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2'-ACETOXY-2-HYDROXY-5-METHOXYBENZOPHENONE

PHOTOCHEMICAL SYNTHESIS, TRANSACYLATION AND CYCLIZATION TO 2-METHOXYXANTHONE

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Abstract—*p*-Methoxyphenyl salicylate **2** gives 2,2' - dihydroxy - 5 - methoxybenzophenone **3** upon irradiation, but the yields are low both in hexane and in methanol. *p*-Methoxyphenyl *o*-acetoxybenzoate **1** undergoes photo-Fries rearrangement, affording 2' - acetoxy - 2 - hydroxy - 5 - methoxybenzophenone **4** in good yield. Compound **4** is not stable in silica gel: it isomerizes to 2' - acetoxy - 2 - hydroxy - 5' - methoxybenzophenone **5**, that is also the major acetylation product of **3** with acetyl chloride. Starting from **1**, 2-methoxyxanthone **7** is obtained in 57% overall yield.

Xanthone derivatives constitute an important group of secondary plant metabolites,[1] which have recently revealed a manifold pharmacological activity (antipsychotic, antiallergic, tuberculostatic, bronchodilator, etc).[2-6] These facts, together with the need for unambiguous structural assignation, have attracted chemists to the total synthesis of the suitably substituted xanthone ring system.[7]

2,2'-Dioxygeated benzophenones are key intermediates in the above sequences, as well as biosynthetic precursors of fungal and lichen xanthones.[8-12] An obvious pathway to them would involve the photo-Fries rearrangement[13,14] of aryl salicylates, a reaction that precludes the use of aluminium chloride or similar Lewis acids, therefore preventing dealkylation. Unfortunately, aryl salicylates are known to undergo photochemical rearrangement only to a low extent,[15,16] probably because of deactivation by intramolecular proton transfer in the excited state.[17,18] To circumvent this difficulty O-methylated derivatives have been tested[19,20] but surprisingly no study has been made concerning the suitability of aryl *o*-acetoxybenzoates as precursors of 2,2'-dioxygenated benzophenones.

Since the photochemical synthesis of condensed γ-pyrones is currently of interest in this laboratory[21,22] we decided to undertake such investigations, obtaining the results that are included in the present report.

RESULTS AND DISCUSSION

Our interest turned to *p*-methoxyphenyl *o*-acetoxybenzoate **1** by two reasons: (1) the *p*-position is blocked and cannot be acylated and (2) the OMe group allows a rapid estimation of the reaction complexity by NMR-spectroscopy. We were also interested in making a comparative study on the photochemistry of *p*-methoxyphenyl salicylate **2** in solvents of different polarity, in order to evaluate the influence of intramolecular H-bonding on the extent of photorearrangement.

Synthesis of p-*methoxyphenyl* o-*acetoxybenzoate*

p-Methoxyphenyl salicylate **2** had previously been prepared by standard procedures,[23] but we could not efficiently synthesize the O-acetyl derivative **1** by simply heating an equimolecular mixture of *o*-acetoxybenzoyl chloride with *p*-methoxyphenol in the absence of solvent. Under these conditions the expected product was obtained (18%), along with **2** (24%) and *p*-methoxyphenyl acetate (42%). This is in accordance with the ambivalent reactivity recently observed for *o*-acetoxybenzoyl chloride, that exists as an equilibrium mixture of open-chain and cyclic tautomers.[24-26]

Addition of pyridine to a solution of the reagents in CCl_4 and keeping the temperature below 5° resulted in almost quantitative yields of *p*-methoxyphenyl *o*-acetoxybenzoate **1**.

Irradiation of p-*methoxyphenyl salicylate*

When hexane was used as solvent, a 69% of starting material was recovered. UV spectroscopy showed that the percentage conversion was not affected by long irradiation times. *p*-Methoxyphenol was a minor side product (2%) and 2,2' - dihydroxy - 5 - methoxybenzophenone **3** was obtained in 8% yield.

The NMR spectrum of **3** evidenced the existence of two different OH groups, and the structure was confirmed by mass spectrometry.

Irradiation of **2** in methanol raised the percentage conversion to 93% and the 2,2' - dihydroxy - 5 - methoxybenzophenone yield to 23%. Other products were *p*-methoxyphenol (45, 8%) and methyl salicylate (5%).

