

Synthesis of the Yeast Antioxidant Benzofuran and Analogues

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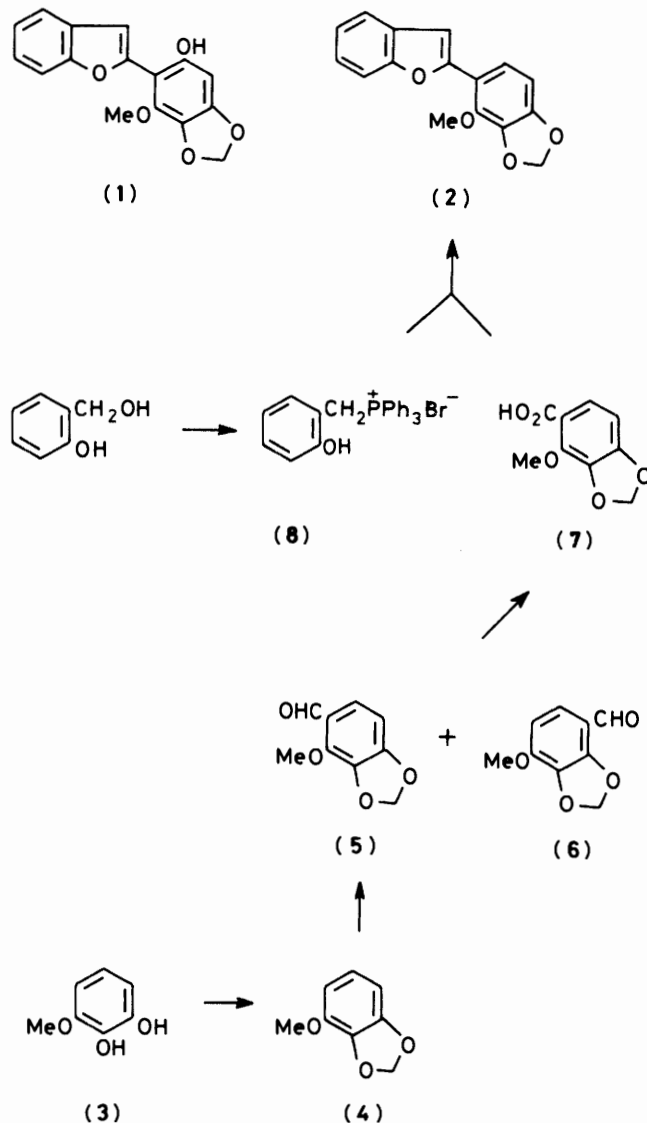
2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)benzofuran, the active antioxidant which occurs in yeasts, and related 2-arylbenzofurans have been synthesized by a convergent route. The key step involves benzofuran formation by an intramolecular Wittig reaction.

Extracts of a variety of yeasts have been found to prevent both liver necrosis and susceptibility to red blood cell hemolysis by dialuric acid in rats kept on a deficient diet. Isolation of an active antioxidant¹ and extensive degradation studies^{2,3} led to the identification of this substance as 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)benzofuran (1). A low yield synthesis of (1) under Hoesch reaction conditions and a lengthy unrelated synthesis of the 6'-deoxy analogue, 2-(2-methoxy-3,4-methylenedioxyphenyl)benzofuran (2), have been described.⁴ We have been examining the formation of arylbenzofurans by the intramolecular Wittig reaction⁵ of esters of *o*-hydroxybenzyltriphenylphosphonium halides with particular applicability to natural product synthesis (phytoalexins,⁶ eupomatenoids,⁷ and benzofuranoquinone⁸), and report here syntheses of the yeast antioxidant benzofuran (1) and analogues by this method.

