

A Novel Photochemical Structural Inversion: The First Methoxy-Hydroxymethyl Isomerization

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Photolysis of 4-methoxybenzo[*b*]furan-3(2*H*)-ones provides the first example of structural inversion of an aryl-methoxy-group to the corresponding hydroxymethyl function. Suitable structural parameters permit subsequent rearrangement of the heterocyclic ring to 5-hydroxyisochroman-4-ones. By contrast photolysis of the isomeric 4-methoxybenzo[*b*]furan-2(3*H*)-one leads directly to the deoxybenzoin analogue.

THE photochemical equivalent of a benzilic acid rearrangement of the 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-one (1) in an aqueous polar solvent system was recently demonstrated by us.¹ We now report the first structure inversion of a phenolic methoxy-function into the isomeric hydroxymethyl function to form a benzyl alcohol based on the photolysis of the same compound in an aprotic medium.

RESULTS AND DISCUSSION

Irradiation of 2-hydroxy-4,6-dimethoxy-2-(*p*-methoxybenzyl)benzo[*b*]furan-3(2*H*)-one [4,4',6-tri-*O*-methylmaesopsin (1)] in anhydrous ethyl acetate gives, besides the previously described¹ benzofuran-2-one (16) (12%), the 3-benzyl-3,5-dihydroxyisochroman-4-one analogue (10) (21%); under similar conditions the full methyl ether, 2,4,4',6-tetra-*O*-methylmaesopsin (2), affords the 4-hydroxymethylbenzofuran-3-one (7) and the α -methoxy-*cis*-chalcone (14), both in low yield (13 and 15%, respectively).

Whereas the chalcone (14) probably arises from a zwitterionic intermediate state of the diradical formed by C-2-O bond homolysis as was previously indicated by us,¹ the slow formation of the 4-hydroxymethylbenzofuran-3-one (7) and 5-hydroxyisochroman (10) may be best rationalized by invoking a free-radical mechanism (Scheme). Hydrogen-transfer from the C-4 methoxy-group *via* a seven-membered cyclic transition state (3) to the n, π^* triplet carbonyl[†] presumably leads to a spiro-oxiran intermediate (4) which could rearrange *via* a six-membered transition state to the 4-hydroxymethyl derivatives [intermediate (5)] and (7). Of these the putative 2-hydroxy-analogue [(5)] is, however, subject to rapid fission of the heterocyclic ring, leading, presumably *via* an α -diketone intermediate (9), to the 5-hydroxyisochroman-4-one (10) by cyclization involving the pre-formed benzylic hydroxy-function. Such formation of the six-membered ring would be favoured by the intramolecular hydrogen bond in the α -diketone (9). Photolysis of the thermally stable 4-hydroxymethyl-2-methoxybenzofuran-3-one (7) under conditions facilitating hydrolysis of the acetal moiety¹ {i.e. (7) \rightarrow [(5)], *cf.* analogous (2) \rightarrow (1) in aqueous acetone¹} also

