# The Chemistry of Fungi. Part 77.[1] The Synthesis of Benzophenones from Phthalides: X-Ray Crystallographic Definition of a Novel Isobenzofuran System

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Reduction of 3,6-dimethoxy-4-methylphthalic anhydride gave a mixture of 3,6-dimethoxy-4-methyl-(1; R¹ = H, R² = Me) and 3,6-dimethoxy-5-methyl- (1; R¹ = Me, R² = H) phthalide.

The condensation of 2,6-dimethoxylithiobenzene with phthalides gives the corresponding 2'-hydroxymethyl-2,6-dimethoxybenzophenones. Treatment of 6-acetoxymethyl-2,5-dibenzyloxy-2',6'-dimethoxy-4-methyl-benzophenone (11; R = H) with boron trichloride gives 1-(2-hydroxy-6-methoxyphenyl)-5-methyl-4,7-dioxo-4,7-dihydroisobenzofuran (13; R = H), the structure of which was defined by X-ray analysis. The crystals are monoclinic, space group $P2_1$ with two molecules in a unit cell of dimensions $a$ = 10.818(1), $b$ = 7.752(1), $c$ = 7.808(3)Å, and $\beta$ = 90.28(1)°. The structure was solved by the direct method using 1 257 reflections and refined by full-matrix least-squares calculations to $R$ = 0.053.

DURING earlier investigations [1,2] directed towards the synthesis of the fungal pigments, type (2) from ergot, we condensed 2,6-dimethoxylithiobenzene with anhydrides to yield 2'-carboxybenzophenones of type (5; R = $CO_2$-H). Cyclisation of the corresponding αβ-unsaturated acid (or ester) [type (6)] gave [2] a spiran (7) rather than the requisite hexahydroxanthone [type (8)]. To circumvent this problem we planned to replace the carboxy-group in (6) with a functionalised alkyl residue, as

Attempts to differentiate unequivocally between these isomers by chemical and spectroscopic means were unsuccessful; however, this was achieved indirectly in the sequel.

Demethylation of (1; R¹ = Me, R² = H) using either boron tribromide or hydrobromic acid gave 3,6-dihydroxy-5-methylphthalide which was readily converted into the 3,6-dibenzyl ether. A minor product from the hydrolysis of 3,6-dimethoxyphthalonitrile (3) was 2-formyl-3,6-dimethoxy-4-methylbenzoic acid (4).

Initial experiments showed that 2,6-dimethoxylithiobenzene condensed readily, in high yield with phthalide and 3,6-dimethoxyphthalide to yield the 6-hydroxymethylbenzophenones (12; R = H) and (12; R = OMe) respectively. Finally, 3,6-dibenzyloxy-5-methylphthalide gave the synthon (11; R = H) from which it was planned to obtain (9; R = $CH_2OH$) by standard methods. However, catalytic removal of the benzyl



(1)



(2)



(3)



(4)
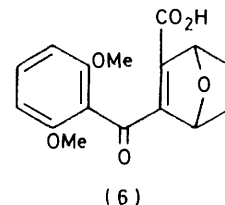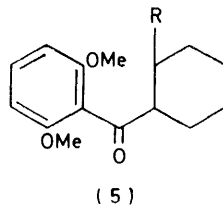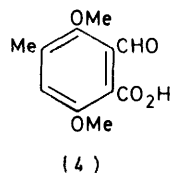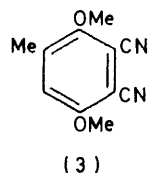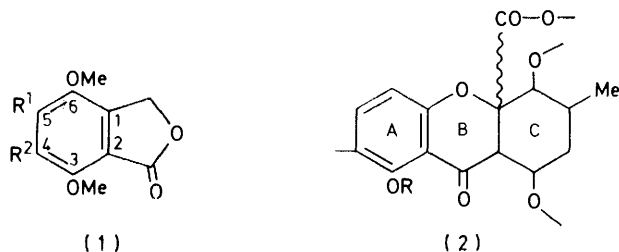
in (5; R = $CH_2OH$), since benzophenones of type (9; R = Me) cyclise [3] to a tricyclic structure of type (10; R = Me). To this end we have developed a route to a potential synthon, 2,5-dibenzyloxy-6-hydroxymethyl-2',6'-dimethoxy-4-methylbenzophenone (11; R = H), for ring c of these metabolites.

We now report the preparation of this synthon together with its unexpected conversion into the isobenzofuran (13).