This is exemplified (Scheme 1) by the synthesis of compound (2), the known 6'-deoxy analogue of the natural antioxidant benzofuran, wherein it was established that the reaction of croweacic acid (7) or the appropriate derivative with *o*-hydroxybenzyltriphenylphosphonium bromide (8) yielded the desired 2-arylbenzofuran (2) directly. The required aryl-carboxylic acid (7) was obtained in three steps from 3-methoxyphenol (3). Methylation of compound (3) by treatment with methylene dibromide and potassium carbonate in dimethylsulphoxide afforded 1-methoxy-2,3-methylenedioxybenzene (4) in about 80% yield. Several reports concerning the Vilsmeier formylation of (4) exist. In the first, Brownell and Weston⁹ reported the isolation of 2-methoxy-3,4-methylenedioxybenzaldehyde (5) as the sole product, a conclusion supported by later findings.¹⁰ In contrast, Wagner and co-workers^{3,11} found that the product was a mixture of the aldehyde (5) and 4-methoxy-2,3-methylenedioxybenzaldehyde (6). This was substantiated by later work of Shulgin¹² and Dallacker,¹³ although there was a wide variation in the ratios of the two aldehydes reported. In our hands, the crude product obtained from compound (4) by treatment with phosphorus oxychloride and dimethylformamide furnished the isomers (5) and (6) in a 2:1 ratio, as estimated from integration of the ¹H n.m.r. spectrum. The mixture was separated by chromatography on silica gel, and the aldehyde (5) oxidized quantitatively to 2-methoxy-3,4-methylenedioxybenzoic acid (croweacic acid) (7) by silver oxide as previously described.³

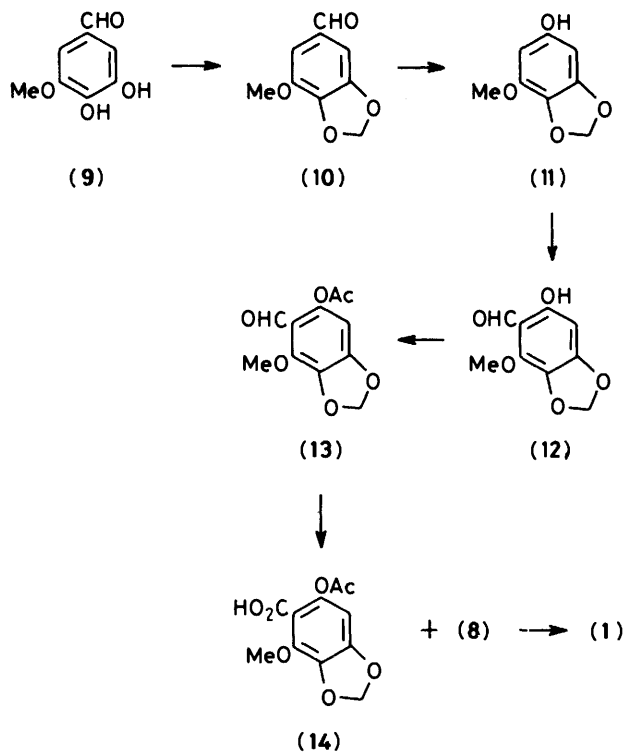
Conversion of the carboxylic acid (7) into the acyl chloride derivative followed by reaction with *o*-hydroxybenzyltriphenylphosphonium bromide¹⁴ and then heating with triethylamine in toluene afforded 2-(2-methoxy-3,4-methylenedioxyphenyl)benzofuran (2) in 56% yield. A significant improvement was also achieved by direct esterification of the phenol by dicyclohexylcarbodi-imide activation of the carboxylic acid in the presence of 4-dimethylaminopyridine.¹⁵ Under these conditions, the arylbenzofuran (2) was isolated in over 80% yield.

Adaptation of this procedure to the synthesis of the natural arylbenzofuran (1) required the preparation of an appropriately substituted piperonylic acid. For this purpose, 6-acetoxy-2-methoxy-3,4-methylenedioxybenzoic acid (14) was chosen, and

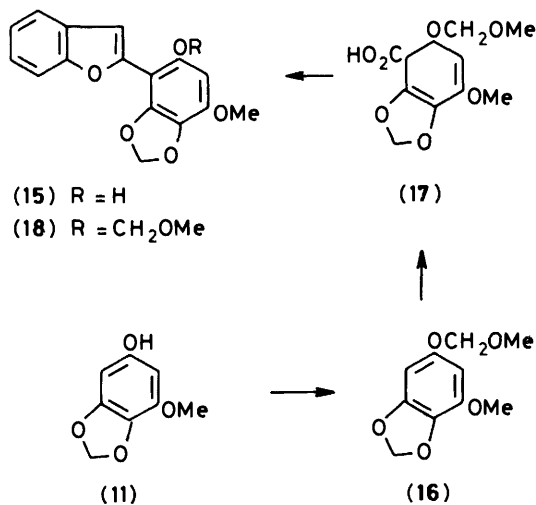


Scheme 1.