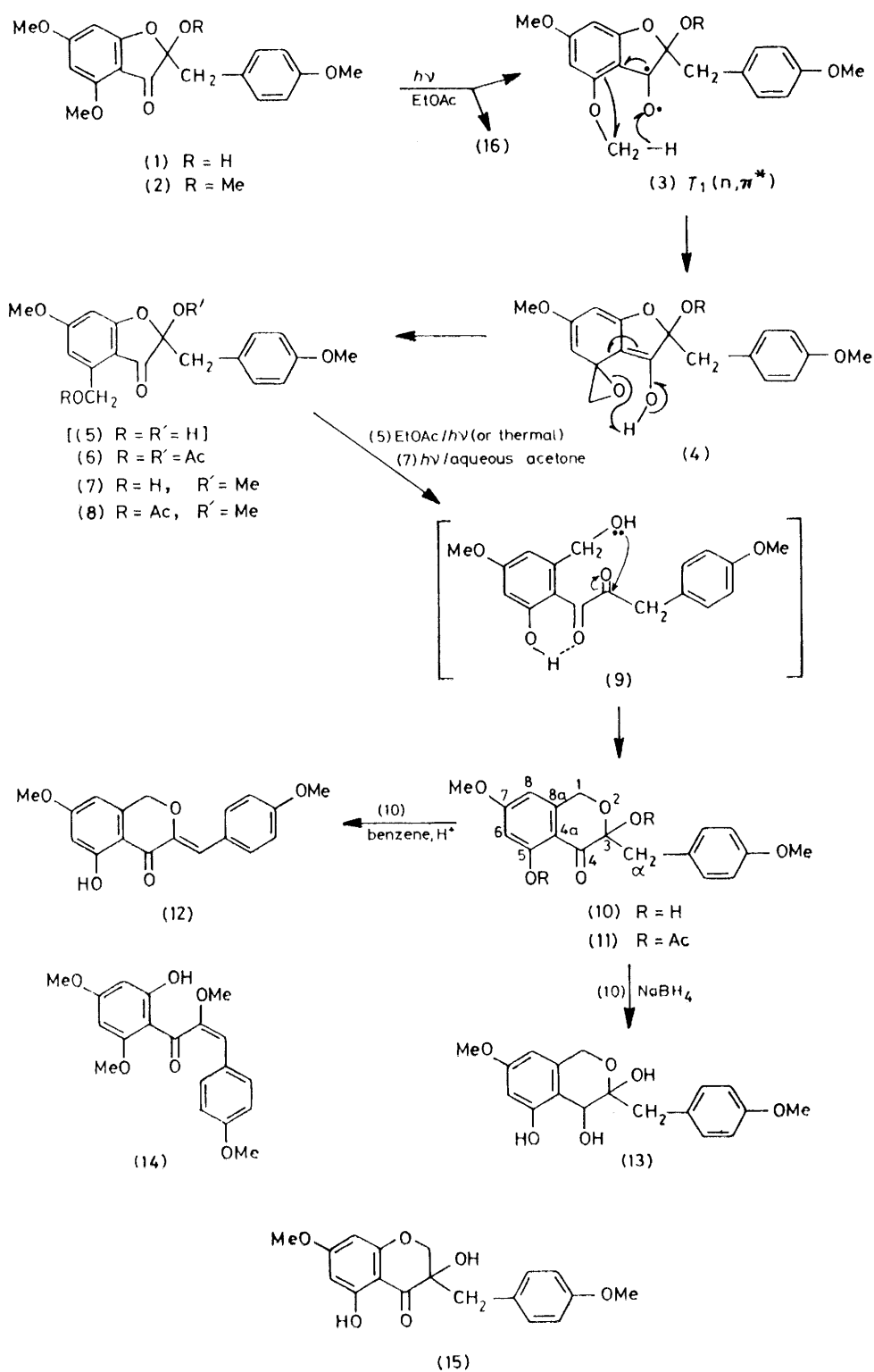
leads to the 5-hydroxyisochroman-4-one (10). Since the presence of the hemiacetal [(5)] could not be substantiated by t.l.c. monitoring, thermal ring opening followed by irreversible conversion to the isochroman-4-one (10) by a ground-state process {i.e. [(5)] $\xrightleftharpoons{\text{heat}}$ [(9)] $\xrightarrow{\text{heat}}$ (10)} might represent a plausible alternative to the proposed two-quantum postulate. This arylmethoxy-hydroxymethyl rearrangement may be considered as the oxygen analogue of the photolytic side-chain isomerization encountered with *t*-butyl-*p*-quinones.²

The influence of solvent polarity on the dual course of these photolytic rearrangements [i.e. the benzilic acid-type rearrangement (1) \rightarrow (16) *vs.* 'methoxy-inversion' (2) \rightarrow (7) and 'methoxy-inversion' plus rearrangement (1) \rightarrow (10), respectively] parallels the dependence of the nature of the excited states of acetophenones in various solvents³ (i.e. polar- π, π^* triplet; non-polar- n, π^* triplet).

Proof of structure of the 3-benzyl-3-hydroxyisochroman-4-one (10) is provided by its dehydration with *p*-toluenesulphonic acid in anhydrous benzene to the α -alkoxy-chalcone analogue (12), and by its smooth reduction to the triol (13) with sodium borohydride, while acetylation with acetic anhydride-pyridine affords two diacetates (6) and (11). Formation of the former, the 2-acetoxy-4-(acetoxymethyl)benzofuran-3-one (6), is explicable in terms of the acidity of the tertiary hydroxy-proton in the parent compound (10) enhanced by adjacent heterocyclic oxygen and carbonyl functions; pyridine is sufficiently basic for abstraction of this proton and subsequent ring-opening to an intermediate α -diketone of type (9), which affords the benzofuranone (6) following successive re-cyclization and acetylation.

