A New Synthesis of Anthraquinones Using Dihydro-oxazoles and Grignard Reagents Derived from Mg(Anthracene)(THF)$_3$[1]

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A general synthesis of anthraquinones which depends on the displacement of the methoxy group from an *o*-methoxyaryldihydro-oxazole by a methoxy substituted benzylmagnesium chloride, generated by using a magnesium–anthracene complex, has been developed. The masked benzylbenzoic acids which result from these reactions are deprotected and then ring-closed to anthrones which on oxidation yield anthraquinones. In this way, the following naturally occurring anthraquinones (or derivatives thereof have been synthesized): chrysophanol (**9**), islandicin (**19**), digitopurpone (**21**), tri-*O*-methylemodin (**26**), and di-*O*-methylsoranjidiol (**29**).

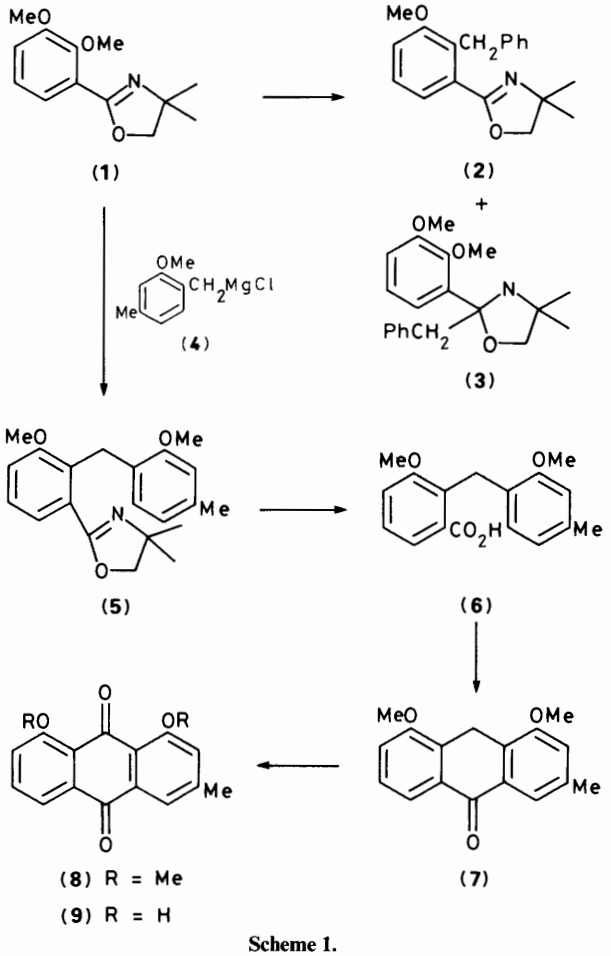
The antitumour properties of the anthracycline antibiotics have provoked a resurgence of interest in the development of new synthetic methods for anthraquinones.[2] The classical method relied on the construction of benzoylbenzoic acids by Friedel–Crafts acylations involving phthalic anhydrides, and subsequent ring closure. Both reactions require harsh conditions and the ring closure is often accompanied by Hayashi rearrangement.[3] We now describe a general synthesis of anthraquinones which employs mild conditions and which precludes the possibility of Hayashi rearrangement.

Meyers and his co-workers[4] have shown that the *o*-methoxy group in *o*-methoxyaryldihydro-oxazoles can be displaced by a variety of nucleophiles. We reasoned that since the dihydro-oxazole entity is a masked carboxylic acid, its reaction with benzylmagnesium halide would constitute a simple synthesis of benzylbenzoic acids which could be elaborated to anthraquinones. Indeed Meyers and his co-workers[4] have touched upon this possibility since they treated the dihydro-oxazole (**1**) (Scheme 1) with a slight excess of benzylmagnesium bromide at 25 °C but the isolated yield of the expected product (**2**) was only 6%.

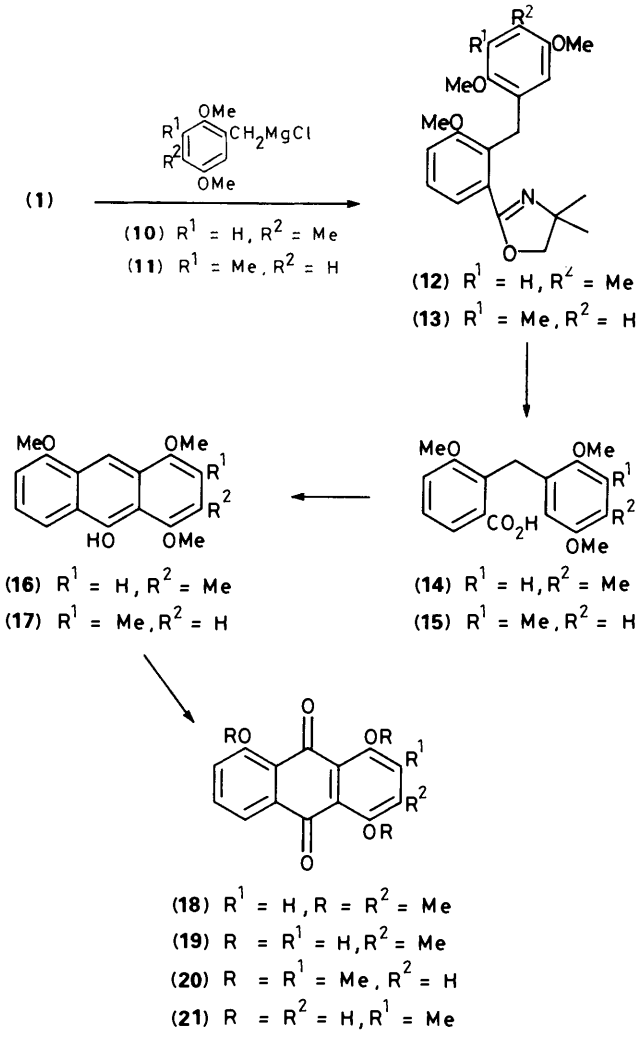
Benzylic halides are prone to undergo Wurtz coupling with magnesium and consequently yields in Grignard reactions involving them are often reduced. It may have been so in the experiment conducted by Meyers and his co-workers.

