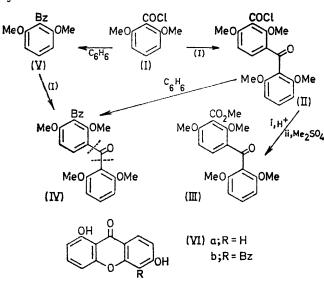
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Synthesis of Benzophenones: Anomalous Friedel–Crafts Reactions

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A Friedel–Crafts reaction between 2,6-dimethoxybenzoyl chloride and benzene yields 2,6-dimethoxybenzophenone and 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone, and under milder conditions, 3-carboxy-2,2',4,6'-tetramethoxybenzophenone. A synthesis and the degradation under acid conditions of 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone are described.

DURING the synthesis of a number of substituted benzophenones for other studies we observed an anomalous Friedel-Crafts reaction. When benzene and 2,6-dimethoxybenzoyl chloride (I) are heated under reflux with aluminium chloride two products are formed, namely 2,6-dimethoxybenzophenone (V) and 3-benzoyl2,2',4,6'-tetramethoxybenzophenone (IV). If the reaction is carried out in ether at room temperature, however, the only product is 3-carboxy-2,2',4,6'-tetramethoxybenzophenone [isolated as the methyl ester (III)]. The structures of the products follow from their analysis and u.v., i.r., and n.m.r. spectral data, and were confirmed in the case of the first two products by independent synthesis.



Under the mild conditions of reaction 2,6-dimethoxybenzoyl chloride (I) presumably reacts initially with itself to form the acid chloride (II), which is converted into the methyl ester during the work-up. The reason why this compound is not obtained under the more severe reaction conditions (refluxing benzene) may be that the acid chloride (II) under these conditions reacts with benzene to give 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone (IV). Alternatively (IV) could arise by the reaction of 2,6-dimethoxybenzoyl chloride with the other product, 2,6-dimethoxybenzophenone (V). It is unlikely that 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone could be cleaved to form the carboxytetramethoxybenzophenone under the acidic conditions employed in the work-up.

Degradation of (IV) by heating under reflux with hydriodic acid yields carbon dioxide, resorcinol, benzoic acid, 1,6-dihydroxyxanthone [isoeuxanthone (VIa)] and 5-benzoyl-1,6-dihydroxyxanthone (VIb). The formation of these products can be explained on the assumption that after initial demethylation at least two reaction sequences occur: (a) cyclisation to the xanthone (VIb) followed by debenzoylation, and (b) cleavage of the diketone at the positions indicated in (IV). Other instances of the cleavage by acids of substituted benzophenones to give phenols and aromatic acids are recorded.1

EXPERIMENTAL

U.v. spectra were measured for solutions in absolute ethanol with a Unicam SP 800 spectrophotometer, i.r. spectra for potassium bromide discs with a Unicam SP 200 spectrophotometer, and n.m.r. spectra with a Perkin-Elmer R10 (unless otherwise stated) operating at 60 MHz for

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solutions in deuteriochloroform with tetramethylsilane as internal standard. Microcombustion analyses were performed by Drs. Weiler and Strauss, Oxford.

Friedel-Crafts Reaction between 2,6-Dimethoxybenzoyl Chloride and Benzene.—Method (a). 2,6-Dimethoxybenzoyl chloride [crude; prepared ² from the acid (10 g.)], freshly sublimed aluminium chloride (20 g.), and benzene (100 ml.) were mixed and heated at 70-75° for 1 hr. then at 75-80° for 45 min. Ice-cold conc. hydrochloric acid was added and the mixture was heated on a water-bath for several hr. The cooled mixture was extracted with ether, the extract was dried, and the solvent was distilled off, leaving a brown tar which was immediately methylated with dimethyl sulphate (13.9 g.) in acetone (150 ml.) containing anhydrous potassium carbonate (28 g.). The acetone was distilled from the filtered solution and the resultant oil was chromatographed on alumina (neutral, B = 1 on Brockmann activity scale), with benzene as eluant. The products were 2,6-dimethoxybenzophenone (0.37 g.), colourless plates from light petroleum (b.p. 80-100°), m.p. 95.5–97.5° (lit., 3 99°), ν_{max} 1675 (benzophenone C=O) and 1600 cm.⁻¹ [Found: C, 74.2; H, 5.7; OMe, 25.4. Calc. for C₁₃H₈O(OMe)₂: C, 74·4; H, 5·8; OMe, 25·5%], and 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone (0.12 g.), colourless needles from light petroleum (b.p. 80-100°), m.p. 227–230°, ν_{max} 1670 and 1595 cm.⁻¹, λ_{max} 221 (log ϵ 4.30), 252 (4.30), and 272 (4.27) nm., τ (Varian A60) 6.48 (s, 2-OMe), 6.30 (s, 2'-, 4-, and 6-OMe), 3.48 (d, 3'- and 5'-H, J 8 Hz), 3.35 (d, 5-H, J 9 Hz), 2.72 (d, 6-H, J 9 Hz), and 2.12-2.67 (5H, m, benzoyl protons) [Found: C, 70.3; H, 5.45; OMe, 31.6. C₂₀H₁₀O₂(OMe)₄ requires C, 70.9; H, 5.45; OMe, 30.5%].

