

**300.** *The Chemistry of Extractives from Hardwoods. Part XXXVII.<sup>1</sup>  
The Synthesis of Furoguaiacin Ethers*

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The synthesis is described of furoguaiacin and *O*-methylfuroguaiacin ethyl ethers, compounds by which the occurrence of these new furanolignans in the heartwood of *Guaiacum officinale* was recently established. These experiments have been extended to include ethers of two as yet hypothetical furanolignans.

THE existence of various lignans in *Guaiacum officinale*, for example furoguaiacin (I; R = Me, H for Et) has recently been demonstrated by the isolation of their ethers from the mixed methylation and ethylation products of a light-petroleum extract of the heartwood (*lignum vitae*).<sup>1</sup> Furoguaiacin dimethyl ether (I; R = Me, Me for Et) is already known, having been obtained from the action of selenium on eudesmin and on pinoresinol

<sup>1</sup> Part XXXVI, King and Wilson, *J.*, 1964, 4011.

and epipinoresinol dimethyl ethers, and its structure has been fully established by synthesis.<sup>2</sup> The diethyl ether, on the other hand, is a new compound, and is of further significance in establishing the hydroxyl pattern of the parent compound which has not yet been isolated as such.

As a preliminary to synthesising the phenolic precursor, possible routes to the mixed ethers were investigated and a product identical with natural diethylfuroguaiacin was obtained. Two similar methods of preparation were employed, depending on the ring-closure of a suitably substituted  $\gamma$ -diketone. In the first synthesis, the diaroylbutane (II; R = Me) was the objective and this was formed by a Wurtz condensation from  $\alpha$ -bromo-4-ethoxy-3-methoxypropiofenone using copper. The required halide was obtained by two alternative procedures. In the first, 4-ethoxy-3-methoxypropiofenone was prepared by ethylation of the phenolic ketone formed from guaiacol propionate by Fries migration<sup>3</sup> and then directly halogenated. Alternatively, the oily secondary alcohol from *O*-ethylvanillin and ethylmagnesium iodide was used as a source of the necessary propiofenone. A variant of this route, namely the coupling by means of iodine of the sodium derivative of ethyl  $\alpha$ -(4-ethoxy-3-methoxybenzoyl)-propionate to give the bis-keto-ester, a method employed by Evans, Baker, and Hibbert<sup>3</sup> in their synthesis of the dimethyl analogue, was unsuccessful.

The second, more successful, synthesis of diethylfuroguaiacin employed  $\alpha\alpha'$ -di(4-ethoxy-3-methoxybenzoyl)-succinate.<sup>4</sup> Ring closure with acetic anhydride-sulphuric acid gave almost quantitatively the furan dicarboxylic ester (I; R = CO<sub>2</sub>Et) with the complete carbon skeleton of the lignan. Conversion of the ethoxycarbonyl group into methyl was readily performed in three stages, namely reduction with lithium aluminium hydride to the bishydroxymethyl compound, then oxidation with chromic acid-pyridine to the dialdehyde from which the bismercaptal was prepared and, without isolation, desulphurised by Raney nickel. The overall yield of diethylfuroguaiacin (I; R = Me) was 45%.

Among the ethylation products of the petroleum-soluble fraction from the heartwood was one designated methylethylfuroguaiacin. Its identification depends on the isolation from the acidic products of permanganate oxidation of a small amount of ethylvanillic acid, thus denoting the natural occurrence of the phenol (III; R = Me, H for Et). The programme of synthesis was therefore extended to the inclusion of asymmetrically substituted furanolignans.

The preparation of the necessary mixed  $\gamma$ -diketone appeared to be feasible from the reaction of the appropriate  $\alpha$ -sodiopropiofenone and an analogous  $\alpha$ -bromo-ketocompound. Numerous instances of the alkylation and acylation of acetophenone derivatives have been described<sup>5</sup> although phenacylation of this kind is apparently unknown. Following the conditions used for the benzylation of propiofenone,<sup>6</sup> sodium *O*-ethylpropiovanillone and  $\alpha$ -bromopropioveratrone afforded two products separated after alumina chromatography by crystallisation from methanol. Only the minor more-soluble product consisted of the required diketone (IV; R = Me). This was cyclised with methanolic hydrochloric acid to a furan shown by mixed melting point to be identical with ethylmethylfuroguaiacin from the natural source. The principal product, which was unaffected by methanolic acid, has not been identified.

To increase the availability of the required  $\gamma$ -diketone other variations of this synthesis were considered, such as the condensation of veratroyl chloride with the appropriate  $\alpha$ -methylphenacylmalonic ester,<sup>7,8</sup> but difficulties were encountered in the preparation of these esters.

<sup>2</sup> Atkinson and Haworth, *J.*, 1938, 1681.

<sup>3</sup> Evans, Baker, and Hibbert, *J. Amer. Chem. Soc.*, 1948, **70**, 62.

<sup>4</sup> Cf. Bruckhausen and Gerhard, *Ber.*, 1939, **72B**, 830.

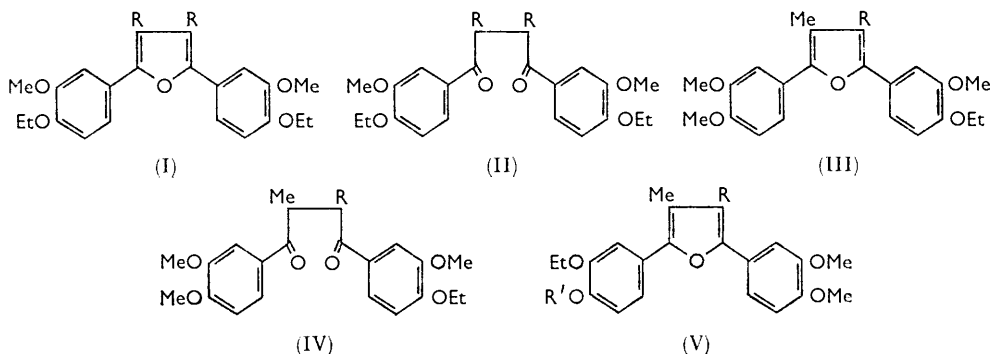
<sup>5</sup> Levine and Fernelius, *Chem. Rev.*, 1954, **54**, 448.

