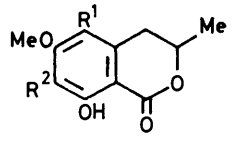
Synthesis of Chlorinated Isocoumarin Derivatives

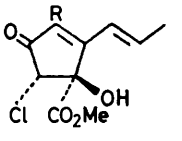
By **Graeme B. Henderson** and **Robert A. Hill,*** Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Syntheses of 5-chloro-, 7-chloro-, and 5,7-dichloro-isocoumarin derivatives, including the fungal metabolites 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (3), 7-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (2), and 5,7-dichloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (1), are described. This is the first total synthesis of compounds (1) and (2) to be reported. The synthetic route involves carboxylation of chlorinated 2,4-dimethoxy-6-methylbenzoic acids, yielding homophthalic acids. The corresponding homophthalic anhydrides were acetylated and decarboxylated to produce isocoumarins. The naturally occurring 7-chloro-8-hydroxy-6-methoxy-3-methylisocoumarin (7) has been synthesised for the first time.

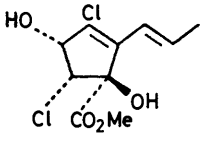
ISOCOUMARINS are important secondary metabolites isolated from fungi,[1] and have been shown to be involved in the biosynthetic pathways of several metabolites.[2] The chlorinated dihydroisocoumarins (1) and (2),[3] together with cryptosporiopsin (4) and its dechloro-derivative (5),[4] have been isolated from *Sporormia affinis*. The chlorinated dihydroisocoumarin (3) and the cyclopentenol (6) have been found in *Periconia macrospinosa*.[5] Recently, the chlorinated isocoumarins (7) and (8) have been isolated from the trunkwood of *Swartzia laevicarpa*.[6]



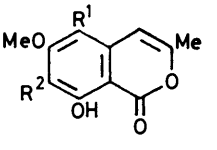
(1) $R^1 = R^2 = Cl$
(2) $R^1 = H, R^2 = Cl$
(3) $R^1 = Cl, R^2 = H$
(27) $R^1 = R^2 = H$



(4) R = Cl
(5) R = H



(6)

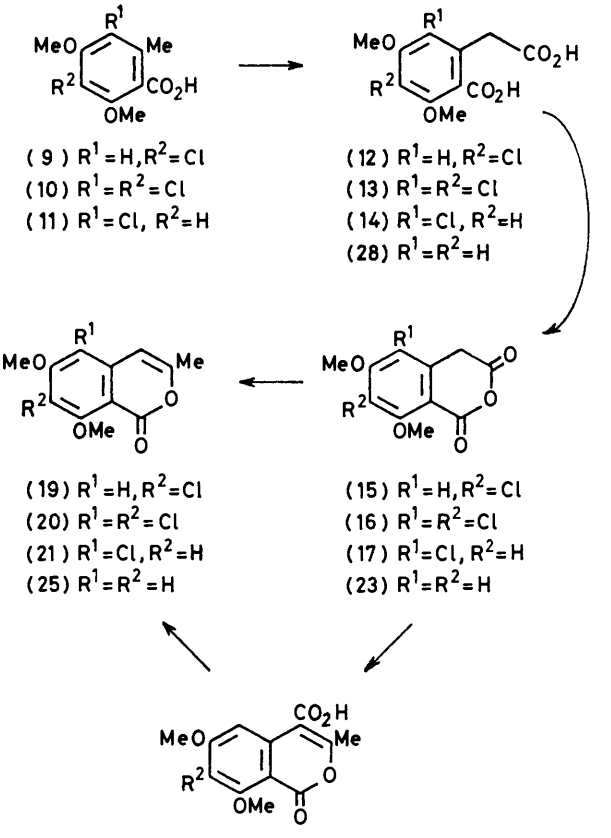


(7) $R^1 = H, R^2 = Cl$
(8) $R^1 = Cl, R^2 = H$

We report in this paper the synthesis of the naturally occurring dihydroisocoumarins (1)—(3), and the naturally occurring isocoumarins (7) and (8). Compounds (3) and (8) have been synthesised recently;[7] we report an improved route to these 5-chloroisocoumarins. We also required the corresponding *O*-demethyl compounds for biosynthetic studies to test the hypothesis[8] that the cyclopentene metabolites (4)—(6) are derived from isocoumarins.

RESULTS AND DISCUSSION

Our synthetic approach (Scheme) starts with the readily available chlorinated 2,4-dimethoxy-6-methylbenzoic acids. These acids were converted into the corresponding homophthalic acids by carboxylation of the dianion produced by di-isopropylamide. Treatment of the homophthalic acids with acetic anhydride produces the isocoumarins.



