APPLICATION OF THE PHOTO-FRIES REARRANGEMENT OF ARYL *N*-CHLOROACETYLANTHRANYLATES AS KEY STEP IN THE SYNTHESIS OF 5-(2-HYDROXYPHENYL)-1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPIN-2-ONES

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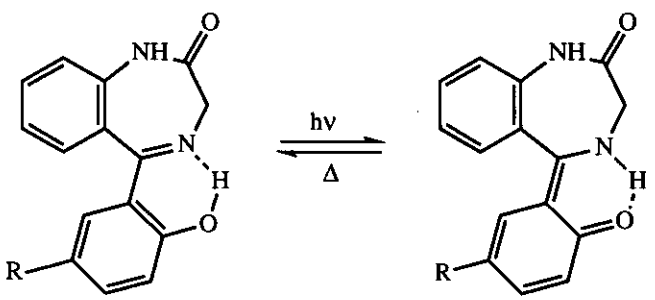
Abstract - Condensation of isatoic anhydride with phenols, followed by treatment of the resulting aryl anthranylates (**4**) with chloroacetyl chloride gives aryl *N*-chloroacetylanthranylates (**5**). Their uv-irradiation results in photo-Fries rearrangement, to afford benzophenones (**6**). Direct treatment of the latter with ammonia gives rise to 1,3-quinazolines (**7**); by contrast, treatment of **6** with potassium iodide and subsequently with ammonia leads to 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (**1**).

The 1,4-benzodiazepines constitute a major therapeutic group, with a wide variety of effects on the central nervous system.[1] Although they present a highly favourable benefit-to-risk ratio, some unwanted side effects associated to their use have been reported, including certain cutaneous alterations which appear in patients taking the drugs upon exposure to sunlight.[2-5] This has promoted a series of studies on the photochemical behaviour of 1,4-benzodiazepines, in an attempt to establish the molecular bases of the phototoxicity observed in clinical practice.[6-10] In some cases, it has been possible to isolate and identify well-defined photoproducts, which appear to

be responsible (at least in part) for their photobiological properties.[10] Singlet oxygen and other active oxygen species have been detected upon photolysis of certain 1,4-benzodiazepines;[11,12] their contribution would also explain the photosensitized damage to biological systems mediated by these drugs.

