The Synthesis of Indan-1-ones and Isocoumarins

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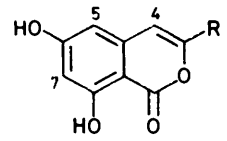
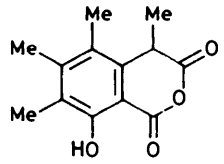
A flexible synthetic route leading *via* indan-1-ones to variously methylated and oxygenated isocoumarins is described. The indanones are prepared by alternative routes involving intramolecular Friedel–Crafts cyclisation of arylpropionic acids or pericyclic ring closure of acrylophenones. The influence of substitution on the rate of the pericyclic reaction is assessed.

THE isocoumarin moiety (1) forms the basis of an important class of secondary metabolites being isolated as end-products or intermediates of many biosynthetic pathways.[1] Thus, for example, the fungal metabolites sclerin (2),[2] canescin (3),[3] sepedonin (4),[4] and ascochitine (5) are considered to derive from various derivatives of



(1)
R = alkyl



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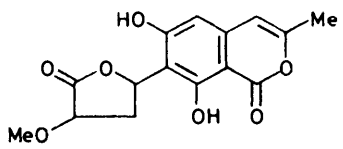

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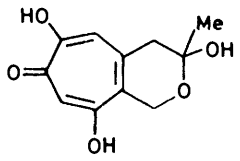

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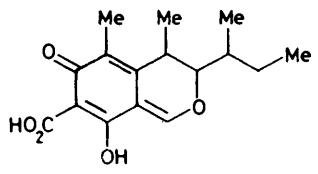


(5)

3-alkyl-6,8-dihydroxyisocoumarins. In order to test some of these hypotheses we needed to synthesise the 3-methylisocoumarins together with a set of derivatives containing one or more additional methyl groups situated at C(4), C(5), and C(7).

RESULTS AND DISCUSSION

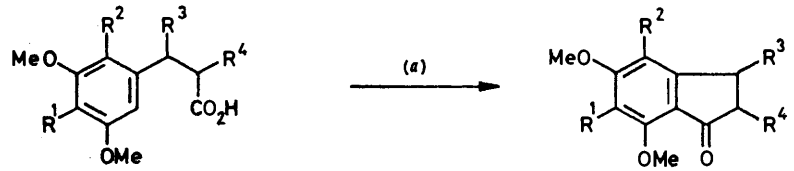
Our synthetic approach (Scheme 1) hinges on the oxidative cleavage of an indanone, which can be effected by the ozonolysis of an enol derivative of the ketone. It is important for the present studies that the synthesis of possible biosynthetic precursors must allow a high specific incorporation of an isotopic label at a selected site of the molecule; an important feature of our strategy is its flexibility which stems from the existence of alternative methods of indanone preparation, designated (*a*) and (*b*). By investigating the preparation of a range of indanones we have shown that these two methods are complementary. We have further synthesised two additional isocoumarins, (36) and (37).

The parent indanone (12) was prepared earlier by route (*a*).[5] This route also proved convenient for the preparation of the *C*-methyl analogues (10), (11), and (13). For the preparation of the more substituted indanones, however, route (*b*) proved more attractive, mainly because of the relative accessibility of the required aromatic starting materials: 1,3-dihydroxybenzene (resorcinol) and its 2-methyl, 4-methyl, and 2,4-dimethyl derivatives. The desired range of acyl substituents was readily introduced by standard methods, though once again it was necessary to employ alternative strategies depending on the substitution pattern. Thus the acrylophenones (18)—(20) and (21)—(24) were prepared using Friedel–Craft conditions with acetyl or propionyl chloride, followed by introduction of the 2,3-ene substituent by the Mannich reaction; whereas the more substituted compounds (25)—(27) and (28)—(31) were conveniently prepared directly by acylation with crotonyl or tiglyl chloride.

Both Lewis and protic acids were investigated as catalysts for the cylisation of the enones. Generally the reactions were slower with a protic acid, but the products were purer and a higher yield was obtained. The ease of cyclisation and the efficiency of the reaction is critically dependent on the substitution pattern. Thus in the absence of a methyl substituent at C(2) of an acrylophenone, no appreciable cyclisation could be achieved without using conditions sufficiently extreme to decompose the product. In addition there needs to be at least one methyl substituent in the aryl ring, although (28) did cyclise in high yield over a period of several days.

The effect of the alkyl substituents can be rationalised in terms of their ability to stabilise the intermediate carbonium ion produced by cyclisation (Scheme 2). A methyl group placed *ortho* to the site of attack has less accelerating effect than one placed *para*, presumably

because it causes a greater degree of steric hindrance. Even so, each additional methyl group in the ring has a net accelerating effect and the highest rate of cyclisation was achieved with the most substituted enone (30), the success of the cyclisation. Both the parent enone (41) [6] and the *o*-monomethoxy-derivative (42) (Scheme 3) cyclise satisfactorily in the presence of concentrated sulphuric acid as catalyst. The presence of the 2-

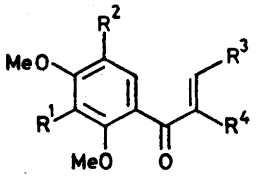


(6) $R^1=R^2=R^3=R^4=H$
(7) $R^1=Me$; $R^2=R^3=R^4=H$
(8) $R^1=R^2=R^3=H$; $R^4=Me$
(9) $R^1=R^2=Me$; $R^3=R^4=H$

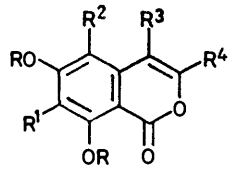
(a)

(b)

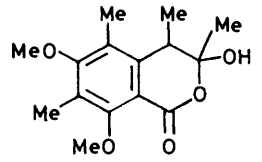
(10) $R^1=R^2=R^3=R^4=H$
(11) $R^1=Me$; $R^2=R^3=R^4=H$
(12) $R^1=R^2=R^3=H$; $R^4=Me$
(13) $R^1=R^4=Me$; $R^2=R^3=H$
(14) $R^1=R^2=R^4=Me$; $R^3=H$
(15) $R^3=R^4=Me$; $R^1=R^2=H$
(16) $R^1=R^3=R^4=Me$; $R^2=H$
(17) $R^1=R^2=R^3=R^4=Me$



(18) $R^1=R^2=R^3=R^4=H$
(19) $R^1=Me$; $R^2=R^3=R^4=H$
(20) $R^1=R^2=Me$; $R^3=R^4=H$
(21) $R^1=R^2=R^3=H$; $R^4=Me$
(22) $R^1=R^4=Me$; $R^2=R^3=H$
(23) $R^1=R^2=R^4=Me$; $R^3=H$
(24) $R^1=R^3=H$; $R^2=R^4=Me$
(25) $R^1=R^2=R^4=H$; $R^3=Me$
(26) $R^2=R^4=H$; $R^1=R^3=Me$
(27) $R^1=R^2=R^3=Me$; $R^4=H$
(28) $R^1=R^2=H$; $R^3=R^4=Me$
(29) $R^2=H$; $R^1=R^3=R^4=Me$
(30) $R^1=R^2=R^3=R^4=Me$
(31) $R^1=H$; $R^2=R^3=R^4=Me$



(32) R =Me; $R^1=R^2=R^3=H$; $R^4=Me$
(33) R =Me; $R^1=R^4=Me$; $R^2=R^3=H$
(34) R =Me; $R^1=R^2=R^3=R^4=Me$
(35) R =H; $R^1=R^2=R^3=H$; $R^4=Me$
(36) R =H; $R^1=R^4=Me$; $R^2=R^3=H$
(37) R =H; $R^1=R^2=R^3=R^4=Me$



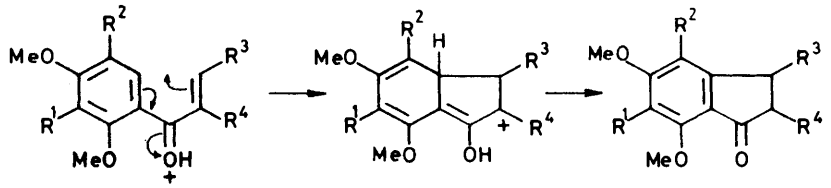
(38)

SCHEME 1

which partly cyclised to the indanone under the mild conditions of the Friedel–Craft reaction used for its preparation ($SnCl_4$ as catalyst).

The two methoxy-substituents do not critically affect methyl substituent in the enone residue is still essential, since the cyclisation failed with both (39) and (40).

For the preparation of 6,8-dihydroxyisocoumarins the two routes to the indanones in Scheme 1 are com-



SCHEME 2

plementary: the less substituted compounds are conveniently prepared from readily available starting materials according to route (*a*), whereas the more heavily substituted derivatives are best prepared by route (*b*). Two of the indanones described above, (13)

(39) $R^1 = R^2 = H$ (43) $R^1 = OMe$; $R^2 = Me$

(40) $R^1 = OMe$; $R^2 = H$

(41) $R^1 = H$; $R^2 = Me$

(42) $R^1 = OMe$; $R^2 = Me$

SCHEME 3

and (17), have been converted into the corresponding isocoumarins (33) and (34) by ozonolysis of the enol trifluoroacetate derivatives. The extra crowding resulting from the higher degree of substitution presented no insurmountable problems in these transformations, though the reactions leading to the more heavily substituted derivative (34) tended on occasion to produce a significant quantity of the hydrate (38) in addition. The lactol was readily converted into the isocoumarin by distillation. Both isocoumarins are smoothly demethylated by treatment with boron tribromide to produce high yields of the dihydroxy-compounds (36) and (37).