(9) $R^1 = H, R^2 = Cl$
(10) $R^1 = R^2 = Cl$
(11) $R^1 = Cl, R^2 = H$

(12) $R^1 = H, R^2 = Cl$
(13) $R^1 = R^2 = Cl$
(14) $R^1 = Cl, R^2 = H$
(28) $R^1 = R^2 = H$

(19) $R^1 = H, R^2 = Cl$
(20) $R^1 = R^2 = Cl$
(21) $R^1 = Cl, R^2 = H$
(25) $R^1 = R^2 = H$

(15) $R^1 = H, R^2 = Cl$
(16) $R^1 = R^2 = Cl$
(17) $R^1 = Cl, R^2 = H$
(23) $R^1 = R^2 = H$

(18) R = Cl
(24) R = H

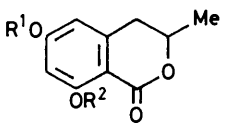
SCHEME

The chlorinated 2,4-dimethoxy-6-methylbenzoic acids (9)—(11) are easily prepared from acetoacetic and crotonic esters.[9,10] Treatment of the benzoic acids (9)—(11) with lithium di-isopropylamide[11] followed by dimethyl carbonate gave the homophthalic acids (12)—(14).

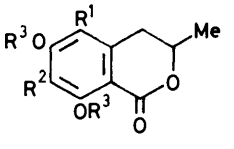
Although it is possible to convert homophthalic acids into isocoumarins without isolating the anhydrides,[12] we found that overall yields were higher if the intermediate anhydrides (15)—(17) were isolated. The efficiency of the acetylation is dependent on the substitution pattern of the homophthalic anhydride, especially at the 2-position. When the 2-position is unsubstituted, as in (15) (and also in the unchlorinated case; see later), the yield is high and the product is the 4-carboxyisocoumarin (18). This is readily decarboxylated by heat to give the isocoumarin (19). A useful feature of this reaction is that the isocoumarin (19) can be obtained quantitatively deuteriated at the 4-position by thermally decarboxylating the acid (18) in which the carboxylic proton has been exchanged with deuterium oxide.

When the 2-chlorohomophthalic anhydrides (16) and (17) were acetylated, the isocoumarins (20) and (21) were formed directly. The yields of these reactions were low, markedly so in the case of the dichloro-compound (16). This is probably due to steric crowding of the site being acetylated. Introduction of the chlorine at a later stage in the synthesis led to a higher overall yield.

We had already found that chlorination of 6,8-dihydroxyisocoumarins proceeded exclusively at the 5-position. The unchlorinated isocoumarin (22) is available by standard methods,[13] but we synthesised it *via* the homophthalic anhydride (23). In this case, as for the reaction with (15), the carboxyisocoumarin (24) was isolated; this was subsequently decarboxylated giving the isocoumarin (25). Reduction of this isocoumarin with borohydride afforded the dihydroisocourmarin (26). This was treated either with boron tribromide, effecting complete demethylation to give (22), or with aluminium trichloride in nitrobenzene, which selectively demethylates the 8-methoxy-group to give (27). Chlorination



(22) $R^1 = R^2 = H$
(26) $R^1 = R^2 = Me$
(27) $R^1 = Me, R^2 = H$



(29) $R^1 = H, R^2 = Cl, R^3 = Me$
(30) $R^1 = Cl, R^2 = H, R^3 = Me$
(31) $R^1 = R^2 = Cl, R^3 = Me$
(32) $R^1 = R^3 = H, R^2 = Cl$
(33) $R^1 = Cl, R^2 = R^3 = H$
(34) $R^1 = R^2 = Cl, R^3 = H$

of (27) with sulphuryl chloride gave the dihydroisocoumarin (3), which was identical with the compound prepared from (21); the spectra of (3) were identical with those of the natural product.

Reduction and partial demethylation of (19) and (20) by standard methods gave the natural dihydroisocoumarins (2) and (1), respectively, in racemic form. Chlorination of (2) produced (1) in better overall yield than was obtained *via* the dichlorophthalic anhydride (16).

The recent report [6] of the isolation of the chlorinated isocoumarins (7) and (8) from *Swartzia laevicarpa* prompted us to synthesise these compounds by partial demethylation of (19) and (21). The physical data for the natural isocoumarin (8) are in agreement with our data and with those of Nozawa *et al.*[7] However the reported n.m.r. data for natural (7) [very similar to those of (8)] differ markedly from our own data. We believe there is an error in the reported data [6] for the following reasons. The chemical shift of H-4 of isocoumarins is influenced by the 5-substituent. When the 5-position is unsubstituted the chemical shift for H-4 for a wide range of compounds is 3.8—3.9 p.p.m., whereas when the 5-substituent is chlorine the shift is in the range 3.4—3.5 p.p.m. Our value for (7) is 3.81, consistent with a hydrogen atom at the 5-position; this is to be compared with the corresponding value for natural (7) reported [6] as 3.36.

