

Photochemical Behaviour of Some 1,2,4-Oxadiazole Derivatives¹

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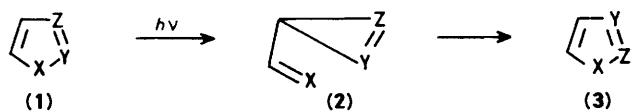
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The photochemical behaviour of some 1,2,4-oxadiazole derivatives in methanol has been studied at 254 nm. On irradiation, 3-amino- (or 3-methylamino-) 5-aryl-1,2,4-oxadiazoles underwent a ring photoisomerization to 1,3,4-oxadiazoles, probably through a 'ring contraction-ring expansion' route. Irradiation of 3-dimethylamino-5-phenyl- and 3,5-diphenyl-1,2,4-oxadiazole gave mainly open chain products derived from reaction of a photolytic intermediate with the nucleophilic solvent. Some mechanistic considerations are reported.

It is well known² that many photoisomerizations of five membered heterocycles can be explained through the 'ring contraction-ring expansion' mechanism, which involves a three membered intermediate (2) and explains the interchange of two adjacent ring atoms (Scheme 1). Other ring photoisomerizations

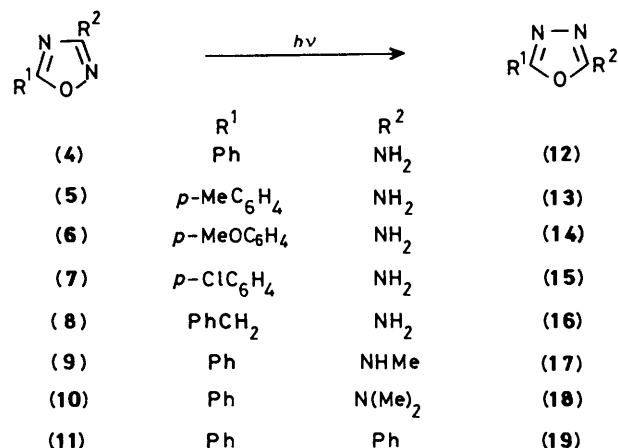


Scheme 1.

are reported² to proceed along an 'internal cyclization-isomerization' route, which involves an initial bicyclic isomer through a 2-5 bond formation, followed by an [1,3] sigmatropic shift, to form the rearranged heterocycles. A general scheme which is a composite of the two outlined mechanisms has also been proposed,³ and, furthermore, a 'zwitterion-tricyclic' route, involving a valence shell expansion of sulphur atom, which seems to be operative in sulphur-containing heterocycles.⁴

Although a large variety of five-membered heterocycles have been studied, the photochemical behaviour of 1,2,4-oxadiazoles has not been systematically investigated. Some examples deal with 1,2,4-oxadiazol-5(4*H*)-ones,⁵ whose photochemistry is characterized by extrusion of CO₂ and formation of intermediates by which the photoproducts have been explained. Dihydro-1,2,4-oxadiazoles have been also studied⁶ and open chain photoproducts have been explained by the cleavage of the weakest O-N bond of the ring. As regards the heteroaromatic 1,2,4-oxadiazole ring, irradiation of the 3,5-diphenyl derivative (11) in aprotic⁷ and protic media has been reported.⁸ The open chain products and the mechanism were explained as arising from a diradical or dipolar species, derived from homolysis or heterolysis of the O-N bond, followed by abstraction of two hydrogen atoms from the medium or by nucleophilic reaction with the solvent, respectively. The occurrence of the supposed⁷ ring photoisomerization to form the corresponding 2,5-diphenyl-1,3,4-oxadiazole (19), likewise the photoisomerization⁹ of 3,5-diphenylisoxazole to 2,5-diphenyloxazole, was not pointed out.

