Naturally Occurring Dibenzofurans. Part 4.[1] Synthesis of Dibenzofurandiols by Annelation of Benzofurans

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Methyl 3-acetylbenzofuran-2-ylacetate (**8**) undergoes *C*-methylation affording methyl 2-(3-acetylbenzofuran-2-yl)propionate (**13**). These compounds and similar oxo esters undergo ready cyclization to dibenzofurandiols on treatment with sodium methoxide in boiling methanol. A convenient synthesis of dimethyl furan-2,5-diyldiacetate (**30**) is described, as are attempts to synthesize 1,3,7,9-tetramethoxy-2,8-dimethyldibenzofuran (**3**).

In an earlier paper[1] we advanced evidence in support of structure (**1**) for rhodomyrtoxin,[2] and structure (**2**) for ψ-rhodomyrtoxin,[3] natural products isolated from the fruit of the Australian finger cherry, *Rhodomyrtus macrocarpa* Benth. In order to verify these structures by synthesis we required the dibenzofuran (**3**) as an intermediate. In the present paper we describe attempts to synthesize this compound. Although these attempts were not successful we believe the results obtained are not without interest.

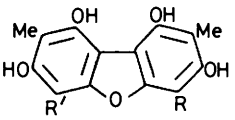
Bentley *et al.*[4] showed that the oxo ester (**4**) on treatment with sodium ethoxide in ethanol gave the naphthalene-1,4-quinone (**5**), presumably by aerial oxidation of the intermediate naphthalene-1,3-diol (**6**). Roberts and his co-workers[5] showed that this reaction was of some generality and constitutes a good synthesis of naphthalene-1,3-diols. We therefore sought to apply this method to the synthesis of dibenzofuran-1,3-diols by using suitably substituted benzofurans as their precursors.

Accordingly methyl benzofuran-2-ylacetate (**7**)[6] was acetylated with acetyl chloride and tin(IV) chloride thus affording the oxo ester (**8**). Treatment with aqueous methanolic sodium hydroxide at room temperature gave the derived acid (**9**). This behaved as a vinylogous β-oxo-acid and, like a β-oxo-acid, it underwent ready decarboxylation. Thus on brief boiling with dilute aqueous sodium hydrogen carbonate it furnished the benzofuran (**10**). On treatment with hot aqueous sodium hydroxide, however, the acid (**9**) gave the ketone (**12**) (Scheme). The intermediate ketone (**10**) presumably suffers conjugate attack by hydroxide and the cleavage of the furan ring affords the β-diketone (**11**) as an intermediate. β-Diketonic fission then results in the ketone (**12**).

The oxo ester (**8**) behaved as a vinylogous β-oxo-ester: it could be *C*-methylated by treatment with an excess of iodomethane and potassium carbonate in *N*,*N*-dimethylformamide at room temperature when it smoothly afforded compound (**13**). This behaviour must be ascribed to the inductive effect of the ring oxygen since neither the furan (**14**) (see later) nor the benzene (**15**)[5] could be similarly *C*-methylated under these mild conditions.

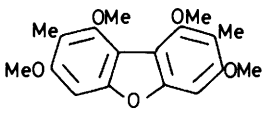
Treatment of the oxo ester (**8**) with concentrated ammonia gave the benzofuro[3,2-*c*]pyridinol (**16**), a reaction presumably involving the intermediacy of the amide.[4] When the oxo ester (**8**) was treated with sodium methoxide in boiling anhydrous methanol under dry nitrogen the dibenzofurandiol (**18**) was obtained in good yield. In a similar manner the oxo ester (**13**) underwent cyclization to the dibenzofurandiol (**19**), and on treatment with ammonia it furnished the benzofuro[3,2-*c*]-pyridinol (**17**).

Propionylation of methyl benzofuran-2-ylacetate (**7**) gave the oxo ester (**22**) which like its lower homologue (**8**), could also be *C*-methylated thus affording the oxo ester (**23**). Compounds (**22**) and (**23**) on separate treatment with methanolic sodium methoxide gave the dibenzofurandiols (**20**) and (**21**).

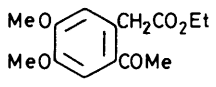


(**1**) R = R′ = $COCH_2CHMe$

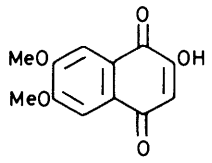
(**2**) R = $COCH_2CHMe_2$, R′ = $COCH(Me)\cdot CH_2Me$



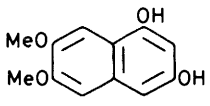
(**3**)



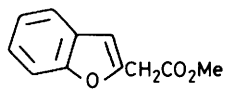
(**4**)



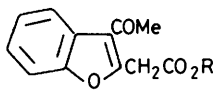
(**5**)



(**6**)

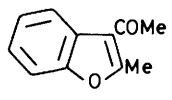


(**7**)

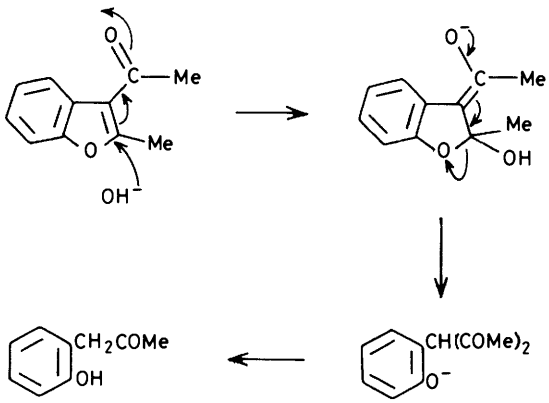


(**8**) R = Me

(**9**) R = H

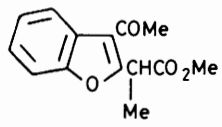


(**10**)



(**12**) (**11**)

Scheme.



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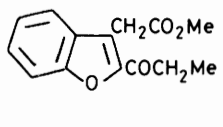

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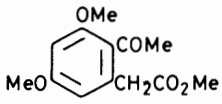

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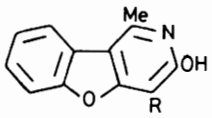
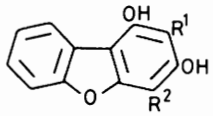
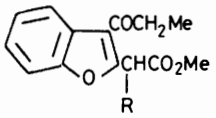


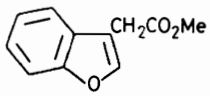
(16) R = H
(17) R = Me



(18) $R^1 = R^2 = H$
(19) $R^1 = H$; $R^2 = Me$
(20) $R^1 = Me$; $R^2 = H$
(21) $R^1 = R^2 = Me$



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



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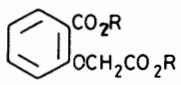
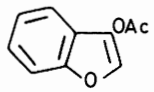


(25) R = Me
(26) R = H



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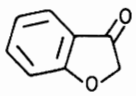

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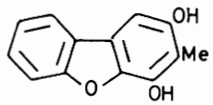
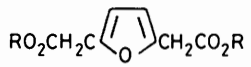


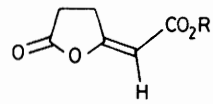
(29)

In order to extend this method to the synthesis of dibenzofuran-2,4-diols we required methyl benzofuran-3-ylacetate (**24**). The starting material for the synthesis of compound (**24**) was obtained by *O*-alkylation of methyl salicylate with methyl bromoacetate. The resultant ester (**25**) was converted into the known dicarboxylic acid (**26**),[7] which was treated with anyhydrous sodium acetate in a boiling mixture of acetic acid and acetic anhydride.[8] This reaction gave 3-acetoxybenzofuran (**27**), which on acidic hydrolysis gave benzofuran-3(2*H*)-one (**28**). Wittig reaction of compound (**28**) with methoxycarbonylmethylenetriphenylphosphorane in boiling toluene gave the benzofuran (**24**), which on propionylation supplied the oxo ester (**14**). This last-mentioned compound on treatment with methanolic sodium methoxide then gave the dibenzofurandiol (**29**).