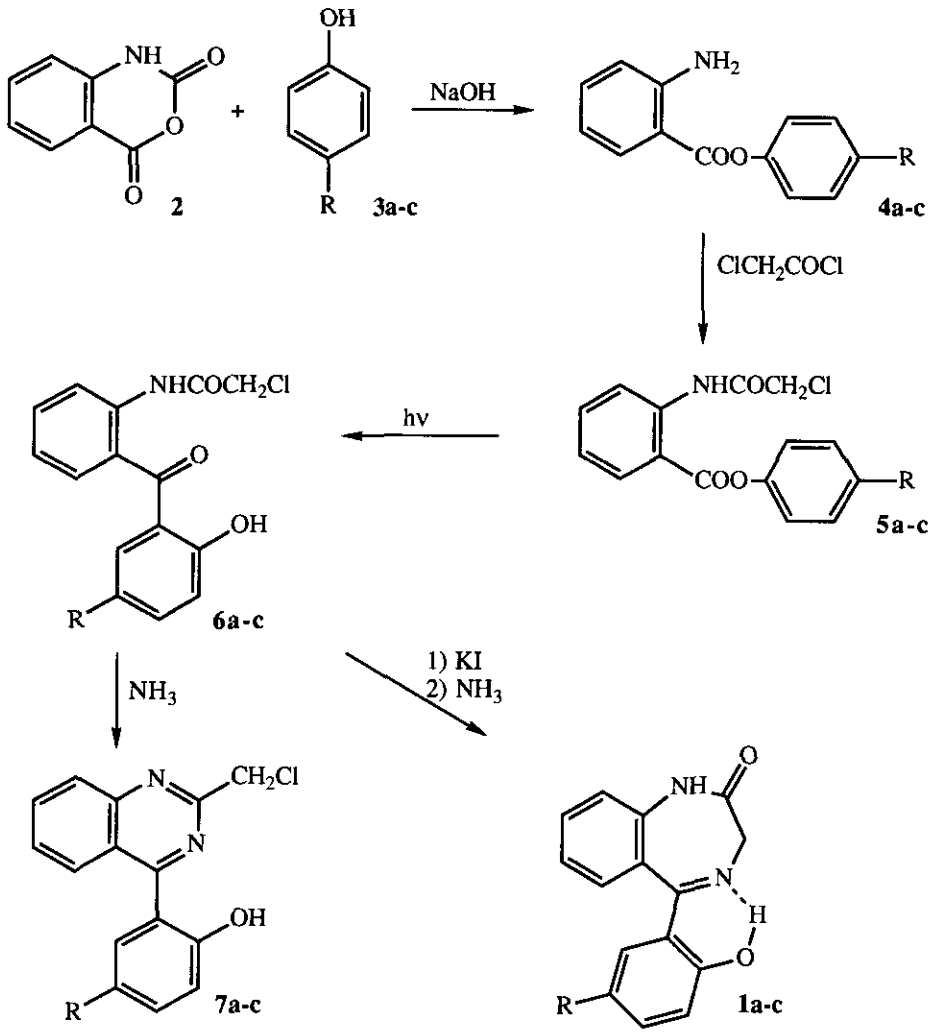
In view of the above precedents, it appeared interesting to synthesize a series of 5-(2-hydroxyphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones (**1**), where chelation of the phenolic hydroxy group with the imino nitrogen atom should provide a very efficient, energy wasting channel for photochemical deactivation.[13-15] In this context, it is well known that intramolecular excited state proton transfer (ESPT) between two heteroatoms, through six membered cyclic transition states, is a general mechanism for the photostabilization of *ortho*-substituted phenols, because it results exclusively in thermally reversible tautomerization processes.[13]



1 **a**: R = H **1′**
b: R = Me
c: R = OMe

The synthetic route employed to prepare the required compounds is based on the photo-Fries rearrangement[16] of aryl *N*-chloroacetylanthranylates (**5**) as key step and constitutes a new approach to the 1,4-benzodiazepine ring system. Nucleophilic opening of isatoic anhydride (**2**) was carried out with good yields (78-98 %) by means of the corresponding phenols (**3**), using dioxane as solvent and NaOH as catalyst.[17-19] This reaction was followed by treatment of the aryl anthranylates (**4**) with chloroacetyl chloride in a biphasic solvent system consisting of chloroform and aqueous sodium bicarbonate. This led to the *N*-chloroacetyl derivatives (**5**) with

reasonable yields (64-75 %). Their photochemistry could follow in principle three different pathways: i) dehalogenation to the *N*-acetyl analogues, ii) dehalogenative cyclization to 2-oxindoles and iii) photo-Fries rearrangement to 2,2′-disubstituted benzophenones (**6**). Pathways i) and ii) are characteristic of α-chloroacetanilides,[20-24] while iii) is common for aryl esters.[16,25] Fortunately, photolysis of the aryl *N*-chloroacetylanthranylates (**5**) gave the rearranged benzophenones (**6**) as single products, although yields were only moderate (35-37 %). A substantial amount of starting material was recovered in the three cases and its recycling allowed to improve the preparative applicability of the method.



The observed predominance of photo-Fries rearrangement can be justified on the basis of electron deficiency at the chloroacetanilide ring, owing to the carboxylate substituent. This prevents excited state electron transfer from the aromatic nucleus to the chloroacetyl side chain, which is the initial step leading to photodehalogenation by both pathways i) and ii).[23]

The final step of the synthetic scheme was cyclocondensation of the benzophenones (**6**) with ammonia. Direct bubling of the latter through solutions of **6** in THF led to the quinazolines (**7**), probably through the corresponding imine intermediates; however, exchange of the halogen by treatment with potassium iodide prior to cyclocondensation with ammonia afforded the desired 1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones (**1**) with reasonable chemical yields (60-75 %).