Photosolvolysis can be explained by intramolecular hydrogen transfer in the excited state,[17,18] followed by nucleophilic attack by the solvent. Earlier work with phenyl salicylate[16] showed that in methanol the intramolecular H-bond is broken and the photo-Fries rearrangement is favored. However neither phenol nor methyl salicylate was found in the reaction mixture. That the observed solvolysis of **2** was light induced could be demonstrated by dark experiments.

Irradiation of p-*methoxyphenyl* o-*acetoxybenzoate*

The synthetic applications of *p*-methoxyphenyl salicylate as photochemical precursor of **3** are of limited value. We expected that acetylation of the OH group

would result in substantial improvement of the yield, as was confirmed later by irradiation of **1**. Using benzene as solvent 2' - acetoxy - 2 - hydroxy - 5 - methoxybenzophenone **4** was obtained and the yield was shown UV and NMR spectroscopically to be 70%. Purification by chromatography on silica gel is in this case not to recommend. Several fractions had to be rejected and the pure one accounted only for 60% of the total product.

Characteristic spectral features of **4** are the singletts at 11.4 (OH), 3.53 (OMe) and 1.92 δ (OCOMe) in NMR.

Transacylation in 2' - acetoxy - 2 - hydroxy - 5 - methoxybenzophenone

Compound **4** was not stable in silica gel, giving rise to 2' - acetoxy - 2 - hydroxy - 5' - methoxybenzophenone **5**. This was observed in the chromatographic purification of **4** and demonstrated by adsorbing the product in silica gel. After 42 hr an equilibrium was reached in which the relation between **4** and **5** was 1/3. Compound **5** exhibits singletts at 11.8 (OH), 3.75 (OMe) and 1.88 δ (OCOMe) in NMR. The IR spectra and MS fragmentation patterns of the two isomers are very similar.

The involved acetyl migration can be envisaged as an intramolecular transesterification, in which the breaking of the H-bond or the nucleophilic attack may be rate determining. Both processes are easier in **4** than in **5** and, therefore, the equilibrium lies over to the right.

This transformation suggested that 2,2' - dihydroxy - 5 - methoxybenzophenone **3** could be selectively acetylated. It was expected that the less strongly chelated OH would be the first in undergoing acetylation. Effectively, although 2 - 2' - diacetoxy - 5 - methoxybenzophenone **6** was the only product in boiling acetic anhydride, a mixture of **5** (80%), **4** (14%) and **6** (5%) resulted when acetyl chloride was used.

It must be emphasized that **4** was always a minor product, except when *p*-methoxyphenyl *o*-acetoxybenzoate was submitted to irradiation. This may be extensible to other 2' - acetoxy - 2 - hydroxybenzophenones.

2-Methoxyxanthone

Benzophenones **3–6** cyclised readily in the presence of 10% NaOH to 2-methoxyxanthone **7**, previously isolated[27,28] and synthesized by other methods.[29–31] Starting from **1** and omitting the chromatographic purification of **4** after irradiation, xanthone **7** was formed in 57% overall yield. All impurities (salicylic acid, *p*-methoxyphenol, hydroxybenzophenones, etc) were retained in the basic solution and a simple extraction with ether allowed the separation of 2-methoxyxanthone of high purity. The main advantages of this route are the use of simple starting materials, non acidic condtions and easy manipulations. Many other xanthones could in principle be prepared by the same way.