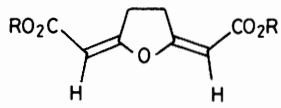
Since the annelation of benzofurans to dibenzofurandiols had been successful it was decided to attempt the reaction in the



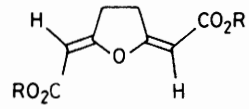
(30) R = Me
(31) R = Et



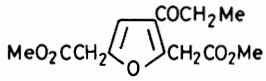
(32) R = Et
(33) R = Me



(34) R = Et
(35) R = Me



(36) R = Et
(37) R = Me

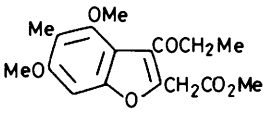


(38)

furan series. We were attracted to this possibility since a short synthesis of the dibenzofuran (**3**) might ensue. We thus required dimethyl furan-2,5-diyldiacetate (**30**) as an intermediate. Soviet workers have described a synthesis of this compound,[9] but the synthesis of the diethyl ester (**31**) by Babidge and Massy-Westropp[10] appeared more attractive. These authors found that Wittig reaction of the *E*-lactone (**32**), available from succinic anhydride by a similar Wittig reaction,[11] with methoxycarbonylmethylenetriphenylphosphorane in carbon tetrachloride at room temperature for 1 week gave a 50% yield of the *E,E*- and *E,Z*-compounds (**34**) and (**36**) in the ratio 5:2. Treatment of the *E,E*-compound (**34**) with trifluoroacetic acid then gave the furan (**31**). In our hands the Wittig reaction of succinic anhydride with 2.4 mol equiv. of methoxycarbonylmethylenetriphenylphosphorane in boiling tetrahydrofuran gave directly the desired furan (**30**) in good yield. It could be isolated conveniently from the reaction mixture by distillation under diminished pressure. A by-product proved to be the *E,E*-compound (**35**). The furan (**30**) could also be secured by treatment of the *E*-lactone (**33**) with methoxycarbonylmethylenetriphenylphosphorane in boiling tetrahydrofuran. In this case the *E,Z*-compound (**37**) was isolated as a by-product.

Dimethyl furan-2,5-diyldiacetate (30) underwent smooth propionylation on treatment with propionic anhydride and tin(IV) chloride. The resultant oxo diester (**38**) could not be cyclized to a benzofurandiol on treatment with a range of bases.

It was therefore reasoned that annelation of the benzofuran (**39**) would provide a route to the dibenzofuran (**3**). The synthesis of the benzofuran (**39**) was therefore investigated. A suitable intermediate for this purpose appeared to be the ester (**40**), available, it was assumed, by a modified Tanaka synthesis,[12] from the salicylaldehyde (**41**). Although this salicylaldehyde is known the syntheses described in the literature are inefficient.[13,14] Hence the boron trichloride induced demethylation of the readily available[15] aldehyde (**42**) was investigated. Although selective demethylation occurred in this reaction it was the more hindered methoxy group which was cleaved and the resultant salicylaldehyde proved to be compound (**43**).[16] We nevertheless carried out the remaining steps in the planned sequence on this compound. Treatment of the salicylaldehyde (**43**) with diethyl bromomalonate and potassium carbonate in *N,N*-dimethylformamide gave the intermediate dihydrobenzofuran (**44**), which underwent deethoxycarbonylation and dehydration on heating with lithium



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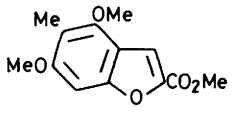

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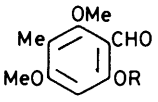
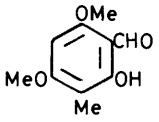


(41) R = H
(42) R = Me



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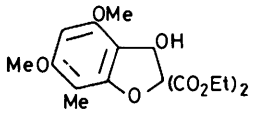

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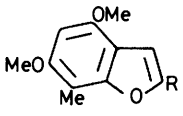
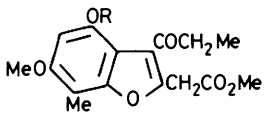
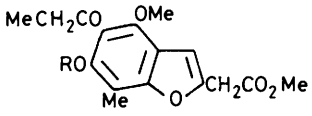


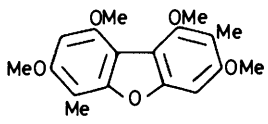
(45) R = CO_2Et
(46) R = CH_2OH
(47) R = CH_2Cl
(48) R = CH_2CN
(49) R = CH_2CO_2Me



(50) R = Me
(51) R = H



(52) R = Me
(53) R = H



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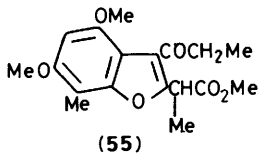

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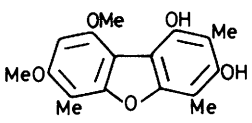

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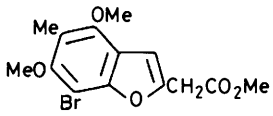

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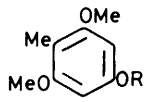
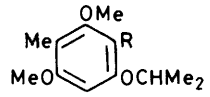
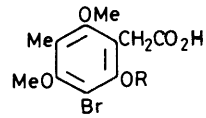


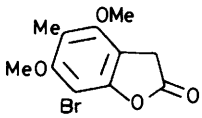
(58) R = H
(59) R = $CHMe_2$



(60) R = CH_2Cl
(61) R = CH_2CN
(62) R = CH_2CO_2H



(63) R = $CHMe_2$
(64) R = H



(65)

Treatment of the phenol (**51**) with methanolic sodium methoxide and subsequent *O*-methylation of the crude product gave, as expected, the known dibenzofuran (**54**).[1,3] The phenol (**51**) on treatment with an excess of iodomethane and potassium carbonate underwent both *O*- and *C*-methylation and provided the benzofuran (**55**). This on cyclization with methanolic sodium methoxide yielded the dibenzofurandiol (**56**).

In order to synthesize the dibenzofuran (**3**) and to prevent the production of a mixture of isomers in the propionylation step we sought a synthesis of the benzofuran (**57**) in which the bromine would serve as a blocking group. The phenol (**58**), available by modification of the method of Seshadri and his co-workers,[18] on isopropylation gave the ether (**59**). This latter compound on chloromethylation under mild conditions gave the unstable chloromethyl compound (**60**), which was converted into the acetic acid (**62**) *via* the acetonitrile (**61**). Bromination of the acid (**62**) afforded compound (**63**), which on treatment with boron trichloride furnished the hydroxyphenylacetic acid (**64**). This underwent ring-closure to the lactone (**65**), in poor yield, on treatment with toluene-*p*-sulphonic acid in boiling benzene. Wittig reaction of this compound with methoxycarbonylmethylenetriphenylphosphorane gave the desired intermediate (**57**). However all attempts to propionylate this compound were unsuccessful, doubtless on account of the considerable steric hindrance at the 3-position.

An alternative synthesis of the dibenzofuran (**3**) has been completed; this will be disclosed in a subsequent publication.

chloride in wet dimethyl sulphoxide thus affording the known benzofuran (**45**).[17] This compound was converted into the benzofuran-2-ylacetate (**49**) *via* the alcohol (**46**), the chloride (**47**), and the nitrile (**48**).

On propionylation the ester (**49**) afforded approximately equal parts of the desired ketone (**50**) and its isomer (**52**) as shown by the ^1H n.m.r. spectrum of the mixture. In order to facilitate separation of these isomers the mixture was treated with boron trichloride. It was expected that only compound (**52**) would suffer selective demethylation under these conditions yielding the phenol (**53**). However compound (**50**) also underwent demethylation affording the phenol (**51**). The mixture of compounds (**51**) and (**53**) was readily separated since the former proved to be cryptophenolic and was hence insoluble in aqueous base.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. Light petroleum was a fraction of b.p. 58—65 °C. All organic extracts were washed with saturated brine and dried over anhydrous sodium sulphate prior to evaporation under reduced pressure. Silica gel was B.D.H. 60—120 mesh, and crude products were pre-adsorbed from dichloromethane prior to chromatography. Alumina was Fluka, neutral activity I (Brockmann). P.l.c. plates (20 × 20 × 0.1 cm) were coated with Merck Kieselgel GF_{254}. Unless stated otherwise n.m.r. spectra were determined at 90 MHz in deuteriochloroform solution using a Brüker HX-90 spectrometer. Others were determined at 60 MHz using a Hitachi–Perkin-Elmer R-24B instrument or at 80 MHz using a Brüker WP-80 instrument in the same solvent. Mass spectra were recorded using a Hewlett-Packard 5986 instrument

operating at 70eV. I.r. spectra were recorded using a Perkin-Elmer 282 spectrophotometer, and electronic spectra with a Varian DMS-80 spectrophotometer.

