Synthesis of Valsarin and 5,7-Dichloroemodin

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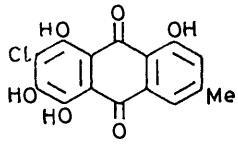
Syntheses of the naturally occurring chloroanthraquinones 5,7-dichloroemodin (2) (1,3-dichloro-2,4,5-trihydroxy-7-methylanthraquinone) and valsarin (1) (3-chloro-1,2,4,5-tetrahydroxy-7-methylanthraquinone) and a new synthesis of 7-chloroemodin (3) (2-chloro-1,3,8-trihydroxy-6-methylanthraquinone) are described.

VALSARIN was isolated by Briggs and Castaing [1] from the fungus *Valsaria rubricosa* and by chemical and spectroscopic methods they deduced that it was a chlorotetrahydroxyanthraquinone. Later Fox *et al.*[2] also isolated a chlorotetrahydroxyanthraquinone from the lichen *Lasallia papulosa* which they named papulosin and for which they deduced structure (1) on spectroscopic grounds. Direct comparison of the two natural products has now demonstrated their identity.[3] Bohman [4] has presented evidence that valsarin co-occurs with an isomeric pigment which she suggested may differ in structure from (1) only by the location of a hydroxy-group. We now describe synthetic work on valsarin as well as a synthesis of the naturally occurring 5,7-dichloroemodin (2) [5] and a new synthesis of 7-chloroemodin (3).[6,7]

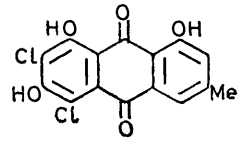
We have previously investigated the chlorination of parietin in our work on the synthesis of 7-chloroemodin (3) and its methyl ether fragilin (4),[6] and consequently we regarded xanthorin (5) [8-10] as a convenient starting material for the synthesis of valsarin (1). Xanthorin (5) was obtained from tri-*O*-methylemodin [6] by a slight modification of the method of Tanaka and Kaneko.[8] As a model for the chlorination of xanthorin (5) we

[1] L. H. Briggs and D. R. Castaing, *Bull. Nat. Inst. Sci. India*, 1965, **28**, 71.
[2] C. H. Fox, W. S. G. Maass, and T. P. Forrest, *Tetrahedron Letters*, 1969, 919.
[3] L. H. Briggs, D. R. Castaing, A. L. Denyer, E. F. Orgias, and C. W. Small, preceding paper.
[4] G. Bohman, *Acta Chem. Scand.*, 1969, **23**, 2241.
[5] I. Yosioka, H. Yamauchi, K. Morimoto, and I. Kitagawa, *Tetrahedron Letters*, 1968, 1149.
[6] M. V. Sargent, D. O'N. Smith, and J. A. Elix, *J. Chem. Soc.* (*C*), 1970, 307.
[7] For the occurrence of this natural product see R. H. Thomson, 'Naturally Occurring Quinones,' 2nd edn., Academic Press, London, 1971.
[8] O. Tanaka and C. Kaneko, *Pharm. Bull.* (*Japan*), 1955, **3**, 284.
[9] W. Steglich, W. Lösel, and W. Reininger, *Tetrahedron Letters*, 1967, 4719.
[10] K.-E. Stensiö and C. A. Wachtmeister, *Acta Chem. Scand.*, 1969, **23**, 144.

investigated the chlorination of 1,4-dihydroxy-2-methoxyanthraquinone (6). With chlorine in cold acetic acid anomalous products were obtained,[11] but chlorination in hot acetic acid in a sealed tube



(1)



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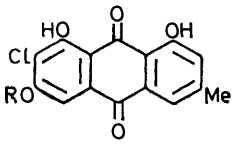
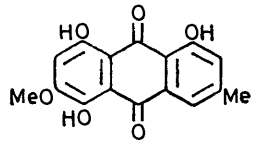
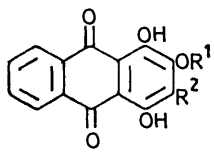


(3) R = H
(4) R = Me

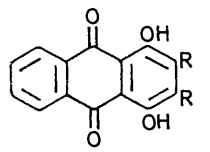


(5)