<sup>6</sup> Arcus, Kenyon, and Levin, *J.*, 1951, 407.

<sup>7</sup> Dhekne and Bhide, *J. Indian Chem. Soc.*, 1951, **28**, 504.

<sup>8</sup> Cooke and Dowd, *Austral. J. Sci. Res.*, 1952, **5A**, 760.

Following Haworth and Kelly's synthesis of ethyl  $\alpha,\beta$ -diveratroylpropionate,<sup>9</sup> the condensation of  $\alpha$ -bromopropioveratrone with the sodio-derivative of 4-ethoxy-3-methoxybenzoylacetate in ether was attempted, but modified conditions were required to obtain the new product (IV; R = CO<sub>2</sub>Et). Though non-crystalline it gave, with methanolic hydrogen chloride, the furan ester (III; R = CO<sub>2</sub>Et) as a crystalline solid in 66% yield.



Thereafter, conversion of the ethoxycarbonyl group into methyl was carried out as in the synthesis of diethylfuroguaiacin with the formation of crystalline intermediates in high yield. The product was shown to be ethylmethylfuroguaiacin (III; R = Me) by melting point and ultraviolet spectroscopy.

The wider applicability of this synthesis of unsymmetrical furanolignans was then demonstrated by the preparation of an isomer of ethylmethylfuroguaiacin and of a higher homologue. The synthesis of the former started from *O*-ethylisovanillin, whence a crystalline alcohol was obtained by the action of ethylmagnesium iodide. Oxidation to the ketone and bromination gave  $\alpha$ -bromo-3-ethoxy-4-methoxypropiofenone which reacted with sodium ethyl veratroylacetate to form a gummy condensate. From this product, ring-closure in the usual way gave the furan monocarboxylic ester (V; R = CO<sub>2</sub>Et, R' = Me) as a crystalline solid. Transformation of the carboxylate residue into methyl was effected as in earlier examples. The resulting diaryl-3,4-dimethylfuran (V; R = Me, R' = Me) had m. p. 129° and the ultraviolet spectrum, fluorescence, and sulphuric acid colour reactions of the analogous furanolignans.

The condensation of sodium ethyl veratroylacetate was similarly carried out with the bromo-derivative of 3,4-diethoxypropiofenone obtained by the Friedel-Crafts synthesis from di-*O*-ethylcatechol and propionyl chloride. The condensate, though gummy, gave a crystalline furan ester (V; R = CO<sub>2</sub>Et, R' = Et), the replacement of the ethoxycarbonyl substituent by methyl being accomplished, with the exception of the mercaptal stage, through the usual well-characterised intermediates to the 3,4-dimethylfuran (V; R = Me, R' = Et).

#### EXPERIMENTAL

**4-Ethoxy-3-methoxypropiofenone.**—(i) A solution of 4-hydroxy-3-methoxypropiofenone<sup>3,10</sup> (31 g.) and ethyl sulphate (64 ml.) in methanol (80 ml.) was warmed to *ca.* 50°. With vigorous agitation, potassium hydroxide (25 g.) in water (70 ml.) was added in three portions and, when the reaction had subsided, the mixture was warmed for 10 min. on a water-bath. Dilution with water and cooling in ice gave a solid product which was washed with water, dried, and recrystallised from light petroleum (b. p. 40–60°). The *ketone* was obtained as large rhombic prisms (32.8 g., 91%), m. p. 60–61° (Found: C, 69.5; H, 7.7. C<sub>12</sub>H<sub>16</sub>O<sub>3</sub> requires C, 69.2; H, 7.7%).

The 2,4-dinitrophenylhydrazone formed red prisms, m. p. 168–169° (from ethanol) (Found: C, 55.7; H, 5.0; N, 14.6. C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub> requires C, 55.7; H, 5.15; N, 14.5%),  $\lambda_{\text{max}}$  298, 395 m $\mu$  (log  $\epsilon$  4.04, 4.44).

<sup>9</sup> Haworth and Kelly, *J.*, 1937, 1645.

<sup>10</sup> Coulthard, Marshall, and Pyman, *J.*, 1930, 280.

(ii) When *O*-ethylvanillin (18 g., 0.1 mol.) in dry ether (130 ml.) was slowly added to the cooled efficiently agitated solution of ethylmagnesium iodide (0.2 mol.) in ether (100 ml.), the complex separated immediately. After being refluxed for 30 min. on a water-bath, the mixture was poured into cold (ice) ammonium chloride solution. The ether layer, combined with an ethereal extract of the aqueous layer, was dried ( $\text{MgSO}_4$ ) and evaporated, leaving the product as a thick oil (21 g.). The crude alcohol (17 g.) in acetone (40 ml.) was oxidised with the chromic acid reagent (6*N* with respect to 0)<sup>11</sup> at *ca.* 20° to give the crude ketone (16 g.) which separated from ether-light petroleum (b. p. 40–60°) as large rhombs (9.0 g.), m. p. 59–60°.

(iii) When the Grignard reaction was carried out in boiling benzene and the complex was decomposed by dilute sulphuric acid the products were isoeugenol ethyl ether, b. p. 128–130°/0.05 mm., which separated from light petroleum (b. p. 40–60°) as lustrous scales, m. p. and mixed m. p. 61–62°, and diethyl di-isoeugenol, remaining after the above distillation, needles, m. p. and mixed m. p. 126–127° (from methanol).