We have recently found,[5] however, that when benzylic Grignard reagents are generated at 0 °C from 0.1 M solutions of benzyl chlorides in tetrahydrofuran using the complex [Mg(anthracene)THF)$_3$], as a source of soluble magnesium, then no Wurtz coupling can be detected. We, therefore, repeated the reaction at 25 °C between the dihydro-oxazole (**1**) and an excess of benzylmagnesium chloride generated from the magnesium–anthracene complex. The isolated yield of the expected product (**2**) was now 80% but it was accompanied by a further product which we have identified from its elemental analysis and its spectroscopic data as the oxazolidine (**3**). This unexpected product presumably arises by addition of the benzylmagnesium chloride to the imine of the dihydro-oxazole (**2**). Grignard reagents do not generally add to these double bonds,[6] but organolithium reagents are known to undergo slow addition at −25 °C.[4]

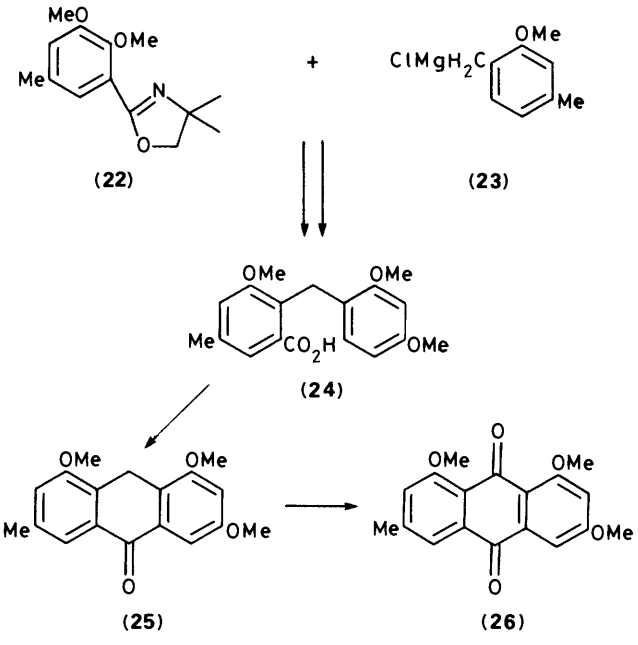
We first attempted the synthesis of chrysophanol (**9**) a common plant anthraquinone.[7] The Grignard reagent (**4**) (1.13 equiv.), available by standard steps from methyl 2-methoxy-4-methylbenzoate,[8] was allowed to react at 25 °C for 18 h with the dihydro-oxazole (**1**). This resulted in the crystalline dihydro-oxazole (**5**) in 86% yield. It was conveniently separated from the anthracene by extraction into acid. Deprotection of this dihydro-oxazole was effected in 90% yield by quaternization with iodomethane and then basic hydrolysis. The resultant benzylbenzoic acid (**6**) was smoothly ring-closed (91%) by brief treatment with trifluoroacetic anhydride in dichloromethane at 0 °C. This reaction gave the anthrone (**7**) which was oxidized with chromium trioxide in acetic acid and afforded di-*O*-methylchrysophanol (**8**) (85%). Demethylation of this compound was accomplished by treatment with boiling hydrobromic acid in acetic acid which gave chrysophanol (**9**) (94%).[9]



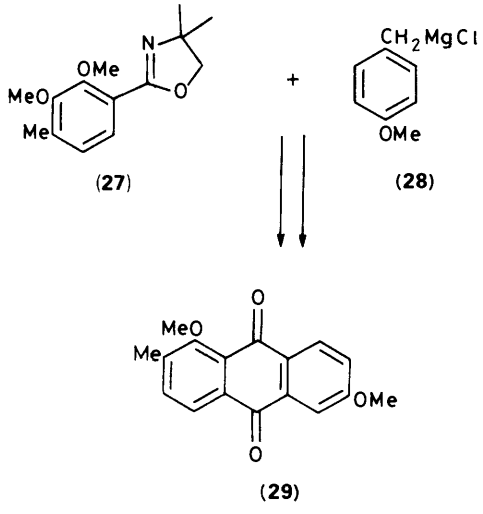
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

We now sought to extend the method to more complex anthraquinones and chose the isomeric compounds islandicin (**19**) (Scheme 2), a mould metabolite,[10] and digitopurpone (**21**), a minor *Digitalis* constituent.[11] For this purpose, we required the Grignard reagents (**10**) and (**11**). Again these were made by standard methods starting from 2,5-dimethoxy-4-methylbenzaldehyde[12] in the case of the former and from 1-bromo-2,5-dimethoxy-3-methylbenzene[13] in the case of the latter. The syntheses proceeded *via* the intermediate dihydro-oxazoles (**12**) and (**13**), the benzylbenzoic acids (**14**) and (**15**), the anthranols (**16**) and (**17**), and finally demethylation of the trimethoxyanthraquinones (**18**) and (**20**) gave the natural products. It is interesting to note that the anthranols (**16**)[14] and (**17**) exist solely as these tautomers as revealed by their ^{1}H n.m.r. spectra recorded in deuteriochloroform solution, whereas the compounds (**7**) and (**25**) (Scheme 3) related respectively to chrysophanol and emodin appear, on the same grounds, to exist exclusively as their anthrone tautomers. In the case of the anthranols (**16**)[14] and (**17**) there are strong intramolecular hydrogen bonds between the hydroxy groups at the 9-positions and the *peri*-methoxy groups since the hydroxy protons resonate as sharp singlets near δ 10 in their ^{1}H n.m.r. spectra. Such interactions are not possible in the anthranol tautomers derived from compounds (**7**) and (**25**).

