Heterocyclic Photorearrangements. Some Investigations of the Photochemical Behaviour of 3-Acylamino-1,2,4-oxadiazoles. Synthesis of the Quinazolin-4-one System

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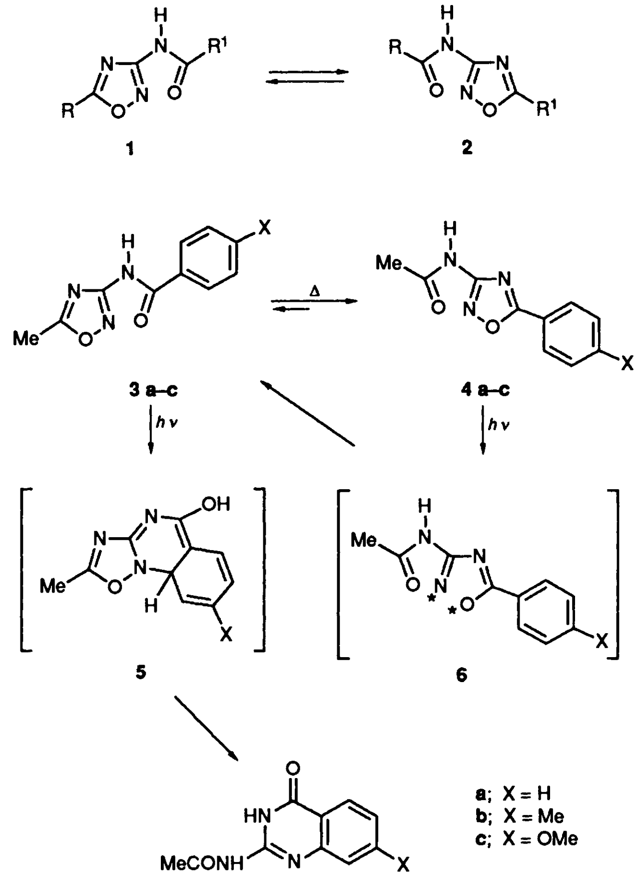
Some mechanistic investigations on the photochemical behaviour of 1,2,4-oxadiazoles are reported. Irradiation of 3-benzoylamino-5-methyl-1,2,4-oxadiazole at λ = 254 nm in methanol involves excitation of the benzoylamino group chromophore to a triplet state species and induces a 6π electrocyclic closure to a tricyclic intermediate. On the other hand, irradiation of 3-acetylamino-5-phenyl-1,2,4-oxadiazole at λ = 254 nm involves excitation of a 5-phenyl-substituted oxadiazole chromophore which leads to the photolysis of the ring O–N bond in a singlet state species. Furthermore, irradiation of some selected 5-phenyl substituted oxadiazoles in the presence of a triplet sensitizer produces an excited triplet state species which collapses in a ring closure reaction involving the C_5-phenyl moiety.

3-Acylamino-1,2,4-oxadiazoles **1** and **2** have furnished interesting examples of thermally induced rearrangements of the isoheterocyclic or degenerate type.[1,2] In this context, 3-aroylamino-5-methyl-1,2,4-oxadiazoles **3** and the corresponding 3-acetylamino-5-aryl-1,2,4-oxadiazoles **4** have been shown to give a thermally induced equilibrium process where the 5-aryl substituted oxadiazole **4** was the thermodynamically favoured component.[1,3]

In connection with our studies on photoinduced rearrangements of 1,2,4-oxadiazoles,[4–9] we have also reported results concerned with the photochemical behaviour of 3-acylamino-oxadiazoles **3** and **4**, pointing out the following:[7,8] irradiation of 3-aroylaminooxadiazoles **3** gave[7] quinazolinone derivatives **7**, whose formation has been suggested to proceed *via* an initial heteroelectrocyclic ring closure to the intermediate **5**, followed by a subsequent ring opening of this latter into **7**. On the other hand, irradiation of 3-acetylamino-5-aryl-1,2,4-oxadiazoles **4** gave[8] at first the 3-aroylaminooxadiazoles **3** (which may be isolated or evidenced by HPLC analyses), and, finally, the expected quinazolinones **7** (see Scheme 1).

Overall, these results showed that the two isoheterocyclic components **3** and **4** behave differently under irradiation, and this fact, as anticipated,[8] could be attributed to the different chromophore (the aroylamino group side chain in one instance and the 5-aryl substituted oxadiazole ring in another), and/or to the different multiplicity of the excited states involved.

