Approaches to the Synthesis of 4-Hydroxypiloquinone

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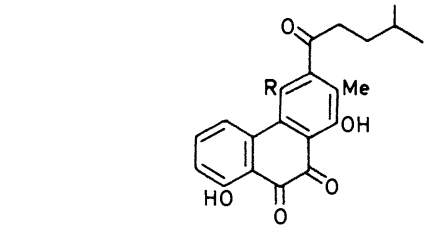
The synthesis of 4-acetoxy-1,8-dihydroxy-2-methyl-3-(4-methylpentanoyl)phenanthrene-9,10-quinone (30) and 1,4,8-trimethoxy-2-methyl-3-(4-methylpentanoyl)phenanthrene-9,10-quinone (33), derivatives of the mould metabolite 4-hydroxypiloquinone [1,4,8-trihydroxy-2-methyl-3-(4-methylpentanoyl)-phenanthrene-9,10-quinone] (2) are described. Photocyclization of methyl 2,2',5,6'-tetramethoxy-3-methylstilbene-4-carboxylate (21) provided methyl 1,4,8-trimethoxy-2-methylphenanthrene-3-carboxylate (22), suitable for further elaboration into the natural derivatives.

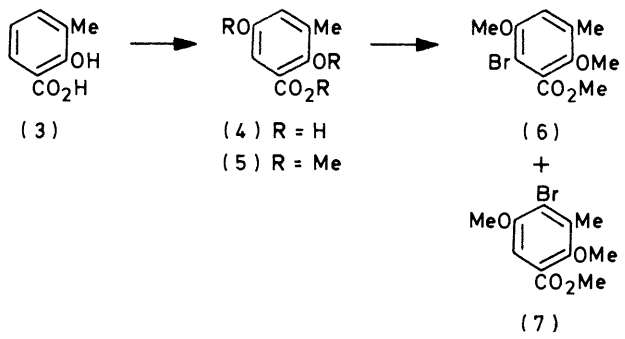
During our synthesis [1] of the mould metabolite piloquinone (1), a rare example of a naturally occurring phenanthrene-9,10-quinone, we observed that 2-methoxystilbenes underwent photocyclization in two modes yielding 1-methoxyphenanthrenes by dehydrocyclization and the corresponding demethoxyphenanthrenes by the alternative loss of methanol. In a later paper [2] we extended the utility of this method to the synthesis of 1-methoxyphenanthrenes from 2,6-dimethoxystilbenes since only loss of methanol can occur in these cases. We now describe approaches to the synthesis of 4-hydroxypiloquinone (2), a minor co-metabolite of piloquinone (1),[3] which exploits the photocyclization of a 2,6-dimethoxystilbene suitable for further elaboration.

For the synthesis of 4-hydroxypiloquinone (2) we therefore required the stilbene (19) (Scheme 3; see later) where the bromo substituent is suitable for the introduction of the 4-methylpentanoyl side-chain by lithium–bromine exchange and further reaction of the lithio derivative. It was expected that the stilbene (19) would readily result from a Wittig reaction between the known aldehyde (18) [2] and the phosphonium salt (17).

The starting material for the synthesis of the phosphonium salt (17) was the commercially available 2-hydroxy-3-methylbenzoic acid (3) (Scheme 1) which was converted into 2,5-dihydroxy-3-methylbenzoic acid (4) by Elbs oxidation using a modification of the method of Still and Snodin.[4] The monobromination of the derived methyl 2,5-dimethoxy-3-methylbenzoate (5) with bromine in acetic acid yielded a 3 : 1 mixture of the two possible isomers. The major isomer was assigned structure (6) on account of its higher field chemical shift (δ 6.75) for the aromatic proton in the ^{1}H n.m.r. spectrum of the mixture. The aromatic proton of the minor isomer (7) resonated at δ 6.94, a value consistent with its *ortho*-relationship to a methoxycarbonyl group. Consequently the bromination of the benzyl bromide (9) (Scheme 2), available by lithium aluminium hydride reduction of the ester (5) and subsequent bromination of the derived alcohol (8) with phosphorus tribromide, was investigated. This resulted in a 4 : 1 mixture of the two possible isomers (10) and (11) which were separated by chromatography. The structural assignments were made by examination of the proton-coupled ^{13}C n.m.r. spectra of the isomers. The spectrum of the major isomer (10) exhibited the carbon signal of the bromomethyl substituent as a triplet (^1J 158 Hz) at δ_C 28.81 p.p.m., whereas the similar signal of the minor isomer (11) occurred as a doublet of triplets (^1J 167, ^3J 6.5 Hz) at δ_C 27.60 p.p.m. Confirmatory evidence for these structural assignments came from the appearance of the methyl carbon signals; that in the major isomer (10) occurred as a doublet of quartets (^1J 123, ^3J 5.9 Hz) at δ_C 14.23 p.p.m. whereas that in the minor isomer (11) appeared as a quartet (^1J 145 Hz) at δ_C 16.48 p.p.m.