Methyl 3-Acetylbenzofuran-2-ylacetate (8).—Methyl benzofuran-2-ylacetate (**7**) (5.0 g),[6] acetyl chloride (2.8 ml), and methylene dichloride (40 ml) were stirred together at 0 °C and tin(IV) chloride (4.6 ml) was added dropwise over 5 min. The solution was then stirred at room temperature for 3.5 h. The mixture was poured on ice and water and extracted with ethyl acetate. The extract was washed in turn with water, saturated sodium hydrogen carbonate solution, water, and finally saturated brine. Distillation of the crude product under diminished pressure gave the *oxo ester* (**8**) (5.4 g, 88%) as a pale yellow liquid, b.p. 200 °C at 1 mmHg (Kugelrohr), which eventually crystallized and formed plates (from light petroleum), m.p. 40—41 °C (Found: C, 67.5; H, 5.45%; M^+, 232. $C_{13}H_{12}O_4$ requires C, 67.25; H, 5.2%; *M*, 232); δ 2.65 (3 H, s, COMe), 3.72 (3 H, s, OMe), 4.21 (2 H, s, CH_2), 7.26—7.55 (3 H, m, 5-, 6-, and 7-H), and 7.74—7.93 (1 H, m, 4-H); $\nu_{max.}$(film) 1 747 (ester), 1 679 (ketone), and 1 575 cm^{-1} (C=C).

3-Acetylbenzofuran-2-ylacetic Acid (**9**).—The ester (**8**) (200 mg) and sodium hydroxide (250 mg) in methanol (10 ml) and water (5 ml) were set aside at room temperature for 22 h. The yellow solution was cooled to 0 °C and acidified with dilute hydrochloric acid. Isolation with ethyl acetate in the usual way gave the *acid* (**9**) (170 mg, 90%), which formed needles (from methylene dichloride–light petroleum), m.p. 122—124 °C (Found: C, 65.9; H, 4.8. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.6%).

1-(2-Methylbenzofuran-3-yl)ethan-1-one (**10**).—The acid (**9**) (150 mg), water (50 ml), and saturated aqueous sodium hydrogen carbonate solution (2 ml) were heated under reflux for 1 h. The cooled mixture was extracted with ethyl acetate and the crude product was subjected to p.l.c. over silica gel with 10% ethyl acetate–light petroleum as developing solvent. The major band afforded the ketone (**10**) (54 mg, 45%) which formed plates (from light petroleum), m.p. 46—47 °C (lit.,[19] 47.4—49.4 °C); δ 2.62 (3 H, s, COMe), 2.76 (3 H, s, Me), 7.22—7.50 (3 H, m, 5-, 6-, and 7-H), and 7.79—8.02 (1 H, m, 4-H); $\nu_{max.}$(CCl_4) 1 678 cm^{-1} (ketone); *m/z* 174 (M^+, 38%), 160 (11), 159 (100), 131 (9), and 77 (10).

1-(2-Hydroxyphenyl)propan-2-one (**12**).—The acid (**9**) (200 mg) was heated at 90 °C under nitrogen with sodium hydroxide (800 mg) in water (30 ml) for 2 h. The cooled mixture was acidified and extracted with ethyl acetate. The crude product crystallized from methylene dichloride–light petroleum (charcoal) as glistening plates (80 mg, 58%) of the ketone (**12**), m.p. 62—63 °C (lit.,[20] 63—64 °C); δ 2.27 (3 H, s, COMe), 3.73 (2 H, s, CH_2CO), and 6.75—7.25 (5 H, m, 4 × ArH and D_2O-exchangeable OH); $\nu_{max.}$(CCl_4) 3 350 (OH) and 1 710 cm^{-1} (ketone); *m/z* 150 (M^+, 36%), 108 (24), 107 (100), and 77 (26).

Methyl 2-(3-Acetylbenzofuran-2-yl)propionate (**13**).—Methyl 3-acetylbenzofuran-2-ylacetate (**8**) (2.5 g), iodomethane (3.0 ml), anhydrous potassium carbonate (4.0 g), and dry *N,N*-dimethylformamide (30 ml) were stirred together for 2 h at room temperature. The mixture was poured into water; isolation with diethyl ether gave the *oxo ester* (**13**), which was distilled at 175 °C at 0.4 mmHg (Kugelrohr) and afforded a solid (2.15 g, 81%) which crystallized from methylene dichloride–light petroleum as prisms, m.p. 50—51 °C (Found: C, 68.35; H, 5.7%; M^+, 246. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.75%; *M*, 246); δ 1.64 (3 H, d, $CHCH_3$), 2.68 (3 H, s, COMe), 3.68 (3 H, s, OMe), 4.82 (1 H, q, *CH*Me), 7.24—7.56 (3 H, m, 5-, 6-, and 7-H), and 7.79—7.91 (1 H, m, 4-H) (irradiation at δ 1.64 caused collapse of the quartet to a singlet); $\nu_{max.}$(film) 1 751 (ester), 1 682 (ketone), and 1 564 cm^{-1} (C=C).

1-Methylbenzofuro[3,2-c]pyridin-3-ol (**16**).—Methyl 3-acetylbenzofuran-2-ylacetate (**8**) (500 mg) was stirred with concentrated ammonia solution (15 ml) for 2 h. The mixture was diluted with ice and water and the precipitate was separated by filtration, washed with water, and then dried *in vacuo*. The *heterocycle* (**16**) (350 mg, 82%) crystallized from methanol as needles, m.p. 267—270 °C (decomp.) (Found: C, 72.15; H, 4.5; N, 7.15. $C_{12}H_9NO_2$ requires C, 72.35; H, 4.55; N, 7.05%); δ(CD_3OD; 80 MHz) 2.75 (3 H, s, Me), 6.29 (1 H, s, 4-H), 7.22—7.48 (3 H, m, 6-, 7-, and 8-H), and 7.73—7.92 (1 H, m, 9-H); *m/z* 199 (M^+, 100%), 171 (32), 170 (39), 115 (11), 85.5 (10), and 75 (14).

Dibenzofuran-1,3-diol (**18**).—Methyl 3-acetylbenzofuran-2-ylacetate (**8**) (500 mg) and sodium methoxide [from sodium (125 mg)] in anhydrous methanol (25 ml) were heated under reflux under dry nitrogen for 2.5 h. The cooled solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed successively with water, saturated sodium hydrogen carbonate solution, water, and finally saturated brine. The *diol* (**18**) (346 mg, 80%) crystallized from chloroform–carbon tetrachloride as prisms, m.p. 173—175 °C (Found: C, 71.6; H, 4.0%; M^+, 200. $C_{12}H_{18}O_3$ requires C, 72.0; H, 4.05%; *M*, 200); δ 5.16 and 5.48 (each 1 H, br, D_2O-exchangeable OH), 6.27 and 6.64 (2 H, AB, *J* 2.0 Hz, 2- and 4-H), 7.31—7.63 (3 H, m, 6-, 7-, and 8-H), and 7.94—8.09 (1 H, m, 9-H). Methylation with iodomethane and potassium carbonate in *N,N*-dimethylformamide at room temperature gave 1,3-dimethoxydibenzofuran as needles (from aqueous methanol), m.p. 72—73 °C (lit.,[12] 72 °C); δ 3.83 and 3.95 (each 3 H, s, OMe), 6.37 and 6.67 (2 H, AB, *J* 2.0 Hz, 2- and 4-H), 7.19—7.52 (3 H, m, 6-, 7-, and 8-H), and 7.92—8.04 (1 H, m, 9-H); $\lambda_{max.}$(EtOH) 214, 223, 225infl, 227infl, 261, 283, 291infl, and 301 nm (ε 36 200, 34 200, 33 600, 33 400, 15 100, 18 800, 14 800, and 13 000).

