Synthesis of Methyl Tri-*O*-methylptilometrate (Methyl 1,6,8-Trimethoxy-3-propylanthraquinone-2-carboxylate)

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A synthesis of the fully *O*-methylated derivative (methyl 1,6,8-trimethoxy-3-propylanthraquinone-2-carboxylate) (2) of the crinoid pigment ptilometric acid is described.

MOST of the quinonoid pigments of marine animals are naphthoquinones but a few crinoids have been shown to produce anthraquinonoid pigments.[1-4] Ptilometric acid (1) is such a pigment which is produced by the crinoids *Ptilometra australis* Wilton and *Tropiometra afra* Hartlaub.[3] We now describe the synthesis of the fully *O*-methylated derivative of ptilometric acid, methyl 1,6,8-trimethoxy-3-propylanthraquinone-2-carboxylate (2).

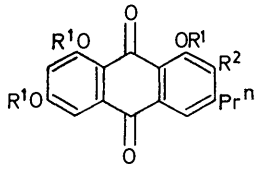
We decided to attempt the synthesis of the ester (2) by nucleophilic displacement of bromide with cyanide from 2-bromo-1,6,8-trimethoxy-3-propylanthraquinone (3) followed by hydrolysis and esterification. Before attempting the synthesis of the bromo-compound (3) we investigated the synthesis of the methyl analogue (6).

It is known that bromination of the benzoylbenzoic acid (11) gives the monobromo-compound (12).[5,6] Anslow and Raistrick claimed that dibromination of the acid (11) probably gave the dibromo-compound (13).[5] We re-investigated this work by brominating the acid (11) and then ring-closing the products to anthraquinones which were *O*-methylated and separated by chromatography. The major dibromo-anthraquinone isolated was the 4,5-isomer (9). Under certain conditions a low yield of the required 2,4-isomer (8) could be secured; this was also accompanied by 4-bromo- (7) and 2,4,5-tribromo-1,6,8-trimethoxy-3-methylanthraquinone (10). It was hoped that α-bromo-substituents could be selectively removed from the anthraquinone nucleus in the presence of β-bromo-substituents by analogy with the chloroanthraquinones.[7] Attempts to remove selectively the α-bromo-substituents from compounds (8) and (10) and thus obtain the required bromo-compound (6) were unsuccessful.

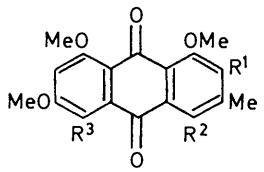
A recent synthesis of anthraquinones by the cyclisation of carbanions of *ortho*-substituted benzophenones has met with some success.[8] This approach to compound

[1] M. D. Sutherland and J. W. Wells, *Austral. J. Chem.*, 1967, **20**, 515.
[2] V. H. Powell, M. D. Sutherland and J. W. Wells, *Austral. J. Chem.*, 1967, **20**, 535.
[3] V. H. Powell and M. D. Sutherland, *Austral. J. Chem.*, 1967, **20**, 541.
[4] T. R. Erdman and R. H. Thomson, *J.C.S. Perkin I*, 1972, 1291.
[5] W. K. Anslow and H. Raistrick, *Biochem. J.*, 1941, **35**, 1006.
[6] H. Brockmann, F. Kluge, and H. Muxfeldt, *Chem. Ber.*, 1957, **90**, 2302.
[7] M. V. Sargent, D.O'N Smith, and J. A. Elix, *J. Chem. Soc.* (*C*), 1970, 307; J. K. K. Lam, M. V. Sargent, J. A. Elix, and D. O'N. Smith, *J.C.S. Perkin I*, 1972, 1466.
[8] J. S. Davies, V. H. Davies, and C. H. Hassall, *J. Chem. Soc.* (*C*), 1969, 1873; C. H. Hassall and B. A. Morgan, *Chem. Comm.*, 1970, 1345; G. M. Holmwood and J. C. Roberts, *J. Chem. Soc.* (*C*), 1971, 3899.