EXPERIMENTAL

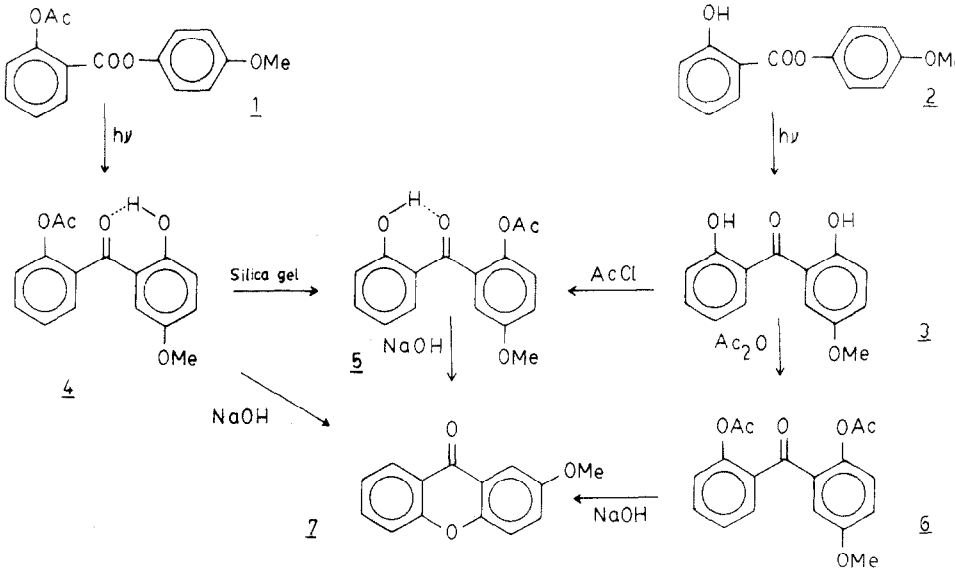
General

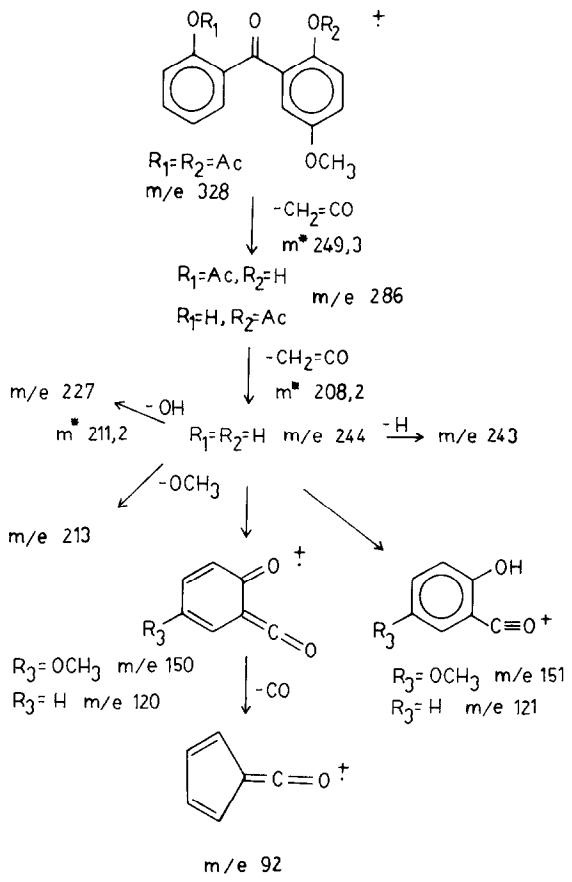
M.ps are uncorrected. Elemental analyses were performed in the Instituto de Química Orgánica (CSIC, Madrid) with a Perkin–Elmer 240 analyzer. IR spectra were obtained in CCl_4 with a Perkin–Elmer 577 spectrometer; for each band $\bar{\nu}_{max}$ (cm^{-1}) is given. NMR spectra were measured in CCl_4 with a 60 MHz Hitachi–Perkin–Elmer R-24 instrument. Chemical shifts are reported in ppm downfield (δ) from TMS. UV spectra were determined in EtOH with a Hitachi–Perkin–Elmer 200 spectrophotometer; absorbed radiation is defined by its wavelength λ_{max} in nm and the figures in brackets are log ϵ. Mass spectra were obtained with a Hitachi–Perkin–Elmer RMU 6 MG spectrometer; the ratios *m/e* and the relative intensities are reported.

To carry out the irradiations a 300 ml immersion well reactor, provided with a quartz sleeve and a 125 W medium pressure mercury lamp, was employed. The progress of the reactions was monitored by UV-spectroscopy. Chromatographic work was done with silica gel Merck PL 60 F_{254} (tlc), 60 PF_{254} (preparative tlc) and 60, 70–230 mesh (cc). Unless otherwise stated a mixture of hexane (2 parts) and ether (1 part) was used as eluent.