Reduction of 3,6-dimethoxy-4-methylphthalic anhydride,[4] by conventional processes formed a mixture of the readily separable phthalides (1; R¹ = Me, R² = H) m.p. 113 °C and (1; R¹ = H, R² = Me), m.p. 168 °C



(5)



(6)



(7)



(8)
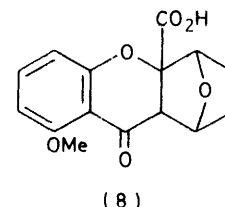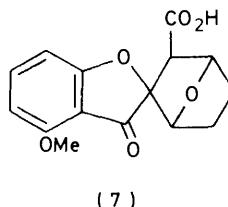
residues from (11; R = H) did not yield (9; R = $CH_2$-OH) but 2-(2,6-dimethoxyphenyl)-5-methyl-4,7-dioxo-4,7-dihydroisobenzofuran (13; R = Me). Because the availability of (13; R = Me) was limited and the spec-
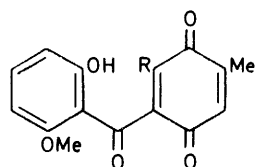
(9)
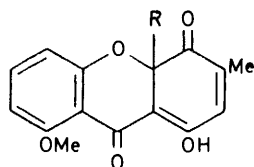


(10)



(11)



(12)



(13)



(14)

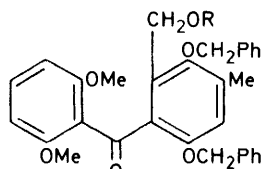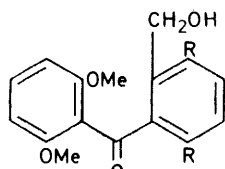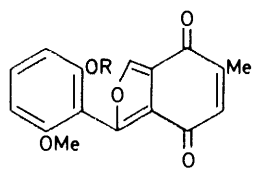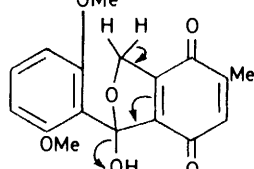tral data were not readily interpreted in terms of a unique structure, this novel isobenzofuran was defined by X-ray crystallography of the demethyl derivative (13; R = H), which was obtained by treatment of the

### TABLE 1

Fractional co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

| Atom | $x$ | $y$ | $z$ |
|---|---|---|---|
| C(1) | 11 922(4) | −2 559 † | 1 729(6) |
| C(2) | 11 649(4) | −4 257(9) | 2 512(6) |
| C(3) | 10 539(4) | −4 590(8) | 3 238(6) |
| C(4) | 9 516(4) | −3 326(8) | 3 366(6) |
| C(5) | 9 720(3) | −1 691(8) | 2 482(6) |
| C(6) | 10 894(4) | −1 318(8) | 1 736(6) |
| C(7) | 10 811(4) | 288(9) | 1 066(7) |
| O(8) | 9 664(3) | 953(7) | 1 359(4) |
| C(9) | 8 985(3) | −271(8) | 2 237(5) |
| C(10) | 7 714(4) | 210(8) | 2 666(6) |
| C(11) | 7 475(4) | 1 809(9) | 3 419(6) |
| C(12) | 6 263(4) | 2 291(9) | 3 831(7) |
| C(13) | 5 315(4) | 1 168(10) | 3 488(8) |
| C(14) | 5 515(4) | −438(10) | 2 721(7) |
| C(15) | 6 718(4) | −892(8) | 2 297(6) |
| O(16) | 12 931(3) | −2 226(8) | 1 122(5) |
| C(17) | 12 679(4) | −5 570(9) | 2 542(8) |
| O(18) | 8 574(3) | −3 679(7) | 4 170(5) |
| O(19) | 8 449(3) | 2 843(8) | 3 773(5) |
| O(20) | 7 009(3) | −2 393(7) | 1 495(4) |
| C(21) | 6 040(5) | −3 611(10) | 1 212(10) |
| H(3) | 10 393 | −5 863 | 3 760 |
| H(7) | 11 545 | 946 | 398 |
| H(12) | 6 081 | 3 527 | 4 416 |
| H(13) | 4 384 | 1 535 | 3 825 |
| H(14) | 4 752 | −1 301 | 2 465 |
| H(171) | 13 478 | −5 053 | 1 895 |
| H(172) | 12 380 | −6 735 | 1 905 |
| H(173) | 12 918 | −5 859 | 3 856 |
| H(19) | 8 070 | 3 923 | 4 278 |
| H(211) | 6 399 | −4 737 | 571 |
| H(212) | 5 329 | −3 026 | 429 |
| H(213) | 5 653 | −3 984 | 2 430 |

† Fixed co-ordinate.

O-acetate (11; R = Ac) with boron trichloride at −70 °C.