$\alpha$ -Bromo-4-ethoxy-3-methoxypropiofenone.—Bromine (9.3 ml.), in chloroform (30 ml.), was added gradually to a solution of 4-ethoxy-3-methoxypropiofenone (34.8 g.) in chloroform (150 ml.). The mixture was set aside for 4 hr. with occasional agitation. Evaporation of the washed (sodium hydrogen carbonate solution and water) and dried ( $\text{MgSO}_4$ ) chloroform solution left a brownish oil, which on being triturated with ether, and diluted with three times the volume of light petroleum (b. p. 40–60°) afforded the bromo-ketone as almost white, feathery needles (30 g., 87%), m. p. 75–76°. Concentration of the mother-liquor gave a further 2.4 g. of product. An analytical sample melted at 76–77° (Found: C, 50.2; H, 5.4; Br, 28.4.  $\text{C}_{12}\text{H}_{15}\text{BrO}_3$  requires C, 50.2; H, 5.3; Br, 27.8%).

The bromo-ketone (0.5 g.) and dinitrophenylhydrazine (0.5 g.) were refluxed in concentrated hydrochloric acid (2.5 ml.), water (2.5 ml.), and ethanol (20 ml.) for 30 min. The osazone separated out after about 15 min., m. p. 233° (from ethyl acetate) (Found: C, 49.8; H, 4.1; N, 18.2.  $\text{C}_{24}\text{H}_{22}\text{N}_8\text{O}_{10}$  requires C, 49.5; H, 3.8; N, 19.2%),  $\lambda_{\text{max}}$  261, 413, 435  $\mu$  (log  $\epsilon$  4.40, 4.67, 4.66).

2,3-Bis-(4-ethoxy-3-methoxybenzoyl)butane (II; R = Me).— $\alpha$ -Bromo-4-ethoxy-3-methoxypropiofenone (11 g.) was heated with freshly precipitated copper (11 g.) in xylene (100 ml.) for 24 hr. The mixture was filtered and the solvent removed under reduced pressure leaving a thick, light brown oil (9.4 g.). Trituration with methanol caused separation of the diketone as a fine white solid. More solvent was added and, when the solid had dissolved and the solution had been filtered, the product separated on cooling (0.55 g., 7%). Recrystallisation from the same solvent afforded needles, m. p. 185–186°. With concentrated sulphuric acid the diketone gave a green colour which rapidly changed to greenish-blue and finally to blue (Found: C, 69.5; H, 7.1; C-Me, 11.9.  $\text{C}_{24}\text{H}_{30}\text{O}_6$  requires C, 69.6; H, 7.2; C-Me, 14.4%),  $\lambda_{\text{max}}$  230, 277, 305  $\mu$  (log  $\epsilon$  4.55, 4.41, 4.34).

The filtrate after removal of the diketone was evaporated under reduced pressure and the residue (8 g.) chromatographed on alumina (180 g.). Elution of the blue fluorescent band (ultraviolet light) with benzene gave a thick oil (5.5 g.) which crystallised on being cooled. Recrystallisation from light petroleum (b. p. 40–60°) gave prisms, m. p. 60–61° which showed no depression on mixing with 4-ethoxy-3-methoxypropiofenone. The 2,4-dinitrophenylhydrazone had m. p. and mixed m. p. 169–170°.

2,5-Bis-(4-ethoxy-3-methoxyphenyl)-3,4-dimethylfuran (I; R = Me).—The diketone (139 mg.) was refluxed in methanolic hydrogen chloride (2.5 ml.) for 1 hr., the furan separating from the mixture (105 mg., 80%). Recrystallisation from methanol afforded fluorescent needles, m. p. and mixed m. p. with the compound from the natural source 151–151.5°. With concentrated sulphuric acid it gave a green colour which slowly became turquoise (Found: C, 72.7; H, 6.8; C-Me, 15.3.  $\text{C}_{24}\text{H}_{28}\text{O}_5$  requires C, 72.7; H, 7.1; C-Me, 15.1%),  $\lambda_{\text{max}}$  250, 326  $\mu$  (log  $\epsilon$  4.10, 4.41).

Ethyl  $\alpha'$ -Di-(4-ethoxy-3-methoxybenzoyl)succinate (II; R =  $\text{CO}_2\text{Et}$ ).<sup>4</sup>—Ethyl 4-ethoxy-3-methoxybenzoylacetate<sup>12</sup> (17.8 g.), in dry ether (300 ml.) and absolute ethanol (20 ml.), was added with efficient stirring to sodium ethoxide prepared from sodium (1.62 g.) in ethanol (50 ml.); stirring was continued for 30 min., most of the sodio-derivative separating out. A solution of iodine (9 g.) in ether (100 ml.) was added dropwise over 30 min. until the mixture became pale brown. It was then washed with water, sodium thiosulphate, and water. As the succinic

<sup>11</sup> Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 461.

<sup>12</sup> Haworth and Kelly, *J.*, 1936, 998.

*ester* began to crystallise out at this stage, the ethereal solution was refrigerated overnight. The prisms (7.3 g.) were collected and the dried ( $\text{MgSO}_4$ ) filtrate evaporated to give a honey-coloured glass (6 g.). Recrystallisation of a small amount of the crystalline fraction yielded colourless prisms, m. p. 162–163° (Found: C, 63.1; H, 6.3.  $\text{C}_{28}\text{H}_{34}\text{O}_{10}$  requires C, 63.4; H, 6.4%).

*Diethyl 2,5-Di-(O-ethylvanillyl)furan-3,4-dicarboxylate* (I; R =  $\text{CO}_2\text{Et}$ ).—The crystalline bis-keto-ester (11.0 g.) was dissolved in warm acetic anhydride (40 ml.) concentrated sulphuric acid (1 drop) added, and the brown solution left for 3 hr. on a gently boiling water-bath. Water was added to the cooled mixture and the crystalline furan separated after several hours. After thorough washing with water and drying *in vacuo* the crude product (10.4 g., 95%) was recrystallised from methanol affording the analytically pure *furan diester* as silky, fluorescent needles, m. p. 91–92° (Found: C, 65.7; H, 6.1.  $\text{C}_{28}\text{H}_{32}\text{O}_8$  requires C, 65.7; H, 6.3%).