synthesized as outlined in Scheme 2. The readily available 3,4-dihydroxy-5-methoxybenzaldehyde (9)¹⁶ was converted into the methylenedioxy derivative (10) by an improved procedure and then into the phenol (11) by Baeyer-Villiger oxidation with performic acid. Gattermann formylation of (11) with zinc cyanide gratifyingly yielded the required aldehyde (12) in over 80% yield. Protection of the phenol functionality by acetylation to give (13), and then oxidation with potassium permanganate in aqueous acetone furnished the carboxylic acid (14).



Scheme 2.



Scheme 3.

Esterification of the phosphonium salt (8) with the acetoxybenzoic acid (14) by the dicyclohexylcarbodi-imide-dimethylaminopyridine (DCC-DMAP) method followed by the Wittig internal cyclization produced the desired final product, the yeast antioxidant benzofuran (1), in 22% yield. Thin layer chromatographic examination of the crude reaction mixture revealed that the desired, but not totally expected, deacetylation^{17,18} of the protected phenol had occurred by reaction with excess of ylide rather than hydrolysis during the subsequent work-up.

That isomer (15) of the natural benzofuran (1) in which the methoxy and methylenedioxy ether functions were interchanged was also synthesized. Treatment of the anion of the phenol (11) with chloromethyl methyl ether gave the methoxymethoxy (MOM) protected derivative (16) (Scheme 3). Metallation of (16)

with *n*-butyl-lithium followed by carboxylation yielded a carboxylic acid mixture from which the major isomer (in a 14:1 ratio) was readily separated by crystallization. The ¹H n.m.r. spectrum of this product strongly supported the structure (17) for this acid. This conclusion was corroborated in the sequel. Subjection of compound (17) to the intramolecular Wittig cyclization with (8), either *via* the acid chloride or the DCC-DMAP method, gave the arylbenzofuran MOM either (18) in 24 and 57% yield respectively; removal of the MOM group by the action of toluene-*p*-sulphonic acid in methanol yielded 2-(6-hydroxy-4-methoxy-2,3-methylenedioxyphenyl)benzofuran (15).

Experimental

M.p.s were determined with a Gallenkamp apparatus and are uncorrected. Varian EM-390 and Bruker FT/90 MHz spectrometers were employed for the determination of ¹H n.m.r. spectra, with tetramethylsilane as internal reference and deuteriochloroform as solvent (unless otherwise stated). The silica gel used for chromatography was J. T. Baker (40–140 mesh) and light petroleum refers to the fraction boiling in the range 54–105 °C. Ether refers to diethyl ether.

1-Methoxy-2,3-methylenedioxybenzene (4).—Anhydrous potassium carbonate (20 g) followed by dibromomethane (10 ml) were added to a solution of 3-methoxyphenol (3) (11.3 g) in dimethyl sulphoxide (250 ml). The mixture was heated at 85 °C for 2 h under nitrogen, then cooled and poured into water (250 ml). Extraction with ether (5 × 100 ml) and evaporation of the washed and dried (MgSO₄) extract yielded an oil, which was distilled (65–75 °C bath temperature at 0.05 mmHg). On standing, the distillate gave compound (4) as light yellow crystals (9.67 g), m.p. 39–41 °C (lit.,¹⁹ m.p. 41 °C); δ 3.88 (3 H, s, OMe), 5.90 (2 H, s, OCH₂O), and 6.45–6.83 (3 H, m, 3-, 4-, and 5-H).