In order to gain information on this aspect of the photochemistry of 1,2,4-oxadiazoles and a greater insight into the photoinduced rearrangements of these five-membered heterocycles, we have now undertaken some mechanistic investigations both on the photophysical properties of the molecules under study and on the mechanism of the photochemical processes. We report results concerning the photochemical behaviour of 3-acylaminooxadiazoles **3** and **4** in the presence of quenchers and sensitizers, and, moreover, in order to generalize about the photochemistry of 1,2,4-oxadiazoles, we report results concerning the photosensitized reaction of some 5-phenyl-substituted 1,2,4-oxadiazoles.



Scheme 1

Results and Discussion

Emission spectra were recorded on a spectrofluorimeter equipped with a low temperature phosphorimeter. Typical spectra for anhydrous methanol solutions of compounds **3a** and **4a** are shown in Fig. 1. They show that compound **3a** has very efficient intersystem crossing, populating the triplet state ($E_t \approx 75$ kcal mol^{-1}),† while compound **4a** decays principally from the singlet state ($E_s \approx 98$ kcal mol^{-1}) and shows very little phosphorescence (from which a value of $E_t \approx 68$ kcal mol^{-1} may be estimated). The emission spectra for compounds **3b**, **c** and **4b**, **c** are similar in behaviour and in the energies of the excited states.

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† 1 cal = 4.184 J.

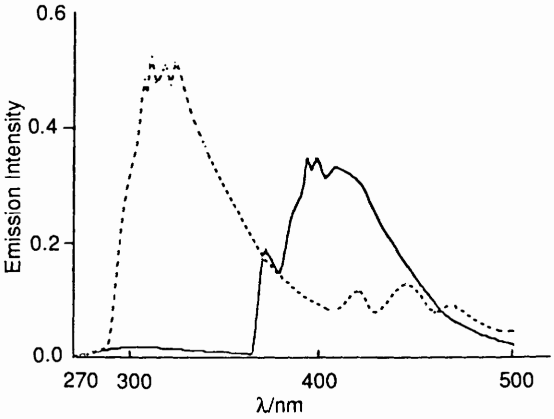


Fig. 1 Plot of the emission intensity *versus* wavelength: (– – – –) fluorescence emission of compound **4a**; (——) phosphorescence emission of compound **3a**

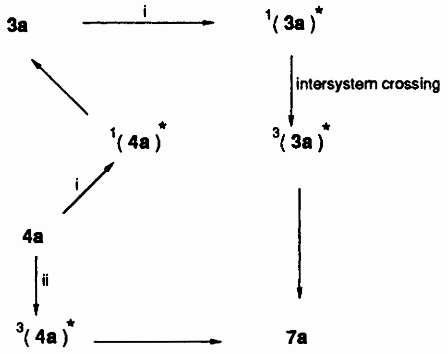
Photochemical investigations were carried out in a Rayonet apparatus, and photoreactions were monitored by HPLC analyses. Irradiations were performed in anhydrous methanol using Hg lamps at λ = 254 nm, and variable amounts of penta-1,3-diene (E_t = 58 kcal mol^{-1}) as quencher.[10] For the photosensitized reactions, irradiations were performed at λ = 300 nm, using a large excess of diphenylacetylene (E_t = 62.5 kcal mol^{-1}) or phenylacetylene (E_t = 72.0 kcal mol^{-1}) as triplet sensitizer.[10]

When the 3-benzoylaminooxadiazole **3a** was irradiated at λ = 254 nm in the presence of increasing amounts of penta-1,3-diene, we observed that the formation of the expected quinazolinone **7a** was quenched thus suggesting that the photorearrangement of compound **3** into **7** should involve a triplet excited state. On the other hand, in the irradiation of the 3-acetylaminooxadiazole **4a** under similar conditions, the expected photoreaction leading to the isoheterocyclic compound **3a** was *not* quenched by penta-1,3-diene. We then examined a photosensitized reaction, by using a large excess of diphenylacetylene or phenylacetylene as triplet sensitizer. The triplet energy of diphenylacetylene, although lower than that of the oxadiazole **4a**, is very close to that of our compound; this should permit the energy transfer to occur.

We have observed that irradiation of compound **4a** at λ = 300 nm [a wavelength at which the oxadiazole **4a** practically does not absorb], gave the unchanged starting material. However, when irradiation of **4a** at λ = 300 nm was carried out in the presence of diphenylacetylene or phenylacetylene, the photoreaction gave the quinazolinone **7a** directly, *i.e.* without 3-benzoylaminooxadiazole **3a** as an intermediate. Irradiation of compound **3a** at λ = 300 nm also gave compound **7a**, whereas when the irradiation of **3a** (E_t ≈ 75 kcal mol^{-1}) was carried out in the presence of a large excess of diphenylacetylene, the photorearrangement of **3a** into **7a** was quenched.