The results obtained in this work have illustrated the applicability of the photo-Fries rearrangement of aryl *N*-chloroacetylanthranylates (**5**) to the synthesis of 5-(2-hydroxyphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones (**1**). Their photochemical and photobiological properties are currently under study.

EXPERIMENTAL

Melting points are uncorrected. Combustion analyses were performed at the Instituto de Química Bio-Orgánica of the C.S.I.C. (Barcelona). Ir spectra were determined in KBr discs or nujol with a Perkin-Elmer 577 spectrophotometer; absorptions (ν, cm^{-1}) are given only for the main bands. ^{1}H-Nmr spectra were recorded in $CDCl_3$ with a 60 MHz Hitachi Perkin-Elmer R-24B or (in the case of **1a-c**) a 300 MHz Varian Gemini; chemical shifts are reported as δ (ppm) values relative to TMS. Ms were measured with a Hewlett-Packard 5930 A spectrometer using direct introduction HDIS; the m/z ratios and relative abundances (in brackets) are given only for the most important peaks. Purification of the crude reaction mixtures was carried out by preparative tlc on silicagel Merck 60 PF_{254}.

Preparation of aryl anthranylates (**4a-c**)

A solution of isatoic anhydride (**2**) (8.15 g, 50 mmol), the corresponding phenol (50 mmol) and NaOH (0.1 g, 2.5 mmol) in dioxane (40 ml) was heated at 90 °C under magnetic stirring for 3 h until no CO_2 was evolved. The reaction mixture was poured into 200 ml of ice-water, under vigorous magnetic stirring. After 15 min the resulting brown precipitate was filtered and washed with cold water. Recrystallization afforded pure samples of **4a-c**.

Preparation of aryl *N*-chloroacetylanthranylates (**5a-c**)

A solution of chloroacetyl chloride (3.78 ml, 41.5 mmol) in chloroform (50 ml) was added dropwise to a biphasic system containing the corresponding anthranylate (32 mmol) in chloroform (50 ml) and a saturated aqueous solution of $NaHCO_3$ (75 ml). After 20 min under magnetic stirring the layers were separated. The organic layer was washed several times with water and dried with anhydrous Na_2SO_4. Evaporation of the solvent followed by recrystallization gave the *N*-chloroacetylanthranylates in pure form.

Irradiations

A solution of aryl *N*-chloroacetylanthranylate (1 g, ca. 3.3 mmol) in benzene (200 ml) was irradiated at room temperature in an immersion well photoreactor equipped with a HQL 125W medium pressure mercury lamp and a quartz cooling jacket. After 5 h, the solvent was removed and the photoproducts were purified by preparative tlc, using a mixture of n-hexane and ethyl acetate (5:2, vol/vol) as eluent. Analytical samples of the benzophenones (**6a-c**) were obtained upon recrystallization.

Reaction of 2-chloroacetylamino-2'-hydroxybenzophenones (**6**) with ammonia

Through a solution of the corresponding benzophenone (500 mg, ca. 1.6 mmol) in tetrahydrofuran (60 ml) ammonia was bubbled during 15 h at room temperature. Then, the solvent was evaporated in vacuo and the residue was purified by preparative tlc, using mixtures of methylene chloride and ethyl acetate (7:1, vol/vol)

(**7c**) or chloroform and ethyl acetate (30:1, vol/vol) (**7a,b**) as eluents. Final recrystallization from cyclohexane (**7c**) or n-hexane (**7a,b**) gave the corresponding 1,3-quinazolines.

Preparation of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (**1**)

To a solution of the corresponding 2-chloroacetylamino-2'-hydroxybenzophenone (200 mg, ca. 0.7 mmol) in dry acetone (50 ml) was added powdered potassium iodide (300 mg, 1.8 mmol). The mixture was refluxed for 3-5 h. After filtration, acetone was removed under reduced pressure. The residue was dissolved in dry tetrahydrofuran (50 ml) and ammonia was bubbled through this solution during 6 h at room temperature. Evaporation of the solvent followed by recrystallization from acetone or ethyl acetate yielded the desired 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (**1a-c**).

