, 2 OMe), 6.18 (2 H, s, $ArCH_2CN$), 6.33 (3 H, s, OMe), 6.35 (3 H, s, OMe), 6.52 (3 H, s, OMe), and 7.70 (3 H, s, ArMe).

Methyl 5-Benzyloxy-3-methoxy-2-(2,4,6-trimethoxy-3-methoxycarbonylbenzoyl)-6-methylphenylacetate (22).—Trifluoroacetic anhydride (40 g, 0.19 mol) was added to a stirred suspension of methyl hydrogen 2,4,6-trimethoxyisophthalate (38.0 g, 0.14 mol) in nitromethane (70 ml) at −10 °C. After all the solid had dissolved the phenylacetate (30) (21.0 g, 0.07 mol) in nitromethane (50 ml) was added and the solution stirred at −10 °C for 40 min. The solution was then poured with stirring into aqueous 10% potassium hydrogen carbonate (500 ml) and extracted with chloroform (4 × 300 ml). The extracts were combined, washed with water (800 ml), dried, and evaporated. Column chromatography [silica (1.0 kg); ethyl acetate–chloroform–hexane (2 : 1 : 1)] gave the *phenylacetate* (22) (34.0 g, 93%) as prisms, m.p. 146—147° (from ethyl acetate) (Found: C, 65.1; H, 5.9. $C_{30}H_{32}O_{10}$ requires C, 65.2; H, 5.8%), M^+ 552, $\nu_{max.}$ 1 748, 1 730, and 1 670 cm^{-1}, τ 2.43—2.63 (5 H, m, ArH), 3.52 (1 H, s, ArH), 3.76 (1 H, s, ArH), 4.87 (2 H, s, OCH_2Ar), 6.10 (6 H, s, 2 OMe), 6.20 (2 H, s, $ArCH_2CO_2Me$), 6.29 (6 H, s, 2 OMe), 6.40 (3 H, s, OMe), 6.43 (3 H, s, OMe), and 7.80 (3 H, s, $ArCH_3$).

6-Benzyloxy-10-cyano-1,3,8-trimethoxy-2-methoxycarbonyl-5-methylanthracen-9-ol (33).—The benzophenone (21) (260 mg, 0.5 mmol) in dry DMF (10 ml) under nitrogen was treated with potassium t-butoxide (112 mg, 1 mmol), and the resulting deep red solution stirred at 90 °C for 1 h. The solution was then cooled, poured into M-HCl (100 ml), and extracted with chloroform (2 × 100 ml.). The extracts were combined, washed with water (4 × 100 ml), dried, and evaporated. The yellow residue was recrystallised from ethyl acetate to give the *anthrol* (33) (236 mg, 95%) as yellow needles, m.p. 180—181° (Found: C, 68.8; H, 5.2; N, 2.8. $C_{28}H_{25}NO_7$ requires C, 69.0; H, 5.2; N, 2.9%), M^+ 487, $\nu_{max.}$ 3 220, 2 205, and 1 740 cm^{-1}, τ −1.56 (1 H, s, exch. D_2O, ArOH), 2.5—2.8 (6 H, m, ArH), 3.56 (1 H, s, ArH), 4.85 (2 H, s, OCH_2Ar), 6.01 (3 H, s, OMe), 6.03 (3 H, s, OMe), 6.08 (3 H, s, OMe), 6.10 (3 H, s, OMe), and 7.15 (3 H, s, ArMe).

6-Benzyloxy-1,3,8-trimethoxy-2-methoxycarbonyl-5-methylanthraquinone (32).—(i) 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 (33) (243 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 15 h before diluting with water (150 ml). The yellow precipitate was collected, washed with water, and dried to give the anthraquinone (32) (229 mg, 96%) as yellow needles, m.p. 194—195° (from ethyl acetate) (Found: C, 68.3; H, 5.3. $C_{27}H_{24}O_8$ requires C, 68.1, H, 5.1%), M^+ 476, $\nu_{max.}$ 1 740, and 1 672 cm^{-1}, τ 2.5—2.7br (6 H, s, ArH), 3.25 (1 H, s, ArH), 4.85 (2 H, s,

OCH_2Ar), 6.04 (3 H, s, OMe), 6.07 (6 H, s, 2 OMe), 6.12 (3 H, s, OMe), and 7.44 (3 H, s, ArMe).

(ii) The benzophenone (22) (1.1 g, 2 mmol) in dry DMF (40 ml) under nitrogen was treated with potassium t-butoxide (450 mg, 4 mmol) and the resulting red solution stirred at 90 °C for 1 h. The solution was then cooled, poured into M-HCl (400 ml), and extracted with dichloromethane (2 × 300 ml). The extracts were combined and evaporated and the orange residue was dissolved in ethanol (150 ml). A solution of hydrogen peroxide (100 mol; 20 ml) and sodium hydroxide (400 mg, 10 mmol) in water (20 ml) was added, and the solution heated at 70 °C for 45 min. After cooling more hydrogen peroxide (100 vol; 20 ml) was added and the solution left for a further 14 h before diluting with water (300 ml). The solution was then extracted with ethyl acetate (3 × 100 ml); the extracts were combined, washed with water (3 × 100 ml), dried, and evaporated. Purification of the residue by column chromatography [silica (30 g); ethyl acetate–chloroform (1 : 1)] gave the *anthraquinone* (32) (390 mg, 41%) as yellow needles, m.p. 194—195° (from ethyl acetate), identical (mixed m.p., t.l.c., and n.m.r. and i.r. spectra) with the sample prepared by method (i).

2,4,6-*Trimethoxy*-3-*methoxycarbonylbenzaldehyde Oxime* (34).—Methyl 3-formyl-2,4,6-trimethoxybenzoate [4] (5.0 g) in ethanol (70 ml) was added to a solution of hydroxylamine hydrochloride (10.0 g) and crystalline sodium acetate (20.0 g) in water (80 ml). The mixture was heated under reflux for 30 min and allowed to cool. The crystalline product was then filtered off washed, with water, and dried to give the *oxime* (34) (5.0 g, 94%) as plates, m.p. 166—167° (Found: C, 53.4; H, 5.5; N, 5.15. $C_{12}H_{15}NO_6$ requires C, 53.3; H, 5.6; N, 5.2%), $\nu_{max.}$ 3 300, 1 720, and 1 600 cm^{-1}.

Methyl 3-*Cyano*-2,4,6-*trimethoxybenzoate* (35).—The oxime (34) (4.0 g) was dissolved in acetic anhydride (20 ml) and the solution heated under reflux for 2 h. The solution was then poured into water (200 ml) and the product left to crystallise. The product was filtered off, washed free of acetic acid, and dried to give the *benzoate* (35) (3.6 g, 96%) as crystals, m.p. 111—112° (Found: C, 57.8; H, 5.1; N, 5.9. $C_{12}H_{13}NO_5$ requires C, 57.4; H, 5.2; N, 5.6%), $\nu_{max.}$ 2 210, 1 710, and 1 600 cm^{-1}.