2-Methoxy-3,4-methylenedioxybenzaldehyde (5).—Phosphorus oxychloride (9.0 ml) was added dropwise during 10 min at room temperature to a solution of compound (4) (5.44 g) in dimethylformamide (7 ml). The mixture was stirred at room temperature for 30 min, then at 50 °C for 1 h and at 90 °C for 2 h, cooled, and diluted with water (50 ml) to yield a yellow precipitate which was dissolved in ether, washed with water, and dried. Evaporation of this extract gave a solid (4.5 g) whose integrated ¹H n.m.r. spectrum indicated the presence of isomers (5) and (6) in a 2:1 ratio. Chromatography of this mixture on silica gel with light petroleum–dichloromethane (3:7) yielded first the aldehyde (5) as needles (2.48 g) from ethanol, m.p. 102–104 °C (lit.,³ m.p. 103–105 °C); δ 4.13 (3 H, s, OMe), 6.00 (2 H, s, OCH₂O), 6.90 (1 H, d, *J* 8 Hz, 5-H), 7.43 (1 H, d, *J* 8 Hz, 6-H), and 10.21 (1 H, s, CHO). Continued elution with the same eluant gave mixtures of isomers (5) and (6), followed by pure 4-methoxy-2,3-methylenedioxybenzaldehyde (6), obtained as a solid (1.3 g), m.p. 82–85 °C (lit.,³ 85–86 °C); δ 3.97 (3 H, s, OMe), 6.10 (2 H, s, OCH₂O), 6.50 (1 H, d, *J* 9 Hz, 5-H), 7.25 (1 H, d, *J* 9 Hz, 6-H), and 9.95 (1 H, s, CHO).

2-Methoxy-3,4-methylenedioxybenzoic Acid (7).—This was prepared from the aldehyde (5) by a modification of a previously described procedure.³ A solution of silver nitrate (4.8 g) in water (10 ml) was added to a solution of the aldehyde (5) (2.48 g) in ethanol (150 ml). To this stirred mixture, a solution of potassium hydroxide (9 g) in water (150 ml) was added dropwise, and, after 2.5 h at room temperature, the mixture was filtered and the acidified (dilute HCl) filtrate extracted with chloroform. Evaporation of the washed and dried extract gave croceic acid (7) as a solid, m.p. 152.5–153.5 °C, raised to m.p. 154–

155 °C on recrystallization from aqueous ethanol (lit.,⁹ m.p. 155 °C); δ 3.88 (3 H, s, OMe), 6.03 (2 H, s, OCH₂O), 6.63 (1 H, d, *J* 9 Hz, 5-H), and 7.75 (1 H, d, *J* 9 Hz, 6-H).

2-(2-Methoxy-3,4-methylenedioxyphenyl)benzofuran (2).—(a) Thionyl chloride (1.2 ml) and dimethylformamide (3 drops) were added to a suspension of the carboxylic acid (7) (870 mg) in toluene (3 ml) and the mixture was heated at 90 °C for 3 h. The residue obtained after removal of the solvent under reduced pressure was redissolved in toluene (175 ml) and *o*-hydroxybenzyltriphenylphosphonium bromide¹⁴ (1.5 g) and triethylamine (2.5 ml) were added. This mixture was then heated at 85 °C for 11 h under nitrogen, cooled, filtered, and evaporated. The product was dissolved in light petroleum–dichloromethane (1:4) and filtered through a column of silica gel (20 g) to give the arylbenzofuran (2) as a solid (670 mg, highly fluorescent on t.l.c. plate) which crystallized from isopropyl alcohol as plates, m.p. 97–99 °C (lit.,⁴ m.p. 95–97 °C); δ [(CD₃)₂CO] 4.13 (3 H, s, OMe), 5.97 (2 H, s, OCH₂O), 6.68 (1 H, d, *J* 8.5 Hz, 5'-H), and 7.13–7.67 (6 H, m, ArH).

(b) To a solution of the carboxylic acid (7) (325 mg) in dichloromethane (15 ml) were sequentially added *p*-dimethylaminopyridine (32 mg), *o*-hydroxybenzyltriphenylphosphonium bromide (1.0 g), and dicyclohexylcarbodi-imide (433 mg in 4.4 ml of dichloromethane). The mixture was stirred at room temperature for 24 h, then toluene (125 ml) was added and the dichloromethane removed by a stream of nitrogen at 70 °C. After the addition of triethylamine (1.3 ml), heating was continued at 100 °C for 6.5 h, and the product (2) then isolated as in (a) in 81% yield.