Method (b). Crude 2,6-dimethoxybenzoyl chloride [from the acid (10 g.) was added during 0.5 hr. with stirring to a mixture of aluminium chloride (10 g.), benzene (8.5 g.), and ether (100 ml.). After 2 days at room temperature the mixture was treated with ice and conc. hydrochloric acid (25 ml.) then heated on a steam-bath. Benzene (150 ml.) was added and the mixture was refluxed for 1.5 hr. The organic layer was dried and distilled, and the brown oil remaining (which gave a positive reaction with ferric ions) was methylated as in method (a). Chromatography on alumina (neutral; B = 1) in benzene yielded 3-methoxycarbonyl-2,2',4,6'-tetramethoxybenzophenone (0.76 g.), colourless plates from light petroleum (b.p. 80-100°), m.p. 120-120.5°, v_{max} 1730, 1660, and 1595 cm.⁻¹, τ 6.33 (s, 2-, 2'-, and 6'-OMe), 6.27 (s, 4-OMe), 6.18 (s, CO₂Me), 3.40 (d, 3'- and 5'-H, J 8 Hz), 3.35 (d, 5-H, J 9 Hz), 2.67 (q, 4'-H, J 8 Hz), and 2.35 (d, 6-H, J 9 Hz) [Found: C, 63.4; H, 5.8; OMe, 44.5. C₁₄H₅O₂(OMe)₅ requires C, 63.3; H, 5.6; OMe, 43.0%]

2,6-Dihydroxybenzophenone.—This was synthesised from 4-methylumbelliferone (17% overall) according to the method 4 used to prepare 2,6-dihydroxyacetophenone; vellow needles from methanol, m.p. 131-133° (lit., 3 135°).

2,6-Dimethoxybenzophenone. 2,6-Dihydroxybenzophenone (20 g.), methylated with dimethyl sulphate (23.5 g.) as already described, gave colourless needles (21.8 g.), m.p. 97.5-98° (from methanol) (lit.,3 99°), identical (mixed m.p., i.r. spectrum) with the compound already obtained.

3-Benzoyl-2,2',4,6'-tetramethoxybenzophenone.-Crude

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2,6-dimethoxybenzoyl chloride [from the acid (9 g.)] was added in portions, with stirring, to a mixture of aluminium chloride (10 g.), 2,6-dimethoxybenzophenone (5.2 g.), and ether (300 ml.) during 0.5 hr. After 24 hr. the mixture was worked up as in method (b). The product formed colourless plates from light petroleum (b.p. 80-100°), m.p. 222-224° (2.7 g., 29%) [Found: C, 69.6; H, 5.45; OMe, 30.8. C₂₀H₁₀O₂(OMe)₄ requires C, 70.9; H, 5.45; OMe, 30.5%].

3-Benzoyl-2,2',4,6'-tetrahydroxybenzophenone. Solutions of 3-benzoyl-2,2',4,6'-tetramethoxybenzophenone (1.45 g.) and boron tribromide (3.93 g.) in methylene dichloride were cooled to -78° and then mixed. The mixture was warmed to room temperature and water (50 ml.) was added. The product was isolated by extraction into ether and formed pale yellow needles from benzene, m.p. 215.5-218.5° (0.1 g., 10%), v_{max} 3500, 3250, 1660, 1615, 1600, and 1590 cm.⁻¹ (Found: C, 68.3; H, 4.05. C₂₀H₁₄O₆ requires C, 68.6; H, 4.05%). 3-Benzoyl-2,2',4,6'-tetrahydroxybenzophenone gave a sherry colour with ferric ions in ethanol.