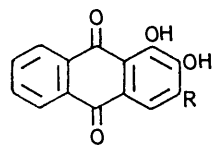
gave the 3-chloro-compound (7), which on demethylation afforded the purpurin (8). Attempted chlorination of 2-ethoxy-1,4-dihydroxyanthraquinone (9), which is appreciably more soluble than the methyl compound (6), with chlorine in cold chloroform gave a complex mixture of products from which the chloro-compound (10) was isolated in only 8% yield. 1,4-Dihydroxyanthraquinone (11) also gave



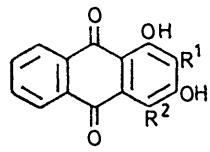
(6) R^1 = Me; R^2 = H
(7) R^1 = Me; R^2 = Cl
(8) R^1 = H; R^2 = Cl
(9) R^1 = Et; R^2 = H
(10) R^1 = Et; R^2 = Cl



(11) R = H
(12) R = Cl



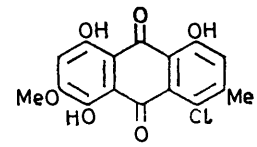
(13) R = H
(14) R = Cl



(15) R^1 = R^2 = H
(16) R^1 = H; R^2 = Cl
(17) R^1 = R^2 = Cl

anomalous products with chlorine in cold acetic acid,[11] but with an excess of chlorine in hot acetic acid in a sealed tube it smoothly gave the dichloro-compound (12). In contrast, treatment of 1,2-dihydroxyanthraquinone (13) with chlorine in cold acetic acid gave the 3-chloro-compound (14). Similarly, treatment of 1,3-dihydroxyanthraquinone (15) with 1 mol. equiv. of chlorine in cold acetic acid yielded the 4-chloro-compound (16), and with 2 mol. equiv. under the same conditions gave the 2,4-dichloro-compound (17).

Treatment of xanthorin (5) with chlorine (1 mol. equiv.) in cold chloroform smoothly furnished the monochloro-compound (18). Further chlorination of compound (18) was achieved by treatment with chlorine in hot acetic acid in a sealed tube when a mixture of the dichloro- (19) and the trichloro-compound (20) resulted. The structures of the chloro-compounds (18) and (19) follow from the n.m.r. spectra of their methyl ethers (see Experimental section). The dichloroxanthorin (19) was converted into the methyl ether (21), which was reduced with hydrazine hydrate and palladised charcoal whereupon the α-chlorine atom was selectively removed [6] to give tetra-*O*-methylvalsarin (22) in 28% yield, identical (mixed m.p.) with that synthesised by an alternative route (see later).



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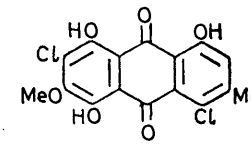
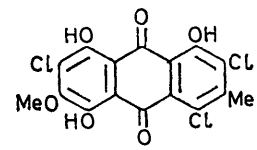
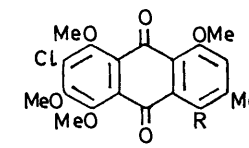


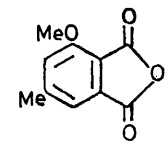
(19)



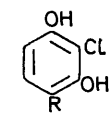
(20)



(21) R = Cl
(22) R = H



(23)



(24) R = H
(25) R = Cl

We have also synthesised valsarin (1) from 5,7-dichloroemodin (2). Friedel–Crafts condensation of 3-methoxy-5-methylphthalic anhydride (23) with 2-chlororesorcinol (24) [12] and subsequent ring-closure of the resultant crude benzoylbenzoic acid was accompanied by demethylation and gave 7-chloroemodin (3), which was identical both with that synthesised previously [6] and with the natural product. A similar sequence starting from 2,4-dichlororesorcinol (25) furnished 5,7-dichloroemodin, which was identical with the natural product.