The synthesis of the naturally occurring dihydroisocoumarins and their demethylated counterparts has been effected in suitably high yields for the synthesis of labelled compounds. Feeding experiments with *Periconia macrospinosa* are in progress.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for potassium bromide discs with a Perkin–Elmer 580 spectrometer. ^1H N.m.r. spectra were recorded with a Perkin–Elmer RB 24 spectrometer for solutions in hexadeuterioacetone unless otherwise stated ($SiMe_4$ as internal standard). Evaporation was performed by rotary evaporator under reduced pressure; solutions in organic solvents were dried over magnesium sulphate.

3,5-*Dichloro*-2,4-*dimethoxy*-6-*methylbenzoic Acid* (10).—Sulphuryl chloride (2 ml) was added to a solution of methyl 3-chloro-2,4-dihydroxy-6-methylbenzoate [10] (5 g) in anhydrous ether (25 ml). The mixture was kept in the dark at room temperature for 2.5 h, then poured into ice–water. The organic layer was washed with water (2 × 10 ml), dried, and evaporated to give methyl 3,5-dichloro-2,4-dihydroxy-6-methylbenzoate. This material was methylated with dimethyl sulphate and potassium carbonate in acetone, and the product hydrolysed with sodium hydroxide solution to give 3,5-*dichloro*-2,4-*dimethoxy*-6-*methylbenzoic acid* (10), m.p. 133—135 °C (from dichloromethane–hexane) (Found: C, 45.7; H, 3.8; Cl, 26.5%; M^+, 264/266/268. $C_{10}H_{10}Cl_2O_4$ requires C, 45.3; H, 3.8; Cl, 26.75%; *M*, 264/266/268); $\nu_{max.}$ 1 700 cm^{-1}; τ 6.1 (6 H, s, OMe) and 7.64 (3 H, s, Me).

3,5-*Dimethoxyhomophthalic Acid* (18).—n-Butyl-lithium (54 ml; 1.5M in hexane) was added to a solution of di-isopropylamine (8.2 g) in tetrahydrofuran (THF) (25 ml) under nitrogen at 0 °C with stirring. After 10 min, the solution was cooled to −78 °C and a solution of 2,4-dimethoxy-6-methylbenzoic acid [9] (4 g) and dimethyl carbonate (4.4 g) in THF (25 ml) was added dropwise during 15 min. The cooling bath was removed and the solution allowed to warm to room temperature. After 4 h, water (30 ml) was added and the suspension stirred for 16 h. The organic solvents were removed by evaporation and the resulting aqueous solution was washed with ether (2 × 20 ml). After acidification with N-hydrochloric acid, the solution was extracted with ethyl acetate (3 × 20 ml). The combined extracts

were dried and evaporated to give 3,5-dimethoxyhomophthalic acid (28) (4 g, 81%), m.p. 165—168 °C (from CH_2Cl_2–hexane) (lit.,[14] 172—173 °C) (Found: C, 54.95; H, 5.05%; M^+, 240. $C_{11}H_{12}O_6$ requires C, 55.0; H, 5.05%; *M*, 240); $\nu_{max.}$ 2 500—3 000, 1 700, 1 605, and 1 580 cm^{-1}; τ 3.43 (2 H, s, ArH), 6.12 (3 H, s, OMe), 6.16 (3 H, s, OMe), and 6.24 (2 H, s, CH_2).

4-*Chloro*-3,5-*dimethoxyhomophthalic Acid* (12).—Treatment of 3-chloro-2,4-dimethoxy-6-methylbenzoic acid [10] by the foregoing method gave the *acid* (12) (88%), m.p. 141—146 °C (from CH_2Cl_2–hexane) (Found: C, 47.9; H, 3.9; Cl, 13.05%; M^+, 274/276. $C_{11}H_{11}ClO_6$ requires C, 48.1; H, 4.05; Cl, 12.9%; *M*, 274/276); $\nu_{max.}$ 2 500—3 000, 1 740, and 1 590 cm^{-1}; τ 2.96 (1 H, s, ArH), 6.00 (3 H, s, OMe), 6.06 (3 H, s, OMe), and 6.13 (2 H, s, CH_2).

6-*Chloro*-3,5-*dimethoxyhomophthalic Acid* (14).—Treatment of 5-chloro-4,6-dimethoxy-6-methylbenzoic acid by the foregoing method gave the acid (14) (90%), m.p. 230—234 °C (from CH_2Cl_2–hexane) (lit.,[15] 215—225 °C) (Found: C, 47.5; H, 3.95; Cl, 12.3%; M^+, 274/276. Calc. for $C_{11}H_{11}ClO_6$: C, 48.1; H, 4.05; Cl, 12.9%; *M*, 274/276); $\nu_{max.}$ 2 500—3 000, 1 705, and 1 595 cm^{-1}; τ 3.19 (1 H, s, ArH), 6.05 (3 H, s, OMe), 6.10 (3 H, s, OMe), and 6.11 (2 H, s, CH_2).