4-Methyldibenzofuran-1,3-diol (**19**).—Methyl 2-(3-acetylbenzofuran-2-yl)propionate (**13**) was treated with boiling methanolic sodium methoxide as described for the preparation of compound (**18**). The *diol* (**19**) (75%) crystallized from methylene dichloride–light petroleum (charcoal) as needles, m.p. 195—196 °C (Found: C, 72.8; H, 4.65% M^+, 214. $C_{13}H_{10}O_3$ requires C, 72.9; H, 4.7%; *M*, 214); δ (80 MHz) 2.36 (3 H, s, Me), 4.88 and 5.24 (each 1 H, br, D_2O-exchangeable OH), 6.28 (1 H, s, 2-H), 7.34—7.65 (3 H, m, 6-, 7-, and 8-H), and 7.94—8.13 (1 H, m, 9-H). Methylation gave 1,3-*dimethoxy*-4-*methyldibenzofuran* as needles (from methanol), m.p. 120—121 °C (Found: C, 74.25; H, 5.95%; M^+, 242. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%; *M*, 242); δ($CDCl_3$; 90 MHz) 2.34 (3 H, s, Me), 3.85 and 3.95 (each 3 H, s, OMe), 6.33 (1 H, s, 2-H), 7.17—7.53 (3 H, m, 6-, 7-, and 8-H), and 7.92—8.05 (1 H, m, 9-H); $\lambda_{max.}$(EtOH) 215, 231, 264, 284, 296, and 308 nm (ε 38 300, 31 500, 12 700, 17 500, 11 000, and 14 700).

Methyl 3-Propionylbenzofuran-2-ylacetate (**22**).—Methyl benzofuran-2-ylacetate (**7**) (5.0 g) was treated with propionyl chloride (3.45 ml) as described for the acetylation of compound (**7**). Distillation gave the *oxo ester* (**22**) (5.17 g, 80%) as a solid, b.p. 190 °C at 0.5 mmHg (Kugelrohr), which crystallized from methylene dichloride–light petroleum as plates, m.p. 76—77 °C (Found: C, 68.25; H, 5.8%; M^+, 246. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.75%; *M*, 246); δ 1.24 (3 H, t, $COCH_2CH_3$), 3.00 (2 H, q, $COCH_2Me$), 3.72 (3 H, s, OMe), 4.23 (2 H, s, CH_2), 7.21—7.55 (3 H, m, 5-, 6-, and 7-H), and 7.73—7.84 (1 H, m, 4-H); $\nu_{max.}$(CCl_4) 1 759 (ester) and 1 684 cm^{-1} (ketone).

Methyl 2-(3-*Propionylbenzofuran*-2-*yl*)*propionate* (**23**).—Methylation of the oxo ester (**22**) (2.5 g) as described for compound (**8**) gave the *oxo ester* (**23**), which distilled at 170 °C and 0.2 mmHg (Kugelrohr) and gave a solid (1.88 g, 71%), which formed prisms (from methylene dichloride–light petroleum), m.p. 65—66 °C (Found: C, 69.15; H, 6.3%; M^+, 260. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%; *M*, 260); δ 1.25 (3 H, t, $COCH_2CH_3$), 1.63 (3 H, d, $CHCH_3$), 3.03 (2 H, q, $COCH_2Me$), 3.68 (3 H, s, OMe), 4.86 (1 H, q, C*H*Me), 7.21—7.60 (3 H, m, 5-, 6-, and 7-H), and 7.76—7.93 (1 H, m, 4-H) (irradiation at δ 1.63 caused collapse of the quartet at δ 4.86 to a singlet); $\nu_{max.}(CCl_4)$ 1 755 (ester) and 1 687 cm^{-1} (ketone).

1,4-*Dimethylbenzofuro*[3,2-c]*pyridin*-3-*ol* (**17**).—Methyl 3-propionylbenzofuran-2-ylacetate (**22**) was treated with ammonia as described for the preparation of compound (**16**). The resultant *heterocycle* (**17**) formed needles (from chloroform–methanol), m.p. 307—310 °C (Found: C, 73.35; H, 5.2; N, 6.8% M^+, 213. $C_{13}H_{11}NO_2$ requires C, 73.25; H, 5.2; N, 6.55%; *M*, 213); δ(CD_3OD; 80 MHz) 2.21 and 2.72 (each 3 H, s, Me), 7.25—7.63 (3 H, m, 6-, 7-, and 8-H), and 7.75—8.00 (1 H, m, 9-H).

2-*Methyldibenzofuran*-1,3-*diol* (**20**).—Methyl 3-propionylbenzofuran-2-ylacetate (**22**) was treated with boiling methanolic sodium methoxide. The *diol* (**20**) (80%) crystallized from methanol–carbon tetrachloride (charcoal) as laths, m.p. 212—213 °C (Found: C, 72.7; H, 4.65%; M^+, 214. $C_{13}H_{10}O_3$ requires C, 72.9; H, 4.7%; *M*, 214); δ(80 MHz) 2.25 (3 H, s, Me), 5.03 and 5.26 (each 1 H, s, D_2O-exchangeable OH), 6.66 (1 H, s, 4-H), 7.31—7.62 (3 H, m, 6-, 7-, and 8-H), and 7.92—8.15 (1 H, m, 9-H). Methylation gave 1,3-*dimethoxy*-2-*methyldibenzofuran* as needles (from methanol), m.p. 66—67 °C (Found: C, 74.1; H, 5.8%; M^+, 242. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%; *M*, 242); δ 2.25 (3 H, s, Me), 3.87 and 3.94 (each 3 H, s, OMe), 6.85 (1 H, s, 4-H), 7.19—7.55 (3 H, m, 6-, 7-, and 8-H), and 7.90—8.04 (1 H, m, 9-H); $\lambda_{max.}$(EtOH) 223, 258, 291, and 298 nm (ε 34 600, 12 400, 17 400, and 17 700).

2,4-*Dimethyldibenzofuran*-1,3-*diol* (**21**).—Methyl 2-(3-propionylbenzofuran-2-yl)propionate (**23**) was treated with boiling methanolic sodium methoxide. The *diol* (21) (77%) formed plates (from chloroform), m.p. 213—214 °C (Found: C, 73.55; H, 5.35%; M^+, 228. $C_{14}H_{12}O_3$ requires C, 73.65; H, 5.3%; *M*, 228); δ (80 MHz) 2.26 and 2.39 (each 3 H, s, Me), 4.86 and 5.09 (each 1 H, s, D_2O-exchangeable OH), 7.31—7.70 (3 H, m, 6-, 7-, and 8-H), and 7.97—8.19 (1 H, m, 9-H).

Methyl 2-*Methoxycarbonylmethoxybenzoate* (**25**).—Methyl bromoacetate (25 ml) was added dropwise over 15 min to a stirred mixture of methyl salicylate (37.5 g) and potassium carbonate (52.5 g) in dry acetone (200 ml). The mixture was then boiled and stirred under reflux for 17 h. The salts were separated by filtration and washed with acetone. The residue left on removal of the acetone was diluted with diethyl ether and the solution was washed successively with water, aqueous sodium carbonate, water, and finally saturated brine. The crude product was distilled under diminished pressure and gave a solid (47.1 g, 85%), b.p. 112—113° at 0.01 mmHg. A sample crystallized from methylene dichloride–light petroleum as prisms of the *benzoate* (**25**), m.p. 49—50 °C (Found: C, 58.7; H, 5.5%; M^+, 224. $C_{11}H_{12}O_5$ requires C, 58.95; H, 5.4%; *M*, 224); δ(CCl_4; 60 MHz) 3.57 and 3.69 (each 3 H, s, OMe), 4.48 (2 H, s, CH_2), and 6.55—7.67 (4 H, m, ArH); $\nu_{max.}(CCl_4)$ 1 774 (aliphatic ester) and 1 740 cm^{-1} (aromatic ester).