3-Methoxy-4,5-methylenedioxybenzaldehyde (10).—Anhydrous potassium carbonate (20 g) and dibromomethane (10 ml) were added to a solution of 3,4-dihydroxy-5-methoxybenzaldehyde (9) (13.5 g) in dimethyl sulphoxide (250 ml) and the mixture was heated at 90 °C for 2.5 h under nitrogen. Dilution of the cooled mixture with water was followed by chloroform extraction (600 ml). Evaporation of the washed and dried extract gave a residual solid which on distillation (110–115 °C at 0.5 mmHg) gave the methoxymethylenedioxy aldehyde (10), m.p. 130–132 °C (lit.,¹⁶ m.p. 131–132 °C).

3-Methoxy-4,5-methylenedioxyphenol (11).—Formic acid (90%; 40 ml) was added to hydrogen peroxide solution (30%; 100 ml) and stirred at 0–5 °C for 1 h. A solution of the benzaldehyde (10) (4.8 g) in formic acid (90%; 100 ml) was then added with continued stirring at 5 °C for 3.5 h, after which additional performic acid (from 5 ml hydrogen peroxide and 20 ml formic acid) was then introduced. After the mixture had been stirred for a further 75 min, the reaction was quenched by the addition of sodium sulphite (10 g) and ice (400 ml) and extracted with ether (600 ml). After being washed with water, the extract was stirred vigorously at room temperature for 30 min with dilute sodium hydroxide solution (pH 12). The dark red basic phase was then separated, acidified with 3% hydrochloric acid, and re-extracted with ether. Evaporation of the washed and dried extract yielded a semi-solid residue which on distillation (ca. 100 °C at 0.1 mmHg) gave the phenol (11) as a light tan solid (2.02 g), m.p. 85–88 °C (lit.,³ m.p. 89–91 °C); δ 3.87 (3 H, s, OMe), 5.08 (2 H, s, OCH₂O), 6.02 (1 H, d, *J* 2.4 Hz, 2- or 6-H), and 6.07 (1 H, d, *J* 2.4 Hz, 6- or 2-H).

6-Hydroxy-2-methoxy-3,4-methylenedioxybenzaldehyde (12).—Zinc cyanide (310 mg) was added to a solution of the phenol (11) (180 mg) in ether (35 ml) and hydrogen chloride bubbled through the stirred mixture for 1.5 h at 0 °C. Stirring was continued for a further 1.5 h after which the ether was decanted. Water (40 ml) was added to the gummy residue, and the mixture

heated on the steam-bath for 15 min, then cooled and filtered. Recrystallization of the solid (175 mg) from light petroleum gave the aldehyde (12) as cream flakes, m.p. 124–125 °C (Found: C, 55.3; H, 4.1. C₉H₈O₅ requires C, 55.1; H, 4.1%); δ 4.10 (3 H, s, OMe), 5.90 (2 H, s, OCH₂O), 6.08 (1 H, s, 5-H), 10.00 (1 H, s, CHO), and 12.53 (1 H, s, OH).

6-Acetoxy-2-methoxy-3,4-methylenedioxybenzaldehyde (13).—A solution of the phenol (12) (317 mg) in acetic anhydride (3.5 ml) and pyridine (2.0 ml) was heated at 80 °C for 14 h, then concentrated under reduced pressure, diluted with water, and extracted with ether (200 ml). Evaporation of the washed and dried extract gave a solid which was dissolved in light petroleum–dichloromethane (1:9) and filtered through silica gel. Crystallization of the eluted light yellow solid (217 mg) from light petroleum–dichloromethane (1:1) gave the acetate (13) as prisms, m.p. 113–115 °C (Found: C, 55.4; H, 4.2. C₁₁H₁₀O₆ requires C, 55.5; H, 4.2%); δ 2.34 (3 H, s, OAc), 4.12 (3 H, s, OMe), 6.00 (2 H, s, OCH₂O), 6.27 (1 H, s, 5-H), and 10.16 (1 H, s, CHO).