Atomic co-ordinates and their standard deviations are given in Table 1 and interatomic distances and angles in Table 2. An ORTEP [5] view of the molecule and of the unit-cell packing are shown in Figures 1 and 2 respectively. The results of the analysis (Figure 1) together with the bond length data, clearly establish the quinonoid structure (13; R = H), from which the

### TABLE 2

Interatomic distances (Å) and angles (°) with estimated standard deviations in parentheses

(a) Bond lengths

| | | | |
|---|---|---|---|
| C(1)−C(2) | 1.481(7) | O(8)−C(9) | 1.384(5) |
| C(1)−C(6) | 1.470(6) | C(9)−C(10) | 1.465(6) |
| C(1)−O(16) | 1.220(5) | C(10)−C(11) | 1.396(7) |
| C(2)−C(3) | 1.355(6) | C(10)−C(15) | 1.404(6) |
| C(2)−C(17) | 1.509(7) | C(11)−C(12) | 1.403(7) |
| C(3)−C(4) | 1.482(6) | C(11)−O(19) | 1.351(6) |
| C(4)−C(5) | 1.460(6) | C(12)−C(13) | 1.370(8) |
| C(4)−O(18) | 1.230(5) | C(13)−C(14) | 1.400(9) |
| C(5)−C(6) | 1.429(6) | C(14)−C(15) | 1.390(6) |
| C(5)−C(9) | 1.371(6) | C(15)−O(20) | 1.359(6) |
| C(6)−C(7) | 1.353(7) | O(20)−C(21) | 1.428(6) |
| C(7)−O(8) | 1.364(6) | | |

(b) Bond angles in degrees (e.s.d.) involving non-hydrogen atoms

| Atom | Angle | Atom | Angle |
|---|---|---|---|
| C(2)−C(1)−C(6) | 115.4(4) | C(7)−O(8)−C(9) | 108.4(4) |
| C(2)−C(1)−O(16) | 121.9(4) | C(5)−C(9)−O(8) | 108.1(3) |
| C(6)−C(1)−O(16) | 122.8(5) | C(5)−C(9)−C(10) | 135.8(4) |
| C(1)−C(2)−C(3) | 121.3(4) | O(8)−C(9)−C(10) | 116.1(4) |
| C(1)−C(2)−C(17) | 117.2(4) | C(9)−C(10)−C(11) | 119.9(4) |
| C(3)−C(2)−C(17) | 121.4(5) | C(9)−C(10)−C(15) | 121.2(4) |
| C(2)−C(3)−C(4) | 124.5(4) | C(11)−C(10)−C(15) | 118.9(4) |
| C(3)−C(4)−C(5) | 115.3(4) | C(10)−C(11)−C(12) | 120.5(4) |
| C(3)−C(4)−O(18) | 120.5(4) | C(10)−C(11)−O(19) | 117.8(4) |
| C(5)−C(4)−O(18) | 124.2(4) | C(12)−C(11)−O(19) | 121.6(5) |
| C(4)−C(5)−C(6) | 120.3(4) | C(11)−C(12)−C(13) | 119.1(5) |
| C(4)−C(5)−C(9) | 132.3(4) | C(12)−C(13)−C(14) | 122.1(4) |
| C(6)−C(5)−C(9) | 107.3(4) | C(13)−C(14)−C(15) | 118.3(5) |
| C(1)−C(6)−C(5) | 122.8(4) | C(10)−C(15)−C(14) | 121.1(4) |
| C(1)−C(6)−C(7) | 130.5(5) | C(10)−C(15)−O(20) | 115.8(4) |
| C(5)−C(6)−C(7) | 106.6(4) | C(14)−C(15)−O(20) | 123.1(4) |
| C(6)−C(7)−O(8) | 110.0(4) | C(15)−O(20)−C(21) | 117.7(4) |

(c) Non-bonded distances <3.4 Å

| | | | |
|---|---|---|---|
| C(2) · · · O(8^I) | 3.337 | O(8) · · · O(19) | 2.730 |
| C(2) · · · O(19^II) | 3.329 | C(14) · · · O(16^IV) | 3.355 |
| C(3) · · · O(19^III) | 3.043 | O(18) · · · O(19^III) | 2.717 |
| C(3) · · · O(19^II) | 3.191 | O(18) · · · H(19^III) | 1.939 |
| C(4) · · · O(19^III) | 3.202 | O(18) · · · O(20) | 2.861 |
| C(4) · · · O(19^II) | 3.258 | | |

The Roman numerals refer to the following equivalent positions:

I  $2 - x, -\frac{1}{2} + y, -z$    III  $x, -1 + y, z$
II  $2 - x, -\frac{1}{2} + y, 1 - z$    IV  $-1 + x, y, z$

orientation of the parent phthalide follows. Thus bonds C(2)−C(3), C(5)−C(9) and C(5)−C(7) are double bonds [mean length 1.360(6) Å]; bonds C(1)−C(2), C(1)−C(6), C(3)−C(4), and C(4)−C(5) are $C(sp^2)$−$C(sp^2)$ single bonds [mean length 1.473(6) Å]. Bond C(5)−C(6) [1.429(6) Å] is shorter than the other $C(sp^2)$−$C(sp^2)$ single bonds and this may result from some slight conjugation effects.

