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PHOTOCHEMISTRY OF 7-ACETOXYBENZOPYRAN DERIVATIVES. SYNTHESIS OF EUPATORIOCHROMENE AND ENCECALIN

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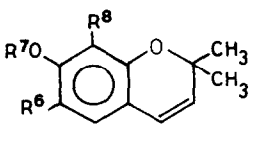
Abstract - The photolysis of the 7-acetoxybenzopyran derivatives **1a-5a** has been carried out. Chromene **1a** was found to undergo extensive photopolymerization. Chromanone **2a** underwent a rather inefficient photo-Fries rearrangement to the 6 - and 8 - acetyl derivatives **2b** and **2c**. Diacetoxychromene **3a** gave the unsaturated ketone **8** as the main product, besides its deacetylation analogue **9** and chromanone **11**. Diacetoxychroman **4a** afforded a mixture of four C-acetyl products: **1b**, **1c**, **2b** and **2c**, together with chromene **1a** and chromanone **2a**. Finally, irradiation of chroman **5a** gave rise to a mixture of the two possible photo-Fries products **5b** (43%) and **5c** (52%). The mechanistic implications of the above results are discussed, with special emphasis on the photoreactivity of the phenyl ester as compared with that of the pyran ring, the enol ester and the benzyl ester moieties. The synthetic applications of these transformations are illustrated with the preparation of eupatoriochromene **1b** and encecalin **1e**.

INTRODUCTION

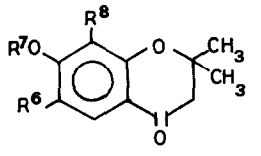
A number of naturally occurring 2,2-dimethyl-2H-chromenes carry an acetyl group, together with one or more oxygenated substituents, at the carbons of the benzene nucleus.[1] These compounds, as well as the chemistry involved in the synthesis of the basic ring system, are known for many years. However, no method for the acetylation of 2H-chromenes was available until very recently, due to resin formation under the acidic conditions usually employed in the Friedel-Crafts reactions. This has been partially circumvented by using weaker acids, but when the electron density of the styrenic double bond is considerably enhanced (for instance, in the case of the 7-methoxy derivative **1d**) resin continues to be the major product.[2]

With this background, we decided to carry out the photolysis of the 7-acetoxybenzopyran derivatives **1a - 5a**. It was expected that photo-Fries rearrangement[3] of the phenyl ester moiety would lead to the corresponding hydroxyketones **1b,c - 5b,c**. Eventually,

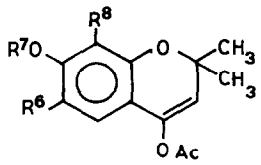
interconversions between the different photo-Fries products could in principle be achieved by well-established procedures. Moreover, the presence of a second interacting moiety with relevant photochemical properties in substrates **1a** (pyran ring), **2a** (aromatic ketone), **3a** (enol ester) and **4a** (benzyl ester) provided excellent models to compare photoreactivities and to establish the structural feature determining the photochemical behaviour, which appeared interesting from the fundamental point of view.



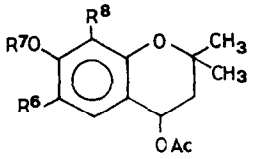
1a, b, c, d, e



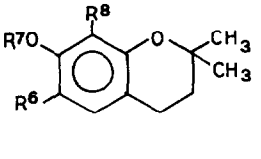
2a, b, c



3a, b, c



4a, b, c



5a, b, c

a: $R^6=R^8=H$, $R^7=COCH_3$
b: $R^6=COCH_3$, $R^7=R^8=H$
c: $R^6=R^7=H$, $R^8=COCH_3$
d: $R^6=R^8=H$, $R^7=CH_3$
e: $R^6=COCH_3$, $R^7=CH_3$, $R^8=H$

