Further Total Syntheses of Chlorine-containing Lichen Xanthones

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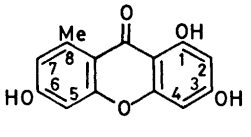
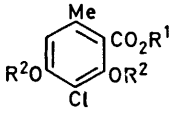
The unambiguous total synthesis of eight chlorine-containing lichen xanthones by ring closure of appropriately substituted benzophenones is described.

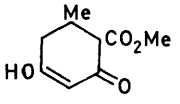
THE lichen xanthones (xanthen-9-ones) are all derivatives of 1,3,6-trihydroxy-8-methylxanthone (*OO*-dinorlichexanthone) (1) and differ only in the number of their chloro-substituents and extent of *O*-methylation. In a previous paper [1] we described the synthesis of lichen xanthones which contained chloro-substituents in the phloroglucinol ring by cyclization of 2-phenoxybenzoic acids available by Ullmann reactions. We have now extended our work to encompass lichen xanthones which contain a 5-chloro-substituent. The cyclization of 2,2'-dihydroxybenzophenones [2,3] or of 2-hydroxy-2'-methoxybenzophenones [4,5] appeared more suitable for this purpose than our earlier method. Hence, in order to prepare the necessary benzophenones, we required a synthesis of the acids (3) and (4). Chlorination [6] of methyl dihydro-orsellinate (5) with 2 mol. equiv. of chlorine gave the chloro-ester (2), the structure of which followed from its hydrolysis and decarboxylation to the chloro-orcinol (6) which differed from its isomer (7).[7] Bromination of methyl dihydro-orsellinate (5) also proceeds in this manner.[8] The ester (2) was then readily converted into the acids (3) and (4).



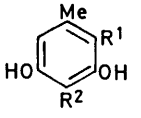
(1)



(2) R^1 = Me, R^2 = H
(3) R^1 = H, R^2 = CH_2Ph
(4) R^1 = H, R^2 = Me

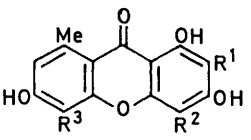


(5)

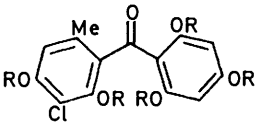


(6) R^1 = H, R^2 = Cl
(7) R^1 = Cl, R^2 = H

Monochloroxanthones.—Santesson isolated a xanthone from the lichen *Lecanora straminea* to which he assigned the structure 2-chlorodi-*O*-norlichexanthone (8).[9] Sundholm [10] has shown by high-pressure liquid chromatography (h.p.l.c.), by ^{1}H n.m.r. spectral studies, and by the synthesis of the 4-chloro-isomer (9) that Santesson's substance was a mixture of the 4- (9) and 5-chloro-isomers (10). Friedel–Crafts reaction between the acid (3) and 1,3,5-trisbenzyloxybenzene [3] gave the benzophenone (11), which on hydrogenolytic debenzylation gave the crude pentahydroxybenzophenone (12). On boiling in aqueous acetone this underwent cyclization [3] to the xanthone (10), identical (h.p.l.c. and ^{1}H n.m.r.) with the natural product.†



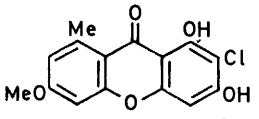
(8) R^1 = Cl, R^2 = R^3 = H
(9) R^1 = R^3 = H, R^2 = Cl
(10) R^1 = R^2 = H, R^3 = Cl



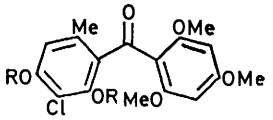
(11) R = CH_2Ph
(12) R = H

Vinetorin, a xanthone from the lichen *Lecanora vinetorum* which grows on vine posts in Austrian vineyards, was initially assigned structure (13) by Poelt and Huneck,[11] but this has been revised to (16) on the grounds of its ^{1}H n.m.r. spectrum.[10,12] This structure is now confirmed by the unambiguous synthesis of compound (16). Condensation of the acid (3) and 1,3,5-trimethoxybenzene gave the benzophenone (17) and thence the dihydroxybenzophenone (18) which can only undergo base-induced cyclization with loss of methanol in one direction thus affording the xanthone (14). The derived acetate (15) on treatment with boron trichloride gave the xanthone (16), identical with the natural product.

