

## Synthesis of Benzofuran *Styrax* Extractives

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Naturally occurring arylbenzofuranpropanols, notably egonol and homoegonol, which may be classified as nor-lignans, have been synthesized by a short reaction pathway.

EGONOL (1), first isolated in 1915 by Okada<sup>1</sup> from the seed oil of *Styrax japonicum*, was formulated by Kawai as 5-(3-hydroxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (1) after extensive degradative studies, which have been reviewed.<sup>2</sup> The proposed

structure was supported by synthesis,<sup>3</sup> and a second synthesis has been described recently.<sup>4</sup> Egonol has also been isolated from other *Styrax* species (*S. formosanus*, *S. obassia*, and *S. americana*), and its spectrometric data

<sup>1</sup> H. Okada, *J. Pharm. Soc. Japan*, 1915, 657.

<sup>2</sup> F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 142.

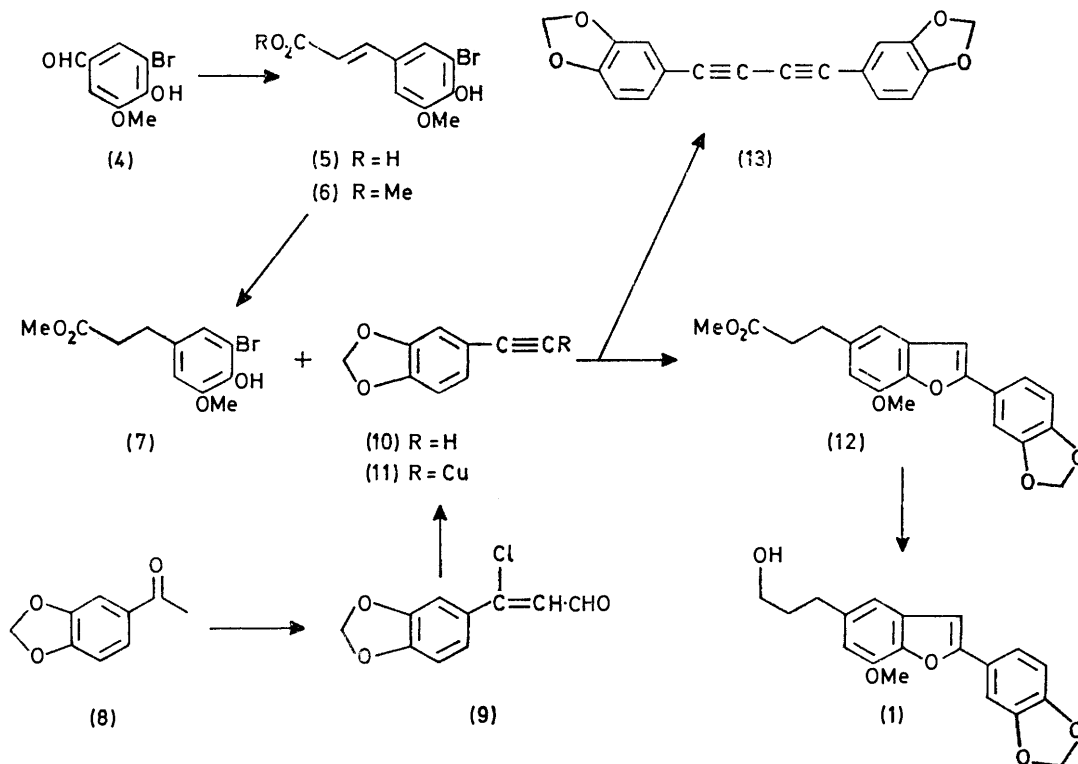
<sup>3</sup> S. Kawai, T. Nakamura, and N. Sugiyama, *Ber.*, 1939, **72**, 1146.