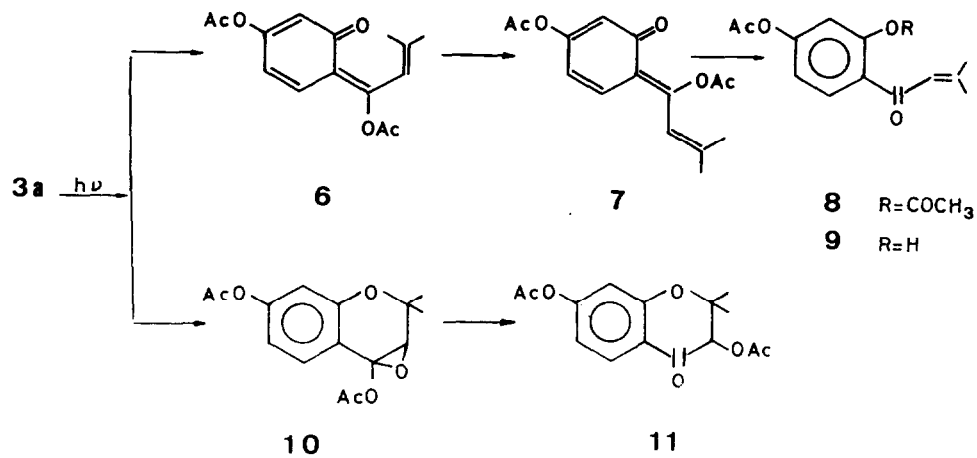
RESULTS AND DISCUSSION

7-Acetoxy-2,2-dimethyl-2H-chromene (**1a**)[4] was found to be extremely photolabile. UV-irradiation of this compound in hexane or benzene resulted in its progressive consumption, accompanied by the appearance of increasing amounts of polymer. No low molecular weight photoproducts could be isolated from the reaction mixtures. Likewise, attempts to detect such photoproducts by GC-MS and/or GC-FTIR failed.

In contrast with this behaviour, 7-acetoxy-2,2-dimethyl-4-chromanone (**2a**)[5] underwent a rather inefficient photorearrangement to the 6- and 8-acetyl derivatives **2b** (7%)[6] and **2c** (7%). Most of the starting material (85%) was recovered unchanged after irradiation during 3 h in hexane. Nonetheless, the reaction was clean, as indicated by the lack of polymer formation. The poor yields obtained for the photo-Fries products **2b** and **2c** clearly indicated that a substantial part of the excitation energy was wasted <u>via</u> the triplet state characteristic of the aromatic ketone moiety, instead of producing cleavage of the ester carbonyl-oxygen bond from the singlet state. This was not surprising, since acyl groups can be considered "deactivating" substituents for the photo-Fries rearrangement of aryl esters.[7]

Blocking of the carbonyl group of chromanone **2a**, via enol acetylation with isopropenyl acetate in the presence of p-toluenesulphonic acid, led to 4,7-diacetoxy-2,2-dimethyl-2H-chromene (**3a**). Photolysis of this compound during 1 h in

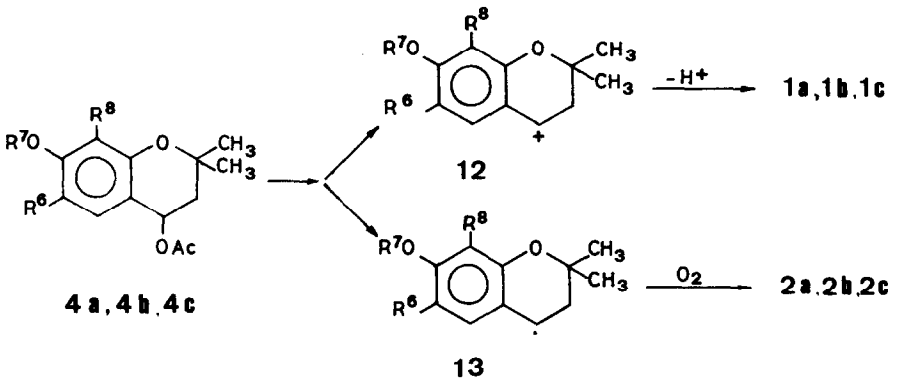
hexane solution afforded a mixture of the unsaturated ketones **8** (26%) and **9** (5%), together with 3,7-diacetoxy-2,2 dimethyl-4-chromanone (**11**,11%) and some unreacted starting material (22%). The formation of **8** can be explained by a photochemical electrocyclic opening of the pyran ring, to give the o-quinoneallide **6**, followed by cis-trans photoisomerization and transacylation. Hydrolysis of the 2-acetoxy group, possibly during the workup, would give rise to compound **9**. Chromanone **11** would arise from the starting chromene via incorporation of air oxygen, probably through a reactive 3,4-epoxide. Similar processes have been reported for the parent 4-acetoxy-2H-chromene,[8] although in that case the major product was a [2+2] cyclobutane dimer and the degree of ring opening to unsaturated ketones was markedly lower. Thus, the results obtained in the photolysis of **3a** show that the photoreactivity of the chromene system prevails over that of the aryl ester and enol ester moieties, being responsible for the photochemical behaviour of this compound.