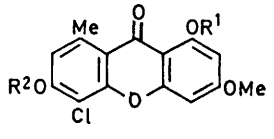
Dichloroxanthones.—Huneck and Höfle [12] have recently isolated a xanthone from the lichen *Pertusaria aleianata* to which they assigned the structure (23) after extensive ^{1}H and ^{13}C n.m.r. studies. This structure is also



(13)



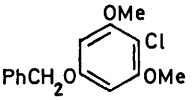
(17) R = CH_2Ph
(18) R = H



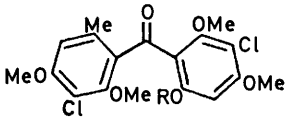
(14) R^1 = Me, R^2 = H
(15) R^1 = Me, R^2 = Ac
(16) R^1 = R^2 = H

† We thank Mr. E. G. Sundholm for these comparisons.

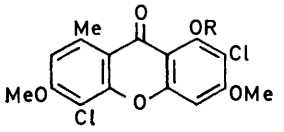
confirmed by unambiguous synthesis. Condensation of the acid (4) with the symmetrical phloroglucinol (19) [13] gave the benzophenone (20) and thence the hydroxy-



(19)



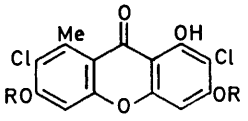
(20) R = CH_2Ph
(21) R = H



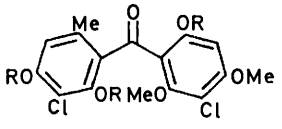
(22) R = Me
(23) R = H

benzophenone (21). Again base-induced ring-closure with loss of methanol can take only one course and the trimethoxyxanthone (22) resulted. On demethylation with boron trichloride the xanthone (22) yielded the hydroxyxanthone (23), identical with the natural product.

Santesson [14] reported that *L. straminea* also contained a xanthone to which he assigned structure (24). Treatment of this xanthone with an excess of diazomethane gave a di-*O*-methyl derivative, assigned structure (25), which was also detected in *Buellia glazionana* by t.l.c. and 'lichen mass spectrometry.' Sundholm, on the grounds of ^1H and ^{13}C n.m.r. data [10,15] and his synthesis of structure (24), has suggested that the natural xanthones should be represented by structures (29) and (31), which we have now synthesized. Thus condensation of the acid (3) with the phloroglucinol (19) gave the benzophenone (26) and thence the trihydroxybenzophenone (27). As expected, base treatment of this last compound gave a dihydroxyxanthone (28). This on demethylation by boiling in aqueous piperidine [5] gave the xanthone (29), identical with the natural product. Methylation of the dihydroxyxanthone (28) gave the trimethoxy compound (30) which on demethylation with boron trichloride gave the dimethoxyxanthone (31), identical with the natural product.

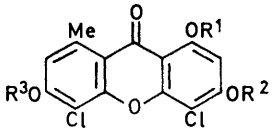


(24) R = H
(25) R = Me

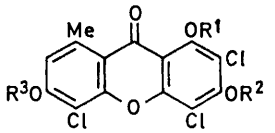


(26) R = CH_2Ph
(27) R = H

Trichloroxanthones.—Huneck and Höfle [12] assigned structure (32) to a xanthone isolated from the *Pertusaria* species mentioned above, on the basis of ^1H and ^{13}C n.m.r. spectral studies. Since the *O*-methyl derivative was identical with the di-*O*-methyl derivative of thuringione [16] and the tri-*O*-methyl derivative of arthothelin,[17,18] the structures of these lichen trichloroxanthones were revised to (34) and (35). Sundholm independently reached the same conclusions.[10] We therefore sought to confirm these structures by unambiguous synthesis. Treatment of the xanthones (22) and (30) with 1 mol equiv. of sulphuryl chloride gave the same trichloroxanthone, which must therefore possess structure (33). This compound was identical with tri-*O*-methylarthothelin, and on demethylation with boron trichloride it gave the xanthone (32), identical with that isolated from the *Pertusaria* lichen. Similar chlorination of the acetate (15) gave a trichloroxanthone assigned structure (36) since it could be converted into tri-*O*-methylarthothelin (33). Treatment of compound (36) with boron trichloride gave thuringione (34), which on boiling with aqueous piperidine gave arthothelin (35).



(28) $R^1 = R^3 = H, R^2 = Me$
(29) $R^1 = R^2 = R^3 = H$
(30) $R^1 = R^2 = R^3 = Me$
(31) $R^1 = H, R^2 = R^3 = Me$



(32) $R^1 = H, R^2 = R^3 = Me$
(33) $R^1 = R^2 = R^3 = Me$
(34) $R^1 = R^3 = H, R^2 = Me$
(35) $R^1 = R^2 = R^3 = H$
(36) $R^1 = R^2 = Me, R^3 = Ac$

EXPERIMENTAL

General directions have been given previously.[19]