In order to obtain substitution patterns other than those restricted by the use of the dihydro-oxazole (**1**), we have used two other dihydro-oxazoles in the anthraquinone synthesis. The dihydro-oxazole (**22**) (Scheme 3), prepared in the usual way,[4] from 2,3-dimethoxy-5-methylbenzoic acid, was allowed to react with the Grignard reagent (**23**) and this synthetic sequence ultimately gave tri-*O*-methylemodin (**26**). The known dihydro-oxazole (**27**)[15] (Scheme 4) was allowed to react with the Grignard reagent (**28**) and this synthetic sequence finally gave di-*O*-methylsoranjidiol (**29**). We have thus demonstrated the versatility and utility of this mild method of anthraquinone synthesis.

Experimental

General directions have been given previously.[16] All experiments involving the use of the magnesium–anthracene complex were conducted under dry argon using the Schlenk technique.

General Method for the Preparation of Benzylic Grignard Reagents.—A solution of the benzyl chloride (15 mmol) in

anhydrous THF (50 ml) was added dropwise to a stirred slurry of [Mg(anthracene)(THF)$_3$] (15 mmol) in THF (100 ml). The orange suspension disappeared with the formation of a deep green solution, which finally became light orange. The concentration of the reagent was established by quenching an aliquot of the solution with 0.1M hydrochloric acid and back-titrating with 0.1M sodium hydroxide. The concentrations were >95%.

Reaction of Benzylmagnesium Chloride with 4,5-*Dihydro*-(2,3-*dimethoxyphenyl*)-4,4-*dimethyloxazole* (**1**).—Benzylmagnesium chloride (21.3 mmol) was added dropwise at room temperature to a stirred solution of the oxazoline (**1**) (2.0 g) in THF (20 ml) and the mixture stirred at room temperature for 24 h. It was then poured into water and the crude product isolated by extraction with ethyl acetate. The extract was washed exhaustively with dilute hydrochloric acid and then the extracts were basified with dilute ammonia solution. The crude basic products were then isolated by extraction with ethyl acetate and, after work-up, subjected to radial chromatography with 30% ethyl acetate–light petroleum as eluant. The first band that was eluted gave 2-*benzyl*-2-(2,3-*dimethoxyphenyl*)-4,4-*dimethyloxazolidine* (**3**) (0.5 g, 18%) as a gum (Found: C, 73.3; H, 7.85. $C_{20}H_{25}NO_3$ requires C, 73.35; H, 7.7%); δ_H(300 MHz) 0.94 and 0.96 (each 3 H, s, 4-Me_2), 2.18 (1 H, b, NH) 3.20 and 3.37 (2 H, AB, *J* 13.6 Hz, PhCH_2), 3.34 and 3.45 (2 H, AB, *J* 7.5 Hz, 5-CH_2), 3.88 and 3.97 (each 3 H, s, OMe), 6.85 (1 H, dd, J_m 1.7, J_o 8.0, 4- or 6-H), 6.92 (1 H, dd, J_o 7.8, 8.0 Hz, 5-H), 7.10 (1 H, dd, J_m 1.7, J_o 7.8 Hz, 4- or 6-H), and 7.18 (5 H, m, Ph); δ_C(75.5 MHz) 27.37 and 27.76 (4-Me_2), 47.03 (Ph*C*H_2), 55.78, (OMe), 58.79 (C-4), 60.92 (OMe), 77.21 (C-5), 98.57 (C-2), 117.70, 119.58, 122.79, 126.35, 127.78, and 131.00 (each Ar*C*H); 137.00, 139.53, 146.55, and 153.26 (each ArC). Further elution gave 2-(2-benzyl-3-methoxyphenyl)-4,5-dihydro-4,4-dimethyloxazole (**2**) (2.0 g, 80%) which crystallized from light petroleum as prisms, m.p. 67—68 °C (lit.,[4] 69—69.5 °C); δ_H(80 MHz) 1.50 (6 H, s, Me_2), 3.85 (3 H, s, OMe), 4.27 (2 H, s, CH_2), 4.42 (2 H, s, ArCH_2), and 6.93—8.02 (8 H, m, ArH).

1,8-*Dihydroxy*-3-*methylanthracene*-9,10-*dione* (*Chrysophanol*) (**9**)

2-*Methoxy*-4-*methylphenylmethanol*.—A solution of methyl 2-methoxy-*p*-toluate[8] (10.0 g) in anhydrous ether (100 ml) was added dropwise with stirring to lithium aluminium hydride (1.5 g) in ether at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C and treated with saturated aqueous sodium sulphate until coagulation occurred. The crude product was distilled under diminished pressure to give an oil (8.2 g, 97%), b.p. 150—153 °C at 0.05 mmHg (Kugelrohr) (lit.,[17] 280—290 °C); δ_H(60 MHz) 2.29 (3 H, s, Me), 2.95 (1 H, s, OH), 3.72 (3 H, s, OMe), and 6.47—7.14 (3 H, m, ArH).