Catalytic hydrogenation of the styrenic double bond of **3a** at atmospheric pressure gave 4,7-diacetoxy-2,2-dimethylchroman (**4a**). Its irradiation during 1 h in hexane gave a mixture of four C-acetyl products: the chromenes **1b**[9] (14%) and **1c** (14%) and the chromanones **2b** (4%) and **2c** (4%), besides 7-acetoxy-2,2-dimethyl-4-chromanone (**2a**, 16%) and some starting material (8%). Obviously, photo-Fries rearrangement of the phenyl ester must be the origin of the C-acylated products. Formation of the chromenes **1b** and **1c** would involve subsequent heterolytic cleavage of the benzylic acetate and deprotonation of the resulting cation **12**, while chromanones **2b** and **2c** would be the result of homolytic cleavage of the same moiety, followed by oxygen trapping of the benzylic radical **13**.[10]

Since irradiation of **1a** under similar conditions did not lead to **1b** or **1c**, it can be ruled out that the C-acetyl chromenes **1b** and **1c** are formed by a combination of the same processes but in the inverse order, i.e, breaking of the benzylic acetate prior to photo-Fries rearrangement. Likewise, the marked photostability of the chromanone **2a**

indicates that most of the C-acetyl chromanones **2b** and **2c** are formed from the C-acetyl chromanes **4b** and **4c** (not isolated), although a minor pathway could also involve the intermediacy of **2a**. Interestingly, irradiation of the diacetoxychroman **4a** during 30 min in benzene allowed isolation of 7-acetoxy-2,2-dimethyl-2H-chromene (**1a**) as the major product (30%), together with **1b** (13%), **1c** (13%), **2a** (9%), **2b** (2%), **2c** (1%) and **4a** (9%). Longer irradiation times produced a rapid disappearance of the chromene **1a**, accompanied by formation of increasing amounts of polymeric material. This contrasts with the fact that the rearranged chromenes **1b** and **1c** are remarkably photostable, which must be attributed to the posibility of hydrogen transfer from the phenolic to the carbonyl oxygen in the excited state, characteristic of the o-hydroxyaryl alkyl ketone moiety.[11] Thus, the results obtained in the photolysis of **4a** show that primary α-cleavage of the phenyl ester competes with β-cleavage of the benzylic ester, the latter being mainly heterolytic in nature.



Finally, irradiation of 7-acetoxy-2,2-dimethylchroman **5a** gave rise to a mixture of the two possible photo-Fries products **5b** and **5c** in very good yields (52 and 43%, respectively). Besides, a 5% of starting **5a** was recovered unchanged. In this case, the desired photorrearrangement of the phenyl ester appears to be the preferred pathway for deactivation of the excited molecule, due to the absence of lower energy chromophores. Hence, the photolysis of **5a** is of synthetic value, specially when coupled with oxidation of the photoproducts with dichlorodicyanoquinone (DDQ). This transformation was carried out under the usual conditions and afforded the C-acetyl chromenes **1b** (eupatoriochromene) and **1c** in almost quantitative yields. Methylation of **5b** with methyl iodide, under phase transfer catalysis conditions, followed by DDQ oxidation gave 6-acetyl-7-methoxy-2,2-dimethyl-2H-chromene **1a** (encecalin)[9] in 75% overall yield.