The aromatic ring C(10)−C(15) is rotated 48.2° about the C(9)−C(10) bond out of the plane of the phthalide system C(1)−C(7), C(8), C(9) to relieve intramolecular overcrowding which would arise between O(18) and O(20),

and O(8) and O(19). This rotation gives rise to O · · · O separations of **2.73** [O(8) · · · O(19)] and **2.86** Å [O(18) · · · O(20)]. Other indications of steric strain are the large difference in bond angles at C(9), *e.g.* C(8)–C(9)–C(10) 116.1(4)° and C(5)–C(9)-C(10) 135.8(4)°. Interestingly,
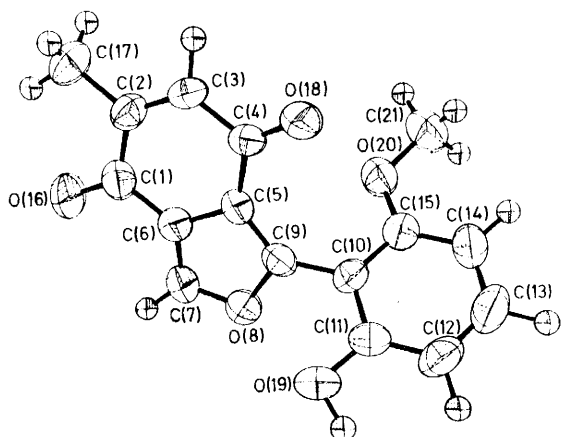


Figure 1 ORTEP view of (9; R = H)

the hydroxy-group of O(19)H hydrogen-bonds intermolecularly to carbonyl oxygen O(18) of a neighbouring molecule related by a *b*-axis translation to produce a chain of molecules in the crystal structure with O–H · · · O 2.72 Å (Figure 2). Presumably no suitable orientation of
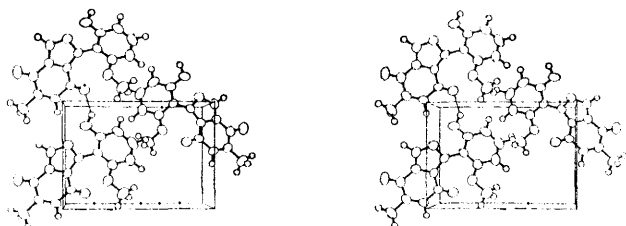


FIGURE 2 Stereo-pair showing the crystal structure and the hydrogen bonding of (9; R = H)

the aromatic ring and its hydroxy-group could give rise to intramolecular hydrogen bonding.

The genesis of these isobenzofurans is presumably by way of the hemiacetal (14), followed by elimination of the elements of water as shown, with the quinone type (9) being a more likely precursor than the corresponding quinol.

EXPERIMENTAL

N.m.r. spectra were determined in solution in CDCl$_3$ at 60 MHz.

*3,6-Dimethoxy-5-methyl- and 3,6-Dimethoxy-4-methyl-phthalide.*—(*a*) A solution of 3,6-dimethoxy-4-methyl-phthalic anhydride (1 g) in acetic acid (50 ml) was maintained at 100 °C whilst zinc dust was slowly added (stir) until the solution was colourless and the initial purple fluorescence had disappeared. The hot mixture was filtered, diluted with water, and extracted with ethyl acetate.

Crystallisation of the product from ethyl acetate gave a mixture of the two isomeric phthalides which were separated by chromatography from benzene–ethyl acetate (50 : 1) on silica to give (i) 3,6-*dimethoxy*-4-*methylphthalide* (0.14 g) as

plates, m.p. 168 °C, from acetone–ether; ν$_{max.}$ 1 760 cm$^{-1}$ (phthalide >C=O); τ 7.7 (s, ArCH$_3$, 3 H), 6.15 (s, OCH$_3$, 3 H), 6.05 (s, OCH$_3$, 3 H), 4.9 (s, ArCH$_2$–O, 2 H), and 3.1 (s, ArH, H) (Found: C, 63.7; H, 5.6%; *M*$^+$ 208. C$_{11}$H$_{12}$-O$_4$ requires C, 63.5; H, 5.8%; *M* 208), and (ii) 3,6-*di-methoxy*-5-*methylphthalide* (0.52 g) as cubes from ethyl acetate, m.p. 113 °C; ν$_{max.}$ 1 745 cm$^{-1}$ (phthalide >C=O); τ 7.65 (s, ArCH$_3$, 3 H), 6.20 (s, OCH$_3$, 3 H), 6.10 (s, OCH$_3$ 3 H), 4.75 (s, ArCH$_2$–O, 2 H), and 3.3 (s, ArH, 1 H) (Found C, 63.5; H, 5.1%; *M*$^+$ 208).

(*b*) Reduction of a suspension of 3,6-dimethoxy-4-methyl-phthalic anhydride (1 g) in alcohol (100 ml) with an excess of sodium borohydride at reflux temperature until the resultant solution was colourless gave 3,6-dimethoxy-4-methylphthalide (0.16 g) and 3,6-dimethoxy-5-methyl-phthalide (0.55 g), identical with the products prepared by route (*a*).