4,6-*Dichloro*-3,5-*dimethoxyhomophthalic Acid* (13).—Treatment of 3,5-dichloro-2,4-dimethoxy-6-methylbenzoic acid (10) by the foregoing method gave the *acid* (13) (89%), m.p. 150—154 °C (from CH_2Cl_2–hexane) (Found: C, 43.15; H, 3.15; Cl, 23.0%; M^+, 308/310/312. $C_{11}H_{10}Cl_2O_6$ requires C, 42.75; H, 3.25; Cl, 22.95%; *M*, 308/310/312); $\nu_{max.}$ 2 500–3 000, 1 715, and 1 570 cm^{-1}; τ 6.03 (6 H, s, OMe) and 6.05 (2 H, s, CH_2).

3,5-*Dimethoxyhomophthalic Anhydride* (23).—3,5-Dimethoxyhomophthalic acid (28) (4 g) was heated at reflux in an excess of acetyl chloride for 30 min, after which time the solution was homogeneous. After cooling, light petroleum (b.p. 40—60 °C) was added; the anhydride slowly crystallised (yield 3.4 g, 91%); m.p. 165—166 °C (from ether–hexane) (lit.,[14] 160—162 °C) (Found: C, 59.4; H, 4.45%; M^+, 222. Calc. for $C_{11}H_{10}O_5$: C, 59.45; H, 4.55%; *M*, 222); $\nu_{max.}$ 1 780, 1 750, 1 605, and 1 585 cm^{-1}; τ 3.20 (2 H, s, ArH), 5.87 (2 H, s, CH_2), and 6.08 (6 H, s, OMe).

4-*Chloro*-3,5-*dimethoxyhomophthalic Anhydride* (15).—4-Chloro-3,5-dimethoxyhomophthalic acid (12) by the foregoing method gave the *anhydride* (15) (90%), m.p. 192—194 °C (from acetone) (Found: C, 51.6; H, 3.4; Cl, 13.55%; M^+, 256/258. $C_{11}H_9ClO_5$ requires C, 51.5; H, 3.55; Cl, 13.8%; *M*, 256/258); $\nu_{max.}$ 1 785, 1 755, 1 590, and 1 575sh cm^{-1}; τ 3.62 (1 H, s, ArH), 6.44 (2 H, s, CH_2), 6.65 (3 H, s, OMe), and 6.78 (3 H, s, OMe).

6-*Chloro*-3,5-*dimethoxyhomophthalic Anhydride* (17).—6-Chloro-3,5-dimethoxyhomophthalic acid (14) by the foregoing method gave the *anhydride* (17) (90%), m.p. 228–234 °C (from ether–hexane) (Found: C, 51.6; H, 3.45; Cl, 13.85%; M^+, 256/258. $C_{11}H_9ClO_5$ requires C, 51.5; H, 3.55; Cl, 13.8%; *M*, 256/258); $\nu_{max.}$ 1 790, 1 755, 1 595, and 1 570 cm^{-1}; τ 3.10 (1 H, s, ArH), 5.89 (2 H, s, CH_2), 5.92 (3 H, s, OMe), and 6.00 (3 H, s, OMe).

4,6-*Dichloro*-3,5-*dimethoxyhomophthalic Anhydride* (16).—4,6-Dichloro-3,5-dimethoxyhomophthalic acid (13) by the foregoing method gave the *anhydride* (16) (85%), m.p. 148—155 °C (decomp.) (from dichloromethane–hexane) (Found: C, 45.1; H, 2.35; Cl, 24.2%; M^+, 290/292/294. $C_{11}H_8Cl_2O_5$ requires C, 45.4; H, 2.75; Cl, 24.35%; *M*, 290/292/294); $\nu_{max.}$ 1 815, 1 757, 1 745sh, and 1 570 cm^{-1}; τ 5.90 (2 H, s, CH_2), 6.00 (3 H, s, OMe), and 6.05 (3 H, s, OMe).

4-*Carboxy*-6,8-*dimethoxy*-3-*methylisocoumarin* (24).—Acetic anhydride (0.15 ml) and pyridine (0.2 ml) were added to a solution of 3,5-dimethoxyhomophthalic anhydride (23) (250 mg) in dry THF (30 ml). The solution was stirred at room temperature for 40 min, then more acetic anhydride (0.2 ml) was added and the solution was heated at gentle reflux for 1 h. After cooling, the solution was evaporated and the residue dissolved in dilute aqueous sodium hydrogen carbonate (10%). The basic solution was washed with ether (2 × 5 ml), then acidified with N-hydrochloric acid and extracted with ethyl acetate (3 × 10 ml). The combined extracts were evaporated to give 4-*carboxy*-6,8-*dimethoxy*-3-*methylisocoumarin* (24) (200 mg, 67%), m.p. 145—147 °C (from ether–hexane) (Found: C, 58.9; H, 4.4%; M^+, 264. $C_{13}H_{12}O_6$ requires C, 59.1; H, 4.6%; 264); $\nu_{max.}$ 1 745, 1 715, 1 650, 1 610, and 1 575 cm^{-1}; τ 3.30 (2 H, m, ArH), 6.03 (3 H, s, OMe), 6.05 (3 H, s, OMe), and 7.36 (3 H, s, Me).

