Heterocyclic Photorearrangements. Photochemical Behaviour of Some 3,5-Disubstituted 1,2,4-Oxadiazoles in Methanol at 254 nm [1]

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Photochemical behaviour of some 3,5-disubstituted 1,2,4-oxadiazoles in methanol at 254 nm has been investigated. Ring photoisomerization to the 1,3,4-oxadiazole heterocycle or formation of open chain compounds involving the nucleophilic solvent was shown to depend on the nature and the position of the substituent. Photoinduced ring closure into the benzimidazole system, involving a 3-*N*-phenylamino side chain sequence and a photolytic intermediate of the oxadiazole heterocycle, is also reported.

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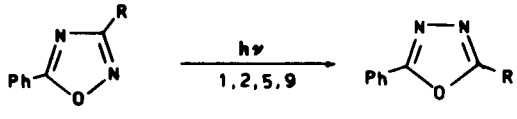
In the context of our research on photochemical behaviour of 1,2,4-oxadiazole systems, we recently reported [2] that irradiation of 3-amino-5-phenyl- (**1**), and 3-methylamino-5-phenyl-1,2,4-oxadiazole (**2**), in anhydrous methanol at 254 nm, gave ring photoisomerization to the corresponding 2-amino-5-phenyl- (**10**) and 2-methylamino-5-phenyl-1,3,4-oxadiazole (**11**). This process, which has been claimed as the first report in the 1,2,4-oxadiazole series, has been related to the well known [3] isoxazole to oxazole photoisomerization and interpreted according to the "ring contraction-ring expansion" route [4]. According to this mechanism, a three membered diazirine intermediate, originated from the photolysis of the *O-N* bond of the 1,2,4-oxadiazole heterocycle, collapses to the photoisomeric 1,3,4-oxadiazole ring through a nitrilimine system. However, the observed photoisomerization process seems to be determined by the presence of a 3-amino or a 3-methylamino group in the 1,2,4-oxadiazole ring. In fact irradiation of 3-dimethylamino-5-phenyl- (**3**) and of 3,5-diphenyl-1,2,4-oxadiazole (**4**) did not give photoisomers **12** and **13**, but open chain compounds **19** and **20**, respectively, derived from the reaction of a photolytic intermediate with the nucleophilic solvent [2] [5].

Scheme 1



1	R= NH_2	10
2	R= NHMe	11
3	R= $N(Me)_2$	12
4	R= Ph	13
5	R= NHPh	14
6	R= N(Me)Ph	15
7	R= CH_2Ph	16
8	R= OMe	17
9	R= OH	18

Continuing our studies in this field, we became interested in how changes in the nature of a substituent in the 1,2,4-oxadiazole heterocycle can influence the photochemical process. In this connection we have now investigated irradiation of some selected 3,5-disubstituted-1,2,4-oxadiazoles in methanol at 254 nm.

Results.

3-Substituted-5-phenyl-1,2,4-oxadiazoles.

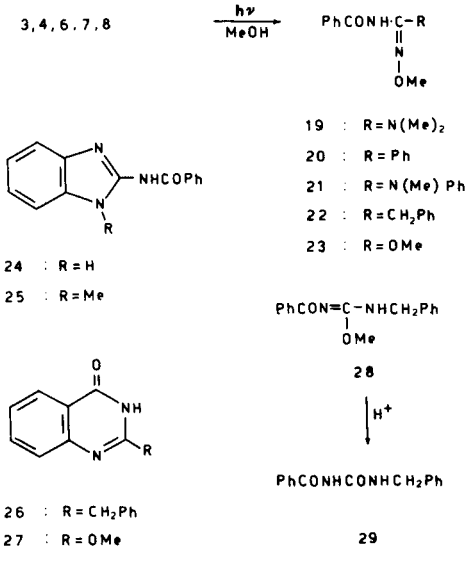
Selected 3-substituted-5-phenyl-1,2,4-oxadiazoles are reported in Scheme 1, where compounds **1-4** were also quoted for comparison utility.

Irradiation of compound **5** mainly gave a mixture of the photoisomer 1,3,4-oxadiazole **14** and the benzimidazole **24**. However, irradiation of compound **6** did not give the photoisomer **15** but it mainly gave the benzimidazole **25** and the open chain product **21**. This means that, in the failure of the photoisomerization process, the disubstituted *N*-Methyl-*N*-phenylamino compound **6** behaves as the disubstituted dimethylamino compound **3** and the 3,5-diphenyl-1,2,4-oxadiazole (**4**).