The *diacid*, obtained by hydrolysis of the diester with 10% methanolic potassium hydroxide, crystallised from methanol as yellow prisms, m. p. 215° (Found: C, 63.1; H, 5.5.  $\text{C}_{24}\text{H}_{24}\text{O}_8$  requires C, 63.2; H, 5.3%).

*2,5-Di-(O-ethylvanillyl)-3,4-bishydroxymethylfuran* (I; R =  $\text{CH}_2\text{OH}$ ).—The diester (10 g.), in dry ether (300 ml.), was added during 15 min. to a suspension of lithium aluminium hydride (2.0 g.) in dry ether (200 ml.). The complex which formed immediately was stirred at room temperature for 6 hr. The ice-cooled mixture was carefully decomposed by the successive addition of ethyl acetate (15 ml.) and dilute ammonium chloride (100 ml.). The *diol* began to crystallise from the ether layer and, after cooling, was collected, thoroughly washed with water, dried *in vacuo*, and recrystallised from methanol as flat, lustrous needles (6.7 g.). A further 0.5 g. were obtained by concentrating the mother-liquor (total 85%). An analytical sample melted at 135° (Found: C, 67.1; H, 6.5.  $\text{C}_{24}\text{H}_{28}\text{O}_7$  requires C, 67.3; H, 6.5%).

The *diacetate* separated from methanol as closely packed clusters of needles, m. p. 125° (Found: C, 65.5; H, 6.1.  $\text{C}_{28}\text{H}_{32}\text{O}_8$  requires C, 65.6; H, 6.2%).

*2,5-Di-(O-ethylvanillyl)-3,4-diformylfuran* (I; R = CHO).—To the complex of chromium trioxide and pyridine, formed as a suspension by carefully adding the powdered oxide (6.6 g.) to dry pyridine (90 ml.), was added a solution of the above diol (5 g.) in pyridine (80 ml.). After 3 hr. at room temperature, the dark green solid was filtered off, washed with pyridine, and the filtrate and washings were diluted with water (2 l.) which precipitated the *dialdehyde* as an orange-yellow solid (3.9 g., 78%). Recrystallisation from methanol afforded orange needles, m. p. 158° (Found: C, 67.9; H, 5.7.  $\text{C}_{24}\text{H}_{24}\text{O}_7$  requires C, 67.8; H, 5.7%).

The *dioxime* formed prisms, m. p. 186–188° (from aqueous methanol) (Found: C, 63.2; H, 5.7; N, 6.2.  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_7$  requires C, 63.4; H, 5.7; N, 6.2%).

*2,5-Di-(O-ethylvanillyl)-3,4-dimethylfuran* (I; R = Me).—The dialdehyde (0.3 g.) was added during 30 min. to a mixture of anhydrous zinc chloride (0.1 g.) anhydrous sodium sulphate (0.1 g.), and ethanethiol (2 ml.), cooled in an ice-bath. The mixture was refrigerated for 36 hr., left at room temperature for 3 hr., poured into ice-water, and extracted with chloroform. On evaporation, the dried ( $\text{MgSO}_4$ ) extract gave a thick gum (0.48 g.) which was refluxed in ethanol (60 ml.) and Raney nickel (*ca.* 10 g.) for 3 hr. The hot mixture was filtered through a layer of Hifo and the residue washed with boiling ethanol. Filtrate and washings were combined and, on cooling, the *furan* crystallised out as flat, lustrous, fluorescent needles (0.24 g., 86%), m. p. 148–150°. The synthetic furan did not depress the melting point of diethylfuroguaiacin, m. p. 151°. An analytical sample, prepared by chromatography on alumina in benzene, crystallised from methanol as flat, fluorescent needles, m. p. 149–150° (Found: C, 72.6; H, 7.2.  $\text{C}_{24}\text{H}_{28}\text{O}_5$  requires C, 72.7; H, 7.1%).

*Ethyl 4-Ethoxy-3-methoxybenzoylmalonate*.<sup>13,14</sup>—Absolute ethanol (5 ml.) and carbon tetrachloride (0.5 ml.) were added to magnesium (5.35 g., 0.22 mol.), and reaction began immediately. The cautious addition of absolute ether (75 ml.) was followed by addition of a solution of malonic ester (35.2 g., 0.22 mol.) in ethanol (20 ml.) and ether (25 ml.) at such a rate that vigorous refluxing was maintained. Refluxing and stirring were continued until almost all the magnesium had dissolved (5 hr.). A solution of *O*-ethylvanilloyl chloride [from the acid (40 g., 0.22 mol.)] in ether (250 ml.) was added during 1 hr., the very pale yellow gummy complex which at first separated out formed a viscous lump. The mixture was stirred and refluxed for a further 1.5 hr. then decomposed by the addition of 10% sulphuric acid. The ethereal layer, with

<sup>13</sup> Cf. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386.

<sup>14</sup> Cf. Drake and Tuemmler, *J. Amer. Chem. Soc.*, 1955, **77**, 1204.

which an ether extract of the aqueous layer was combined, was washed with water and dried ( $\text{MgSO}_4$ ), and on evaporation left a thick oil (70.5 g.) which crystallised on standing. Recrystallisation from 70% ethanol gave the ester as small needles (58.5 g.). A further amount (2.3 g.) was obtained by cooling the mother-liquors (total 91%). An analytical sample melted at 57—58° (Found: C, 60.4; H, 6.3.  $\text{C}_{17}\text{H}_{22}\text{O}_7$  requires C, 60.4; H, 6.5%).

*Ethyl Veratroylmalonate*.—The above method was used to prepare this compound, glistening plates (84%), m. p. 70° (from 50% aqueous ethanol) (Found: C, 59.6; H, 6.1.  $\text{C}_{16}\text{H}_{20}\text{O}_7$  requires C, 59.3; H, 6.2%).