The routes described are ideally suited for the introduction of specific isotopic labels at key sites from readily available labelled building blocks such as malonate or methyl iodide. The way is now open, therefore, for the preparation of the wide range of variously substituted 6,8-dihydroxyisocoumarins required for biosynthetic studies.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 spectrophotometer for solutions in chloroform, unless otherwise stated. ^{1}H N.m.r. were recorded with a Varian HA100 or Perkin-Elmer RB12 spectrometer for solutions in deuteriochloroform, unless otherwise stated ($SiMe_4$ as internal standard).

3-(3,5-*Dimethoxyphenyl*)*propionic Acid* (6).—3,5-Dimethoxybenzaldehyde (0.92 g), malonic acid (1.1 g), and piperidine (0.5 ml) were dissolved in dry pyridine (24 ml) and the mixture heated with stirring for 5 h at 110 °C. On cooling, the solution was poured onto crushed ice (60 g) and hydrochloric acid (35 ml) and the solid which precipitated was removed by filtration and dried. Recrystallisation from 95% ethanol gave 3-(3,5-*dimethoxyphenyl*)*propenoic acid* (1.12 g, 94%) as white needles, m.p. 174—176 °C (Found: C, 63.4; H, 5.75. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.77%); $\lambda_{max.}$ 228, 270(sh), and 284 nm; $\nu_{max.}$ 1 690s and 1 640s cm^{-1}; δ 3.82 (6 H, S, OMe), 6.42 (1 H, AB d, *J* 16 Hz, –CH=), 6.50 (1 H, t, *J* 3 Hz, Ar-H), 6.69 (2 H, d, *J* 3 Hz, Ar-H), and 7.72 (1 H, AB d, *J* 16 Hz, –CH=); *m/e* 208 (M^+). 3-(3,5-Dimethoxyphenyl)propenoic acid (0.5 g) was dissolved in absolute ethanol (25 ml) and 5% palladium–charcoal (0.05 g) added. The mixture was hydrogenated at 20 °C and atmospheric pressure until hydrogen uptake ceased (4 h). After filtration through Hyflosupercel, the solution was evaporated *in vacuo* to give an oily residue which crystallised on standing. Recrystallisation from cyclohexane gave 3-(3,5-dimethoxyphenyl)propionic acid (6) as white crystals (0.48 g, 96%), m.p. 59—61 °C (lit.,[7] 58—60 °C); $\lambda_{max.}$ 223, 275, and 283(sh) nm; $\nu_{max.}$ 1 730s cm^{-1}; δ 2.82 (4 H, A_2B_2M, CH_2CH_2), 2.79 (6 H, s, OMe), 6.38 (3 H, s, Ar-H), and 11.34 (1 H, br s, CO_2H, exchanges with D_2O); *m/e* 210 (M^+).

3-(3,5-*Dimethoxy*-4-*methylphenyl*)-2-*methylpropionic Acid* (9).—3,5-Dimethoxy-4-methylbenzaldehyde[8] (2.4 g) was dissolved in dry benzene (30 ml); diethyl malonate (2.1 ml, 2.0 g), piperidine (0.05 ml, 0.043 g), and glacial acetic acid (0.15 ml) were added. The mixture was refluxed in a Dean–Stark apparatus for 15 h (0.2 ml water collected, theoretical amount 0.23 ml); after cooling, ether (20 ml) was added and the solution washed with 3N sulphuric acid (20 ml), 10% sodium hydrogencarbonate solution (20 ml), 5% acetic acid (20 ml), and water (20 ml) twice, then dried and evaporated to give an oil which was distilled at 160 °C/0.1 Torr to give *diethyl* 3,5-*dimethoxy*-4-*methylbenzylidenemalonate* (4.0 g, 93%) as colourless prisms from hexane, m.p. 83—85 °C (Found: C, 63.3; H, 6.8. $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88%); $\lambda_{max.}$ 225 and 311 nm; $\nu_{max.}$ 2 960(br), 1 710s, 1 620, 1 580, and 1 450 cm^{-1}; δ 1.30 (3 H, t, *J* 7 Hz, CO_2CH_2*Me*), 1.32 (3H, t, *J* 7 Hz, CO_2CH_2*Me*), 2.08 (3 H, s, Ar-*Me*), 3.76 (6 H, s, OMe), 4.28 (2 H, q, *J* 7 Hz, $COCH_2$*Me*), 4.32 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.64 (2 H, s, Ar-H), and 7.66 (1 H, s, Ar–CH=); *m/e* 322 (M^+).

Diethyl 3,5-dimethoxy-4-methylbenzylidenemalonate (0.38 g) was dissolved in dry ethyl acetate (20 ml); 5% palladium–charcoal (0.2 g) was added and the mixture hydrogenated at 20 °C and atmospheric pressure for 2 h. After filtration through Hyflosupercel, the solution was evaporated and the resulting oil distilled at 150 °C/0.05 Torr to give *diethyl* (3,5-*dimethoxy*-4-*methylbenzyl*)*malonate* (0.36 g, 95%) as colourless needles from hexane, m.p. 78—79 °C (Found: C, 63.15; H, 7.7. $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46%); $\lambda_{max.}$ 225(sh), 271, and 280 nm; $\nu_{max.}$ 2 940, 1 730s, 1 590, 1 450, and 1 140 cm^{-1}; δ 1.20 (6 H, t, *J* 7 Hz, CO_2-CH_2*Me*), 2.20 (3 H, s, Ar–Me), 3.18 (2 H, *J* 7 Hz, Ar–CH_2–), 3.66 (1 H, *J* 7 Hz, Ar–CH_2–*C*H–), 3.74 (6 H, s, OMe), 4.16 (4 H, *q*, *J* 7 Hz, CO_2CHMe), and 6.36 (2 H, s, Ar-H); *m/e* 324 (M^+).

Diethyl-(3,5-dimethoxy-4-methylbenzyl)malonate (0.37 g) in dry ethanol (2 ml) was added to a solution of sodium (0.07 g) in dry ethanol (12 ml). The mixture was refluxed for 1 h, then methyl iodide (0.195 g) in ethanol (2 ml) was added slowly and heating continued for 1 h. After cooling the solution was concentrated; ether was added, the solution washed with water, 3N sulphuric acid, and 10% sodium hydroxide, then dried and evaporated, giving *diethyl* (3,5-*dimethoxybenzyl*)*methylmalonate* (0.35 g, 95%) as a yellow oil which was not further purified; $\lambda_{max.}$ 224, 272, and 280 nm; $\nu_{max.}$ 2 980, 1 730, and 1 610 cm^{-1}; δ 1.26 (6 H. t, *J* 7 Hz, CO_2CH_2*Me*), 1.36 (3 H, s, Me), 2.02 (3 H, s, Ar–Me), 3.20 (2 H, s, Ar–CH_2–), 3.68 (6 H, s, OMe), 4.16 (4 H, q, *J* 7 Hz, CO_2CH_2Me), and 6.28 (2 H, s, Ar-H); *m/e* 338 (M^+).

Diethyl (3,5-dimethoxybenzyl)methylmalonate (1.9 g) was added to a solution of potassium hydroxide (0.6 g) in water (6 ml) and the mixture refluxed for 30 h. After

cooling, sulphuric acid (1.2 g) in water (1.8 ml) was added and heating continued for 25 h. The product was extracted with ether (2 × 10 ml), and the ethereal solution was washed with 10% sodium hydrogencarbonate (2 × 5 ml). The acidified aqueous solution was extracted with ether (2 × 10 ml) and the combined ether extracts dried and evaporated to give a yellow oil, which crystallised on standing. Recrystallisation from cyclohexane or ether gave 3-(3,5-*dimethoxyphenyl*)-2-*methylpropionic acid* (9) (1.1 g, 82%) as colourless crystals, m.p. 118—120 °C (Found: C, 65.7; H, 7.5. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%); $\lambda_{max.}$ 213, 225, and 272 nm; $\nu_{max.}$ 3 300—2 800w(br), 2 940, and 1 710 cm^{-1}; δ 1.20 (3 H, d, *J* 6 Hz, Me), 2.04 (3 H, s, Ar–Me), 2.5—3.1 (3 H, complex m, Ar–CH_2–C*H*), 3.76 (6 H, s, OMe), and 10.5 (1 H, br, CO_2H); *m/e* 238 (M^+).

3-(3,5-*Dimethoxy*-4-*methylphenyl*)*propionic Acid* (7).—Following the procedure described above for the preparation of (6), 3,5-dimethoxy-4-methylbenzaldehyde (5.5 g) was converted into 3-(3,5-*dimethoxy*-4-*methylphenyl*)*propenoic acid* (5.9 g, 96%). Recrystallisation from 95% ethanol gave white needles, m.p. 165—166 °C (Found: C, 64.8; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.31%); $\lambda_{max.}$ 231 and 304 nm; $\nu_{max.}$ 2 940, 1 690, and 1 635 cm^{-1}; δ 2.12 (3 H, s, Ar–Me), 3.84 (6 H, s, OMe), 6.39 (1 H, AB d, *J* 15 Hz, –CH=), 6.70 (2 H, s, Ar-H), 7.72 (1 H, AB d, *J* 15 Hz, –CH=), and 9.34 (1 H, br s, CO_2H, exchanges with D_2O); *m/e* 222 (M^+).

3-(3,5-Dimethoxy-4-methylphenyl)propenoic acid (0.2 g) was hydrogenated to give 3-(3,5-*dimethoxy*-4-*methylphenyl*)-*propionic acid* (7) (0.19 g, 98%), m.p. 102—104 °C (from cyclohexane) (Found: C, 64.35; H, 7.15. $C_{12}H_{16}O_4$ requires C, 64.32; H, 7.14%); $\lambda_{max.}$ 219, 271, and 280(sh) nm; $\nu_{max.}$ 1 725 cm^{-1}; δ 2.06 (3 H, s, Ar–Me), 2.81 (4 H, A_2B_2M, –CH_2CH_2–), 3.79 (6 H, s, OMe), 6.38 (2 H, s, Ar-H), and 10.93 (1 H, br s, CO_2H, exchanges with D_2O); *m/e* 224 (M^+).