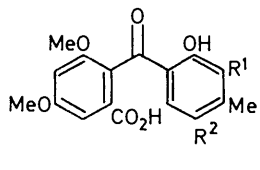
(6) was therefore investigated. Methyl 2,6-dimethoxy-4-methylbenzoate (14) on bromination gave methyl 3-bromo-2,6-dimethoxy-4-methylbenzoate (15) which was converted into the chloride (17) by way of the acid (16). Friedel–Crafts condensation of the chloride (17) with 3,5-dimethoxyphenylacetonitrile (18) gave the benzophenone (19) in moderate yield. This smoothly underwent base catalysed ring-closure and subsequent oxidation, and gave the required bromo-compound (6) as well as the isomer (7) which was identical with that synthesised previously (see above).



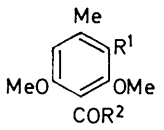
(1) $R^1 = H$, $R^2 = CO_2H$
(2) $R^1 = Me$, $R^2 = CO_2Me$
(3) $R^1 = Me$, $R^2 = Br$
(4) $R^1 = Me$, $R^2 = CN$
(5) $R^1 = Me$, $R^2 = H$



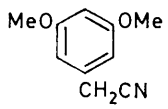
(6) $R^1 = Br$, $R^2 = R^3 = H$
(7) $R^1 = R^3 = H$, $R^2 = Br$
(8) $R^1 = R^2 = Br$, $R^3 = H$
(9) $R^1 = H$, $R^2 = R^3 = Br$
(10) $R^1 = R^2 = R^3 = Br$



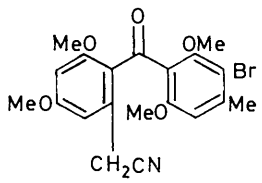
(11) $R^1 = R^2 = H$
(12) $R^1 = H$, $R^2 = Br$
(13) $R^1 = R^2 = Br$



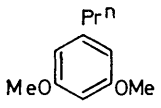
(14) $R^1 = H$, $R^2 = OMe$
(15) $R^1 = Br$, $R^2 = OMe$
(16) $R^1 = Br$, $R^2 = OH$
(17) $R^1 = Br$, $R^2 = Cl$



(18)

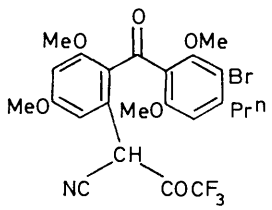


(19)



(20)

(21) $R^1 = H$, $R^2 = OH$
(22) $R^1 = H$, $R^2 = OMe$
(23) $R^1 = Br$, $R^2 = OMe$
(24) $R^1 = Br$, $R^2 = OH$
(25) $R^1 = Br$, $R^2 = Cl$



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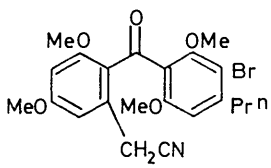

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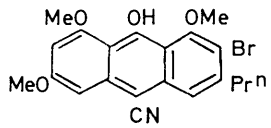

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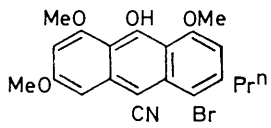

(29)

The only condensation product isolated, however, was the trifluoroacetyl compound (26) which must have arisen by an acid catalysed aldol type reaction between the imino-tautomer of the phenylacetonitrile (27) and trifluoroacetic anhydride. When the acid chloride (25) was condensed with 3,5-dimethoxyphenylacetonitrile (18) with titanium(IV) chloride as catalyst the required benzophenone (27) was obtained in 44% yield.

The benzophenone (27) underwent smooth base

This on bromination gave the bromo-compound (23) which was hydrolysed to the acid (24). In an attempt to improve the yield in the Friedel–Crafts reaction the acid (24) was condensed with 3,5-dimethoxyphenylacetonitrile (18) in the presence of trifluoroacetic anhydride.[9]

[9] J. B. Hendrickson, M. V. J. Ramsay, and T. R. Kelly, *J. Amer. Chem. Soc.*, 1972, **94**, 6834.