Products

Phenyl anthranylate (**4a**), (98%), recrystallized from n-hexane, mp 71-72 °C (lit.,[18] 72 °C).

4-Methylphenyl anthranylate (**4b**), (72%), recrystallized from n-hexane, mp 70 °C (lit.,[19] 69-70 °C).

4-Methoxyphenyl anthranylate (**4c**), (75%), recrystallized from n-hexane, mp 102-103 °C (lit.,[19] 103 °C).

Phenyl *N*-chloroacetylanthranylate (**5a**), (64%), recrystallized from n-hexane, mp 106-108 °C; Anal. Calcd for $C_{15}H_{12}NO_3Cl$: C, 62.19; H, 4.17; N, 4.83; Cl, 12.24. Found: C, 62.25; H, 4.17; N, 5.03; Cl, 12.18; ir (KBr) 3260, 1705, 1675; ^{1}H-nmr 8.8-6.8 (m, 9H, ArH), 4.1 (s, 2H, $COCH_2Cl$).

4-Methylphenyl *N*-chloacetylanthranylate (**5b**), (70%), recrystallized from n-hexane, mp 98-100 °C; Anal. Calcd for $C_{16}H_{14}NO_3Cl$: C, 63.27; H, 4.65; N, 4.61; Cl, 11.67. Found: C, 63.46; H, 4.67; N, 4.55; Cl, 11.64; ir (KBr) 3260, 1720, 1680; ^{1}H-nmr 8.8-6.8 (m, 8H, ArH), 4.1 (s, 2H, $COCH_2Cl$), 2.4 (s, 3H, Ar-CH_3).

4-Methoxyphenyl *N*-chloroacetylanthranylate (**5c**), (75%), recrystallized from

cyclohexane, mp 121-123 °C; Anal. Calcd for $C_{16}H_{14}NO_4Cl$: C, 60.10; H, 4.41; N, 4.38; Cl, 11.09. Found: C, 60.19; H, 4.40; N, 4.36; Cl, 11.12; ir (KBr) 3220, 1710, 1670; ^{1}H-nmr 8.9-6.5 (m, 8H, ArH), 4.1 (s, 2H, $COCH_2Cl$), 3.7 (s, 3H, OCH_3).

2-Chloroacetylamino-2'-hydroxybenzophenone (**6a**), (37%), recrystallized from ether/cyclohexane, mp 107-108 °C; Anal. Calcd for $C_{15}H_{12}NO_3Cl$: C, 62.19; H, 4.17; N, 4.83. Found: C, 62.14; H, 4.16; N, 4.83; ir (nujol) 1690, 1620; ^{1}H-nmr 11.8 (s, 1H, OH), 10.5 (s,1H, NH), 9.0-6.5 (m, 8H, ArH), 4.2 (s, 2H, $COCH_2Cl$).

2-Chloroacetylamino-2'-hydroxy-5'-methylbenzophenone (**6b**), (35%), recrystallized from ether/n-hexane, mp 101-103 °C; Anal. Calcd for $C_{16}H_{14}NO_3Cl$: C, 63.27; H, 4.65; N, 4.61; Cl, 11.67. Found: C, 63.45; H, 4.71; N, 4.65; Cl, 11.41; ir (nujol) 1670, 1620; ^{1}H-nmr 11.4 (s, 1H, OH), 10.2 (s, 1H, NH), 8.5-6.5 (m, 7H, ArH), 4.1 (s, 2H, $COCH_2Cl$), 2.2 (s, 3H, Ar-CH_3).