Methyl 3-Chloro-2,4-dihydroxy-6-methylbenzoate (2).—This method is an adaptation of that of Grossman.[6] Chlorine (14.0 g) in cold acetic acid (100 ml) was added with stirring and ice-cooling over 10 min to a solution of methyl dihydroorsellinate (5) [8] (18.4 g) in acetic acid (50 ml) in a closed system. The solution was stirred at room temperature for 0.5 h and at 60 °C (bath) for 2.5 h, and then poured into iced water. The precipitate was separated by filtration, washed with water, and dried *in vacuo*. The ester (2) (8.3 g) formed lustrous laths (from dichloromethane–light petroleum), m.p. 129—130° (lit.,[6] 139—140°) (Found: C, 50.2; H, 4.4; Cl, 16.5%; M^+, 216/218. Calc. for $C_9H_9ClO_4$: C, 49.9; H, 4.2; Cl, 16.35%; *M*, 216/218); δ($CDCl_3$; 60 MHz) 2.43 (3 H, s, Me), 3.90 (3 H, s, OMe), 5.89 (1 H, s, D_2O exchangeable OH), 6.36 (1 H, s, ArH), and 11.99 (1 H, s, D_2O-exchangeable OH).

4-Chloro-3,5-dihydroxytoluene (6).—The ester (2) (1.5 g) and aqueous sodium hydroxide (5%; 75 ml) were boiled under reflux under nitrogen for 3 h. The solution was poured into ice and hydrochloric acid and extracted with ethyl acetate. The crude product crystallized from benzene (charcoal) as prisms (0.5 g), m.p. 137—138°, or needles, m.p. 112—115° (lit.,[10] 138—138.5°) (Found: C, 53.4; H, 4.7; Cl, 22.2%; M^+, 158/160. Calc. for $C_7H_7ClO_2$: C, 53.0; H, 4.45; Cl, 22.35%; *M*, 158/160); δ($CDCl_3$; CD_3SOCD_3; 60 MHz) 2.12 (3 H, s, Me), 6.23 (2 H, s, ArH), and 6.90 (2 H, s, OH). The n.m.r. spectrum and the R_F values in several solvent systems were different to those of an authentic sample of 2-chloro-3,5-dihydroxytoluene (7).[7]

2,4-Bisbenzyloxy-3-chloro-6-methylbenzoic Acid (3).—The ester (2) (5.7 g), benzyl bromide (7 ml), and potassium carbonate (15 g) were stirred in dry *NN*-dimethylformamide (30 ml) under dry nitrogen for 15 h. Work-up in the usual way followed by removal of the excess of benzyl bromide in steam gave *methyl 2,4-bisbenzyloxy-3-chloro-6-*

methylbenzoate (10.4 g) which formed laths (from dichloromethane–light petroleum), m.p. 99—100° (Found: C, 69.9; H, 5.5; Cl, 8.85%; M^+, 396/398. $C_{23}H_{21}ClO_4$ requires C, 69.6; H, 5.35; Cl, 8.95%; *M*, 396/398). The ester (10.3 g) and potassium hydroxide (10.3 g) were stirred with water (10 ml) and dimethyl sulphoxide (150 ml) for 6 h on a steam-bath. The usual work-up gave the *acid* (3) (9.7 g), which formed prisms (from dichloromethane–light petroleum), m.p. 142—143° (Found: C, 69.0; H, 5.4; Cl, 9.45%; M^+, 382/384. $C_{22}H_{19}ClO_4$ requires C, 69.0; H, 5.0; Cl, 9.25%; *M*, 382/384).

3-*Chloro*-2,4-*dimethoxy*-6-*methylbenzoic Acid* (4).—Methylation of the ester (2) (8.2 g) with dimethyl sulphate and potassium carbonate in acetone followed by hydrolysis as above gave the *acid* (4) (7.9 g) as prisms (from dichloromethane–light petroleum), m.p. 154—155° (Found: C, 52.3; H, 4.7; Cl, 15.55%; M^+, 230/232. $C_{10}H_{11}ClO_4$ requires C, 52.1; H, 4.8; Cl, 15.35%; *M*, 230/232).

4-*Benzyloxy*-1-*chloro*-2,6-*dimethoxybenzene* (19).—4-Chloro-3,5-dimethoxyphenol (9.6 g),[1] benzyl bromide (9.1 g), and potassium carbonate (14 g) were stirred in dry *NN*-dimethylformamide (75 ml) under dry nitrogen for 24 h. The usual work-up followed by removal of the excess of benzyl bromide in steam gave the product (19) (13.6 g) as plates (from ether–light petroleum), m.p. 97.5—98° (lit.,[13] 97—98°); δ($CDCl_3$; 60 MHz) 3.73 (6 H, s, OMe), 4.91 (2 H, s, CH_2), 6.10 (2 H, s, ArH), and 7.23 (5 H, s, Ph).