1-(2,4-*Dimethoxyphenyl*)*prop*-2-*en*-1-*one* (18).—2,4-Dimethoxyacetophenone (10 g), paraformaldehyde (2.1 g), dimethylamine hydrochloride (6 g), and three drops of concentrated hydrochloric acid were refluxed in ethanol for 8 h. Ether (100 ml) was added and the solution left at 0 °C for the Mannich salt to crystallise. The ether supernatant was decanted and the residual tacky salt dissolved in dilute hydrochloric acid (15 ml) and washed with ether (2 × 15 ml). Dilute ammonia was added to release the free amine, which was then extracted into ether (3 × 25 ml), dried, and evaporated to give 3-(NN-*dimethylamino*)-1-(2,4-*dimethoxyphenyl*)*propan*-1-*one* as an orange-brown oil which could be distilled at 125—127 °C/0.5 Torr (Found: M^+, 237.164 3. $C_{13}H_{19}O_3N$ requires *M*, 237.164 7); $\lambda_{max.}$ 229, 268, and 308 nm; $\nu_{max.}$ 2 820, 2 780, and 1 685s cm^{-1}; δ 2.80 (6 H, s, NMe_2), 2.65 and 3.10 (each 2 H, t, *J* 7.5 Hz, distorted), 3.75 and 3.82 (each 3 H, s, OMe), 6.45 (1 H, d, *J* 3 Hz), 6.55 (1 H, q, *J* 11, 3 Hz), and 7.72 (1 H, d, *J* 11 Hz); *m/e* 237, 192, and 165. This amine (5.67 g) was dissolved in ether (30 ml) and methyl iodide (4.6 g) added slowly. After standing overnight at 0 °C, the methiodide salt (7.2 g) was removed by filtration and dried. The methiodide salt (400 mg) was distilled at 170 °C/0.2 Torr to give a yellow oil (180 mg, 90%) which could be further purified by p.l.c. using ether as eluant to give 1-(2,4-*dimethoxyphenyl*)*prop*-2-*en*-1-*one* (18) (Found: C, 68.05; H, 6.65. $C_{11}H_{12}O_3$ requires C, 68.64; H, 6.25%); $\lambda_{max.}$ 231, 283, and 316 nm; $\nu_{max.}$ 3 040, 2 840, and 1 660 cm^{-1}; δ 3.82, and 3.85 (each 3 H, s, OMe), 5.65 (1 H, q, *J* 9, 2 Hz, CH_2=C*H*CO), 6.25 (1 H, q, *J* 18, 2.5 Hz, CH_2 *cis* to CO), 6.45 (1 H, q, *J* 9, 2.5 Hz, 5-H), 6.45 (1 H, s, 3-H), 7.2 (1 H, q, *J* 18, 9 Hz, CH_2 *trans* to CO), and 7.65 (1 H, d, *J* 9 Hz); *m/e* 192, 165, and 112.

1-(2,4-*Dimethoxy*-3-*methylphenyl*)-2-*methylprop*-2-*en*-1-*one* (22).—1,3-Dihydroxy-2-methylbenzene (5.0 g) was added slowly with stirring to boron trifluoride–diethyl ether (10 ml) (freshly distilled from calcium hydride) and the solution cooled to 0 °C. Propionic anhydride (5.85 g) was added dropwise during 20 min and the solution allowed to warm to 20 °C, then heated at 75 °C for 6 h. On cooling, the coagulum was poured, with vigorous stirring, into ice–water (100 ml), left overnight at 4 °C, and the resulting yellow precipitate filtered off. Recrystallisation from a large volume of boiling water gave 2,4-*dihydroxy*-3-*methylpropiophenone* as colourless crystals (6.1 g, 84%), m.p. 124—125 °C (Found: C, 66.55; H, 6.65. $C_{10}H_{12}O_3$ requires C, 66.66; H, 6.66%); $\lambda_{max.}$ 227 and 270 nm; $\nu_{max.}$ 1 660 cm^{-1}; δ 1.15 (3 H, *J* 7 Hz, CH_2*Me*), 2.20 (3 H, s, Ar–*Me*), 2.96 (2 H, q, *J* 7 Hz, CH_2Me), 6.24 (1 H, AB d, *J* 16 Hz, Ar-H), and 7.37 (1 H, AB d, *J* 10 Hz, Ar-H); *m/e* 180 (M^+).

2,4-Dihydroxy-3-methylpropiophenone (5.0 g) was dissolved in dry acetone (500 ml), and potassium carbonate (30 g) and dimethyl sulphate (30 ml) were added with stirring; the solution was stirred under reflux for 48 h. After cooling and filtration, the solvent was evaporated *in vacuo*. The residue was stirred with concentrated ammonia (100 ml) for 1 h and then dissolved in water (250 ml) and ether (250 ml). The ethereal layer was separated and washed with water (4 × 250 ml), then dried and evaporated giving pale orange crystals of 2,4-*dimethoxy*-3-*methylpropiophenone*, which were recrystallised from light petroleum (b.p. 60—80 °C) to give colourless prisms (4.8 g, 86%), m.p. 40—41 °C (Found: C, 69.35; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.23; H, 7.69%); $\lambda_{max.}$ 227 and 273 nm; $\nu_{max.}$ 1 660 cm^{-1}; δ 1.18 (3 H, t, *J* 10 Hz, CH_2*Me*), 2.16 (3 H, s, Ar–*Me*), 2.95 (2 H, q, *J* 10 Hz, CH_2Me), 3.72 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.67 (1 H, AB d, *J* 9 Hz, Ar-H), and 7.53 (1 H, AB d, *J* 9 Hz, Ar-H); *m/e* 208 (M^+), 193, and 179.

1-(2,4-Dimethoxy-3-methylphenyl)-2-methylprop-2-en-1-one (22) was prepared from 2,4-dimethoxy-3-methylpropiophenone by two methods.

Method a. 2,4-Dimethoxy-3-methylpropiophenone (3.41 g), dimethylamine hydrochloride (1.75 g), paraformaldehyde (1.05 g), and concentrated hydrochloric acid (0.5 ml) were dissolved in absolute ethanol (25 ml) and the mixture heated refluxed. After 18 h more paraformaldehyde (0.3 g) was added and the reaction continued for a further 24 h. On cooling, the mixture was poured into an excess of ether (200 ml) and left overnight at 0 °C for the Mannich salt to crystallise. The supernatant was decanted off and the salt dissolved in hydrochloric acid (25 ml) and washed with ether (2 × 25 ml). Saturated sodium hydrogencarbonate solution (25 ml) was added carefully to the acidic solution, which was then extracted with ether (4 × 50 ml); the ethereal layers were dried and evaporated to give an orange oil, which was purified by distillation at 150 °C/0.5 Torr giving 3-(NN-*dimethylamino*)-1-(2,4-*dimethoxy*-3-*methylmethylphenyl*)-2-*methylpropan*-1-*one* as a pale yellow oil (2.8 g, 67%) (Found: C, 67.9; H, 8.6; N, 5.25. $C_{15}H_{23}NO_3$ requires C, 67.92; H, 8.67; N, 5.28%); $\lambda_{max.}$ 227 and 273 nm; $\nu_{max.}$ 1 665 cm^{-1}; δ 1.16 (3 H, d, *J* 7 Hz, Me), 2.16 (3 H, s, Ar–Me), 2.22 (6 H, s, NMe_2), 3.48 (2 H, q, C$H_2$$NMe_2$), 3.1—3.6 (1 H, m, COC*H*Me), 3.76 (3 H, s, OMe), 3.87 (3 H, s,

OMe), 6.65 (1 H, AB d, *J* 8 Hz, Ar-H), and 7.44 (1 H, AB d, *J* 8 Hz, Ar-H); *m/e* 265 (M^+). The methiodide salt of this amine was made by dissolving the amine (2.43 g) in ether (100 ml) with an excess of methyl iodide (25 ml). The solution was left overnight at 0 °C; the white precipitate 3.79 g) was filtered off and dried, m.p. 184—185 °C (Found: C, 46.95; H, 6.4; N, 3.2. $C_{16}H_{26}INO_3$ requires C, 47.19; H, 6.39; N, 3.44%). When heated *in vacuo* to 170 °C, the methiodide salt yielded a yellow oil of 1-(2,4-*dimethoxy*-3-*methylphenyl*)-2-*methylprop*-2-*en*-1-*one* (22), b.p. 130 °C/0.1 Torr (Found: C, 70.95; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.91; H, 7.27%); $\lambda_{max.}$ 223 and 281 nm; $\nu_{max.}$ 1 650 cm^{-1}; δ 2.03 (3 H, d, *J* 1 Hz, Me), 2.14 (3 H, s, Ar–*Me*), 3.68 (3 H, s, OMe), 3.82 (3 H, s, OMe), 5.58 (1 H, m, C*H cis* to Me), 5.83 (1 H, m, CH *trans* to Me), 6.60 (1 H, AB d, *J* 8 Hz, Ar-H), and 7.13 (1 H, AB d, *J* 8 Hz, Ar-H); *m/e* 220 (M^+).

