JOC*Note*

Competing Ring-Photoisomerization Pathways in the 1,2,4-Oxadiazole Series. An Unprecedented Ring-Degenerate Photoisomerization‡

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Abstract: The irradiation of some 5-alkyl-3-amino-1,2,4-oxadiazoles at $\lambda = 254$ nm in methanol in the presence of triethylamine (TEA) gave ring-photoisomerization both into 2-alkyl-5-amino-1,3,4-oxadiazoles and, unprecedently, into the ring-degenerate 3-alkyl-5-amino-1,2,4-oxadiazoles. The competing ring contraction−ring expansion route and the internal cyclization−isomerization mechanism explain the results.

Ring photoisomerizations of aromatic five-membered heterocycles are well-known reactions and their possible mechanisms have been systematized.[1−6] A theoretical approach also has been evaluated to rationalize these reactions in terms of the relative energies of presumed intermediates and multiplicity of corresponding excited states.[6,7] Among the different mechanisms, two widely observed pathways are represented by (i) the "ring contraction−ring expansion" route, which involves a three-membered-ring intermediate and explains the interchange of adjacent ring atoms, and (ii) the "internal cyclization−isomerization" route (also named "electrocyclic ring closure−heteroatom migration" pathway), which assumes an initial bicyclic species through the formation of a bond between positions 2 and 5 of the rearranging ring, followed by sigmatropic shifts and final ring-isomerization.

For a given five-membered heterocycle, competing pathways involving both ring contraction and electrocyclic ring closure have been documented.[2,3] This is the case, e.g., of pyrazole,[8] oxazole,[9,10] or isothiazole,[11] for which competing pathways were shown to depend on the structure of the starting ring (the nature of substituents and their position), as well as on the photoreaction medium. Interestingly, in the isothiazole series the occurrence of the above competing routes is also affected by addition of TEA to the irradiation medium.[11] As for O−N bond containing azoles, isoxazoles are historically known[2,3,6] to undergo the isoxazole-to-oxazole rearrangement via the ring contraction mechanism along azirine intermediates, isolable in some cases. Moreover, 1,2,5-oxadiazoles (furazans) are known to give rearrangements by a photofragmentation pattern.[2,12] In turn, 1,2,4-oxadiazoles undergo photocleavage of the ring O−N bond, and the resulting photolytic species develop into different products depending on their structure, as well as on the irradiation conditions and medium.[12,13] The ring-photoisomerization of 1,2,4-oxadiazoles into 1,3,4-oxadiazoles appears restricted[14] to oxadiazoles containing an XH moiety at C(3) of the ring and, moreover, favored by addition of a base to the photoreaction medium.[15] Thus, in the irradiation of 3-amino- or 3-methylamino-5-phenyl-1,2,4-oxadiazoles at $\lambda = 254$ nm in methanol, yields of the ring-isomers 2-amino- or 2-methylamino-5-phenyl-1,3,4-oxadiazoles increased when irradiations were carried out in the presence of TEA. To explain these results, the acidity of the NH moiety at C(3) (at least in the excited state) has been invoked, and a ring contraction−ring expansion mechanism has been suggested.[15]

Following our studies on the photochemistry of O−N bond containing azoles, in this note we now report clear evidence for the occurrence of competing ring-photoisomerization pathways in the 1,2,4-oxadiazole series, and, interestingly, for an unprecedented ring-degenerate process involving interchange between positions 3 and 5 of the oxadiazole ring.

Irradiations of the 3-aminooxadiazoles **1a**,**b** at $\lambda = 254$ nm in methanol gave the expected ring isomers 2-amino-1,3,4-oxadiazoles **2a**,**b** by the ring contraction mechanism. However, different results were obtained when the irradiation of compounds **1a**,**b** was carried out in methanol containing TEA. In fact, under these conditions, photoconversion of the starting material increased but mixtures of compounds **2** and the ring-degenerate isomers **4** were formed. An independent synthesis of compounds **4** by ammonolysis[16] of the 5-trichloromethyl

‡ This paper is dedicated to Professor Domenico Spinelli on the occasion of his 70th birthday.