*3,6-Dihydroxy-5-methylphthalide.*—(*a*) A solution of 3,6-dimethoxy-5-methylphthalide (0.4 g) in benzene (20 ml) was stirred during addition of a 10% solution of boron tribromide (2 ml) in benzene: 1 h later, after addition of water, the solid product was collected. Trituration with ether gave 3,6-*dihydroxy*-5-*methylphthalide* as a semicrystal-line light-brown solid (0.05 g), m.p. 168—169 °C, exhibiting an intense dark brown ferric chloride test: ν$_{max.}$ 3 600—3 300 (OH), 1 730 cm$^{-1}$ (phthalide >C=O); τ [(CD$_3$)$_2$CO] 7.75 (s, ArCH$_3$, 3 H), 4.8 (s, OH, 2 H replaceable with D$_2$O), 4.75 (s, ArCH$_2$O, 2 H), 3.3 (s, ArH, 1 H) (Found: C, 59.9; H, 4.6%; *M*$^+$ 180. C$_9$H$_8$O$_4$ requires C, 60.0; H, 4.5%; *M* 180).

Extraction with ethyl acetate of the aqueous liquid remaining after separation of the solid gave 6-*hydroxy*-3-*methoxy*-5-*methylphthalide* (0.3 g) as needles, m.p. 254 °C from ethyl acetate having a negative ferric reaction in alcohol; ν$_{max.}$ 3 530—3 100 (OH), 1 745 cm$^{-1}$ (phthalide >C=O); τ [(CD$_3$)$_2$CO] 7.65 (s, ArCH$_3$, 3 H), 7.05 (s, OH, 1 H, replaceable with D$_2$O), 6.15 (s, OCH$_3$, 3 H), and 4.28 (s, ArCH$_2$O, 2 H) (Found: C, 61.4; H, 5.3%; *M*$^+$ 194. C$_{10}$-H$_{10}$O$_4$ requires C, 61.8; H, 5.2%; *M* 194).

(*b*) A solution of 3,6-dimethoxy-5-methylphthalide (0.25 g) in acetic acid (5 ml) containing 48% hydrobromic acid (8 ml) was refluxed (nitrogen) for 3 h. The dark solution was diluted with water (250 ml), neutralised by the addition of excess of sodium hydrogencarbonate, and extracted with ether to yield 3,6-dihydroxy-5-methylphthalide (0.15 g) identical with that prepared by method (*a*).

A solution of 3,6-dihydroxy-5-methylphthalide (0.15 g) in acetone (15 ml) containing benzyl bromide (2 ml) and anhydrous potassium carbonate (2 g) was refluxed for 4 h. The resultant 3,6-*dibenzyloxy*-5-*methylphthalide* was purified by p.t.l.c. on silica using benzene–ethyl acetate (19 : 1) as eluant, then from benzene–light petroleum (b.p. 40—60 °C) as plates (0.12 g), m.p. 106 °C; ν$_{max.}$ 1 755 cm$^{-1}$ (phthalide >C=O); τ [(CD$_3$)$_2$CO] 7.7 (s, ArCH$_3$, 3 H), 5.0 (s, ArCH$_2$, 2 H), 3 0 (s, ArH, 1 H), and 2.6 (m, ArH, 10 H) (Found: C, 76.6; H, 5.8%; *M*$^+$ 360. C$_{23}$H$_{20}$O$_4$ requires C, 76.7; H, 5.6%; *M* 360).

Reduction of a solution of 3,6-dimethoxy-5-methyl-phthalide (0.25 g) in boiling ether (100 ml) containing lithium aluminium hydride (1 g) during 2 h, gave 3,6-*dimethoxy*-4-*methylphthalyl alcohol* (0.2 g) which formed cubes, m.p. 87 °C, from acetone; ν$_{max.}$ 3 640—3 080 cm$^{-1}$ (OH); τ 7.7 (s, ArCH$_3$, 3 H), 7.0 (s, ArOH, 2 H replaceable by D$_2$O), 6.25 (s, ArCH$_2$O 2 H), 6.0 (s, ArCH$_2$, 2 H), and 3.3 (s, ArH, 1 H) (Found: C, 62.1; H, 7.7%; *M*$^+$ 212. C$_{11}$H$_{16}$O$_4$ requires C, 62.3; H, 7.6%; *M* 212).

2-*Formyl*-3,6-*dimethoxy*-4-*methylbenzoic Acid* (4).—The mother-liquors from the hydrolysis of 3,6-dimethoxy-4-methylphthalonitrile (10 g) were extracted with ethyl acetate: this extract was washed with 2N-sodium hydrogen-carbonate solution. Acidification of the resultant alkaline solution gave 2-*formyl*-3,6-*dimethoxy*-4-*methylbenzoic acid* (0.6 g) which formed cubes, m.p. 194 °C from ethyl acetate: $\nu_{max.}$ 1 730 (carboxylic C=O), 1 600 cm$^{-1}$ (formyl C=O) (Found: C, 58.6; H, 5.5%; $M^+$ 224. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%; $M$, 224).