(1) R = H
(2) R = OH

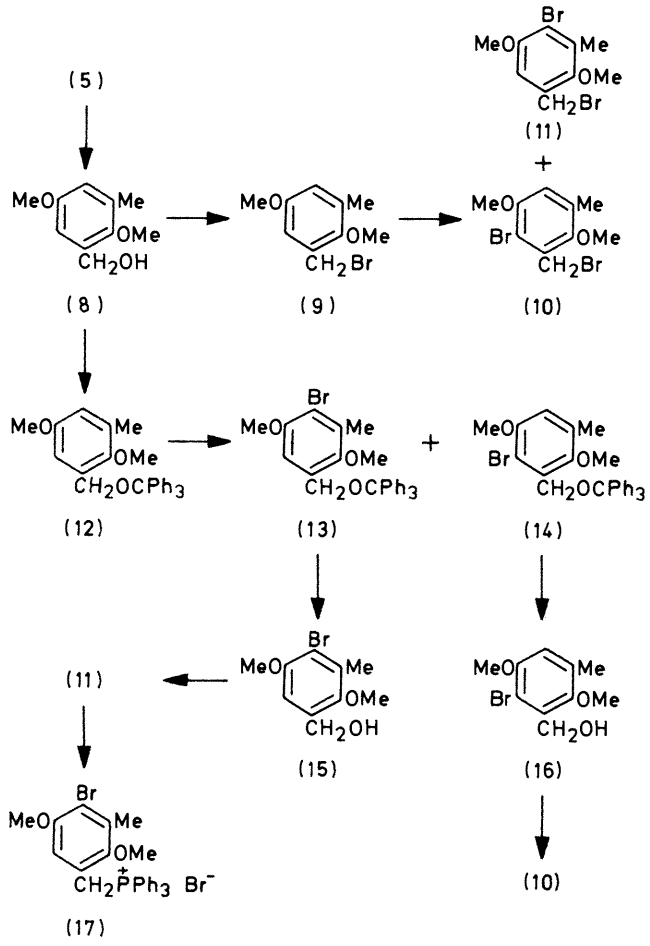


(3) (4) R = H (5) R = Me (6) + (7)

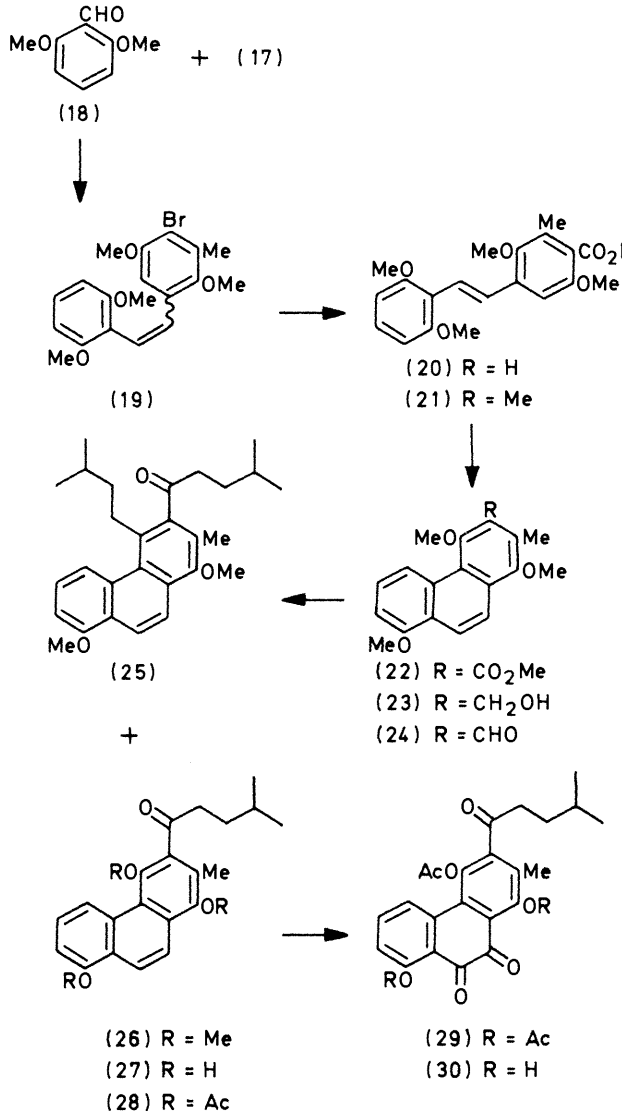
Scheme 1.

In order to increase the proportion of the desired isomer it was reasoned that the steric effect of the bulky triphenylmethyl ether group in compound (12) would hinder bromination at the 6-position. This expectation was realized and the ratio of the isomers (13) and (14) produced on bromination was now 4 : 1, in favour of the desired isomer (13). Removal of the protecting groups afforded a mixture of the alcohols (15) and (16) from which the major isomer (15) was conveniently separated by crystallization. The derived benzyl bromide (11) was then converted into the phosphonium salt (17) which, on Wittig reaction by the *in situ* method in methanol with 2,6-dimethoxybenzaldehyde (18) (Scheme 3), afforded the stilbene (19) as a mixture of isomers in which the (*E*)-isomer predominated.

The pure (*E*)-isomer was subjected to lithium–bromine exchange followed by carboxylation with solid carbon dioxide and the resultant acid (20) was converted into its methyl ester



Scheme 2.



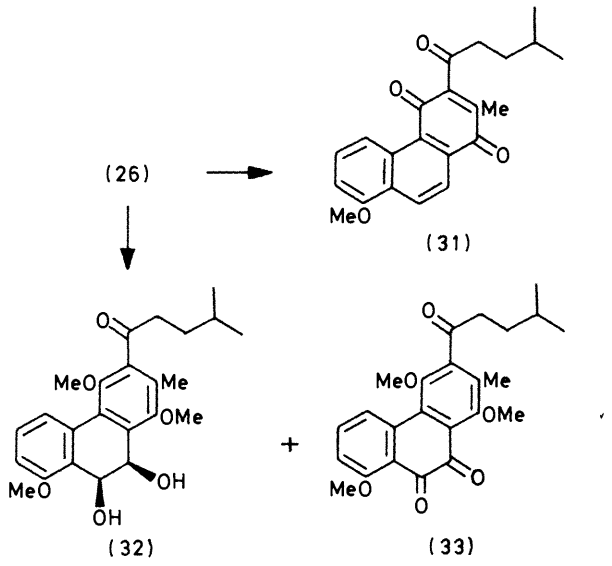
Scheme 3.