catalysed ring-closure and yielded the anthrols (28) and (29) which were readily distinguished on the grounds of their n.m.r. spectra. The anthrol (28) on oxidation in alkaline hydrogen peroxide gave the bromo-anthraquinone (3). This on reaction in boiling *NN*-dimethylformamide with copper(I) cyanide followed by methylation, gave the nitrile (4). A minor product of this reaction was the known 1,6,8-trimethoxy-3-propylanthraquinone (5). Hydrolysis of the nitrile (4) followed by methylation then gave methyl tri-*O*-methylptilometrate (2) which was identical with the natural derivative.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. Silica gel was B.D.H. 60—120 mesh material. Plates (20 × 20 × 0·1 cm) for p.l.c. were Merck Kieselgel GF_{254}. Light petroleum was a fraction b.p. 58—65°. N.m.r. spectra were determined at 60 MHz using a Varian A60-A spectrometer for deuteriochloroform solutions unless stated otherwise. Mass spectra were determined using a Varian MAT CH7 spectrometer operating at 70 eV.

2-(2-*Hydroxy*-4-*methylbenzoyl*)-3,5-*dimethoxybenzoic Acid* (11).—This was prepared by the method of Brockmann *et al.*,[6] as prisms from methanol, m.p. 233—234° (lit.,[6] 233°).

Bromination and Ring-closure of the Benzoylbenzoic Acid (11).—(*a*) This experiment was modelled on that of Anslow and Raistrick.[5] The benzoylbenzoic acid (11) (4·0 g) in acetic acid (150 ml) was stirred and treated at 50° with a solution of bromine (4·3 g) in acetic acid (43 ml). The mixture was stirred at 50° for 2 h and the solvent was then removed under reduced pressure. The residue was crystallised twice from ethanol to give a pale yellow crystalline solid (4·7 g), m.p. 217—270°. This solid (505 mg) and boric oxide (2·7 g) were stirred in oleum [15 ml, prepared from concentrated sulphuric acid (2 parts) and 20% oleum (1 part)] at 90° for 15 min. The mixture was poured on ice (100 g) and the red precipitate was washed well with water and dried *in vacuo*. This material was methylated with methyl sulphate and potassium carbonate in acetone in the usual way. The crude product was separated by p.l.c. (3 plates, 30% ethyl acetate–benzene). The faster band gave 4-bromo-1,6,8-trimethoxy-3-methylanthraquinone (7) (197 mg), as yellow needles, m.p. 230—231° (lit.,[6] 234°) (from methanol), *m/e* 392/390 (M^+), τ 2·80 and 3·28 (2H, ABq, *J* 2·5 Hz, 7- and 5-H), 2·83 (1H, s, 2-H), 6·02, 6·04, and 6·06 (each 3H, s, OMe), and 7·45 (3H, s, Me). The slower band yielded 4,5-*dibromo*-1,6,8-*trimethoxy*-3-*methylanthraquinone* (9) (76 mg) which crystallised from chloroform–methanol as golden-yellow prisms, m.p. 239·5—241° (Found: Br, 33·7%; M^+, 472/470/468. $C_{18}H_{14}Br_2O_5$ requires Br, 34·0%; *M*, 472/470/468), τ 2·94 (1H, s, 2-H), 3·34 (1H, s, 7-H), 6·01 (6H, s, 2 OMe), 6·05 (3H, s, OMe), and 7·47 (3H, s, Me).

(*b*) The foregoing partially brominated benzoylbenzoic acid (4·14 g) in acetic acid (120 ml) was treated at 50° with bromine (2·1 g) in acetic acid (21 ml) and the mixture was stirred for 3 h. The solvent was removed under reduced pressure and the residue crystallised from ethanol to afford yellow prisms (3·46 g), m.p. 210—275°. This material (3·4 g) and boric oxide (19 g) were stirred in oleum (105 ml) as before. The crude product obtained after methylation was chromatographed over silica gel (800 g) by gradient elution using ethyl acetate–benzene. The first material eluted was 2,4-*dibromo*-1,6,8-*trimethoxy*-3-*methylanthraquinone* (8) (133 mg), as yellow needles (from chloroform–methanol), m.p. 219·5—221° (Found: C, 45·95; H, 3·65; Br, 34·0%; M^+, 472/470/468. $C_{18}H_{15}Br_2O_5$ requires C, 46·0; H, 3·0; Br, 34·0%; *M*, 472/470/468), τ 2·83 and 3·28 (2H, ABq, *J* 2·5 Hz, 5- and 7-H), 5·96, 6·03, and 6·04 (each 3H, s, OMe), and 7·20 (3H, s, Me). This was followed by 2,4,5-*tribromo*-1,6,8-*trimethoxy*-3-*methylanthraquinone* (10) (806 mg), as yellow prisms (from chloroform–methanol), m.p. 225—226° (Found: C, 39·55; H, 2·8; Br, 43·5. $C_{18}H_{13}Br_3O_5$ requires C, 39·4; H, 2·4; Br, 43·65%), τ 3·31 (1H, s, 7-H), 5·97 (9H, s, OMe), and 7·23 (3H, s, Me). This was followed by 4-bromo-1,6,8-trimethoxy-3-methylanthraquinone (7) (382 mg) and 4,5-dibromo-1,6,8-trimethoxy-3-methylanthraquinone (9) (1·04 g).

