PYRAZOLES AND ISOXAZOLES DERIVED FROM 2-HYDROXY-ARYL PHENYLETHYNYL KETONES: SYNTHESIS AND SPECTROPHOTOMETRIC EVALUATION OF THEIR POTENTIAL APPLICABILITY AS SUNSCREENS

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Abstract - Reaction of the acetylenic ketones (**1**) with hydrazine or hydroxylamine leads to the pyrazoles (**2**) or the isoxazoles (**3**), respectively. Spectrophotometric evaluation of the UV-photoprotecting ability as compared to p-aminobenzoic acid (PABA) shows that the predicted effectiveness of **2** and the 3-phenylisoxazoles (**3B**) is very close to that of PABA, while that of the 5-phenylisoxazoles (**3A**) is clearly lower. The pyrazoles (**2**) are more stable than PABA upon UV-irradiation in cyclohexane solution.

Heterocycles containing a phenolic hydroxy group intramolecularly hydrogen bonded to nitrogen or oxygen are interesting because of their applicability in the protection against UV-irradiation damage.[1] These compounds have attracted considerable attention[1] from the practical point of view as potential sunscreens, but also in connection with the

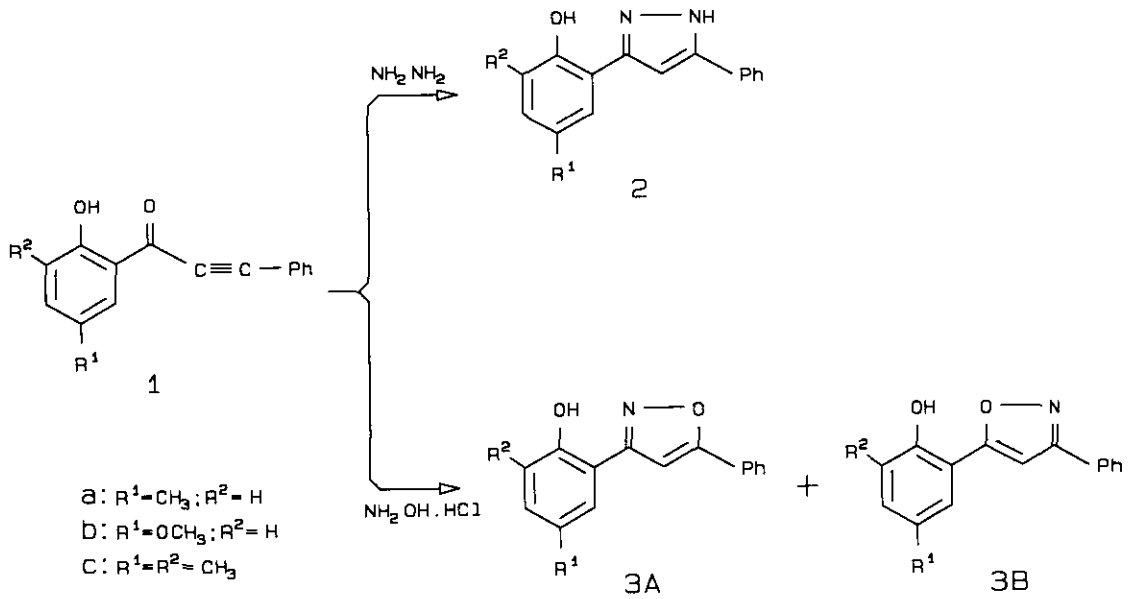
possibility of proton transfer in their excited states,[2] as a nonradiative deactivation pathway responsible for their photostability.[1,2] For these reasons we interested in the reaction of 2-hydroxyaryl phenylethynyl ketones (**1**) with hydrazine or hydroxylamine as potential source of the pyrazoles (**2**) or the isoxazoles (**3**), respectively. In spite of being the dehydrogenated analogues of the well-known o-hydroxychalcones,[3] the chemistry of acetylenic ketones such as **1** remains almost unexplored.[4]

On the other hand, the literature reports dealing with the preparation of phenolic heterocycles analogous to **2** or **3** are very scarce,[5] being specially noteworthy that, with few exceptions,[5d,f] a wrong structure has been assigned to the isoxazoles.

The required 2-hydroxyaryl phenylethynyl ketones (**1**) were prepared by photo-Fries rearrangement of the corresponding aryl esters as previously described.[4a] The reaction of **1** with aqueous hydrazine in ethanol at room temperature afforded the phenolic pyrazoles (**2**) with yields ranging from 52 to 59%. Likewise, treatment of the acetylenic ketones (**1**) with hydroxylamine hydrochloride in boiling ethanol gave rise to mixtures of the isomeric isoxazoles (**3A**) and (**3B**), except in the case of **1b** which was converted into a single regioisomer (**3Ab**).