3-*Acetoxybenzofuran* (**27**).—Hydrolysis of the ester (**25**) with boiling aqueous methanolic sodium hydroxide gave the derived dicarboxylic acid (**26**), m.p. 190 °C (lit.,[7] 190 °C). This acid (20 g), anhydrous sodium acetate (20 g), acetic acid (60 ml), and acetic anhydride (100 ml) were boiled and stirred under reflux for 4 h. The cooled mixture was diluted with water and extracted with light petroleum. The extract was washed in turn with water, saturated sodium hydrogen carbonate solution, water, and finally saturated brine. The residue left on removal of the solvent was distilled under diminished pressure and gave the *benzofuran* (**27**) (9.8 g, 55%) as an oil, b.p. 110 °C at 0.1 mmHg (Kugelrohr) (Found: C, 68.15; H, 4.35%; M^+, 176. $C_{10}H_8O_3$ requires C, 68.2; H, 4.6%; *M*, 176); δ(60MHz) 2.29 (3 H, s, Me), 7.00—7.50 (4 H, m, ArH), and 7.80 (1 H, s, 2-H; $\nu_{max.}$(film) 1 777 (ester), 1 628 (C=C), and 1 587 cm^{-1} (C=C).

Benzofuran-3(2H)-*one* (**28**).—3-Acetoxybenzofuran (**27**) (8.8 g), water (20 ml), methanol (80 ml), and concentrated hydrochloric acid (2 ml) were heated under reflux for 50 min. The cooled solution was diluted with water. Isolation with diethyl ether and crystallization from light petroleum (charcoal) gave the benzofuranone (**28**) (4.6 g, 69%) as needles, m.p. 100—101 °C (lit.,[21] 100 °C); δ(60 MHz) 4.45 (2 H, s, CH_2) and 6.97—7.63 (4 H, m, ArH).

Methyl Benzofuran-3-*ylacetate* (**24**).—Benzofuran-3(2*H*)-one (**28**) (4.96 g) and methoxycarbonylmethylenetriphenylphosphorane (13.7 g) were stirred and heated under reflux in dry toluene (140 ml) for 35 h. The solvent was removed under reduced pressure and the residue was filtered through a column of silica gel with 10% ethyl acetate–light petroleum as eluant. The product (**24**) was then distilled under diminished pressure and gave an oil (5.0 g, 71%), b.p. 130 °C at 0.7 mmHg (Kugelrohr) (lit.,[22] 90—93 °C at 0.25 mmHg) (Found: C, 69.2; H, 5.25%; M^+, 190. Calc. for $C_{11}H_{10}O_3$: C, 69.45; H, 5.3%; *M*, 190); δ(CCl_4) 3.61 (2 H, d, J_{2,CH_2} 1.0 Hz, CH_2), 3.67 (3 H, s, OMe), 7.09—7.54 (4 H, m, ArH), and 7.57 (1 H, t, $J_{CH_2,2}$ 1.0 Hz, 2-H); $\nu_{max.}$(film) 1 747 cm^{-1} (ester).

Methyl-2-*Propionylbenzofuran*-3-*ylacetate* (**14**).—Propionylation of methyl benzofuran-3-ylacetate (**24**) (1.85 g) with propionyl chloride (1.3 ml) during 21 h, as described for the acetylation of compound (**7**), gave a crude product. This was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum as eluant. The major fraction was distilled under diminished pressure and gave the *oxo ester* (**14**) (1.2 g, 50%) as a solid, b.p. 160 °C at 0.01 mmHg (Kugelrohr). It crystallized from light petroleum as needles, m.p. 62—63 °C (on rapid crystallization, or plates, m.p. 73—74 °C (on slow crystallization) (Found: C, 68.2; H, 5.75%; M^+, 246. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.75%; *M*, 246); δ(60 MHz) 1.19 (3 H, t, CH_3CH_2), 2.97 (2 H, q, $MeCH_2$), 3.60 (3 H, s, OMe), 4.09 (2 H, s, CH_2), and 7.01—7.69 (4 H, m, ArH).

3-*Methyldibenzofuran*-2,4-*diol* (**29**).—Treatment of the oxo ester (**14**) with boiling methanolic sodium methoxide gave the *diol* (**29**) (81%) as prisms (from carbon tetrachloride–methanol), m.p. 204—205 °C (Found: C, 72.8; H, 4.75%; M^+, 214. $C_{13}H_{10}O_3$ requires C, 72.9; H, 4.7%; *M*, 214); δ(80 MHz) 2.31 (3 H, s, Me), 4.71 and 5.36 (each 1 H, s, D_2O-exchangeable OH), 6.88 (1 H, s, 1-H), 7.31—7.59 (3 H, m, 6-, 7-, and 8-H), and 7.94 (1 H, m, 9-H). Methylation gave a crude product, b.p. 200 °C at 0.2 mmHg (Kugelrohr), which formed prisms (from light petroleum) of 2,4-*dimethoxy*-3-*methyldibenzofuran*, m.p. 46—47 °C (Found: C, 74.1; H, 5.9%; M^+, 242. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.8%; *M*, 242); δ 2.27 (3 H, s, Me), 3.91 and 4.17 (each 3 H, s, OMe), 7.07 (1 H, s, 1-H), 7.19—7.79 (3 H, m, 6-, 7-, and 8-H), and 7.79—7.91 (1 H, m, 9-H); $\lambda_{max.}$(EtOH) 212, 218, 255, 290, and 318infl nm (ε 31 500, 32 200, 13 700, 17 100, and 4 700).

(E)-*Methyl* (4,5-*Dihydro*-5-*oxofuran*-2-(3H)-*ylidene*)*acetate* (**33**).—Succinic anhydride (0.71 g) and methoxycarbonyl-

methylenetriphenylphosphorane (2.5 g) were heated under reflux in dry benzene (20 ml) for 14 h. The residue left on removal of the solvent was chromatographed over a column of silica gel with 20% ethyl acetate–light petroleum as eluant. The *lactone* (**33**) (791 mg, 71%) formed plates (from methylene dichloride–light petroleum), m.p. 109—109.5 °C (Found: C, 53.95; H, 5.05%; M^+, 156. $C_7H_8O_4$ requires C, 53.85; H, 5.15%; *M*, 156); δ 2.62—2.82 (2 H, m, 4-H_2), 3.28—3.48 (2 H, m, 3-H_2), 3.71 (3 H, s, OMe), and 5.71 (1 H, t, *J* 2.0 Hz, CH).

Wittig Reaction of (E)-*Methyl* (4,5-*Dihydro*-5-*oxofuran*-2-(3H)-*ylidene*)*acetate* (**33**) *and Methoxycarbonylmethylenetriphenylphosphorane*.—The lactone (**33**) (500 mg) and the title ylide (1.18 g) were heated under reflux in dry tetrahydrofuran (40 ml) for 72 h. Chromatography of the crude product over silica gel with 20% ethyl acetate–light petroleum as eluant gave dimethyl furan-2,5-diyldiacetate (**30**) (423 mg, 62%) as an oil, b.p. 135 °C at 0.4 mmHg (Kugelrohr) (lit.,[9] 117—118 °C at 1 mmHg); δ(60 MHz) 3.58 (4 H, s, 2 × CH_2), 3.64 (6 H, s, 2 × OMe), and 6.06 (2 H, s, 3- and 4-H). Further elution gave (E,Z)-*dimethyl* 2,2′-(3,4-*dihydrofuran*-2,5-*diylidene*)*bisacetate* (**37**) (90 mg, 13%), which formed stout needles (from methylene dichloride-light petroleum), m.p. 136—137.5 °C (Found: C, 56.7; H, 5.8%; M^+, 212. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%; *M*, 212); δ 2.74—2.96 (2 H, m, CH_2), 3.10—3.32 (2 H, m, CH_2), 3.70 (6 H, s, 2 × OMe), 5.15 (1 H, t, *J* 1.5 Hz, CH of *Z*-system), and 5.78 (1 H, t, *J* 2.0 Hz, CH of *E*-system).