6-Acetoxy-2-methoxy-3,4-methylenedioxybenzoic Acid (14).—A solution of potassium permanganate (500 mg), in aqueous acetone (1:1; 100 ml) was added dropwise (4–5 h) with stirring to a solution of the acetate-aldehyde (13) (450 mg) in acetone (30 ml). After 14 h, additional potassium permanganate (100 mg) in water (50 ml) was introduced and stirring continued for a further 7 h. The mixture was then concentrated under reduced pressure, dilute hydrochloric acid and sodium metabisulphite added, and the solution extracted with ethyl acetate (100 ml). The organic phase was extracted with saturated sodium hydrogen carbonate solution, and this extract was acidified (to pH 1) and re-extracted with ethyl acetate. Removal of the dried ethyl acetate solution gave a solid (140 mg) which, after crystallization from dichloromethane–light petroleum, gave the pure acid (14), m.p. 104–106 °C (Found: C, 51.9; H, 3.95. C₁₁H₁₀O₇ requires C, 52.0; H, 4.0%); δ 2.26 (3 H, s, OAc), 4.06 (3 H, s, OMe), 5.98 (2 H, s, OCH₂O), 6.37 (1 H, s, 5-H), and 10.58 (1 H, br s, CO₂H).

2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)benzofuran (1).—To a solution of the acid (14) (140 mg) in dichloromethane (5 ml) were added in turn *p*-dimethylaminopyridine (ca. 10 mg), *o*-hydroxybenzyltriphenylphosphonium bromide (313 mg), and dicyclohexylcarbodi-imide (140 mg, in 2.0 ml of dichloromethane). The mixture was stirred at room temperature for 24 h (precipitate formed) after which toluene (40 ml) was added with heating to 85 °C under a stream of nitrogen for 15 min. After addition of triethylamine (0.4 ml), heating was continued at 85 °C for 5 h. The mixture was then poured into water, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was shaken with sodium hydroxide solution (2M; 75 ml), and this base extract acidified and re-extracted with ether. Evaporation of the dried ether extract gave a residual solid (64 mg) which was dissolved in dichloromethane–light petroleum (1:1) and filtered through silica gel to yield the benzofuran (1) as fine needles from light petroleum, m.p. 117.5 °C (lit.,¹ m.p. 118 °C); δ [(CD₃)₂CO] 3.94 (3 H, s, OMe), 5.96 (2 H, s, OCH₂O), 6.30 (1 H, s, 5'-H), 6.91 (1 H, d, *J* 0.9 Hz, 3-H), 7.16–7.33 (2 H, m, 5- and 6-H), and 7.44–7.64 (2 H, m, 4- and 7-H).

1-Methoxy-5-methoxymethoxy-2,3-methylenedioxybenzene (16).—A solution of the phenol (11) (200 mg) in dimethylformamide was added to a suspension of sodium hydride (112 mg of a 60% dispersion in oil, washed with cyclohexane) in dimethylformamide (5 ml) and heated at 50 °C for 1 h. The temperature was then lowered to 40 °C and chloromethyl methyl ether (0.2 ml) added with continued stirring at this

temperature for 75 min. The reaction was quenched by careful addition of methanol, dilution with water, and extraction with ether. Evaporation of the washed and dried extract gave the *methoxymethyl ether* (**16**) as a yellow oil, purified by distillation (b.p. 103 °C at 0.25 mmHg) to a colourless glass (m.p. 31–32 °C) (Found: C, 56.4; H, 5.7. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%); δ 3.48 (3 H, s, OCH_2OMe), 3.87 (3 H, s, ArOMe), 5.05 (2 H, s, OCH_2OMe), 5.88 (2 H, s, OCH_2O), 6.20 (1 H, d, J 2.2 Hz, 4- or 6-H), and 6.29 (1 H, d, J 2.2 Hz, 6- or 4-H).