(21). Photocyclization of the stilbene (21) then gave the phenanthrene (22) which was converted into the alcohol (23) by reduction with lithium aluminium hydride and thence into the aldehyde (24) by oxidation with manganese dioxide. Grignard reaction of the aldehyde (24) with 3-methylbutylmagnesium bromide and subsequent oxidation of the crude secondary alcohol product with Jones' reagent afforded two products. The major product was the desired ketone (26) and the minor product was assigned structure (25) from its microanalytical and spectroscopic data (see Experimental). The latter compound must result from conjugate addition of the Grignard reagent at the 4-position of the phenanthrene (24) and subsequent reaction of the Grignard reagent at the carbonyl group.

Demethylation of the ketone (26) was achieved by treatment with boron tribromide and the crude triol (27) was acetylated affording the triacetate (28) which was oxidized with chromium trioxide in acetic acid thus providing a poor yield of the triacetoxyquinone (29). Attempted purification of this compound by chromatography resulted in partial deacetylation and a monoacetoxyquinone resulted. This was assigned structure (30) on account of its i.r. spectrum which exhibited a non-bonded ketone carbonyl band at 1 710 cm^{-1}. Attempts by a number of methods to deacetylate 4-acetoxypiloquinone (30), including exposure of the compound to dilute aqueous sodium carbonate or sodium hydroxide solutions, or to a trace of concentrated sulphuric acid in ethyl acetate,[5] or treatment with boron trichloride,[6] resulted only in extensive decomposition. The acetate (30) was unaffected by exposure in ethyl acetate to neutral alumina.[7]

In an alternative approach to 4-hydroxypiloquinone (2) the oxidation of the tri-*O*-methyl compound (26) was investigated. Oxidation of compound (26) (Scheme 4) with chromium trioxide in acetic acid did not occur at the 9,10-double bond but instead afforded the phenanthrene-1,4-quinone (31). The structure of this compound followed from its ^1H n.m.r. spectrum which confirmed that the 9- and 10-proton were unaffected by the oxidation and also revealed the presence of only one methoxy group. The i.r. spectrum exhibited a quinone carbonyl band at 1 664 cm^{-1} and a ketone carbonyl band at 1 704 cm^{-1}.

Oxidation of the tri-*O*-methyl compound (26) with osmium tetraoxide followed by chromatography of the crude product over silica gel afforded predominantly the *cis*-diol (32) and a trace of the quinone (33). Oxidation of the diol (32) with pyridinium chlorochromate afforded the quinone (33) but attempts to obtain 4-hydroxypiloquinone (2) by demethylation of this compound with boron trichloride or boron tribromide were again frustrated by the extensive decomposition which occurred. Unfortunately, insufficient natural material was



Scheme 4.

available to allow its conversion into the synthetic derivatives (30) and (33).

Experimental

Unless otherwise stated i.r. spectra were measured for Nujol mulls, using a Perkin-Elmer 237 spectrophotometer, and n.m.r. spectra for solutions in deuteriochloroform with tetramethylsilane as internal reference. ^{1}H N.m.r. spectra were recorded at 100 MHz with a Varian XL-100 spectrometer, and ^{13}C n.m.r. spectra were obtained using a Brüker WH-90 spectrometer. Unless otherwise stated column chromatography was carried out on wet columns with Merck Kieselgel 60 (30—70 mesh). For dry columns Merck Kieselgel 60 (70—230 mesh) was used. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel $60F_{254}$. Light petroleum refers to the fraction boiling in the range 60—80 °C. The phrase ' residue obtained upon work-up ' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Photochemical reactions were performed under nitrogen with a 450-W high-pressure Hanovia mercury vapour photoreactor.

Methyl 2,5-*Dimethoxy*-3-*methylbenzoate* (5).—Crude 2,5-dihydroxy-3-methylbenzoic acid (4) was obtained by a modification of the method of Still and Snodin [4] in which 2-hydroxy-3-methylbenzoic acid (3) (40 g) was oxidized with a saturated solution of potassium peroxodisulphate (*ca.* 100 g) in water (1 700 ml). After removal of most of the starting material as described by Still and Snodin, the crude 2,5-dihydroxy-3-methylbenzoic acid (4) was further purified by heating under reflux with light petroleum. The hot solution was filtered to remove residual starting material in solution. The solid remaining in the filter afforded pure 2,5-dihydroxy-3-methylbenzoic acid (4) (24.7 g, 56%).

This material was dissolved in dry acetone (225 ml) and anhydrous potassium carbonate (96 g) and a solution of dimethyl sulphate (75 ml) in acetone (225 ml) were then added in turn. The flask contents were heated and stirred under reflux for 20 h. The residue was removed by filtration, the filtrate was evaporated, and the product was dissolved in diethyl ether. The ethereal solution was washed successively with concentrated ammonia, water, and then dilute hydrochloric acid, and was then evaporated and the dark residual oil was chromatographed (10% ethyl acetate in light petroleum as eluant). The resulting oil (27.0 g, 91%) could be distilled at 100 °C (bath) at 0.4 mmHg to afford the *product* (5) which slowly crystallized, m.p. 81—82 °C (Found: C, 62.6; H, 6.5. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%); δ_H 1.28 (3 H, s, Me), 3.76 (6 H, s, 2 × OMe), 3.88 (3 H, s, OMe), and 6.85 and 7.11 (together 2 H, AB, *J* 3 Hz, 4- and 6-H).