Halogen atoms at the α-positions of the anthraquinone

[11] See M. A. Sargent, D. O'N. Smith, and J. A. Elix, *Tetrahedron Letters*, 1970, 2065.
[12] N. Schamp, *Bull. Soc. chim. belges*, 1964, **73**, 35.

nucleus may be replaced by hydroxy-groups by treatment with sulphuric and boric acids at elevated temperature.[13] In particular α-halogen atoms may be so replaced in presence of β-halogeno-substituents. Thus Mettler[14] found that 2,4-dichloro-1,3-dihydroxyanthraquinone (17) was converted into 3-chloro-1,2,4-trihydroxyanthraquinone (8) under these conditions. When this method was applied to 5,7-dichloroemodin (2) conversion into valsarin (1) occurred. The i.r. spectra of the synthetic material and its tetra-acetate were virtually identical with those of authentic natural material.

EXPERIMENTAL

General procedures have been described previously.[6]

1-Bromo-2,4,5-trimethoxy-7-methylanthraquinone (*5-Bromo-tri-O-methylemodin*).—The following modification of the method of Tanaka and Kaneko[8] was used. Tri-*O*-methyl emodin[6] (500 mg), bromine (256 mg), and fused sodium acetate (439 mg) were heated at 100° in glacial acetic acid (24·4 ml) for 6 h. The mixture was poured into hot water (110 ml) and set aside for 12 h. The yellow precipitate was separated by filtration and dried *in vacuo*. The filtrate was exhaustively extracted with ethyl acetate, and the extracts were washed in turn with sodium hydrogen carbonate solution, water, and saturated brine, and then dried ($MgSO_4$). The solvent was removed and the combined crude product was crystallised (×2) from toluene to give yellow prisms (428 mg, 69%) of the quinone, m.p. 234—237° (lit.,[8] 232—234°), τ 2·36br (1H, s, 4-H), 2·82br (1H, s, 2-H), 3·10 (1H, s, 7-H), 5·93 (6H, s, OMe), 5·96 (3H, s, OMe), and 7·52 (3H, s, Me).

1,4,5-Trihydroxy-2-methoxy-7-methylanthraquinone (*Xanthorin*) (5).—The foregoing bromo-compound (1·44 g), manganese dioxide (1·60 g), and potassium hydroxide (42 g) were heated under reflux in methanol (480 ml) for 14 h. The cooled mixture was poured into water and extracted exhaustively with chloroform. The extracts were washed with water and saturated brine, and then dried ($MgSO_4$). The residue left on removal of the solvent was heated under reflux for 0·5 h with glacial acetic acid (50 ml) and hydrogen bromide in glacial acetic acid (25 ml; 45% w/v). The cooled mixture was then poured into water and the precipitate separated by filtration and dried *in vacuo*. The crude product was pre-adsorbed from chloroform on to silica gel and chromatographed over a column of the same material (total 750 g). On gradient elution with 40% pentane–benzene to benzene a red band was eluted which afforded the quinone (327 mg, 29%) as red needles from benzene, m.p. 245—247° (lit.,[8-10] 245—246, 253, 250—251°), $\lambda_{max.}$($CHCl_3$) 233, 259, 308, and 492 nm (ε 22,400, 28,200, 9800, and 14,800), $\lambda_{infl.}$ 464, 514, and 528 nm (ε 11,200, 10,600, and 10,400), τ −3·67, −2·88, and −2·34 (all 1H, s, OH), 2·27br (1H, s, 4-H), 2·85br (1H, s, 2-H), 3·29 (1H, s, 7-H), 5·97 (3H, s, OMe), and 7·54 (3H, s, Me).

1,4-Dihydroxy-2-methoxyanthraquinone (6).—1,2,4-Trimethoxyanthraquinone[15] (1·82 g) in glacial acetic acid (50 ml) was heated under gentle reflux with aqueous 48% hydrobromic acid (30 ml) for 0·5 h. The cooled mixture was diluted with water and the product separated by filtration as orange-red needles (1·44 g, 87%), m.p. 239—240° (from acetic acid) (lit.,[16] 240°).

