Naturally Occurring Dibenzofurans. Part 9.[1] A Convenient Synthesis of Phthalides: The Synthesis of Methyl Di-*O*-methylporphyrilate

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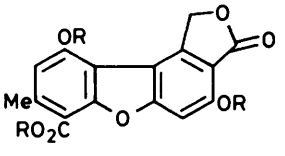
A convenient synthesis of phthalides [isobenzofuran-1(3*H*)-ones] from *o*-halogenobenzyl alcohols is described. This method is then applied to the synthesis of methyl di-*O*-methylporphyrilate (methyl 1,3-dihydro-4,10-dimethoxy-8-methyl-3-oxoisobenzofuro[5,4-*b*]benzofuran-7-carboxylate) (**2**), a derivative of the lichen dibenzofuran porphyrilic acid (**1**).

Porphyrilic acid is a dibenzofuran first isolated by Zopf[2] from the lichens *Haematomma coccineum* (Dicks.) Körb. and *H. porphyrium* (Pers.) Zopf. Structure (**1**) was proposed by Wachtmeister on the grounds of classical degradations.[3,4] In continuation of our studies on the total synthesis of naturally occurring dibenzofurans we were attracted to the problem of porphyrilic acid, the most complex of the fully aromatic lichen dibenzofurans.

The difficulty in the synthesis of porphyrilic acid (**1**) was envisaged to be the construction of the phthalide moiety. Although many phthalides [isobenzofuran-1(3*H*)-ones] are naturally occurring substances, and although phthalides are important intermediates in the synthesis of naphthalenes,[5] anthraquinones,[6] benzophenones,[7] and polyketides,[8,9] the methods available for their synthesis are few. The classical methods are those of Fritsch,[10,11] in which an appropriately substituted benzoic acid is condensed with chloral under acidic conditions and the resultant product is subjected to further transformations, and of Perkin,[12,13] which depends on the chloromethylation of a benzoic acid. The yields are often low. More recent methods depend on the lithiation of 3-methoxybenzyl alcohols at the 2-position and subsequent carboxylation; again the yields are often low.[6,8,14]

We now describe a convenient synthesis of phthalides which has been applied to the synthesis of methyl di-*O*-methylporphyrilate (**2**). Renson and Colliene[15] have shown that 2-(hydroxymethyl)benzonitrile exhibits in its i.r. spectrum a C=N stretching frequency at 1 685 cm^{-1} as well as a nitrile stretching band at 2 225 cm^{-1} so that the ψ-phthalimidine tautomer (**3**)[16] is present. On being kept in moist air for several days 2-(hydroxymethyl)benzonitrile is completely transformed into phthalide; no doubt the hydroxy group provides anchimeric assistance to the hydrolysis of the nitrile. Hence a synthesis of 2-(hydroxymethyl)benzonitriles would constitute a good method for the synthesis of phthalides. Since bromo or iodo substituents on aromatic rings can easily be replaced by nitriles by the agency of copper(I) cyanide in *NN*-dimethylformamide (DMF)[17] 2-(hydroxymethyl)benzonitriles are therefore readily available from 2-bromo- or 2-iodo-benzyl alcohols. The readily available iodo compounds (**4**)—(**7**) and the bromo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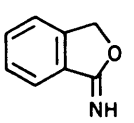
(2) R = Me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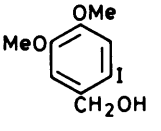
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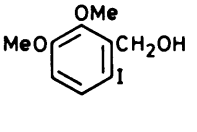
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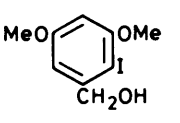
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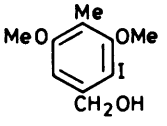
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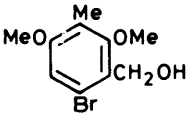
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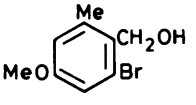
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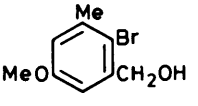
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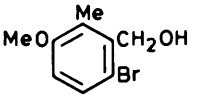
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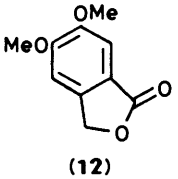
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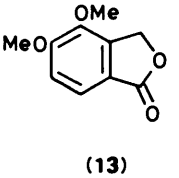
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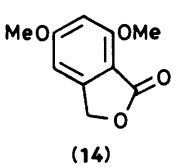
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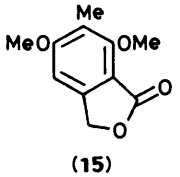
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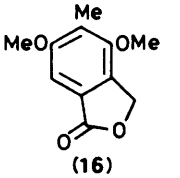
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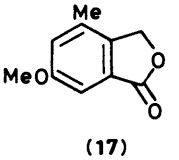
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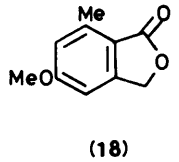
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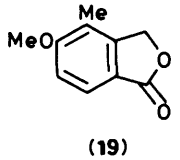
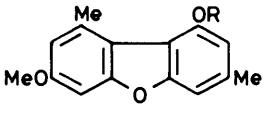

(19)

compounds (**8**)—(**11**) were therefore treated separately with copper(I) cyanide in hot DMF and the crude nitriles so obtained were then hydrolysed with boiling aqueous methanolic potassium hydroxide thereby providing the phthalides (**12**)—(**19**) in 71—94% yield.