The structures of the cyclocondensation products were unequivocally assigned by spectroscopic methods and elemental analysis. Mass spectrometry was of critical importance to differentiate between structures **3A** and **3B** for the hydroxylamine adducts. Thus, isoxazoles with nitrogen linked to the carbonyl carbon atom (**3A**) underwent predominant cleavage to the benzoyl cation (m/z 105), which was always the base peak.[6] The complementary ions [M^+ - 105] were also observable. The isomeric isoxazoles (**3B**) gave also the substituted benzoyl cations, but their most salient spectroscopic feature was an unprecedent 1,5 hydrogen migration from oxygen to the C-4 carbon, followed by fragmentation of the

heterocyclic ring to the ions with m/z 117 and [M^+ - 117]. The former were the most prominent peaks of the spectra.



After realizing that the reaction of 2-hydroxyaryl phenylethynyl ketones (**1**) *with hydrazine and hydroxylamine affords* phenolic heterocycles of potential use in UV-photoprotection, we performed a preliminary evaluation of this property based on spectrophotometric absorption measurements of the obtained products. Since our interest was mainly focused on the possible application as sunscreens in dermatology or cosmetics, it was necessary to take into account a weighting factor derived from the combination of the solar spectrum at the earth's surface with the erythemal action spectrum for human skin, in order to give the appropiate importance to each particular wavelength.[7] Table 1 summarizes the photoprotecting ability of compounds (**2**) and (**3**). The numerical values given are relative to p-aminobenzoic acid (PABA), one of the most common active ingredients of sunscreen preparations.[8]

Table 1. Photoprotecting ability of the heterocycles (**2**) and (**3**).

Compound	λmax (nm)	log ε	Photoprotection[a]
2a	301	3.8	0.60
2b	315	3.9	0.66
2c	302	3.9	0.71
3Aa	305	3.7	0.43
3Ab	323	3.8	0.44
3Ac	311	3.7	0.49
3Ba	316	4.0	0.75
3Bc	314	4.0	0.82

[a]Calculated as the overlap of the absorption spectra with the combination of the solar spectrum at the earth's surface and the erythemal action spectrum. Values are related to that of PABA, taken arbitrarily as being equal to 1.

According of these data, the predicted effectiveness of the pyrazoles (**2**) and the isoxazoles (**3B**) is very close to that of PABA, while the isomeric isoxazoles (**3A**) are clearly less effective.

A further important point concerning the usefulness of sunscreens or any other ultraviolet stabilizers is their reluctance to undergo photochemical degradation.[2] In fact, one of the most immportant drawbacks of PABA is associated to its photolability, which appears to be responsible for the known photosensitizing properties of this compound.[9] We have followed spectrophotometrically the behavior of cyclohexane solutions of the obtained heterocycles upon UV-irradiation and found that the pyrazoles (**2**) are substantially more stable than PABA under the same conditions (Figures 1a,b).