3-Chloro-1,4-dihydroxy-2-methoxyanthraquinone (7).—The foregoing quinone (226 mg) and chlorine (650 mg) in acetic acid (25 ml) were heated in a sealed tube at 130° for 41·5 h. The cooled mixture was then poured into water, and the product separated by filtration, and dried *in vacuo*. It was pre-adsorbed on to silica gel and chromatographed over a column of the same material with benzene as eluant. The *chloroquinone* (178 mg, 70%) formed orange-red needles, m.p. 215—216° (from benzene) (Found: C, 58·9; H, 2·9. $C_{15}H_9ClO_5$ requires C, 59·1; H, 3·0%), τ −3·91 and −3·57 (each 1H, s, OH), 1·55 (2H, m, 5- and 8-H), 2·05 (2H, m, 6- and 7-H), and 5·78 (3H, s, OMe). The *bis*(*methyl ether*) formed pale yellow needles, m.p. 141—142° (from methanol) (Found: C, 61·65; H, 3·9. $C_{17}H_{13}ClO_5$ requires C, 61·4; H, 3·95%), τ 1·72 (2H, m, 5- and 8-H), 2·13 (2H, m, 6- and 7-H), and 5·91 (9H, s, OMe).

3-Chloro-1,2,4-trihydroxyanthraquinone (8).—The chloro-compound (7) (88·9 mg) was maintained at 160° (bath) with pyridine hydrochloride (10 g) for 9 h. The cooled melt was treated with water and the suspension exhaustively extracted with ethyl acetate. The extracts were washed with saturated brine and dried ($MgSO_4$). The solvent was removed and the residue crystallised from glacial acetic acid to give red needles (57·3 mg, 68%), m.p. 280—282°. A sample sublimed at 175° and 0·1 mmHg to give red needles, m.p. 281—283° (lit.,[14] 270—273°) (Found: C, 58·05; H, 2·65%; *M*, 290, 292. Calc. for $C_{14}H_7ClO_5$: C, 57·85; H, 2·45%; *M*, 290, 292).

2-Ethoxy-1,4-dihydroxyanthraquinone (9).—This was prepared in the same way as the methyl analogue (6). The *quinone* crystallised from acetone as orange-red needles, m.p. 206·5—208° (Found: C, 67·4; H, 4·1. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·25%), τ 1·56 (2H, m, 5- and 8-H), 2·09 (2H, m, 6- and 7-H), 3·26 (1H, s, 3-H), 5·74 (2H, q, CH_2), and 8·44 (3H, t, Me).

3-Chloro-2-ethoxy-1,4-dihydroxyanthraquinone (10).—The foregoing quinone (255 mg) and chlorine (70·1 mg) in ethanol-free chloroform (6·4 ml) were set aside in the dark in a sealed flask for 17 h. T.l.c. revealed the product to be a complex mixture. The solution was concentrated and applied to a layer plate which was developed with 50% cyclohexane–benzene. The *chloroquinone* (23·3 mg, 8%) was obtained from an orange-red band, and formed orange-red leaflets, m.p. 160—161° (from cyclohexane) (Found: C, 60·65; H, 3·2. $C_{16}H_{11}ClO_5$ requires C, 60·3; H, 3·5%) τ −4·05 and −3·77 (each 1H, s, OH), 1·48 (2H, m, 5- and 8-H), 2·01 (2H, m, 6- and 7-H), 5·46 (2H, q, CH_2), and 8·42 (3H, t, Me).

2,3-Dichloro-1,4-dihydroxyanthraquinone (12).—1,4-Dihydroxyanthraquinone (200 mg) and chlorine (670 mg) in glacial acetic acid (25 ml) were heated in a sealed tube at 130° for 46·5 h. The chloroquinone, obtained as above, formed orange platelets (173 mg, 67%), m.p. 249·5—251° (from acetone) (lit.,[17] 242°) (Found: C, 54·4; H, 2·2.

[13] F. Bayer and Co., G.P. 203,083; H. Plath, *Ber.*, 1877, **10**, 614; F. Ullmann and W. Schmidt, *ibid.*, 1919, **52**, 2098; F. Ullmann and A. Conzetti, *ibid.*, 1920, **53**, 826; R. Eder and O. Manoukian, *Helv. Chim. Acta*, 1926, **9**, 51; A. Locher and H. E. Fierz, *ibid.*, 1927, **10**, 642; M. Hayashi, *J. Chem. Soc.*, 1927, 2516; A. Eckert and J. Hampel, *Ber.*, 1927, **60**, 1693; K. Keimatsu and I. Hirano, *J. Pharm. Soc. Japan*, 1931, **51**, 695.