Method b. 2,4-Dimethoxy-3-methylpropiophenone (1.0 g), piperidine hydrochloride (0.6 g), paraformaldehyde (0.025 g), and concentrated hydrochloric acid (0.2 ml) were refluxed in dry ethanol; after 1 h more paraformaldehyde (0.225 g) was added and the solution refluxed overnight. On cooling, the mixture was poured into ether (100 ml) and left for 24 h at 0 °C. The supernatant was decanted off leaving the Mannich salt, which was dissolved in saturated sodium hydrogencarbonate solution (50 ml) then extracted with ether (4 × 50 ml). The ethereal solution was dried and evaporated giving 3-*piperidino*-2-*methyl*-1-(2,4-*dimethoxy*-3-*methylphenyl*)*propan*-1-*one* as a yellow-orange oil, which gave a pale yellow oil (61%) on distillation at 160 °C/0.5 Torr (Found: C, 71.15; H, 8.8; N, 4.6. $C_{17}H_{27}NO_3$ requires C, 70.80; H, 8.85; N, 4.60%); $\lambda_{max.}$ 225 and 273 nm; $\nu_{max.}$ 1 680 cm^{-1}; δ 1.18 (3 H, d, *J* 7 Hz, Me), 1.60—2.10 (6 H, m, $CH_2CH_2CH_2$), 2.20 (3 H, s, Ar–*Me*), 2.90—3.30 (5 H, m, COC*H*Me and CH_2–N–CH_2), 3.74 (3 H, s, OMe), 3.88 (3 H, s, OMe), 6.60 (1 H, *J* 8 Hz, Ar-H), and 7.40 (1 H, *J* 8 Hz, Ar-H); *m/e* 305 (M^+). The piperidino-hydrochloride salt (3.1 g) was dissolved in water (250 ml) and steam-distilled; 2 l of distillate were collected and extracted with ether (3 × 1 l). The etheral solution was dried and evaporated giving (22) as a colourless oil (1.92 g, 88%).

1-(2,4-*Dimethoxyphenyl*)*but*-2-*en*-1-*one* (25).—1,3-Dimethoxybenzene (175 mg) was stirred at reflux with tin(IV) chloride (0.5 ml) and crotonyl chloride (0.2 ml) in AnalaR carbon disulphide (10 ml). After 2 h, the solvent was removed and the residue decomposed with ice–concentrated hydrochloric acid. After extraction into ether (3 × 5 ml), the combined organic layers were dried and evaporated to give 1-(2,4-*dimethoxyphenyl*)*but*-2-*en*-1-*one* (25) as a red oil, which was further purified by column chromatography on silica using dichloromethane as eluant to give a yellow oil (200 mg, 80%), b.p. 125 °C/0.3 Torr (Found: M^+, 206.093 7. $C_{12}H_{14}O_3$ requires *M*, 206.094 2); $\lambda_{max.}$ 232, 272, and 312 nm; $\nu_{max.}$ 2 830, 1 655, and 1 130 cm^{-1}; δ 1.95 (3 H, d, *J* 7 Hz, Me), 3.82 and 3.85 (each 3 H, s, OMe), 6.80 (1 H, s, COC*H*–), 6.85 (1 H, q, *J* 7 Hz, MeC*H*), 6.48 (1 H, br, H-3′), 6.58 (1 H, q, *J* 10, 2 Hz, H-5′), and 7.70 (1 H, d, *J* 10 Hz, H-6′); *m/e* 206 (M^+), 190, 188, 166, and 150.

1-(2,4-*Dimethoxyphenyl*)-2-*methylbut*-2-*en*-1-*one* (28).—1,3-Dimethoxybenzene (0.63 g) was dissolved in AnalaR carbon disulphide (30 ml) and stirred at reflux for 2 h with tin(IV) chloride (2 ml) and tiglyl chloride (0.65 g) until a red-brown layer had separated. The solvent was then removed and the viscous residue decomposed with ice–concentrated hydrochloric acid and extracted into ether (3 × 20 ml). The organic layers were dried and evaporated to give an oil (1.0 g) which was further purified by column chromatography on silica using dichloromethane as eluant to give 1-(2,4-*dimethoxyphenyl*)-2-*methylbut*-2-*en*-1-*one* (28) as a pale oil (0.8 g, 75%), b.p. 125 °C/0.4 Torr (Found: C, 71.4; H, 7.55. $C_{13}H_{16}O_3$ requires C, 70.90; H, 7.27%); $\lambda_{max.}$ 272(sh), 280, and 298 nm; $\nu_{max.}$ 2 950, 2 830, 1 630, 1 600, 1 570, and 1 140 cm^{-1}; δ 1.75 (3 H, d, *J* 7 Hz, COC=CH*Me*), 1.85 (3 H, s, COC*Me*), 3.61 and 3.78 (each 3 H, s, OMe), 6.44 (2 H, m, H-3′ and MeC*H*), 6.44 (1 H, d, *J* 7 Hz, H-5), and 7.13 (1 H, d, *J* 7 Hz, H-6′); *m/e* 220 (M^+), 206, 165, and 122.

1-(2,4-*Dimethoxy*-3-*methylphenyl*)*prop*-2-*en*-1-*one* (19).—Treatment of 2,4-dihydroxy-3-methylbenzene (5.0 g) in acetic anhydride and boron trifluoride–ether as described for (22) gave 2,4-*dihydroxy*-3-*methylacetophenone* (83%) as white needles from water, m.p. 165—166 °C (lit.,[9] 156—157 °C); $\lambda_{max.}$ 233, 288, and 317(sh) nm; $\nu_{max.}$ 1 655 cm^{-1}; δ 1.98 (3 H, s, CO*Me*), 2.20 (3 H, s, Ar–*Me*), 6.26 (1 H, *J* 16 Hz, Ar-H), and 7.39 (1 H, *J* 10 Hz, Ar-H); *m/e* 166 (M^+). By treatment of this compound with dimethyl sulphate and potassium carbonate, 2,4-*dimethoxy*-3-*methylacetophenone* was prepared in 82% yield as a colourless solid on distillation at 90 °C/0.1 Torr, m.p. 30—31 °C (Found: C, 68.0; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.04; H, 7.22%); $\lambda_{max.}$ 234 and 285 nm; $\nu_{max.}$ 1 670 cm^{-1}; δ 2.03 (3 H, s, COMe), 2.48 (3 H, s, Ar–*Me*), 3.70 (3 H, s, OMe), 3.82 (3 H, s, OMe), 6.38 (1 H, *J* 7 Hz, Ar-H), and 7.53 (1 H, *J* 7 Hz, Ar-H); *m/e* 194 (M^+).

1-(2,4-Dimethoxy-3-methylphenyl)prop-2-en-1-one (19) was prepared from 2,4-dimethoxy-3-methylacetophenone by two methods.

Method a. Treatment with paraformaldehyde–dimethylamine hydrochloride gave 3-dimethylamino-1-(2,4-dimethoxy-3-methylphenyl)propan-1-one (71%) as a yellow oil, b.p. 140 °C/0.3 Torr (Found: C, 66.95; H, 8.35; N, 5.5. $C_{14}H_{21}NO_3$ requires C, 66.93; H, 8.36; N, 5.57%); $\lambda_{max.}$ 230 and 273 nm; $\nu_{max.}$ 1 665 cm^{-1}; δ 2.15 (3 H, s, Ar–*Me*), 2.25 (6 H, s, NMe_2), 2.50—3.50 (4 H, m, CH_2CH_2), 3.74 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.69 (1 H, *J* 8 Hz, Ar-H), and 7.60 (1 H, *J* 8 Hz, Ar-H); *m/e* 251 (M^+). The methiodide salt of this amine melts at 178—181 °C (Found: C, 45.75; H, 6.1; N, 3.55; I, 32.7. $C_{15}H_{24}INO_3$ requires C, 45.80; H, 6.10; N, 3.56; I, 32.31%). Distillation of the methiodide salt (400 mg) gave 1-(2,4-*dimethylamino*-3-*methylphenyl*)-*prop*-2-*en*-1-*one* (19) in 75% yield as a straw-coloured oil (Found: C, 69.96; H, 6.82. $C_{12}H_{14}O_3$ requires C, 69.90; H, 6.79%); $\lambda_{max.}$ 230 and 284 nm; $\nu_{max.}$ 1 660 cm^{-1}; δ 2.14 (3 H, s, Ar–*Me*), 3.67 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.70—6.40 (2 H, ABX multiplet, $=CH_2$), 6.70—7.35 (1 H, ABX, multiplet =CH–), 6.68 (1 H, *J* 8 Hz, Ar-H), and 7.52 (1 H, *J* 9 Hz, Ar-H); *m/e* 206 (M^+).

Method b. Treatment with piperidine hydrochloride and formaldehyde gave 3-*piperidino*-1-(2,4-*dimethoxy*-3-*methylphenyl*)*propan*-1-*one* in 56% yield (Found: C, 70.15; H, 8.55; N, 4.7. $C_{17}H_{25}NO_3$ requires C, 70.10; H, 8.59; N, 4.81%); $\lambda_{max.}$ 224 and 273 nm; $\nu_{max.}$ 1 675 cm^{-1}; δ 1.60—2.10 (6 H, m, $CH_2CH_2CH_2$), 2.18 (3 H, s, Ar–*Me*), 2.80—3.30 (6 H, m, COC*H*Me and CH_2–N–CH_2), 3.76 (3 H, s, OMe), 3.88 (3 H, s, OMe), 6.56 (1 H, *J* 8 Hz, Ar-H), and 7.38 (1 H, *J* 8 Hz, Ar-H); *m/e* 291 (M^+). Steam-distillation of this amine hydrochloride (3.0 g) led to (19), (85%).