Similar results have been obtained on irradiation of the 3-benzyl- **7** and the 3-methoxy- compound **8**, in which photoisomerization to the corresponding 1,3,4-oxadiazoles **16** and **17**, respectively, was not observed. In fact, irradiation of **7** and **8** mainly gave **22** and **23**, respectively. In addition, quinazolones **26** and **27** were isolated, and, in the case or irradiation of compound **7**, the open chain product **28** was also obtained. On the basis that tautomeric forms due to amino or monosubstituted amino groups could determine the photoisomerization process, we investigated irradiation of the 3-hydroxyoxadiazole **9**. In this instance,

as forecast on the basis of our hypothesis, irradiation gave the photoisomer 1,3,4-oxadiazole **18** (See Scheme 2).

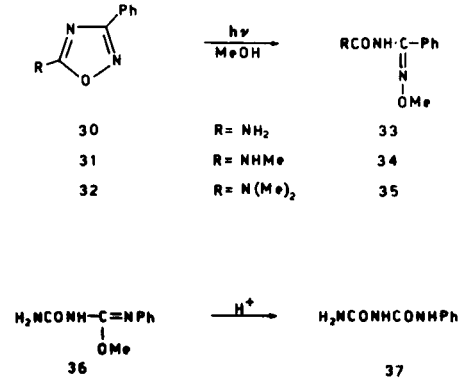
Scheme 2



5-Substituted-3-phenyl-1,2,4-oxadiazoles.

In order to gain insight into the influence of an amino or substituted amino group in the photochemical reaction, we investigated irradiation of 5-amino-3-phenyl- (**30**), 5-methylamino-3-phenyl- (**31**), and of 5-dimethylamino-3-phenyl-1,2,4-oxadiazole (**32**). However, we have observed that none of these compounds gave the corresponding photoisomer 1,3,4-oxadiazole. In fact, the photoreaction, which was proved to proceed more easily than that observed for the 3-amino series (see Experimental), gave open chain compounds **33-35**. Only on irradiation of compound **30**, trace amounts of the photoisomer **10** have been observed. Moreover, in this experiment the open chain compound **36** has also been isolated (See Scheme 3).

Scheme 3



Comments.

All of the present and the previously reported [2] results allows us to point out that two distinct photochemical processes can be recognized in the 1,2,4-oxadiazole system: a ring photoisomerization to the 1,3,4-oxadiazole heterocycle, and formation of open chain compounds derived from the reaction of a photolytic intermediate with the nucleophilic solvent. Clearly, the two processes must proceed through different pathways, depending on the nature and the position of the substituent present in the 1,2,4-oxadiazole heterocycle.

The ring photoisomerization occurs only when the 3-substituent was a tautomerizable group such as NH_2, NHMe, NHPh, or OH. This result suggests that the photoisomerization process should involve tautomeric forms in the starting oxadiazole and/or in the three membered ring intermediate which comes from the photolysis of the *O-N* bond through a "ring contraction" route. In turn, the

Table 1

UV Data of Compounds **5-9**, **30-32**, and **43**

Compound	λ max nm (MeOH)	log ε (254 nm)
5	252	4.59
6	252	4.47
7	251	4.24
8	254	4.08
9	255	4.10
30	225	3.48
31	230	3.45
32	230	3.48
43	250	4.22

Table 2

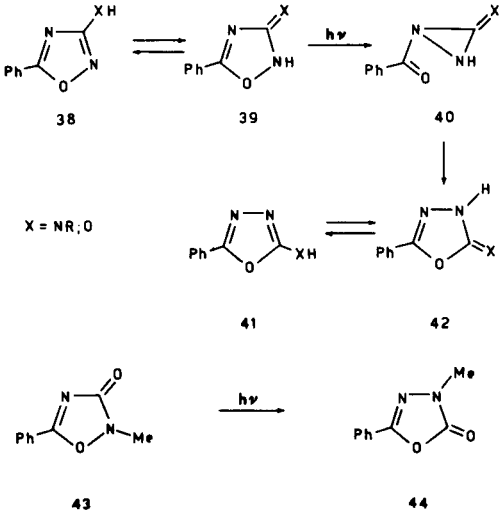
Irradiation of 1,2,4-oxadiazoles **5-9**, **30-32**, and **43**