4-Methoxy-6-methoxymethoxy-2,3-methylenedioxybenzoic Acid (**17**).—A solution of the ether (**16**) (400 mg) in ether (5 ml) was added with stirring at 0 °C to a solution of *n*-butyl-lithium (1.2 ml of a 1.7M solution in hexane) in ether (10 ml). After the mixture had been stirred for 100 min, dry carbon dioxide was bubbled through for 5 min, then dilute hydrochloric acid added. The layers were separated and the aqueous phase extracted with chloroform. The combined layers were washed, dried, and evaporated to yield a solid (390 mg) shown by 1H n.m.r. examination to be a 14:1 mixture of isomeric arylcarboxylic acids. Trituration with dichloromethane–light petroleum gave the acid (**17**) as a solid, m.p. 129–132 °C (Found: C, 51.4; H, 4.75. $C_{11}H_{12}O_7$ requires C, 51.6; H, 4.7%); δ 3.57 (3 H, s, OCH_2OMe), 3.97 (3 H, s, ArOMe), 5.33 (2 H, s, OCH_2OMe), 6.12 (2 H, s, OCH_2O), and 6.46 (1 H, s, 5-H).

When the same experiment was conducted with added tetramethylenediamine (0.25 ml), the same mixture of acids in a 4:1 ratio was obtained. The 1H n.m.r. spectrum of the minor (not isolated) constituent, 2-methoxy-6-methoxymethoxy-3,4-methylenedioxybenzoic acid, was δ 3.46 (3 H, s, OCH_2OMe), 4.01 (3 H, s, ArOMe), 5.09 (2 H, s, OCH_2OMe), 5.91 (2 H, s, OCH_2O), and 6.47 (1 H, s, 5-H).

2-(4-Methoxy-6-methoxymethoxy-2,3-methylenedioxyphenyl)benzofuran (**18**).—(a) Triethylamine (0.08 ml) and oxalyl chloride (0.1 ml) were added to a suspension of the acid (**17**) (125 mg) in benzene (23 ml). The mixture was stirred at room temperature for 10 h, then taken to dryness under reduced pressure, and the residue suspended in toluene (50 ml). The phosphonium salt (**8**) (265 mg) and triethylamine (0.4 ml) were added and the mixture heated at 100 °C for 12 h, then cooled and filtered. The filtrate was evaporated and the residue dissolved in light petroleum–dichloromethane (1:4) and filtered through silica gel (15 g). Elution with the same solvent gave the benzofuran (**18**) as a solid, which crystallized from light petroleum as small needles (38 mg), m.p. 93–95 °C (Found: C, 66.3; H, 4.8. $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9%); δ 3.53 (3 H, s, OCH_2OMe), 3.96 (3 H, s, ArOMe), 5.18 (2 H, s, OCH_2OMe), 6.04 (2 H, s, OCH_2O), 6.45 (1 H, s, 5'-H), 7.11 (1 H, d, J 0.9 Hz, 3-H), 7.16–7.32 (2 H, m, 5- and 6-H), and 7.47–7.62 (2 H, m, 4- and 7-H).

(b) Reaction of the acid (**17**) and the salt (**8**) by the dicyclohexylcarbodi-imide–dimethylaminopyridine method and work-up as in the previous cases gave the benzofuran (**18**) in 57% yield.

2-(6-Hydroxy-4-methoxy-2,3-methylenedioxyphenyl)benzofuran (**15**).—Toluene-*p*-sulphonic acid (30 mg) was added to a solution of the methoxymethoxy ether (**18**) (75 mg) in methanol (60 ml), concentrated to 10 ml by heating and passage of a nitrogen stream, then diluted with water. The mixture was extracted with ether and the extract shaken with 1M-sodium hydroxide solution (2 × 25 ml). The separated alkaline solution was acidified with dilute hydrochloric acid and re-extracted with ether. Evaporation of the washed and dried ether layer gave a solid (53 mg) which crystallized from light petroleum–dichloromethane as rosettes, m.p. 122–124 °C (Found: C, 67.5; H, 4.1. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.26%); δ [(CD_3) $_2CO$] 3.88 (3 H, s, OMe), 6.03 (2 H, s, OCH_2O), 6.28 (1 H, s, 5'-H), 7.18–7.33 (2 H, m, 5- and 6-H), 7.21 (1 H, d, J 0.9 Hz, 3-H), and 7.43–7.67 (2 H, m, 4- and 7-H).

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