Bromination of Methyl 2,5-*Dimethoxy*-3-*methylbenzoate* (5).—A solution of bromine (0.65 g) in acetic acid (10 ml) was added dropwise to a stirred solution of the ester (5) (0.84 g) and anhydrous sodium acetate (0.4 g) in acetic acid (10 ml). The mixture was boiled under reflux for 1.25 h, cooled slightly, and the solvent removed under reduced pressure. The crude product in chloroform was washed in turn with saturated aqueous sodium hydrogen carbonate and water. The residue (1.06 g) obtained upon work-up was examined by ^{1}H n.m.r. spectroscopy which indicated that it was a mixture of methyl 6-bromo-2,5-dimethoxy-3-methylbenzoate (6) * and the 4-bromoisomer (7) in the ratio 3 : 1 (see Discussion).

2,5-*Dimethoxy*-3-*methylbenzyl Alcohol* (8).—A solution of the ester (5) (23.6 g) in dry diethyl ether (300 ml) was added dropwise to lithium aluminium hydride (5.5 g) in diethyl ether (200 ml) and the mixture was heated under reflux for 3 h. Saturated ammonium chloride was added to the cooled solution and the mixture was then dried ($MgSO_4$) and evaporated to give the alcohol (8) (19.5 g, 95%) as an oil, $\nu_{max.}$ (film) 3 400 cm^{-1} (OH); δ_H 2.23 (3 H, s, Me), 2.59 (1 H, t, *J* 6 Hz, OH), 3.65 and 3.69 (each 3 H, s, OMe), 4.61 (2 H, d, *J* 6 Hz, CH_2), and 6.58 and 6.72 (together 2 H, AB, *J* 3 Hz, 2 × ArH).

Preparation and Bromination of 2,5-*Dimethoxy*-3-*methylbenzyl Bromide* (9).—A solution of the alcohol (8) (2.18 g) in dry benzene (30 ml) was stirred at room temperature for 20 h with phosphorus tribromide (1.26 g). The solution was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water. The residue (2.86 g, 97%) obtained upon work-up proved to be the bromo compound (9), δ_H 2.31 (3 H, s, Me), 3.77 and 3.83 (each 3 H, s, OMe), 4.55 (2 H, s, CH_2), and 6.69 and 6.76 (together 2 H, AB, *J* 3 Hz, 2 × ArH).

A solution of the product (9) (2.85 g) in acetic acid (50 ml) was treated with a solution of bromine (1.9 g) in acetic acid (20 ml) and the mixture was stirred at room temperature for 5 h. The acetic acid was evaporated under reduced pressure and the residue in diethyl ether was washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue obtained upon work-up afforded a mixture of 6-bromo-2,5-dimethoxy-3-methylbenzyl bromide (10) † and the 4-bromo isomer (11) in the ratio 4 : 1. These compounds were separated by p.l.c. and were shown to be identical with those described below.

2,5-*Dimethoxy*-3-*methylbenzyl Triphenylmethyl Ether* (12).—A solution of the alcohol (8) (18.2 g) in dry pyridine (100 ml) was stirred overnight with an excess of triphenylmethyl chloride (47.9 g). Most of the solvent was removed under reduced pressure, and dry diethyl ether (100 ml) was added to the residue. The precipitate was removed by filtration and was washed with more dry diethyl ether. The organic layer was evaporated to yield the crude ether (12) (38.0 g) contaminated with triphenylmethanol. A small portion was chromato-

* Systematic name: methyl 2-bromo-3,6-dimethoxy-5-methylbenzoate.

† Alternative name: α,2-dibromo-3,6-dimethoxy-5-methyltoluene.

graphed (chloroform) to afford an analytical sample as an *oil* (Found: C, 82.5; H, 6.8. $C_{29}H_{28}O_3$ requires C, 82.05; H, 6.65%); δ_H 2.23 (3 H, s, Me), 3.48 and 3.78 (each 3 H, s, OMe), 4.22 (2 H, s, CH_2), 6.65 and 7.06 (together 2 H, AB, *J* 3 Hz, 2 × ArH), and 7.05—7.70 (15 H, m, 3 × Ph).

4-*Bromo*-2,5-*dimethoxy*-3-*methylbenzyl Triphenylmethyl Ether* (13).—A solution of the crude ether (12) (45.3 g) (containing *ca.* 32 g ether contaminated with triphenylmethanol, as estimated by ^1H n.m.r.) in dry chloroform (120 ml) containing pyridine (7 g) was treated dropwise with a solution of bromine (12.86 g) in chloroform (50 ml). The mixture was stirred at ambient temperature for 4 h, and then the solvent and pyridine were removed under reduced pressure. The residue was dissolved in methylene dichloride and washed with water, and the solution was dried and evaporated to *yield an oil* (56.0 g). A small portion was chromatographed with 20% ethyl acetate in light petroleum as eluant to give the *product* (13), m.p. 225 °C (from chloroform–light petroleum) (Found: C, 69.6; H, 5.4. $C_{29}H_{27}BrO_3$ requires C, 69.2; H, 5.4%); δ_H 2.34 (3 H, s, Me), 3.48 and 3.90 (each 3 H, s, OMe), 4.24 (2 H, s, CH_2), 7.04 (1 H, s, 6-H), and 7.10—7.65 (15 H, m, 3 × Ph).