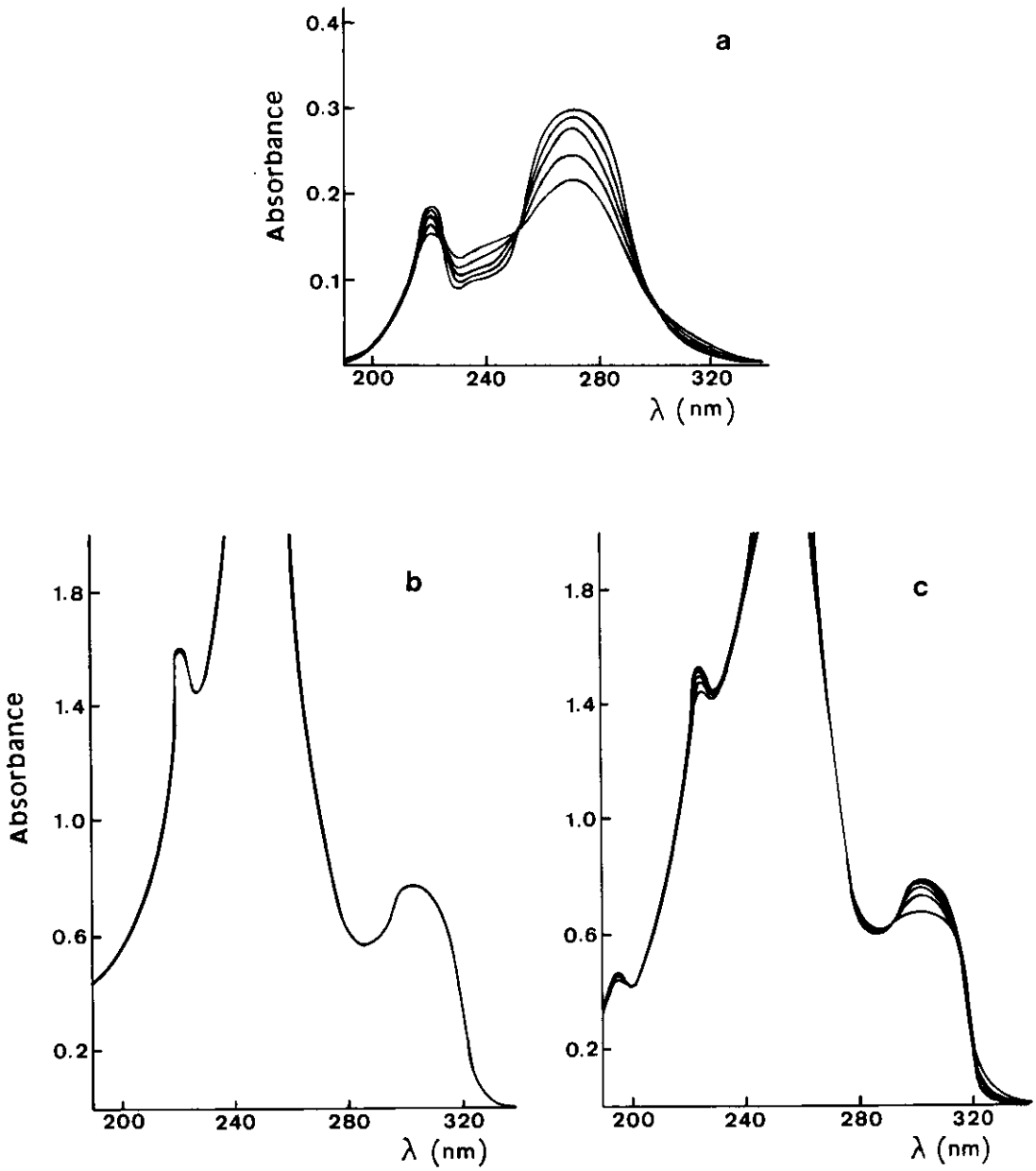


Figure 1.- Photostability of the pyrazole (**2a**) in ciclohexane (Part b) as compared to PABA in ciclohexane (Part a) and to **2a** in methanol (Part c), under the same irradiation conditions (see experimental). Spectra were recorded after 0, 5, 10, 20 and 40 min irradiation for the three experiments.

By contrast, the isoxazoles (**3**) were markedly less stable and underwent extensive photodegradation upon prolonged exposure to UV-light. That the intramolecular hydrogen bond plays an important role in the photostability of the pyrazoles (**2**) could be convincingly demostrated by repeating the irradiation experiments in methanol, in order to favor the formation of intermolecular hydrogen bonds. This led to a slow but clearly progressive diminution of the original absorption maxima at $\lambda \approx 310$ nm with formation of two isosbestic points at $\lambda \approx 290$ and 320 nm (Figure 1c).

In summary, the reaction of the 2-hydroxyaryl phenylethynyl ketones (**1**) with hydrazine or hydroxylamine leads to the formation of the phenolic pyrazoles (**2**) or isoxazoles (**3**) respectively. The structures of the latter can be unequivocally assigned by means of mass spectromtry. The pyrazoles (**2**) are potentially effective in UV-protection and present a marked photostability, presumably associated to the formation of intramolecular hydrogen bonds.

EXPERIMENTAL

Melting points are uncorrected. Combustion analyses were performed at the Instituto de Química Orgánica of CSIC (Madrid). Ir spectra were determined in CCl_4 solutions as KBr pellets with a Perkin-Elmer 577 spectrophotometer; absorption (ν, cm^{-1}) are given only for the main bands. ^{1}H-Nmr spectra were measured with a Hitachi Perkin-Elmer R-24-B instrument, using CCl_4, $CDCl_3$ or DMSO-d_6 as solvent; chemical shifts are reported in ppm downfield (δ) from TMS. Uv-vis spectra were determined in methanol or cyclohexane solution with a Hewlett Packard-8452-A Diode Array instrument.