Methyl 2,6-*Dimethoxy*-4-*methylbenzoate* (14).—2,6-Dimethoxy-4-methylbenzoic acid was prepared by the method of Ridley *et al.*[10] It formed plates, m.p. 187—190° (lit.,[11] 179—180°), from aqueous methanol. This acid (36·6 g) and potassium carbonate (110 g) in acetone (1·2 l) were stirred and treated dropwise with methyl sulphate (31 ml). After the addition the mixture was stirred at room temperature for 15 h and then under reflux for 2 h. Work-up in the usual way gave the product (38·4 g, 98%) which formed prisms from dichloromethane–light petroleum, m.p. 79—81° (lit.,[11] 86°), τ 3·62 (2H, s, ArH), 6·14 (3H, s, CO_2Me), 6·23 (6H, s, OMe), and 7·65 (3H, s, Me).

Methyl 3-*Bromo*-2,6-*dimethoxy*-4-*methylbenzoate* (15).—A solution of the foregoing methyl ester (14) (6·43 g) and anhydrous sodium acetate (20 g) in acetic acid (100 ml) was stirred at room temperature during the rapid dropwise addition of bromine (4·91 g) in acetic acid (25 ml). After the addition the mixture was stirred for 2·5 min longer and then poured onto ice–water. The mixture was extracted with dichloromethane and the extract was washed in turn with water, saturated sodium hydrogen carbonate solution until effervescence ceased, water, and finally dried (Na_2SO_4). The residue left on removal of the solvent was crystallised from ether–light petroleum and gave the ester (15) (8·60 g, 97%), as prisms, m.p. 84—85° (lit.,[12] 89°) (Found: C, 45·5; H, 4·65; Br, 27·25. Calc. for $C_{11}H_{13}BrO_4$: C, 45·65; H, 4·55; Br, 27·65%), τ 3·37 (1H, s, ArH), 6·11, 6·15, and 6·22 (each 3H, s, OMe), and 7·61 (3H, s, Me).

3-*Bromo*-2,6-*dimethoxy*-4-*methylbenzoic Acid* (16).—The foregoing ester (15) (6·3 g) and sodium hydroxide (12 g) were heated under reflux with methanol (125 ml) and water (125 ml). The cooled solution was acidified with concentrated hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and with saturated brine and dried (Na_2SO_4). The residue left on removal of the solvent was crystallised from aqueous methanol to yield the product (5·7 g, 95%) as blades, m.p. 180—181·5° (lit.,[12] 180°) (Found: C, 43·55; H, 4·2; Br, 28·95%. Calc. for $C_{10}H_{11}BrO_4$: C, 43·65; H, 4·05; Br, 29·05%).

Friedel–Crafts Reaction between 3-*Bromo*-2,6-*dimethoxy*-4-*methylbenzoyl Chloride* (17) *and* 3,5-*Dimethoxyphenylacetonitrile* (18).—The foregoing acid (16) (4·5 g) and phosphorus pentachloride (4·3 g) were heated under reflux in dry carbon tetrachloride (90 ml) for 5 h. The phosphoryl

[10] D. D. Ridley, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1968, **21**, 2982.