1-(2,4-*Dimethoxy*-3,5-*dimethylphenyl*)*prop*-2-*en*-1-*one* (20).—2,4-Dimethoxy-3,5-dimethylacetophenone was prepared from 1,3-dimethoxy-2,4-dimethylbenzene (1.66 g)[10] as a

pale oil (1.40 g, 76%), b.p. 110—120 °C/0.5 Torr, by treatment with acetyl chloride and tin(IV) chloride (Found: C, 69.35; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.23; H, 7.69%); $\lambda_{max.}$ 268 nm; $\nu_{max.}$ 2 930, 2 820, and 1 705 cm^{-1}; δ 2.23 (6 H, s, Ar–*Me*), 2.58 (3 H, s, CO*Me*), 3.70 (6 H, s, OMe), and 7.22 (1 H, s, Ar-H); *m/e* 208 (M^+), 193, 181, 169, 155, and 143. Treatment of 2,4-dimethoxy-3,5-dimethylacetophenone (0.5 g) with dimethylamine hydrochloride and paraformaldehyde as described for (22) gave 3-(NN-*dimethylamino*)-1-(2,4-*dimethoxy*-3,5-*dimethylphenyl*)*prop*-2-*en*-1-*one* (78%), b.p. 130—140 °C/0.5 Torr (Found: M^+, 265.168 5. $C_{15}H_{23}NO_3$ requires *M*, 265.167 7); $\lambda_{max.}$ 227, 259, and 282(sh) nm; $\nu_{max.}$ 2 880 and 1 680 cm^{-1}; δ 2.16 (6 H, s, Ar–*Me*), 2.30 (6 H, s, NMe_2), 2.68—3.16 (4 H, m, $COCH_2CH_2$NMe), 3.74 (6 H, s, OMe), and 7.31 (6 H, s, Ar-H); *m/e* 265 (M^+), 246, 220. The methiodide salt of this amine melts at 170—172 °C (Found: C, 46.8; H, 6.3; N, 3.45. $C_{16}H_{26}INO_3$ requires C, 47.17; H, 6.38; N, 3.44%). Distillation *in vacuo* of the methiodide salt (203 mg) gave 1-(2,4-*dimethoxy*-3,5-*dimethylphenyl*)*prop*-2-*en*-1-*one* (20) (95 mg, 80%), b.p. 105—110 °C/0.5 Torr (Found: M^+, 220.109 3. $C_{13}H_{16}O_3$ requires M^+, 220.109 9); $\lambda_{max.}$ 225 and 280 nm; $\nu_{max.}$ 1 660 cm^{-1}; δ 2.25 (6 H, s, Ar–*Me*), 3.54 and 3.75 (each 3 H, s, OMe), 5.82 (1 H, d, *J* 2 Hz, $COCHCH_2$), 6.27 (1 H, dd, *J* 2, 18 Hz, COCHC*H trans* to CO), 7.08 (1 H, m, *J* 9, 18 Hz, COCHC*H cis* to CO), and 7.28 (1 H, s, Ar-H); *m/e* 220, 204, 193, and 180.

1-(2-*Methoxyphenyl*)*prop*-2-*en*-1-*one* (40).—2-Methoxyacetophenone [11] (20 g) was treated with dimethylamine hydrochloride and paraformaldehyde in ethanol to give 3-(NN-*dimethylamino*)-1-(2-*methoxyphenyl*)*propan*-1-*one* (16 g, 65%) as a viscous oil; $\lambda_{max.}$ 212, 247, and 304 nm; $\nu_{max.}$ 2 730, 1 680s, and 1 610s cm^{-1}; δ 2.28 (6 H, s, NMe_2), 3.69 (2 H, t, *J* 8 Hz, 3-CH_2), 3.17 (2 H, t, *J* 8 Hz, 2-CH_2), 3.87 (3 H, s, OMe), and 7.30 (4 H, m, Ar-H); *m/e* 207 (M^+). The methiodide salt gave on distillation, 1-(2-*methoxyphenyl*)*prop*-2-*en*-1-*one* (6.0 g, 76%) as a colourless oil; $\lambda_{max.}$ 216 and 312 nm; $\nu_{max.}$ 2 850, 1 675s, and 1 605 cm^{-1}; δ 3.91 (3 H, s, OMe), and 5.6—7.7 (7 H, complex m, Ar-H and olefinic H); *m/e* 162 (M^+).

1-(2,4-*Dimethoxyphenyl*)-2-*methylprop*-2-*en*-1-*one* (21).—1,3-Dimethoxybenzene (2.8 g) was treated with propionyl chloride and tin(IV) chloride, in a manner similar to that described for (25) and (30), to give 2,4-*dimethoxypropiophenone* (3.6 g, 80%) as white needles, m.p. 66—67 °C from light petroleum (b.p. 40—60 °C) (lit.,[9] 67 °C); $\lambda_{max.}$ 228, 267, and 302 nm; $\nu_{max.}$ 2 230 and 1 658 cm^{-1}; δ 1.14 (3 H, t, *J* 6.5 Hz, $COCH_2Me$), 2.95 (2 H, q, *J* 6.5 Hz, $COCH_2$Me), 3.82 and 3.86 (each 3 H, s, OMe), 6.45 (1 H, d, *J* 2 Hz, H-3), 6.60 (1 H, d, *J* 9 Hz, H-5), and 7.85 (1 H, d, *J* 9 Hz, H-6); *m/e* 194 (M^+), 166, 155, and 149.

2,4-Dimethoxypropiophenone (0.96 g) was treated with dimethylamine hydrochloride and paraformaldehyde in ethanol as described for (22) to give 3-(NN-*dimethylamino*)-2-*methyl*-1-(2,4-*dimethoxyphenyl*)*propan*-1-*one* (1.0 g, 80%) as a yellow oil (Found: M^+, 251.153 0. $C_{14}H_{21}NO_3$ requires *M*, 251.152 0); $\lambda_{max.}$ 215, 230, and 268 nm; $\nu_{max.}$ 3 500(br), 2 820, 2 760, and 1 660 cm^{-1}; δ 1.18 (3 H, d, *J* 7 Hz, C*H*Me), 2.23 (6 H, s, NMe_2), 2.2—2.8 (2 H, dq, CH_2NMe_2), 3.76 (1 H, m, C*H*Me), 3.84 and 3.90 (each 3 H, s, OMe), 6.48 (1 H, d, *J* 2 Hz, H-3), 6.52 (1 H, dd, *J* 9, 2 Hz, H-5), and 7.72 (1 H, d, *J* 9 Hz, H-6); *m/e* 251, 236, and 220. The methiodide salt melts at 101—105 °C (Found: C, 45.7; H, 6.2; N, 3.55; I, 31.95. $C_{15}H_{24}INO_3$ requires C, 45.81; H, 6.11; N, 3.56; I, 32.2%). When distilled at 170°C/0.2 Torr, the methiodide salt (440 mg) gave 1-(2,4-*dimethoxyphenyl*-2-*methylprop*-2-*en*-1-*one* (21) as a pale yellow oil (220 mg, 95%) (Found: M^+, 206.094 7. $C_{12}H_{14}O_3$ requires *M*, 206.094 2); $\lambda_{max.}$ 226, 277, and 302 nm; $\nu_{max.}$ 2 920, 2 830, 1 650, and 1 630 cm^{-1}; δ 2.00 (3 H, d, *J* 1 Hz, Me), 3.86 and 4.00 (each 3 H, s, OMe), 5.54 (1 H, M, CH *trans* to CO), 5.75 (1 H, q, *J* 1.5 Hz, CH *trans* to Me), 6.44 (1 H, d, *J* 2 Hz, H-3), 6.48 (1 H, dd, *J* 10, 2 Hz, H-5), and 7.26 (1 H, d, *J* 10 Hz, H-6); *m/e* 206 (M^+), 189, 177, 165, and 151.

1-(2,4-*Dimethoxy*-3,5-*dimethylphenyl*)-2-*methylprop*-2-*en*-1-*one* (23).—1,3-Dimethoxy-2,4-dimethylbenzene (3.32 g) was treated with propionyl chloride and tin(IV) chloride in AnalaR carbon disulphide giving 2′,4′-*dimethoxy*-3′,5′-*dimethoxypropiophenone* (3.8 g, 87%) as an oil, b.p. 120 °C/0.5 Torr (lit.,[12] 155—158 °C/12 Torr); $\lambda_{max.}$ 258 and 300 nm; $\nu_{max.}$ 1 680 cm^{-1}; δ 1.18 (3 H, t, *J* 8 Hz, $COCH_2Me$), 2.26 (6 H, s, Ar–*Me*), 2.98 (2 H, q, *J* 8 Hz, $COCH_2$Me), 3.72 and 3.75 (each 3 H, s, OMe), and 7.20 (1 H, s, Ar-H); *m/e* 222 (M^+).

2′,4′-Dimethoxy-3′,5′-dimethylpropiophenone (0.5 g) was treated with dimethylamine hydrochloride and formaldehyde in ethanol to give 3-(*NN*-dimethylamino)-2-methyl-1-(2,4-dimethoxy-3,5-dimethylphenyl)propan-1-one as an oil (20—40%), b.p. 145 °C/0.5 Torr (Found: M^+, 279.184. $C_{16}H_{25}NO_3$ requires *M*, 279.183); $\lambda_{max.}$ 227, 259, and 282 nm; $\nu_{max.}$ 2 880 and 1 680 cm^{-1}; δ 1.17 (3 H, d, *J* 10 Hz, CH*Me*), 2.15 (6 H, s, NMe_2), 2.3—3.0 (2 H, m, CH_2NMe_2), 3.50 (1 H, M, *J* 10 Hz, C*H*Me), 3.50 and 3.70 (each 3 H, s, OMe), and 7.05 (1 H, s, Ar-H); *m/e* 279 (M^+). Distillation of the corresponding methiodide salt (800 mg) gave 1-(2,4-*dimethoxy*-3,5-*dimethylphenyl*)-2-*methylprop*-2-*en*-1-*one* (23) (355 mg, 89%) as a pale yellow oil, b.p. 130—140 °C/0.1 Torr (lit.,[12] 122—124 °C/0.4 Torr) (Found: M^+, 234.127 5. $C_{14}H_{18}O_3$ requires *M*, 234.125 6); $\lambda_{max.}$ 212 and 273 nm; $\nu_{max.}$ 1 650s and 1 115 cm^{-1}; δ 2.05 (3 H, d, *J* 2 Hz, olefinic Me), 2.28 (6 H, s, Ar–*Me*), 3.64 and 3.72 (each 3 H, s, OMe), 5.64 (1 H, m, CH *cis* to CO), 5.88 (1 H, m, CH *trans* to CO), and 6.90 (1 H, s, Ar-H); *m/e* 234 (M^+), 220, 193, and 179.