The ¹H n.m.r. spectra of these 'methoxy-inverted' derivatives, either as hydroxymethyl [(6)–(8)] or cyclic [(10)–(13)] analogues exhibit characteristic secondary benzylic splitting of their *ortho*-ring-A protons (*J ca.* 0.8 Hz). This convincingly differentiates this new class of compound from the closely related but dissimilar isomeric homoisoflavonoid (15), obtained synthetically by the method of Heller *et al.*⁴ Diagnostic chemical-shift comparisons of the isochroman (10) and the corresponding homoisoflavonoid derivative (15) in both ¹³C [C-3 for (10) δ 95.77 (s), for (15) 71.5 (s)] and ¹H n.m.r.

[†] Complete quenching of the reaction by naphthalene is considered as indicative of the triplet nature of the excited carbonyl.



spectra [H-1 for (10) δ 4.50, for (15) 5.03 (J 15.3); H-2 for (10) 3.97, for (15) 4.16 (J 11.2)] are in line with their structural differences.

Considering the facile photo-enolization of *o*-alkylbenzophenones⁵ and related compounds,⁶ logical extension of this novel photochemical methoxy-rearrangement to *o*-methoxyacetophenones was attempted, aimed at furnishing a general method of access to aromatic hydroxymethyl functionality. 2,4,6-Trimethoxyacetophenone under identical conditions, however, gives no reaction, presumably because either the stereoelectronic

for 48 h, while acetylations were carried out with acetic anhydride-pyridine. M.p.s were determined with a Reichert hot-stage apparatus. Hydrogen-1 and ¹³C (20.1 MHz) n.m.r. spectra were recorded on a Bruker WP-80 spectrometer for solutions in CDCl₃ with SiMe₄ as internal standard, and mass-spectral data on a Varian CH-5 instrument. Analyses (C and H) were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, Germany.

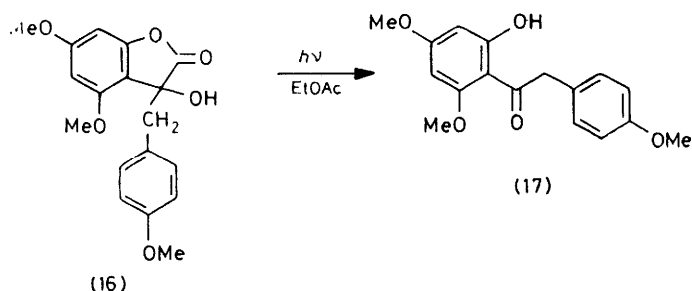
Photoreactions of Benzofuranones (Maesopsin Derivatives).—(a) 2-Hydroxy-4,6-dimethoxy-2-(*p*-methoxybenzyl)benzo[b]furan-3(2H)-one (1). The benzofuranone (1) (400 mg) in anhydrous ethyl acetate (150 ml) was irradiated for 25 h, the solvent evaporated, and the mixture separated by p.l.c. with benzene-acetone (19 : 1). Three bands, R_F 0.26 (71 mg, red), 0.31 (41 mg, olive-green), and 0.40 (70 mg, red) were obtained.

The first fraction consisted of unconsumed starting material, while the R_F 0.31 band gave (\pm)-3-hydroxy-4,6-dimethoxy-3-(*p*-methoxybenzyl)benzo[b]furan-2(3H)-one (16) as an amorphous pale yellow solid, with spectral data identical to that of an authentic sample.¹