Action of Hydriodic Acid on 3-Benzoyl-2,2',4,6'-tetramethoxybenzophenone.--The title compound (1 g.) was gently heated under reflux with hydriodic acid ($d \cdot 7$; 60 ml.) for 3 hr. while a slow stream of nitrogen was passed through the mixture. The effluent gases were passed into a Dreschel bottle containing saturated barium hydroxide solution. A white precipitate of barium carbonate formed as the reaction proceeded. The reaction mixture was diluted with water (60 ml.) and left overnight. Some crystallisation occurred. The suspension was extracted with ether $(4 \times 50 \text{ ml.})$ and the extract was washed with sodium hydrogen carbonate solution (retained), then a little water, and dried (Na_2SO_4) . Removal of the solvent yielded a gum which was dissolved in benzene and chromatographed on a column of silica gel MFC. The eluate yielded resorcinol (0.1 g.), needles, m.p. and mixed m.p. 106-108° [dibenzoate, m.p. 115-116° (lit.,⁵ 117°)], and 5-benzoyl-1,6-dihydroxyxanthone (0.07 g.), pale yellow needles, m.p. 198-201° (from methanol), olivegreen colour with ferric ions in ethanol, ν_{max} 1675, 1650, and 1603 cm.⁻¹ (Found: C, 71.1; H, 3.45. C₂₀H₁₂O₅ requires C, 72.3; H, 3.65%). (Prolonged drying did not improve these figures.) Later fractions yielded 1,6-dihydroxyxanthone (0.02 g.) as pale yellow needles, m.p. 246-248.5° (from methanol) (lit.,6 245-246°), olive-green colour with ferric ions in ethanol, ν_{max} 1640 and 1603 cm.⁻¹, λ_{max} 231 (log ε 4·43), 248 (4·21), 265 (3·98), 305 (4·04), and 351 (3·82)

The sodium hydrogen carbonate extract was acidified nm. with dil. hydrochloric acid and extracted with ether $(2 \times 50 \text{ ml.})$. Removal of the solvent left colourless needles of benzoic acid (0.025 g.), m.p. and mixed m.p. 120-122°.

2,2',4,6'-Tetramethoxybenzophenone.—Crude 2,6-dimethoxybenzoyl chloride [from the acid (10 g.)] was added with stirring to a mixture of aluminium chloride (10 g.) 1,3-dimethoxybenzene (7.6 g.), and ether (100 ml.). The reaction was carried out as described in method (b). 2,2',4,6'-Tetramethoxybenzophenone (8.2 g., 69%) separated from benzene as colourless prisms, m.p. $125 \cdot 5 - 126 \cdot 5^{\circ}$, ν_{max} 1645, 1600, and 1580 cm.⁻¹, τ 6.38 (s, 2-, 2'-, and 6'-OMe), 6.27 (s, 4-OMe), 3.60 (d, 3-H meta-coupled to 5-H; J 2.5 Hz), 3.58 (d, 5-H, J 9 Hz), 3.48 (d, 3'- and 5'-H, J 8 Hz), 2.80 (q, 4'-H, J 8 Hz), and 2.32 (d, 6-H, J 9 Hz).

1,6-Dihydroxyxanthone. 2,2',4,6'-Tetramethoxybenzophenone (1 g.) was refluxed with hydriodic acid (60 ml.) for 3 hr. The product was isolated by extraction into ether, distillation, and chromatography of the residue on silica gel MFC, with benzene as eluant. 1,6-Dihydroxyxanthone (0.1 g.) separated from methanol as pale yellow needles, m.p. 246-248.5°. Methylation with dimethyl sulphatepotassium carbonate-acetone gave 1,6-dimethoxyxanthone, m.p. 181.5-183° (0.025 g.), colourless needles from light petroleum (b.p. 60–80°), ν_{max} 1655, 1625, 1605, and 1570 cm.⁻¹ [Found: C, 70·2; H, 4·65; OMe, 24·7. $C_{13}H_6O_2$ -(OMe)₂ requires C, 70.3; H, 4.7; OMe, 24.2%].

5-Benzoyl-1,6-dimethoxyxanthone.—Prepared by methylation of 5-benzoyl-1,6-dihydroxybenzophenone (0.057 g.) by the dimethyl sulphate-potassium carbonate method, the product (0.025 g.) separated from light petroleum (b.p. 60—80°) as colourless needles, m.p. 259·5—261°, ν_{max} 1660, 1620, and 1605 cm.⁻¹, τ (Varian A60A) 6.12 and $\overline{5.98}$ (each s, 1- and 6-OMe), 3.33 and 3.20 (each d, 2- and 3-H), 2.96 (d, 7-H, J 9 Hz), 2.00-2.58 (5H, m, benzovl hydrogens), and 1.58 (d, 8-H, J 9 Hz) [Found: C, 72.7; H, 4.55; OMe, 16.5. C₂₀H₁₀O₃(OMe)₂ requires C, 73.3; H, 4.4; OMe, 17.2%].

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