[14] C. Mettler, *Ber.*, 1912, **45**, 800.

[15] L. H. Briggs and G. A. Nicholls, *J. Chem. Soc.*, 1951, 1138.

[16] C. Graebe and H. Bernhard, *Annalen*, 1906, **349**, 222.

[17] H. Dimroth, Dissertation, University of Würzburg, 1927, p. 33.

Calc. for $C_{14}H_6Cl_2O_4$: C, 54·4; H, 1·95%). The *diacetate* formed pale yellow needles, m.p. 249—251° (from ethanol) (Found: C, 55·0; H, 2·6. $C_{18}H_{10}Cl_2O_6$ requires C, 55·0; H, 2·55%), τ 1·33 (2H, m, 5- and 8-H), 1·73 (2H, m, 6- and 7-H), and 7·44 (6H, s, OAc).

3-*Chloro*-1,2-*dihydroxyanthraquinone* (14).—A solution of 1,2-dihydroxyanthraquinone (1·3 g) in glacial acetic acid (400 ml) was saturated with chlorine and set aside for 19 h. The excess of chlorine was then removed by passage of nitrogen and the crude product was separated by filtration. and crystallised from chloroform to form orange needles (950 mg, 64%), m.p. 270—271° (lit.,[18] 270—271°). The *bis*(*methyl ether*) formed yellow needles, m.p. 139—140° (from methanol) (Found: C,6 4·0; H, 3·7. $C_{16}H_{11}ClO_4$ requires C, 6·35; H, 3·65%), τ 1·84 (2H, m, 5- and 8-H), 1·93 (1H, s, 4-H), 2·55 (2H, m, 6- and 7-H), and 5·96 and 6·00 (each 3H, s, OMe).

4-*Chloro*-1,3-*dihydroxyanthraquinone* (16).—1,3-Dihydroxyanthraquinone (240 mg) and chlorine (76 mg) in glacial acetic acid (50 ml) were set aside for 46 h. The solvent was then removed under reduced pressure and the crude product crystallised from carbon tetrachloride to give the *product* (200 mg, 73%) as orange needles, m.p. 210—213° (Found: C, 59·9; H, 2·9%; *M*, 274, 276. $C_{14}H_7ClO_4$ requires C, 61·2; H, 2·55%; *M*, 274, 276). The *bis*(*methyl ether*) formed yellow needles, m.p. 175—177° (from methanol) (Found: C, 63·85; H, 3·65. $C_{16}H_{11}ClO_4$ requires C, 63·5; H, 3·65%), τ 1·80 (2H, m, 5- and 8-H), 2·25 (2H, m, 6- and 7-H), 3·17 (1H, s, 2-H), and 5·95 (6H, s, OMe).

2,4-*Dichloro*-1,3-*dihydroxyanthraquinone* (17).—1,3-Dihydroxyanthraquinone (240 mg) and chlorine (152 mg) in glacial acetic acid (50 ml) were set aside for 36 h. The residue (290 mg) left on removal of the solvent was applied to three layer plates which were developed with benzene. The major band yielded the dichloro-compound which formed orange needles, m.p. 235—238° (from carbon tetrachloride) (lit.,[14] 236—238°). The *bis*(*methyl ether*) formed pale yellow needles, m.p. 164·5—166° (from methanol) (Found: C, 56·6; H, 2·9%; *M*, 336, 338, 340. $C_{16}H_{10}Cl_2O_4$ requires C, 57·0; H, 3·0%; *M*, 336, 338, 340) ,τ 1·83 (2H, m, 5- and 8-H), 2·24 (2H, m, 6- and 7-H), and 5·96 (6H, s, OMe).