2-*Hydroxymethyl*-2',6'-*dimethoxybenzophenone*.—Excess of a solution of 2,6-dimethoxyphenyl-lithium in ether was added dropwise during 5 min, to a solution of phthalide (3 g) in ether (300 ml) with stirring in an atmosphere of nitrogen. After $\frac{1}{2}$ h, the mixture was acidified with 2N-sulphuric acid, diluted with water (200 ml), and the ethereal layer separated, washed, dried, and evaporated. Purification from ether gave 2-*hydroxymethyl*-2',6'-*dimethoxy-benzophenone* (4 g) as needles, m.p. 107 °C; $\nu_{max.}$ 3 650—3 100 (OH) and 1 665 cm$^{-1}$ (C=O); τ [(CD$_3$)$_2$CO] 7.1 (s, O*H*, H, replaceable +D$_2$O), 6.3 (s, 2 × OC*H$_3$*, 6 H), 5.0 (s, C*H$_2$*OH, 2 H), 3.3—3.15 (Ar*H*, 2 H), 2.8—2.1 (Ar*H*, 4 H), and 2.7—2.45 (Ar*H*, 1 H) (Found: C, 70.8; H, 6.1%; $M^+$ 272. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%; $M$ 272).

Oxidation of a solution of this alcohol (1 g) in acetone (30 ml) with an excess of Jones' reagent gave 2-(2',6'-dimethoxy-benzoyl)benzoic acid (0.6 g), m.p. and mixed m.p. with an authentic specimen 202 °C (Found: C, 67.1; H, 4.9. Calc. for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9%).

3,6-*Dimethoxyphthalide*.—Zinc dust was added (stir) to a solution of 3,6-dimethoxyphthalic anhydride (1 g) in acetic acid (50 ml) at 100 °C until the initially purple, fluorescent solution became colourless. The hot reaction mixture was filtered and the filtrate diluted with water (250 ml) and extracted with ethyl acetate to yield 3,6-*dimethoxyphthalide* (0.8 g) as light yellow rhombs, m.p. 171 °C from ethyl acetate; $\nu_{max.}$ 1 700 cm$^{-1}$ (phthalide C=O) (Found: C, 61.7; H, 5.5. $C_{10}H_{10}O$ requires C, 61.9; H, 5.2%).

6-*Hydroxymethyl*-2',2',5,6'-*tetramethoxy*-4-*methylbenzo-phenone*.—Prepared from the addition of an excess of a solution in ether of 2,6-dimethoxylithium to a solution of 3,6-dimethoxy-5-methylphthalide (0.9 g) in ether (200 ml), 6-*hydroxymethyl*-2',2',5,6'-*tetramethoxy*-4-*methylbenzophenone* formed prisms (0.6 g), m.p. 132—134 °C, from acetone; $\nu_{max.}$ 3 560—3 420 (OH), 1 655 cm$^{-1}$ (C=O); τ [(CD$_3$)$_2$CO] 7.7 (s, ArC*H$_3$*, 3 H), 7.25 (s, O*H*, 1 H, replaceable +D$_2$O), 6.55 (s, OC*H$_3$*, 3 H), 6.35 (s, 2 × OC*H$_3$*, 6 H), 6.2 (s, OC*H$_3$*, 3 H), 5.4 (s, C*H$_2$*OH, 2 H), 3.4—2.25 (Ar*H*, 2 H), 3.15 (Ar*H*, 1 H), and 2.8—2.5 (Ar*H*, 1 H) (Found: C, 65.4; H, 6.5%; $M^+$ 346. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%; $M$ 346).

Prepared similarly in 55% yield, from 3,6-dimethoxy-4-methylphthalide, 6-*hydroxymethyl*-2',2',5,6'-*tetramethoxy*-3-*methylbenzophenone* formed cubes, m.p. 134—136 °C, from ether; $\nu_{max.}$ 3 510 (OH) and 1 655 cm$^{-1}$ (>C=O): [(CD$_3$)$_2$-CO] 7.8 (s, ArC*H$_3$*, 3 H), 7.05 (s, O*H*, 1 H, replaceable +D$_2$O), 6.7 (s, OC*H*, 3 H), 6.3 (s, 2 × OC*H$_3$*, 6 H), 6.15 (s, OC*H$_3$*, 3 H), 5.45 (s, C*H$_2$*OH, 2 H), 3.35—3.20 (Ar*H*, 2 H), 3.0 (Ar*H*, 1 H), and 2.75—2.45 (Ar*H*, 1 H) (Found: C, 66.1; H, 6.4%; $M^+$ 346).