In connection with our interest¹⁰ on five membered heterocyclic rearrangements, and in order to confirm a ring photoisomerization, we investigated the photochemical behaviour of 1,2,4-oxadiazole systems as a function of the substituents in the heteroaromatic ring. Here we report results concerning the irradiation of 3-amino (or substituted amino)-5-aryl-1,2,4-oxadiazoles (4)–(10) in methanol at 254 nm. In order to compare our results with the literature,⁷ the photochemistry of the diphenyl derivative (11) (Scheme 2) was reinvestigated.



Scheme 2.

Results and Discussion

On irradiation of compounds (4)–(9) for 8 h, we observed a photoisomerization reaction to the corresponding 1,3,4-oxadiazoles (12)–(17) which were isolated in *ca.* 10% yield and compared with authentic samples. H.p.l.c. on the photoreaction mixture at low conversion showed no other significant components. However, the 1,3,4-oxadiazole derivatives remained essentially unchanged when irradiated under similar experimental conditions, although they showed comparable absorption values. Compounds (4)–(9) did not exhibit significant phosphorescence emission. Moreover, photoisomerization of compound (4) (λ_F 414 nm) to compound (12) was not quenched by penta-1,3-diene ($E_T = 58$ kcal mol⁻¹), neither was it sensitized by diphenylacetylene ($E_T = 62.5$ kcal mol⁻¹) on irradiation at 300 nm, a wavelength at which starting compound does not absorb.

Different results were obtained when the 3-dimethylamino compound (10) was examined. Irradiation of compound (10) gave mainly the open chain compound (20) together with some guanidine (22), which originated from subsequent photoreaction on compound (20) as verified by means of a separate experiment. H.p.l.c. analysis performed on enriched chromatography fractions of the photoreaction mixture revealed the

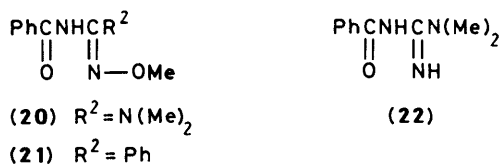


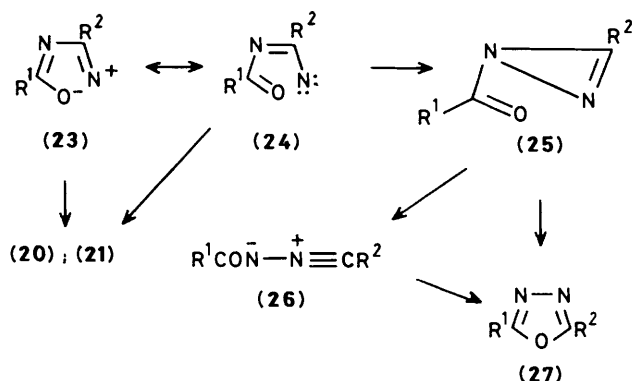
Table. Spectroscopic data of compounds (4)—(11)

Compound	$\lambda_{\max.}$ (MeOH)/ nm	log ϵ (254 nm)
(4)	240	3.90
(5)	247	4.18
(6)	278	4.13
(7)	248	4.14
(8)	230sh	2.70
(9)	242	4.09
(10)	244	4.09
(11)	244	4.30

presence of only a small amount of the photoisomer 1,3,4-oxadiazole (18). On reinvestigation of compound (11), we confirmed the literature report⁸ in that the main photoproduct was the open chain compound (21). However, as in the previous case, h.p.l.c. analysis revealed the presence of trace amounts of the photoisomer (19). The significant spectroscopic data are given in the Table.

From the results, it is possible to point out that two distinct photochemical processes are operative in the 1,2,4-oxadiazole system: ring photoisomerization to the 1,3,4-oxadiazole heterocycle, and formation of open chain products characterized by a reaction with the solvent. The first process may be recognized only for 3-amino or 3-methylamino-5-aryl-1,2,4-oxadiazoles (4)—(9), and is, to our knowledge, the first report of such a process for 1,2,4-oxadiazoles. The second process is operative for 3-dimethylamino-5-phenyl- (10) and 3,5-diphenyl-1,2,4-oxadiazole (11), and formation of compounds (20) and (21) could be explained through the zwitterion species (23).