- EXPERIMENTAL -

General. Melting points were determined with a Büchi 510 apparatus and are uncorrected. Ir-spectra were obtained in CCl_4 solns with a Perkin-Elmer 781 spectrophotometer; $\bar{\nu}$ max (cm^{-1}) is given only for the main bands. ^{1}H-nmr spectra were measured in CCl_4 with a 60-MHz Varian 360 EM instrument; chemical shifts are reported in δ (ppm) values, using TMS as internal standard. Mass spectra were obtained with a Hewlett-Packard 5988 A spectrometer; the ratios m/e and the relative intensities (%) are reported. The combustion analyses were performed at the Instituto de Química Bio-Orgánica of C.S.I.C. in Barcelona. Isolation and purification were done by flash column chromatography on silica gel Merck 60, 70-230 mesh, using hexane as eluent, or alternatively by means of a Waters isocratic HPLC equipment provided with a semipreparative microporasil column, using hexane-ethyl acetate as eluent.

Preparation of 4,7-Diacetoxy-2,2-dimethyl-2H-chromene **3a**

To a solution of 7-hydroxy-2,2-dimethyl-4-chromanone (2g, 10 mmol) in pyridine (10 ml) was added acetic anhydride (2g), and the mixture was refluxed for 1 h. After cooling, the resulting solution was poured into concentrated hydrochloric acid (10 ml) and ice (50 g), and then extracted with dichloromethane. The organic layer was washed with aqueous sodium hydroxide (10%) and water, dried and evaporated to give pure 7-acetoxy-2,2-dimethyl-4-chromanone (**2a**) in quantitative yield.

The chromanone (1 g, 4 mmol), p-toluenesulphonic acid (0,2 g) and isopropenyl acetate (25 ml) were heated together at about 90°C, acetone being collected by distillation as it was formed. The reaction was monitored by NMR spectroscopy and was stopped at approximately 90% completion. The mixture was then partitioned between ether and water and the organic layer was washed with 10% $NaHCO_3$, dried and concentrated. The oily residue was purified by column chromatography, giving 0,75 g (75%) of **3a**. Analysis: C 65.53 H 6.15% (Calcd for $C_{15}H_{16}O_5$. C 65.21 H 5.83%); ir: 1760 (C=O), ^{1}H-nmr: 7.00 (d, J=9 Hz, 1H, 5-ArH), 6.53 (m, 2H, 6,8-ArH), 5,38 (s, 1H, CH=), 2.20 (s, 6H, 2 x $OCOCH_3$), 1.46 (s, 6H, 2 x CH_3); Ms: 276 (6), 261(7), 219(43), 191(5), 177(100), 148(4), 137(8), 91(3).

Preparation of 4,7 - Diacetoxy - 2,2 - dimethylchroman **4a**

The chromene **3a** (1g, 3.6 mmol) in ethyl acetate (25 ml) was hydrogenated in the presence of palladium on charcoal (11%) (0.1 g) until consumption of 85 ml of hydrogen. The solution was filtered and on evaporation afforded the pure chroman **4a** in quantitative yield. Oil; analysis: C 64.70 H 6.51% (Calcd for $C_{15}H_{18}O_5$: C 64.97 H 6.54%); ir: 1720 and 1750 (C=O); ^{1}H-nmr : 7.23 (d, J=7Hz, 1H, 5-ArH), 6.63 (m, 2H, 6,8-Ar H), 5.96 (t, J=6Hz, 1H, $CHOCOCH_3$), 2.25 (m, 2H, CH_2), 2.26 and 2.10 (s+s, 6H, 2 x $OCOCH_3$), 1.41 and 1.36 (s+s,

6H, 2 x CH_3); Ms : 278 (17), 236 (28), 177 (35), 176 (13), 161 (100), 139 (14), 138 (10), 137 (10).