4-*Chloromethyl*-2-*methoxytoluene*.—Freshly distilled thionyl chloride (11.6 g) was added to a solution of the foregoing alcohol (5.0 g) in benzene (50 ml) containing pyridine (2.0 ml) and the solution was heated under reflux for 3 h. It was then cooled, diluted with ethyl acetate, and washed in turn with water, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. Removal of the solvent gave the chloride (5.1 g, 91%) which decomposed on attempted distillation under reduced pressure; δ_H(60 MHz) 2.17 (3 H, s, Me), 3.62 (3 H, s, OMe), 4.45 (2 H, s, CH_2), and 6.50—7.15 (3 H, m, ArH).

4,5-*Dihydro*-2-[2-(2′-*methoxy*-4′-*methylbenzyl*)-3-*methoxyphenyl*]-4,4-*dimethyloxazole* (**5**).—The Grignard reagent (**4**), prepared from the foregoing chloride (2.27 g), was added at room temperature to a stirred solution of the oxazoline (**1**) (3.0 g) in THF (30 ml). The solution was stirred at room temperature for 18 h and then poured into water. The crude product was isolated by extraction with ethyl acetate and the organic phase was exhaustively extracted with dilute hydrochloric acid. The combined aqueous layers were basified with ammonia solution and the crude oxazoline was isolated by extraction with ethyl acetate and purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. The *oxazoline* (**5**) (2.7 g, 86%) crystallized from light petroleum as laths, m.p. 155—156.5 °C (Found: C, 74.1; H, 7.75; N, 4.15%; *M*,$^+$ 339. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.4; N, 4.15%; *M*, 339); δ_H(80 MHz) 1.19 (6 H, s, Me_2), 2.35 (3 H, s, Me), 3.71 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 3.86 (2 H, s, CH_2), 4.26 (2 H, s, ArCH_2), and 6.68—7.16 (6 H, m, ArH).

2-(2′-*Methoxy*-4′-*methylbenzyl*)-3-*methoxy*-5-*methylbenzoic Acid* (**6**).—A solution of the oxazoline (**5**) (1.0 g) in nitromethane (5.0 ml) was stirred and heated at 70 °C (bath) with iodomethane (1.4 ml) for 18 h. The solvent was removed under reduced pressure and the residue was heated under reflux with aqueous sodium hydroxide (20%; 35 ml) and methanol (35 ml) for 44 h. The cooled solution was diluted with water and then extracted with ethyl acetate; this extract was discarded. The aqueous phase was acidified with hydrochloric acid and the crude acid was isolated by extraction with ethyl acetate. The *acid* (**6**) (0.64 g, 90%) crystallized from dichloromethane–light petroleum as needles, m.p. 175—176.5 °C (Found: C, 71.15; H, 6.35%; *M*,$^+$ 286. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%; *M*, 286); δ_H(80 MHz) 2.37 (3 H, s, Me), 3.75 (9 H, s, 3 × OMe), 4.23 (2 H, s, CH_2), and 6.25—7.34 (5 H, m, ArH).

4,5-*Dimethoxy*-2-*methylanthracen*-9(10H)-*one* (**7**).—Trifluoroacetic anhydride (2.5 ml) was added dropwise at 0 °C to a stirred solution of the benzylbenzoic acid (**6**) (0.5 g) in dichloromethane (15 ml) at 0 °C. The solution was stirred at room temperature for 0.5 h and then poured into water and extracted with ethyl acetate. The extract was washed in turn with water, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. The *anthrone* (**7**) (0.43 g, 91%) crystallized from dichloromethane–light petroleum as needles, m.p. 187.5—189 °C (Found: C, 75.85; H, 5.95%; *M*$^+$, 268. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%; *M*, 268); δ_H(80 MHz) 2.46 (3 H, s, Me), 3.96 and 3.97 (each 3 H, s, OMe), 4.01 (2 H, s, CH_2), and 6.94—8.04 (5 H, m, ArH).

1,8-*Dimethoxy*-3-*methylanthracene*-9,10-*dione* (**8**).—Chromium trioxide (0.3 g) was added in portions to a solution of the anthrone (**7**) (0.3 g) in acetic acid (30 ml) which was heated on a steam-bath. After 15 min the solution was poured into an excess of saturated aqueous sodium hydrogen carbonate and the crude product was isolated by extraction with ethyl acetate. The anthraquinone (**8**) (0.27 g, 85%) crystallized from ethyl acetate as yellow prisms, m.p. 191—191.5 °C (lit.,[9] 190 °C); δ_H(80 MHz) 2.47 (3 H, s, Me), 4.00 (6 H, s, 2 × OMe), and 7.22—7.90 (5 H, m, ArH); *m*/*z* 282 (41%, *M*$^+$), 268(18), and 267(100).

1,8-*Dihydroxy*-3-*methylanthracene*-9,10-*dione* (*Chrysophanol*) (**9**).—The foregoing anthraquinone (**8**) (0.20 g) was heated under reflux for 0.5 h in acetic acid (10 ml) and hydrobromic acid (48%; 10 ml). The mixture was poured on ice and neutralized by the addition of saturated aqueous sodium hydrogen carbonate. The product was isolated by extraction with ethyl acetate. Chrysophanol (**9**) (0.17 g, 94%) crystallized from ethyl acetate as bronze laths, m.p. 194—195 °C (lit.,[9] 190 °C); δ_H(80 MHz) 2.45 (3 H, s, Me), 7.07—7.87 (5 H, m, ArH), and 11.97 and 12.08 (each 1 H, s, OH); *m*/*z* 254 (100%, *M*$^+$), 255(16), and 226(11).