3-*Cyano*-2,4,6-*trimethoxybenzoic Acid* (39).—The ester (35) (3.1 g) was added to a solution of potassium hydroxide (6 g) in methanol (30 ml) and water (30 ml) and the mixture heated under reflux for 2 h. The resulting light yellow solution was acidified (pH *ca.* 2) with dilute HCl and extracted with ethyl acetate (3 × 60 ml). The extracts were combined, washed with water (2 × 100 ml), dried, and evaporated to give the *acid* (39) (2.6 g, 89%) as a white powder, m.p. 190—191° (Found: C, 55.5; H, 4.7; N, 5.7. $C_{11}H_{11}NO_5$ requires C, 55.7; H, 4.7; N, 5.9%), M^+ 237, $\nu_{max.}$ 3 300—2 500, 2 215, and 1 700 cm^{-1}.

Methyl 2-(3-*Cyano*-2,4,6-*trimethoxybenzoyl*)-3,5-*dimethoxyphenylacetate* (3).—Trifluoroacetic anhydride (25.2 g, 0.12 mol) was added to a stirred suspension of 3-cyano-2,4,6-trimethoxybenzoic acid (39) (26 g, 0.11 mol) in nitromethane (100 ml). After all the solid had dissolved the solution was cooled to −10 °C, a solution of methyl 3,5-dimethoxyphenylacetate (14.7 g, 0.07 mol) in nitromethane (10 ml) was added, and stirring was continued at this temperature for 70 min. The solution was then poured into aqueous 10% potassium hydrogen carbonate (400 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 200 ml); the combined organic layers were washed with water (2 × 300 ml), dried, and evaporated to give a red gum (*ca.* 40 g). Column chromatography [silica (700); ethyl acetate–chlorform (1 : 1)] gave the *phenylacetate* (3) (19.1 g, 63%) as crystals, m.p. (from ethyl acetate–ether) 167—167.5° (Found: C, 61.4; H, 5.3; N, 3.35. $C_{22}H_{23}NO_8$ requires C, 61.5; H, 5.4; N, 3.3%), M^+ 429, $\nu_{max.}$ 2 225, 1 740, and 1 660 cm^{-1}, τ 3.48 (1 H, d, *J* 2.5 Hz, ArH), 3.61 (1 H, d, *J* 2.5 Hz, ArH), 3.79 (1 H, s, ArH), 6.02 (3 H, s, OMe), 6.15 (3 H, s, OMe), and 6.22 (11 H, m, 3 OMe and $ArCH_2CO_2R$).

Methyl 2-*Cyano*-9-*hydroxy*-1,3,6,8-*tetramethoxyanthracene*-10-*carboxylate* (5).—The benzophenone (3) (1.075 g, 2.5 mmol) was dissolved in dry DMF (20 ml) and treated, under nitrogen, with potassium t-butoxide (660 mg, 5 mmol). The resulting deep purple solution was stirred at 90 °C for 30 min, cooled, poured into 2M-HCl (180 ml), and extracted with chloroform (3 × 150 ml). The extracts were combined, washed with water (4 × 200 ml), dried, and evaporated, and the residue was recrystallised from dichloromethane–ethyl acetate to give the *anthrol* (5) (615 mg, 83%) as brown-yellow crystals, m.p. 224—226° (Found: C, 63.2; H, 4.7; N, 3.7. $C_{21}H_{19}NO_7$ requires C, 63.5; H, 4.8; N, 3.5%), M^+ 397, $\nu_{max.}$ 3 270, 2 220, and 1 710 cm^{-1}, τ −1.12 (1 H, s, exch. D_2O, ArOH), 3.22 (1 H, s, ArH), 3.33 (1 H, d, *J* 2 Hz, ArH), 3.63 (1 H, d, *J* 2 Hz, ArH), 5.86 (3 H, s, OMe), 5.89 (3 H, s, OMe), 5.92 (3 H, s, OMe), 6.04 (3 H, s, OMe), and 6.10 (3 H, s, OMe).

Cyclisation of the Benzophenone (9).—Potassium t-butoxide (168 mg, 1.5 mmol) was added to a stirred solution of the benzophenone (9) (386 mg, 0.76 mmol) in DMF (10 ml) to produce an immediate dark red solution. The mixture was stirred at 20 °C for 10 min and then poured into 2M-HCl (100 ml) to give a bright yellow precipitate. The suspension was extracted with ether (3 × 80 ml) and the extracts were washed with water (6 × 250 ml), dried, and evaporated to yield an orange gum (207 mg). This was separated into two fractions by column chromatography [silica (30 g)]. Elution with ether–light petroleum (b.p. 40—60 °C) (1 : 1) yielded the less polar material as a bright orange solid (48 mg), m.p. 152—187°, M^+ 417, $\nu_{max.}$ 3 330, 1 735, 1 680, 1 640, 1 625, 1 600, 1 585, and 1 535 cm^{-1}, $\lambda_{max.}$ 281, 300sh, 362sh, and 378 nm (log ε 4.65, 3.43, 3.57, and 3.73), τ −0.765 (0.7 H, s, ArOH), −0.72 (0.3 H, s, ArOH), 2.50 (0.3 H, s, ArH), 2.62 (0.7 H, s, ArH), 3.35 (1 H, d, *J* 2 Hz, ArH), 3.60 (1 H, d, *J* 2 Hz, ArH), 5.88 (3 H, s, OMe), 5.97 (3 H, s, OMe), 5.98 (6 H, s, 2 OMe), and 6.07 (3 H, s, OMe). This material was formulated as a mixture of methyl 9-hydroxy-1,3,6,8-tetramethoxy-2-nitroanthracene-4-carboxylate (41) and methyl 9-hydroxy-1,3,6,8-tetramethoxy-4-nitroanthracene-2-carboxylate (40). When the eluting solvent was changed to ether the more polar material was obtained as a bright yellow crystalline solid (119 mg), m.p. 165—187°, M^+ 475, $\nu_{max.}$ 1 740, 1 720, 1 685, 1 610, 1 585, 1 575, and 1 540 cm^{-1}, $\lambda_{max.}$ 244, 297, and 327 nm (log ε 4.27, 3.99, and 4.05), τ 3.39 (1 H, d, *J* 2 Hz, ArH), 3.49 (1 H, d, *J* 2 Hz, ArH), 4.86 (0.66 H, s, 10-H), 5.04 (0.33 H, s, 10-H), 5.91 (3 H, s, OMe), 5.98 (3 H, s, OMe), 6.02, 6.03, 6.05, and 6.06 (total 6 H, 2 OMe), 6.10 (3 H, s, OMe), and 6.36 and 6.39 (total 3 H, ratio 1 : 2, OMe). This material was formulated as a mixture of dimethyl 9,10-dihydro-1,3,6,8-tetramethoxy-4-nitro-9-oxoanthracene-2,-10-dicarboxylate (43) and dimethyl 9,10-dihydro-1,3,6,8-tetramethoxy-2-nitro-9-oxoanthracene-4,10-dicarboxylate (44), in the ratio 1 : 2.