5-*Chloro*-1,3,6-*trihydroxy*-8-*methylxanthen*-9-*one* (10).—Trifluoroacetic anhydride (5 ml) in dry dichloromethane (10 ml) was added dropwise at 0 °C over 2 min to a stirred solution of the acid (3) (1.4 g) and 1,3,5-trisbenzyloxybenzene [3] (1.5 g) in dry dichloromethane (30 ml). The solution was stirred for a further 10 min at 0 °C and then diluted with ether and washed in turn with water, aqueous ammonia, water, and finally saturated brine. Removal of the solvent gave 2,2′,4,4′,6-pentakisbenzyloxy-3′-chloro-6′-methylbenzophenone (11) (2.7 g) as a thick oil homogeneous on t.l.c.; δ($CDCl_3$; 60 MHz) 2.03 (3 H, s, Me), 4.58 (6 H, s, 3 × CH_2), 4.87 and 4.94 (each 2 H, s, CH_2), 5.98 (2 H, s, 3- and 5-H), 6.19 (1 H, s, 5′-H), and 6.70—7.40 (25 H, m, Ph). The benzophenone (11) (2.7 g) and 10% palladized charcoal (0.5 g) were stirred under hydrogen in ethyl acetate (400 ml) containing concentrated hydrochloric acid (5 drops) until absorption ceased. The crude product (950 mg) was boiled with aqueous acetone and was then crystallized from acetone to give yellow needles of the *xanthone* (10), m.p. 304—305° (Found: C, 57.6; H, 3.2; Cl, 11.9%; M^+, 292/294. $C_{14}H_9ClO_5$ requires C, 57.45; H, 3.1; Cl, 12.1%; *M*, 292/294); δ(CD_3COCD_3; 90 MHz) 2.76 (3 H, d, $J_{7\text{-H, Me}}$ 0.9 Hz, Me), 6.22 and 6.41 (2 H, AB, $J_{2,4}$ 2.1 Hz, 2- and 4-H), and 6.87 (1 H, narrow m, $W_{\frac{1}{2}}$ 2.0 Hz, 7-H).

3-*Chloro*-2,4-*dihydroxy*-2′,4′,6′-*trimethoxy*-6-*methylbenzophenone* (18).—Condensation of the acid (3) (2.5 g) and 1,3,5-trimethoxybenzene (1.3 g) in the presence of trifluoroacetic anhydride (10 ml) as above gave a crude product which was chromatographed over silica gel with 5—20% ethyl acetate–light petroleum as eluant. Early fractions gave 2,2,2-trifluoro-2′,4′,6′-trimethoxyacetophenone (0.7 g), which formed needles (from dichloromethane–light petroleum), m.p. 54—55° (lit.,[20] 59—60°) (Found: C, 50.0; H, 4.1%; M^+, 264. Calc. for $C_{11}H_{11}F_3O_4$: C, 50.0; H, 4.2%; *M*, 264); δ($CDCl_3$; 60 MHz) 3.69 (6 H, s, 2 × OMe), 3.76 (3 H, s, OMe), and 6.00 (2 H, s, ArH). Later fractions gave 2,4-bisbenzyloxy-3-chloro-2′,4′,6′-trimethoxy-6-methylbenzophenone (17) (2.7 g) as a gum homogeneous on t.l.c.; δ($CDCl_3$; 60 MHz) 2.25 (3 H, s, Me), 3.41 (6 H, s, 2 × OMe), 3.72 (3 H, s, OMe), 4.72 and 5.21 (each 2 H, s, CH_2), 5.90 (2 H, s, 3′- and 5′-H), 6.60 (1 H, s, 5-H), and 7.14 and 7.32 (each 5 H, s, Ph). Hydrogenolysis of this benzophenone (17) gave the *benzophenone* (18) as pale yellow needles (from methanol), m.p. 175—177° (Found: C, 58.05; H, 5.1; Cl, 10.05%; M^+, 352/354. $C_{17}H_{17}ClO_6$ requires C, 57.9; H, 4.85; Cl, 10.05%; *M*, 352/354); δ($CDCl_3$; CD_3SOCD_3; 60 MHz) 1.92 (3 H, s, Me), 3.61 (6 H, s, 2 × OMe), 3.76 (3 H, s, OMe), 6.00 (2 H, s, 3′- and 5′-H), and 6.16 (1 H, s, 5-H).