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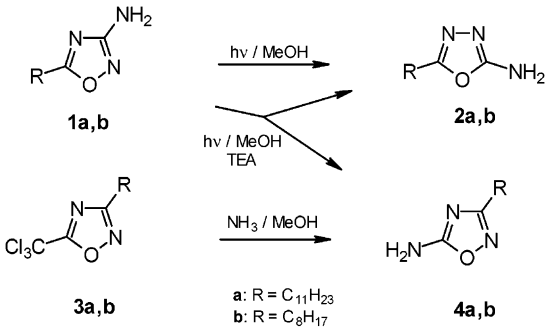
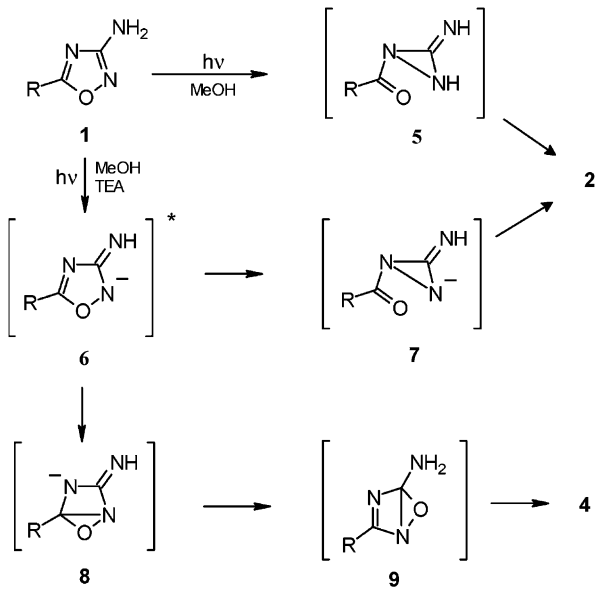
SCHEME 1



oxadiazoles **3** confirmed their identity. Analysis of photolyzates obtained under different molar ratios of TEA showed that the photoconversion of the starting material was accelerated even by addition of small amounts of TEA. In a typical experiment, HPLC analyses of photolyzates (15 min of irradiation) in the absence or in the presence of the base (0.5/1 TEA/**1a** molar ratio) showed that photoconversion was increased from 14% to 28%, respectively. In turn, yields of the ring-degenerate isomer **4a** increased from zero (in methanol) to 6% (in methanol/TEA), whereas yields of the ring isomer **2a** increased from 14% to 22%, respectively. Moreover, increasing the TEA/**1a** molar ratio also increased the **4a**/**2a** ratio. For example, when an excess of TEA was used (molar ratio of about 5/1), photoisomers **2** and **4** were present in 20% and 12% yields, respectively. Essentially comparable results were also observed when the irradiations were carried out in methanol with the addition of methanolic ammonia or aqueous sodium hydrogen carbonate, and this observation allow us to exclude (at least in a first-glance hypothesis) the possibility of an electron-transfer mechanism in the photorearrangement reactions.[11,15]

Since oxadiazoles **2** and **4** do not interconvert with each other under photoreaction conditions, they must be considered primary photoproducts arising from two competing and independent pathways. The formation of 1,3,4-oxadiazoles **2** can be clearly explained by the ring contraction mechanism with formation of a three-membered transient intermediate. Formation of the ring-degenerate oxadiazoles **4** most likely involves the internal cyclization mechanism. Since both mechanisms are working when irradiations were carried out in the presence of the base, an intriguing hypothesis suggests the anionic species **6** (at least in the excited state) as a common precursor.[17] On one hand, species **6** will develop through a heterolytic cleavage of the ring O−N bond leading to the three-membered anion **7** and then to the 1,3,4-oxadiazole ring. On the other hand, **6** will develop through an internal cyclization−isomerization route, involving the electrocyclic ring-closure between N(2) and C(5) into the transient bicyclic intermediate **8**, followed by oxygen migration and protonation to form **9** from which the ring-degenerate 1,2,4-oxadiazoles **4** will finally arise (see Scheme 2). In the case of irradiations in the absence of base, only the ring contraction mechanism