1,4,5-*Trihydroxy*-2-*methylanthracene*-9,10-*dione* (*Islandicin*) (**19**)

2,5-*Dimethoxy*-4-*methylphenylmethanol*.—A solution of sodium borohydride (2.0 g) in aqueous sodium hydroxide (10%; 50 ml) was added dropwise at 0 °C to a stirred solution of 2,5-dimethoxy-4-methylbenzaldehyde[12] (9.4 g) in THF (100 ml). The solution was stirred at room temperature for 0.5 h and then poured into an excess of dilute hydrochloric acid at 0 °C. The crude product was isolated by extraction with ethyl acetate and the alcohol (8.1 g, 85%) crystallized from ether as needles, m.p. 80—81 °C (lit.,[12] 77—78 °C); δ_H(60 MHz) 2.20 (3 H, s, Me), 3.70 (6 H, s, 2 × OMe), 4.62 (2 H, s, CH_2), and 6.65 and 6.75 (each 1 H, s, ArH).

4-*Chloromethyl*-2,5-*dimethoxytoluene*.—The foregoing alcohol was converted into the chloride (89%) by a method similar to that described above. The benzyl chloride crystallized from dichloromethane–light petroleum as needles, m.p. 144—145 °C (lit.,[18] 144—146 °C); δ_H(60 MHz) 2.22 (3 H, s, Me), 3.70 and 3.75 (each 3 H, s, Me), 4.62 (2 H, s, CH_2), and 6.70 and 6.80 (each 1 H, s, ArH).

2-(2′,5′-*Dimethoxy*-4′-*methylbenzyl*)-3-*methoxybenzoic Acid* (**14**).—The Grignard reagent (**10**) derived from the foregoing benzyl chloride (15 mmol) was allowed to react with the oxazoline (**1**) (2.34 g, 10 mmol) by a method similar to that described for the preparation of compound (**5**). Work-up after 1 h gave the oxazoline (**12**) (3.6 g, 95%) as an oil; δ_H(60 MHz) 1.25 (6 H, s, Me_2), 2.10 (3 H, s, Me), 3.72 (6 H, s, 2 × OMe), 3.68 (3 H, s, OMe), 3.92 (2 H, s, CH_2), 4.22 (2 H, s, ArCH_2), and 6.28—7.25 (5 H, m, ArH). This was deprotected by a method similar to that described for compound (**5**). The benzylbenzoic acid (**14**) (2.1 g, 71%) crystallized from ethyl acetate as needles, m.p. 191.5—192.5 °C (lit.,[14] 196—197 °C); δ_H[60 MHz, $(CD_3)_2SO$] 2.06 (3 H, s, Me), 3.45, 3.65 and 3.70 (each 3 H, s, OMe), 6.25 and 6.65 (each 1 H, s, ArH), and 7.05—7.30 (3 H, m, ArH).

1,4,5-*Trimethoxy*-2-*methylanthracene*-9,10-*dione* (**18**).—Ring closure of the benzylbenzoic acid (**14**) (1.0 g) by a method similar to that described for compound (**7**) gave the crude anthranol (**16**) (0.94 g).[14] Jones reagent (7.0 ml) was added dropwise to a stirred solution of this anthranol in acetone (70 ml) and stirring was continued at room temperature for 1 h. After this the mixture was poured into water and the crude product was isolated by extraction with ethyl acetate in the usual way and then chromatographed over silica gel with 50% ethyl acetate–benzene as eluant. The quinone (**18**) (0.69 g, 69%) crystallized from methanol as yellow needles, m.p. 160.5—161 °C (lit.,[14] 160.5—162.5 °C); δ_H(60 MHz) 2.35 (3 H, s, Me), 3.85, 3.90, and 3.94 (each 3 H, s, OMe), and 7.08—7.76 (4 H, m, ArH).

1,4,5-*Trihydroxy*-3-*methylanthracene*-9,10-*dione* (*Islandicin*) (**20**).—Demethylation of the foregoing quinone (**18**) (0.21 g) by a method similar to that described for compound (**8**) gave islandicin (**19**) (0.17 g, 94%) as deep red plates (from ethyl acetate), m.p. 223.5—224 °C (lit.,[10] 218 °C); δ_H(80 MHz) 2.38 (3 H, d, $J_{Me,3}$ 1.0 Hz, Me), 7.15 (1 H, s, $W_{h/2}$ 2.2 Hz, 3-H), 7.35 (1 H, dd, $J_{8,7}$ 7.5 Hz, $J_{8,6}$ 1.6 Hz, 8-H), 7.59 (1 H, dd, $J_{7,8}$ 7.5 Hz, $J_{7,6}$ 8.1 Hz, 7-H), 7.90 (1 H, dd, $J_{6,7}$ 8.1 Hz, $J_{6,8}$ 1.6 Hz, 6-H) and 12.27, 12.32, and 13.48 (each 1 H, s, D_2O exchangeable OH); irradiation at the frequency of the methyl group sharpened the 3-H signal; *m*/*z* 271(16), 270 (100%, M^+), and 121(13).

1,4,5-*Trihydroxy*-3-*methylanthracene*-9,10-*dione* (*Digitopurpone*) (**21**)

2,5-*Dimethoxy*-3-*methylbenzonitrile*.—1-Bromo-2,5-dimethoxy-3-methylbenzene[13] (9.5 g) and copper(I) cyanide (9.7 g) were stirred and heated under reflux in *NN*-dimethylformamide (100 ml) under argon for 6 h. The mixture was poured into an excess of ethylenediamine and water, and the crude product was isolated by extraction with ethyl acetate in the usual way. The *nitrile* (6.8 g, 94%) crystallized from light petroleum as needles, m.p. 83—83.5 °C (Found: C, 67.75; H, 6.3; N, 7.95%; M^+, 177. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%; *M*, 177); δ_H(80 MHz) 2.28 (3 H, s, Me), 3.77 and 3.91 (each 3 H, s, OMe), and 6.89 and 6.93 (2 H, AB, *J* 3.6 Hz, ArH).