Preparation of **1**

Procedure A. 5.88 g (29.6 mmoles) *o*-acetoxybenzoyl chloride[32] and 3.68 g (29.6 mmoles) *p*-methoxyphenol were heated together at 100° for 1 hr. Column chromatography of the mixture afforded the following products: p-*methoxyphenyl salicylate* **2**[27] (1.76 g; 24.3%), m.p. 91–92°. IR: 1690 (C=O, ester); NMR: 10.40 (s, 1H, OH), 8.15–6.70 (m, 8 aromatic H), 3.80 (s, 3H, OCH_3); UV: 240 (4.1), 277 (3.6), 283 (3.6), 310 (3.7); MS: 244 (18), 124 (67), 123 (5), 121 (100), 120(2), 109(18), 95.8 (metastable), 93(10), 92(8), 71.5 (metastable); p-*methoxyphenyl acetate*, m.p. 30–32° (2.1 g, 42.3%); p-*methoxyphenyl* o-*acetoxybenzoate* **1** (1.92 g, 18.2%), m.p. 103° (cyclohexane). (Found: C 66.91 and H 5.08. Calc. for $C_{16}H_{14}O_5$: C 67.12 and H 4.92%). IR: 1765 (CH_3C=O) and 1740 (ArC=O); NMR: 8.17–6.60 (m, 8 aromatic H), 3.70 (s, 3H, OCH_3), 2.20 (s,





FRAGMENTATION PATTERN OF BENZOPHENONES

3H, $OCOCH_3$); UV: 227 (4.2), 279 (3.6), 283 (3.6); MS: 286 (1), 244 (2), 163 (36), 124 (24), 123 (10), 121 (100), 120 (7), 109 (8), 93 (12), 92 (11), 89.6 (metastable), 71.5 (metastable).

Procedure B. To a soln of 2.48 g (20 mmoles) *p*-methoxyphenol and 1.42 g (18 mmoles) pyridine in 25 ml CCl_4 were added dropwise 2.97 g (15 mmoles) *o*-acetoxybenzoyl chloride in 25 ml CCl_4. The mixture was maintained at 0°C during the addition (1 hr) and then allowed to stand for 3 hr. The crude was concentrated, extracted with ether, washed with water, dried (Na_2SO_4) and evaporated, giving 3.65 g of **1** (85.3%).

Irradiation of **2**

In hexane. 1 g of **2** was irradiated for 4 hr in hexane. The resulting soln was concentrated and the residue purified by column chromatography. Following products were isolated: 690 mg of starting material (69%); 8 mg of *p*-methoxyphenol (2%); 80 mg of 2,2' - *dihydroxy* - 5 - *methoxybenzophenone* **3** (8% yield), m.p. 93° (EtOH/water). (Found: C 68.52 and H 5.14. Calc. for $C_{14}H_{12}O_4$: C 68.84 and H 4.95%). IR: 1615 (C=O); NMR: 10.70 (s, 1H, 2'-OH), 10.10 (s, 1H, 2-OH), 7.70–6.60 (m, 7 aromatic H), 3.70 (s, 3H, OMe); UV; 261 (3.9), 345 (3.5); MS: 244 (81), 243 (9), 227 (38), 213 (6), 151 (26), 150 (100), 138 (37), 135 (14), 121 (43), 120 (72), 107 (13), 93 (17), 92 (81).

In methanol. Irradiation of **2** (1 g) for 11 hr in this solvent gave after work-up in the same way: 70 mg of starting material (7%); 50 mg of *methyl salicylate* (5%); 230 mg of **3** (23%) and 230 mg of *p*-methoxyphenol (45.8%).

In the absence of light and maintaining all other conditions, **2** was shown to be markedly stable.

