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 arylmethoxy-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 described [1] 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).

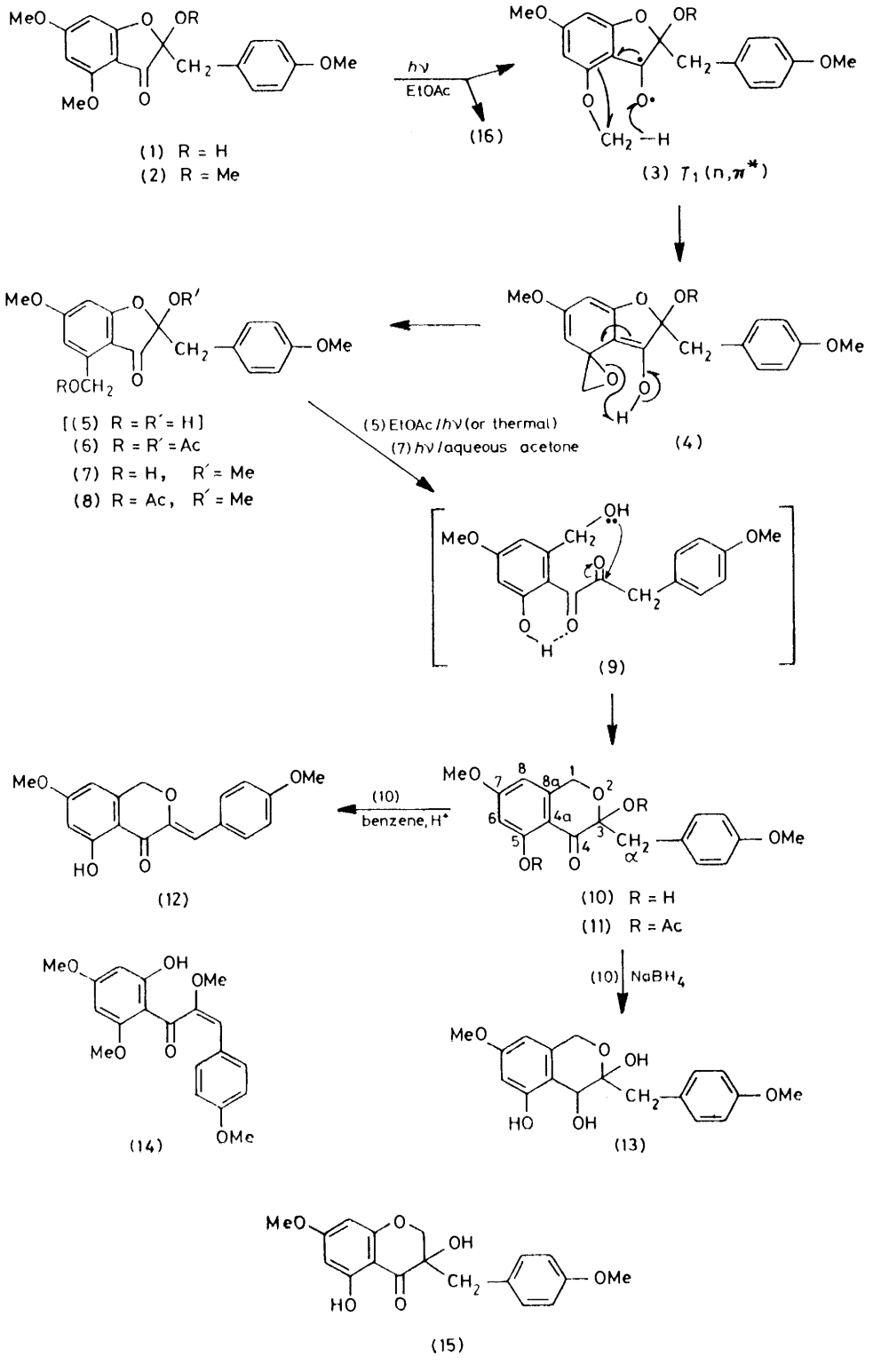
Whereas the chalcone (14) probably arises from a zwitterionic intermediate state of the diradical formed by C-2–O bond homolysis as was previously indicated by us,[1] the slow formation of the 4-hydroxymethylbenzofuran-3-one (7) and 5-hydroxyisochroman (10) may be best rationalized by invoking a free-radical 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 preformed 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 moiety [1] {i.e. (7) ⟶ [(5)], *cf.* analogous (2) ⟶ (1) in aqueous acetone [1]} 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)] $\overset{\text{heat}}{\rightleftharpoons}$ [(9)] $\overset{\text{heat}}{\longrightarrow}$ (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) ⟶ (16) *vs.* 'methoxy-inversion' (2) ⟶ (7) and 'methoxy-inversion' plus rearrangement (1) ⟶ (10), respectively] parallels the dependence of the nature of the excited states of acetophenones in various solvents [3] (*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.