SCHEME 2



takes place. In this case, the amphoteric solvent can promote the rearrangement reaction through the neutral three-membered species **5**, but to a lesser extent. On the other hand, collapse of **5**, too, will be favored by the base. The fact that the internal cyclization route takes place only when the base is present corroborates the involvement of an anionic species such as **6** (in which a higher electron density at N(2) is expected) collapsing into the stabilized anion **8**. Furthermore, it is worthy to note that the competing internal cyclization route also appears to be determined by the nature of the substituent at C(5) of the starting ring. In fact, in the irradiation of 3-amino-5-phenyl-1,2,4-oxadiazole under similar conditions we were not able to detect the corresponding ring-degenerate isomerization. This observation would suggest that, depending on the nature of the substituent (alkyl or aryl) at C(5) of the oxadiazole ring, the involvement of different electronic transitions (and then different excited states) could be envisaged. Further mechanistic investigations are necessary to verify this point, as well as the role of photochemical conditions in selectivity between the above competing pathways.

Experimental Section

Materials and Methods. For instruments and general procedures see our previous papers.[13,14,17] IR spectra were recorded from Nujol mulls (and in $CHCl_3$ when indicated). ^1H NMR spectra (250 MHz) were taken with TMS as internal standard. HPLC analyses were performed by using a Chromolith RP-18e 100-4.6 column, and eluting with water−acetonitrile (70/30 v/v). Flash chromatography was performed by using mixtures of light petroleum (fraction boiling in the range of 40−60 °C) and ethyl acetate in varying ratios, or, when necessary, with ethyl acetate, and elution was carefully monitored by HPLC. Anhydrous methanol and triethylamine (99.9%) were used as received.

Compound **1a** was prepared as reported.[18] Compound **1b** was prepared by adopting the procedure described for **1a**, using nonanoyl chloride as the acylating reagent.

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3-Amino-5-octyl-1,2,4-oxadiazole (1b) had mp 72−74 °C (from light petroleum); IR 3340, 3300, 3220, 3180, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.70 (m, 2H), 2.75 (t, J = 7 Hz, 2H), 6.21 (s, exch., 2H); MS m/z 197 (M^+, 100), 111 (19), 85 (5). Anal. Calcd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.60; H, 9.60; N, 21.10.

Samples of **4a** and **4b** for comparison were obtained by ammonolysis[16] of the 5-trichloromethyloxadiazoles **3a** and **3b**, respectively (see after).

Photochemical reactions were carried out in anhydrous methanol by using a Rayonet RPR-100 photoreactor fitted with 16 Hg lamps irradiating at λ = 254 nm (in 20 mL Quartz vessels) and a merry-go-round apparatus. All the solutions were purged by bubbling nitrogen (10 min) before irradiation. In the case of analytical scale photoreactions, quantitative determinations were accomplished by HPLC.

Irradiation of 3-Amino-5-undecyl-1,2,4-oxadiazole (1a) in Methanol. A sample of the oxadiazole **1a** (0.2 g; 0.8 mmol) in methanol (170 mL), apportioned into nine quartz tubes, was irradiated for 30 min. After removal of the solvent, chromatography of the residue returned starting material (0.14 g; 70%) and gave 2-amino-5-undecyl-1,3,4-oxadiazole (**2a**) (0.02 g; 10%), mp 148 °C (from benzene) (lit.[19] mp 148−149 °C).

Irradiation of 3-Amino-5-undecyl-1,2,4-oxadiazole (1a) in Methanol in the Presence of Triethylamine (TEA). A sample of the oxadiazole **1a** (0.2 g; 0.8 mmol) in methanol (170 mL) was apportioned into nine quartz tubes and the solutions were purged by bubbling nitrogen. An excess of TEA (molar ratio 10/1) was added and then all the samples were irradiated for 30 min. After removal of the solvent, chromatography of the residue returned starting material (0.1 g; 50%) and gave 5-amino-3-undecyl-1,2,4-oxadiazole (**4a**) (0.03 g; 15%) and 2-amino-5-undecyl-1,3,4-oxadiazole (**2a**) (0.03 g; 15%). Compound **4a** had mp 68−69 °C (from light petroleum); IR 3460, 3300, 3260, 3190, 3150, 1690 cm^{-1}; IR ($CHCl_3$) 3500, 3400, 3310, 3260, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.91 (t, J = 7 Hz, 3H), 1.29 (m, 16H), 1.62 (m, 2H), 2.44 (t, J = 7 Hz, 2H), 7.67 (s, exch., 2H); MS m/z 239 (M^+, 16), 223 (8), 197 (10), 154 (13), 141 (15), 123 (20), 112 (81), 99 (100), 83 (42). Anal. Calcd for $C_{13}H_{25}N_3O$: C, 65.23; H, 10.53; N, 17.55. Found: C, 65.00; H, 10.40; N, 17.40.