<sup>4</sup> E. Ritchie and W. C. Taylor, *Austral. J. Chem.*, 1969, **22**, 1329.

were then reported.<sup>5</sup> From the glycosidic fraction obtained from the seeds of *S. officinalis*, Segal *et al.*<sup>6</sup> isolated, by acidic hydrolysis, egonol and the veratryl analogue, which has been indexed as homoegonol (2).<sup>7</sup> Most recently, a demethoxy-analogue (3) has been reported as a constituent of *S. obassia*.<sup>8</sup>

Although the structure of egonol did not initially lend

with malonic acid, to give the cinnamic acid (5),<sup>18,19</sup> followed by catalytic hydrogenation of the derived methyl ester (6).<sup>20</sup> The acetylene (10) was prepared as recently described<sup>21</sup> from methylenedioxyacetophenone (8) by a Vilsmeier reaction to give the  $\beta$ -aryl- $\beta$ -chloroacrylaldehyde (9), which yielded (10) on treatment with hot aqueous base. Coupling in pyridine solution of the



itself readily to biogenetic classification,<sup>9</sup> the structural relationship to the eupomatenooids<sup>10-12</sup> strongly suggests that it is a bisarylpropanoid ('lignan'<sup>10</sup> or 'neolignan') having lost one phenylpropanoid  $\gamma$ -carbon atom.

We report here a simple synthesis of egonol and congeners based upon the method of benzofuran construction introduced by Castro,<sup>13-16</sup> and consisting of reaction of an *o*-halogenophenol with a copper(I) arylacetylide.

The arylpropionate ester (7) was obtained from 5-bromovanillin (4)<sup>17</sup> by a Doebner-Knoevenagel reaction

copper(I) arylacetylide (11) [prepared from (10) by treatment with copper sulphate and hydroxylamine hydrochloride in ammonium hydroxide] with the bromophenol (7) yielded methyl egonoate (12) accompanied by the diaryldiyne (13). Reduction of the ester (12) by lithium aluminium hydride in tetrahydrofuran gave egonol (1) in high yield. In terms of economy and experimental ease, this synthesis is preferable to those previously reported.

For the preparation of homoegonol (2), not previously synthesized, the same bromophenol (7) was coupled with the copper salt of 3,4-dimethoxyphenylacetylene (14)<sup>22</sup>

<sup>5</sup> C. Y. Hopkins, D. F. Ewing, and M. J. Chisholm, *Canad. J. Chem.*, 1967, **45**, 1425.

<sup>6</sup> R. Segal, I. Milo-Goldzweig, S. Sokoloff, and D. V. Zaitshchek, *J. Chem. Soc. (C)*, 1967, 2402.

<sup>7</sup> T. K. Devon and A. I. Scott, 'Handbook of Naturally Occurring Compounds,' vol. I, Academic Press, New York, 1975.

<sup>8</sup> M. Takanashi, Y. Takizawa, and T. Mitsuhashi, *Chem. Letters*, 1974, 869.

<sup>9</sup> J. H. Richards and J. B. Hendrickson, 'The Biosynthesis of Steroids, Terpenes and Acetogenins,' Benjamin, New York, 1964.

<sup>10</sup> R. S. McCredie, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1969, **22**, 1011.

<sup>11</sup> B. F. Bowden, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1972, **25**, 2659.

<sup>12</sup> K. Picker, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1973, **26**, 1111.

<sup>13</sup> C. E. Castro and R. D. Stephens, *J. Org. Chem.*, 1963, **28**, 2163.

<sup>14</sup> R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.

<sup>15</sup> C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.

<sup>16</sup> C. E. Castro, R. Havlin, V. K. Honwad, A. Malte, and S. Moje, *J. Amer. Chem. Soc.*, 1969, **91**, 6464.

<sup>17</sup> R. L. Shriner and P. McCutchan, *J. Amer. Chem. Soc.*, 1959, **81**, 2193.

<sup>18</sup> N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535.

<sup>19</sup> W. M. Whaley, M. Meadow, and W. L. Dean, *J. Org. Chem.*, 1954, **19**, 1022.