Methyl 2-*Hydroxy*-4,6-*dimethoxybenzoate* (36).—A solution

of methyl 2,4,6-trimethoxybenzoate (263 g, 1.16 mol) in dichloromethane (2.4 l) was cooled to −70 °C and a solution of boron trichloride (150 g, 1.28 mol) in dichloromethane (300 ml) added slowly with stirring. The mixture was allowed to warm up to 20 °C then poured into a stirred solution of conc. HCl (200 ml) in water (2.1 l). The layers were separated and the aqueous layer extracted with dichloromethane (5 × 100 ml). The combined extracts were washed with water (5 × 250 ml), dried, and evaporated to give the phenol (36) as a light brown crystalline solid (246 g, 99%), m.p. 105—106.5° (lit.,[13] 105—106°).

Methyl 3-Formyl-2-hydroxy-4,6-dimethoxybenzoate (37).—Phosphoryl chloride (295 g, 1.92 mol) was added dropwise to stirred dimethylformamide (360 ml) at 0 °C. The cooling bath was removed and the phenol (36) (109.2 g, 0.51 mol) was added. The mixture was stirred at 20 °C for 18 h then poured into ice–water (9.0 l) and set aside for 1 h. The solid was filtered off, washed with water, and dried to yield the crude product (97.32 g). This was crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to give the pure *aldehyde* (37) (64.71 g, 52%), m.p. 130—132° (Found: C, 55.1; H, 5.0. $C_{11}H_{12}O_6$ requires C, 55.0; H, 5.0%), M^+ 240, $\nu_{max.}$ 1 715 and 1 630 cm^{-1}, τ −2.70 (1 H, s, ArOH), −0.07 (1 H, s, CHO), 4.03 (1 H, s, ArH), and 6.07 (9 H, s, 3 OMe).

Methyl 2-Ethoxy-3-formyl-4,6-dimethoxybenzoate (38).—A mixture of the phenol (37) (84.83 g, 0.35 mol), bromoethane (123.9 g, 1.14 mol), and anhydrous potassium carbonate (80 g, 0.58 mol) in dimethylformamide (800 ml) was stirred at 60 °C under reflux for 4 h. Further bromoethane (36.5 g, 0.33 mol) was added and the mixture stirred at 60 °C for a further 2.5 h. The mixture was then poured into ice–water (6.0 l) and the solid filtered off, washed with water, and dried to yield the *ethoxy-aldehyde* (38) (89.40 g, 94%), m.p. 118—118.5° (Found: C, 58.0; H, 6.0. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%), M^+ 268, $\nu_{max.}$ 1 735 and 1 680 cm^{-1}, τ −0.30 (1 H, s, CHO), 3.73 (1 H, s, ArH), 5.95 (2 H, q, *J* 6.5 Hz, OCH_2·CH$_3$), 6.07 (3 H, s, OMe), 6.11 (6 H, s, 2 OMe), and 8.67 (3 H, t, *J* 6.5 Hz, OCH$_2$·CH_3).

Methyl 2-Ethoxy-3-formyl-4,6-dimethoxy-5-nitrobenzoate (16).—The aldehyde (38) (100.0 g, 0.37 mol) was added with stirring to conc. H_2SO_4 (400 ml) at 0 °C. Potassium nitrate (80.0 g, 0.79 mol) was added gradually and the mixture stirred at 0 °C for 25 min, then poured into ice–water (2.0 l). The resulting bright yellow suspension was extracted with chloroform (3 × 500 ml) and the combined extracts were washed with water (3 × 500 ml), dried, and evaporated. The product was purified by column chromatography [silica (1.75 kg); ether–light petroleum (b.p. 40—60 °C) (1 : 1)] to give the *nitro-aldehyde* (16) (46.07 g, 40%) as a white crystalline solid, m.p. 60° (Found: C, 49.7; H, 4.7; N, 4.5. $C_{13}H_{15}NO_8$ requires C, 49.85; H, 4.8; N, 4.5%), M^+ 313, $\nu_{max.}$ 1 730, 1 690, 1 590, 1 550, and 1 540 cm^{-1}, τ −0.70 (1 H, s, CHO), 5.87 (2 H, q, *J* 6.5 Hz, OCH_2·CH$_3$), 6.00 and 6.03 (total 9 H, 3 OMe), and 8.60 (3 H, t, *J* 6.5 Hz, CH$_2$·CH_3).

Methyl Hydrogen-2-Ethoxy-4,6-dimethoxy-5-nitroisophthalate (17).—The acid (16) was synthesised by a similar procedure to that for the homologous acid (14). The *ethoxy-acid* (17) was obtained as a white crystalline solid, m.p. 66° (Found: C, 47.3; H, 4.6; N, 4.35. $C_{13}H_{15}NO_9$ requires C, 47.4; H, 4.6; N, 4.3%), M^+ 329, $\nu_{max.}$ 3 200br 1 735, 1 705, 1 600, 1 580, and 1 535 cm^{-1}, τ 0.73br (1 H, s, exch. D_2O, CO_2H), 5.80 (2 H, q, *J* 7 Hz, OCH_2·CH$_3$), 5.97 (3 H, s, OMe), 6.00 (6 H, s, 2 OMe), and 8.63 (3 H, t, *J* 7 Hz, CH$_2$·CH_3).

Methyl 3-Chloroformyl-2-ethoxy-4,6-dimethoxy-5-nitrobenzoate (18).—The acid (17) (32.90 g, 0.10 mol) was suspended in benzene (200 ml) and oxalyl chloride (19.0 g, 0.15 mol) was added. The mixture was stirred at 20 °C for 48 h and evaporated to dryness. The residue was dissolved in benzene and the solution evaporated to yield the acid chloride (18), which was used without further purification.

Methyl 2-(2-Ethoxy-4,6-dimethoxy-3-methoxycarbonyl-5-nitrobenzoyl)-3,5-dimethoxyphenylacetate (10).—A solution of the acid chloride (18) (34.77 g, 0.10 mol) and methyl 3,5-dimethoxyphenylacetate (21.00 g, 0.10 mol) in nitromethane (200 ml) was stirred at 0 °C and titanium tetrachloride (28.5 g, 0.15 mol) was added to give an immediate dark red colour. The mixture was stirred at 0 °C for 85 min and then poured into 5% sodium hydrogen carbonate solution (2.0 l). This solution was extracted with chloroform (3 × 1.0 l), acidified, and extracted again with chloroform (2 × 500 ml). The combined extracts containing acidic material were dried and evaporated to yield the acid (17) (9.97 g, 30%).