1-(2,4-*Dimethoxy*-5-*methylphenyl*)-2-*methylprop*-1-*en*-2-*one* (24).—1,3-Dimethoxy-4-methylbenzene (0.23 g) was treated with tin(IV) chloride and propionyl chloride in carbon disulphide to give 2′,4′-*dimethoxy*-5′-*methylpropiophenone* (270 mg, 80%) as white needles from light petroleum (b.p. 40—60 °C), m.p. 72.5—73.5 °C (Found: C, 69.25; H, 7.95. $C_{12}H_{16}O_3$ requires C, 69.23; H, 7.95%); $\lambda_{max.}$ 228, 265, and 311 nm; $\nu_{max.}$ 1 720 and 1 650 cm^{-1}; δ 1.20 (3 H, t, *J* 8 Hz, $COCH_2Me$), 2.18 (3 H, s, Ar–*Me*), 2.94 (2 H, q, *J* 8 Hz, $COCH_2$Me), 3.85 and 3.90 (each 3 H, s, OMe), 6.44 (1 H, s, H-3) and 7.68 (1 H, s, H-6); *m/e* 208 (M^+), 179, 165, and 150. Treatment with dimethylamine hydrochloride and paraformaldehyde in ethanol gave 3-(*NN*-dimethylamino)-2-methyl-1-(2,4-dimethoxy-5-methylphenyl)propan-1-one (70 mg from 52 mg ketone), b.p. 140 °C/0.5 Torr (Found: M^+, 265.166 8. $C_{15}H_{23}NO_3$ requires *M*, 265.167 7); $\lambda_{max.}$ 231, 271, and 313 nm; $\nu_{max.}$ 1 658, 1 605, and 3 500(br) cm^{-1}; δ 1.14 (3 H, d, *J* 7 Hz, Me), 2.12 (3 H, s, Ar–*Me*), 2.1—2.7 (2 H, m, CH_2NMe_2), 2.20 (6 H, s, NMe_2), 3.85 and 3.88 (each 3 H, s, OMe) and 7.50 (1 H, s, Ar-H); *m/e* 265 (M^+), 250, 233, 220, and 180. The corresponding methiodide salt melts at 190—192 °C (Found: C, 47.1; H, 6.5; N, 3.35. $C_{16}H_{26}INO_3$ requires C, 47.19; H, 6.39; N, 3.44%). Distillation of the methiodide salt (50 mg) at 150 °C/0.5 Torr gave 1-(2,4-*dimethoxy*-5-*methylphenyl*)-2-*methylprop*-2-*en*-1-*one* (24) (Found: M^+, 220.109 5. $C_{13}H_{16}O_3$ requires *M*, 220.109 9); $\lambda_{max.}$ 228, 275, and 312 nm; $\nu_{max.}$ 1 645, 1 655,

and 1 610 cm^{-1}; δ 2.03 (3 H, s, COCMe), 2.16 (3 H, s, Ar–Me), 3.79 and 3.88 (each 3 H, s, OMe), 5.55 (1 H, m), 5.74 (2 H, m), and 7.71 (1 H, s, Ar-H); *m/e* 220, 205, 180, and 179.

1-(2-*Methoxyphenyl*)-2-*methylprop*-2-*en*-1-*one* (42).—2-Hydroxypropiophenone [13] (20 g) was treated with dimethyl sulphate and potassium carbonate, as described in the preparation of (22), to give 2-*methoxypropiophenone* (15.4 g, 70%) as an oil, b.p. 134—136 °C/22 Torr (Found: C, 73.3; 4, 7.2. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%); $\lambda_{max.}$ 211, 245, and 302 nm; $\nu_{max.}$ (film) 1 675s, 1 600s, 1 485, and 1 285 cm^{-1}; δ 1.16 (3 H, t, *J* 7 Hz, Me), 3.04 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 3.86 (3 H, s, OMe), and 6.8—7.7 (4 H, m, Ar-H); *m/e* 164 (M^+). 2-Methoxypropiophenone (11 g) was treated with dimethylamine hydrochloride and paraformaldehyde in methanol to give 3-(NN-*dimethylamino*)-1-(2-*methoxyphenyl*)-2-*methylpropan*-1-*one* (9.9 g, 75%); $\lambda_{max.}$ 217, 250, and 305 nm; $\nu_{max.}$ (film) 1 680s, 1 600, 1 485, and 1 285 cm^{-1}; δ 1.05 (3 H, d, *J* 7 Hz, CH*Me*), 2.07 (6 H, s, NMe_2), 2.2—2.7 (2 H, m, C*H*$_2$$NMe_2$), 3.55 (1 H, m, *J* 7 Hz, C*H*Me), 3.78 (3 H, s, OMe), and 6.8—7.5 (4 H, m, Ar-H); *m/e* 219 (M^+), 176, and 139. The methiodide salt melts at 129—130 °C (Found: C, 86.8; H, 5.8; N, 3.9; I, 35.0. $C_{14}H_{22}INO_2$ requires C, 46.6; H, 5.6; N, 3.9; I, 35.1%). Pyrolysis of the hydrochloride salt (10 g) of this amine at 160 °C for 3 h gave 1-(2-methoxyphenyl)-2-methylprop-2-en-1-one (42) as an oil (5.5 g, 70%); $\lambda_{max.}$ 215 and 280 nm; $\nu_{max.}$ 1 665s, 1 600, 1 250, and 750 cm^{-1}; δ 1.20 (3 H, s, Me), 3.71 (3 H, s, OMe), 5.57 (1 H, m, olefinic H), 5.85 (1 H, m, olefinic H), and 6.8—7.4 (4 H, m, Ar-H); *m/e* 176 (M^+).

1-(2,4-*Dimethoxy*-3-*methylphenyl*)*but*-2-*en*-1-*one* (26).—1,3-Dimethoxy-2-methylbenzene (1.0 g) was treated with crotonyl chloride and tin(IV) chloride as described for (25) to give 1-(2,4-dimethyl-3-methylphenyl)but-2-en-1-one (26) as an oil, b.p. 130—140 °C/0.4 Torr (Found: M^+, 220.110. $C_{13}H_{16}O_3$ requires *M*, 220.109 9); $\lambda_{max.}$ 210 and 292 nm; $\nu_{max.}$ 1 660 cm^{-1}; δ 1.96 (3 H, d, *J* 5 Hz, *Me*CH), 2.2 (3 H, s, Ar–*Me*), 3.72 and 3.89 (each 3 H, s, OMe), 6.90 (1 H, s, CH*CH*CHMe), 6.92 (1 H, q, *J* 5 Hz, Me*CH*), 6.68 (1 H, d, *J* 8 Hz, H-5), and 7.48 (1 H, d, *J* 8 Hz, H-6); *m/e* 220, 205, 203, and 179.

1-(2,4-*Dimethoxy*-3,5-*dimethylphenyl*)*but*-2-*en*-1-*one* (27).—Treatment of 1,3-Dimethoxy-2,4-dimethylbenzene (0.83 g) with crotonyl chloride and tin(IV) chloride in AnalaR carbon disulphide gave 1-(2,4-*dimethoxy*-3,5-*dimethylphenyl*)-*but*-2-*en*-1-*one* (27) as an oil (1.0 g, 82%), b.p. 110—120 °C/0.4 Torr (Found: C, 71.05; H, 7.7%; *m/e* 234.125 4. $C_{14}H_{18}O_3$ requires C, 71.80; H, 7.69%; *m/e* 234.125 6); $\lambda_{max.}$ 223 and 269 nm; $\nu_{max.}$ 1 665 cm^{-1}; δ 1.95 (3 H, d, *J* 6 Hz, *Me*CH), 2.25 and 2.28 (each 3 H, s, Ar–*Me*), 3.70 and 3.76 (each 3 H, s, OMe), 6.81 (1 H, s, COC*H*CHMe), 6.88 (1 H, q, *J* 6 Hz, C*H*Me), and 7.21 (1 H, s, Ar-H); *m/e* 234, 219, 205, 193, 181, 169, and 155.

1-(2,4-*Dimethoxy*-3-*methylphenyl*)-2-*methylbut*-2-*en*-1-*one* (29).—Treatment of 1,3-dimethoxy-3-methylbenzene (1.5 g) with tiglyl chloride and tin(IV) chloride in AnalaR carbon disulphide, as described in the preparation of (28), gave 1-(2,4-dimethoxy-3-methylphenyl)-2-methylbut-2-en-1-one (1.8 g, 82%) as an oil, b.p. 130 °C/0.5 Torr (Found: C, 71.55; H, 7.9. $C_{14}H_{18}O_3$ requires C, 71.80; H, 7.63%); $\lambda_{max.}$ 231 and 276 nm; $\nu_{max.}$ 2 920, 2 830, 1 630, 1 580, and 1 115 cm^{-1}; δ 1.78 (3 H, d, *J* 8 Hz, *Me*CH), 1.90 (3 H, d, *J* 1 Hz, COCH*Me*), 2.11 (3 H, s, Ar–*Me*), 3.62 and 3.79 (each 3 H, s, OMe), 6.32 (1 H, q, *J* 8 Hz, H-3), 6.56 (1 H, d, *J* 8 Hz, H-5′), and 6.98 (1 H, d, *J* 8 Hz, H-6′); *m/e* 220 (M^+), 219, 205, 179, and 165.