2,5-*Dibenzyloxy*-6-*hydroxymethyl*-2',6'-*dimethoxy*-4-*methyl-benzophenone*.—Prepared from an excess of 2,6-dimethoxy-phenyl-lithium and 3,6-dibenzyloxy-5-methylphthalide (2 g), the title benzophenone (1 g) formed prisms, m.p. 155—157 °C from ether, or cubes, m.p. 118 °C from ethyl acetate–light petroleum (b.p. 60—80 °C); $\nu_{max.}$ 3 510 (OH) and

1 655 cm$^{-1}$ (C=O); τ[(CD$_3$)$_2$CO] 7.7 (s, ArC*H$_3$*, 3 H), 7.1 (s, O*H*, 1 H, replaceable + D$_2$O), 6.5 (s, 2 × OC*H$_3$*, 6 H), 5.4 (s, C*H$_2$*OH, 2 H), 5.15 (s, ArC*H$_2$*, 2 H), 5.0 (s, ArC*H$_2$*, 2 H), 3.5—3.35 (m, Ar*H*, 2 H), 3.05 (s, Ar*H*, 1 H), 3.1—2.35 (m, Ar*H*, 11 H) (Found: C, 74.7; H, 6.2%; $M^+$ 498. $C_{31}H_{30}O_6$ requires C, 74.7; H, 6.1%; $M$ 498).

Prepared quantitatively by the pyridine–acetic anhydride method, the O-*acetate* formed rhombs, m.p. 163 °C from acetone; $\nu_{max.}$ 1 730 (acetate C=O) and 1 675 cm$^{-1}$ (C=O) (Found: C, 73.6; H, 5.9%; $M^+$ 540. $C_{33}H_{32}O_7$ requires C, 73.3; H, 6.0; $M$ 540). The corresponding O-*benzoate* formed prisms, m.p. 116 °C from ethyl acetate–light petroleum (b.p. 60—80 °C) (Found: C, 75.2; H, 5.6. $C_{38}H_{34}O_7$ requires C, 75.7; H, 5.7%).

5-*Benzyloxy*-6-*hydroxymethyl*-2,2',6'-*trimethoxy*-4-*methyl-benzophenone*.—Benzylation of 6-hydroxy-3-methoxy-5-methylphthalide by the acetone–potassium carbonate–benzyl bromide method gave 6-*benzyloxy*-3-*methoxy*-5-*methylphthalide* as rhombs, m.p. 86 °C from ethyl acetate (Found: C, 71.8; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%).

Prepared from this phthalide (1 g) and 2,6-dimethoxy-phenyl-lithium, 5-*benzyloxy*-6-*hydroxymethyl*-2,2',6'-*tri-methoxy*-4-*methylbenzophenone* (0.6 g) formed needles, m.p. 140 °C from ethyl acetate; $\nu_{max.}$ 3 510 (OH) and 1 645 cm$^{-1}$ (C=O) (Found: C, 70.6; H, 6.2%; $M^+$ 422. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2%; $M$ 422).

This benzophenone (0.3 g) dissolved in dichloromethane (30 ml) was stirred at 70 °C whilst a solution of boron tribromide (0.5 g) in the same solvent was added. After 1 h, the mixture was allowed to attain room temperature. Next day the product was isolated and purified by t.l.c. on silica using benzene–ethyl acetate (95 : 5) to yield (i) 6-*formyl*-5,6'-*dihydroxy*-2,2'-*dimethoxy*-4-*methylbenzophenone* (0.06 g) as yellow needles, m.p. 163 °C from ether, and having an intense green ferric reaction in alcohol; $\nu_{max.}$ 3 650—3 250 (OH), 1655 (HC=O), and 1 610 cm$^{-1}$ (chelated C=O); τ [(CD$_3$)$_2$CO] 7.65 (s, ArC*H$_3$*, 3 H), 7.25 (O*H*, 2 H, replaceable + D$_2$O), 6.50 (s, OC*H$_3$*, 3 H), 6.30 (s, OC*H*, 3 H), 3.55—3.4 (m, Ar*H*, 2 H), 3.30 (s, Ar*H*, 1 H), 2.75—2.45 (m, Ar*H*, 1 H), and 0.05 (s, C*H*O, 1 H) (Found: C, 64.5; H, 5.0%; $M^+$ 316. $C_{17}H_{16}O_6$ requires C, 64.6; H, 5.1%; $M$ 316), and (ii) 6-*formyl*-5-*hydroxy*-2,2',6-'*trimethoxy*-5-*hydroxybenzophenone* (0.03 g) as yellow needles, m.p. 136 °C from ether, having a negative ferric reaction in alcohol; τ [(CD$_3$)$_2$CO] 7.70 (s, ArC*H$_3$*, 3 H), 7.15 (OH, 1 H, replaceable with D$_2$O), 6.50 (s, OC*H$_3$*, 3 H), 6.2 (s, 2 × OC*H$_3$*, 6 H), 3.3—3.10 (m, Ar*H*, 3 H), and 2.75—2.45 5.0%; $M^+$ 330. $C_{18}H_{18}O_6$ requires C, 65.5; H, 5.5%; $M$ 330).