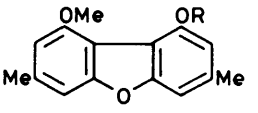
In order to apply this method of phthalide synthesis to the case of methyl di-*O*-methylporphyrilate (**2**) we required the iodo compounds (**32**). We have previously reported the synthesis of the acid (**29**) which was an intermediate in our synthesis of schizopeltic acid.[18] The derived ester (**30**) was therefore adopted as the key intermediate in the present synthesis. The *O*-methylpannarol (**20**) is an intermediate in the synthesis of the acid (**29**)[18] and since the methyl ether (**21**) is readily available[19] we attempted its selective demethylation with boron trichloride.[20] However, compound (**21**) was unchanged on prolonged treatment with boron trichloride so that the methyl group at the 9-position does not provide sufficient steric compression for demethylation to occur. However, the isomeric compound (**22**) underwent selective demethylation with boron trichloride to give the benzofuranol (**23**). Surprisingly the tetramethoxynaphthalene (**24**)[21] underwent no demethylation on prolonged treatment with boron trichloride.

The synthesis of the acid (**29**) has however been shortened. The intermediate (**26**) has now been prepared by alkylation of everninaldehyde with bromoacetal, thus providing the protected dialdehyde (**25**). On boiling compound (**25**) in acetic acid[22] the major product was the required aldehyde (**26**) accompanied by the benzofuran (**27**) and the tribenzofurylmethane (**28**).

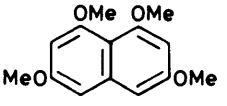
The ester (**30**) was prepared by methylation of the acid (**29**) and then subjected to radical bromination. The crude product of this reaction was treated with an excess of anhydrous sodium



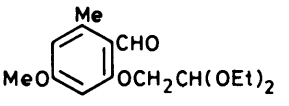
(**20**) R = H
(**21**) R = Me



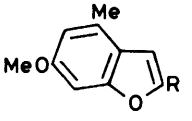
(**22**) R = Me
(**23**) R = H



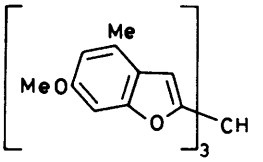
(**24**)



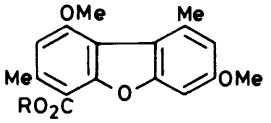
(**25**)



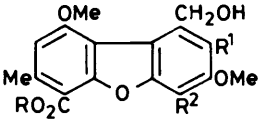
(**26**) R = CHO
(**27**) R = H



(**28**)



(**29**) R = H
(**30**) R = Me



(**31**) $R^1 = R^2 = H$
(**32**) $R^1 = I$, $R^2 = H$
(**33**) $R^1 = H$, $R^2 = I$

acetate in DMF and the mixture of acetates so obtained was hydrolysed with aqueous methanolic sodium hydroxide. Under these conditions the acetate derived from functionalization of the 3-methyl group in compound (**30**) would form a lactone. Thus the basic solution was extracted and the crude product so obtained on purification by chromatography yielded the hydroxymethyl compound (**31**) in 40% yield.

Iodination of the hydroxymethyl compound (**31**) with a solution of iodine in chloroform in the presence of silver trifluoroacetate provided a mixture of two monoiodo compounds, which were separated by radial chromatography and were obtained in 60 and 21% yield. The high-resolution n.m.r. spectra of these compounds revealed that they had both undergone iodination on the ring bearing the hydroxymethyl substituent. The minor isomer proved to be compound (**33**) since saturation of the methylene signal of the hydroxymethyl group in its ^1H n.m.r. spectrum gave a 17.6% n.O.e. at the adjacent 8-proton. Hence the major isomer was compound (**32**), and on treatment with copper(I) cyanide in DMF followed by basic hydrolysis and methylation it furnished methyl di-*O*-methylporphyrilate (**2**) in 94% yield. This compound proved to be identical with the derivative of the natural product, thus confirming Wachtmeister's structural assignment for porphyrilic acid (**1**).

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. Light petroleum was a fraction b.p. *ca.* 55—65 °C. All organic extracts were washed with saturated brine, and were then dried over anhydrous sodium sulphate prior to evaporation under reduced pressure. Radial chromatography was carried out on a Harrison Research Chromatotron with plates coated with Merck Kieselgel $60PF_{254}$. Unless otherwise stated, n.m.r. spectra, recorded for solutions in deuteriochloroform, were determined at 80 MHz with a Bruker WP-80 instrument. Those recorded at 300 MHz were obtained with a Bruker AM-300 instrument. Mass spectra were recorded with a Hewlett-Packard 5986 instrument operating at 35 eV. The i.r. spectrum was recorded with a Perkin-Elmer 282 spectrophotometer. Ether refers to diethyl ether.