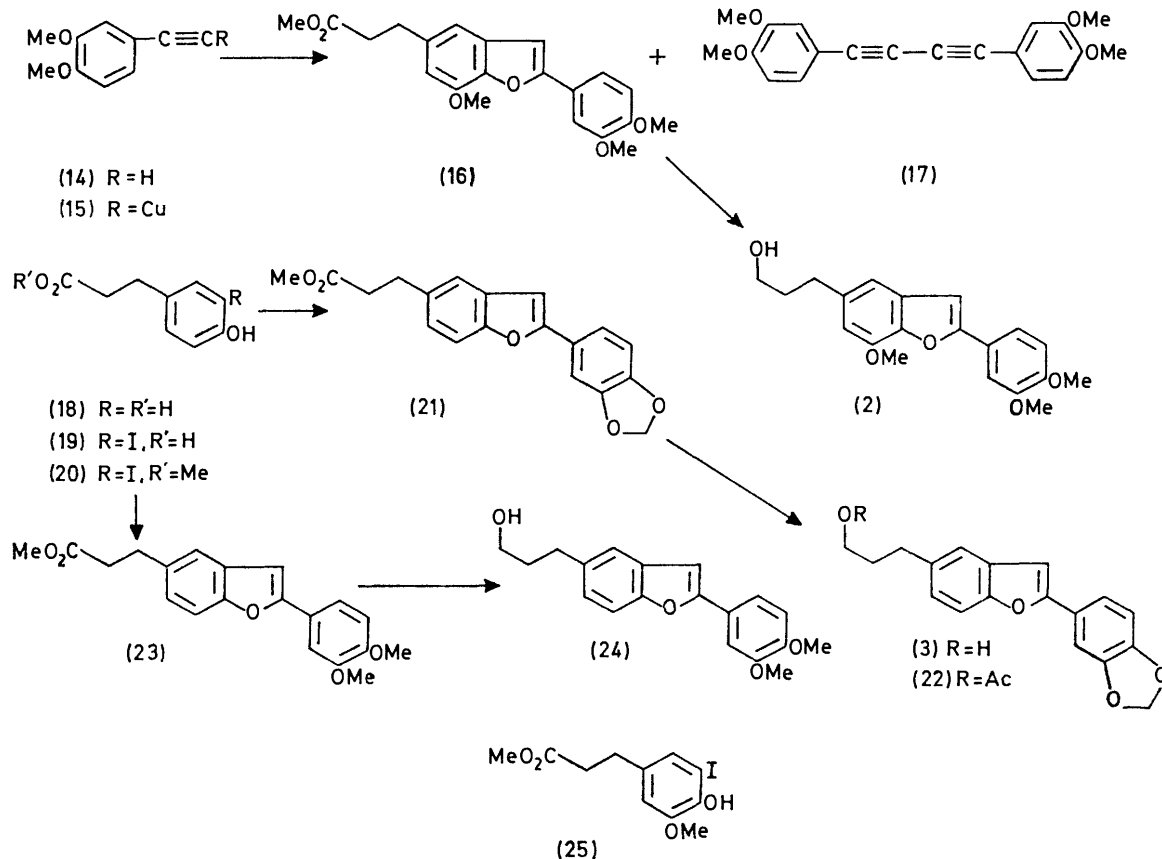
<sup>20</sup> H. Hellmann and W. Elser, *Annalen*, 1961, **639**, 77.

<sup>21</sup> R. Ahmed and R. Stevenson, *Org. Prep. Proc. Int.*, 1975, **7**, 79.

<sup>22</sup> K. Bodendorf and R. Mayer, *Chem. Ber.*, 1965, **98**, 3554.

to give the benzofuran methyl ester (16) and the diaryldiyne (17) in the ratio *ca.* 4 : 1 as determined from the  $^1\text{H}$  n.m.r. spectrum of the crude reaction mixture. These products were separated by chromatography on silica gel

quence, the formation of the homoegonol precursor (16) by use of the iodophenol (25) instead of the bromophenol (7) was examined, and the anticipated improvement was realized.



or by basic hydrolysis of the total product mixture followed by separation of a neutral (diyne) fraction and acid fraction, and re-esterification of the latter to yield the ester (16). Reduction of (16) with lithium aluminium hydride then cleanly yielded homoegonol (2).

For the synthesis of the demethoxy-analogue (3), we employed the commercially available phloretic acid (*p*-hydroxydihydrocinnamic acid) (18) which on iodination gave the known 4-hydroxy-3-iododihydrocinnamic acid (19).<sup>23,24</sup> Coupling of the derived methyl ester (20) with the copper(I) salt (11) yielded, in over 90% yield, the benzofuran ester (21), reduction of which as in the previous cases yielded the benzofuranpropanol (3), characterized as the acetate (22) and with physical constants in good agreement with those reported. To complete the series, the dimethoxyphenyl analogue (24), although not yet reported as a natural product, was prepared by coupling of (20) with (15) followed by reduction of the ester product (23).