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

[12] F. Fuzikawa, *Ber.*, 1935, **68**, 72.

chloride and carbon tetrachloride were removed under reduced pressure and the residue and 3,5-dimethoxyphenylacetonitrile [13] (18) (2·89 g) in dry dichloromethane (150 ml) were treated dropwise with titanium(IV) chloride (4·5 ml). The blood-red solution was stirred at room temperature for 5·75 h and then poured onto ice–water (350 g) containing concentrated hydrochloric acid (25 ml). After the ice had melted the suspension was extracted exhaustively with dichloromethane. The extract was washed in turn with dilute sodium hydroxide solution, water, and saturated brine, and dried (Na_2SO_4). The solution was concentrated and pre-adsorbed on silica gel and chromatographed over a column of silica gel (total 800 g) with gradient elution using ethyl acetate–light petroleum as eluant. This gave 2-(3-*bromo*-2,6-*dimethoxy*-4-*methylbenzoyl*)-3,5-*dimethoxyphenylacetonitrile* (19) (1·86 g, 26%) which crystallised from methanol as prisms, m.p. 139—140·5° (Found: C, 55·55; H, 4·7; Br, 18·1; N, 3·0. $C_{20}H_{20}BrNO_5$ requires C, 55·3; H, 4·65; Br, 18·4; N, 3·2%), τ 3·24 and 3·39 (2H, ABq, *J* 2 Hz, 6- and 4-H), 3·39 (1H, s, 5-H), 5·98 (2H, s, CH_2), 6·15 and 6·49 (each 3H, s, OMe), 6·34 (6H, s, 2 OMe), and 7·57 (3H, s, Me).

Ring-closure and Alkaline Hydrogen Peroxide Treatment of the Benzophenone (19).—A stream of dry, oxygen-free nitrogen was passed through a solution of the foregoing benzophenone (19) (2·40 g) in dry dimethyl sulphoxide (150 ml). Dry sodium methoxide (4·1 g) was added and the red solution was heated rapidly to 140—144° and kept at that temperature for 15 min. The cooled solution was acidified with dilute hydrochloric acid and then extracted with dichloromethane. The extract was washed with water and with saturated brine and dried (Na_2SO_4). The residue left on removal of the solvent was dissolved in tetrahydrofuran (900 ml), sodium hydroxide solution (N; 600 ml), and water (250 ml). The solution was stirred at room temperature for 72 h and 30% hydrogen peroxide (50 ml) was added every 12 h. The mixture was then extracted with dichloromethane and the extract was washed in turn with iron(II) sulphate solution, water, and saturated brine, and dried (Na_2SO_4). The solution was concentrated and pre-adsorbed on silica gel and chromatographed over a column of silica gel (total 250 g) with gradient elution using ethyl acetate–benzene. The first material eluted was 2-*bromo*-1,6,8-*trimethoxy*-3-*methylanthraquinone* (6) (780 mg) which crystallised from dichloromethane–methanol as yellow needles, m.p. 221·5—222·5° (Found: C, 55·5; H, 3·8; Br, 20·5. $C_{18}H_{15}BrO_5$ requires C, 55·25; H, 3·85; Br, 20·45%), τ 2·11 (1H, s, 4-H), 2·68 and 3·23 (2H, ABq, *J* 2·5 Hz, 5- and 7-H), 5·98, 6·03, and 6·06 (each 3H, s, OMe), and 7·45 (3H, s, Me). Later fractions gave 4-bromo-1,6,8-trimethoxy-3-methylanthraquinone (7) (720 mg) identical with that prepared before.