2-Chloroacetylamino-2'-hydroxy-5'-methoxybenzophenone (**6c**), (37%), recrystallized from ethyl acetate/n-hexane, mp 150-152 °C; Anal. Calcd for $C_{16}H_{14}NO_4Cl$: C, 60.10; H, 4.41; N, 4.38; Cl, 11.09. Found: C, 59.51; H, 4.35; N, 4.34; Cl, 11.53; ir (KBr) 1700, 1620; ^{1}H-nmr 11.2 (s, 1H, OH), 10.4 (s, 1H, NH), 8.5-6.5 (m, 7H, ArH), 4.1 (s, 2H, $COCH_2Cl$), 3.6 (s, 3H, OCH_3).

2-Chloromethyl-4-(2-hydroxyphenyl)quinazoline (**7a**), (43%), recrystallized from n-hexane, mp 117-119 °C; Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.65; H, 4.10; N, 10.26; Cl, 13.09. Found: C, 66.61; H, 4.14; N, 10.26; Cl, 12.85; ^{1}H-nmr 11.3 (s, 1H, OH), 8.0-6.5 (m, 8H, ArH), 4.7 (s, 2H, CH_2Cl); ms 272 (17), 271 (36), 270 (62), 269 (100), 235 (31), 233 (56), 206 (20), 205 (16), 139 (18).

2-Chloromethyl-4-(2-hydroxy-5-methylphenyl)quinazoline (**7b**), (35%), recrystallized from n-hexane, mp 103-105 °C; Anal. Calcd for $C_{16}H_{13}N_2OCl$: C, 67.46; H, 4.60; N, 9.84; Cl, 12.45. Found: C, 67.46; H, 4.65; N, 9.85; Cl, 12.34; ^{1}H-nmr 11.2 (s, 1H, OH), 8.5-6.5 (m, 7H, ArH), 4.8 (s, 2H, CH_2), 2.3 (s, 3H, Ar-CH_3); ms 286 (34), 285 (42), 284 (80), 283 (100), 269 (26), 249 (34), 248 (31), 247 (38), 102 (18).

2-Chloromethyl-4-(2-hydroxy-5-methoxyphenyl)quinazoline (**7c**), (39%), recrystallized from cyclohexane, mp 152-153 °C; Anal. Calcd for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.36; N, 9.31; Cl, 11.79. Found: C, 63.91; H, 4.41; N, 9.29; Cl, 11.48; ^{1}H-nmr

11.0 (s, 1H, OH), 8.5-6.5 (m, 7H, ArH), 4.7 (s, 2H, CH_2), 3.6 (s, 3H, OCH_3); ms 302 (29), 301 (24), 300 (86), 299 (31), 287 (28), 286 (16), 285 (100), 257 (30), 221 (33), 193 (27), 192 (16), 167 (25), 166 (43), 140 (23), 127 (17).

5-(2-Hydroxyphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**1a**), (60%), recrystallized from ethyl acetate, mp > 250 °C (decomp.); Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.38; H, 4.78; N, 10.96; ir (KBr) 1690; ^{1}H-nmr 7.6-6.6 (m, 8H, ArH), 4.6 + 3.8 (d+d, J=12 Hz, 2H, CH_2).

5-(2-Hydroxy-5-methylphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**1b**), (68%), recrystallized from acetone, mp > 250 °C (decomp.); Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.16; H, 5.29; N, 10.45; ir (KBr) 1690; ^{1}H-nmr 8.5-7.0 (m, 7H, ArH), 4.6+3.8 (d+d, J=12 Hz, 2H, CH_2), 2.4 (s, 3H, CH_3).

5-(2-Hydroxy-5-methoxyphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**1c**), (75%), recrystallized from acetone, mp >240 °C (decomp.); Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 4.99; N, 9.92. Found: C, 68.11; H, 5.01; N, 9.87; ir (KBr) 1690; ^{1}H-nmr 7.7-6.6 (m, 7H, ArH), 4.7+3.8 (d+d, J=12 Hz, 2H, CH_2), 3.6 (s, 3H, OCH_3).

ACKNOWLEDGEMENT

Financial Support by the Spanish DGICYT (Grant No. PB 91-0540) is gratefully acknowledged.

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Received, 28th May, 1993