2,5-*Dimethoxy*-3-*methylbenzoic Acid*.—The foregoing nitrile (5.5 g) was boiled under reflux with potassium hydroxide (8.0 g), water (60 ml) and methanol (70 ml) for 72 h. Most of the methanol was removed by distillation and the cooled solution was extracted with ether; this extract was discarded. The aqueous phase was acidified and the crude acid was isolated by extraction with ethyl acetate; it crystallized from dichloromethane–light petroleum as spars (5.6 g, 92%), m.p. 79.5—80.5 °C (lit.,[19] 80—82 °C).

2,5-*Dimethoxy*-3-*methylphenylmethanol*.—A solution of the foregoing acid (5.2 g) in anhydrous THF (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.0 g) in THF (50 ml) at room temperature. After 2 h the usual work-up gave the alcohol (4.7 g, 97%) as an oil, b.p. 115 °C at 0.01 mmHg (Kugelrohr) (lit.,[20] 94—96 °C at 0.1 mmHg) (Found: C, 65.8; H, 7.65%; M^+, 182. Calc. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.75%; *M*, 182); δ_H(80 MHz) 2.27 (3 H, s, Me), 3.72 and 3.76 (each 3 H, s, OMe), 4.26 (1 H, s, OH), 4.68 (2 H, s, CH_2), and 6.65 and 6.74 (2 H, AB, *J* 4.0 Hz, ArH).

1-*Chloromethyl*-2,5-*dimethoxy*-3-*methylbenzene*.—The foregoing alcohol was converted into the chloride (92%) by a method similar to that described above. The chloride was obtained as an oil which decomposed with time.

4,5-*Dihydro*-2-[2-(2′,5′-*dimethoxy*-3′-*methylbenzyl*)-2-*methoxyphenyl*]-4,4-*dimethyloxazole* (**13**).—The oxazoline (**1**) was treated with the Grignard reagent (**11**) derived from the foregoing benzyl chloride (2.2 equiv.) in a similar manner to that described for compound (**5**). Work-up after 24 h at room temperature followed by radial chromatography of the crude product with 30% ethyl acetate–light petroleum as eluant gave the *oxazoline* (**13**) (67%) which crystallized from light petroleum as prisms, m.p. 73—74 °C (Found: C, 71.65; H, 7.7; N, 3.85%; M^+, 369. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.35; N, 3.8%; *M*, 369); δ_H 1.37 (6 H, s, Me_2), 2.28 (3 H, s, Me), 3.60, 3.72, and 3.79 (each 3 H, s, OMe), 4.10 (2 H, s, CH_2), 4.37 (2 H, s, ArCH_2), 6.06 and 6.51 (2 H, AB, *J* 3.0 Hz, 4- and 6-H), and 7.13—7.58 (3 H, m, ArH).

2-(2′,5′-*Dimethoxy*-3′-*methylbenzyl*)-3-*methoxybenzoic Acid* (**15**).—Deprotection of the oxazoline (**13**) in a manner similar to that described above gave the *benzylbenzoic acid* (**15**) (83%) which crystallized from methanol as needles, m.p. 179—180 °C (Found: C, 68.35; H, 6.65%; M^+, 316. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%; *M*, 316); δ_H(300 MHz) 2.28 (3 H, s, Me), 3.62, 3.67, and 3.75 (each 3 H, s, OMe), 4.39 (2 H, s, CH_2), 6.10 and 6.50 (2 H, AB, $J_{4',6'}$ 3.2 Hz, 4′- and 6′-H), 7.06 (1 H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 1.1 Hz, 4-H), 7.31 (1 H, dd, $J_{5,8} = J_{5,6}$ 8.0 Hz, 5-H), and 7.57 (1 H, dd, $J_{6,5}$ 8.0, $J_{6,4}$ 1.1 Hz, 6-H).

1,4,5-*Trimethoxy*-3-*methylanthracen*-9-*ol* (**17**).—Ring closure

of the benzylbenzoic acid (**15**) by a method similar to that described above gave the *anthranol* (**17**) (95%) which crystallized from dichloromethane–light petroleum as yellow needles, m.p. 180—181 °C (Found: C, 72.45; H, 6.35%; M^+, 298. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%; *M*, 298); δ_H(300 MHz), 2.43 (3 H, s, Me), 3.93, 4.06, and 4.08 (each 3 H, s, OMe), 6.45 (1 H, s, 2-H), 6.77 (1 H, d, $J_{6,7}$ 7.4 Hz, 6-H), 7.31 (1 H, dd, $J_{7,8}$ 8.7, $J_{7,6}$ 7.4 Hz, 7-H), 7.97 (1 H, d, $J_{8,7}$ 8.7 Hz, 8-H), 8.42 (1 H, s, 10-H), and 10.17 (1 H, s, OH).

1,4,8-*Trimethoxy*-2-*methylanthracene*-9,10-*dione* (**19**).—Oxidation of the anthrone (**17**) with chromium trioxide by a method similar to that described above gave the anthraquinone (**19**) which was purified by radial chromatography with 50% ethyl acetate–light petroleum as eluant; it crystallized from dichloromethane–light petroleum as yellow plates (95%), m.p. 162—164 °C (lit.,[21] 163 °C); δ_H(300 MHz) 2.41 (1 H, d, $J_{Me,3}$ 0.9 Hz, Me), 3.93, 3.96, and 4.00 (each 3 H, s, OMe), 7.08 (1 H, s, 3-H), 7.21 (1 H, dd, $J_{7,6}$ 8.0, $J_{7,5}$ 1.0 Hz, 7-H), 7.61 (1 H, dd, $J_{6,7} = J_{6,5}$ = 8.0 Hz, 6-H), and 7.74 (1 H, dd, $J_{5,6}$ 8.0, $J_{5,7}$ 1.0 Hz, 5-H); *m*/*z* 312 (M^+, 33%).