General Method for Synthesis of Phthalides from o-*Halogenobenzyl Alcohols.*—The *o*-halogenobenzyl alcohol (10 mmol) and copper(I) cyanide (15 mmol) were stirred in anhydrous DMF (15 ml) under dry nitrogen or argon at 110 °C (bath) [for iodo compounds] or under reflux (for bromo compounds) until examination by t.l.c. indicated that no starting material was left. This time was usually 0.5 h for iodo compounds and 1 h for bromo compounds. The reaction mixture was poured into aqueous sodium cyanide (5%; 100 ml) and the crude product was isolated with ethyl acetate. The crude product was then boiled under reflux with water (10 ml), methanol (10 ml), and potassium hydroxide (5 g). When the evolution of ammonia could no longer be detected the mixture was cooled and diluted with water. The basic aqueous phase was extracted with ether and this extract was discarded. The aqueous layer was acidified and extracted with ethyl acetate and after drying and evaporation of the solvent the residue was crystallized.

5,6-*Dimethoxyisobenzofuran*-1(3H)-*one* (m-*Meconin*) (**12**).—Sodium borohydride (0.5 g) in ice-cold aqueous sodium hydroxide (5%; 5 ml) was added dropwise to a stirred solution of 2-iodo-4,5-dimethoxybenzaldehyde[23] (1.90 g) in tetrahydrofuran (THF) (25 ml) at room temperature. The solution was stirred for 15 min after the addition, and the excess of borohydride was destroyed by the addition of dil. hydrochloric acid. Isolation of the product with ethyl acetate gave 2-*iodo*-4,5-*dimethoxybenzyl alcohol* (**4**) (1.70 g, 89%) as plates (from dichloromethane–light petroleum), m.p. 103—104 °C (Found: C, 37.1; H, 3.8; I, 43.0%; M^+, 294. $C_9H_{11}IO_3$ requires C, 36.75; H, 3.75; I, 43.15%; *M*, 294); δ 2.15 (1 H, s, OH), 3.86 (6 H, s,

2 × OMe), 4.60 (2 H, s, CH_2), and 7.00 and 7.22 (each 1 H, s, ArH).

This was converted into *m*-meconin (**12**) (85%) which formed needles, m.p. 158—159 °C (from dichloromethane–light petroleum) (lit.,[12] 155—157 °C); δ 3.94 and 3.98 (each 3 H, s, OMe), 5.23 (2 H, s, CH_2), 6.91 (1 H, s, 4-H), and 7.32 (1 H, s, 7-H); irradiation at δ 5.23 sharpened the 4-H signal.

4,5-*Dimethoxyisobenzofuran*-1(3H)-*one* (ψ-*Meconin*) (**13**).—6-Iodo-2,3-dimethoxybenzyl alcohol (**5**), m.p. 77—79 °C (lit.,[24] 69—70 °C) was similarly converted into ψ-meconin (**13**) (81%) which formed needles, m.p. 123—124 °C (lit.,[25] 123—124 °C), from methanol; δ 3.96 and 3.97 (each 3 H, s, OMe), 5.23 (2 H, s, CH_2), and 7.07 and 7.62 (2 H, AB, *J* 8.6 Hz, 6- and 7-H).

5,7-*Dimethoxyisobenzofuran*-1(3H)-*one* (**14**).—A solution of iodine (4.45 g) in chloroform (150 ml) was added dropwise to a stirred solution of 3,5-dimethoxybenzyl alcohol[26] (2.95 g) in chloroform (25 ml) containing suspended silver trifluoroacetate (3.90 g). The suspension was stirred for a further 15 min and the silver iodide was separated by filtration through Celite and washed with dichloromethane. The filtrate was washed in turn with water, aqueous sodium thiosulphate, and finally with saturated brine. The crude product crystallized from dichloromethane–light petroleum as needles (4.85 g, 94%) of 2-*iodo*-3,5-*dimethoxybenzyl alcohol* (**6**), m.p. 96—97 °C (Found: C, 36.95; H, 3.7; I, 43.4%; M^+, 294. $C_9H_{11}IO_3$ requires C, 36.75; H, 3.75; I, 43.15%; M^+, 294); δ 2.50 (1 H, s, OH), 3.81 and 3.85 (each 3 H, s, OMe), 4.64 (2 H, s, CH_2), and 6.35 and 6.71 (2 H, AB, *J* 2.9 Hz, ArH).