5-*Chloro*-6-*hydroxy*-1,3-*dimethoxy*-8-*methylxanthen*-9-*one* (14).—The benzophenone (18) (1.0 g) was boiled under reflux with ethanolic potassium hydroxide (1%; 100 ml) for 1.5 h. The usual work-up gave the *xanthone* (14) (850 mg) as microscopic aggregates of plates (from aqueous dimethyl sulphoxide), m.p. 325—327° (decomp.) (Found: C, 59.8; H, 4.3; Cl, 10.8%; M^+, 320/322. $C_{16}H_{13}ClO_5$ requires C, 59.9; H, 4.1; Cl, 11.05%; *M*, 320/322). The *acetate* (15) (pyridine–acetic anhydride at 90 °C) formed felted needles (from chloroform–methanol), m.p. 240—241° with sublimation from 220° (Found: C, 59.5; H, 4.45; Cl, 9.5%; M^+, 362/364. $C_{18}H_{15}ClO_6$ requires C, 59.6; H, 4.15; Cl, 9.75%; *M*, 362/364); δ($CDCl_3$; 60 MHz), 2.37 (3 H, s, MeCO), 2.82 (3 H, s, Me), 3.82 and 3.90 (each 3 H, s, OMe), 6.22 and 6.41 (2 H, AB, $J_{2,4}$ 2.5 Hz, 2- and 4-H), and 6.74 (1 H, s, 7-H).

5-*Chloro*-1,6-*dihydroxy*-3-*methoxy*-8-*methylxanthen*-9-*one* (*Vinetorin*) (16).—The acetate (15) (445 mg) in dry dichloromethane (100 ml) was stirred at 0 °C and treated rapidly with boron trichloride (3.0 g) in dry dichloromethane (50 ml). The solution was stirred at 0 °C for 1 h and then poured into water and extracted with ethyl acetate. The usual work-up gave *vinetorin* (16) (336 mg) as yellow needles (from ethyl acetate), m.p. 254—255°. A slightly impure sample of authentic vinetorin provided by Dr. S. Huneck had m.p. 248—250° (with some sweating from 220°) (lit.,[11] 243—245°) and on admixture with synthetic material it had m.p. 253—255°. The R_F values of the two samples were identical in four solvent systems, although the natural sample had a slight impurity of higher R_F. The mass spectra of the two samples were identical, but the natural sample contained a trace of material with one more chlorine atom [11] (Found: C, 58.75; H, 4.0; Cl, 11.5%; M^+, 306/308. $C_{15}H_{11}ClO_5$ requires C, 58.75; H, 3.6; Cl, 11.55%; *M*, 306/308); δ($CDCl_3$; 80 MHz) 2.52 (3 H, d, $J_{Me,8\text{-H}}$ 1.1 Hz, Me), 3.89 (3 H, s, OMe), 6.07 (1 H, s, OH), 6.34 and 6.46 (2 H, AB, $J_{2,4}$ 2.4 Hz, 2- and 4-H), 6.82 (1 H, s, 7-H), and 13.16 (1 H, s, OH); identical with that of the natural sample.

6′-*Benzyloxy*-3,3′-*dichloro*-2,2′,4,4′-*tetramethoxy*-6-*methylbenzophenone* (20).—Trifluoroacetic anhydride (15 ml) in dry dichloromethane (15 ml) was added dropwise at 0 °C to a stirred solution of the acid (4) (3.0 g) and the phloroglucinol (19) (14.0 g) in dry dichloromethane (100 ml). After the addition the solution was stirred at room temperature for 5 h. The usual work-up gave a crude product which was chromatographed over silica gel with 5—20% ethyl acetate–light petroleum as eluant. This gave the *benzophenone* (20) (5.8 g) as rosettes of needles (from dichloromethane–light petroleum), m.p. 138—139° (Found: C, 60.95; H, 4.8; Cl, 14.5%; M^+, 490/492/494. $C_{25}H_{24}Cl_2O_6$ requires C, 61.1; H, 4.9; Cl, 14.45%; *M*, 490/492/494); δ($CDCl_3$; 60 MHz) 2.17 (3 H, s, Me), 3.43 and 3.72 (each 3 H, s, OMe), 3.78 (6 H, s, 2 × OMe), 4.77 (2 H, s,

CH_2), 6.19 and 6.24 (each 1 H, s, ArH), and 6.80—7.27 (5 H, m, Ph).

3,3′-*Dichloro*-6-*hydroxy*-2,2′,4,4′-*tetramethoxy*-6-*methylbenzophenone* (21).—Hydrogenolysis of the benzophenone (20) as above gave the *benzophenone* (21) as pale yellow *prisms* (from chloroform–methanol), m.p. 147—148° (Found: C, 54.2; H, 4.65; Cl, 18.0%; M^+, 400/402/404. $C_{18}H_{18}Cl_2O_6$ requires C, 53.9; H, 4.5; Cl, 17.65%; *M*, 400/402/404); δ($CDCl_3$; 60 MHz) 2.14 (3 H, s, Me), 3.28 and 3.74 (each 3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 6.33 and 6.51 (each 1 H, s, ArH), and 13.25 (1 H, s, OH).