4-*Carboxy*-7-*chloro*-6,8-*dimethoxy*-3-*methylisocoumarin* (18).—4-Chloro-3,5-dimethoxyhomophthalic anhydride (15) by the foregoing method gave the *isocoumarin* (75%), m.p. 164 °C (decomp.) (from ether–hexane) (Found: C, 52.15; H, 3.55; Cl, 11.3%; M^+, 298/300. $C_{13}H_{11}ClO_6$ requires C, 52.3; H, 3.7; Cl, 11.85%; *M*, 298/300); $\nu_{max.}$ 1 765, 1 655, and 1 590 cm^{-1}; τ 2.75 (1 H, s, ArH), 5.90 (3 H, OMe), 6.09 (3 H, s, OMe), and 7.28 (3 H, s, Me).

5-*Chloro*-6,8-*dimethoxy*-3-*methylisocoumarin* (21).—Acetic anhydride (0.5 ml) and pyridine (0.1 ml) were added to a solution of 6-chloro-3,5-dimethoxyhomophthalic anhydride (17) (280 mg) in benzene (20 ml). The solution turned yellow on heating and heating was continued under reflux for 8 h. The cooled solution was washed with N-hydrochloric acid (10 ml) and water (10 ml). The organic solution was dried and evaporated to small volume; 5-chloro-6,8-dimethoxy-3-methylisocoumarin (21) crystallised (190 mg, 68%); m.p. 198—202 °C (from chloroform–hexane) (lit.,[7] 204 °C) (Found: C, 57.0; H, 4.35; Cl, 13.6%; M^+, 254/256. $C_{12}H_{11}ClO_4$ requires C, 56.6; H, 4.35; Cl, 13.9%; *M*, 254/256); $\nu_{max.}$ 1 730, 1 665, and 1 590 cm^{-1}; $\tau(CDCl_3)$ 3.42 (1 H, d, *J* 1 Hz, H-4), 3.51 (1 H, s, H-7), 6.00 (6 H, s, OMe), and 7.76 (3 H, d, *J* 1 Hz, Me).

5,7-*Dichloro*-6,8-*dimethoxy*-3-*methylisocoumarin* (19).—4,6-Dichloro-3,5-dimethoxyhomophthalic anhydride (16) by the foregoing method gave the *isocoumarin* (25%), m.p. 140—144 °C (Found: C, 49.75; H, 3.5; Cl, 24.15%; M^+, 288/290/292. $C_{12}H_{10}Cl_2O_4$ requires C, 49.85; H, 3.5; Cl, 24.5%; *M*, 288/290/292); $\nu_{max.}$ 1 740, 1 660, 1 565, and 1 540 cm^{-1}; $\tau(CDCl_3)$ 3.41 (1 H, s, H-4), 6.03 (6 H, s, OMe), and 7.73 (3 H, s, Me).

6,8-*Dimethoxy*-3-*methylisocoumarin* (25).—4-Carboxy-6,8-dimethoxy-3-methylisocoumarin (24) (250 mg) was heated to just below its m.p. (140—150 °C) for 10 min; carbon dioxide evolution had then ceased. The residue was chromatographed over silica gel (ethyl acetate as eluant) to give 6,8-dimethoxy-3-methylisocoumarin (25) (190 mg, 91%), m.p. 156—169 °C (lit.,[13] 157—158 °C), showing properties (n.m.r., i.r.) identical with those reported.[13]

7-*Chloro*-6,8-*dimethoxy*-3-*methylisoccumarin* (20).—4-Carboxy-7-chloro-6,8-dimethoxy-3-methylisocoumarin (18) by the foregoing method gave the *isocoumarin*, m.p. 187—200 °C (decomp.) (from ethyl acetate–hexane) (Found: C, 55.8; H, 4.35; Cl, 13.7%; M^+, 254/256. $C_{12}H_{11}ClO_4$ requires C, 56.6; H, 4.35; Cl, 13.9%; *M*, 254/256); $\nu_{max.}$

1 720, 1 670, 1 590, and 1 555 cm^{-1}; τ($CDCl_3$) 3.47 (1 H, s, H-5), 3.88 (1 H, br, s, H-4), 6.03 (6 H, s, OMe), and 7.80 (3 H, br, s, Me).