1-*Chloro*-4,5,8-*trihydroxy*-7-*methoxy*-2-*methylanthraquinone* (4-*Chloroxanthorin*) (18).—Chlorine (5·46 mg) in ethanol-free chloroform (0·125 ml) was added to a solution of xanthorin (5) (21·0 mg) in chloroform (2·0 ml). The solution was set aside in the dark for 24 h. The solvent was then removed and the residue was crystallised from methanol to give the *chloroquinone* (20·5 mg, 88%) as red needles, m.p. 232—234° (Found: C, 57·2; H, 3·85. $C_{16}H_{11}ClO_6$ requires C, 57·4; H, 3·3%), $\lambda_{max.}$ (MeOH) 238, 258, 304, and 500 nm (ε 25,200, 30,100, 8000, and 14,800), and $\lambda_{infl.}$ 474, 490, 526, and 537 nm (ε 11,700, 14,100, 10,500, and 9200), τ 3·38 (1H, s, 7-H), 5·98 (3H, s, OMe), and 7·51 (3H, s, Me); the resonance due to the 2-proton was obscured by the chloroform resonance. The *tris*(*methyl ether*) formed yellow plates, m.p. 210—211° (from methanol) (Found: C, 60·35; H, 4·2. $C_{19}H_{17}ClO_6$ requires C, 60·55; H, 4·55%), τ([$^2H_6$]Me_2CO) 2·48br (1H, s, 2-H), 2·82 (1H, s, 7-H), 5·91 (3H, s, OMe), 6·00 (6H, s, OMe), 6·04 (3H, s, OMe), and 7·50 (3H, s, Me).

2,5-*Dichloro*-1,4,8-*trihydroxy*-3-*methoxy*-6-*methylanthraquinone* (4,7-*Dichloroxanthorin*) (19) *and* 1,3,6-*Trichloro*-4,5,8-*trihydroxy*-7-*methoxy*-2-*methylanthraquinone* (2,4,7-*Trichloroxanthorin*) (20).—The foregoing quinone (18) (100 mg) and chlorine (233 mg) in acetic acid (12·9 ml) were heated at 125° for 64 h in a sealed tube. The cooled solution was then poured into water (500 ml) and the precipitate collected by filtration, washed with water, and dried *in vacuo*. The crude product, in chloroform, was applied to two layer plates which were developed with 20% cyclohexane–benzene. A red band afforded the *dichloro-compound* (41·3 mg, 37%) as brown-yellow needles, m.p. 211·5—213° (from chloroform) (Found: C, 52·2; H, 2·4. $C_{16}H_{10}Cl_2O_6$ requires C, 52·05; H, 2·75%), $\lambda_{max.}$ ($CHCl_3$) 242, 263, 308, and 505 nm (ε 27,400, 29,200, 8500, and 15,800), $\lambda_{infl.}$ 494, 528, and 542 nm (ε 15,500, 11,900, and 9200), τ 2·73 (1H, s, 2-H), 5·81 (3H, s, OMe), and 7·50 (3H, s, Me). The *tris*(*methyl ether*) (21) formed pale yellow needles, m.p. 204—206° (from methanol) (Found: *M*, 410·0326. $^{12}C_{19}{}^1H_{16}{}^{35}Cl_2{}^{16}O_6$ requires *M*, 410·0324), τ ([$^2H_6$]Me_2CO) 2·48 (1H, s, 2-H), 5·98 (3H, s, OMe), 6·01 (6H, s, OMe), 6·05 (3H, s, OMe), and 7·54 (3H, s, Me). A slower moving, purple band afforded the *trichloro-compound* (11·8 mg, 10%) as deep red needles, m.p. 257—258° (from chloroform) (Found: C, 47·35; H, 1·85. $C_{16}H_9Cl_3O_6$ requires C, 47·6; H, 2·25%), $\lambda_{max.}$ ($CHCl_3$) 244, 268, 316, and 508 nm (ε 30,600, 37,000, 10,700, and 18,000), and $\lambda_{infl.}$ 482, 500, 531, and 544 nm (ε 14,700, 17,300, 14,000, and 11,300).