This was converted into the phthalide (**14**) (75%) which formed plates (from methanol), m.p. 151—153 °C (lit.,[27] 151—153 °C) undepressed on admixture with an authentic sample.[28]

5,7-*Dimethoxy*-6-*methylisobenzofuran*-1(3H)-*one* (O-*Methylnidulol*) (**15**).—A solution of methyl 3,5-dimethoxy-4-methylbenzoate[29] (5.0 g) in anhydrous ether (100 ml) was added to a stirred suspension of lithium aluminium hydride (0.90 g) in ether (50 ml). The mixture was stirred at room temperature for 3 h and then cooled in ice and treated with an excess of saturated aqueous magnesium sulphate solution. Isolation with ethyl acetate gave 3,5-*dimethoxy*-4-*methylbenzyl alcohol* (4.25 g, 92%) which formed plates from dichloromethane–light petroleum, m.p. 68—69 °C (Found: C, 65.8; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.75%); δ 1.97 (1 H, s, D_2O-exchangeable OH),2.07 (3 H, s, Me), 3.81 (6 H, s, 2 × OMe), 4.61 (2 H, s, CH_2), and 6.52 (2 H, s, ArH). Iodination of this compound by a method similar to that described for compound (**6**) gave 2-*iodo*-3,5-*dimethoxy*-4-*methylbenzyl alcohol* (**7**) (95%) as needles (from dichloromethane–light petroleum), m.p. 81—82 °C (Found: C, 39.55; H, 4.3; I, 41.15. $C_{10}H_{13}IO_3$ requires C, 39.0; H, 4.25; I, 41.2%); δ 2.20 (3 H, s, Me), 2.31 (1 H, s, D_2O-exchangeable OH), 3.74 and 3.83 (each 3 H, s, OMe), 4.64 (2 H, s, CH_2), and 6.84 (1 H, s, ArH).

This was converted into *O*-methylnidulol (**15**) (80%) which formed laths from dichloromethane–light petroleum, m.p. 174—176 °C (lit.,[30] 172—173 °C) (Found: C, 63.2; H, 5.8%; M^+, 208. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.8%; *M*, 208); δ 2.14 (3 H, s, Me), 3.92 and 4.03 (each 3 H, s, OMe), 5.18 (2 H, s, CH_2), and 6.66 (1 H, s, ArH). Chromatography of a portion of the product obtained after the benzyl alcohol had been allowed to react with copper(I) cyanide gave 6-*hydroxymethyl*-2,4-*dimethoxy*-3-*methylbenzonitrile* as felted needles (from dichloromethane–light petroleum), m.p. 105—106 °C (Found: C, 64.05; H, 6.4; N, 6.55%; M^+, 207. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.75%; *M*, 207); δ 2.12 (3 H, s, Me), 3.91 and 3.93 (each 3 H, s, OMe), 4.84 (2 H, s, CH_2), and 6.88 (1 H, s, ArH).

4,6-*Dimethoxy*-5-*methylisobenzofuran*-1(3H)-*one* (**16**).—Reduction of methyl 6-bromo-2,4-dimethoxy-3-methylbenzoate[31] with lithium aluminium hydride in a manner similar to that described above gave 6-*bromo*-2,4-*dimethoxy*-3-*methylbenzyl alcohol* (**8**) (90%) as needles (from ether–light petroleum), m.p. 63—64 °C (Found: C, 46.2; H, 5.0; Br, 30.45; M^+, 260/262. $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0; Br, 30.6%; *M*, 260/262); δ 2.09 (1 H, t, *J* 5.7 Hz, D_2O-exchangeable OH), 2.09 (3 H, s, Me), 3.80 and 3.81 (each 3 H, s, OMe), 4.77 (2 H, d, *J* 5.7 Hz, CH_2OH; collapsed to a singlet on addition of D_2O), and 6.85 (1 H, s, ArH). Compound (**8**) was converted into the phthalide (**16**) (71%) which formed needles (from methanol), m.p. 159—160 °C (lit.,[32] 160 °C; δ 2.20 (3 H, s, Me), 3.89 (6 H, s, 2 × OMe), 5.34 (2 H, s, CH_2), and 7.08 (1 H, s, ArH).

6-*Methoxy*-4-*methylisobenzofuran*-1(3H)-*one* (**17**).—Reduction of methyl 2-bromo-4-methoxy-6-methylbenzoate[33] with lithium aluminium hydride in a manner similar to that described above gave 2-*bromo*-4-*methoxy*-6-*methylbenzyl alcohol* (**9**) (95%) as prisms (from dichloromethane–light petroleum), m.p. 79—80 °C (Found: C, 47.1; H, 4.75; Br, 34.75%; M^+, 230/232. $C_9H_{11}BrO_2$ requires C, 46.8; H, 4.8; Br, 34.6%; *M*, 230/232); δ 1.80 (1 H, s, OH), 2.45 (3 H, s, Me), 3.78 (3 H, s, OMe), 4.77 (2 H, s, CH_2), and 6.69 and 6.96 (2 H, AB, *J* 2.9 Hz, 5-and 3-H).

Compound (**9**) was converted into the phthalide (**17**) (80%) which formed needles (from dichloromethane–light petroleum), m.p. 105—106 °C (lit.,[11] 105.5 °C); δ 2.32 (3 H, s, Me), 3.86 (3 H, s, OMe), 5.19 (2 H, s, CH_2), and 7.05 and 7.19 (2 H, AB, *J* 2.3 Hz, 5- and 7-H).