*Reaction of  $\alpha$ -Bromopropioveratrone with the Sodio-derivative of O-Ethylpropiovanillone*.—A suspension of sodamide (0.4 g.) in dry benzene (15 ml.) was added over 2 hr. to a well-stirred and gently refluxing solution of *O*-ethylpropiovanillone (1.94 g.) in benzene (10 ml.) with rigorous exclusion of moisture. As the sodio-derivative began to form, ammonia was evolved and the solution became yellow. Stirring and refluxing were continued for 4 hr. until almost all the sodamide had reacted, then the bromo-ketone<sup>15</sup> (2.73 g.) in dry benzene (20 ml.) was added during 2 hr. The mixture was refluxed and stirred for a further 12 hr., cooled, washed well with water, and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvent left a pale brown gum (3.0 g.) which was chromatographed on alumina (75 g.) in benzene. The benzene eluate gave an almost colourless gum (1.9 g.) from which white crystals (0.9 g.) (A) were obtained on crystallisation from methanol. Two further recrystallisations from methanol afforded needles, m. p. 115—117° (Found: C, 70.4, 70.7; H, 6.6, 6.8%; *M*, 348),  $\lambda_{\text{max}}$  291  $\text{m}\mu$  ( $E_{1\text{cm}}^{1\%}$  670). The substance was recovered unchanged after being refluxed with 5% methanolic hydrogen chloride.

From the mother-liquors of (A) more crystals (B) separated after several days at 0°. Two recrystallisations from methanol afforded lustrous small plates (0.08 g.), m. p. 161°, which, with concentrated sulphuric acid, gave a green colour which changed rapidly to blue. Substance (B) gave a satisfactory analysis for the  $\gamma$ -diketone, 2-veratroyl-4-ethoxy-3-methoxybenzoylbutane (IV; R = Me) (Found: C, 68.8; H, 7.0.  $\text{C}_{23}\text{H}_{28}\text{O}_6$  requires C, 69.0; H, 7.0%).

*Cyclisation of (B)*.—The compound (50 mg.) was refluxed for 1 hr. in methanolic hydrogen chloride (ca. 5%) (2 ml.). The needles which separated on cooling were collected, washed with methanol, and recrystallised from the same solvent to give 2-(3,4-dimethoxyphenyl)-5-(*O*-ethylvanillyl)-3,4-dimethylfuran (III; R = Me) as fluorescent needles, m. p. 139—140°, alone or mixed with the natural product (Found: C, 72.3; H, 6.8.  $\text{C}_{23}\text{H}_{26}\text{O}_5$  requires C, 72.2; H, 6.8%).

*Ethyl 2-(3,4-Dimethoxyphenyl)-5-O-ethylvanillyl-3-methylfuran-4-carboxylate* (III; R =  $\text{CO}_2\text{Et}$ ).—Ethyl 4-ethoxy-3-methoxybenzoylacetate (9.8 g., 0.37 mol.) in absolute ethanol (60 ml.) was added to a solution of sodium ethoxide [from sodium (0.85 g., 0.37 mol.) and absolute ethanol (30 ml.)] and the sodio-derivative began to separate out almost immediately. The bromo-ketone (10.5 g., 0.37 mol.) in ethanol (80 ml.) was then added and the mixture left at room temperature for 4 days. Addition of water precipitated an oil which was isolated with ether as a viscous, almost colourless gum (17.1 g.) which could not be crystallised. The product was dissolved in methanolic hydrogen chloride (ca. 5%) (70 ml.) and the solution refluxed for 1.25 hr. Cooling gave a mass of fluffy needles (12.0 g., 66%), m. p. 88—89° (from methanol). The furan exhibited a brilliant fluorescence in ultraviolet light and gave a negative ferric reaction (Found: C, 68.4; H, 6.4.  $\text{C}_{25}\text{H}_{28}\text{O}_7$  requires C, 68.2; H, 6.4%). The acid was obtained by hydrolysis of the ester with 10% methanolic potassium hydroxide and crystallised in fluffy, pale yellow needles, m. p. 180—181.5° (from methanol) (Found: C, 67.3; H, 5.9.  $\text{C}_{23}\text{H}_{24}\text{O}_7$  requires C, 67.0; H, 5.8%).

2-(3,4-Dimethoxyphenyl)-5-O-ethylvanillyl-4-hydroxymethyl-3-methylfuran (III; R =  $\text{CH}_2\text{OH}$ ).—To a suspension of powdered lithium aluminium hydride (0.9 g., 1 mol. excess) in dry ether (150 ml.), the ester (10 g.) in dry ether (250 ml.) was added during 15 min. with efficient agitation. The mixture was then gently refluxed for 3 hr., cooled, and the excess of reducing agent decomposed by careful addition of ethyl acetate (20 ml.) with vigorous swirling. The addition of water (50 ml.) and dilute hydrochloric acid (50 ml.) followed, whereupon the alcohol began to crystallise from the ether layer. After refrigeration for 3 hr. the product was filtered off, washed with water, and dried *in vacuo*. The crude alcohol (7.8 g.) and a further amount (0.3 g.) obtained by concentrating the ethereal layer of the filtrate were recrystallised from methanol to yield tiny, blue fluorescent needles (7.3 g., 80%), m. p. 141° (Found: C, 69.2; H, 6.6.  $\text{C}_{23}\text{H}_{26}\text{O}_6$  requires C, 69.3; H, 6.5%). The benzoate was obtained as feathery needles, m. p. 118° (from methanol) (Found: C, 71.5; H, 6.1.  $\text{C}_{30}\text{H}_{30}\text{O}_7$  requires C, 71.7; H, 6.0%).

<sup>15</sup> Haworth and Woodcock, *J.*, 1938, 809.