The chloroform extracts containing non-acidic material were washed with water (2 × 1.0 l), dried, and evaporated to leave a red gum (50.15 g). This was chromatographed [silica (1.90 kg); ether–light petroleum (b.p. 40—60 °C) (1 : 1; 14.0 l); ether (14.0 l)] to yield methyl 3,5-dimethoxyphenylacetate (2.98 g, 14%) and the *phenylacetate* (10), obtained as a white crystalline solid (26.62 g, 51%), m.p. 84° (Found: C, 55.2; H, 5.3; N, 2.9. $C_{24}H_{27}NO_{12}$ requires C, 55.3; H, 5.2; N, 2.7%), M^+ 521, $\nu_{max.}$ ($CHCl_3$) 1 740, 1 650, 1 600, 1 580, and 1 540 cm^{-1}, τ 3.54 (1 H, d, *J* 2 Hz, ArH), 3.65 (1 H, d, *J* 2 Hz, ArH), 6.08, 6.10, and 6.14 (10 H, 2 OMe, 2 CH$_2$), 6.20 (3 H, s, OMe), 6.26 (3 H, s, OMe), 6.30 (3 H, s, OMe), 6.42 (3 H, s, OMe), and 8.96 (3 H, t, *J* 7 Hz, CH$_2$·CH_3).

The more polar isomer, *methyl 4-(2-ethoxy-4,6-dimethoxy-3-methoxycarbonyl-5-nitrobenzoyl)-3,5-dimethoxyphenylacetate* (12) (2.28 g, 4%) was obtained as a gum, M^+ 521, τ 3.51 (2 H, s, 2 ArH), 6.08 and 6.10 (6 H, 2 OMe), 6.19, 6.27, and 6.28 (total 13 H, 3 OMe, 2 CH$_2$), 6.40 (3 H, s, OMe), and 8.90 (3 H, t, *J* 7 Hz, CH$_2$·CH_3).

Cyclisation of the Benzophenone (10).—Potassium t-butoxide (300 mg, 2.67 mmol) was added to a stirred solution of the benzophenone (10) (633 mg, 1.21 mmol) in dimethylformamide (25 ml) to give a dark red solution. The mixture was stirred at 20 °C for 12 min then poured into 2M-HCl (200 ml). The resulting bright yellow suspension was extracted with chloroform (2 × 100 ml) and the combined extracts were washed with water (5 × 200 ml), dried, and evaporated to an orange gum. Purification by column chromatography [silica (100 g); ether–light petroleum (b.p. 40—60 °C) (1 : 2; 300 ml); ether–light petroleum (b.p. 40—60 °C) (1 : 1; 1.67 l); ether–light petroleum (b.p. 40—60 °C) (2 : 1; 1.2 l); ether–light petroleum (b.p. 40—60 °C) (3 : 1; 1.0 l)] yielded four anthracenic products. *Methyl 1-ethoxy-9-hydroxy-3,6,8-trimethoxy-4-nitroanthracene-2-carboxylate* (42) was obtained as a red microcrystalline solid (41 mg, 8%), m.p. 167—169° (Found: M^+, 431.121 5. $C_{21}H_{21}NO_9$ requires *M*, 431.121 6), $\nu_{max.}$ ($CHCl_3$) 3 350, 1 735, 1 680, 1 630, 1 625, 1 600, 1 580, and 1 540 cm^{-1}, $\lambda_{max.}$ 280, 362sh, and 378 nm (log ε 4.74, 3.62, and 3.82), τ −0.72 (1 H, s, ArOH), 2.62 (1 H, s, ArH), 3.34 (1 H, d, *J* 2 Hz, ArH), 3.60 (1 H, d, *J* 2 Hz, ArH), 5.80 (2 H, q, *J*

[13] P. Holmes, D. E. White, and I. H. Wilson, *J. Chem. Soc.*, 1950, 2810.

7 Hz, $OCH_2{\cdot}CH_3$), 5.91 (3 H, s, OMe), 6.02 (3 H, s, OMe), 6.03 (3 H, s, OMe), 6.10 (3 H, s, OMe), and 8.55 (3 H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$).

Methyl 9-hydroxy-1,3,6,8-tetramethoxy-2-nitroanthracene-4-carboxylate (41) was obtained as an orange solid (85 mg, 17%), m.p. 172—175° (Found: M^+, 417.105 9. $C_{20}H_{19}NO_9$ requires *M*, 417.105 9), $\nu_{max.}$ 3 340, 1 735, 1 675, 1 640, 1 625, 1 600, 1 585, and 1 540 cm^{-1}, $\lambda_{max.}$ 281, 340sh, 362sh, and 378 nm (log ε 4.65, 3.43, 3.57, and 3.73), τ −0.78 (1 H, s, ArOH), 2.62 (1 H, s, ArH), 3.34 (1 H, d, *J* 2 Hz, ArH), 3.59 (1 H, d, *J* 2 Hz, ArH), 5.90 (3 H, s, OMe), 5.99 (3 H, s, OMe), 6.00 (3 H, s, OMe), and 6.10 (3 H, s, OMe).

Dimethyl 1-ethoxy-9,10-dihydro-3,6,8-trimethoxy-4-nitro-9-oxoanthracene-2,10-dicarboxylate (45) was obtained as a bright yellow solid (118 mg, 20%), m.p. 125—128° (Found: C, 56.4; H, 4.9; N, 2.8. $C_{23}H_{23}NO_{11}$ requires C, 56.4; H, 4.7; N, 2.9%), M^+ 489, $\nu_{max.}$ ($CHCl_3$) 1 750, 1 680, 1 610, 1 595, 1 590, and 1 545 cm^{-1}, $\lambda_{max.}$ 244, 295, and 327 nm (log ε 4.21, 3.98, and 4.03), τ 3.39 (1 H, d, *J* 2 Hz, ArH), 3.50 (1 H, d, *J* 2 Hz, ArH), 5.04 (1 H, s, 10-H), 5.75 (2 H, q, *J* 7 Hz, $OCH_2{\cdot}CH_3$), 6.00 (6 H, s, 2 OMe), 6.06 (3 H, s, OMe), 6.10 (3 H, s, OMe), 6.36 (3 H, s, OMe), and 8.48 (3 H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$).