In those two coupling reactions which involved aryl iodides, the absence of the diynes (13) and (17) as products led to simplified isolation and higher yields of the required benzofurans (21) and (23). As a conse-

#### EXPERIMENTAL

N.m.r. spectra were determined for solutions in [ $^2\text{H}$ ]chloroform (unless otherwise stated) with tetramethylsilane as internal standard. For t.l.c., silica gel PF 254 + 366 was employed.

*Methyl 3-(3-Bromo-4-hydroxy-5-methoxyphenyl)propionate* (7).—Palladium-carbon (10%; *ca.* 100 mg) was added to a suspension of methyl 3-bromo-4-hydroxy-5-methoxycinnamate<sup>20</sup> (6) (8.61 g) in acetic acid (100 ml) and the mixture stirred under hydrogen at atmospheric pressure. When uptake was complete, the filtered solution was evaporated to give the methyl ester (7) as a viscous oil which slowly solidified (lit.,<sup>20</sup> m.p. 81–82°);  $\delta$  2.41–2.97 (m,  $\text{CH}_2\text{-CH}_2$ ), 3.65 (s,  $\text{CO}_2\text{Me}$ ), 3.82 (s, ArOMe), 6.23br (s, OH), 6.68 (d,  $J$  2 Hz, aryl H-6), and 6.93 (d,  $J$  2 Hz, aryl H-2).

*Copper(I) 3,4-Methylenedioxyphenylacetylde* (11).—Hydroxylamine hydrochloride (764 mg) was added to a stirred solution of copper sulphate pentahydrate (1.37 g) in concentrated ammonium hydroxide (6 ml) and water (25 ml) under nitrogen. After the dark blue-purple colour had faded to light blue, a solution of 3,4-methylenedioxyphenylacetylene<sup>21</sup> (803 mg) in ethanol (30 ml) was added with vigorous stirring under nitrogen to disperse the yellow pasty precipitate.

<sup>23</sup> J. Runeberg, *Acta Chem. Scand.*, 1958, **12**, 188.

<sup>24</sup> A. Nishinaga and T. Matsuura, *J. Org. Chem.*, 1964, **29**, 1812

pitite, which was collected, washed with water, ethanol, and ether, and vacuum dried. The dark yellow powder (1.09 g) was stored over phosphorus pentoxide.

**Methyl 3-[7-Methoxy-2-(3,4-methylenedioxyphenyl)benzofuran-5-yl]propanoate (12).**—To a suspension of copper(I) 3,4-methylenedioxyphenylacetylde (236 mg) in pyridine (12 ml) was added a solution of the methyl ester (7) (365 mg) in the same solvent (8 ml) and the mixture was heated under reflux (nitrogen atmosphere) for 22 h. It was then cooled, diluted with ether, and washed successively with saturated brine, *N*-hydrochloric acid, saturated sodium carbonate solution, and brine. Evaporation of the dried ethereal extract yielded a brown oily solid (358 mg), crystallization of which from acetone-methanol, then acetone gave 1,4-dipiperonylbuta-1,3-diyne (13) as pale yellow needles (45 mg), m.p. 195–198° (Found: C, 74.4; H, 3.8. C<sub>18</sub>H<sub>10</sub>O<sub>4</sub> requires C, 74.5; H, 3.45%);  $\delta$  5.98 (s, OCH<sub>2</sub>O), 6.77 (d, *J* 8 Hz, aryl H-5), 6.97 (d, *J* 2 Hz, aryl H-2), and 7.10 (dd, *J* 8 and 2 Hz, aryl H-6). Evaporation of the filtrate was followed by preparative t.l.c. of the residue [with benzene-acetone (9:1)] yielding a zone (*R<sub>F</sub>* 0.57) which, by elution with acetone, afforded a yellow oil which crystallized. Recrystallization from aqueous methanol gave methyl egonoate as soft needles (23%), m.p. 114–115° (lit.,<sup>5</sup> 105–107°) (Found: C, 67.7; H, 5.2. C<sub>20</sub>H<sub>18</sub>O<sub>6</sub> requires C, 67.8; H, 5.1%);  $\nu_{\max}$  (CCl<sub>4</sub>) 1 740, 1 620, and 1 600 cm<sup>-1</sup>;  $\delta$  2.43–3.25 (m, CH<sub>2</sub>·CH<sub>2</sub>), 3.67 (s, CO<sub>2</sub>Me), 4.02 (s, ArOMe), 5.99 (s, OCH<sub>2</sub>O), 6.63 (d, *J* 1.5 Hz, H-6), 6.78 (s, H-3), 6.88 (d, *J* 9 Hz, phenyl H-5), 6.98 (d, *J* 1.5 Hz, H-4), 7.29 (d, *J* 2 Hz, phenyl H-2), and 7.42 (dd, *J* 9 and 2 Hz, phenyl H-6).