Wittig Reaction of Succinic Anhydride with 2.4 *Mol Equiv. of Methoxycarbonylmethylenetriphenylphosphorane*.—Succinic anhydride (2.0 g) and the title ylide (14.8 g) were heated under reflux in dry tetrahydrofuran (50 ml) for 26 h. The crude product was distilled under diminished pressure to afford dimethyl furan-2,5-diyldiacetate (**30**) (2.85 g, 67%) as an oil, b.p. 170 °C at 0.6 mmHg (Kugelrohr), identical with the sample just described. Chromatography of the pot residue over silica gel with 20% ethyl acetate–light petroleum as eluant gave (E,E)-*dimethyl* 2,2′-(3,4-*dihydrofuran*-2,5-*diylidene*)*bisacetate* (**35**) (420 mg, 10%) as glistening plates (from light petroleum), m.p. 131.5—132.5 °C (Found: C, 56.6; H, 5.8%; M^+, 212. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%; *M*, 212); δ 3.56 (4 H, d, *J* 0.6 Hz, 2 × CH_2), 3.70 (6 H, s, 2 × OMe), and 5.60 (2 H, s, 2 × CH).

Dimethyl 3-*Propionylfuran*-2,5-*diyldiacetate* (**38**).—Tin(IV) chloride (572 mg) was added at 0 °C to a stirred solution of dimethyl furan-2,5-diyldiacetate (**30**) (423 mg) and propionic anhydride (288 mg) in dry 1,2-dichloroethane. The solution was stirred at room temperature for 23 h, and then diluted with ethyl acetate and washed in turn with water, saturated aqueous sodium hydrogen carbonate, and finally saturated brine. Removal of the solvent gave the *ketone* (**38**) (520.5 mg, 97%), which distilled at 150 °C at 0.03 mmHg as an oil (Found: C, 58.53; H, 5.8%; M^+, 268. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%; *M*, 268); δ 1.13 (3 H, t, *J* 7.5 Hz, CH_3CH_2), 2.74 (2 H, q, *J* 7.5 Hz, CH_3CH_2), 3.68 (2 H, s, 5-CH_2), 3.70 and 3.73 (each 3 H, s, OMe), 4.05 (2 H, s, 2-CH_2), and 6.55 (1 H, s, 4-H); $\nu_{max.}$(film) 1 740 (ester) and 1 678 cm^{-1} (ketone).

2-*Hydroxy*-4,6-*dimethoxy*-3-*methylbenzaldehyde* (**43**).—2,4,6-Trimethoxy-3-methylbenzaldehyde (**42**) (17.3 g)[15] in dry methylene dichloride (30 ml) was added with stirring at −10 °C to a solution of boron trichloride (38.9 g) in methylene dichloride (175 ml). The solution was then stirred at −10 °C for 1.5 h, and then diluted with ethyl acetate. The usual work-up gave the aldehyde (**43**) (16.0 g, 99%), which formed plates (from methylene dichloride–light petroleum), m.p. 168—169 °C (lit.,[16] 169 °C); δ(60 MHz) 1.92 (3 H, s, Me), 3.78 and 3.79 (each 3 H, s, OMe), 5.80 (1 H, s, ArH), 9.98 (1 H, s, CHO), and 12.23 (1 H, s, OH).

Diethyl 2,3-*Dihydro*-3-*hydroxy*-4,6-*dimethoxy*-7-*methylbenzofuran*-2,2-*dicarboxylate* (**44**).—The aldehyde (**43**) (16.0 g), diethyl bromomalonate (21.0 g), and dry potassium carbonate (25.0 g) were stirred in dry *N*,*N*-dimethylformamide (200 ml) at room temperature under dry nitrogen for 23 h. The mixture was diluted with water and extracted with diethyl ether. The extract was washed in turn with water, dilute aqueous sodium hydroxide solution, water, and finally saturated brine. The crude product crystallized from methylene dichloride–light petroleum (charcoal) as prisms of the *benzofuran* (**44**) (19.6 g, 68%), m.p. 138—139 °C (Found: C, 57.5; H, 6.25%; M^+, 354. $C_{17}H_{22}O_8$ requires C, 57.65; H, 6.25%; *M*, 354); δ 1.26 and 1.31 (each 3 H, t, CH_2CH_3), 2.06 (3 H, s, Me), 2.72 (1 H, d, *J* 7.5 Hz, D_2O-exchangeable OH), 3.79 and 3.83 (each 3 H, s, OMe), 4.25 and 4.33 (each 2 H, q, CH_2Me), 5.93 (1 H, d, *J* 7.5 Hz, 3-H), and 6.03 (1 H, s, 5-H) (irradiation at δ 5.93 caused collapse of the OH resonance to a singlet as did addition of D_2O).

Ethyl 4,6-*Dimethoxy*-7-*methylbenzofuran*-2-*carboxylate* (**45**).—The diester (**44**) (11.1 g), lithium chloride (1.5 g), water (1.1 ml), and dimethyl sulphoxide (100 ml) were heated and stirred at 165 °C (bath) under nitrogen for 1 h. The mixture was poured on ice and isolation with ethyl acetate gave the product (**45**) (6.95 g, 86%) as needles (from methanol), m.p. 126.5—127 °C (lit.,[17] 126 °C); δ 1.39 (3 H, t, CH_2CH_3), 2.31 (3 H, s, Me), 3.87 and 3.90 (each 3 H, s, OMe), 4.38 (2 H, q, CH_2Me), 6.33 (1 H, s, 5-H), and 7.52 (1 H, s, 3-H).

4,6-*Dimethoxy*-7-*methylbenzofuran*-2-*ylmethanol* (**46**).—The ester (**45**) (6.9 g) in dry tetrahydrofuran (200 ml) was added with stirring to lithium aluminium hydride (1.0 g) in dry diethyl ether (200 ml). The mixture was stirred and heated under reflux for 1 h. The usual work-up gave the *alcohol* (**46**) (5.7 g, 96%) as rosettes of needles (from methylene dichloride–light petroleum), m.p. 94—95 °C (Found: C, 64.8; H, 6.35%; M^+, 222. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%; *M*, 222).

Methyl 4,6-*Dimethoxy*-7-*methylbenzofuran*-2-*ylacetate* (**49**).—The alcohol (**46**) (4.75 g) and pyridine (2.1 g) in anhydrous benzene (120 ml) were stirred at room temperature during the dropwise addition of thionyl chloride (2.9 g) in benzene (60 ml). The solution was stirred at room temperature for 1 h and then poured on ice. The organic layer was separated and washed with saturated sodium hydrogen carbonate solution and with saturated brine. The crude product (**47**) in dry *N*,*N*-dimethylformamide (50 ml) was stirred with powdered potassium cyanide (2.8 g) under dry nitrogen for 3 h. Dilution with water and isolation with ethyl acetate gave the crude product. A small portion was chromatographed over silica gel with 10% ethyl acetate–light petroleum as eluant. 4,6-*Dimethoxy*-7-*methylbenzofuran*-2-*ylacetonitrile* (**48**) formed prisms (from cyclohexane), m.p. 98—100 °C (Found: C, 67.55; H, 5.7; N, 5.75%; M^+, 231. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%; *M*, 231); δ 2.27 (3 H, s, Me), 3.84 (2 H, d, *J* 1.2 Hz, CH_2), 3.87 and 3.91 (each 3 H, s, OMe), 6.36 (1 H, s, 5-H), and 6.72 (1 H, t, *J* 1.2 Hz, 3-H) (irradiation at δ 3.84 caused collapse of the 3-H signal to a singlet). The crude nitrile and potassium hydroxide (10 g) were heated under reflux in methanol (160 ml) and water (160 ml) for 4 d. Acidification and isolation of the acid with ethyl acetate and then saturated sodium hydrogen carbonate solution gave the crude acid, which was methylated with iodomethane and potassium carbonate in *N*,*N*-dimethylformamide at room temperature. The crude product was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum as eluant. The *ester* (**49**) (3.4 g, 60%) formed rosettes of needles (from

methylene dichloride–light petroleum), m.p. 94—95 °C (Found: C, 63.55; H, 6.1%; M^+, 264. $C_{14}H_{16}O_5$ requires C, 63.65; H, 6.1%; *M*, 264); δ 2.27 (3 H, s, Me), 3.71 (3 H, s, OMe), 3.77 (2 H, d, *J* 0.8 Hz, CH_2), 3.84 and 3.88 (each 3 H, s, OMe), 6.33 (1 H, s, 5-H), and 6.61 (1 H, t, *J* 0.8 Hz, 3-H); $\nu_{max.}$($CHCl_3$) 1 745 (ester), 1 631 (C=C), and 1 609 cm^{-1} (C=C).