4-*Bromo*-2,5-*dimethoxy*-3-*methylbenzyl Alcohol* (15) *and* 2-*Bromo*-3,6-*dimethoxy*-5-*methylbenzyl Alcohol* (16).—The above crude mixture of bromo ethers (13) and (14) (55.0 g) was heated under reflux in glacial acetic acid–water (4 : 1; 100 ml) for 10 min. The solution was cooled in ice and the precipitated triphenylmethanol was removed by filtration and washed with a little cold acetic acid. The filtrate was evaporated and the residue chromatographed rapidly with chloroform to separate residual triphenylmethanol from the mixture of slower running bromo alcohols (15) and (16). This latter mixture was crystallised from methylene dichloride–light petroleum to afford 4-*bromo*-2,5-*dimethoxy*-3-*methylbenzyl alcohol* (15) (11.0 g), m.p. 87—88 °C (Found: C, 46.05; H, 5.05. $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0%); δ_H 2.36 (3 H, s, Me), 2.56 (1 H, br, OH), 3.69 and 3.85 (each 3 H, s, OMe), 4.66 (2 H, s, CH_2), and 6.80 (1 H, s, 6-H). The mother liquors from the above crystallization were evaporated and chromatographed (eluant 20% ethyl acetate–light petroleum). Earlier fractions afforded 2-*bromo*-3,6-*dimethoxy*-5-*methylbenzyl alcohol* (16) (3.5 g), m.p. 69—70 °C (from light petroleum) (Found: C, 46.1; H, 4.85%); δ_H 2.28 (3 H, s, Me), 2.42 (1 H, t, *J* 7 Hz, OH), 3.77 and 3.85 (each 3 H, s, OMe), 4.84 (2 H, d, *J* 7 Hz, CH_2), and 6.90 (1 H, s, 4-H). Later fractions afforded more of the alcohol (15).

4-*Bromo*-2,5-*dimethoxy*-3-*methylbenzyl Bromide* (11).*—The alcohol (15) (8.2 g) was allowed to react (5 h) with phosphorus tribromide (3.3 g), in the manner described above for compound (8), to afford the desired intermediate *dibromide* (11) (8.2 g, 80%), m.p. 85—86 °C (from ethanol) (Found: C, 37.2; H, 3.6. $C_{10}H_{12}Br_2O_2$ requires C, 37.0; H, 3.7%); δ_H 2.39 (3 H, s, Me), 3.92 and 3.89 (each 3 H, s, OMe), 4.56 (2 H, s, CH_2), and 6.78 (1 H, s, 6-H).

6-*Bromo*-2,5-*dimethoxy*-3-*methylbenzyl Bromide* (10).†—The alcohol (16) was brominated as in the preceding case to give the *dibromide* (10), m.p. 102—103 °C (from ethanol) (Found: C, 37.2; H, 3.6%); δ 2.30 (3 H, s, Me), 3.88 (6 H, s, 2 × OMe), 4.75 (2 H, s, CH_2), and 6.73 (1 H, s, 4-H).

* α,4-Dibromo-2,5-dimethoxy-3-methyltoluene.

† Alternative name: α,2-dibromo-3,6-dimethoxy-5-methyltoluene.

4-*Bromo*-2,5-*dimethoxy*-3-*methylbenzyltriphenylphosphonium Bromide* (17).—To a solution of the bromide (11) (21.77 g) in dry benzene (75 ml) was added triphenylphosphine (21.25 g). The mixture was stirred and boiled under reflux for 20 h, during which time precipitation of the product occurred. The mixture was cooled in ice and filtered, and the precipitate was washed with cold dry diethyl ether. Crystallization afforded the *phosphonium salt* (17) (36.4 g, 92%), m.p. 212—213 °C (from methylene dichloride–diethyl ether) (Found: C, 56.8; H, 5.1. $C_{28}H_{27}Br_2O_2P$ requires C, 57.3; H, 4.6%); δ_H 2.18 (3 H, s, Me), 3.53 (6 H, s, 2 × OMe), 5.20 (2 H, d, *J* 14 Hz, CH_2), 6.83 (1 H, d, *J* 2 Hz, 6-H), and 7.45—7.95 (15 H, m, 3 × Ph).

4-*Bromo*-2,2′,5,6′-*tetramethoxy*-3-*methylstilbene* (19).—The phosphonium salt (17) (18.3 g) and 2,6-dimethoxybenzaldehyde [2] (18) (5.2 g) were dissolved in dry methanol (250 ml) under dry nitrogen. A solution of lithium methoxide [from lithium (217 mg)] in dry methanol (35 ml) was then added dropwise at room temperature to the stirred mixture which became pale yellow and was then heated under reflux for 2 h. The solution was cooled and evaporated, and the residue chromatographed (eluant 10% ethyl acetate–light petroleum) to afford the product (19) (11.3 g, 92%) as a mixture of (*Z*) and (*E*) isomers, the latter predominating. Crystallization from methylene dichloride–light petroleum afforded the pure (*E*)-*isomer*, m.p. 94—95 °C (Found: C, 58.0; H, 5.35. $C_{19}H_{21}BrO_4$ requires C, 58.0; H, 5.4%); δ_H 2.40 (3 H, s, Me), 3.72 (3 H, s, OMe), 3.90 (6 H, s, 2 × OMe), 3.93 (3 H, s, OMe), 6.59 (2 H, d, *J* 8 Hz, 3′- and 5′-H), 7.05 (1 H, s, 6-H), 7.17 (1 H, t, *J* 8 Hz, 4′-H), and 7.37 and 7.79 (together 2 H, AB, *J* 16 Hz, *trans* CH=CH).