Methyl 2,6-*Dimethoxy*-4-*propylbenzoate* (22).—To a stirred solution of phenyl-lithium [from lithium (2·019 g) and bromobenzene (20·1 g)] in dry ether (120 ml) under dry nitrogen was added 3,5-dimethoxypropylbenzene [14] (20) (21·7 g) in dry ether (80 ml). The mixture was stirred and heated under reflux for 20 h and then poured onto solid carbon dioxide (1 kg). When the mixture had attained room temperature it was acidified with dilute hydrochloric acid and extracted exhaustively with ether. The extract was washed with saturated sodium carbonate solution until effervescence ceased. The aqueous extract was acidified and extracted with ether. The extract was washed with water and dried (Na_2SO_4). The residue from evaporation was crystallised from aqueous methanol and gave prisms (13·0 g, 48%) of 2,6-*dimethoxy*-4-*propylbenzoic acid* (21), m.p. 146—147° (Found: C, 64·05; H, 7·45. $C_{12}H_{16}O_4$ requires C, 64·25; H, 7·2%), τ 1·33br (1H, s, CO_2H), 3·54 (2H, s, ArH), 6·12 (6H, s, 2 OMe), 7·37 (2H, deformed t, CH_2CH_2Me), 8·32 (2H, m, CH_2CH_2Me), and 9·03 (3H, deformed t, Me). Methylation as before gave the title ester (22) as an oil (12·5 g, 94%), b.p. 136—142° at 0·2 mmHg, τ (CCl_4) 3·90 (2H, s, 3- and 5-H), 6·28 (3H, s, CO_2Me), 6·38 (6H, s, 2 OMe), 7·54 (2H, deformed t, CH_2CH_2Me), 8·41 (2H, m, CH_2CH_2Me), and 9·09 (3H, deformed t, Me).

Methyl 3-*Bromo*-2,6-*dimethoxy*-4-*propylbenzoate* (23).—Bromination of the foregoing ester (22) (12·45 g) as before gave the *ester* (23) (16·3 g, 99%) which crystallised from aqueous methanol as plates, m.p. 54·5—55·5° (Found: C, 49·2; H, 5·4; Br, 25·2. $C_{13}H_{17}BrO_4$ requires C, 49·1; H, 5·3; Br, 24·95%), τ 3·58 (1H, s, ArH), 6·20, 6·24, and 6·30 (each 3H, s, OMe), 7·32 (2H, deformed t, CH_2CH_2Me), 8·38 (2H, m, CH_2CH_2Me), and 9·03 (3H, deformed t, Me).

3-*Bromo*-2,6-*dimethoxy*-4-*propylbenzoic Acid* (24).—The foregoing ester (23) (15·5 g) on hydrolysis in the usual way gave the *acid* (24) (14·7 g, 99%) which crystallised from aqueous methanol as plates, m.p. 156—158° (Found: C, 47·6; H, 5·1; Br, 26·25. $C_{12}H_{15}BrO_4$ requires C, 47·55; H, 5·0; Br, 26·35%).

[2-(3-*Bromo*-2,6-*dimethoxy*-4-*propylbenzoyl*)-3,5-*dimethoxyphenyl*]*trifluoroacetylacetonitrile* (26).—3,5-Dimethoxyphenylacetonitrile (18) (322 mg) was added to a stirred solution of the foregoing benzoic acid (24) (552 mg) in dry dichloromethane (5 ml) and trifluoroacetic anhydride (3 ml). The solution instantly turned dark red and was stirred at room temperature for 48 h. The gum left on removal of the solvents under diminished pressure was dissolved in dichloromethane and washed with dilute sodium hydroxide solution and with water, and dried (Na_2SO_4). The crude product was purified by p.l.c. (10% ethyl acetate–light petroleum) to give the *acetonitrile* (26) (268 mg, 26%) as red prisms (from dichloromethane–methanol), m.p. 234·5—236·5° (Found: C, 51·9; H, 4·15; N, 2·45%; M^+, 559/557. $C_{24}H_{23}BrF_3NO_6$ requires C, 51·65; H, 4·15; N, 2·5%; *M*, 559/557), τ 1·88 (1H, s, α-H), 3·45 (1H, s, 5-H), 3·60 and 3·97 (2H, ABq, *J* 2 Hz, 4- and 6-H), 6·06 (3H, s, OMe), 6·33 (6H, s, 2 OMe), 6·47 (3H, s, OMe), 7·20 (2H, deformed t, CH_2CH_2Me), 8·32 (2H, m, CH_2CH_2Me), and 8·99 (3H, deformed t, Me).