Dimethyl 9,10-dihydro-1,3,6,8-tetramethoxy-2-nitro-9-oxoanthracene-4,10-dicarboxylate (44) was obtained as a bright yellow solid (236 mg, 41%), m.p. 155—159° (Found: C, 55.5; H, 4.5; N, 3.0. $C_{22}H_{21}NO_{11}$ requires C, 55.6; H, 4.5; N, 2.95%), M^+ 475, $\nu_{max.}$ 1 740, 1 735, 1 685, 1 605, 1 585, and 1 545 cm^{-1}, $\lambda_{max.}$ 246, 296, and 328 nm (log ε 4.25, 4.01, and 4.08), τ 3.40 (1 H, d, *J* 2 Hz, ArH), 3.51 (1 H, d, *J* 2 Hz, ArH), 4.88 (1 H, s, 10-H), 5.92 (3 H, s, OMe), 5.97 (3 H, s, OMe), 6.04 (3 H, s, OMe), 6.06 (3 H, s, OMe), 6.09 (3 H, s, OMe), and 6.38 (3 H, s, OMe).

2-(2,4-Dichlorobenzoyl)-3,5-dimethoxyphenylacetonitrile (47) *and 4-(2,4-Dichlorobenzoyl)-3,5-dimethoxyphenylacetonitrile* (49).—Titanium tetrachloride (15 ml) was added to a stirred solution of 3,5-dimethoxyphenylacetonitrile[14] (10.0 g, 58 mmol) and 2,4-dichlorobenzoyl chloride (13.0 g, 62 mmol) in dichloromethane (500 ml). The solution was stirred at room temperature for 5 h and poured into ice–water (500 g); the dichloromethane layer was separated, washed with water (2 × 500 ml), dried, and evaporated. The residue was pre-adsorbed from dichloromethane on silica and chromatographed over a silica column [500 g; hexane–ethyl acetate (3 : 1)]. The first material eluted was the *benzophenone* (47) (2.98 g, 18%), as prisms, m.p. (from methanol) 97—98° (Found: C, 58.25; H, 3.8; N, 4.1. $C_{17}H_{13}Cl_2NO_3$ requires C, 58.3; H, 3.7; N, 4.0%), $\nu_{max.}$ 2 250 and 1 645 cm^{-1}, τ 2.55—2.67 (3 H, m, ArH), 3.18 (1 H, d, *J* 2 Hz, ArH), 3.55 (1 H, d, *J* 2 Hz, ArH), 6.01 (2 H, s, $ArCH_2CN$), 6.06 (3 H, s, OMe), and 6.42 (3 H, s, OMe). Later fractions gave the *benzophenone* (49) (2.92 g, 18%) as prisms, m.p. (from methanol) 102—103° (Found: C, 58.2; H, 3.8; N, 4.0. $C_{17}H_{13}Cl_2NO_3$ requires C, 58.3; H, 3.8; N, 4.0%), $\nu_{max.}$ 2 250 and 1 675 cm^{-1}, τ 2.31—2.78 (3 H, m, ArH), 3.40 (2 H, s, ArH), 6.20 (2 H, s, $ArCH_2CN$), and 6.25 (6 H, s, 2 OMe).

6-Chloro-10-cyano-1,3-dimethoxyanthracen-9-ol (50).—The benzophenone (47) (350 mg, 1 mmol) in dry dimethylformamide (5 ml), under nitrogen, was treated with potassium t-butoxide (224 mg, 2 mmol) and the resulting red solution stirred at 100 °C for 20 min. The solution was then cooled, poured into M-HCl (100 ml), and extracted with dichloromethane (2 × 100 ml). The dichloromethane extracts were combined, washed with water (4 × 100 ml), dried, and evaporated, and the residue was recrystallised from dichloromethane–ethyl acetate to give the *anthrol* (50) (143 mg, 46%) as dark yellow needles, m.p. 249—250° (Found: C, 64.8; H, 3.9; N, 4.3. $C_{17}H_{12}ClNO_3$ requires C, 65.1; H, 3.9; N, 4.5%), M^+ 313/315, $\nu_{max.}$ 3 340, 2 200, 1 630, 1 615, 1 590, and 1 580 cm^{-1}, τ 1.73 (1 H, d, *J* 9 Hz, ArH), 1.91 (1 H, d, *J* 2 Hz, ArH), 2.71 (1 H, dd, *J* 9 and 2 Hz, ArH), 2.99 (1 H, d, *J* 2 Hz, ArH), 3.62 (1 H, d, *J* 2 Hz, ArH), 5.87 (3 H, s, OMe), and 6.01 (3 H, s, OMe).

Methyl 2-(2-Chloro-6-methoxybenzoyl)-3,5-dimethoxyphenylacetate (48).—2-Chloro-6-methoxybenzoic acid[15] (0.50 g, 2.68 mmol) was added to a stirred solution of methyl 3,5-dimethoxyphenylacetate (0.565 g, 2.68 mmol) in trifluoroacetic anhydride (10 ml) and dichloromethane (10 ml) at 0 °C. The mixture was stirred at 0 °C for 2.5 h and then poured into ice-cold 5% sodium hydrogen carbonate solution (300 ml) and extracted with dichloromethane (2 × 150 ml). The combined extracts were washed with water (250 ml), dried, and evaporated to yield an orange gum (0.555 mg). This was crystallised from ether–light petroleum (b.p. 40—60 °C) to give the *benzophenone* (48) (0.249 g, 25%) as a white crystalline solid, m.p. 105.5—106.5° (Found: C, 60.4; H, 5.1; Cl, 9.5. $C_{19}H_{19}ClO_6$ requires C, 60.2; H, 5.05; Cl, 9.4%), M^+ 378/380, $\nu_{max.}$ 1 745 and 1 670 cm^{-1}, τ 2.80—3.27 (3 H, m, 3 ArH), 3.51 (1 H, d, *J* 2 Hz, ArH), 3.67 (1 H, d, *J* 2 Hz, ArH), 6.16 (3 H, s, OMe), 6.20 (2 H, s, $ArCH_2{\cdot}CO_2Me$), 6.25 (3 H, s, OMe), 6.31 (3 H, s, OMe), and 6.52 (3 H, s, OMe).

Methyl 3-Bromo-2,6-dimethoxybenzoate (51).—Bromine (120.0 g, 0.75 mol) was added to a stirred solution of methyl 2,6-dimethoxybenzoate (147.15 g, 0.75 mol) in chloroform (1.15 l) over 5 h. The solution was evaporated to yield the bromo-ester (51) (204.32 g, 99%) as a white crystalline solid, m.p. 91—92.5° (lit.,[16] 81°) (Found: C, 43.8; H, 4.0; Br, 29.4. Calc. for $C_{10}H_{11}BrO_4$: C, 43.7; H, 4.0; Br, 29.05%), M^+ 274/276, $\nu_{max.}$ 1 737 cm^{-1}, τ 2.52 (1 H, d, *J* 9 Hz, ArH), 3.42 (1 H, d, *J* 9 Hz, ArH), 6.18 (3 H, s, OMe), 6.20 (3 H, s, OMe), and 6.27 (3 H, s, OMe).