2-(3,4-Dimethoxyphenyl)-5-O-ethylvanillyl-4-formyl-3-methylfuran (III; R = CHO).—To the complex formed by the careful addition of powdered chromium trioxide (2 g.) to dry pyridine (25 ml.) a solution of the above alcohol (3.2 g.) in pyridine (25 ml.) was added. After 2 hr. at room temperature the dark green precipitate was filtered off and washed with pyridine. Filtrate and washings were poured into a large volume of water and after 24 hr. the crystalline, yellow aldehyde was collected, washed well with water, and dried (2.9 g., 91%). Recrystallisation from methanol gave soft, yellow needles, m. p. 121° (Found: C, 69.9; H, 5.8.  $C_{23}H_{24}O_6$  requires C, 69.7; H, 6.1%). The oxime crystallised from methanol as needles (Found: C, 67.3; H, 5.9; N, 3.4.  $C_{23}H_{25}NO_6$  requires C, 67.1; H, 6.1; N, 3.4%).

*Bis(ethyl Mercaptal) of the above Aldehyde.*—The aldehyde (1.5 g.) was slowly added to a cooled mixture of fused zinc chloride (0.3 g.), anhydrous sodium sulphate (0.3 g.), and ethanethiol (10 ml.). The mixture was shaken for 5 min., refrigerated for 24 hr., and, after 4 hr. at room temperature, poured into a separating funnel containing ice and water. Extraction with ether and a little benzene was followed by another ether extraction. Removal of the solvent at ca. 40° under reduced pressure left the mercaptal as a yellow gum which crystallised from methanol as silky needles (1.55 g., 82%), m. p. 86° (Found: C, 64.4; H, 6.8; S, 13.8.  $C_{27}H_{34}O_5S_2$  requires C, 64.5; H, 6.8; S, 12.8%).

2-(3,4-Dimethoxyphenyl)-5-O-ethylvanillyl-3,4-dimethylfuran (III; R = Me).—The mercaptal (0.6 g.) and Raney nickel (ca. 10 g.) were refluxed in 95% ethanol (70 ml.) for 2 hr. The catalyst was filtered through a layer of Hifo and washed several times with boiling ethanol (70 ml.). The filtrate and washings were concentrated to ca. 50 ml. and on slow cooling the fluorescent solution deposited needles (0.3 g., 66%), m. p. 139°, undepressed when mixed with the natural ether, m. p. 140°. Like the natural product the synthetic furan gave, with concentrated sulphuric acid, a vivid green colour which slowly changed to turquoise (Found: C, 72.0; H, 7.9; C-Me, 10.8.  $C_{23}H_{26}O_5$  requires C, 72.2; H, 6.8; 3C-Me, 11.8%),  $\lambda_{max}$  251, 327 m $\mu$  (log  $\epsilon$  4.10, 4.49).

1-(O-Ethylisovanillyl)propan-1-ol.—With efficient agitation a solution of O-ethylisovanillin (19 g., 0.1 mol.) in dry ether (100 ml.) was added to cooled ethylmagnesium iodide (0.2 mol.) in ether (100 ml.) over 30 min.; immediate separation of the complex occurred. After refluxing for 1 hr. on a steam-bath, the mixture was cooled and carefully decomposed by pouring into iced ammonium chloride solution. The ether layer, to which an ether extract of the aqueous layer was added, was dried ( $Na_2SO_4$ ) and evaporated leaving a thick oil (20.7 g.) which crystallised on standing. From ether-light petroleum (b. p. 40–60°) the alcohol crystallised in needles (15.0 g., 71%), m. p. 73.5°, and was used without further purification for the next step. The analytical sample melted at 79° (from methanol) (Found: C, 68.7; H, 8.4.  $C_{12}H_{15}O_3$  requires C, 68.6; H, 8.6%).

O-Ethylpropioisovanillone.—The above alcohol (14.0 g.) in purified acetone (70 ml.) was oxidised by titration with the chromic acid reagent (6N with respect to O) <sup>14</sup> the temperature being kept below 30°; 14 ml. were required. The mixture was diluted with water, refrigerated overnight, and the crystalline ketone was collected, washed well with water, and dried *in vacuo*. The crude product (11.2 g.) was recrystallised from methanol giving prisms (8.4 g., 62%), m. p. 66–67° (Found: C, 69.3; H, 7.8.  $C_{12}H_{16}O_3$  requires C, 69.2; H, 7.7%).

The oxime, needles from aqueous methanol, melted at 98–100° (Found: C, 64.5; H, 7.6; N, 6.6.  $C_{12}H_{17}NO_3$  requires C, 64.6; H, 7.6; N, 6.3%).

$\alpha$ -Bromo-O-ethylpropioisovanillone.—A solution (3 ml.) of bromine (2.4 ml.) in chloroform (10 ml.) was added to the above ketone (10 g.) in chloroform (40 ml.). Decolorisation and evolution of hydrogen bromide began after 30 min., when the remainder of the bromine solution was slowly added. The mixture was left for 3 hr. and shaken intermittently after which the hydrogen bromide was removed in a stream of dry air. The chloroform solution was washed with sodium hydrogen carbonate and water and dried ( $Na_2SO_4$ ). Removal of solvent left a thick oil which rapidly crystallised. Two recrystallisations from ether-light petroleum (b. p. 40–60°) gave the bromo-ketone as white, fluffy needles (9 g., 65%). An analytical sample melted at 91° (Found: C, 50.1; H, 5.1; Br, 27.7.  $C_{12}H_{15}BrO_3$  requires C, 50.2; H, 5.3; Br, 27.8%).