Irradiation of **1**

2 g of **1** were irradiated for 11 hr in benzene. The resulting soln was concentrated and the crude was column chromatographed, affording the following pure fractions: starting material (70 mg, 3.5%); *p*-methoxyphenol (50 mg, 6%) and 2' - *acetoxy* - 2 - *hydroxy* - 5 - *methoxybenzophenone* **4** (800 mg, 40%). Yellow oil. (Found: C 66, 83 and H 5.02. Calc. for $C_{16}H_{14}O_5$: C67.12 and H 4.92%). IR: 1770 (C=O, ester), 1635 (C=O, ketone); NMR: 11.40 (s, 1H, OH), 7.55–6.50 (m, 7 aromatic H), 3.53 (s, 3H, OCH_3), 1.92 (s, 3H; OCHMe); UV: 261 (4.0), 335 (3.8); MS: 286 (22), 244 (62), 243 (21), 227 (46), 213 (7), 208.2 (metastable), 163 (5), 151 (24), 150 (100), 135 (9), 121 (44), 120 (3), 107 (13), 93 (12), 92 (10).

Transacylation of **4** *in silica gel*

To a soln of 720 mg of **4** in 50 ml ether were added 2.4 g of silica gel Merck 60 HF_{254}. After elimination of the solvent, the powder was allowed to stand at room temp. Periodically were taken aliquots, extracted with ether and concentrated, the residues being examined by NMR spectroscopy. New signals appeared, whose intensities increased with the time. After 42 hr no further change was observed. Extraction with ether, followed by elimination of the solvent, left a residue that crystallized partially on standing. Crystals were washed with ether and recrystallized from CCl_4/ether (m.p. 70–3°), pure 2' - *acetoxy* - 2 - *hydroxy* - 5' - *methoxybenzophenone* **5** (Found: C 67.21 and H 5.32. Calc. for $C_{16}H_{14}O_5$: C 67.12 and H 4.92%). IR: 1770 (C=O, ester), 1630 (C=O, ketone); NMR: 11.80 (s, 1H, OH), 7.70–6.50 (m, 7 aromatic H), 3.75 (s, 3H, OMe), 1.88 (s, 3H, OCOMe); MS: 286 (6), 244 (71), 243 (12), 227 (43), 213 (6), 211.2 (metastable), 151 (32), 150 (100), 135 (9), 122 (11), 121 (36), 120 (3), 107 (13), 93 (12), 92 (10). **5** constituted 75% and **4** 25% of the equilibrium mixture (measured NMR spectroscopically).

Acetylation of **3**

In acetic anhydride. **3** (1 g, 4.1 mmoles), pyridine (2 ml) and Ac_2O (20 ml) were refluxed for 2 hr and then poured into 100 ml

ice-water. After extraction with ether, the organic phase was washed with 10% $NaHCO_3$, dried (Na_2SO_4) and vacuum concentrated, giving 2,2' - *diacetoxy* - 5 - *methoxybenzophenone* **6** in quantitative yield, m.p. 67–69° (CCl_4/ether). (Found: C 65.63 and H 5.02. Calc. for $C_{18}H_{16}O_6$: C 65.84 and H 4.91%). IR: 1770 (C=O, ester), 1675 (C=O, ketone); NMR: 7.60–6.40 (m, 7 aromatic H), 3.72 (s, 3H, OMe), 1.93 (s, 3H, 2'-OCOMe), 1.85 (s, 3H, 2-$OCOCH_3$); UV: 255 (4.0), 290 (Sh); MS: 328 (2), 286 (61), 249.3 (metastable), 244 (100), 243 (15), 227 (37), 213 (4), 211.2 (metastable), 208.2 (metastable), 151 (18), 150 (86), 135 (5), 122 (4), 121 (18), 120 (1), 107 (8), 93 (7), 92 (7).

In acetyl chloride. To 1 g of **3** in 20 ml acetyl chloride was added a drop of pyridine and the mixture was refluxed for 30 min. After elimination of the excess acetyl chloride and preparative TLC of the residue were isolated **4** (150 mg, 14%), **5** (880 mg, 80%) and **6** (70 mg, 5%).

Cyclization to 2-methoxyxanthone **7**

General procedure. The appropriate benzophenone (2 mmoles) was refluxed in 10% NaOH (50 Ml) for 48 hr. The mixture was cooled and extracted with ether. Elimination of the solvent left 2-methoxyxanthone of high purity (360 mg, 80%).

This method was valid for compounds **3–6**. Using the crude photomixture from 1 g of **1** and operating as before, 450 mg of **7** were obtained (57% overall yield).

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