1,4,8-*Trihydroxy*-2-*methylanthracene*-9,10-*dione* (*Digitopurpone*) (**21**).—Demethylation of the foregoing compound (**19**) with hydrobromic acid in boiling acetic acid in a manner similar to that described above gave digitopurpone (**21**) (92%) which was sublimed at 110 °C at 0.01 mmHg and formed orange–red needles, m.p. 209—211 °C (lit.,[11] 209—211 °C); δ_H(300 MHz) 2.37 (3 H, d, $J_{Me,3}$, 0.9 Hz, Me), 7.17 (1 H, s, 3-H), 7.30 (1 H, dd, $J_{7,6}$ 8.4, $J_{7,5}$ 1.2 Hz, 7-H), 7.70 (1 H, dd, $J_{6,7}$ 8.4, $J_{6,5}$ 7.6 Hz, 6-H), 7.87 (1 H, dd, $J_{5,6}$ 7.6, $J_{5,7}$ 1.2 Hz, 5-H), and 12.23, 12.71, and 13.09 (each 1 H, s, OH); *m*/*z* 270 (M^+, 100%).

1,3,8-*Trimethoxy*-6-*methylanthracene*-9,10-*dione* (*Tri*-O-*methylemodin*) (**26**)

4,5-*Dihydro*-2-(2,3-*Dimethoxy*-5-*methylphenyl*)-4,4-*dimethyloxazole* (**22**).—Creosol was formylated by the method of Vierhapper *et al.*,[22] and the resultant aldehyde was methylated with iodomethane and potassium carbonate in *NN*-dimethylformamide at 75 °C during 4 h. Permanganate oxidation of the derived 2,3-dimethoxy-5-methylbenzaldehyde by the method of Manske and Ledingham[23] gave 2,3-dimethoxy-5-methylbenzoic acid. This acid (18.9 g) and thionyl chloride (22.0 ml) were stirred at room temperature for 19 h. The excess of thionyl chloride was removed under reduced pressure and the residue was azeotroped with tetrachloromethane. The resultant acid chloride dissolved in dichloromethane (50 ml) was added dropwise to a stirred solution of 2-amino-2-methylpropan-1-ol (17.2 g) in dichloromethane at 0 °C, and the mixture stirred for 1 h at room temperature. The precipitated salt was filtered off and washed with a little dichloromethane. The filtrate and washings were evaporated under reduced pressure and the residue was dissolved in dichloromethane (50 ml) and stirred and treated at 0 °C by the dropwise addition of thionyl chloride (25 ml). The solution was stirred at room temperature for 1 h and then poured into ice and water. The aqueous layer was separated and the organic phase was washed several times with water. The combined aqueous extracts were basified at 0 °C with ammonia and the crude oxazoline was isolated by extraction with ethyl acetate. The *oxazoline* (**22**), distilled under diminished pressure, was obtained as an oil (18.6 g, 77%), b.p. 165 °C at 0.7 mmHg (Kugelrohr) (Found: C, 67.7; H, 7.65%; *M*, 249. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.7%; *M*, 249); δ_H(80 MHz) 1.38 (6 H, s, Me_2), 2.30 (3 H, s, Me), 3.81 and 3.85 (each, s, OMe), 4.10 (2 H, s, CH_2), and 6.80—7.15 (2 H, m, ArH).

1-*Chloromethyl*-2,4-*dimethylbenzene*.—A cooled and stirred solution of 2,4-dimethoxyphenylmethanol (**22**) (1.0 g) in anhydrous dichloromethane (5.0 ml) and anhydrous pyridine (1.0 ml) was treated dropwise with freshly distilled thionyl chloride (1.5 g) in anhydrous dichloromethane (1.5 ml) so that the reaction temperature was −15 to −5 °C. The solution was then poured into ice and water and extracted with dichloromethane. The extract was washed with ice-cold water and with ice-cold aqueous sodium hydroxide (10%) and then dried (K_2CO_3) at −10 °C. The solvent was removed under reduced pressure at room temperature to give the benzyl chloride (0.74 g, 67%), which polymerized after *ca.* 1 h at 0 °C; δ_H(60 MHz) 3.55 and 3.60 (each 3 H, s, OMe) 4.42 (2 H, s, CH_2), and 6.18—7.09 (3 H, m, ArH).

2-(2′,4′-*Dimethoxybenzyl*)-3-*methoxy*-5-*methylbenzoic Acid* (**24**).—The Grignard reagent (**23**) (15 mmol) derived from the foregoing chloride was added dropwise at room temperature to a stirred solution of the oxazoline (**22**) (2.0 g) in THF (50 ml). The solution was stirred and heated under reflux for 18 h. Work-up gave a crude product which was purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. 4,5-Dihydro-2-[2-(2′,4′-dimethoxybenzyl)-3-methoxy-4-methylphenyl]-4,4-dimethyloxazole (2.56 g, 86%) was obtained as a viscous oil; δ_H(80 MHz) 1.21 (6 H, s, Me_2), 2.34 (3 H, s, Me), 3.72 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 3.88 (2 H, s, CH_2), 4.17 (2 H, s, ArCH_2), and 6.19—7.25 (5 H, m, ArH); *m*/*z* 369 (M^+, 100). Deprotection of this oxazoline by a method similar to that described above gave the *benzylbenzoic acid* (**24**) (84%) which crystallized from dichloromethane–light petroleum as needles, m.p. 172—174 °C (Found: C, 68.1; H, 6.6%; M^+, 316. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%; *M*, 316); δ_H(80 MHz) 2.37 (3 H, s, Me), 3.75 (9 H, s, 3 × OMe), 4.23 (2 H, s, CH_2), and 6.25—7.34 (5 H, m, ArH).