Syntheses of the pyrazoles (**2**)

To a solution of 200 mg (ca. 0.7 mmol) of the corresponding 2-hydroxyaryl phenylethynyl ketone (**1**) in 20 ml of ethanol was added 0.1 ml (2.5 mmol) of an aqueous solution of hydrazine (80%); the mixture was stirred for 30 min at room temperature. Then, the reaction mixture was concentrated in vacuo, dissolved in ether and washed with water. Finally, the organic residue was dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was submitted to purification by thick layer (2 mm) chromatography on silica gel (Merck Art. No. 7747), using dichloromethane as eluent, affording the corresponding pyrazoles (**2**).

Syntheses of the isoxazoles (**3**)

A mixture of the corresponding 2-hydroxyaryl phenylethynyl ketone (**1**) (200 mg, ca. 0.7 mmol) with hydroxylamine hydrochloride (200 mg, 2.9 mmol) and potassium carbonate (100 mg, 0.73 mmol) in 20 ml of ethanol was refluxed during 5 h. After this time, the reaction mixture was concentrated in vacuo and submitted to the same treatment described in the preparation of the pyrazoles (**2**), to give the corresponding isoxazoles (**3A**) and (**3B**).

Evaluation of the potential applicability of the pyrazoles (**2**) and the isoxazoles (**3**) as sunscreens.

The potential applicability of the compounds (**2**) and (**3**) as sunscreens was evaluated by determination of the SPF (sun protection factor), analyzing the absorption spectra of their solutions in methanol by comparison with p-aminobenzoic (PABA).

The mathematical model used in this study is based on the equation:

$$SPF = \frac{1}{T} = \frac{\Sigma EE\ (\lambda) \times I\ (\lambda)}{\Sigma EE\ (\lambda) \times I\ (\lambda) \times T\ (\lambda)}$$

EE (λ) = erythemic efficiency
I (λ) = solar spectra
ΣEE (λ) x I (λ) = 1.0 (normalized)
λ = 290 - 320 nm (increments 5 mm)
$T(\lambda) = 10^{-abs\ (\lambda)}$
abs (λ) = the absorption of a solution of the corresponding compound in methanol (concentration 0.02 g/l)

PABA was used as reference compound and its SPF was taken arbitrarily as the unity. The SPF of the different compounds studied are relative to PABA.

Evaluation of the photostability

One mg of the compound was dissolved in 50 ml of methanol or cyclohexane. The resulting solution was irradiated at room temperature for 40 min, with a 125W medium pressure mercury lamp inside a quartz immersion well photoreactor. The photostability was controlled by periodically recording absorption spectra at 0, 5, 10, 20 and 40 min.

Products

5-(2-Hydroxy-5-methylphenyl)-3-phenylpyrazole (**2a**), recrystallized from CCl_4, mp 166-167°C. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20. Found: C, 77.03; H, 5.65; N, 11.28; uv-vis 301 (3.8), 255 (4.4), 223 (4.2); ir 3340 (vs), 1510 (m), 1490 (w), 1455 (s), 1280 (w), 1260 (w), 1245 (vs), 1190 (w), 1170 (vw), 970 (w); ^{1}H-nmr 9.36 (s, 2H, OH + NH), 7.83-6.72 (m, 8H, Ar-H), 6.89 (s, 1H, H in C-4), 2.49 (s, 3H, CH_3); ms 250

(100), 249 (16), 221 (11), 178 (3), 145 (31), 125 (9), 104 (7), 91 (9), 77 (14), 51 (10).

5-(2-Hydroxy-5-metoxyphenyl)-3-phenylpyrazole (**2b**), recrystallized from cyclohexane, mp 130-140°C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 72.13; H, 5.66; N, 10.90; uv-vis 315 (3.9), 256 (4.4), 222 (4.3); ir 3445 (m), 1555 (w), 1505 (s), 1490 (vs), 1460 (s), 1430 (vw), 1250 (vw), 1190 (vw), 1170 (vw), 1040 (w); ^{1}H-nmr 9.17 (s, 2H, OH + NH), 7.82-6.70 (m, 8H, Ar-H), 6.86 (s, 1H, H in C-4), 3.85 (s, 3H, OCH_3); ms 266 (83), 251 (100), 205 (3), 194 (3), 151 (4), 149 (4), 123 (5), 97 (21), 83 (29), 77 (14), 51 (7).

5-(2-Hydroxy-3,5-dimethylphenyl)-3-phenylpyrazole (**2c**), recrystallized from CCl_4, mp 188-189°C. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.18; H, 6.18; N, 10.66; uv-vis 302 (3.9), 259 (4.5), 224 (4.3); ir 3345 (vs), 2880 (m), 1485 (m), 1450 (s), 1380 (w), 1280 (w), 1230 (m), 1180 (w), 750 (vs), 740 (w); ^{1}H-nmr 9.43 (s, 2H, OH + NH), 7.80-6.90 (m, 7H, Ar-H), 6.93 (s, 1H, H in C-4), 2.33 (s, 6H, 2 x CH_3); ms 264 (100), 263 (17), 250 (7), 249 (10), 235 (10), 221 (6), 132 (9), 117 (8), 77 (13), 51 (7).