2,5-*Dichloro*-1,3,6-*trimethoxy*-8-*methylxanthen*-9-*one* (22).—Ring-closure of the benzophenone (21) with ethanolic potassium hydroxide as before gave the *xanthone* (22) as felted needles (from chloroform–methanol), m.p. 208—209° (lit.,[12] 205—206°) (Found: C, 55.5; H, 3.85; Cl, 19.2%; M^+, 368/370/372. $C_{17}H_{14}Cl_2O_5$ requires C, 55.3; H, 3.8; Cl, 19.2%; *M*, 368/370/372); δ($CDCl_3$; 90 MHz) 2.84 (3 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, Me), 3.97, 3.99, and 4.00 (each 3 H, s, OMe), 6.44 (1 H, s, $W_{\frac{1}{2}}$ 2.8 Hz, 7-H), and 6.74 (1 H, s, 4-H); irradiation at δ 2.84 sharpened the 7-H signal.

2,5-*Dichloro*-1-*hydroxy*-3,6-*dimethoxy*-8-*methylxanthen*-9-*one* (23).—Demethylation of the xanthone (22) with boron trichloride as above gave the title *xanthone* (23) as pale yellow needles (from ethyl acetate), m.p. 314—315°, undepressed on admixture with an authentic sample which had m.p. 313—315° (lit.,[12] 299—300°). The R_F values of the two samples were identical in three solvent systems (Found: C, 54.5; H, 3.45; Cl, 19.6%; M^+, 354/356/358. $C_{16}H_{12}Cl_2O_5$ requires C, 54.1; H, 3.4; Cl, 19.95%; *M*, 354/356/358). The *acetate* formed needles (from chloroform–methanol), m.p. 248—250°, undepressed on admixture with an authentic sample which had m.p. 247—250° (with some previous sweating) (lit.,[12] 234—235°). The R_F values of the two samples were identical in three solvent systems (Found: C, 54.15; H, 3.6; Cl, 17.9%; M^+, 396/398/400. $C_{18}H_{14}Cl_2O_6$ requires C, 54.4; H, 3.55; Cl, 17.85%; *M*, 396/398/400); δ($CDCl_3$; 60 MHz) 2.43 (3 H, s, MeCO), 2.73 (3 H, s, Me), 3.89 and 3.93 (each 3 H, s, OMe), and 6.55 and 6.75 (each 1 H, s, 7- and 4-H).

2,4,6′-*Trisbenzyloxy*-3,3′-*dichloro*-2′,4′-*dimethoxy*-6-*methylbenzophenone* (26).—The acid (3) (5.0 g) and the phloroglucinol (19) (9.1 g) were treated as described for the preparation of the benzophenone (20). The *benzophenone* (26) (5.1 g) formed rosettes of needles (from dichloromethane–light petroleum), m.p. 161—162° (Found: C, 68.8; H, 5.1; Cl, 11.7. $C_{37}H_{32}Cl_2O_6$ requires C, 69.05; H, 5.0; Cl, 11.0%); δ($CDCl_3$; 60 MHz) 2.15 (3 H, s, Me), 3.71 (6 H, s, 2 × OMe), 4.60, 4.63, and 5.01 (each 2 H, s, CH_2), 6.06 and 6.35 (each 1 H, s, 5′- and 5-H), and 6.73—7.43 (15 H, m, Ph).

3,3′-*Dichloro*-2,4,6′-*trihydroxy*-2′,4′-*dimethoxy*-6-*methylbenzophenone* (27).—Hydrogenolysis of the benzophenone (26) gave the *benzophenone* (27) as pale yellow plates (from dichloromethane–light petroleum), m.p. 164—165° (Found: C, 51.45; H, 3.6; Cl, 19.25%; M^+, 372/374/376. $C_{16}H_{14}Cl_2O_6$ requires C, 51.5; H, 3.8; Cl, 19.0%; *M*, 372/374/376); δ($CDCl_3$; 60 MHz) 2.10 (3 H, s, Me), 3.31 and 3.89 (each 3 H, s, OMe), 6.30 and 6.39 (each 1 H, s, ArH)