**5-(3-Hydroxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (Egonol) (1).**—A solution of methyl egonoate (104 mg) in tetrahydrofuran (10 ml) was added to a stirred suspension of lithium aluminium hydride (500 mg) in the same solvent (10 ml) at 0°C under nitrogen. The mixture was allowed to come to room temperature, stirred for 4 h, then worked up in the usual way. The product (91 mg) was purified by t.l.c. [*R<sub>F</sub>* 0.31 in benzene-acetone (9:1)] and crystallized from aqueous methanol to give egonol as needles, m.p. 112.5–113°,  $\lambda_{\max}$  (MeOH) 217 ( $\epsilon$  34 200), 302 (25 200), 317.5 (29 500), and 330 nm (22 800), with i.r. and n.m.r. spectra in agreement with those recorded.<sup>5</sup>

**Copper(I) 3,4-Dimethoxyphenylacetylde (15).**—This was prepared as for the piperonyl analogue (11), as a bright yellow powder (4.01 g), from 3,4-dimethoxyphenylacetylene (14) (3.15 g), copper sulphate pentahydrate (4.87 g), and hydroxylamine hydrochloride (2.71 g).

**Coupling of the Acetylde (15) and Methyl 3-(3-Bromo-4-hydroxy-5-methoxyphenyl)propionate (7).**—To a suspension of the salt (15) (251 mg) in pyridine (12 ml) under nitrogen was added a solution of the methyl ester (7) (324 mg) in the same solvent (8 ml) and the mixture heated under reflux for 22 h. Work-up as before gave a product which was dissolved in benzene and chromatographed on a column (45 × 2 cm) of silica gel. Elution with benzene (500 ml) gave 1,4-diveratrylbuta-1,3-diyne (17) as yellow needles, m.p. 183–185° (from methanol) (Found: C, 74.55; H, 5.65. C<sub>20</sub>H<sub>18</sub>O<sub>4</sub> requires C, 74.5; H, 5.65%);  $\nu_{\max}$  (KBr) 2 140 cm<sup>-1</sup> (C≡C);  $\delta$  3.90 (s, OMe), 6.82 (d, *J* 8 Hz, aryl H-5), 7.05 (d, *J* 2 Hz, aryl H-2), and 7.20 (dd, *J* 8 and 2 Hz, aryl H-6). Elution with benzene-ether and ether yielded a solid which crystallized from methanol as needles, to give methyl 3-[7-methoxy-2-(3,4-dimethoxyphenyl)benzofuran-5-yl]propanoate (16), m.p. 119–121° (Found: C, 68.05; H, 5.8. C<sub>21</sub>H<sub>22</sub>O<sub>6</sub> requires C, 68.1; H, 6.0%);  $\nu_{\max}$  (KBr) 1 730, 1 615, and

1 600 cm<sup>-1</sup>;  $\delta$  2.5–3.2 (m, CH<sub>2</sub>·CH<sub>2</sub>), 3.68 (CO<sub>2</sub>Me), 3.92 and 3.97 (s, phenyl 3- and 4-OMe), 4.03 (s, 7-OMe), 6.65 (d, *J* 1.5 Hz, H-6), 6.83 (s, H-3), 6.87–7.00 (m, phenyl H-5, and H-4), 7.27 (d, *J* 2 Hz, phenyl H-2), and 7.46 (dd, *J* 9 and 2 Hz, phenyl H-6).