Preparation of 7-Acetoxy-2,2-dimethyl chroman **5a**

7-Hydroxy-2,2-dimethyl-4-chromanone (1 g, 5 mmol) was dissolved in dry tetrahydrofuran (75 ml) and treated with an excess of lithium aluminium hydride (336 mg, 5 mmol). The reaction mixture was stirred for 2h, quenched with a few drops of saturated aqueous sodium sulphate and partitioned between brine and ethyl acetate. The organic extract was washed with water, dried and evaporated. To the resulting oil was added pyridine (10 ml) and acetic anhydride (2g) and the reaction mixture was refluxed for 1h. After cooling the solution was then poured into a mixture of concentrated hydrochloric acid (10 ml) and ice (50 g). The products were extracted with dichloromethane and the extracts were washed with aqueous sodium hydroxide (10%) and water, dried and evaporated. The residue was purified by chromatography on a short silica gel column using dichlorometane as eluent, affording 7-acetoxy-2,2-dimethyl-2H-chromene (**1a**) in 60% yield. A stirred solution of the chromene **1a** (1g, 4.6 mmol) in ethyl acetate (25 ml) was hydrogenated with palladium/charcoal (10%) (0.1 g) for 2 h and then filtered. The resulting filtrate was evaporated to give the pure chroman **5a** in quantitative yield. M.p. 60°C; analysis: C 70.98 H 7.34% (Calcd for $C_{13}H_{16}O_3$: C 70.88 H 7.33%); ir: 1740 (C=O); ^{1}H-nmr : 7.10 (d, J=10 Hz, 1H, 5-ArH), 6.60 (m, 2H, 6,8-ArH), 2.80 (t, J=6 Hz, 2H, 4-CH_2) 2.26 (s, 3H, $OCOCH_3$); 1.80 (t, J=6Hz, 2H, 3-CH_2) 1.33 (s, 6H, 2 x CH_3); Ms : 220 (11), 178 (31), 163 (15), 123 (100), 110 (3), 107 (3), 91 (4).

General irradiation procedure. A soln of 1g of the substrate in 400 ml of freshly distilled hexane or benzene was irradiated at r.t with a 125 W medium pressure mercury lamp inside a quartz immersion well. The photoproducts were isolated, after removal of the solvent, with silica gel flash-column chromatography, using hexane as eluent, and subsequently by HPLC.

Spectral and analytical data of the photoproducts

8-Acetyl-7-hydroxy-2,2-dimethyl-2H-chromene **4a**

Oil; analysis: C 71.32 H 6.91% (Calcd for $C_{13}H_{14}O_3$: C 71.54 H 7.16%); ir : 1620 (C=O); ^{1}H-nmr: 13.06 (s, 1H, OH), 7.06 (d, J=8 Hz, 1H, 5-ArH), 6.45 (d, J=8Hz, 1H, 6-ArH),, 6.25 and 5.48 (AB, J=10Hz, 2H, CH=CH), 2.73 (s, 3H, $COCH_3$), 1.50 (s, 6H, 2 x CH_3); Ms : 218 (18), 203 (100), 185 (42), 161 (3), 131 (3), 128 (6), 115 (3), 94 (10).

8-Acetyl-7-hydroxy-2,2-dimethyl-4-chromanone **2c**

M.p. 96°C; analysis: C 67.23 H 6.04% (Calcd for $C_{13}H_{14}O_4$: C 66.65 H 6.02%); ir : 1680 (C=O ketone), 1620 (C=O chelated ketone); ^{1}H-nmr : 13.75 (s, 1H, OH), 7.92 (d, J=10Hz, 1H, 5-ArH), 6.50 (d, J=10Hz, 1H, 6-ArH), 2.63 (s, 3H, $COCH_3$), 2.58 (s, 2H, CH_2), 1.51 (s, 6H, 2 x CH_3); Ms: 234 (66), 219 (100), 201 (15), 179 (50), 163 (60), 161 (24), 150 (88).

6-Acetyl-7-hydroxy-2,2-dimethylchroman **5b**

M.p. 85°C; analysis : C 70.51 H 7.18% (Calcd for $C_{13}H_{16}O_3$: C 70.88 H 7.33%); ir: 1640 (C=O); ^{1}H-nmr : 12.40 (s, 1H, OH), 7.46 (s, 1H, 5-ArH), 6,36 (s, 1H, 8-ArH), 2.73 (t, J=6Hz, 2H, 4-CH_2), 2.56 (s, 3H, $COCH_3$), 1.80 (t, J=6Hz, 2H, 3CH_2), 1.36 (s, 6H, 2 x CH_3), Ms : 220 (33), 205 (21), 177 (3), 165 (100), 163 (6), 149 (7), 147 (11), 121 (4).