1-(2,4-*Dimethoxy*-3,5-*dimethylphenyl*)-2-*methylbut*-2-*en*-1-*one* (30).—1,3-Dimethoxy-2,4-dimethylbenzene (0.83 g) was reacted with tiglyl chloride and tin(IV) chloride in AnalaR carbon disulphide to give 5,7-dimethoxy-2,3,4,6-tetramethylindan-1-one (17) (1.05 g) and 1-(2,4-*dimethoxy*-3,5-*dimethylphenyl*)-2-*methylbut*-2-*en*-1-*one* (30) (0.04 g), b.p. 120—125 °C/0.3 Torr (Found: C, 72.45; H, 8.25. $C_{15}H_{20}O_3$ requires C, 72.58; H, 8.06%); $\lambda_{max.}$ 230 and 270 nm; $\nu_{max.}$ 1 660 and 1 635 cm^{-1}; δ 1.85 (3 H, d, *J* 7 Hz, Me), 1.90 (3 H, s, CH*Me*), 2.2 (6 H, s, Ar–*Me*), 3.62 and 3.70 (each 3 H, s, OMe), 6.2—6.3 (1 H, m, C*H*Me), and 6.8 (1 H, s, Ar-H); *m/e* 248 (M^+).

1-(2,4-*Dimethoxy*-5-*methylphenyl*)-2-*methylbut*-2-*en*-1-*one* (31).—1,3-Dimethoxy-4-methylbenzene (300 mg) was treated with tiglyl chloride and tin(IV) chloride in AnalaR carbon disulphide to give 5,7-*dimethoxy*-2,3,4-*trimethylindan*-1-*one* (213 mg) and 1-(2,4-dimethoxy-5-methylphenyl)-2-methylbut-2-en-1-one (31) (80 mg) (Found: M^+, 234.125 6. $C_{14}H_{18}O_3$ requires *M*, 234.125 6); $\lambda_{max.}$ 220, 277, and 307 nm; $\nu_{max.}$ 1 630 cm^{-1}; δ 2.28 (3 H, s, Ar–*Me*), 3.80 and 3.92 (each 3 H, s, OMe), 6.51 (1 H, s, Ar-H), and 7.07 (1 H, s, Ar-H); *m/e* 234.

5,7-*Dimethoxyindan*-1-*one* (10).—3-(3,5-Dimethoxyphenyl)propionic acid (6) (0.9 g) was added with stirring to polyphosphoric acid (30 ml) at 65 °C. The mixture was stirred for 75 min at 65 °C, then poured into ice–water (100 ml) with vigorous stirring. The solution was adjusted to pH 6 with sodium hydroxide solution, then extracted with benzene (4 × 100 ml). The benzene solution was washed with 10% sodium hydroxide (2 × 100 ml) and water (100 ml), then evaporated *in vacuo* leaving pale yellow crystals of 5,7-dimethoxyindan-1-one, which were recrystallised from benzene–light petroleum (1 : 1) as colourless needles (0.8 g, 90%), m.p. 98—99 °C (lit.,[7] 98.5—99.5 °C); $\lambda_{max.}$ 228, 273, and 300(sh) nm; $\nu_{max.}$ 1 690s and 1 600s cm^{-1}; δ 2.60 (2 H, m, CH_2), 2.96 (2 H, m, CH_2), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.25 (1 H, d, *J* 1 Hz, Ar-H), and 6.42 (1 H, d, *J* 1 Hz, Ar-H); *m/e* 192 (M^+).

5,7-*Dimethoxy*-6-*methylindan*-1-*one* (11).—Freshly distilled trifluoroacetic acid anhydride (4 ml) was added to a solution of 3-(3,5-dimethoxy-4-methylphenyl)propionic acid (7) (0.9 g) in trifluoracetic acid (16 ml). The mixture was stirred at 0 °C for 30 min, then evaporated to small volume (*ca.* 2 ml) and taken up in ether (25 ml). The ether solution was washed with 10% sodium hydroxide (2 × 25 ml), water (25 ml), then dried and evaporated to give an orange solid which was recrystallised from ethyl acetate–hexane (1 : 1) as pale yellow prisms of 5,7-*dimethoxy*-6-*methylindan*-1-*one* (11) (0.7 g, 77%), m.p. 113—115 °C (Found: C, 69.9; H, 6.8. $C_{12}H_{14}O_3$ requires C, 69.91; H, 6.79%); $\lambda_{max.}$ 230, 278, and 304(sh) nm; $\nu_{max.}$ 1 690s and 1 600s cm^{-1}; δ 2.10 (3 H, s, Me), 2.60 (2 H, m, CH_2), 2.96 (2 H, m, CH_2), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), and 6.50 (1 H, s, Ar-H); *m/e* 208 (M^+).

5,7-*Dimethoxy*-2,6-*dimethylindan*-1-*one* (13).—*Method a.* Trifluoroacetic anhydride (3.5 ml) was added to a solution of 3-(3,5-dimethoxy-4-methylphenyl)-2-methylpropionic acid (9) in trifluoracetic acid (15 ml). The mixture was stirred at 0 °C for 30 min, then evaporated to small volume, taken up in ether (25 ml) and washed with dilute sodium hydroxide solution (2 × 25 ml), then water (25 ml). The ethereal solution was dried and evaporated to give a yellow oil which could be recrystallised from light petroleum (b.p. 40—60 °C) as white needles of 5,7-*dimethoxy*-2,6-*dimethylindan*-1-*one* (0.36 g, 68%), m.p. 59—60 °C (Found: C, 70.65; H, 7.4.

$C_{13}H_{16}O_3$ requires C, 70.88; H, 7.32%); $\lambda_{max.}$ 227 and 275 nm; $\nu_{max.}$ 1 690 cm^{-1}; δ 1.25 (3 H, d, *J* 7 Hz, Me), 2.10 (3 H, s, Ar–*Me*), 2.4—2.8 (2 H, m, CH_2), 3.2—3.4 (1 H, m, CH), 3.86 (3 H, s, OMe), 3.92 (3 H, s, OMe), and 6.60 (1 H, s, Ar-H); *m/e* 220 (M^+).

Method b. 1-(2,4-Dimethoxy-3-methylphenyl)-2-methylprop-2-en-1-one (22) (2.0 g) and fluorosulphonic acid (1 ml) were dissolved in dry chloroform (25 ml) and the solution stirred at 20 °C for 1 week. The solvent was removed *in vacuo* and the residue partitioned between ether (50 ml) and water (50 ml). The ether solution was washed with 10% sodium hydroxide (25 ml) and water (2 × 25 ml), dried, and evaporated to give a white solid which was recrystallised from light petroleum (b.p. 40—60 °C) to give (13) as white needles (1.89, 95%).

7-*Methoxy*-2-*methylindan*-1-*one* (43).—Concentrated sulphuric acid (2 ml) was mixed with 1-(2-methoxyphenyl)-2-methylprop-2-en-1-one (42) (200 mg) at room temperature and stirred for 15 h. The mixture was added to water (20 ml), extracted with ether (2 × 25 ml), dried, and evaporated to give 7-*methoxy*-2-*methylindan*-1-*one* (43) (150 mg, 75%); $\lambda_{max.}$ 223, 267, 285, and 295 nm; $\nu_{max.}$ 1 690s, 1 600s, 1 460, and 1 260 cm^{-1}; δ 1.25 (3 H, d, *J* 7 Hz, Me), 2.61 (2 H, m, *J* 14 Hz, CH_2), 3.32 (1 H, m, *J* 8 Hz, C*H*Me), 3.86 (3 H, s, OMe), 6.80 (2 H, m, Ar-H), and 7.61 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 176 (M^+).

5,7-*Dimethoxy*-2,3,4,6-*tetramethylindan*-1-*one* (17).—1,3-Dimethoxy-2,4-dimethylbenzene (0.83 g) was dissolved in AnalaR carbon disulphide (30 ml). Tin(IV) chloride (2 ml) and tiglyl chloride (0.5 ml) were added and the solution stirred at reflux for 1—2 h until a red-brown solid had separated. After removal of solvent (water-bath), the gummy residue was decomposed with ice–hydrochloric acid and extracted into ether (3 × 30 ml). The organic layers were dried, then evaporated to give a brown oil (1.3 g) which was further purified by column chromatography on silica gel with dichloromethane as eluant. The relative yields of (31) and (17) were variable, but typically a pale yellow oil (1.03 g, 83%) was obtained, which distilled at 125—130 °C/0.5 Torr to give 5,7-dimethoxy-2,3,4,6-tetramethylindan-1-one;[14] $\lambda_{max.}$ 260 and 302 nm; $\nu_{max.}$ 2 840, 1 695s, 1 585, 1 325, and 1 120 cm^{-1}; δ 1.1—1.4 (6 H, m, *J* 7, 8.5 Hz, Me, mixture of isomers), 2.24 (3 H, s, Ar–*Me*), 2.30 (3 H, s, Ar–*Me*), 2.7—3.0 (1 H, m, Ar–C*H*Me), and 3.0—4.0 (1 H, m, CO*CH*Me); *m/e* 248 (M^+).

5,7-*Dimethoxy*-2,3-*dimethylindan*-1-*one* (15).—This was obtained in trace amounts from the reaction of 1,3-dimethoxybenzene with tiglyl chloride; alternatively, cyclisation of 1-(2,4-dimethoxyphenyl)-2-methylbut-2-en-1-one (28) with fluorosulphonic acid as described for (13) gave 5,7-*dimethoxy*-2,3-*dimethylindan*-1-*one* [15] (15), b.p. 130 °C/0.4 Torr (Found: M^+, 220.109 6. $C_{13}H_{16}O_3$ requires *M*, 220.109 9); $\lambda_{max.}$ 225, 273, and 298(sh) nm; $\nu_{max.}$ 1 685 cm^{-1}; δ 1.0—1.4 (6 H, m, COCH*Me* and ArCH*Me*), 2.0—3.5 (2 H, m, Ar–C*H* and COC*H*–), 3.90 (6 H, s, OMe), 6.28 (1 H, s, Ar-H), and 6.45 (1 H, s, Ar-H); *m/e* 220 (M^+).