Methyl 4-Amino-2,6-dimethoxybenzoate (52).—Sodium (1.91 g, 0.083 mol) was added in small pieces to a solution of iron(III) chloride (0.60 g) in liquid ammonia (1.1 l). The grey suspension was stirred and refluxed for 10 min and more sodium (61.6 g, 2.68 mol) was added in small pieces. The mixture was cooled to −70 °C and the bromo-ester (51) (204.32 g, 0.74 mol) was added. The suspension was stirred and refluxed for 1.5 h then cooled to −50 °C and ammonium chloride (191.6 g, 3.58 mol) added. The condenser was removed and the ammonia allowed to evaporate overnight. Ether (750 ml) and 2M-HCl (2.5 l) were added to the residue and stirred to dissolve the solid. Layers were separated and the aqueous solution washed with more ether (750 ml). The aqueous solution was stirred and cooled as 10M-sodium hydroxide solution (550 ml) was added to precipitate a light brown solid which was filtered off, washed with water, and dried. Crystallisation from ether–light petroleum (b.p. 40—60 °C) yielded the amine (52) as a white crystalline solid (139.61 g, 89%), m.p. 140—141° (lit.,[17] 143—144°) (Found: C, 56.8; H, 6.15; N, 6.7. Calc. for $C_{10}H_{13}NO_4$: C, 56.8; H, 6.2; N, 6.6%), M^+ 211; $\nu_{max.}$

[14] A. Bhati, *Tetrahedron*, 1962, **18**, 1519.
[15] T. P. C. Mulholland, R. I. W. Honeywood, H. D. Preston, and D. T. Rosevear, *J. Chem. Soc.*, 1965, 4939.
[16] F. P. Doyle, J. H. C. Nayler, H. R. J. Waddington, J. C. Hanson, and G. R. Thomas, *J. Chem. Soc.*, 1963, 497.
[17] W. J. Leanza, B. G. Christensen, E. F. Rogers, and A. A. Patchett, *Nature*, 1965, **207**, 1395.

3 460, 3 360, and 1 720 cm^{-1}, τ 4.05 (2 H, s, 2 ArH), 4.75br (2 H, s, exchanged D_2O, NH_2), and 6.43 (9 H, s, 3 OMe).

Methyl 4-Chloro-2,6-dimethoxybenzoate (53).—The amine (52) (139.61 g, 0.66 mol) was dissolved in conc. HCl (690 ml) and the solution stirred and cooled to 0 °C to precipitate the hydrochloride as a fine solid. A solution of sodium nitrite (51.0 g, 0.74 mol) in water (320 ml) was added over 15 min, with the temperature of the mixture kept below 2 °C. The solution was stirred at 0 °C for a further 45 min, then added over 25 min at 0 °C to a stirred solution of copper(I) chloride [from copper(II) sulphate (231.0 g, 0.925 mol)] in conc. HCl (315 ml), covered with ether (300 ml). More ether (210 ml) was added during the addition, to prevent excessive frothing. The mixture was allowed to warm to 20 °C and stirred for a further 2 h. It was then poured into water (2.2 l) and the layers were separated. The aqueous solution was extracted with ether (3 × 1.5 l) and the combined extracts were washed with water (3 × 1.5 l), dried, and evaporated to yield the *product* (53) (119.28 g, 78%) as a pale yellow crystalline solid, m.p. 78° (Found: C, 52.1; H, 4.8; Cl, 15.2. $C_{10}H_{11}ClO_4$ requires C, 52.1; H, 4.8; Cl, 15.4%), M^+ 230/232, $\nu_{max.}$ 1 743 cm^{-1}, τ 3.40 (2 H, s, 2 ArH), 6.10 (3 H, s, OMe), and 6.18 (6 H, s, 2 OMe).

Methyl 4-Chloro-2-hydroxy-6-methoxybenzoate (54).—A solution of boron trichloride (67.2 g, 0.57 mol) in dichloromethane (350 ml) was added over 40 min to a stirred solution of methyl 4-chloro-2,6-dimethoxybenzoate (53) (119.28 g, 0.52 mol) in dichloromethane (1.175 l) at −70 °C. The cooling bath was removed and the mixture stirred for 2.5 h, forming a thick precipitate. 2M-Hydrochloric acid (170 ml) was added gradually over 1 h and the mixture poured into further 2M-HCl (400 ml). Layers were separated and the organic solution was washed with water (3 × 800 ml), dried, and evaporated to yield the *phenol* (54) (110.90 g, 99%) as a cream solid, m.p. (from ether–light petroleum) 82—82.5° (Found: C, 50.1; H, 4.2; Cl, 16.3. $C_9H_9ClO_4$ requires C, 49.9; H, 4.2; Cl, 16.4%), M^+ 216/218, $\nu_{max.}$ 3 500—2 500, 1 660, 1 610, and 1 580 cm^{-1}, τ −1.17 (1 H, s, ArOH), 3.33 (1 H, d, *J* 2 Hz, ArH), 3.55 (1 H, d, *J* 2 Hz, ArH), 6.03 (3 H, s, OMe), and 6.08 (3 H, s, OMe).

Methyl 4-Chloro-3-formyl-2-hydroxy-6-methoxybenzoate (55).—Titanium tetrachloride (195.0 g, 1.03 mol) was added to a stirred solution of the phenol (54) (110.90 g, 0.51 mol) in dichloromethane (2.0 l) over 45 min at 20 °C. The solution was cooled to −7 °C and 1,1-dichloromethyl methyl ether (88.5 g, 0.77 mol) was added over 10 min. The mixture was stirred at 2—5 °C for 18 h and then 2M-HCl (330 ml) was added slowly. The resulting mixture was poured into 2M-HCl (1.3 l) and the layers were separated. The organic solution was washed with 2M-HCl (2 × 800 ml) and water (3 × 800 ml), dried, and evaporated to give the *aldehyde* (55) (113.65 g, 91%) as a pale yellow solid, m.p. 99—100° (Found: C, 49.1; H, 3.9; Cl, 14.5. $C_{10}H_9ClO_5$ requires C, 49.1; H, 3.7; Cl, 14.5%), M^+ 244/246, $\nu_{max.}$ 1 740 and 1 700 cm^{-1}, τ −2.45 (1 H, s, ArOH), −0.16 (1 H, s, CHO), 3.26 (1 H, s, ArH), and 6.06 (6 H, s, 2 OMe).