5-*Methoxy*-7-*methylisobenzofuran*-1(3H)-*one* (**18**).—Reduction of methyl 2-bromo-5-methoxy-3-methylbenzoate[34] with lithium aluminium hydride in a manner similar to that described above gave 2-*bromo*-5-*methoxy*-3-*methylbenzyl alcohol* (**10**) (90%) as needles (from ether–light petroleum), m.p. 48—49 °C (Found: C, 47.2; H, 4.95; Br, 34.6%; M^+, 230/232. $C_9H_{11}BrO_2$ requires C, 46.8; H, 4.8; Br, 34.6%; *M*, 230/232); δ 2.13 (1 H, t, *J* 6.3 Hz, D_2O-exchangeable OH), 3.79 (3 H, s, OMe), 4.71 (2 H, d, *J* 6.3 Hz; collapsed to a singlet on addition of D_2O), and 6.73 and 6.90 (2 H, AB, *J* 3.1 Hz, ArH).

Compound (**10**) was converted in the usual manner into the *phthalide* (**18**) (89%) which crystallized from methanol as needles, m.p. 175—175.5 °C (Found: C, 67.15; H, 5.7%; M^+, 178. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.65%; *M*, 178); δ 2.64 (3 H, s, Me), 3.87 (3 H, s, OMe), 5.12 (2 H, s, CH_2), and 6.73 and 6.78 (2 H, AB, *J* 2.0 Hz, ArH).

5-*Methoxy*-4-*methylisobenzofuran*-1(3H)-*one* (**19**).—Reduction of methyl 6-bromo-3-methoxy-2-methylbenzoate[35] with lithium aluminium hydride gave 6-*bromo*-3-*methoxy*-2-*methylbenzyl alcohol* (**11**) (94%) which crystallized from ether–light petroleum as plates, m.p. 86—87 °C (Found: C, 46.6; H, 4.8; Br, 34.75%; M^+, 230/232. $C_9H_{11}BrO_2$ requires C, 46.8; H, 4.8; Br, 34.6%; *M*, 230/232); δ 1.94 (1 H, s, D_2O-exchangeable OH), 2.32 (3 H, s, Me), 3.78 (3 H, s, OMe), 4.82 (2 H, s, CH_2), and 6.67 and 7.34 (2 H, AB, *J* 8.8 Hz, 4- and 5-H).

The alcohol (**11**) was converted into the phthalide (**19**) (89%) which crystallized from methanol as laths, m.p. 171—172 °C (lit.,[36] 168—169 °C); δ 2.15 (3 H, s, Me), 3.94 (3 H, s, OMe), 5.19 (2 H, s, CH_2), and 6.94 and 7.74 (2 H, AB, *J* 8.6 Hz, 7- and 6-H).

Demethylation of 1,9-*Dimethoxy*-3,7-*dimethyldibenzofuran* (**22**).—A solution of boron trichloride (916 mg) in dichloromethane (2 ml) was added to a stirred solution of the substrate (**22**)[19] (223 mg) in dichloromethane (10 ml) at 0 °C. The solution was then stirred at room temperature for 6.5 h. The solution was cooled in ice, and water and ethyl acetate were added. Isolation and crystallization of the crude product from

cyclohexane gave 9-*methoxy*-3,7-*dimethyldibenzofuran*-1-*ol* (**23**) (199 mg, 95%), m.p. 136—137 °C (Found: C, 74.45; H, 5.8%; M^+, 242. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%; *M*, 242); δ 2.48 and 2.43 (each 3 H, s, Me), 4.07 (3 H, s, OMe), 6.59, 6.63, 6.84, and 6.98 (each 1 H, br s, 2-, 8-, 4-, and 6-H), and 8.40 (1 H, s, D_2O-exchangeable OH).

Attempted Demethylation of 1,7-*Dimethoxy*-3,9-*dimethyldibenzofuran* (**21**).—Treatment of the substrate (**21**)[19] in a similar manner to that described for compound (**22**) during 5 h and work-up gave the starting material.

Attempted Demethylation of 1,3,6,8-*Tetramethoxynaphthalene* (**24**).—This compound was prepared by the method of Morishita and Shibata[21] and formed prisms (from ether–light petroleum), m.p. 111—113 °C (lit.,[21] 111 °C); δ 3.83 and 3.88 (each 6 H, s, 2 × OMe) and 6.35 and 6.59 (4 H, AB, *J* 2.0 Hz, 2-, 7-, and 4-,5-H). It was recovered unchanged after treatment with an excess of boron trichloride in dichloromethane at room temperature for 25 h or under reflux for 6.5 h.