Crystallization of the R_F 0.40 fraction from hexane-ethyl acetate (9 : 1) afforded (\pm)-3,5-dihydroxy-3-(*p*-methoxybenzyl)-7-methoxyisochroman-4-one (10) as hexagonal needles, m.p. 108–109 °C; m/e 330 (M^+ , 1.1%), 312(8), 267(7.1), 210(5.3), 209(53), 181 (7.7), 164(11.5), 137(5.1), 122(52), and 121(100); δ_H 10.68 (s, 5-OH), 7.16 (d, 2'- and 6'-H, J 8.5 Hz), 6.75 (d, 3'- and 5'-H, J 8.5 Hz), 6.22 (d, 6-H, J 2.0 Hz), 6.06 (dd, 8-H, J 2.0 and 0.8 Hz), 5.03 (dd, 1-H_{eq}, J 15.3 and 0.8 Hz), 4.50 (d, 1-H_{ax}, J 15.3 Hz), 3.76 (s, OMe), 3.73 (s, OMe), 3.38 and 3.06 (dd, α -CH₂, J 13.6 Hz), and 2.61 (s, 3-OH); δ_C 191.5 (s, 4-C), 164.8, 163.9, 157.2 (s, aromatic oxygenated carbon atoms), 142.3 (t, 8a-C, J 3.0 Hz), 130.6 (dq, 2'- and 6'-C, J 157, 12, and 5 Hz), 123.8 (m, 1'-C), 112.5 (dd, 3'- and 5'-C, J 157 and 5 Hz), 105.7 (m, 4a-C), 101.4 (d, 8-C, J 162 Hz), 98.3 (dq, 6-C, J 157, 7.5, and 5 Hz), 95.77 (d, 3-C, J 3.75 Hz), 60.3 (td, 1-C, J 143.8 and 5 Hz), 55.0 (q, OMe, J 142.5 Hz), 54.7 (q, OMe, J 142.5 Hz), and 39.8 (tt, α -C, J 127.5 and 3.75 Hz) (Found: C, 65.4; H, 5.6. C₁₈H₁₈O₆ requires C, 65.5; H, 5.5%).

Acetylation of the isochroman-4-one (10) (50 mg) followed by p.l.c. separation [benzene-ethyl acetate (19 : 1)] gave two fractions, R_F 0.39 (30 mg, red), and 0.43 (14 mg, red). Crystallization of the latter from methanol afforded 2-acetoxy-4-(*acetoxy*methyl)-6-methoxy-2-(*p*-methoxybenzyl)-benzo[b]furan-3(2H)-one (6) as white cubic needles, m.p. 112–113 °C; δ 7.02 (d, 2'- and 6'-H, J 8.5 Hz), 6.63 (d, 3'- and 5'-H, J 8.5 Hz), 6.42 (m, 5-H), 6.21 (d, 7-H, J 2.0 Hz), 5.26 (s, CH₂O), 3.75 (s, OMe), 3.66 (s, OMe), 3.22 and 2.99 (dd, α -CH₂, J 13.75 Hz), 2.12 (s, 2-OAc), and 2.03 (s, CH₂OAc); m/e 414 (M^+ , 8.3%), 355(31), 354(47), 313(17.6), 312(35), 311(47), 251(24), 210(12.9), 209(45), 191(27), 182(21), 181(47), 180(17), 164(34), and 121(100). The R_F 0.39 fraction gave the *diacetate* (11) as an amorphous powder; δ 7.04 (d, 2'- and 6'-H, J 8.5 Hz), 6.65 (d, 3'- and 5'-H, J 8.5 Hz), 6.43 and 6.37 (m, 6- and 8-H), 5.16 (dt, 1-H_{eq}, J 14.5 and 0.8 Hz), 4.59 (d, 1-H_{ax}, J 14.5 Hz), 3.78 (s, OMe), 3.69 (s, OMe), 3.22 and 2.98 (dd, α -CH₂, J 13.25 Hz), 2.37 (s, 5-OAc), and 2.03 (s, 3-OAc); m/e 414 (M^+ , 2.8%), 356(14.1), 355(37), 354(52), 314(13.1), 313(37), 312(38), 311(14.6), 285(12.9), 284(34), 269(15), 251(37), 223(33), 210(36), 209(71), 206(18), 181(39), 166(11.5), 165(37), 164(66), 148(32), 135(25), 122(40), and 121(100).

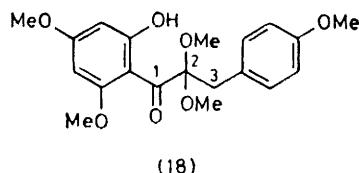
The isochroman-4-one (10) (27 mg) in ethanol (10 ml) was



requirements (*i.e.* planarity between carbonyl and *o*-methoxy-function) are not met, in contrast to the maesopsin analogues (1) and (2), or the predominant π, π^* nature of the excited methoxyacetophenone does not permit hydrogen abstraction.