3,4-Dihydro-6,8-dimethoxy-3-methylisocoumarin (26).—4-Carboxy-6,8-dimethoxy-3-methylisocoumarin (24) (250 mg) was heated under reflux in aqueous 10% sodium hydroxide (15 ml) for 1 h. Sodium borohydride (50 mg) was added with stirring and the mixture heated under reflux for 30 min; more sodium borohydride (50 mg) was then added and heating continued for 30 min. The hot solution was filtered and the filtrate acidified with hydrochloric acid, then cooled to 0 °C. 3,4-Dihydro-6,8-dimethoxy-3-methylisocoumarin (26) crystallised from the solution (yield 175 mg, 70%); m.p. 125—126 °C (from ether–hexane) (lit.,[13] 125—126 °C), showing properties identical with those reported.[13]

7-Chloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (29).—This was prepared by the foregoing method from 4-carboxy-7-chloro-6,8-dimethoxy-3-methylisocoumarin (18). The product was isolated by chromatography over silica gel (ethyl acetate as eluant) to produce *crystals* (60%), m.p. 154—157 °C (from dichloromethane–hexane) (Found: C, 56.45; H, 4.95; Cl, 13.95%; M^+, 256/258. $C_{12}H_{13}ClO_4$ requires C, 56.15; H, 5.1; Cl, 13.8%; *M*, 256/258); $\nu_{max.}$ 1 712 and 1 595 cm^{-1}; τ($CDCl_3$) 3.44 (1 H, s, H-5), 5.44 (1 H, br, q, H-3), 6.05 (6 H, s, OMe), 7.12 (1 H, br, s, H-4), 7.22 (1 H, br, s, H-4), and 8.55 (3 H, d, *J* 7 Hz, Me).

5-Chloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (30).—5-Chloro-6,8-dimethoxy-3-methylisocoumarin (21) by the foregoing method gave the isocoumarin (30) (65%), m.p. 134—136 °C (lit.,[7] 134 °C) (Found: C, 56.35; H, 5.1; Cl, 13.45%; M^+, 256/258. Calc. for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.1; Cl, 13.8%; *M*, 256/258); $\nu_{max.}$ 1 720 and 1 595 cm^{-1}; τ($CDCl_3$) 3.5 (1 H, s, H-7), 5.5 (1 H, m, H-3), 6.03 (3 H, s, OMe), 6.07 (3 H, s, OMe), 6.75 (1 H, dd, *J* 3 and 17 Hz, H-4), 7.33 (1 H, dd, *J* 11 and 17 Hz, H-4), and 8.50 (3 H, d, J 6 Hz, Me).

5,7-Dichloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (31).—5,7-Dichloro-6,8-dimethoxy-3-methylisocoumarin (19) by the foregoing method gave the isocoumarin (31). The product was isolated by chromatography on silica gel (ethyl acetate as eluant), yielding *crystals* (60%), m.p. 76–80 °C (decomp.) (Found: C, 48.0; H, 4.15%; M^+, 290/292/294. $C_{12}H_{12}Cl_2O_4$ requires C, 49.5; H, 4.15%; *M*, 290/292/294); $\nu_{max.}$ 1 725 and 1 565 cm^{-1}; τ($CDCl_3$) 5.45 (1 H, m, H-3), 6.03 (3 H, s, OMe), 6.05 (3 H, s, OMe), 6.79 (1 H, dd, *J* 3 and 18 Hz, H-4), 7.30 (1 H, dd, *J* 11 and 18 Hz, H-4), and 8.52 (3 H, d, *J* 6 Hz, Me).

3,4-Dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (27).—Aluminium chloride (150 mg) was added to a solution of 3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (26) (50 mg) in freshly distilled nitrobenzene (4 ml). The solution was stirred at 50—60 °C for 6 h, then poured into ice–water and acidified with dilute hydrochloric acid. The acidic solution was extracted with ether (3 × 10 ml), then the combined extracts were extracted with aqueous 10% sodium hydroxide (2 × 10 ml). The basic solution was extracted with ether, acidified, and again extracted with ether. The last extract was evaporated, and the residue purified by p.l.c. (silica gel; ethyl acetate as eluant) to give 3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (27) (38 mg, 80%), m.p. 96 °C (from ether–hexane) (lit.,[16] 95—97 °C), showing spectra identical with those reported.[17]

7-Chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (2).—7-Chloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (29) by the foregoing method gave the *isocoumarin* (2) (80%), m.p. 168—171 °C (Found: C, 54.7; H, 4.5; Cl, 14.35%; M^+, 242/244. $C_{11}H_{11}ClO_4$ requires C, 54.45; H, 4.55; Cl, 14.6%; *M*, 242/244); $\nu_{max.}$ 1 660, 1 620, and 1 580 cm^{-1}; τ($CDCl_3$) 3.68 (1 H, s, H-5), 5.30 (1 H, m, H-3), 6.05 (3 H, s, OMe), 7.08 (1 H, br, s, H-4), 7.16 (1 H, br, s, H-4), and 8.52 (3 H, d, *J* 6 Hz, Me).