Ethyl 2-(3,4-Dimethoxyphenyl)-5-O-ethylisovanillyl-4-methylfuran-3-carboxylate (V; R =  $CO_2Et$ , R' = Me).—Ethyl veratroylacetate (8.8 g.) in absolute ethanol (50 ml.) was added to sodium ethoxide from sodium (8 g.) and absolute ethanol (40 ml.) and, to the cloudy orange solution thus formed, the bromo-ketone (10 g.) in ethanol (100 ml.) was added. The mixture was shaken for 5 min. and left at room temperature for 4 days. The oil which separated when

the mixture was poured into water was isolated with ether as a honey-coloured gum (15.5 g.). After refluxing in methanolic hydrogen chloride (*ca.* 5%) (50 ml.) for 45 min., the dark brown solution was filtered and on cooling deposited a mass of rosettes (9 g., 60%). An analytical sample melted at 76° (from methanol). The *furan* was insoluble in alkali, gave a negative ferric reaction, and its solution in methanol had an intense blue fluorescence in ultraviolet light (Found: C, 67.9; H, 6.1.  $C_{25}H_{28}O_7$ , requires C, 68.2; H, 6.4%).

Hydrolysis of the ester with 10% methanolic potassium hydroxide gave the *acid*, fluffy pale yellow needles, m. p. 191° (from methanol) (Found: C, 66.8; H, 5.6.  $C_{23}H_{24}O_7$ , requires C, 67.0; H, 5.8%).

2-(3,4-Dimethoxyphenyl)-5-O-ethylisovanillyl-3-hydroxymethyl-4-methylfuran (V; R = CH<sub>2</sub>OH, R' = Me).—A solution of the above ester (8 g.) in dry ether (200 ml.) was added slowly during 15 min. to a suspension of lithium aluminium hydride (0.8 g.) also in dry ether (120 ml.), efficient agitation being maintained throughout. The mixture was refluxed for 4 hr. on a water-bath, cooled in ice, and the excess of reducing agent destroyed by careful addition of ethyl acetate (10 ml.) followed by water and dilute hydrochloric acid. The *alcohol* crystallised from the ethereal solution during this procedure and, after refrigeration for one night, was collected. The crude product was recrystallised from methanol as very pale yellow needles (4.5 g., 62%), m. p. 103—104° (Found: C, 69.5; H, 6.7.  $C_{23}H_{26}O_6$ , requires C, 69.3; H, 6.5%).

2-(3,4-Dimethoxyphenyl)-5-O-ethylisovanillyl-3-formyl-4-methylfuran (V; R = CHO, R' = Me).—The above alcohol (4 g.) in dry pyridine (25 ml.) was added to the complex formed by carefully adding powdered chromium trioxide (2.7 g.) to dry pyridine (30 ml.). The mixture was left at room temperature for 3 hr. and the dark green precipitate filtered off and washed with pyridine. The filtrate and washings were poured into water (500 ml.) and after 24 hr. the yellow *aldehyde* was collected, washed well with water, and dried. Crystallisation of the crude product from ethanol afforded yellow plates (2.3 g., 58%), m. p. 102—103° (Found: C, 69.5; H, 6.7.  $C_{23}H_{24}O_6$ , requires C, 69.7; H, 6.1%).

2-(3,4-Dimethoxyphenyl)-3,4-dimethyl-5-O-ethylisovanillylfuran (V; R = R' = Me).—The above aldehyde (2 g.) was added during 30 min. to a mixture of anhydrous sodium sulphate (0.4 g.), anhydrous zinc chloride (0.4 g.), anhydrous zinc chloride (0.4 g.), and ethanethiol (12 ml.) cooled in ice, the mixture becoming brownish as the aldehyde dissolved. The mixture was shaken thoroughly for 5 min. and refrigerated for 20 hr. After 5 hr. at room temperature the mixture was poured into a separating-funnel containing water and ice. The mercaptal was extracted with a mixture of ether and benzene and the extract was evaporated under reduced pressure without drying, leaving a crystalline residue (2.5 g., 98%). Recrystallisation of a small amount from ethanol gave cream needles, m. p. 127°, which did not give a satisfactory analysis. The mercaptal (2.0 g.) was refluxed with Raney nickel (*ca.* 10 g.) in 90% ethanol (100 ml.) for 4 hr. The catalyst was filtered off, washed with boiling alcohol, and the filtrate and washings were reduced in volume. On cooling, the *furan* separated as needles (1.45 g.). Chromatography in benzene on a small column of alumina gave a white product which recrystallised from methanol to give fluffy needles (1.22 g., 80%), m. p. 129° (Found: C, 72.5; H, 7.0; C-Me, 10.1.  $C_{23}H_{26}O_5$ , requires C, 72.2; H, 6.8; 3C-Me, 11.3%),  $\lambda_{max}$  250, 325 m $\mu$  (log  $\epsilon$  4.14, 4.48). The furan was intensely fluorescent (blue) in ultraviolet light and, with concentrated sulphuric acid, gave a bright green colour which slowly changed to turquoise.

3,4-Diethoxypropiophenone.—A solution of 1,2-diethoxybenzene (39 g.) and propionyl chloride (23 g.) in benzene (50 ml.) was added dropwise over 20 min. to a well-stirred mixture of powdered anhydrous aluminium chloride (40 g.) in benzene (100 ml.). Reaction began immediately and the mixture began to reflux gently with the development of a light red colour which gradually changed to deep blood-red. After being refluxed for 40 min. on a water-bath, the mixture was cooled and decomposed by pouring on to ice and sulphuric acid. The benzene layer and an ether extract of the aqueous layer were evaporated and the residue was steam-distilled to remove unchanged 1,2-diethoxybenzene. The *ketone* was isolated with ether as a colourless oil (25.3 g., 49%), b. p. 119—121°/0.5 mm., which slowly crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave needles (20.6 g.), m. p. 36—39°. For analysis a small amount was distilled from a bulb-tube, b. p. 100—103° (bath)/0.1 mm. (Found: C, 70.4; H, 7.9.  $C_{13}H_{18}O_3$ , requires C, 70.3; H, 8.1%).

The 2,4-dinitrophenylhydrazone was obtained in the usual way as purple needles with a pronounced metallic lustre, m. p. 161—162° (Found: C, 56.7; H, 5.7; N, 14.1.  $C_{19}H_{22}N_4O_8$ , requires C, 56.7; H, 5.5; N, 13.9%).