3-*Chloro*-1,2,4,5-*tetramethoxy*-7-*methylanthraquinone* (*Tetra*-O-*methylvalsarin*) (22).—The methyl ether (21) (55 mg) and 100% hydrazine hydrate (6·5 mg) in ethanol (6·3 ml) were heated under reflux with 10% palladised charcoal (100 mg) for 0·5 h. More hydrazine hydrate (10 mg) in ethanol (2 ml) was then added and heating continued for a further 0·5 h, when hydrazine hydrate (20 mg) in ethanol (4 ml) was added and heating again continued for 0·5 h. The solution was cooled and the catalyst was separated by filtration. The filtrate was diluted with ethyl acetate and washed in turn with water, dilute hydrochloric acid, and saturated brine, and dried (Na_2SO_4). The solution was concentrated and applied to two layer plates which were developed with 2% ethyl acetate–benzene. The major yellow band was removed and extracted with dichloromethane. The solvent was removed and the residue was crystallised from dichloromethane–light petroleum as yellow needles (14·2 mg, 28%) of the *tetrakis*(*methyl ether*), m.p. 176—177·5° (lit.,[2,3] 173—174, 180—180·5°) undepressed on mixture with that prepared later (Found: C, 60·3; H, 4·5%; *M*, 376, 378. $C_{19}H_{17}ClO_6$ requires C, 60·55; H, 4·55%; *M*, 376, 378).

3-*Methoxy*-5-*methylphthalic anhydride* (23).—This was prepared (39%) by the method of Birch and Hextall,[19] except that the intermediate diene was not conjugated before reaction with the acetylene.[20] It formed needles, m.p. 169—172° (from benzene) (lit.,[19] 167—168°). The methyl ester was obtained as prisms, m.p. 85—86° (from light petroleum) (lit.,[19] 84·5—85·5°), τ (CCl_4) 2·65br (1H, s, 4-H), 3·13br (1H, s, 6-H), 6·18 (9H, s, OMe), and 7·63 (3H, s, Me).

2-*Chloro*-1,3,8-*trihydroxy*-6-*methylanthraquinone* (7-*Chloroemodin*) (3).—Powdered aluminium chloride (2·67 g) was added to a stirred suspension of the foregoing anhydride

[18] G. Heller, *Ber.*, 1913, **46**, 2703.
[19] A. J. Birch and P. Hextall, *Austral. J. Chem.*, 1955, **8**, 96.
[20] See A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, 1967, **23**, 87.

(1·92 g), and 2-chlororesorcinol [12] (1·45 g) in dry benzene (20 ml). The temperature was gradually brought to 100° over 3 h and the mixture was then cooled and set aside for 12 h. Ice and concentrated hydrochloric acid (2 ml) were then added and the benzene was driven off in a current of steam. The aqueous residue was cooled and the precipitate was extracted into ethyl acetate. The solution was exhaustively extracted with dilute sodium hydroxide solution and the alkaline extracts were saturated with carbon dioxide, filtered, and acidified with concentrated hydrochloric acid. The pale yellow precipitate (1·90 g) was collected by filtration and dried *in vacuo*. The crude benzoylbenzoic acid (300 mg), boric oxide (1 g), and concentrated sulphuric acid (18 ml) were stirred for 12 h at 90° and then poured on to ice. The aqueous suspension was extracted exhaustively with ethyl acetate and the extracts were washed with water and saturated brine, and then dried (Na_2SO_4). The residue (285 mg) left on removal of the solvent was crystallised from methanol to afford the quinone (190 mg) as orange needles, m.p. 281—283° (lit.,[5,6] 286—287, 281—283°) undepressed on admixture with authentic material (Found: C, 59·3; H, 3·2%; *M*, 304, 406. Calc. for $C_{15}H_9ClO_5$: C, 59·15; H, 3·0%; *M*, 304, 306). The synthetic and natural products had the same R_F on t.l.c. in a number of solvent systems.

2,4-*Dichlororesorcinol* (25).—Sulphuryl chloride (1·40 g) was added dropwise to a stirred solution of 2-chlororesorcinol (1·45 g) in dry ether (25 ml). Evolution of gas occurred immediately and the ether was removed. The residue was crystallised from carbon tetrachloride as needles (1·40 g, 79%), which after drying over concentrated sulphuric acid *in vacuo*, had m.p. 84—85° (lit.,[21] 82·5—84°), τ (CCl_4) 2·86 and 3·43 (2H, ABq, *J* 8·5 Hz, 5- and 6-H), and 4·41 (2H, s, OH).