5-Chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (3).—5-Chloro-3,4-dihydro-6,8-dimethoxyisocoumarin (30) by the foregoing method gave the isocoumarin (3) (82%), m.p. 119—122 °C (from ethyl acetate–hexane) (lit.,[7] 119 °C) (Found: C, 54.35; H, 4.45; Cl, 14.35%; M^+, 242/244. Calc. for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.55; Cl, 14.6%; *M*, 242/244); $\nu_{max.}$ 2 500—3 200, 1 655, 1 620, and 1 580 cm^{-1}; τ($CDCl_3$) 3.57 (1 H, s, H-7), 5.35 (1 H, m, H-3), 6.09 (3 H, s, OMe), 6.75 (1 H, dd, *J* 3 and 17 Hz, H-4), 7.25 (1 H, dd, *J* 11 and 17 Hz, H-4), and 8.50 (3 H, d, *J* 6 Hz, Me). Also (3) was prepared from (27) by the following method, in 85% yield, giving an identical product.

5,7-Dichloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (1).—This was prepared either from 5,7-dichloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (31) by the foregoing method (67%), or by the following method. Sulphuryl chloride (0.5 ml) was added to 7-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (2) (100 mg) in ether (20 ml). The solution was kept in the dark for 1 h at room temperature, then water was added to destroy the excess of sulphuryl chloride. The organic solution was dried and evaporated and the residue purified by p.l.c. on silica gel (ethyl acetate as eluant) to give *crystals*, m.p. 121—125 °C (from chloroform–hexane) (Found: C, 47.7; H, 3.7; Cl, 25.15%; M^+, 276/278/280. $C_{11}H_{10}Cl_2O_4$ requires C, 47.7; H, 3.65; Cl, 25.6%; *M*, 276/278/280); ν_{max} 1 685 and 1 595 cm^{-1}; τ($CDCl_3$) 5.30 (1 H, m, H-3), 6.04 (3 H, s, OMe), 6.25 (1 H, dd, *J* 3 and 17 Hz, H-4), 7.25 (1 H, dd, *J* 11 and 17 Hz, H-4), and 8.45 (3 H, d, *J* 6 Hz, Me).

3,4-Dihydro-6,8-dihydroxy-3-methylisocoumarin (22).—Boron tribromide (0.5 ml) was added to 3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (26) (100 mg) in dichloromethane (25 ml) at −70 °C. The solution was kept at this temperature for 24 h, then allowed to warm to room temperature over 12 h. Ether (10 ml) was added, then water (10 ml). The organic layer was dried and evaporated and the residue purified by chromatography on silica gel [ethanol–hexane (1 : 5) as eluant] to give crystals (80 mg, 82%), m.p. 214—215 °C (from acetone–hexane) (lit.,[13] 214—215 °C), showing spectra identical with those reported.[13]

7-Chloro-3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (32).—7-Chloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (29) by the foregoing method gave the *isocoumarin* (32) (60%), m.p. 193—196 °C (from ethyl acetate–hexane) (Found: C, 52.75; H, 4.15; Cl, 15.3%; M^+, 228/230. $C_{10}H_9ClO_4$ requires C, 52.55; H, 3.95; Cl, 15.5%; *M*, 228/230); $\nu_{max.}$ 3 400, 1 665, 1 615, and 1 505 cm^{-1}; τ 3.50 (1 H, s, H-5), 5.28 (1 H, m, H-3), 7.00 (1 H, d, *J* 11 Hz, H-4), 7.15 (1 H, d, *J* 7 Hz), and 8.55 (3 H, d, *J* 7 Hz, Me).

5-Chloro-3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (33).—5-Chloro-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (30) by the foregoing method gave the *isocoumarin* (33) (65%), m.p. 179—181 °C (from acetone) (Found: C, 52.6; H, 3.75; Cl, 15.75%; M^+, 228/230. $C_{10}H_9ClO_4$ requires C, 52.55; H, 3.95; Cl, 15.5%; *M*, 228/230); $\nu_{max.}$ 3 400, 1 663, 1 630, and 1 615 cm^{-1}; τ($CDCl_3$) 2.43 (1 H, s, H-7), 3.75 (1 H, br, s, D_2O exch., OH), 5.31 (1 H, m, H-3),

6.79 (1 H, dd, *J* 3 and 17 Hz, H-4), 7.29 (1 H, dd, *J* 11 and 17 Hz, H-4), and 8.47 (3 H, d, *J* 6 Hz, Me).

5,7-*Dichloro*-3,4-*dihydro*-6,8-*dihydroxy*-3-*methylisocoumarin* (34).—Sulphuryl chloride (0.3 ml) was added to a solution of 7-chloro-3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (32) (50 mg) in ether (20 ml). The solution was kept in the dark for 1 h at room temperature. The excess of sulphuryl chloride was destroyed with water and the organic layer was dried and evaporated. The residue was purified by chromatography over silica gel (ethyl acetate as eluant) to give *crystals* (50 mg, 87%), m.p. 230—234 °C (from acetone) (Found: C, 45.6; H, 2.95%; M^+, 262/264/266. $C_{10}H_8Cl_2O_4$ requires C 45.65; H, 3.05%; *M*, 262/264/266); $\nu_{max.}$ 3 630, 1 665, 1 650, and 1 610 cm^{-1}; τ 5.20 (1 H, m, H-3), 4.69 (1 H, dd, *J* 3 and 17 Hz, H-4), 3.19 (1 H, dd, *J* 11 and 17 Hz, H-4), and 8.49 (3 H, d, *J* 6 Hz, Me).