The photoisomerization process seems to be related to the 'ring contraction—ring expansion' mechanism, a generally accepted^{2,9,12} route for the isoxazole heterocycle which differs from the 1,2,4-oxadiazole in presenting a CH group in place of an N atom at position 4, but which also possesses a weak O—N bond. Therefore, we can reasonably propose a photoisomerization pathway through the diazirine* (25) which could collapse into the photorearrangement product through the nitrilimine (26). However, on the basis of results obtained from the photochemistry of 1,2,4-oxadiazol-5(4H)-ones⁵ or isoxazoles,¹³ a common azomethine nitrene of type (24) could be operative in both processes; depending on the nature of the substituent R² (dimethylamino or phenyl in one side, amino or methylamino in the other) the azomethine nitrene (24) could collapse through a



* Diazirines are well documented in the photochemistry of sydnone (see e.g., ref. 2d).

reaction with the nucleophilic solvent or through the diazirine (25) and then the ring rearrangement, respectively (Scheme 3).

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (Nujol mulls) were determined with a Perkin-Elmer 257 instrument, u.v. spectra (in MeOH) with a Beckmann DU-6 spectrophotometer, emission spectra with an Aminco Bowman MPF instrument, ¹H n.m.r. spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). H.p.l.c. analyses were performed on a Jasco instrument with silica column Hibar SI-60. Flash chromatography¹⁴ 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 reported¹⁵ and was used freshly prepared.

Compounds (4),¹⁶ (8),^{16,17} (10),¹⁸ (11),¹⁹ (12),²⁰ (13),²⁰ (14),²⁰ (15),²⁰ (16),²¹ (17),²² (18),²³ and (19)²⁴ were prepared as reported.

3-Methylamino-5-phenyl-1,2,4-oxadiazole (9), prepared by the reaction of 3-chloro-5-phenyl-1,2,4-oxadiazole²⁵ with an excess of ethanolic methylamine, had m.p. 123 °C (from aqueous ethanol) (Found: C, 61.6; H, 5.2; N, 23.8. C₉H₉N₃O requires C, 61.70; H, 5.18; N, 23.99%); $\nu_{\max.}$ 3 320 cm⁻¹ (NH); $\delta[(\text{CD}_3)_2\text{SO}]$ 3.75 (3 H, d, Me; s after exchange with D₂O), 6.80 (1 H, br q, NH), and 7.45—8.10 (5 H, m, Ph); m/z 175 (M^+).

Compounds (5), (6), and (7) were prepared by reaction between the appropriate aroylcyanamide and hydroxylamine hydrochloride in pyridine, as for compounds (4) and (8). They have also been formed from a reaction between *N*-cyanoamidine and hydroxylamine hydrochloride.²⁶ (For a criticism of this method see ref. 27.)

Compound (5) had m.p. 199 °C (from ethanol) (lit.,²⁶ 160 °C) (Found: C, 61.7; H, 5.2; N, 23.9. C₉H₉N₃O requires C, 61.70; H, 5.18; N, 23.99%); $\nu_{\max.}$ 3 420, 3 305, 3 220, and 3 180 (NH₂); $\delta[(\text{CD}_3)_2\text{SO}]$ 2.35 (3 H, s, Me), 6.35 (2 H, s, NH₂), and 7.25—8.10 (4 H, m, ArH); m/z 175 (M^+).

Compound (6) had m.p. 165 °C (from ethanol) (lit.,²⁶ 165 °C) (Found: C, 56.5; H, 4.8; N, 21.9. C₉H₉N₃O₂ requires C, 56.54; H, 4.75; N, 21.98%); $\nu_{\max.}$ 3 340 and 3 180 (NH₂); $\delta[(\text{CD}_3)_2\text{SO}]$ 3.80 (3 H, s, Me), 6.25 (2 H, s, NH₂), and 6.95—8.10 (4 H, m, ArH); m/z 191 (M^+).