*α*-Bromo-3,4-diethoxypropiofenone.—The foregoing ketone (13.4 g.) was dissolved in chloroform (50 ml.), bromine (3 ml.) in chloroform (9 ml.) was added gradually, and the mixture set aside for 4 hr. with occasional shaking. Washing with sodium hydrogen carbonate and water was followed by evaporation of the solvent, leaving an oil which crystallised from ether-light petroleum (b. p. 40–60°) to yield needles (13.7 g., 72%). Recrystallisation from the same solvent gave the pure *bromo-ketone*, m. p. 80° (Found: C, 61.7; H, 5.5; Br, 26.5. C<sub>13</sub>H<sub>17</sub>BrO<sub>3</sub> requires C, 61.8; H, 5.7; Br, 26.6%).

*Ethyl 2-(3,4-Dimethoxyphenyl)-5-(3,4-diethoxyphenyl)-4-methylfuran-3-carboxylate* (V; R = CO<sub>2</sub>Et, R' = Et).—*α*-Bromo-3,4-diethoxypropiofenone (5.5 g.) dissolved in absolute ethanol (40 ml.) was added to the sodio-derivative prepared from ethyl veratroylacetate (4.67 g.) in ethanol and sodium ethoxide (15 ml.) [from sodium (0.42 g.)] and the mixture left at room temperature for 4 days, poured into water, and the precipitated oil extracted with ether. Removal of the solvent left a honey-coloured glass (8.0 g.) which could not be crystallised, but, on being refluxed for 1 hr. in *ca.* 5% methanolic hydrogen chloride (30 ml.), gave, after filtration and cooling, clusters of felted needles (4.4 g., 54%). Recrystallisation of a sample from the same solvent gave creamy needles, m. p. 83° (Found: C, 68.6; H, 6.3. C<sub>26</sub>H<sub>30</sub>O<sub>7</sub> requires C, 68.7; H, 6.6%). The *furan ester* exhibited an intense blue fluorescence in ultraviolet light, was insoluble in alkali, and gave a negative ferric reaction.

Hydrolysis of the ester with 10% methanolic potassium hydroxide gave the *acid*, creamy needles, m. p. 169–171° (from methanol) (Found: C, 67.4; H, 5.9. C<sub>24</sub>H<sub>26</sub>O<sub>7</sub> requires C, 67.6; H, 6.1%).

*2-(3,4-Dimethoxyphenyl)-5-(3,4-diethoxyphenyl)-3-hydroxymethyl-4-methylfuran* (V; R = CH<sub>2</sub>OH, R' = Et).—A solution of the above ester (3.5 g.) in dry ether was added dropwise to a suspension of lithium aluminium hydride (0.4 g.) in dry ether (160 ml.) with thorough agitation. The mixture was gently refluxed on a water-bath for 3.5 hr., cooled (ice), and ethyl acetate added to consume the excess of reducing agent. When water and dilute hydrochloric acid were added, the *alcohol* began to crystallise from the ether layer. The mixture was refrigerated overnight and the product collected, washed well with water, and dried. The crude alcohol (3.0 g., 93%) and a further amount (0.2 g.) obtained by concentration of the dried ether layer of the filtrate were recrystallised from methanol to give pale yellow needles, m. p. 118–120° (Found: C, 70.0; H, 7.0. C<sub>24</sub>H<sub>28</sub>O<sub>6</sub> requires C, 69.7; H, 6.8%).

*2-(3,4-Dimethoxyphenyl)-5-(3,4-diethoxyphenyl)-3-formyl-4-methylfuran* (V; R = CHO, R' = Et).—The above alcohol (2.9 g.) in pyridine (30 ml.) was added to a suspension of the chromium trioxide-pyridine complex obtained by the careful addition of the oxide (2.0 g.) to pyridine (25 ml.), and the mixture set aside at room temperature for 2.5 hr. The dark green precipitate was filtered off and washed with pyridine, and the washings and filtrate were poured into water (400 ml.) and left for 18 hr. The orange-yellow aldehyde was collected, washed well with water, and dried *in vacuo* giving a crude product (2.4 g.) which crystallised from methanol as yellow needles (2.1 g., 72%), m. p. 120–121° (Found: C, 70.2; H, 6.2. C<sub>24</sub>H<sub>26</sub>O<sub>6</sub> requires C, 70.2; H, 6.3%).

*2-(3,4-Dimethoxyphenyl)-5-(3,4-diethoxyphenyl)-3,4-dimethylfuran* (V; R = Me, R' = Et).—The above aldehyde (2 g.) was slowly added to a mixture of powdered anhydrous zinc chloride (0.4 g.), anhydrous sodium sulphate (0.4 g.), and ethanethiol (8 ml.) cooled in an ice-bath. The mixture was well shaken for 5 min. and refrigerated for 24 hr. After 3 hr. at room temperature it was poured into ice-water and extracted with chloroform. The yellow extract was filtered from a small amount of flocculent precipitate, dried, and on evaporation left a yellow gum (2.2 g.) which could not be crystallised. The gum was refluxed with Raney nickel (*ca.* 15 g.) in 90% ethanol (100 ml.) for 2 hr. The catalyst was filtered off through a layer of Hiflo, washed with boiling ethanol, and the filtrate and washings were concentrated to *ca.* 40 ml. On cooling, the product separated as flat needles (1.2 g.). Chromatography in benzene on a short column of alumina afforded a fluorescent crystalline product which, on recrystallisation from methanol, gave the analytically pure *furan* (0.9 g., 47%), m. p. 122.5° (Found: C, 72.6; H, 6.8; C-Me, 15.2. C<sub>24</sub>H<sub>28</sub>O<sub>5</sub> requires C, 72.7; H, 7.1; 4C-Me, 15.1%), λ<sub>max.</sub> 249, 326 mμ (log ε 4.14, 4.49). The furan exhibited an intense blue fluorescence in ultraviolet light and with concentrated sulphuric acid gave a bright green colour which slowly changed to turquoise.

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