7-*Chloro*-8-*hydroxy*-6-*methoxy*-3-*methylisocoumarin* (7).—Aluminium trichloride (75 mg) was added to a solution of 7-chloro-6,8-dimethoxy-3-methylisocoumarin (20) (100 mg) in freshly distilled nitrobenzene (10 ml). The mixture was stirred at 50—60 °C for 5 h, then poured on to ice–water. Concentrated hydrochloric acid (1 ml) was added and the solution extracted with ether (4 × 25 ml). The combined extracts were extracted with aqueous 10% sodium hydroxide. The basic solution was acidified with hydrochloric acid, then extracted with ether. The organic solution was dried and evaporated and the residue purified by chromatography over silica gel (ethyl acetate as eluant) to give crystals (70 mg, 73%), m.p. 208—215 °C (decomp.) (from ether) (lit.,[6] 163—165 °C) (Found: C, 54.85; H, 3.8; Cl, 14.85%; M^+, 240/242. Calc. for $C_{11}H_9ClO_4$: C, 54.9; H, 3.75; Cl, 14.75%; *M*, 240/242); $\nu_{max.}$ 1 680, 1 645, 1 610, 1 560, 1 520, 1 475 and 1 420 cm^{-1}; $\tau(CDCl_3)$ — 1.53 (1 H, s, D_2O exch., OH), 3.68 (1 H, s, H-5), 3.81 (1 H, m, H-4), 6.02 (3 H, s, OMe), and 7.75 (3 H, s, Me).

5-*Chloro*-8-*hydroxy*-6-*methoxy*-3-*methylisocoumarin* (8).—5-Chloro-6,8-dimethoxy-3-methylisocoumarin (21) similarly gave the isocoumarin (8) (75%), m.p. 156—158 °C (from hexane) (lit.,[6] 155—157 °C; lit.,[7] 146—147 °C) (Found: C, 54.8; H, 3.8; Cl, 14.85%; M^+, 240/242. $C_{11}H_9ClO_4$ requires C, 54.9; H, 3.7; Cl, 14.75%; *M*, 240/242); $\nu_{max.}$ 1 690, 1 655, 1 610, and 1 575 cm^{-1}; $\tau(CDCl_3)$ — 1.18 (1 H, s, D_2O exch., OH), 3.38 (1 H, s, H-7), 3.48 (1 H, m, H-4), 6.04 (3 H, s, OMe), and 7.72 (3 H, m, Me).

We thank the S.R.C. for financial support. We are indebted to Dr. W. J. McGahren for spectra of the natural dihydroisocoumarins.

[1/1689 *Received*, 29*th October*, 1981]

REFERENCES

[1] W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971, ch. 5.
[2] A. J. Birch, F. Geger, L. Mo, A. Pelter, and J. J. Wright, *Aust. J. Chem.*, 1969, **22**, 2429; A. G. McInnes, D. G. Smith, L. C. Vining, and L. Johnson, *Chem. Commun.*, 1971, 325; R. A. Hill, R. H. Carter, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1975, 380; M. J. Garson and J. Staunton, *ibid.*, 1978, 158.
[3] W. J. McGahren and L. A. Mitscher, *J. Org. Chem.*, 1968, **33**, 1577.
[4] W. J. McGahren, J. H. van den Hende, and L. A. Mitscher, *J. Am. Chem. Soc.*, 1969, **91**, 157.
[5] D. Giles and W. B. Turner, *J. Chem. Soc.*, 1969, 157.
[6] R. B. Filho, M. P. L. de Mornes, and O. R. Gottlieb, *Phytochemistry*, 1980, **19**, 2003.
[7] K. Nozawa, S. Nakajuna, M. Yamada, and K.-I. Kawai, *Chem. Pharm. Bull.*, 1980, **24**, 1622.
[8] J. S. E. Holker and K. Young, *J. Chem. Soc., Chem. Commun.*, 1975, 525.
[9] J. Santesson, *Acta Chem. Scand.*, 1970, **24**, 3373.
[10] L. Fitzpatrick, T. Sala, and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1980, 85.
[11] F. M. Hauser and R. Rhee, *Synthesis*, 1972, 245.
[12] R. B. Tirodkar and R. S. Usgaonkar, *J. Indian Chem. Soc.*, 1969, **46**, 935.
[13] R. H. Carter, R. M. Colyer, R. A. Hill, and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1438.
[14] E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, 1966, **49**, 1283.
[15] K. Nozawa, S. Nakajuna, and K.-I. Kawai, *Chem. Pharm. Bull.*, 1980, **24**, 1112.
[16] H. L. Slates, S. Weber, and N. L. Wendler, *Chimia*, 1967, **21**, 468.
[17] E. Sondheimer, *J. Am. Chem. Soc.*, 1957, **79**, 5036.