In an alternative work-up procedure, the product (250 mg) from (15) (225 mg) and (7) (290 mg) was dissolved in methanol (50 ml) and heated under reflux with sodium hydroxide (230 mg) in water (10 ml) for 1 h. Dilution with water and concentration yielded a solid (41 mg), which on one crystallization from methanol gave the diyne (17) as long yellow needles, m.p. 177–182°. Acidification of the basic filtrate precipitated a solid, which was collected, dried, and heated with methanol (30 ml) and sulphuric acid (10 drops) for 1 h. Work-up in the usual way gave the methyl ester (16) as needles (146 mg), m.p. 119–121°.

**2-(3,4-Dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran (2).**—A suspension of the ester (16) (51 mg) was reduced with lithium aluminium hydride (as for egonol). T.l.c. [*R<sub>F</sub>* 0.28 in benzene-acetone (9:1)] yielded homoeconol (2) as needles (27 mg) (from aqueous methanol), m.p. 124.5–126° (lit.,<sup>6</sup> m.p. 120–122°);  $\delta$  1.93 (m,  $\beta$ -CH<sub>2</sub>), 2.42 (s, OH), 2.77 (m,  $\alpha$ -CH<sub>2</sub>), 3.68 (t, *J* 6 Hz,  $\gamma$ -CH<sub>2</sub>), 3.88, 3.95, and 4.01 (s, 3 OMe), and 6.59–7.55 (m, 5 ArH);  $\lambda_{\max}$  (EtOH) 216 (34 100), 301 (28 300), 314 (32 900), and 327 nm (23 400).

**3-(4-Hydroxy-3-iodophenyl)propanoic Acid (19).**—This was prepared essentially by the method of Runeberg;<sup>23</sup>  $\delta$ [(CD<sub>3</sub>)<sub>2</sub>CO] 2.35–3.00 (m, CH<sub>2</sub>·CH<sub>2</sub>), 6.78 (d, *J* 8 Hz, H-5), 7.06 (dd, *J* 8 and 2 Hz, H-6), 7.55 (d, *J* 2 Hz, H-2), 8.58br (s, OH), and 9.73br (s, CO<sub>2</sub>H). Esterification with methanol-sulphuric acid gave the methyl ester (20) as an oil,  $\delta$  2.33–2.98 (m, CH<sub>2</sub>·CH<sub>2</sub>), 3.62 (s, CO<sub>2</sub>Me), 6.72 (d, *J* 8.5 Hz, H-5), 6.94 (dd, *J* 8.5 and 2 Hz, H 6), and 7.42 (d, *J* 2 Hz, H-2), which was used without further purification.

**Methyl 3-[2-(3,4-Methylenedioxyphenyl)benzofuran-5-yl]propanoate (21).**—To a suspension of copper(I) 3,4-methylenedioxyphenylacetylde (145 mg) in pyridine (12 ml) was added a solution of the methyl iodophenylpropanoate (20) (218 mg) in the same solvent (8 ml). The mixture was treated as in the previous coupling experiments, yielding a solid (224 mg) which crystallized from methanol to give the methyl benzofuranylpropanoate (21) as needles, m.p. 125–128° (Found: C, 70.1; H, 4.8. C<sub>19</sub>H<sub>16</sub>O<sub>5</sub> requires C, 70.35; H, 5.0%);  $\nu_{\max}$  (KBr) 1 730, 1 610, and 1 575 cm<sup>-1</sup>;  $\delta$  2.3–3.3 (m, CH<sub>2</sub>·CH<sub>2</sub>), 3.67 (s, CO<sub>2</sub>Me), 6.02 (s, OCH<sub>2</sub>O), and 6.82–7.5 (m, ArH).