5,7-*Dimethoxy*-2,3,6-*trimethylindan*-1-*one* (16).—Cyclisation of 1-(2,4-dimethoxy-3-methylphenyl)-2-methylbut-2-en-1-one (29) with fluorosulphonic acid gave 5,7-*dimethoxy*-2,3,6-*trimethylindan*-1-*one* (16) as an oil, b.p. 135 °C/0.5 Torr (Found: C, 71.75; H, 7.75. $C_{14}H_{18}O_3$ requires C, 71.80; H, 7.69%); $\lambda_{max.}$ 273 nm; $\nu_{max.}$ 1 690 cm^{-1}; δ 1.35 (6 H, s, ArCH*Me* and COCH*Me*), 2.0—3.5 (2 H, m, ArC*H*– and COC*H*Me), 2.10 (3 H, s, Ar–Me), 3.90 and 3.92 (each 3 H, s, OMe), and 6.61 (1 H, s, Ar-H); *m/e* 234 (M^+).

5,7-*Dimethoxy*-2,4,6-*trimethylindan*-1-*one* (14).—Cyclisation of 1-(2,4-dimethoxy-3,5-dimethylphenyl)-2-methylprop-2-en-1-one (23) with fluorosulphonic acid gave 5,7-dimethoxy-2,4,6-trimethylindan-1-one (14), b.p. 110—115 °C/0.1 Torr (lit.,[12] 145—148 °C/3 Torr); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 2 840, 1 685, and 1 140 cm^{-1}; δ 1.30 (3 H, d, *J* 8.5 Hz, COCH*Me*), 2.20 (6 H, s, Ar–*Me*), 2.5—3.5 (3 H, m, Ar–CH_2, COCH_2, and CO*CH*Me), and 3.75 and 3.92 (each 3 H, s, OMe); *m/e* 234 (M^+), 220, 205, and 191.

6,8-*Dimethoxy*-3,7-*dimethylisocoumarin* (33).—A solution of 5,7-dimethoxy-2,6-dimethylindan-1-one (13) (0.58 g) in freshly distilled trifluoracetic anhydride (20 ml) was stirred at 20 °C for 40 min. The solvent was removed *in vacuo* and the brown residue distilled at 130 °C/0.1 Torr to give 5,7-*dimethoxy*-2,6-*dimethyl*-1-*trifluoracetoxyindene* as a pale yellow oil which crystallised on standing (0.66 g, 79%), m.p. 70—72 °C (Found: C, 57.55; H, 5.05. $C_{15}H_{15}F_3O_4$ requires C, 56.96; H, 4.78%); $\lambda_{max.}$ 247, 269, 277, 289, and 324 nm; $\nu_{max.}$ 1 720s and 1 600s cm^{-1}; δ 2.15 (3 H, s, Me), 2.20 (3 H, s, Me), 3.30 (2 H, s, CH_2), 3.80 (3 H, s, OMe), 3.86 (3 H, s, OMe), and 6.80 (1 H, s, Ar-H); *m/e* 316 (M^+). This unstable enol trifluoracetate (0.66 g) was dissolved in dry ethyl acetate (100 ml) and cooled to −78 °C. Ozone was passed through the solution until it became pale blue, then the solution was flushed with N_2. Dimethyl sulphide (10 ml) was added and the solution stirred at 20 °C overnight, when the solvent was removed *in vacuo* and the residue dissolved in ether (50 ml). The ethereal solution was washed with water (2 × 30 ml), then dried and evaporated. Colourless crystals of 6,8-*dimethoxy*-3,7-*dimethylisocoumarin* (33) were obtained from methanol (0.65 g, 75%), m.p. 153—156 °C (Found: C, 66.35; H, 6.05. $C_{13}H_{14}O_4$ requires C, 66.37; H, 6.02%); $\lambda_{max.}$ 248, 270, 288, and 324 nm; $\nu_{max.}$ 1 720 and 1 600 cm^{-1}; δ 2.14 (3 H, s, Me), 2.20 (3 H, s, Me), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.15 (1 H, s, CH), and 6.45 (1 H, s, Ar-H); *m/e* 234 (M^+).

6,8-*Dihydroxy*-3,7-*dimethylisocoumarin* (36).—6,8-Dimethoxy-3,7-dimethylisocoumarin (33) (0.2 g) was dissolved in dry dichloromethane (25 ml) at −78 °C. Boron tribromide (1 ml) was added slowly with stirring and the solution allowed to warm up to 20 °C overnight. Most of the solvent was removed *in vacuo* and ether added cautiously. The white precipitate which formed was removed by filtration and washed with ether (5 ml), then water (5 ml). Sublimation at 160 °C/0.5 Torr gave 6,8-*dihydroxy*-3,7-*dimethylisocoumarin* (36) as a white powder (0.167 g, 90%), m.p. 230 °C (sublimes) (Found: C, 64.15; H, 4.85. $C_{11}H_{10}O_4$ requires C, 64.07; H, 4.85%); $\lambda_{max.}$ 245, 279, and 327 nm; $\nu_{max.}$ 1 670 cm^{-1}; δ 2.05 (3 H, s, Me), 2.21 (3 H, s, Ar–*Me*), 6.23 (1 H, s), and 6.27 (1 H, s); *m/e* 206 (M^+).

6,8-*Dimethoxy*-3,4,5,7-*tetramethylisocoumarin* (34).—Freshly distilled 2,3,4,6-tetramethyl-5,7-dimethoxyindan-1-one (17) (84 mg) was dissolved in freshly prepared trifluoroacetic anhydride; the solution was stirred for 3—4 h, during which time a pink colour developed. The solution was then evaporated to give 5,7-*dimethoxy*-2,3,4,6-*tetramethyl*-1-*trifluoroacetoxyindene* as a dark oil (90 mg) which was not further purified; $\lambda_{max.}$ (hexane) 234, 241(sh), 252, 259, 266, and 269 nm; $\nu_{max.}$ 1 765, 1 160, 1 125, 1 095, and 900 cm^{-1}; δ 1.35 (3 H, d, *J* 7.5 Hz, ArC*H*Me), 1.9 (3 H, s, Me–C=), 3.22 and 3.32 (each 3 H, s, Ar–*Me*), 3.0—3.5 (1 H, m, ArC*H*Me), and 3.70 and 3.75 (each 3 H, s, OMe); *m/e* 344 (M^+) and 248. The crude enol trifluoracetate (90 mg) was dissolved in dry ethyl acetate (50 ml) and ozonised at −78 °C. After removal of excess of ozone, dimethyl sulphide (0.5 ml) was

added and the solution allowed to warm to room temperature overnight. Evaporation of the solvent, finally at high vacuum, gave a brown oil (110 mg) which was shown to be 6,8-dimethoxy-3-hydroxy-3,4,5,7-tetramethyl-3,4-dihydroisocoumarin [14] (38) by its n.m.r. data. It distilled as the isocoumarin (34) and could not be purified by t.l.c.; $\lambda_{max.}$ 255 and 301 nm; $\nu_{max.}$ 1 715 cm^{-1}; δ 1.25 (3 H, d, *J* 7 Hz, ArCH*Me*), 1.65 [3 H, s, C(OH)*Me*], 2.21 (6 H, s, Ar–*Me*), 3.72 and 3.78 (each 3 H, s, OMe), and 4.4 (1 H, s, OH); *m/e* 280(w), 262 ($M^+ - 18$), and 248. The crude lactol (38), when distilled at 130—140 °C/0.3 Torr with toluene-*p*-sulphonic acid, gave a pale yellow oil which solidified on standing. Recrystallisation from acetone–light petroleum (b.p. 40—60 °C) gave 6,8-*dimethoxy*-3,4,5,7-*tetramethylisocoumarin* as white needles, m.p. 144—145 °C (lit.,[16] 144.5—145 °C); $\lambda_{max.}$ 245, 260, 278, 287, and 343 nm; $\nu_{max.}$ 1 720 and 1 645 cm^{-1}; δ 3.30 (9 H, Me), 3.55 (3 H, s, Me), and 3.88 and 3.92 (each 3 H, s, OMe); *m/e* 262 (M^+), 260, 248, 234, and 218.

6,8-*Dihydroxy*-3,4,5,7-*tetramethylisocoumarin* (37).—6,8-Dimethoxy-3,4,5,7-tetramethylisocoumarin (34) (10 mg) was dissolved in dry dichloromethane (10 ml) and cooled to − 78 °C. Boron tribromide (0.2 ml) was added with stirring and the reaction allowed to warm to room temperature overnight. Ether (10 ml) was added cautiously, followed by water (3 × 10 ml). The combined aqueous layers were extracted into ether (3 × 10 ml) and the combined organic layers then dried and evaporated to give 6,8-*dihydroxy*-3,4,5,7-*tetramethylisocoumarin* (37) as a white powder (8 mg) which was recrystallised from methanol as a white powder, m.p. 223—224 °C (lit.,[16] 224 °C); $\lambda_{max.}$ 247, 267, 285, 293, and 345 nm; $\nu_{max.}$ 3 200(br), 1 728, 1 662, and 1 618 cm^{-1}; δ 1.29 (2 H, br, OH), 2.18 (3 H, s, Ar-C*Me*), 2.29 and 2.32 (each 3 H, s, Ar–*Me*), and 2.44 (3 H, s, ArCH*Me*); *m/e* 234 (M^+).

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