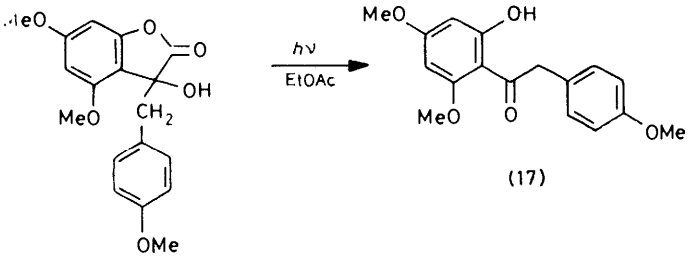
The ^{1}H n.m.r. spectra of these 'methoxy-inverted' derivatives, either as hydroxymethyl [(6)—(8)] or cyclic [(10)—(13)] analogues exhibit characteristic secondary benzylic splitting of their *ortho*-ring-A protons (*J ca.* 0.8 Hz). This convincingly differentiates this new class of compound from the 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 ^{13}C [C-3 for (10) δ 95.77 (s), for (15) 71.5 (s)] and ^{1}H n.m.r.

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


(1) R = H
(2) R = Me
hν
EtOAc
(16)
(3) $T_1(n,\pi^*)$
(4)
[(5) R = R′ = H]
(6) R = R′ = Ac
(7) R = H, R′ = Me
(8) R = Ac, R′ = Me
(5) EtOAc/hν (or thermal)
(7) hν/aqueous acetone
(9)
(10) R = H
(11) R = Ac
(10) benzene, H+
(12)
(10) NaBH4
(13)
(14)
(15)

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*-alkylbenzophenones [5] 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

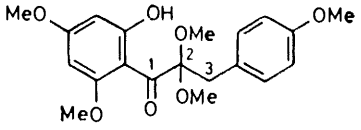


(16) (17)

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(3*H*)-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(2*H*)-one analogues (1) and (2).

An interesting observation made during the course of



(18)

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-dimethoxypropiophenone (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 F_{254} (0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40 : 1) after development. Colours indicated are those obtained with this reagent. Preparative plates [Kieselgel PF_{254} (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 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 ^{13}C (20.1 MHz) n.m.r. spectra were recorded on a Bruker WP-80 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ 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 Gummbersbach 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 (±)-3-hydroxy-4,6-dimethoxy-3-(*p*-methoxybenzyl)benzo[*b*]furan-2(3*H*)-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 (±)-*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-CH_2, *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. $C_{18}H_{18}O_6$ 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-(-acetoxymethyl)-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, CH_2O), 3.75 (s, OMe), 3.66 (s, OMe), 3.22 and 2.99 (dd, α-CH_2, *J* 13.75 Hz), 2.12 (s, 2-OAc), and 2.03 (s, CH_2OAc); *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-CH_2, *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

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 ([$^2H_6$]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-CH_2, *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-CH_2, *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-CH_2), 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, CH_2OH, *J* 7.25 Hz), 4.19 (t, CH_2OH, *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-CH_2, *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. $C_{19}H_{20}O_6$ 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, CH_2OAc, *J* 14.5 Hz), 3.78 (s, OMe), 3.66 (s, OMe), 3.20 (s, 2-OMe), 3.16 and 2.97 (dd, α-CH_2, *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, CH_2), 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 (±)-2′-hydroxy-3-(4-methoxyphenyl)-2,2,4′,6′-tetramethoxypropiophenone (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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