Friedel–Crafts Reaction between 3-*Bromo*-2,6-*dimethoxy*-4-*propylbenzoyl Chloride* (25) *and* 3,5-*Dimethoxyphenylacetonitrile* (18).—A suspension of 3-bromo-2,6-dimethoxy-4-propylbenzoic acid (24) (10·8 g) and phosphorus pentachloride (9·0 g) in dry carbon tetrachloride (150 ml) was stirred and heated under reflux for 45 min. The solvent and phosphoryl chloride were removed under reduced pressure and the residue and 3,5-dimethoxyphenylacetonitrile (18) (6·11 g) in dry dichloromethane (300 ml) were treated with titanium(IV) chloride (9 ml). The solution was stirred at room temperature for 4·5 h and then poured on ice–water (500 g). Work-up as before gave the crude product which was pre-adsorbed from dichloromethane onto silica gel and chromatographed over a column of silica gel (total 850 g) with gradient elution using ethyl acetate–light

[13] R. Adams, S. MacKenzie, jun., and S. Loewe, *J. Amer. Chem. Soc.*, 1948, **70**, 664.

[14] Y. Asahina, *Ber.*, 1936, **69**, 1643; C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.*, 1939, **61**, 232.

petroleum. This afforded 2-(3-*bromo*-2,6-*dimethoxy*-4-*propylbenzoyl*)-3,5-*dimethoxyphenylacetonitrile* (27) (7·0 g, 44%), as prisms (from methanol), m.p. 110—112° (Found: C, 57·1; H, 5·5; Br, 17·45; N, 2·75. $C_{22}H_{24}BrNO_5$ requires, C, 57·15; H, 5·25; Br, 17·3; N, 3·05%), τ 3·48 and 3·95 (2H, ABq, *J* 2 Hz, 6- and 4-H), 3·76 (1H, s, 5-H), 6·18 (2H, s, CH_2CN), 6·24, 6·40, 6·46, and 6·60 (each 3H, s, OMe), 7·35 (2H, deformed t, CH_2CH_2Me), 8·38 (2H, m, CH_2CH_2Me), and 9·01 (3H, deformed t, Me).

Ring-closure of the Benzophenone (27).—The foregoing benzophenone (6·1 g) was subjected to ring-closure as described above. The crude product was pre-adsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (total 460 g) with gradient elution using ethyl acetate–light petroleum. The first material eluted was 2-*bromo*-9-*hydroxy*-1,6,8-*trimethoxy*-3-*propylanthracene*-10-*carbonitrile* (28) (1·78 g, 31%), as orange-yellow prisms (from dichloromethane–methanol), m.p. 230—231·5° (Found: C, 58·85; H, 4·75; Br, 19·0; N, 3·1. $C_{21}H_{20}BrNO_4$ requires C, 58·6; H, 4·7; Br, 18·55; N, 3·25%), τ −1·27 (1H, s, OH), 2·16 (1H, s, 4-H), 2·94 and 3·61 (2H, ABq, *J* 2 Hz, 5- and 7-H), 5·89 (3H, s, OMe), 6·02 (6H, s, 2 OMe), 7·05 (2H, deformed t, CH_2CH_2Me), 8·30 (2H, m, CH_2CH_2Me), and 8·91 (3H, deformed t, Me). Later fractions gave 1-*bromo*-10-*hydroxy*-4,5,7-*trimethoxy*-2-*propylanthracene*-9-*carbonitrile* (29) (1·59 g, 28%), as orange-yellow prisms (from dichloromethane–methanol), m.p. 158—160° (Found: C, 58·85; H, 4·95; N, 3·5. $C_{21}H_{20}BrNO_4$ requires C, 58·6; H, 4·7; N, 3·25%), τ −1·53 (1H, s, OH), 2·70 and 3·61 (2H, ABq, *J* 2 Hz, 8- and 6-H), 3·46 (1H, s, 3-H), 5·96 (3H, s, OMe), 6·00 (6H, s, OMe), 7·12 (2H, deformed t, CH_2CH_2Me), 8·26 (2H, m, CH_2CH_2Me), and 8·94 (3H, deformed t, Me).