Methyl 4-Chloro-3-formyl-2-hydroxy-6-methoxy-5-nitrobenzoate (56).—Conc. H_2SO_4 (1.64 l) was stirred and cooled to −6 °C. The aldehyde (55) (37.88 g, 0.15 mol) was added over 15 min. Powdered sodium nitrate (26.57 g, 0.31 mol) was added over 15 min The mixture was stirred at 0 °C for 30 min, and was then allowed to warm up to 20 °C and stirred for a further 40 min. It was poured slowly into ice–water (6.3 l) and the resulting bright yellow suspension was extracted with chloroform (3 × 500 ml). The combined extracts were washed with water (3 × 1.0 l), dried, and evaporated to a dark orange gum (39.94 g). This was crystallised from ether to yield the *product* (56) (17.48 g, 39%) as a yellow crystalline solid, m.p. 97—98° (Found: C, 41.5; H, 2.7; Cl, 12.0; N, 4.9. $C_{10}H_8ClNO_7$ requires C, 41.5; H, 2.8; Cl, 12.25; N, 4.8%), M^+ 289/291, $\nu_{max.}$ 1 750, 1 680, 1 655, 1 610, 1 580, and 1 560 cm^{-1}, τ −2.90 (1 H, s, ArOH), −0.30 (1 H, s, CHO), 5.97 (3 H, s, OMe), and 6.00 (3 H, s, OMe).

Methyl 4-Chloro-3-formyl-2,6-dimethoxy-5-nitrobenzoate (57).—A mixture containing the phenol (56) (52.44 g, 0.15 mol), anhydrous potassium carbonate (96.7 g, 0.70 mol), and dimethyl sulphate (36.2 g, 0.29 mol) in dry acetone (4.5 l) was stirred under reflux for 4.5 h. The mixture was cooled and filtered, and the filtrate evaporated to yield the *product* (57) (42.33 g, 77%) as a pale yellow solid, m.p. 92° (Found: C, 43.6; H, 3.3; Cl, 11.45; N, 4.4. $C_{11}H_{10}ClNO_7$ requires C, 43.5; H, 3.3; Cl, 11.7; N, 4.6%), M^+ 303/305, $\nu_{max.}$ 1 750, 1 715, 1 590, and 1 560 cm^{-1}, τ −0.43 (1 H, s, CHO) and 6.28 (9 H, s, 3 OMe).

Methyl Hydrogen 2-Chloro-4,6-dimethoxy-5-nitroisophthalate (58).—The acid (58) was synthesised by a similar procedure to that employed for the acid (14). The *chloro-acid* (58) was obtained as a pale yellow oil which crystallised, m.p. (from ether–light petroleum) 102° (Found: C, 41.2; H, 3.1; Cl, 10.85; N, 4.2. $C_{11}H_{10}ClNO_8$ requires C, 41.3; H, 3.15; Cl, 11.1; N, 4.4%), M^+ 319/321, $\nu_{max.}$ ($CHCl_3$) 3 400—2 400, 1 745, 1 735, 1 590, 1 570, and 1 555 cm^{-1}, τ 1.45br (1 H, s, CO_2H), 5.97 (3 H, s, OMe), and 5.98 (6 H, s, 2 OMe).

Methyl 4-Chloro-3-chloroformyl-2,6-dimethoxy-5-nitrobenzoate (59).—A suspension of the acid (58) (19.18 g, 60 mmol) in oxalyl chloride (22.71 g, 179 mmol) and benzene (120 ml) was stirred and refluxed for 18 h. The solution was evaporated to dryness, and the residue was dissolved in benzene. This solution was evaporated to give the acid chloride (59) as a brown gum which was used without further purification.

Methyl 2-(2-Chloro-4,6-dimethoxy-3-methoxycarbonyl-5-nitrobenzoyl)-3,5-dimethoxyphenylacetate (60).—Titanium tetrachloride (25.0 g, 130 mol) was added to a stirred solution of the acid chloride (59) (20.3 g, 60 mmol) and methyl 3,5-dimethoxyphenylacetate (12.6 g, 60 mmol) in nitromethane (240 ml) at 0 °C. The dark red solution was stirred at 0 °C for 1 h then poured into 5% sodium hydrogen carbonate solution (1.5 l). The mixture was extracted with dichloromethane (3 × 500 ml) and the combined extracts were washed with water (2 × 1 l), dried, and evaporated to yield an orange solid (29.90 g). Column chromatography [silica (2.0 kg); ether–light petroleum (b.p. 40—60 °C) (1 : 1)] yielded the *benzophenone* (60) (15.44 g, 50%) as a white crystalline solid, m.p. 109° (Found: C, 51.8; H, 4.3; Cl, 7.0; N, 2.6. $C_{22}H_{22}ClNO_{11}$ requires C, 51.6; H, 4.3; Cl, 7.0; N, 2.7%), M^+ 511/513, $\nu_{max.}$ 1 740, 1 660, 1 600, 1 560 cm^{-1}, τ 3.32 (1 H, d, *J* 2 Hz, ArH), 3.65 (1 H, d, *J* 2 Hz, ArH), 6.05 (3 H, s, OMe), 6.06 (3 H, s, OMe), 6.14 (5 H, s, OMe, $ArCH_2{\cdot}CO_2Me$), 6.26 (3 H, s, OMe), 6.32 (3 H, s, OMe), and 6.42 (3 H, s, OMe).

Dimethyl 9,10-Dihydro-1,3,6,8-tetramethoxy-4-nitro-9-oxoanthracene-2,10-dicarboxylate (43).—Potassium t-butoxide (0.544 g, 4.8 mmol) was added to a solution of the benzophenone (60) (1.087 g, 2.1 mmol) in dimethylformamide (11 ml.). The dark red solution was stirred at 20 °C for 25 min, then poured into stirred 2M-HCl (170 ml). The bright yellow suspension was extracted with chloroform (2 × 200

ml) and the combined extracts were washed with water (6 × 200 ml), dried, and evaporated. The crude product was purified by column chromatography [silica (117 g); ether–light petroleum (b.p. 40—60 °C) (1 : 1)] to yield the pure *anthrone* (43) (0.754 g, 75%) as bright yellow crystals, m.p. 163—164° (Found: C, 55.4; H, 4.4; N, 2.9. $C_{22}H_{21}NO_{11}$ requires C, 55.6; H, 4.45; N, 2.95%), M^+ 475, $\nu_{max.}$ ($CHCl_3$) 1 750, 1 685, 1 610, 1 600, 1 590, and 1 545 cm^{-1}, $\lambda_{max.}$ 244, 299, and 328 nm (log ε 4.25, 3.99, and 4.09), τ 3.38 (1 H, d, *J* 2 Hz, ArH), 3.48 (1 H, d, *J* 2 Hz, ArH), 5.04 (1 H, s, 10-H), 5.95 (3 H, s, OMe), 6.02 (3 H, s, OMe), 6.03 (3 H, s, OMe), 6.07 (3 H, s, OMe), 6.10 (3 H, s, OMe), and 6.36 (3 H, s, OMe).