Methyl 4-Hydroxy-6-methoxy-7-methyl-3-propionylbenzofuran-2-ylacetate (**51**).—The ester (**49**) (1.02 g) and propionyl chloride (7.5 ml) in dry methylene dichloride (60 ml) were stirred at 0 °C and treated dropwise with tin(IV) chloride (3.7 ml) in methylene dichloride (15 ml). The mixture was stirred at room temperature for 1.75 h and then worked up in the usual way. Examination of the crude product by ^1H n.m.r. spectroscopy indicated that it was a mixture of the 3-isomer (**50**) and the 5-isomer (**52**) in approximately equal proportions. The crude product in dry methylene dichloride (50 ml) was added at −10 °C with stirring to a solution of boron trichloride (3.0 g) in methylene dichloride (50 ml). After 50 min water and diethyl ether were added and the usual work-up gave the crude product, which was dissolved in diethyl ether and extracted with dilute aqueous potassium hydroxide. The organic layer was separated and on work-up afforded the *oxo ester* (**51**) (515 mg, 44%) as yellow needles (from methylene dichloride–light petroleum), m.p. 145—146 °C (Found: C, 62.8; H, 6.05; M^+, 306. $C_{16}H_{18}O_6$ requires C, 62.75; H, 5.9%; *M*, 306); δ 1.20 (3 H, t, CH_2CH_3), 2.17 (3 H, s, Me), 2.83 (2 H, q, CH_2Me), 3.74 and 3.81 (each 3 H, s, OMe), 4.06 (2 H, s, CH_2CO_2Me), 6.38 (1 H, s, 5-H), and 10.80 (1 H, s, D_2O-exchangeable OH) (irradiation of the signal at δ 2.17 caused sharpening of the 5-H signal); $\nu_{max.}$($CHCl_3$) 1 750 (ester), 1 659 (bonded ketone), 1 639 (C=C), and 1 612 cm^{-1} (C=C).

Methyl 2-(4,6-Dimethoxy-7-methyl-3-propionylbenzofuran-2-yl)propionate (**55**).—Methylation of the benzofuranol (**50**) with an excess of iodomethane and potassium carbonate in *N,N*-dimethylformamide at room temperature followed by filtration of the crude product through silica gel with 10% ethyl acetate–light petroleum as eluant, afforded the *product* (**55**) (85%) as needles (from methylene dichloride–light petroleum), m.p. 96—97 °C (Found: C, 64.15; H, 6.6%; M^+, 334. $C_{18}H_{22}O_6$ requires C, 64.65; H, 6.65%; *M*, 334); δ (80 MHz) 1.15 (3 H, t, CH_2CH_3), 1.59 (3 H, d, $CHCH_3$), 2.27 (3 H, s, Me), 3.11 (2 H, q, CH_2Me), 3.68, 3.89, and 3.91 (each 3 H, s, OMe), 4.32 (1 H, q, *CH*Me), and 6.42 (1 H, s, ArH); $\nu_{max.}$ ($CHCl_3$) 1 746 (ester), 1 680 (ketone), 1 638 (C=C), and 1 610 cm^{-1} (C=C).

1,3,7,9-*Tetramethoxy-2,6-dimethyldibenzofuran* (**54**).—The benzofuranol (**51**) (50 mg) was treated with boiling methanolic sodium methoxide. The crude triol was methylated and the crude product was then purified by p.l.c. using 10% ethyl acetate–light petroleum. The dibenzofuran (**54**) (31 mg, 60%) formed needles from light petroleum, m.p. 115—116 °C (lit.,[3] 116 °C) (Found: C, 68.85; H, 6.75. Calc. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.35%); $\lambda_{max.}$(EtOH) 221infl, 232, 268, 287, 297infl, and 309 nm (ε 36 500, 37 000, 15 300, 17 100, 12 300, and 14 900).

7,9-*Dimethoxy-2,4,6-trimethyldibenzofuran-1,3-diol* (**56**).—The oxo ester (**55**) was treated with boiling methanolic sodium methoxide and this gave the *diol* (**56**) (70%) as needles (from methylene dichloride–light petroleum), m.p. 203—205 °C (Found: C, 67.35; H, 6.0%; M^+, 302. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.0%; *M*, 302); δ(80 MHz) 2.23 (3 H, s, Me), 2.34 (6 H, s, 2 × Me), 3.90 and 4.07 (each 3 H, s, OMe), 4.42—5.09 (1 H, D_2O-exchangeable OH), 6.39 (1 H, s, ArH), and 8.44 (1 H, s, D_2O-exchangeable OH). Methylation during 2 h with an excess of iodomethane and potassium carbonate in *N,N*-dimethylformamide followed by p.l.c. of the crude product using 10% ethyl acetate–light petroleum gave 3,7,9-*trimethoxy-2,4,6-trimethyldibenzofuran-1-ol* as needles (from methylene dichloride–light petroleum), m.p. 139—140 °C (Found: C, 67.9; H, 6.5%; M^+, 316. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%; *M*, 316); δ(80 MHz) 2.27, 2.34, and 2.40 (each 3 H, s, Me), 3.76, 3.91, and 4.08 (each 3 H, s, OMe), 6.41 (1 H, s, ArH), and 8.45 (1 H, s, D_2O-exchangeable OH); $\lambda_{max.}$(EtOH) 218, 234, 278, 288infl, and 305infl (ε 36 700, 37 500, 21 000, 19 700, and 2 800).

Formylation of 3,5-Dimethoxyphenol.—Phosphoryl chloride (29.9 g) was added dropwise to the phenol (20.0 g) in dry *N,N*-dimethylformamide (40 ml) at 0 °C with stirring. The mixture was then stirred at room temperature for 18 h. An excess of ice and water was added and the mixture was stirred at room temperature for 16 h. The precipitate (23.5 g) was separated by filtration, washed with water, and dried *in vacuo*. It was extracted exhaustively with boiling light petroleum. Work-up of the extract afforded 2-hydroxy-4,6-dimethoxybenzaldehyde (10.5 g, 44%) as needles (from methylene dichloride–light petroleum), m.p. 68—70 °C (lit.,[23] 70 °C); δ (60 MHz) 3.71 (6 H, s, 2 × OMe), 5.75 and 5.86 (2 H, AB, *J* 2 Hz, ArH), 9.90 (1 H, s, CHO), and 12.31 (1 H, s, OH). The residue, a red powder (11.0 g, 47%) was 4-hydroxy-2,6-dimethoxybenzaldehyde, pure enough for the next step. A sample crystallized from ethanol (charcoal) formed sparkling yellow plates, m.p. 226—229 °C (lit.,[14] 222—224 °C); δ($CDCl_3$–CD_3SOCD_3; 60 MHz) 3.75 (6 H s, 2 × OMe), 6.00 (2 H, s, ArH), and 10.10 (1 H, s, CHO).

3,5-*Dimethoxy-4-methylphenol* (**58**).—4-Hydroxy-2,6-dimethoxybenzaldehyde (11.0 g), zinc amalgam [from zinc dust (87 g) and mercury(II) chloride (6.6 g)], acetic acid (80 ml), water (150 ml), and concentrated hydrochloric acid (150 ml) were stirred and heated under reflux for 2 h. The spent amalgam was separated by filtration through Kieselguhr and the filtrate was cooled and diluted with water. Isolation with ethyl acetate gave the phenol (**58**) (8.0 g, 79%) which formed cream prisms (from methylene dichloride–light petroleum), m.p. 147—149 °C (lit.,[24] 148—150 °C); δ 60 MHz) 1.90 (3 H, s, Me), 3.62 (6 H, s, 2 × OMe), 5.85b (1 H, OH), and 5.93 (2 H, s, ArH).