1-(2,6-*Dimethoxyphenyl*)-5-*methyl*-4,7-*dioxo*-4,7-*dihydro-isobenzofuran*.—A solution of 2,5-dibenzyloxy-6-hydroxy-methyl-2',6'-dimethoxy-4-methylbenzophenone (0.5 g) in acetone (150 ml) containing 10% palladium–charcoal (0.1 g) was shaken in an atmosphere of hydrogen, until the absorption of two equivalents was complete and the solution had become yellow. Isolated in the normal manner the *dioxoisobenzofuran* (0.3 g) formed yellow needles, m.p. 183—184 °C from ether; τ 7.85 (s, C*H$_3$*, 3 H), 6.2 (s, 2 × OC*H$_3$*, 6 H), 3.4—3.25 (m, Ar*H*, 3 H), 2.7—2.4 (t, C*H*=CMe, 1 H), and 1.8 (s, OC*H*=, 1 H) (Found: C, 68.7; H, 4.6%; $M^+$ 298. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%; $M$ 298).

1-(2-*Hydroxy*-6-*methoxyphenyl*)-5-*methyl*-4,7-*dioxo*-4,7-*dihydroisobenzofuran*.—A solution of 6-acetoxymethyl-2,5-dibenzyloxy-2',6'-dimethoxy-4-methylbenzophenone (1 g) in dichloromethane (150 ml) was treated at −70 °C with

10% boron trichloride–dichloromethane (100 ml). After 1 h, the solution was allowed to attain room temperature and 12 h later the product was isolated to yield the title *dioxo-isobenzofuran* (0.2 g) [after chromatography on silica from ethyl acetate–light petroleum (b.p. 60—80 °C)] as yellow prisms, m.p. 175—176 °C (Found: C, 67.4; H, 4.3%; $M^+$ 284. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.3%; $M$ 284).

*X-Ray Analysis.*—Crystals of (9; R=H) crystallised from ether as pale yellow plates with well defined faces. Preliminary cell and space-group data were obtained from Weissenberg and precession photographs, and accurate unit-cell dimensions were obtained by least-squares refinement of the setting angles of twelve reflections measured on an automatic diffractometer.

*Crystal Data.*—$C_{16}H_{12}O_5$, $M = 284.3$. Monoclinic, $a = 10.818(1)$, $b = 7.752(1)$, $c = 7.808(3)$ Å, $\beta = 90.28(1)°$, $U = 654.8$ Å$^3$, $Z = 2$, $D_c = 1.44$, $F(000) = 296$. Space group $P2_1$ ($C_2^2$, No. 4) or $P2_1/m$ ($C_{2h}^2$, No. 11) from systematic absences $0k0$ for $k$ odd. $P2_1$ chosen, and confirmed by the analysis. Mo-radiation, $\lambda = 0.710$ 69 Å, $\mu$(Mo-$K_\alpha$) = 0.66 cm$^{-1}$.

Three-dimensional intensity data were collected on a Hilger and Watts four-circle diffractometer controlled by a PDP-8 computer, in our usual way.[6] A total of 2 039 unique reflections was measured in the range $1 < \theta < 30°$ of which 1 257 with $I > 3\sigma(I)$ were used in the refinement of the structure. The data were corrected for Lorentz and polarisation effects but not for absorption which is insignificant.

*Structure Analysis.*—The structure was solved by direct methods using MULTAN 78.[7] The first $E$-map calculated using the phases with the highest combined figure-of-merit gave a chemically recognisable (but unexpected) 16-atom fragment. A subsequent $F_o$ Fourier synthesis phased with contribution from these atoms revealed the remaining non-hydrogen atoms of the molecule. Full-matrix least-squares refinement with weights derived from counting statistics and anisotropic thermal parameters, lowered $R = \Sigma||F_o| - |F_o|\Sigma|F_o|$ to 0.102. The scattering factors of ref.

8 were used for hydrogen, and from ref. 9 for carbon and oxygen.

A difference synthesis revealed peaks of height 0.25—0.51 e Å$^3$ in positions consistent with the hydrogen atoms. These were allowed for in chemically expected positions with C–H 1.08 Å and $U_{iso}$ 0.063 Å$^2$ in the final least-squares calculations. Refinement converged at $R = 0.053$ and $R' = [\Sigma w|F_o - F_c|^2|\Sigma w|F_o|^2]^{\frac{1}{2}} = 0.059$. A final difference synthesis was featureless.

A list of observed and calculated structure factors, thermal parameters, and mean plane data has been deposited as Supplementary Publication No. SUP 22850 (11 pp.).*

* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1979, Index issue.

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