(E)-*Methyl* 2,2′,5,6′-*Tetramethoxy*-3-*methylstilbene*-4-*carboxylate* (21).—A solution of the bromostilbene (19) as the pure (*E*)-isomer (0.5 g) in dry diethyl ether (50 ml) was treated dropwise with butyl-lithium (0.55 ml of a 15.5% solution in hexane) under dry nitrogen. The mixture was stirred at room temperature for 30 min and was then poured onto an excess of solid carbon dioxide. The solution was extracted with dilute aqueous sodium hydroxide and the basic layer was acidified with dilute hydrochloric acid and extracted with chloroform. Evaporation of the extract afforded crude (*E*)-2,2′,5,6′-tetramethoxy-3-methylstilbene-4-carboxylic acid (20) (0.44 g, 97%).

This acid was methylated with dimethyl sulphate (0.16 g) and anhydrous potassium carbonate (0.5 g) in *N*,*N*-dimethylformamide (10 ml) during 20 h at room temperature. The usual work-up afforded the *product* (21) as an oil. A sample was purified for analysis by p.l.c. (5% ethyl acetate–light petroleum) (Found: C, 67.3; H, 6.8. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%); δ_H 2.24 (3 H, s, Me), 3.72 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.91 (9 H, s, 3 × OMe), 6.59 (2 H, d, *J* 8 Hz, 3′- and 5′-H), 7.04 (1 H, s, 6-H), 7.18 (1 H, t, *J* 8 Hz, 4′-H), and 7.38 and 7.82 (together 2 H, AB, *J* 16 Hz, *trans* CH=CH).

Methyl 1,4,8-*Trimethoxy*-2-*methylphenanthrene*-3-*carboxylate* (22).—A solution of the stilbene ester (21) (2.94 g) in cyclohexane (800 ml) was irradiated through quartz (Vycor sleeve) for 3 h. The crude product was chromatographed (eluant 10% ethyl acetate–light petroleum) to afford the *phenanthrene* (22) (1.16 g, 43%), m.p. 121—122 °C (from methanol) (Found: C, 70.9; H, 6.3. $C_{20}H_{20}O_5$ requires C, 70.6; H, 5.9%); δ_H 2.41 (3 H, s, Me), 3.84 and 3.87 (each 3 H, s, OMe), 4.02 (6 H, s, 2 × OMe), 6.99 (1 H, d, *J* 9 Hz, 7-H), 7.52 (1 H, t, *J* 9 Hz, 6-H), 8.00 and 8.32 (together 2 H, AB, *J* 9.5 Hz, 9- and 10-H), and 8.96 (1 H, d, *J* 9 Hz, 5-H).

1,4,8-*Trimethoxy*-2-*methyl*-3-*phenanthrylmethanol* (23).—A solution of the ester (22) (1.04 g) in dry tetrahydrofuran (THF) (30 ml) was added dropwise at room temperature to a suspension of lithium aluminium hydride (0.6 g) in the same solvent (70 ml), and the mixture was stirred for 4 h. Work-up as for compound (8) afforded the *alcohol* (23) (0.90 g, 95%), m.p. 144—145 °C (from methanol) (Found: C, 72.8; H, 6.5. $C_{19}H_{20}O_4$ requires C, 73.1; H, 6.4%); δ_H 2.44 (1 H, br, OH), 2.54 (3 H, s, Me), 3.80, 3.86, and 4.02 (each 3 H, s, OMe), 4.98 (2 H, s, CH_2), 6.98 (1 H, d, *J* 9 Hz, 7-H), 7.51 (1 H, t, *J* 9 Hz, 6-H), 7.98 and 8.27 (together 2 H, AB, *J* 9.5 Hz, 9- and 10-H), and 9.02 (1 H, d, *J* 9 Hz, 5-H).

1,4,8-*Trimethoxy*-2-*methylphenanthrene*-3-*carbaldehyde* (24).—A solution of the alcohol (23) (1.55 g) in chloroform (150 ml) was heated under reflux with activated manganese dioxide for 30 h. The solution was cooled, filtered, and evaporated, and the residue was chromatographed (dry column; eluant 2.5% ethyl acetate–light petroleum). Earlier fractions afforded the *aldehyde* (24) (1.19 g, 77%), m.p. 138—139 °C (from methanol) (Found: C, 73.35; H, 6.0. $C_{19}H_{18}O_4$ requires C, 73.55; H, 5.85%); $\nu_{max.}$ 1 679 cm^{-1} (C=O); δ_H 2.69 (3 H, s, Me), 3.88 (6 H, s, 2 × OMe), 4.05 (3 H, s, OMe), 7.05 (1 H, d, *J* 9 Hz, 7-H), 7.60 (1 H, t, *J* 9 Hz, 6-H), 8.03 and 8.44 (together 2 H, AB, *J* 9.5 Hz, 9- and 10-H), 9.03 (1 H, d, *J* 9 Hz, 5-H), and 10.79 (1 H, s, CHO). Later fractions afforded 8-methoxy-3-methoxymethyl-2-methylphenanthrene-1,4-quinone (40 mg, 2%), m.p. 150—151 °C (from methylene dichloride–light petroleum); *m/z* 296 (M^+); $\nu_{max.}$ ($CHCl_3$) 1 660 cm^{-1} (C=O); δ_H 2.28 (3 H, s, Me), 3.46 (3 H, s, CH_2O*Me*), 4.02 (3 H, s, OMe), 4.54 (2 H, s, CH_2), 6.94 (1 H, d, *J* 9 Hz, 7-H), 7.58 (1 H, t, *J* 9 Hz, 6-H), 8.10 and 8.62 (together 2 H, AB, *J* 9 Hz, 9- and 10-H), and 9.03 (1 H, d, *J* 9 Hz, 5-H).