2-(2,2-*Diethoxyethoxy*)-4-*methoxy*-6-*methylbenzaldehyde* (**25**).—Everninaldehyde[18] (10.0 g), 1-bromo-2,2-diethoxyethane (13.05 g), and dry potassium carbonate (9.0 g) were stirred and boiled under reflux in anhydrous DMF (30 ml) under dry nitrogen for 2 h. The mixture was poured into water–ice, and the crude product was isolated with ether. Distillation under diminished pressure gave the *aldehyde* (**25**) (13.75 g, 81%) as an oil, b.p. 138—140 °C at 0.01 mmHg (Found: C, 64.0; H, 7.7%; M^+, 282. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%; *M*, 282); δ 1.24 (6 H, t, 2 × OCH_2Me), 2.57 (3 H, s, Me), 3.73 and 3.70 (each 2 H, q, OCH_2Me), 3.83 (3 H, s, OMe), 4.05 (2 H, d, OCH_2CH), 4.86 (1 H, t, OCH_2CH), 6.33 (2 H, s, ArH), and 10.51 (1 H, s, CHO).

6-*Methoxy*-4-*methylbenzofuran*-2-*carbaldehyde* (**26**).—The foregoing aldehyde (**25**) (2.32 g) was stirred and heated under reflux in acetic acid (10 ml) under dry nitrogen for 12 h. The cooled mixture was diluted with water and extracted with ethyl acetate. The extract was washed in turn with dil. aqueous sodium hydroxide (× 2), water, and finally with saturated brine. The crude product was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum as eluant. Early fractions afforded 6-*methoxy*-4-*methylbenzofuran* (**27**) (200 mg, 15%) as an oil, b.p. 175 °C at 25 mmHg (Kugelrohr) (Found: C, 74.2; H, 6.35%; M^+, 162. $C_{10}H_{10}O_2$ requires C, 74.05; H, 6.2%; *M*, 162); δ (300 MHz; assignments by spin decoupling and convolution difference) 2.47 (3 H, apparent q, Me), 3.83 (3 H, s, OMe), 6.69 (1 H, dq, $J_{5,7}$ 2.2, $J_{5,Me}$ 0.8 Hz, 5-H), 6.70 (1 H, dd, $J_{3,2}$ 2.2, $J_{3,7}$ 1.0 Hz, 3-H), 6.87 (1 H, m, $J_{7,5}$ 2.2, $J_{7,3}$ 1.0 Hz, and further fine coupling to Me, 7-H), and 7.52 (1 H, d, $J_{2,3}$ 2.2 Hz, 2-H).

Further elution gave *tris*-(6-*methoxy*-4-*methylbenzofuran*-2-*yl*)*methane* (**28**) (109 mg) which crystallized from methanol as fine needles, m.p. 166—167 °C (Found: C, 74.7; H, 5.75%; M^+, 496. $C_{31}H_{28}O_6$ requires C, 75.0; H, 5.9%; *M*, 496); δ (300 MHz; assignments by spin decoupling), 2.42 (9 H, br s, $W_{\frac{1}{2}}$ 1.8 Hz, 3 × Me), 3.81 (9 H, s, 3 × OMe), 5.84 (1 H, q, $J_{CH,3}$ 0.9 Hz, CH), 6.56 (3 H, dd, $J_{3,CH}$ 0.9, $J_{3,7}$ 0.9 Hz, 3 × 3-H), 6.67 (3 H, dq, $J_{5,7}$ 2.2, $J_{5,Me}$ 0.8 Hz, 3 × 5-H), and 6.85 (3 H, m, $J_{7,5}$ 2.2, $J_{7,3}$ 0.9 Hz, and further fine coupling to Me, 3 × 7-H).

Further elution gave the title aldehyde (**26**) (1.00 g, 64%) as needles (from methanol), m.p. and mixed m.p. 129—130 °C (lit.,[18] 129—130 °C).

Methyl 1,7-*Dimethoxy*-3,9-*dimethyldibenzofuran*-4-*carboxylate* (**30**).—Methylation of 1,7-dimethoxy-3,9-dimethylbenzofuran-4-carboxylic acid (**29**) with iodomethane and potassium carbonate in DMF at room temperature afforded the *ester* (**30**) as plates, m.p. 141—142.5 °C (from dichloromethane–light petroleum) (Found: C, 68.5; H, 5.65%; M^+, 314. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.75%; *M*, 314); δ 2.63 and 2.80 (each 3 H, s, 3- and 9-Me), 3.86, 3.98, and 4.00 (each 3 H, s, OMe), 6.59 (1 H, s, 2-H), and 6.72 and 6.92 (2 H, AB, *J* 2.9 Hz, 8-and 6-H); irradiation at the frequency of the 3-Me signal sharpened the 2-H signal, and irradiation at the 9-Me signal sharpened the AB system.