6-Benzyloxy-8-methoxy-5-methyl-2-trifluoroacetyl-1-(2,4,6-trimethoxy-3-methoxycarbonylphenyl)isoquinolin-3-one (61).—Trifluoroacetic anhydride (9 ml) was added to a solution of 3-benzyloxy-5-methoxy-2-methylphenylacetonitrile (28) (2.67 g, 10 mmol) and 1-methyl hydrogen 2,4,6-trimethoxyisophthalate (2.70 g, 10 mmol) in dry nitromethane (10 ml). The deep red solution was stirred at 20 °C for 75 min, poured into aqueous 5% potassium hydrogen carbonate (300 ml), and extracted with chloroform (3 × 100 ml). The extracts were combined, washed with water (2 × 100 ml), dried, and evaporated to give a dark red gum. Column chromatography [silica (50 g); ethyl acetate–chloroform (1 : 1)] gave the *nitrile* (28) (1.5 g), followed by the benzophenone (21) (1.32 g, 25%) as prisms, m.p. (from ethyl acetate) 169—170°. Later fractions gave the *isoquinolin-3-one* (61) as red prisms (0.65 g, 10.5%), m.p. (from ethyl acetate) 220—222° (Found: C, 60.3; H, 4.4; N, 2.2. $C_{31}H_{28}F_3NO_9$ requires C, 60.5; H, 4.6; N, 2.3%), M^+ 615, $\nu_{max.}$ 1 745, 1 640, 1 610, and 1 595 cm^{-1}, $\lambda_{max.}$ 290, 342.5, 358, and 501 nm (log ε 4.66, 4.14, 4.16, and 4.11), τ 1.65 (1 H, s, ArH), 2.59 (5 H, s, ArH), 3.60 (1 H, s, ArH), 3.72 (1 H, s, ArH), 4.68 (2 H, s, OCH_2Ar), 6.08 (3 H, s, OMe), 6.12 (3 H, s, OMe), 6.28 (3 H, s, OMe), 6.38 (3 H, s, OMe), 6.44 (3 H, s, OMe), and 7.68 (3 H, s, ArMe).

1-(2,6-Dimethoxy-4-methylphenyl)-6,8-dimethoxy-2-trifluoroacetylisoquinolin-3-one (63).—2-(2,6-Dimethoxy-4-methylbenzoyl)-3,5-dimethoxyphenylacetonitrile [4] (2.0 g) in dichloromethane (40 ml) was treated with trifluoroacetic anhydride (20 ml) and the orange solution was stirred at room temperature, under nitrogen, for 2 days. The solution was then poured into aqueous 10% potassium hydrogen carbonate (200 ml) and extracted with dichloromethane (3 × 75 ml). The combined extracts were washed with water, dried, and evaporated to give an orange residue, which was recrystallised from dichloromethane–ethyl acetate to give the *isoquinolin-3-one* (63) (1.41 g, 55%) as orange crystals, m.p. 283—284° (Found: C, 58.5; H, 4.3; N, 3.1. $C_{22}H_{20}F_3NO_6$ requires C, 58.5; H, 4.5; N, 3.1%), M^+ 451, $\nu_{max.}$ 1 645, 1 615, 1 595, and 1 585 cm^{-1}, $\lambda_{max.}$ (EtOH) 285, 338, and 458 nm (log ε 4.54, 3.86, and 3.93), τ [$CDCl_3$–$(CD_3)_2SO$] 1.87 (1 H, s, ArH), 3.37 (1 H, d, *J* 2 Hz, ArH), 3.53 (2 H, s, ArH), 3.78 (1 H, d, *J* 2 Hz, ArH), 5.97 (3 H, s, OMe), 6.26 (6 H, s, OMe), 6.41 (3 H, s, OMe), and 7.56 (3 H, s, ArMe).

6,8-Dimethoxy-2-trifluoroacetyl-1-(2,4,6-trimethoxy-3-methoxycarbonylphenyl)-2-isoquinolin-3-one (62).—3,5-Dimethoxy-2-(2,4,6-trimethoxy-3-methoxycarbonylbenzoyl)phenylacetonitrile (1) (22.0 g) in dichloromethane (200 ml) was treated with trifluoroacetic anhydride (40 ml) and the orange solution was kept at room temperature for 9 days. The solution was then poured into aqueous 10% potassium hydrogen carbonate (500 ml) and the product extracted with dichloromethane (3 × 200 ml). The combined extracts were washed with water, dried, and evaporated. The orange residue was recrystallised from dichloromethane–ethyl acetate to give the *isoquinolin-3-one* (62) (5.8 g, 21%) as orange crystals, m.p. 254—255° (Found: C, 54.8; H, 4.1; N, 2.6. $C_{24}H_{22}F_3NO_9$ requires C, 54.9; H, 4.2; N, 2.7%), M^+ 525, $\nu_{max.}$ 1 735, 1 650, 1 625, 1 610, and 1 600 cm^{-1}, $\lambda_{max.}$ 287, 328, and 464 nm (log ε 4.68, 4.04, and 4.10), τ 1.80 (1 H, s, ArH), 3.55 (1 H, d, *J* 2 Hz, ArH), 3.72 (1 H, s, ArH), 3.89 (1 H, d, *J* 2.5 Hz, ArH), 6.01 (3 H, s, OMe), 6.09 (3 H, s, OMe), 6.11 (3 H, s, OMe), 6.23 (3 H, s, OMe), 6.36 (3 H, s, OMe), and 6.40 (3 H, s, OMe).

6,8-Dimethoxy-1-(2,4,6-trimethoxy-3-methoxycarbonylphenyl)isoquinolin-3-one (66).—Methanol (90 ml) and aqueous ammonia (2M; 90 ml) were added to a stirred solution of the isoquinolin-3-one (62) (1.78 g) in dichloromethane (100 ml). After 2.5 h the dichloromethane layer was separated, washed with water (2 × 50 ml), dried, and evaporated. The residue was recrystallised from dichloromethane–ethyl acetate to give the *isoquinolin-3-one* (66) (1.05 g, 61%) as yellow needles, m.p. 251—253° (Found: C, 61.3; H, 5.5; N, 3.3. $C_{22}H_{23}NO_8$ requires C, 61.5; H, 5.4; N, 3.3%), M^+ 429, $\nu_{max.}$ 1 735, 1 645, 1 630, 1 610, 1 590, and 1580 cm^{-1}, $\lambda_{max.}$ 254 and 415 nm (log ε 3.76 and 4.69), τ 3.45 (1 H, s, ArH), 3.73 (1 H, s, ArH), 3.80 (1 H, d, *J* 2 Hz, ArH), 4.14 (1 H, d, *J* 2 Hz, ArH), 6.09 (3 H, s, OMe), 6.11 (3 H, s, OMe), 6.13 (3 H, s, OMe), 6.29 (3 H, s, OMe), 6.50 (3 H, s, OMe), and 6.57 (3 H, s, OMe).

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