1-(1,4,8-*Trimethoxy*-2-*methyl*-3-*phenanthryl*)-4-*methylpentan*-1-*one* (26).—A solution of isopentyl bromide (3.10 g) in dry diethyl ether (20 ml) was added to magnesium (0.50 g) to prepare the Grignard reagent in the usual way. A solution of the aldehyde (24) (1.08 g) in dry THF (20 ml) was added dropwise followed by further THF (20 ml). The mixture was heated under reflux for 30 min. An excess of saturated aqueous ammonium chloride was added, and the mixture was worked up (ethyl acetate). The crude product was dissolved in acetone (15 ml) and Jones' reagent (4.3 ml) was added dropwise to the solution at room temperature. The solution was stirred for 30 min and then partitioned between water and chloroform. Work-up of the organic layer afforded a crude product (1.57 g) which showed two products on t.l.c. The reaction mixture was separated by p.l.c. (1% ethyl acetate–light petroleum). A fast band afforded 1-(4-*isopentyl*-1,8-*dimethoxy*-2-*methyl*-3-*phenanthryl*)-4-*methylpentan*-1-*one* (25) (0.094 g, 6%) as a clear oil (Found: C, 80.05; H, 8.55. $C_{28}H_{36}O_3$ requires C, 79.95; H, 8.65%); δ_H 0.97 (12 H, t, 4 × Me), 1.70 (6 H, m, 2 × CH_2CH_2CHMe$_2$), 2.32 (3 H, s, ArMe), 2.78 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 3.20 (2 H, br, $ArCH_2$), 3.86 and 4.01 (each 3 H, s, OMe), 6.98 (1 H, d, *J* 9 Hz, 7-H), 7.45 (1 H, t, *J* 9 Hz, 6-H), 8.03 (1 H, d, *J* 9 Hz, 9- or 10-H), and 8.28 (2 H, d, *J* 9 Hz, 5- and 10- or 9-H). A second band gave the required *ketone* (26) (0.66 g, 50%) m.p. 76—77 °C (from methanol) (Found: C, 75.8; H, 7.6. $C_{24}H_{28}O_4$ requires C, 75.75; H, 7.4%); $\nu_{max.}$ 1 692 cm^{-1} (C=O); δ_H 0.95 (6 H, d, *J* 6 Hz, 2 × Me), 1.69 (3 H, m, CH_2CHMe$_2$), 2.34 (3 H, s, ArMe), 2.95 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 3.74, 3.87, and 4.00 (each 3 H, s, OMe), 6.98 (1 H, d, *J* 9 Hz, 7-H), 7.52 (1 H, t, *J* 9 Hz, 6-H), 7.99 and 8.30 (together 2 H, AB, *J* 9.5 Hz, 9- and 10-H), and 8.97 (1 H, d, *J* 9 Hz, 5-H).

1-(1,4,8-*Triacetoxy*-2-*methyl*-3-*phenanthryl*)-4-*methylpentan*-1-*one* (28).—A solution of the ketone (26) (0.6 g) in dry methylene dichloride was added dropwise to a stirred solution of boron tribromide (1.43 g) in dry methylene dichloride (15 ml) at −78 °C. The mixture was stirred at −78 °C for 1 h and then at room temperature for 2 h. Water was cautiously added and the mixture was shaken until the complex decomposed. The residue obtained upon work-up afforded the crude triol (27) (0.45 g, 84%), δ_H 0.88 (6 H, d, *J* 6 Hz, 2 × Me), 1.66 (3 H, m, CH_2CHMe$_2$), 2.45 (3 H, s, ArMe), 2.88 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 4.85 and 5.75 (each 1 H, br, OH), 6.94 (1 H, d, *J* 9 Hz, 7-H), 7.40 (1 H, t, *J* 9 Hz, 6-H), 7.88 and 8.27 (together 2 H, AB, *J* 9 Hz, 9- and 10-H), 9.28 (1 H, d, *J* 9 Hz, 5-H), and 12.90 (1 H, s, 4-OH).

The crude triol (27) was acetylated with acetic anhydride and pyridine (90 °C; 2 h) in the usual way. The *acetate* (28) was obtained as needles, m.p. 205—206 °C (from methanol–methylene dichloride) (Found: C, 69.7; H, 6.25. $C_{27}H_{28}O_7$ requires C, 69.8; H, 6.1%); $\nu_{max.}$ 1 756 (acetate C=O) and 1 694 cm^{-1} (ketone C=O); δ_H 0.96 (6 H, d, *J* 6 Hz, 2 × Me), 1.68 (3 H, m, CH_2CHMe$_2$), 2.24, 2.39, 2.46, and 2.50 (each 3 H, s, together 3 × Ac and ArMe), 2.90 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 7.36 (1 H, d, *J* 8 Hz, 7-H), 7.60 (1 H, t, *J* 8 Hz, 6-H), 7.68 and 7.89 (together 2 H, AB, *J* 9 Hz, 9- and 10-H), and 8.82 (1 H, d, *J* 8 Hz, 5-H).