1,3-*Dichloro*-2,4,5-*trihydroxy*-7-*methylanthraquinone* (5,7-*Dichloroemodin*) (2).—Condensation of 2,4-dichlororesorcinol (1·82 g) and 3-methoxy-5-methylphthalic anhydride (1·92 g) (see before) gave the crude benzoylbenzoic acid (2·80 g). This (1·78 g) and boric oxide (5·4 g) were stirred in concentrated sulphuric acid (120 ml) at 98° for 12 h. The mixture was poured on to ice and the precipitate was extracted into ethyl acetate. The extracts were washed with water and with saturated brine, and then dried (Na_2SO_4). Removal of the solvent left a brownish residue (1·58 g) which was sublimed at 175° and 0·1 mmHg and then crystallised from benzene to give the *quinone* as orange needles, m.p. 274—275° (lit.,[5] 267—269°) undepressed on admixture with authentic material (Found: C, 53·3; H, 2·75%; *M*, 338, 340, 342. $C_{15}H_8Cl_2O_5$ requires C, 53·15; H, 2·9%; *M*, 338, 340, 342). The mass spectra of the synthetic and natural products, determined under the same conditions, were identical. The *triacetate* formed pale yellow needles, m.p. 218—219° (from benzene–light petroleum) (Found: C, 54·4; H, 3·3. $C_{21}H_{14}Cl_2O_8$ requires C, 54·2; H, 3·05%), τ 2·04br (1H, s, 4-H), 2·75br (1H, s, 2-H), 7·49 (3H, s, OAc), 7·53 (6H, s, OAc), and 7·60 (3H, s, Me). The *tris*(*methyl ether*) formed yellow needles, m.p. 227—228° (from methanol) (Found: C, 56·95; H, 4·05. $C_{18}H_{14}Cl_2O_5$ requires C, 56·7; H, 3·7%), τ 2·43br (1H, s, 4-H), 2·89br (1H, s, 2-H), 5·92 (3H, s, OMe), 6·00 (6H, s, OMe), and 7·51 (3H, s, Me).

3-*Chloro*-1,2,4,5-*tetrahydroxy*-7-*methylanthraquinone* (*Valsarin*) (1).—The foregoing quinone (2) (700 mg), boric acid (1·0 g), and concentrated sulphuric acid (20 ml) were stirred at 160° for 19 h. The mixture was poured into a large excess of water which was then heated under reflux for 15 min. The dark red precipitate was separated by filtration, washed with water, and dried *in vacuo*. The crude product was twice crystallised from ethanol to give material (104 mg) which was sublimed at 190° and 1 mmHg to afford red needles (64 mg) of *valsarin*, m.p. 273—274° (lit.,[1-3] 273—274, 268—269, 285—286° (Found: C, 55·95; H, 3·3%; *M*, 320, 322. $C_{15}H_9ClO_6$ requires C, 56·2; H, 2·85%; *M*, 320, 322). The i.r. spectrum (KBr) was virtually identical with that of the natural material. The tetra-acetate formed pale yellow needles from ethyl acetate–light petroleum, m.p. 222—223° (lit.,[1] 221·5—222°) (Found: C, 56·5; H, 3·7. Calc. for $C_{23}H_{17}ClO_{10}$: C, 56·5; H, 3·5%), τ 2·14br (1H, s, 4-H), 2·81br (1H, s, 2-H), 7·52 7·55, and 7·59 (total 15H, each s, OAc and Me). The i.r. spectrum (KBr) was identical with that of the natural acetate. The tetrakis(methyl ether) formed yellow needles, m.p. 176—177·5° (from methanol) (lit., see before) (Found: C, 60·6; H, 4·9. Calc. for $C_{23}H_{17}ClO_{10}$: C, 60·55; H, 4·55%. Found: *M*, 376·0713. Calc. for $^{12}C_{23}{}^{1}H_{17}{}^{35}Cl^{16}O_{10}$: *M*, 376·0714), τ 2·44br (1H, s, 4-H), 2·90br (1H, s, 2-H), 5·94, 5·98, and 6·00 (total 12H, each s, OMe), and 7·51 (3H, s, Me).

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[21] C. v. d. Stelt, B. G. Suurmond, and W. T. Nauta, *Rec. Trav. chim.*, 1954, **73**, 1022.