4-*Isopropoxy-2,6-dimethoxytoluene* (**59**).—The phenol (**58**) (2.45 g), 2-bromopropane (1.97 g), and dry potassium carbonate (2.51 g) in dry *N,N*-dimethylformamide (15 ml) were stirred together at 50 °C (bath) for 72 h. The usual work-up gave the crude product, which was filtered through a plug of neutral alumina with light petroleum as eluant; the *ether* (**59**) (2.47 g, 81%) was obtained as an oil, b.p. 85 °C at 0.01 mmHg (Found: C, 68.3; H, 8.5%; M^+, 210. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%; *M*, 210), δ 1.33 [6 H, d, *J* 6.0 Hz, $(CH_3)_2CH$], 2.01 (3 H, s, Me), 3.77 (6 H, s, 2 × OMe), 4.51 (1 H, septet, *J* 6.0 Hz, CH), and 6.13 (2 H, s, ArH).

6-*Isopropoxy-2,4-dimethoxy-3-methylphenylacetic Acid* (**62**).—Dry hydrogen chloride was bubbled through a stirred suspension of paraformaldehyde (730 mg, 24.4 mmol) and the toluene (**59**) (3.41 g, 16.2 mmol) in dry 1,2-dichloroethane (80 ml) at 0 °C over 2 h. The mixture was then diluted with ethyl acetate and washed with water, and with saturated brine. Removal of the solvent gave 6-isopropoxy-2,4-dimethoxy-3-methylbenzyl chloride (**60**) (4.1 g, 98%) as an oil which decomposed rapidly; δ (60 MHz) 1.34 [6 H, d, *J* 7.5 Hz, $(CH_3)_2CH$], 2.02 (3 H, s, Me), 3.72 and 3.75 (each 3 H, s, OMe), 4.52 (1 H, septet, *J* 7.5 Hz, CH), 4.65 (2 H, s, CH_2), and 6.22 (1 H, s, ArH). When this experiment was repeated in the same way with the toluene (**59**) (1.0 g, 4.76 mmol) and paraformaldehyde (158 mg, 5.3 mmol) the product was *bis-(6-isopropoxy-2,4-dimethoxy-3-methylphenyl)methane* (0.5 g, 49%) which formed prisms (from methylene dichloride–light petroleum), m.p. 165—166.5 °C (Found: C, 69.35; H, 8.5%; M^+, 432. $C_{25}H_{36}O_6$

requires C, 69.4; H, 8.4%; *M*, 432); δ 1.10 [12 H, d, *J* 6.0 Hz, 2 × $(CH_3)_2CH$], 2.07 (6 H, s, 2 × Me), 3.52 and 3.75 (each 6 H, s, 2 × OMe), 3.95 (2 H, s, CH_2), 4.38 (2 H, septet, CH), and 6.22 (2 H, s, ArH). The crude benzyl chloride (**60**) (4.10 g) and powdered sodium cyanide (1.17 g) were stirred in dry *N,N*-dimethylformamide (20 ml) at room temperature under dry nitrogen for 20.5 h. The usual work-up gave 6-isopropoxy-2,4-dimethoxy-3-methylphenylacetonitrile (**61**) (3.88 g, 98%) as a brown oil which decomposed on attempted distillation; δ (60 MHz) 1.33 [6 H, d, *J* 6.0 Hz, $(CH_3)_2CH$], 2.02 (3 H, s, Me), 3.52 (2 H, s, CH_2), 3.67 and 3.70 (each 3 H, s, OMe), 4.47 (1 H, septet, *J* 6.0 Hz, CH), and 6.30 (1 H, s, ArH). The crude nitrile (**61**) (3.53 g) and potassium hydroxide (10 g) were heated under reflux in methanol (75 ml) and water (50 ml) for 8 d. The usual work-up gave the *acid* (**62**) (2.60 g, 68%) as plates (from methylene dichloride–light petroleum), m.p. 126—127 °C (Found: C, 62.75; H, 7.75%; M^+, 268. $C_{14}H_{20}O_5$ requires C, 62.65; H, 7.5%; *M*, 268); δ 1.30 [6 H, d, *J* 6.0 Hz, $(CH_3)_2CH$], 3.64 (2 H, s, CH_2), 3.68 and 3.77 (each 3 H, s, OMe), 4.51 (1 H, septet, *J* 6.0 Hz, CH), 6.27 (1 H, s, ArH), and 11.22br (1 H, OH). When the reaction was terminated after 18 h the major product was *6-isopropoxy-2,4-dimethoxy-3-methylphenylacetamide*, which formed needles (from methylene dichloride–light petroleum), m.p. 130—132 °C (Found: C, 62.6; H, 7.95; N, 5.2%; M^+, 267. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.25%; *M*, 267); δ 1.34 [6 H, d, *J* 6.0 Hz, $(CH_3)_2CH$], 2.09 (3 H, s, Me), 3.54 (2 H, s, CH_2), 3.72 and 3.80 (each 3 H, s, OMe), 4.55 (1 H, septet, *J* 6.0 Hz, CH), 5.87br (2 H, NH_2), and 6.31 (1 H, s, ArH).

3-Bromo-2-hydroxy-4,6-dimethoxy-5-methylphenylacetic Acid (**63**).—Bromine (1.55 g) in methylene dichloride (7.5 ml) was added dropwise to a stirred solution of the acid (**62**) (2.60 g) in methylene dichloride (50 ml). The solution was then stirred for 0.5 h and worked up in the usual way to yield the product (**63**) as a gum. This in methylene dichloride (30 ml) was treated, with stirring and cooling to −10 °C, with boron trichloride (3.29 g) in methylene dichloride (12 ml). After 0.5 h the usual work-up gave the crude product, which was purified by extraction into aqueous sodium hydrogen carbonate solution in the usual way. The *acid* (**64**) (1.80, 61%) formed plates (from benzene–light petroleum), m.p. 147—149 °C (Found: C, 43.15; H, 4.6; Br, 26.15%; M^+, 304/306. $C_{11}H_{13}BrO_5$ requires C, 43.3; H, 4.3; Br, 26.2%; *M*, 304/306); δ 2.20 (3 H, s, Me), 3.71 and 3.78 (each 3 H, s, OMe), 3.75 (2 H, s, CH_2), and 7.68 (2 H, br, 2 × OH).

7-Bromo-4,6-dimethoxy-5-methylbenzofuran-2(3H)-one (**65**).—The acid (**64**) (2.60 g), toluene-*p*-sulphonic acid (50 mg), and dry benzene (250 ml) were stirred and heated in a Dean–Stark apparatus for 19 h. The usual work-up and flash chromatography with 10% ethyl acetate–light petroleum as eluant gave the *lactone* (**65**) (370 mg, 15%) as fine needles (from methylene dichloride–light petroleum), m.p. 131.5—132 °C (Found: C, 45.65; H, 4.0%; M^+, 286/288. $C_{11}H_{11}BrO_4$ requires C, 46.0; H, 3.85%; *M*, 286/288); δ 2.17 (3 H, s, Me), 3.79 and 3.87 (each 3 H, s, OMe), and 3.92 (2 H, s, CH_2).

Methyl 7-Bromo-4,6-dimethoxy-5-methylbenzofuran-2-ylacetate (**57**).—The lactone (**65**) (270 mg) and methoxycarbonylmethylenetriphenylphosphorane (377 mg) were stirred and heated under reflux in dry xylene (15 ml) under dry nitrogen for 4 h. The usual work-up and chromatography of the crude product over silica gel with 10% ethyl acetate–light petroleum as eluant gave the ester as a yellow gum (268 mg, 83%); δ (60 MHz) 2.20 (3 H, s, Me), 3.68 (3 H, s, OMe), 3.74 (5 H, s, CH_2 and OMe), 3.89 (3 H, s, OMe), and 6.68 (1 H, s, 3-H); *m/z* 344 (90%, M^+), 342 (86, M^+), 329 (20), 327 (20), 285 (100), 283 (82), 255 (15), 253 (15), 250 (10), 189 (18), 159 (25), and 146 (10).

Acknowledgement

We thank the Australian Research Grants Committee for financial support.

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Received 24*th November* 1983; *Paper* 3/2119