Compound (7) had m.p. 255 °C (from ethanol) (lit.,²⁶ 190 °C) (Found: C, 49.1; H, 3.0; N, 21.5. C₈H₆N₃OCl requires C, 49.10; H, 3.07; N, 21.48%); $\nu_{\max.}$ 3 375, 3 340, and 3 200 (NH₂); $\delta[(\text{CD}_3)_2\text{SO}]$ 6.40 (2 H, s, NH₂) and 7.50—8.10 (4 H, m, ArH); m/z 195 (M^+).

Photochemical Reactions. General Procedure.—A solution of the oxadiazole (4)—(11) (500 mg) in freshly prepared anhydrous methanol (100 ml), in a quartz tube, was degassed by nitrogen bubbling (20 min), and then irradiated in an immersion well apparatus with a low-pressure mercury lamp (Helios Italquarz 17 W). In order to avoid the formation of secondary products from subsequent photoreactions, we decided to work at low conversion of the starting material. The solvent was evaporated off under reduced pressure and the residue was subjected to chromatography. Elution with light petroleum—ethyl acetate in varying ratios gave, at first, unchanged starting material and then photoproducts. Minor components were discarded.

Irradiation of Compounds (4)—(9) to form Photoisomers (12)—(17).—Irradiation for 8 h gave the starting material (80—85%) and photoisomers (12)—(17) which were isolated in ca. 10% yield, and identified by comparison with authentic

samples. H.p.l.c. analysis of the photoreaction mixture revealed no significant amounts of other components.

Samples (10 ml) of a methanol solution of compound (4) (500 mg in 250 ml), containing variable amounts (to a molar ratio of 1:1) of penta-1,3-diene ($E_T = 58 \text{ kcal mol}^{-1}$) were irradiated in the Rayonet apparatus at 254 nm for 2.5 h. Quantitative h.p.l.c. analysis revealed that the photoisomerization of compound (4) to compound (12) was not quenched.

Irradiation of compound (4) at 300 nm in the Rayonet apparatus, in the presence of an excess of diphenylacetylene ($E_T = 62.5 \text{ kcal mol}^{-1}$) as sensitizer, did not give photoisomerization.

Irradiation of Compound (10).—Irradiation for 6 h gave unchanged starting material (80%), compound (20) (8%), and compound (22) (10%). Compound (20) had m.p. 80–83 °C (from light petroleum) (Found: C, 59.6; H, 6.7; N, 18.8. $C_{11}H_{15}N_3O_2$ requires C, 59.71; H, 6.83; N, 18.99%); v_{\max} . 3 300 and 3 240 cm^{-1} (NH); $\delta[(CD_3)_2SO]$ 2.65 (6 H, s, 2 × Me), 3.55 (3 H, s, Me), 7.40–8.05 (5 H, m, Ph), and 9.65 (1 H, s, NH); m/z 221 (M^+). Compound (22) had m.p. 130 °C (dec.) (from light petroleum–ethyl acetate) (Found: C, 62.7; H, 6.8; N, 21.9. $C_{10}H_{13}N_3O$ requires C, 62.80; H, 6.85; N, 21.98%); v_{\max} . 3 300 and 3 160 cm^{-1} (NH); $\delta[(CD_3)_2SO]$ 3.00 (6 H, s, 2 × Me), 7.30–8.25 (5 H, m, Ph), and 8.50 (2 H, br s, 2 × NH); m/z 191 (M^+). Compound (22) has also been produced on reduction of compound (10) with zinc dust in acetic acid.²⁸

T.l.c. and h.p.l.c. analysis performed on enriched chromatography fractions of the photoreaction mixture revealed the presence of trace amounts of the photoisomer (18).

Irradiation of Compound (11).—Irradiation for 3.5 h gave unchanged starting material (80%) and compound (21) (13%), m.p. 150–152 °C (from methanol) (lit.,⁸ m.p. 150–152 °C). T.l.c. and h.p.l.c. analysis performed on enriched fractions of the photoreaction mixture revealed the presence of trace amounts of the photoisomer (19).

Acknowledgements

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