A sample of **4a** was prepared by ammonolysis of **3a**. Thus, a mixture of dodecanamidoxime[20] (1 g; 4.7 mmol) and trichloroacetic anhydride (1 mL; 5.5 mmol) in anhydrous toluene (30 mL) was refluxed for 2 h. After removal of the solvent, the residue was treated with water and then extracted with ethyl acetate. The organic layers were washed with aqueous (10%) sodium hydrogencarbonate, dried, and evaporated. Chromatography of the residue gave crude 5-trichloromethyl-3-undecyl-1,2,4-oxadiazole (**3a**) (1 g, 63%) as an oil; ^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7 Hz, 3H), 1.32 (m, 16H), 1.59 (m, 2H), 2.54 (t, J = 7 Hz, 2H); MS m/z 340 (M^+ , 100), 304 (11), 276 (16), 222 (24), 194 (30). To a solution of compound **3a** (0.4 g; 1.17 mmol) in methanol (30 mL) was added an excess of methanolic ammonia and the mixture was allowed to stand at room temperature for 12 h. After removal of the solvent, the residue was taken up as usual affording **4a** (0.22 g; 80%), mp 68−69 °C (from light petroleum).

Irradiation of 3-Amino-5-octyl-1,2,4-oxadiazole (1b) in Methanol. Irradiation of **1b** (0.2 g; 1 mmol) in methanol (170 mL) for 30 min and chromatography returned starting material (0.14 g; 70%) and gave 2-amino-5-octyl-1,3,4-oxadiazole (**2b**) (0.03 g; 15%), mp 148−150 °C (from benzene); IR 3290, 3250, 3100, 1655 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.91 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.64 (m, 2H), 2.66 (t, J = 7 Hz, 2H), 6.87 (s, exch., 2H); MS m/z 197 (M^+, 100), 140 (7), 111 (27). Anal. Calcd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.70; H, 9.60; N, 21.20.

Irradiation of 3-Amino-5-octyl-1,2,4-oxadiazole (1b) in Methanol in the Presence of Triethylamine (TEA). Irradiation of **1b** (0.2 g; 1 mmol) in methanol (170 mL) and TEA (10/1 TEA/**1b** molar ratio) returned starting material (0.1 g; 50%) and gave 5-amino-3-octyl-1,2,4-oxadiazole (**4b**) (0.03 g; 15%) and then 2-amino-5-octyl-1,3,4-oxadiazole (**2b**) (0.03 g; 15%). Compound **4b** had mp 57−59 °C (from light petroleum); IR 3450, 3300, 3250, 3190, 3150, 1690, 1640 cm^{-1}; IR ($CHCl_3$) 3500, 3400, 3310, 3260, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.91 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.62 (m, 2H), 2.47 (t, J = 7 Hz, 2H), 7.67 (s, exch., 2H); MS m/z 197 (M^+, 100), 180 (9), 154 (21). Anal. Calcd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.70; H, 9.60; N, 21.10.

Like **4a**, a sample of **4b** was prepared by ammonolysis of **3b**. By adopting the same procedure used for **3a**, the nonanamidoxime[21] gave 5-trichloromethyl-3-octyl-1,2,4-oxadiazole (**3b**) (60%) as an oil; ^1H NMR (DMSO-d_6) δ 0.9 (t, J = 7 Hz, 3H), 1.30 (m, 10H), 1.59 (m, 2H), 2.50 (t, J = 7 Hz, 2H); MS m/z 298-(M^+, 100), 234 (43), 180 (13), 162 (33), 119 (24). Ammonolysis of **3b** gave **4b** (80%), mp 57−59 °C (from light petroleum).

Analytical Photoreactions. A solution of **1a** (0.06 g; 0.21 mmol) in methanol (60 mL) was apportioned into different quartz tubes. Variable amounts of TEA, methanolic ammonia, or aqueous sodium hydrogen carbonate, respectively, were added to each sample to obtain different molar ratios betweeen the base and **1a**. The samples were simultaneously irradiated for 15 min, and photolyzates were analyzed by HPLC.

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