2,4,5-*Trimethoxy*-7-*methylanthracen*-9(10H)-*one* (**25**).—Ring closure of the foregoing benzylbenzoic acid (**24**) during 10 min by a method similar to that described above gave the *anthrone* (**25**) (99%) which crystallized from dichloromethane–light petroleum as tan needles, m.p. 190—191.5 °C (Found: C, 72.8; H, 6.25%; M^+, 298. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%; *M*, 298); δ_H(80 MHz) 2.46 (3 H, s, Me), 3.92 (9 H, s, 3 × OMe), 3.94 (2 H, s, CH_2), 6.72 and 7.43 (2 H, AB, $J_{1,3}$ 2.4 Hz, 3- and 1-H), and 6.94 and 7.79 (each 1 H, s, $W_{h/2}$ 4 Hz, 6- and 8-H).

1,3,8-*Trimethoxy*-6-*methylanthracene*-9,10-*dione* (*Tri*-O-*methylemodin* (**26**).—Oxidation of the anthrone (**25**) with chromium trioxide by a method similar to that described above gave the anthraquinone (**26**) (82%) which crystallized from dichloromethane–light petroleum as yellow needles, m.p. and mixed m.p. 223—224 °C (lit.,[25] 224—226 °C); *m*/*z* 312 (M^+, 52%), 298 (17), 297 (100), 295 (27), 165 (18), 153 (15), and 152 (17).

1,6-*Dimethoxy*-2-*methylanthracene*-9,10-*dione*-(*Di*-O-*methylsoranjidiol*) (**29**)

4,5-*Dihydro*-2-(2,3-*dimethoxy*-4-*methylphenyl*)-4,4-*dimethyloxazole* (**27**).—2,3-Dimethoxy-4-methylbenzoic acid[26] was converted into the oxazoline (**27**) (88%) by the general method described above. It was distilled under reduced pressure and soon crystallized as prisms, m.p. 49—50 °C (lit.,[15] 48—49 °C) (Found: C, 67.15; H, 7.8. Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.8%); δ_H(80 MHz) 1.42 (6 H, s, Me_2), 2.26 (3 H, s, Me), 3.93 (6 H, s, 2 × OMe), 4.06 (2 H, s, CH_2), and 6.92 and 7.44 (2 H, AB, *J* 8 Hz, ArH).

2-(4′-*Methoxybenzyl*)-3-*methoxy*-4-*methylbenzoic Acid*.—The Grignard reagent (**28**) (2.5 equiv.) derived from 1-chloro-

methyl-4-methoxybenzene[27] was added dropwise to the foregoing oxazoline (**27**) (3.0 g) in THF (50 ml). The solution was next heated under reflux for 18 h. Work-up gave a crude product which was purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. 4,5-Dihydro-2-[2-(4′-methoxybenzyl)-3-methoxy-4-methylphenyl]-4,4-dimethyloxazole (3.34 g, 82%) was obtained as a viscous oil; δ_H(80 MHz) 1.17 (6 H, s, Me_2), 2.26 (3 H, s, Me), 3.52 and 3.65 (each 3 H, s, OMe), 3.83 (2 H, s, CH_2), 4.34 (2 H, s, $ArCH_2$), and 5.56—7.40 (6 H, m, ArH); *m*/*z* 369 (M^+, 67%). Deprotection of this oxazoline by the method described above gave 2-(*4′-methoxybenzyl*)-3-*methoxy*-4-*methylbenzoic acid* (96%) which crystallized from dichloromethane–light petroleum as needles, m.p. 98—99 °C (Found: C, 71.25; H, 6.45%; M^+, 286. $C_{17}H_{16}O_3$ requires C, 71.3; H, 6.35%; *M*, 286); δ_H(80 MHz) 2.36 (3 H, s, Me), 3.59 and 3.73 (each 3H, s, OMe), 4.42 (2 H, s, $ArCH_2$), 6.74 and 7.15 (2 H, AA′BB′, 2′, -3′, -5′, and 6′-H), and 7.23 and 7.73 (2 H, AB, $J_{5,6}$ 8 Hz, 5- and 6-H).

1,6-*Dimethoxy*-2-*methylanthracene*-9,10-*dione* (*Di*-O-*methylsoranjidiol* (**29**).—Ring closure of the foregoing benzylbenzoic acid by a method similar to that described above gave the crude anthrone which was oxidized with chromium trioxide during 30 min by a method similar to that described above. The anthraquinone (**29**) (80%) crystallized from dichloromethane–light petroleum as bright yellow needles, m.p. 198—199 °C (lit.,[28] 195 °C) (Found: C, 72.25; H, 5.15. Calc. for $C_{17}H_{14}O_4$: C, 72.35; H, 5.0%); δ_H(80 MHz) 2.43 (3 H, s, Me), 3.93 and 3.97 (each 3 H, s, OMe), 7.25 (1 H, dd, $J_{7,8}$ 8.7 Hz, $J_{7,5}$ 2.5 Hz, 7-H), 7.56 and 8.04 (2 H, AB, $J_{3,4}$ 7.87 Hz, 3- and 4-H), 7.66 (1 H, d, $J_{5,7}$ 2.7 Hz, 5-H), and 8.23 (1 H, d, $J_{8,7}$ 8.7 Hz, 8-H); *m*/*z* 282 (M^+, 100%), 253 (37), 249 (27), 165 (32), 153 (29), 152 (40), and 139 (29).

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