**5-(3-Hydroxypropyl)-2-(3,4-methylenedioxyphenyl)benzofuran (3).**—Reduction of the methyl ester (21) (58 mg) with lithium aluminium hydride (500 mg) as before gave a product (55 mg) which was purified by t.l.c. [*R<sub>F</sub>* 0.32 in benzene-acetone (9:1)] to give the propanol (3), crystallized from aqueous methanol as needles (82%), m.p. 124–125° (lit.,<sup>8</sup> 118–119°); n.m.r. spectrum in close agreement with that reported;<sup>8</sup>  $\lambda_{\max}$  (EtOH) 214 ( $\epsilon$  35 200), 317 (32 300), and 331 nm (26 200). Acetylation with pyridine-acetic anhydride gave the acetate (22) as shiny flakes, m.p. 90–91° (from aqueous methanol or light petroleum);  $\lambda_{\max}$  (EtOH) 214 ( $\epsilon$  33 100), 305sh (23 000), 320 (31 600), and 335sh nm (25 800), with the n.m.r. spectrum again in excellent agreement.<sup>8</sup>

**Methyl 3-[2-(3,4-Dimethoxyphenyl)benzofuran-5-yl]propanoate (23).**—Coupling of the acetylde (15) and the methyl iodophenylpropanoate (20) in the usual way gave, in quantitative yield, a solid product which crystallized from

aqueous methanol, affording the *methyl ester* (23) as needles, m.p. 113—115° (Found: C, 70.4; H, 5.75.  $C_{20}H_{20}O_5$  requires C, 70.55; H, 5.9%);  $\nu_{\max}$  1 730, 1 603, and 1 572  $cm^{-1}$ ;  $\delta$  2.42—3.17 (m,  $CH_2 \cdot CH_2$ ), 3.60 (s,  $CO_2Me$ ), 3.82 and 3.88 (s, OMe), and 6.68—7.43 (m, ArH).

*2-(3,4-Dimethoxyphenyl)-5-(3-hydroxypropyl)benzofuran* (24).—Reduction of the methyl ester (23) with lithium aluminium hydride, purification as before (t.l.c.  $R_F$  0.2), and crystallization from aqueous methanol gave the *benzofuran* (24), m.p. 108—110° (softens at 102°) (Found: C, 73.4; H, 6.45.  $C_{19}H_{20}O_4$  requires C, 73.05; H, 6.45%);  $\nu_{\max}$  (KBr) 3 530, 1 603, 1 590, and 1 570  $cm^{-1}$ ;  $\delta$  1.74—2.08 (m,  $\beta-CH_2$ ), 2.45—2.95 (m,  $\alpha-CH_2$ ), 3.67 (t,  $J$  6.5 Hz,  $\gamma-CH_2$ ), 3.87 and 3.93 (s, OMe), and 6.77—7.53 (m, ArH);  $\lambda_{\max}$  (EtOH) 214.5 ( $\epsilon$  33 000), 303sh (25 400), 317 (36 100), and 331 nm (28 100).

*Methyl 4-Hydroxy-5-iodo-3-methoxydihydrocinnamate* (25).—To a solution of dihydroferulic acid (1.29 g) in concentrated ammonium hydroxide solution (130 ml) was added a solution of potassium iodide (5.4 g) and iodine (1.7 g) in water (13.5 ml). The mixture was stirred for 2 h, then

evaporated to dryness under reduced pressure; the residue was redissolved in water (50 ml), acidified, and worked up *via* ether to give a mixture of starting and iodo-substituted acids which was esterified (methanol-sulphuric acid) to afford, after fractional crystallization from aqueous methanol, the *methyl ester* (25) as plates (45 mg), m.p. 113—114° (Found: C, 39.45; H, 3.8.  $C_{11}H_{13}IO_4$  requires C, 39.3; H, 3.9%);  $\delta$  2.45—2.98 (m,  $CH_2 \cdot CH_2$ ), 3.70 (s,  $CO_2Me$ ), 3.87 (s, ArOMe), 6.15 (s, OH), 6.72 (d,  $J$  2 Hz, H-2), and 7.17 (d,  $J$  2 Hz, H-6).

*Coupling of the Acetylide (15) and Methyl 4-Hydroxy-5-iodo-3-methoxydihydrocinnamate* (25).—Reaction of the acetylide (15) (123 mg) and the iodophenol (25) (168 mg) in the usual way yielded a product (182 mg) which on crystallization from methanol gave the methyl benzofuranylpropanoate (16) as needles (135 mg), m.p. 116—120°.

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