4,5-*Dichloro*-1,6-*dihydroxy*-3-*methoxy*-8-*methylxanthen*-9-*one* (28).—Ring-closure of the benzophenone (27) with ethanolic potassium hydroxide as above gave the *xanthone* (28) as felted yellow needles (from ethyl acetate), m.p. 255—256° (Found: C, 52.9; H, 3.0; Cl, 20.15%; M^+, 340/342/344. $C_{15}H_{10}Cl_2O_5$ requires C, 52.8; H, 2.95; Cl, 20.8%; *M*, 340/342/344); δ($CDCl_3$; 80 MHz) 2.84 (3 H, s, Me), 3.99 (3 H, s, OMe), and 6.43 and 6.86 (each 1 H, s, 2- and 7-H). The *di*-O-*methyl ether* (30) (iodomethane–potassium carbonate–*NN*-dimethylformamide) formed needles (from chloroform–methanol), m.p. 254—255° (lit.,[14] 203—207°) (Found: C, 55.4; H, 4.0; Cl, 19.2%; M^+, 368/370/372. $C_{17}H_{14}Cl_2O_5$ requires C, 55.3; H, 3.8; Cl, 19.2%; *M*, 368/370/372); δ($CDCl_3$; 60 MHz), 2.81 (3 H, s, Me), 3.94 (9 H, s, 3 × OMe), and 6.31 and 6.60 (each 1 H, s, 2- and 6-H).

4,5-*Dichloro*-1,3,6-*trihydroxy*-8-*methylxanthen*-9-*one* (29).—The xanthone (28) (630 mg) was boiled under reflux in piperidine (15 ml) and water (15 ml) for 66 h. The cooled solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. The *xanthone* (29) (520 mg) formed pale yellow needles (from cyclohexane–ethyl acetate), m.p. 292—294° (slight decomp.). An authentic sample of the xanthone from *L. straminea* had m.p. 291—293° (slight decomp.) [lit.,[14] 273—274° (decomp.)], undepressed on admixture with the synthetic material. The R_F values in three solvent systems and the n.m.r. and mass spectra of the two samples were identical (Found: C, 51.1; H, 2.3; Cl, 21.75%; M^+, 326/328/330. $C_{14}H_8Cl_2O_5$ requires C, 51.4; H, 2.45; Cl, 21.7%; *M*, 326/328/330); δ($CDCl_3$; 60 MHz) 2.69 (3 H, s, Me), and 6.29 and 6.69 (each 1 H, s, 2- and 7-H).

4,5-*Dichloro*-1-*hydroxy*-3,6-*dimethoxy*-8-*methylxanthen*-9-*one* (31).—The xanthone (30) was demethylated with boron trichloride as above. The *xanthone* (31) formed silky pale yellow needles (from ethyl acetate), m.p. 285—286.5°. An authentic sample of this xanthone had m.p. 271—275° (with previous sweating) (lit.,[14] 250—251°) and on admixture with the synthetic material it had m.p. 282—285°. The R_F values in three solvent systems and the mass spectra of the two samples were identical (Found: C, 54.35; H, 3.6; Cl, 19.9%; M^+, 354/356/358. $C_{16}H_{12}Cl_2O_5$ requires C, 54.1; H, 3.4; Cl, 19.95%; *M*, 354/356/358). The *acetate* formed needles (from chloroform–methanol), m.p. 235—237° (with slight previous sweating) (Found: C, 54.2; H, 3.65; Cl, 18.2%; M^+, 396/398/400. $C_{18}H_{14}Cl_2O_6$ requires C, 54.45; H, 3.55; Cl, 17.85%; *M*, 396/398/400); δ($CDCl_3$; 60 MHz) 2.46 (3 H, s, MeCO), 2.80 (3 H, s, Me), 3.98 (6 H, s, 2 × OMe), and 6.58 and 6.67 (each 1 H, s, 2- and 7-H).

2,4,5-*Trichloro*-1,3,6-*trimethoxy*-8-*methylxanthen*-9-*one* (33).—(*a*) Freshly distilled sulphuryl chloride (265 mg) in 1,2-dichloroethane (20 ml) was added dropwise to a solution of the xanthone (22) (657 mg) in 1,2-dichloroethane (65 ml). The solution was stirred for 5.5 h and then worked up in the usual way. The crude product was crystallized from chloroform–methanol and then sublimed at 145 °C and 0.01 mmHg; the *xanthone* (33) (460 mg) was obtained as needles, m.p. 212—214° (lit.,[12] 201—202°; lit.,[16] 202—203°), identical (mixed m.p., R_F values in three solvent systems, mass and n.m.r. spectra) with an authentic sample of tri-*O*-methylarthothelin (Found: C, 50.65; H, 3.3; Cl, 26.8%; M^+, 402/404/406/408. $C_{17}H_{13}Cl_3O_5$ requires C, 50.6; H, 3.25; Cl, 26.35%; *M*, 402/404/406/408); δ($CDCl_3$; 90 MHz) 2.83 (3 H, d, $J_{7,Me}$ 0.9 Hz, Me), 4.00 (6 H, s, 2 × OMe), 4.03 (3 H, s, OMe), and 6.70 (1 H, s, $W_{\frac{1}{2}}$ 2.1 Hz, ArH); irradiation at δ 2.83 sharpened the ArH signal.