2-*Bromo*-1,6,8-*trimethoxy*-3-*propylanthraquinone* (3).—The foregoing anthracene (28) (700 mg) in tetrahydrofuran (250 ml), sodium hydroxide solution (N; 200 ml), and sufficient water so that the solution was homogeneous was stirred for 60 h and treated every 12 h with 30% hydrogen peroxide (50 ml). Work-up as before gave the crude product which crystallised from dichloromethane–methanol as yellow needles (540 mg, 79%) of the *anthraquinone*, m.p. 142·5—144·5° (Found: C, 57·55; H, 4·65; Br, 19·05. $C_{20}H_{19}BrO_5$ requires C, 57·3; H, 4·55; Br, 19·05%), τ 2·15 (1H, s, 4-H), 2·68 and 3·24 (2H, ABq, *J* 2·5 Hz, 5- and 7-H), 5·99, 6·04, and 6·06 (each 3H, s, OMe), 7·13 (2H, deformed t, CH_2CH_2Me), 8·34 (2H, m, CH_2CH_2Me), and 8·97 (3H, deformed t, Me).

2-*Cyano*-1,6,8-*trimethoxy*-3-*propylanthraquinone* (4).—The foregoing bromo-compound (3) (905 mg) and copper(I) cyanide (333 mg) were heated under reflux in *NN*-dimethylformamide (20 ml) for 12 h. The hot solution was poured into a solution of hydrated iron(III) chloride (7·5 g) in hydrochloric acid (2N; 800 ml) and was kept at 60—75° for 20 min. The cooled mixture was extracted with dichloromethane and the extract was washed well with dilute hydrochloric acid, and with water, and dried (Na_2SO_4). The solution was concentrated and pre-adsorbed on silica gel and chromatographed over a column of silica gel (total 180 g) with gradient elution using ethyl acetate–benzene. The first material eluted had M^+ at *m/e* 351 and it was therefore methylated with methyl sulphate and potassium carbonate in acetone. Work-up in the usual way gave the *nitrile* (4) (520 mg, 66%), as long yellow needles (from dichloromethane–methanol), m.p. 168—170° (Found: C, 69·05; H, 5·5; N, 3·6. $C_{21}H_{19}NO_5$ requires C, 69·05; H, 5·25, N, 3·85%), τ 2·09 (1H, s, 4-H), 2·67 and 3·19 (2H, ABq, *J* 2·5 Hz, 5- and 7-H), 5·84, 6·01, and 6·03 (each 3H, s, OMe), 7·06 (2H, deformed t, CH_2CH_2Me), 8·17 (2H, m, CH_2CH_2Me), and 8·95 (3H, deformed t, Me). Later fractions gave 1,6,8-trimethoxy-3-propylanthraquinone (5) (74 mg), as yellow needles (from methanol), m.p. 170—171·5° (lit.,[15] 169—170°), τ 2·34 and 2·89 (2H, ABq, *J* 1·6 Hz, 4- and 2-H), 2·67 and 3·22 (2H, ABq, *J* 2·5 Hz, 5- and 7-H), 6·00, 6·04, and 6·07 (each 3H, s, OMe), 7·29 (2H, deformed t, CH_2CH_2Me), 8·33 (2H, m, CH_2CH_2Me), and 9·00 (3H, deformed t, Me).

Methyl 1,6,8-*Trimethoxy*-3-*propylanthraquinone*-2-*carboxylate* (*Methyl Tri*-O-*methylptilometrate*) (2).—The foregoing nitrile (4) (150 mg) was suspended in 10% sodium hydroxide solution (50 ml) and the mixture was heated under reflux under nitrogen for 40 h. The cooled solution was acidified and then extracted with ethyl acetate. The extract was washed exhaustively with saturated sodium hydrogen carbonate solution. The aqueous extract was acidified and extracted with ethyl acetate and the extract was washed with water and dried (Na_2SO_4). The material (32 mg) remaining on removal of the solvent was methylated using methyl sulphate and potassium carbonate in acetone. The crude product so obtained was purified by p.l.c. (2·5% ethyl acetate–benzene) and the major band afforded the *ester* (2) (23 mg) which formed yellow needles from methanol, m.p. 148·5—151° (lit.,[3] 155—156°) (Found: C, 66·0; H, 5·55%; M^+, 398. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·55%; *M*, 398). It was identical (mixed m.p., t.l.c., n.m.r., and i.r. spectra) with a sample of the natural derivative kindly provided by Professor M. D. Sutherland.

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[15] A. J. Birch and C. J. Moye, *J. Chem. Soc.*, 1961, 4691.