Methyl 9-*Hydroxymethyl*-1,7-*dimethoxy*-3-*methyldibenzofuran*-4-*carboxylate* (**31**).—A solution of the substrate (**29**) (896 mg) in tetrachloromethane (20 ml) was boiled under reflux over a 250 W tungsten lamp during the dropwise addition of a solution of bromine (465 mg) in CCl_4 (10 ml). The solution was heated for a further 5 min after the addition and then cooled, diluted with dichloromethane, and washed in turn with water and saturated brine. The crude product was stirred in DMF (20 ml) with anhydrous sodium acetate (5.0 g) for 18 h. Dilution with water and isolation with ethyl acetate gave a crude product, which was stirred at room temperature with sodium hydroxide (2.0 g) in a mixture of methanol (40 ml) and water (10 ml) for 2.5 h. The mixture was then diluted with water and extracted with ethyl acetate. The crude product was subjected to radial chromatography with 10—40% ethyl acetate–light petroleum as eluant. Early fractions gave a trace of starting material and this was followed by the *alcohol* (**31**) (367 mg, 40%) which formed needles (from dichloromethane–light petroleum), m.p. 157—158 °C (Found: C, 65.3; H, 5.45%; M^+, 330. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%; *M*, 330); δ 1.59 (1 H, br s, D_2O-exchangeable OH) 2.64 (3 H, s, 3-Me), 3.88, 4.01, and 4.07 (each 3 H, s, OMe), 5.00 (2 H, s, CH_2), 6.66 (1 H, s, 2-H), and 6.91 and 7.06 (2 H, AB, *J* 2.3 Hz, 8- and 6-H); irradiation at δ 5.00 sharpened the AB system.

Iodination of Methyl 9-*Hydroxymethyl*-1,7-*dimethoxy*-3-*methyldibenzofuran*-4-*carboxylate* (**31**).—A solution of iodine (168 mg) in chloroform (30 ml) was added dropwise during 10 min to a stirred solution of the substrate (218 mg) in chloroform (15 ml) containing suspended silver trifluoroacetate (150 mg). The usual work-up gave a crude product, which was subjected to radial chromatography with 40% ethyl acetate–light petroleum as eluant. The first band that was eluted gave *methyl* 9-*hydroxymethyl*-8-*iodo*-1,7-*dimethoxy*-3-*methyldibenzofuran*-4-*carboxylate* (**32**) (180.5 mg, 60%) as needles (from dichloromethane–light petroleum), m.p. 207—208 °C (Found: C, 47.6; H, 3.7; I, 29.5%; M^+, 456. $C_{18}H_{17}IO_6$ requires C, 47.4; H, 3.75; I, 27.8%; *M*, 456); δ (300 MHz) 2.64 (3 H, s, Me), 3.06 (1 H, t, *J* 6.2 Hz, OH), 3.96, 4.02, and 4.10 (each 3 H, s, OMe), 5.41 (2 H, d, *J* 6.2 Hz, CH_2), 6.67 (1 H, s, 2-H), and 7.05 (1 H, s, 6-H); irradiation at δ 2.64 sharpened the 2-H signal.

Further elution gave *methyl* 9-*hydroxymethyl*-6-*iodo*-1,7-*dimethoxy*-3-*methyldibenzofuran*-4-*carboxylate* (**33**) (62.6 mg, 21%) as needles (from methanol), m.p. 217—219 °C (Found: C, 47.8; H, 3.8; I, 27.8%; M^+, 456); δ (300 MHz) 2.67 (3 H, s, Me), 3.21 (1 H, t, *J* 6.2 Hz, OH), 3.98, 4.06, and 4.08 (each 3 H, s, OMe), 5.03 (2 H, d, *J* 6.2 Hz, CH_2), and 6.65 and 6.85 (each 1 H, s, 2- and 8-H); irradiation at δ 2.67 sharpened the 2-H signal, and irradiation at δ 5.03 sharpened the 8-H signal; saturation of the CH_2 signal gave a 17.6% n.O.e. at the 8-H signal.

Methyl 1,3-*Dihydro*-4,10-*dimethoxy*-8-*methyl*-3-*oxoisobenzofuro*[5,4-b]*benzofuran*-7-*carboxylate* (**2**).—The iodo compound (**32**) (175 mg), copper(I) cyanide (100 mg), and DMF (4 ml) were stirred and heated at 110 °C (bath) under dry nitrogen for 30 min. The cooled solution was diluted with aqueous sodium cyanide (10%; 20 ml) and extracted exhaustively with chloroform. The crude product was heated under reflux with methanol (9 ml), water (9 ml), and potassium hydroxide (2.0 g)