4-*Acetoxy*-1,8-*dihydroxy*-2-*methyl*-3-(4-*methylpentanoyl*)-*phenanthrene*-9,10-*quinone* (4-*Acetoxypiloquinone*) (30).—A mixture of chromium trioxide (55 mg) in acetic acid (0.5 ml) and water (0.3 ml) was added dropwise to a solution of the ketone (28) (50 mg) in acetic acid (2.5 ml). The reaction mixture was stirred and heated at 65 °C for 0.75 h, poured into water (50 ml) and then extracted exhaustively with methylene dichloride. The extract was washed successively with saturated aqueous sodium hydrogen carbonate and water. The residue obtained upon work-up was subjected to p.l.c. (eluant 20% ethyl acetate–light petroleum). A maroon band was removed which gave the *quinone* (30) (10 mg, 23%) as maroon needles, m.p. 180—182 °C (Found: C, 67.15; H, 5.7. $C_{23}H_{22}O_7$ requires C, 67.3; H, 5.4%); $\nu_{max.}$ ($CHCl_3$) 1 780 (acetate C=O), 1 710 (ketone C=O), and 1 632 cm^{-1} (quinone C=O); δ_H 0.95 (6 H, d, *J* 6 Hz, 2 × Me), 1.64 (3 H, m, CH_2CHMe$_2$), 2.18 and 2.25 (each 3 H, s, Ac and ArMe), 2.74 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 7.00 (1 H, d, *J* 8 Hz, 7-H), 7.54 (1 H, t, *J* 8 Hz, 6-H), 7.80 (1 H, d, *J* 8 Hz, 5-H), and 12.40 and 13.06 (each 1 H, s, OH).

8-*Methoxy*-2-*methyl*-3-(4-*methylpentanoyl*)*phenanthrene*-1,4-*quinone* (31).—The phenanthrene (26) (50 mg) was dissolved in acetic acid (2.5 ml) at 70 °C. A solution of chromium trioxide (55 mg) in acetic acid (0.5 ml) and water (0.3 ml) was added dropwise and the reaction mixture was stirred and heated at 65 °C for 0.75 h. Work-up and p.l.c. as for the oxidation of compound (28) afforded the quinone (31) (13 mg, 28%) as red needles, m.p. 135—137 °C; *m/z* 350 (M^+); $\nu_{max.}$ ($CHCl_3$) 1 704 (ketone C=O) and 1 644 cm^{-1} (quinone C=O); δ_H 0.96 (6 H, d, *J* 6 Hz, 2 × Me), 1.64 (3 H, m, CH_2CHMe$_2$), 2.10 (3 H, s, ArMe), 2.79 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 4.04 (3 H, s, OMe), 6.98 (1 H, d, *J* 8 Hz, 7-H), 7.63 (1 H, t, *J* 8 Hz, 6-H), 8.13 and 8.68 (together 2 H, AB, *J* 9 Hz, 9- and 10-H), and 9.04 (1 H, d, *J* 8 Hz, 5-H).

Oxidation of 1-(1,4,8-*Trimethoxy*-2-*methyl*-3-*phenanthryl*)-4-*methylpentan*-1-*one* (26).—A mixture of the phenanthrene (26) (51 mg) and osmium tetraoxide (100 mg) in dry pyridine (15 ml) was stirred at room temperature for 7 d. The pyridine was evaporated and the crude product was purified by chromatography (eluant 10—20% ethyl acetate–light petrol-

eum). Three fractions were obtained. That of highest R_F was starting material (26) (13 mg); this was followed by the quinone (33) (3 mg) and finally the diol (32) (17 mg) was obtained as a solid, $\nu_{max.}$ ($CHCl_3$) 3 440 (OH) and cm^{-1} 1 700 (ketone C=O); δ_H 0.95 (6 H, d, *J* 6 Hz, 2 × Me), 1.64 (3 H, m, CH_2CHMe_2), 2.18 (3 H, s, ArMe), 2.82 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 3.44, 3.88, and 3.94 (each 3 H, s, OMe), 4.02 (2 H, br, OH), 5.06 and 5.16 (together 2 H, AB, *J* 4 Hz, 9- and 10-H), 6.90 (1 H, d, *J* 8 Hz, 7-H), 7.32 (1 H, t, *J* 8 Hz, 6-H), and 8.00 (1 H, d, *J* 8 Hz, 5-H).

A mixture of the diol (32) (22.3 mg) and pyridinium chlorochromate (36.5 mg) in dry methylene dichloride (5 ml) was stirred at room temperature for 20 h. Dry diethyl ether (25 ml) was added to the mixture and the brown precipitate was separated by filtration and the filtrate was evaporated under reduced pressure. The resulting oil was chromatographed (eluant chloroform) to afford 1,4,8-*trimethoxy*-2-*methyl*-3-(4-*methylpentanoyl*)*phenanthrene*-9,10-*quinone* (33) (19.3 mg, 87%) as yellow platelets, m.p. 139—140 °C (Found: C, 69.85; H, 6.3. $C_{24}H_{26}O_6$ requires C, 70.2; H, 6.4%); δ_H 0.96 (6 H, d, *J* 6 Hz, 2 × Me), 1.66 (3 H, m, CH_2CHMe_2), 2.15 (3 H, s, ArMe), 2.81 (2 H, deformed t, *J* 7 Hz, $COCH_2$), 3.55, 3.87, and 3.95 (each 3 H, s, OMe), 7.00 (1 H, d, *J* 8 Hz, 7-H), 7.62 (1 H, t, *J* 8 Hz, 6-H), and 8.13 (1 H, d, *J* 8 Hz, 5-H).

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