Irradiation of the isomeric 3-benzyl-3-hydroxybenzo[b]furan-2(3H)-one (16) in anhydrous ethyl acetate results in decarbonylation of the heterocycle *via* a Norrish type I process, leading to the deoxybenzoin (17), in complete contrast with the behaviour of the benzo[b]furan-3(2H)-one analogues (1) and (2).

An interesting observation made during the course of



the above work is that under identical conditions (irradiation at 350 nm; ethyl acetate solution) the α -methoxy-*cis*-chalcone (14) and 3-aryl-2,2-dimethoxypropionophenone (18)⁷ are converted into one of the starting materials in the above sequences, tetra-*O*-methylmaesopsin (2), in 58 and 22% yields, respectively.

EXPERIMENTAL

Irradiation of compounds in anhydrous ethyl acetate in a quartz vessel was carried out in a slow current of nitrogen (*ca.* 1 ml min⁻¹) in a Rayonet photochemical reactor at 350 nm. T.l.c. was performed on DC-Plastikfolin Kieselgel 60 F₂₅₄ (0.25 mm) and the plates sprayed with H₂SO₄-HCHO (40 : 1) after development. Colours indicated are those obtained with this reagent. Preparative plates [Kieselgel PF₂₅₄ (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol-diethyl ether at -15 °C

stirred for 2 h at room temperature with sodium borohydride (5 mg). The mixture was poured onto ice containing 3M hydrochloric acid (5 ml) and extracted with ether (3 × 25 ml). The extract was washed with water (3 × 25 ml) and the solvent evaporated. Crystallization from methanol afforded the *triol* (13) (21 mg) as white needles, m.p. 135–137 °C; δ ($^{13}\text{H}_6$)acetone 7.28 (d, 2'- and 6'-H, J 8.5 Hz), 6.69 (d, 3'- and 5'-H, J 8.5 Hz), 6.2 (d, 6-H, J 2 Hz), 6.03 (m, 8-H), 4.78 and 4.47 (dd, 1-CH₂, J 15.5 Hz), 4.28 (s, 4-H), 3.71 (s, OMe), 3.64 (s, OMe), and 3.25 and 2.89 (dd, α -CH₂, J 13.25 Hz); m/e 314 (M^+ - 18, 31%), 312(10), 194(12.8), 193(39), 191(22), 183(18.9), 167(24), 166(41), 165(72), 164(25), 137(19.4), 135(22), 123(19.8), 122(46), and 121(100).

The isochroman-4-one (10) (50 mg) in anhydrous benzene (50 ml) was refluxed for 5 min with toluene-*p*-sulphonic acid (10 mg). The mixture was washed with water (3 × 25 ml) and the solvent evaporated. P.l.c. separation [benzene-acetone (17 : 3)] followed by crystallization from acetone gave the *trans-chalcone analogue* (12), R_F 0.43, red (9 mg) as light-yellow needles, m.p. 144–145 °C; δ 10.0 (s, 5-OH), 7.69 (d, 2'- and 6'-H, J 8.5 Hz), 6.91 (s, α -H), 6.78 (d, 3'- and 5'-H, J 8.5 Hz), 6.28 (d, 6-H, J 2.0 Hz), 6.13 (m, 8-H), 5.05 (br s, 1-CH₂), 3.80 (s, OMe), and 3.78 (s, OMe); m/e 312 (M^+ , 88%), 284(28), 269(27), 176(11.5), 165(12.1), 164(100), 156(10.1), 136 (17.1), and 121(10.4).

(b) **2,4,6-Trimethoxy-2-(p-methoxybenzyl)benzo[b]furan-3(2H)-one** (2). The benzofuranone (2) (1 g) in anhydrous ethyl acetate (500 ml) was irradiated for 20 h. Evaporation of the solvent followed by p.l.c. [benzene-acetone (17 : 3)] afforded three fractions, R_F 0.71 (53 mg), red-brown; 0.53 (600 mg) red; and 0.44 (60 mg), red-brown.