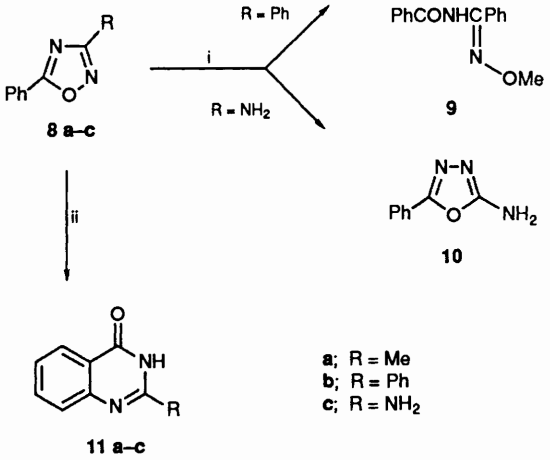
The above results suggest that photorearrangement of 3-aroylaminooxadiazoles **3** into **7** should involve the excitation of the aroylamino group chromophore in a triplet state species and the reaction implies a 6π electrocyclic ring closure into a tricyclic intermediate of the type **5**. On the other hand, the isoheterocyclic photorearrangement of 3-acetylaminooxadiazole **4a** into 3-benzoylaminooxadiazole **3a** should involve the excitation of the 5-phenyl-substituted oxadiazole chromophore in a singlet state species, and the reaction implies the initial photolysis of the oxadiazole O–N bond, followed by the new oxadiazole ring closure with the NCO sequence of the acetylamino group.

Irradiation of the 3-acetylaminooxadiazole **4a** at λ = 300 nm and in the presence of diphenylacetylene should excite the oxadiazole chromophore too, implying the ring O–N bond photolysis, but in a triplet state species. This one, at variance with the singlet species, collapses to the quinazolinone **7a** directly, by a new ring closure involving the phenyl moiety linked at the C-5 of the oxadiazole (Scheme 2).



Scheme 2 *Reagents and conditions:* i, *hν*, λ = 254 nm; ii, *hν*, λ = 300 nm, triplet sensitizer

This observation prompted us to exploit the irradiation of a 5-phenyl-substituted 1,2,4-oxadiazole system, in the presence of a triplet sensitizer, as a tool for the synthesis of the quinazolin-4-one system. With this aim, we irradiated 3-methyl-5-phenyl-**8a**, and 3,5-diphenyl-1,2,4-oxadiazole **8b** (which show strong fluorescence but not phosphorescence emission) at λ = 300 nm in methanol and in presence of diphenylacetylene. As expected on the basis of the above results, such irradiations gave the 2-methyl-**11a** and 2-phenylquinazolin-4-one **11b**, respectively, in about 40% yield. It is noteworthy that irradiation of compounds **8a** and **b** at λ = 300 nm in the absence of the triplet sensitizer gave the unchanged starting material. Moreover, it has been reported[4,11] that irradiation of the oxadiazole **8b** at λ = 254 nm in methanol gave essentially the solvent addition product **9** which arises from a reaction of the photolytic intermediate with the solvent.



Scheme 3 *Reagents and conditions:* i, *hν*, λ = 254 nm; ii, *hν*, λ = 300 nm, triplet sensitizer

We have also extended this treatment to the 3-amino-5-phenyl-1,2,4-oxadiazole **8c**. This compound, as well as oxadiazoles **8a** and **8b**, shows strong fluorescence but not phosphorescence emission; but, for example, considering that the energy of the singlet state for **8c** is much lower (87 kcal mol^{-1}) than that of compound **4a** (E_s ≈ 98 kcal mol^{-1}), we can safely estimate its triplet state energy to be lower than 68 kcal mol^{-1}. For the oxadiazole derivative **8c** we had reported[4] that irradiation at λ = 254 nm in methanol induces a photoisomerization into the 2-amino-1,3,4-oxadiazole **10**, and the reaction has been interpreted as proceeding *via* a ring contraction–ring expansion pathway, involving a singlet excited species. Now, in accordance with the above results, we have observed that irradiation of 3-aminooxadiazole **8c** at λ = 300 nm in the presence of diphenylacetylene or phenylacetylene did not give the photoisomer **10** but instead the 2-aminoquinazolin-4-one **11c** (10%).