8-Acetyl-7-hydroxy-2,2-dimethylchroman **5c**

M.p. 44-45°C; analysis: C 70.57 H 7.30% (Calcd for $C_{13}H_{16}O_3$: C 70.88 H : 7.33%); ir : 1620 (C=O); ^{1}H-nmr : 13.10 (s, 1H, OH), 7.10 (d, J=8Hz, 1H, 5-ArH), 6.45 (d, J=8Hz, 1H, 6-ArH), 2.70 (t, J=6Hz, 2H, 4-CH_2) 1.80 (t, J=6Hz, 2H, 3-CH_2), 1.40 (s, 6H, 2 x CH_3); Ms: 220 (37), 205 (9), 203 (7), 177 (5), 165 (10), 149 (9), 147 (22), 121 (5).

1-(2,4-Diacetoxyphenyl)-3-methyl-2-buten-1-one **8**

Oil, ir : 1760 (C=O ester), 1660 (C=O ketone); ^{1}H-nmr: 7.66 (d, J=9Hz, 1H, 6-ArH), 7.00 (m, 2H, 3,5-ArH), 6.40 (bs, 1H, -CH=), 2.16 (s, 6H, 2 x $OCOCH_3$), 2.10 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$), 1.90 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$); Ms : 276 (0.3), 261 (11), 219 (30), 177 (100), 107 (2), 69 (2).

1-(4-Acetoxy-2-hydroxyphenyl)-3-methyl-2-buten-1-one **9**

M.p. 53-55°C; analysis : C 66.59 H 6,36% (Calcd for $C_{13}H_{14}O_4$: C 66.66 H 6.02%); ir : 1760 (C=O ester), 1630 (C=O ketone); ^{1}H-nmr : 12.80 (s, 1H, OH), 7.66 (d, J=8Hz, 1H, 6-ArH), 6.65 (m, 3H, 3,5-ArH, -CH=), 2.25 (s, 6H, $OCOCH_3$, $H\diagup C = C\diagup^{CH_3}_{CH_3}$), 2.03 (s, 3H, $H\diagup C = C\diagup^{CH_3}_{CH_3}$); Ms : 234 (3), 219 (29), 191 (4), 177 (100), 137 (15), 115 (4), 108 (7).

3,7-Diacetoxy-2,2-dimethyl-4-chromanone **11**

M.p. 138°C; analysis : C 62.02 H 5.44% (Calcd for $C_{15}H_{16}O_6$: C 61.64 H 5.51%); ir : 1760 (C=O ester), 1700 (C=O ketone); ^{1}H-nmr : 7.83 (d, J=9 Hz, 1H, 5-ArH), 6.76 (m, 2H, 6,8-ArH), 5.56 (s, 1H, CH), 2.30 and 2.23 (s+s, 6H, 2 x $OCOCH_3$), 1.53 and 1.35 (s+s, 6H, 2

x CH_3); Ms : 292 (7), 250 (9), 190 (19), 179 (28), 137 (100), 108 (8).

Preparation of eupatoriochromene **1b**

The chroman **5b** (300 mg) and DDQ (400 mg) in 50 ml of dry benzene were refluxed 1 h under argon atmosphere. Filtration and evaporation gave the pure chromene **1b** in quantitative yield.

Preparation of encecalin **1e**

To a magnetically stirred solution of **5b** (300 mg, 1.3 mmol) in NaOH 25% (2.5 ml) were added tetraethyl-ammonium hydroxide (100 mg, 0.68 mmol) and subsequently methyl iodide (225 mg, 1.58 mmol). The reaction mixture was maintained at 60-65°C for 1 h and then poured in water (20 ml) and extracted with dichloromethane. The solvent was evaporated and the crude residue was dissolved in 50 ml of benzene and treated with DDQ (400 mg) for 1 h a reflux temperature. Filtration and evaporation gave chromene **1e** in 80% yield.

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6 Attempts to isolate this compound failed. However, its presence and percentage in the photolysis mixture was assessed by GC-MS: 234(60), 219(100), 179(55), 163(42), 150(28), 95(18).

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