Crystallization of the former from methanol gave 2'-hydroxy- α ,4,4',6'-tetramethoxy-*cis*-chalcone (14) as light-yellow needles, m.p. 114–115 °C (lit.⁷ 116 °C). Spectral data were identical to those reported. The R_F 0.53 band was unchanged starting material.

The R_F 0.44 fraction afforded 4-hydroxymethyl-2,6-dimethoxy-2-(p-methoxybenzyl)benzo[b]furan-3(2H)-one (7) as a colourless amorphous solid; δ 7.03 (d, 2'- and 6'-H, J 8.5 Hz), 6.59 (3'- and 5'-H, J 8.5 Hz), 6.31 (m, 5-H), 6.22 (d, 7-H, J 2.0 Hz), 4.59 (d, CH₂OH, J 7.25 Hz), 4.19 (t, CH₂OH, J 7.25 Hz), 3.79 (s, OMe), 3.66 (s, OMe), 3.22 (s, 2-OMe), and 3.19 and 3.0 (dd, α -CH₂, J 13.75 Hz); m/e 344 (M^+ , 21%), 224(10.7), 223(80), 180(16.2), 135(10.6), 122(18.6), and 121(100) (Found: C, 66.3; H, 5.8. C₁₈H₂₀O₆ requires C, 66.3; H, 5.9%).

Acetylation of the benzofuran-3-one (7) followed by crystallization from methanol gave the *mono-acetate* (8) as white platelets, m.p. 104–105 °C; δ 7.0 (d, 2'- and 6'-H, J 8.5 Hz), 6.59 (d, 3'- and 5'-H, J 8.5 Hz), 6.36 (m, 5-H), 6.23 (d, 7-H, J 2.0 Hz), 5.37 and 5.17 (dd, CH₂OAc, J 14.5 Hz), 3.78 (s, OMe), 3.66 (s, OMe), 3.20 (s, 2-OMe), 3.16 and 2.97 (dd, α -CH₂, J 13.5 Hz), and 1.94 (s, OAc); m/e 386

(M^+ , 7.7%), 279(5.3), 265(42), 223(10.4), 191(5.3), 167(5.8), 149(32), 122(10.5), and 121(100).

Irradiation of the benzofuran-3-one (7) (40 mg) in acetone-water (1 : 1) (100 ml) for 6 h and subsequent p.l.c. separation gave the isochroman-4-one (10) (5 mg) with spectral data identical to those previously described.

Related Photolytic Transformations.—2-(p-Methoxyphenyl)-2'-hydroxy-4',6'-dimethoxyacetophenone (17). The benzofuran-2-one (16) (40 mg) in anhydrous ethyl acetate (50 ml) was irradiated for 9 h at 300 nm. Evaporation of solvent and p.l.c. separation in benzene-ethyl acetate (19 : 1) gave the deoxybenzoin (17) (10 mg), R_F 0.54 as white needles (from acetone), m.p. 87–88 °C (lit.⁸ 88–89 °C); δ 8.66 (s, OH), 7.03 and 6.73 (2-, 6-, 3-, and 5-H, J 8.5 Hz), 5.97 and 5.83 (dd, 3'- and 5'-H, J 2.5 Hz), 4.19 (s, CH₂), 3.78 (s, OMe), 3.75 (s, OMe), and 3.73 (s, OMe); m/e 302 (M^+ , 14.9%), 181(100), and 121(5.3).

2,4,6-Trimethoxy-2-(p-methoxybenzyl)benzo[b]furan-3(2H)-one (2). The 2'-hydroxy- α ,4,4',6'-tetramethoxy-*cis*-chalcone (14) (100 mg) in dry ethyl acetate (50 ml) was irradiated for 24 h. P.l.c. separation [benzene-ethyl acetate (17 : 3)] gave the benzofuranone (2) (35 mg), R_F 0.60, m.p. 130–131 °C (from methanol) (lit.⁹ 130–131 °C).

Similar treatment of (\pm)-2'-hydroxy-3-(4-methoxyphenyl)-2,2,4',6'-tetramethoxypropionophenone (18) (100 mg) also gave the benzofuranone (2) (17 mg).

Synthesis of the Homoisoflavanone (16).—An authentic specimen of the homoisoflavanone (16) was obtained *via* the method of Heller *et al.*⁴

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