On the basis of these results, we can therefore suggest a general feature for the photochemical behaviour of 5-phenyl-substituted 1,2,4-oxadiazoles in the presence of a triplet sensitizer: the photolytic intermediate arising from the ring O–N bond cleavage collapses through a ring closure involving the phenyl moiety linked at the C-5 of the oxadiazole heterocycle, thus furnishing an interesting approach to the quinazolin-4-one system.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus; photochemical reactions were performed with a RPR-100 Rayonet apparatus equipped with RPR-2537 Å (λ = 254 nm) and RPR-3000 Å (λ = 300 nm) Hg lamps; emission spectra (in methanol) were obtained with a JASCO FP 770 spectrofluorimeter equipped with a PMA-280 phosphorescence accessory (λ_{ex} = 254 nm). HPLC analyses were performed with a Perkin-Elmer Series 10 instrument, by using a C-18 SIL-X-10 Perkin-Elmer column (25 cm × 4.6 mm diameter) eluting with water–acetonitrile (7:3 v/v) (3:7 v/v in the case of compounds **8a** and **b**) at flow rate of 2.0 cm^3 min^{-1}, monitoring the absorbance at λ = 230 nm (λ = 235 nm in the case of compounds **8a**, **b**). Flash chromatography[12] was performed on Merck silica gel (0.040–0.063 mm). Light petroleum refers to that fraction boiling in the range 40–60 °C. Methanol was purified as reported[13] and was used freshly prepared. Penta-1,3-diene (piperylene; mixture of isomers), diphenylacetylene and phenylacetylene were obtained from Aldrich Chemical Co.

Compounds **3a**,[1] **4a**,[1] **7a**,[7] **8a**,[14] **8b**,[14] **8c**,[15] **9**,[4,11] **10**,[16] **11a**,[17] **11b**[18] and **11c**,[19] which were used for irradiations or as pure samples for comparison, were prepared as reported.

Photochemical Reactions: General Procedures.—A solution of the oxadiazole in anhydrous methanol, in a quartz tube, was degassed by nitrogen bubbling (20 min), and then irradiated in the Rayonet apparatus. In the case of preparative photoreactions, the solvent was removed under reduced pressure and the residue chromatographed by using mixtures of light petroleum–ethyl acetate in varying ratios as the eluent. Quantitative HPLC analyses were performed by using correction factors determined from pure samples.

Irradiation of Acylaminooxadiazoles **3a** *and* **4a** *in the Presence of Quenchers.*—A solution of the oxadiazole **3a** or **4a** (100 mg) in anhydrous methanol (50 cm^3), was apportioned in four quartz tubes containing variable amounts (until attaining a molar ratio of 1/6) of penta-1,3-diene (piperylene) and then irradiated at λ = 254 nm for 10 min. Quantitative HPLC analyses showed that the formation of **7a** from **3a** was quenched, while the formation of **3a** from **4a** was not.

Sensitized Irradiation of Acylaminooxadiazoles **3a** *and* **4a**.—A mixture of the oxadiazole **4a** (20 mg), anhydrous methanol (10 cm^3) and an excess of diphenylacetylene or phenylacetylene (100 mg), was irradiated at λ = 300 nm for 60 min. HPLC analyses revealed the formation of compound **7a** (18%) and the unchanged starting material (80%). The presence of the *iso*-heterocyclic compound **3a** was not observed. Irradiation of **4a** alone at λ = 300 nm for 60 min produced no change.

A mixture of the oxadiazole **3a** (20 mg), anhydrous methanol (10 cm^3) and an excess of diphenylacetylene (100 mg) was irradiated at λ = 300 nm for 60 min. HPLC analyses revealed only trace amounts of compound **7a** (1.5%), and the unchanged starting material (95%). Irradiation of **3a** (20 mg) in anhydrous methanol (10 cm^3) at λ = 300 nm for 60 min, gave compound **7a** (30%) and the unchanged starting material (65%) (HPLC analyses).

Sensitized Irradiation of Oxadiazoles **8a–c**.—A mixture of the oxadiazole **8a** or **8b** (20 mg), anhydrous methanol (10 cm^3) and an excess of diphenylacetylene (100 mg) was irradiated at λ = 300 nm for 11 h. HPLC analyses revealed the formation of compounds **11a** or **11b** (44%), respectively and the unchanged starting material (50%). For a preparative photoreaction, a mixture of the oxadiazole **8a** or **8b** (400 mg), anhydrous methanol (80 cm^3) and diphenylacetylene (2.5 g), was irradiated at λ = 300 nm for 6 h. Evaporation of the solvent and chromatography of the residue gave **11a** (40%) [m.p. 236–238 °C (from EtOH), lit.,[17] 236–238 °C], or **11b** (40%) [m.p. 232–236 °C (from EtOH), lit.,[18] 233–234 °C]. In the irradiation of **8b** HPLC analyses did not show the presence of compound **9**.

A mixture of the oxadiazole **8c** (20 mg), anhydrous methanol (10 cm^3) and diphenylacetylene or phenylacetylene (100 mg) was irradiated at λ = 300 nm for 11 h. HPLC analyses revealed the formation of compound **11c** (10%) and the unchanged starting material (85%). Compound **10** was not detected. Irradiation at λ = 300 nm in the absence of diphenylacetylene or phenylacetylene gave the unchanged starting material only.

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