during 16 h. The solution was diluted with water (20 ml) and acidified with conc. hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried *in vacuo*. Methylation of this product during 4 h with excess of iodomethane and potassium carbonate in DMF, and isolation with ethyl acetate, gave the *porphyrilate* (**2**) (129 mg, 94%) which crystallized from ethyl acetate as needles, m.p. 280—282 °C (lit.,[3,37] 270—272 °C, 266 °C) (Found: C, 63.9; H, 4.5. $C_{19}H_{16}O_7$ requires C, 64.05; H, 4.55%); *m/z* [37] 357 (19%), 356 (100, M^+), 341 (6), 328 (9), 327 (48), 326 (5), 325 (23), 324 (8), 323 (35), 312 (11), 311 (9), 310 (24), 309 (6), 297 (12), 296 (8), 295 (5), 282 (10), 281 (8), 280 (5), 269 (4), 268 (4), 267 (5), 253 (12), 252 (7), 251 (7), 250 (5), 239 (6), 238 (6), 237 (5), 226 (4), 225 (8), 224 (5), 223 (6), 211 (8), 210 (7), and 209 (6); δ[$(CD_3)_2SO$] 2.59 (3 H, s, Me), 3.93, 3.98, and 4.02 (each 3 H, s, OMe), 5.56 (2 H, s, CH_2), 6.92 (1 H, s, 9(H), and 7.43 (1 H, s, 5-H); irradiation at δ 5.56 sharpened the 5-H signal and irradiation at δ 2.59 sharpened the 9-H signal; $\nu_{max.}$(KBr) 1 765 (lactone C=O) and 1 705 cm^{-1} (ester C=O). The product was identical by mixed m.p. (268—269 °C, open capillary, Al block), i.r. spectrum, and t.l.c. (in three different solvent systems) with an authentic sample.

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References

1 Part 8, C. F. Carvalho and M. V. Sargent, *Aust. J. Chem.*, in the press.
2 W. Zopf, *Justus Liebig's Ann. Chem.*, 1906, **346**, 82.
3 C. A. Wachtmeister, *Acta Chem. Scand.*, 1954, **8**, 1433.
4 C. A. Watchtmeister, *Acta Chem. Scand.*, 1956, **10**, 1404.
5 F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1978, **43**, 178; N. J. P. Broom and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1978, 162; G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, 2263.
6 D. J. Dodsworth, M. P. Calcagno, E. U. Ehrmann, B. Devadas, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2120.
7 J. Ahad, R. Banham, W. B. Whalley, G. Ferguson, and P. Y. Siew, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2445.
8 B. M. Trost, G. T. Rivers, and J. M. Gold, *J. Org. Chem.*, 1980, **45**, 1835.
9 S. Mahalingam, P. C. Kuzma, J. Y. C. Lee, and T. M. Harris, *J. Am. Chem. Soc.*, 1985, **107**, 7760.
10 P. Fritsch, *Justus Liebig's Ann. Chem.*, 1897, **296**, 344; 1898, **301**, 359.
11 A. N. Meldrum, *J. Chem. Soc.*, 1911, 1712.
12 G. A. Edwards, W. H. Perkin, Jr., and F. W. Stoyle, *J. Chem. Soc.*, 1925, 195.
13 E. H. Charlesworth, R. P. Rennie, J. E. Sinder, and M. M. Yau, *Can. J. Res., Sect. B*, 1945, **23**, 17 (*Chem. Abstr.*, 1945, **39**, 2063).
14 P. D. Noire and R. W. Franck, *Synthesis*, 1980, 882; M. Uemura, S. Tokuyama, and, S. Sakau, *Chem. Lett.*, 1975, 1195.
15 M. Renson and R. Colliene, *Bull. Soc. Chim. Belg.*, 1964, **73**, 491.
16 S. Gabriel and W. Landsberger, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 2732.
17 L. Friedman and H. Schechter, *J. Org. Chem.*, 1961, **26**, 2522.
18 M. V. Sargent and P. O. Stransky, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2373.
19 M. V. Sargent and P. O. Stransky, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1605.
20 C. F. Carvalho, A. V. Russo, and M. V. Sargent, *Aust. J. Chem.*, 1985, **38**, 777.
21 E. Morishita and S. Shibata, *Chem. Pharm. Bull.*, 1967, **15**, 1765.
22 M. Descamps and F. Henaux, Fr. P. 1 537 206/1968 (*Chem. Abstr.*, 1969, **71**, 61198).
23 D. M. Piatak, G. Flynn, K. Yim, and J. Roosenberg, *J. Org. Chem.*, 1977, **42**, 1068.
24 A. Cowell and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4193.
25 O. Salomon, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 883.
26 A. Bhati, *Tetrahedron*, 1962, **18**, 1519.
27 W. R. Logan and G. T. Newbold, *J. Chem. Soc.*, 1957, 1946.
28 N. M. Rana, M. V. Sargent, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1992.
29 S. Huneck and M. V. Sargent, *Aust. J. Chem.*, 1976, **29**, 1059.
30 A. J. Birch and R. A. Russell, *Aust. J. Chem.*, 1971, **24**, 1975.
31 M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1982, 403.
32 H. Achenbach, A. Mühlenfeldt, and G. U. Brillinger, *Liebigs Ann. Chem.*, 1985, 1596.
33 C. F. Carvalho, M. V. Sargent, and E. Stanojevic, *Aust. J. Chem.*, 1984, **37**, 2111.
34 M. V. Sargent, P. Vogel, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1986.
35 T. M. Cresp, R. G. F. Giles, M. V. Sargent, C. Brown, and D. O'N. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2435.
36 D. Bhattacharjee and F. D. Popp, *J. Heterocycl. Chem.*, 1980, **17**, 315.
37 S. Huneck, C. Djerassi, D. Becker, M. Barber, M. von Ardenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, 1968, **24**, 2707.

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