(*b*) The xanthone (30) on chlorination as above gave the xanthone (33), m.p. and mixed m.p. 212—214°.

2,4,5-*Trichloro*-1-*hydroxy*-3,6-*dimethoxy*-8-*methylxanthen*-9-*one* (32).—Demethylation of the xanthone (33) with

boron trichloride gave the *xanthone* (32), which was crystallized from ethyl acetate and then sublimed at 200 °C and 0.05 mmHg; it formed pale yellow needles, m.p. 225—227° (lit.,[12] 221—223°), identical (mixed m.p., R_F values in three solvent systems, and mass spectra) with an authentic sample (Found: C, 49.05; H, 2.9; Cl, 27.7. $C_{16}H_{11}Cl_3O_5$ requires C, 49.3; H, 2.85; Cl, 27.3%). The *acetate* formed needles (from chloroform–methanol), m.p. 200—202° (lit.,[12] 202—203°) (Found: C, 50.3; H, 3.05; Cl, 24.3. $C_{18}H_{13}Cl_3O_6$ requires C, 50.1; H, 3.05; Cl, 24.65%); δ($CDCl_3$; 90 MHz) 2.50 (3 H, s, MeCO), 2.79 (3 H, d, $J_{7,Me}$ 0.9 Hz, Me), 4.00 and 4.06 (each 3 H, s, OMe), and 6.71 (1 H, s, $W_{\frac{1}{2}}$ 2.2 Hz, ArH); irradiation at δ 2.79 sharpened the ArH signal.

6-*Acetoxy*-2,4,5-*trichloro*-1,3-*dimethoxy*-8-*methylxanthen*-9-*one* (36).—The xanthone (15) (3.6 g) was chlorinated with sulphuryl chloride in dichloromethane as before. The *acetate* (36) (3.0 g) formed needles (from chloroform–methanol), m.p. 180—183° (Found: C, 49.85; H, 3.2; Cl, 24.8. $C_{18}H_{13}Cl_3O_5$ requires C, 50.1; H, 3.05; Cl, 24.65%); δ($CDCl_3$; 90 MHz) 2.39 (3 H, s, MeCO), 2.85 (3 H, d, $J_{7,Me}$ 0.9 Hz, Me), 4.01 and 4.03 (each 3 H, s, OMe), and 6.96 (1 H, s, $W_{\frac{1}{2}}$ 1.9 Hz, ArH); irradiation at δ 2.85 sharpened the ArH.

2,4,5-*Trichloro*-1,6-*dihydroxy*-3-*methoxy*-8-*methylxanthen*-9-*one* (*Thuringione*) (34).—The xanthone (36) was treated with boron trichloride as above. The product *xanthone* (34) formed pale yellow needles (from ethyl acetate–light petroleum), m.p. 278—280° (lit.,[16] 278—279°), identical (mixed m.p. and R_F values in three solvent systems) with an authentic sample (Found: C, 47.95; H, 2.6; Cl, 28.4. $C_{15}H_9Cl_3O_5$ requires C, 47.95; H, 2.4; Cl, 28.3%); δ($CDCl_3$; CD_3SOCD_3; 90 MHz) 2.76 (3 H, s, Me), 4.02 (3 H, s, OMe), and 6.85 (1 H, s, $W_{\frac{1}{2}}$ 2.1 Hz, ArH); irradiation at δ 2.76 sharpened the ArH signal. The di-*O*-methyl ether (33) was identical with that described above.

2,4,5-*Trichloro*-1,3,6-*trihydroxy*-8-*methylxanthen*-9-*one* (*Arthothelin*) (35).—The xanthone (34) (500 mg) was boiled under reflux with piperidine (10 ml) and water (10 ml) for 3 h. The usual work-up gave *arthothelin* (35) (385 mg) as yellow needles (from ethyl acetate), m.p. 283—285° (lit.,[18] 269—271°; lit.,[17] 275—276°) (Found: C, 46.65; H, 2.15; Cl, 29.7. $C_{14}H_7Cl_3O_5$ requires C, 46.5; H, 1.95; Cl, 29.4%); δ(CD_3SOCD_3; 90 MHz) 2.55 (3 H, s, Me) and 6.69 (1 H, s, ArH). The tri-*O*-methyl ether (33) was identical with that described above.

We thank Dr. S. Huneck and Mr. E. G. Sundholm for authentic samples and the Australian Research Grants Committee for financial support.

[9/301 *Received*, 26*th February*, 1979]

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