3-(2-Hydroxy-5-methylphenyl)-5-phenylisoxazole (**3Aa**), recrystallized from hexane, mp 101-102°C. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.35; H, 5.11; N, 5.62; uv-vis 305 (3.7), 266 (4.2) 247 (4.1); ir 3290 (w), 1630 (m), 1590 (m), 1575 (s), 1500 (vs), 1450 (w), 1430 (w), 1400 (m), 1290 (s), 1250 (vs); ^{1}H-nmr 9.15 (s, 1H, OH), 8.00-6.69 (m, 8H, Ar-H), 6.80 (s, 1H, H in C-4), 2.35 (s, 3H, CH_3); ms 251 (64), 250 (19), 224 (2.5), 179 (9), 146 (15), 105 (100), 77 (46), 51 (12).

3-(2-Hydroxy-5-metoxyphenyl)-5-phenylisoxazole (**3Ab**), recrystallized from ethanol, mp 129-130°C. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.62; H, 4.84; N, 5.09; uv-vis 323 (3.8), 265 (4.4), 247 (4.3); ir 1570 (vw), 1500 (vs), 1400 (vw), 1260 (vw), 1240 (w); ^{1}H-nmr 9.25 (s, 1H, OH), 8.10-7.00 (m, 8H, Ar-H), 6.85 (s, 1H, H in C-4), 3.85

(s, 3H, OC<u>H</u>$_3$); ms 267 (50), 252 (24), 190 (2), 162 (3), 134 (2), 133 (4), 105 (100), 77 (39), 51 (10).

<u>3-(2-Hydroxy-3,5-dimethylphenyl)-5-phenylisoxazole</u> (**3Ac**), recrystallized from hexane, mp 133-134°C. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.72; H, 5.76; N, 5.28; uv-vis 311 (3.7), 265 (4.4), 222 (4.0); ir 1620 (m), 1590 (m), 1570 (s), 1500 (s), 1490 (vs), 1450 (m), 1440 (m), 1240 (vs), 1120 (m); ^{1}H-nmr 9.55 (s, 1H, O<u>H</u>), 8.10-6.90 (m, 7H, Ar-<u>H</u>), 6.85 (s, 1H, H in C-4), 2.30 (s, 6H, 2 x C<u>H</u>$_3$); ms 265 (38), 264 (10), 250 (2), 236 (2), 160 (22), 132 (3), 105 (100), 77 (56), 51 (8).

<u>5-(2-Hydroxy-5-methylphenyl)-3-phenylisoxazole</u> (**3Ba**), recrystallized from hexane, mp 211-212°C. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.27; H, 5.43; N, 5.22; uv-vis 316 (4.0), 265 (4.2), 243 (4.3), 224 (4.3); ir 3110 (s), 1610 (m), 1560 (m), 1510 (s), 1465 (s), 1450 (s), 1390 (ws), 1250 (ws), 1210 (m); ^{1}H-nmr 10.4 (s, 1H, O<u>H</u>), 8.15-6.89 (m, 8H, Ar-<u>H</u>), 6.80 (s, 1H, H in C-4), 2.35 (s, 3H, C<u>H</u>$_3$); ms 251 (64), 250 (122), 174 (0.2), 148 (7), 147 (4), 135 (27), 134 (18), 117 (100), 91 (7), 77 (33), 51 (12).

<u>5-(2-Hydroxy-3,5-dimethylphenyl)-3-phenylisoxazole</u> (**3Bc**), recrystallized from ethanol, mp 210-211°C. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C,76.82; H, 5.96; N, 5.25; uv-vis 314 (4.0), 270 (4.3), 226 (4.0); ir 3200 (vs), 1565 (vs), 1480 (vs), 1465 (vs), 1440 (vs), 1390 (vs), 1300 (vs), 1250 (vs), 1200 (vs), 1170 (vs); ^{1}H-nmr 9.20 (s, 1H, O<u>H</u>), 8.20-7.10 (m, 9H, Ar-<u>H</u>), 2.35 (s, 6H, 2 x C<u>H</u>$_3$); ms 265 (76), 264 (19), 162 (6), 149 (26), 148 (42), 120 (32), 117 (100), 91 (28), 77 (58), 51 (23).

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