Compound	Time (hours)	Starting Material %	Products (%)
5	5	75	**14** (5) [a], **24**, (10) [a]
6	9	15	**21** (45), **25**, (30) [a]
7	8	25	**22** (40), **26** (10) [a], **28** (20)
8	2	85	**23** (12), **27** (trace) [a]
8	6	80	**23** (5), **27** (10) [b]
9	6	80	**18** (10) [a]
30	1	50	**33** (35), **36** (5), **10** (trace) [a]
31	0.5	75	**34** (20)
32	0.25	80	**35** (13)
43	2	75	**44** (12) [a] [c]

[a] Compared with authentic sample. [b] In a separate experiment, irradiation of **23** gave ring closure into **27**. [c] Significant amounts of other photoproduct were also present.

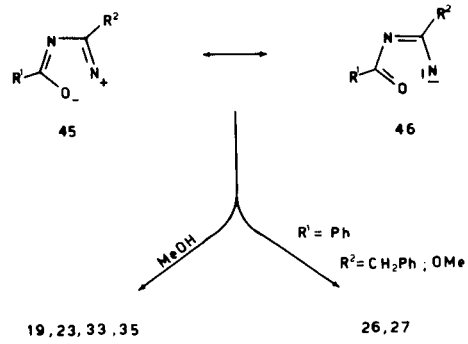
three membered ring intermediate could collapse to the photoisomer heterocycle through a nitrilimine system [2] (see Scheme 4). In accordance with this hypothesis claiming tautomeric forms, we have observed that irradiation of 2-methyl-5-phenyl-Δ^4-1,2,4-oxadiazolin-3-one (**43**) under controlled experimental conditions gave the corresponding 3-methyl-5-phenyl-Δ^4-1,3,4-oxadiazolin-2-one (**44**). (See Scheme 4).

Scheme 4



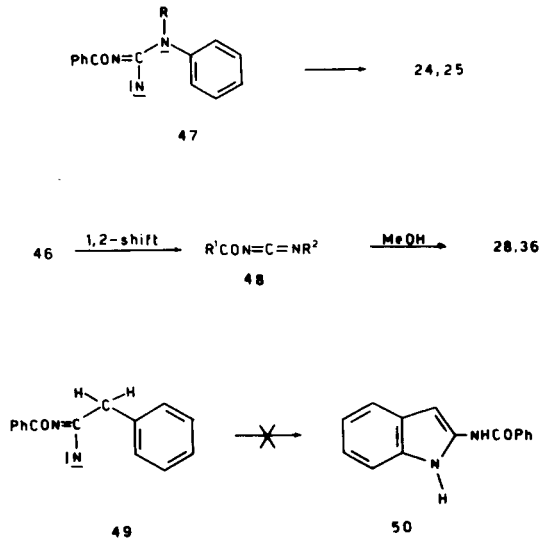
A part from these special structures, the photochemical reactivity of the 1,2,4-oxadiazole ring in methanol at 254 nm could be explained through a zwitterion **45** or a nitrene species **46** originating from a photolysis of the *O-N* bond of the ring (see Scheme 5). The electrophilic nitrogen atom of the photolytic intermediate can react: i) with the nucleophilic solvent [5] [6], to give compounds **19-23**, and **33-35**; ii) with the phenyl ring of the benzoyl moiety [5] (see **45** or **46**; R^1 = Ph), to give compounds **26** and **27**; iii) with the phenyl ring of the phenylamino group [7] [8] (see **47**), to give compounds **24** and **25**. Clearly, formation of **28** and **36** implies a 1,2-shift of the benzyl or phenyl group,

Scheme 5



respectively, in **46** (R^2 = CH_2Ph or Ph), followed by addition of methanol to the carbodiimide intermediate **48**. On irradiation of the 3-benzyl derivative **7** we have not observed formation of the indole **50** as supposed by a reaction of the nitrogen atom of the photolytic intermediate **49** on the phenyl ring of the benzyl group, likewise the formation of benzimidazoles **24** and **25**. As supported by literature [7] [8], this different behaviour could be explained on the basis of the fact that in the benzimidazole formation, ring closure may be assisted by electronic delocalization in an aromatic transition state, whereas a similar assistance to indole ring formation is unavailable.

Scheme 6



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. The ir spectra (Nujol) were determined with a Perkin-Elmer 257 instrument, uv spectra with a Beckmann Du-6 spectrophotometer, ^{1}H nmr spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as the internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). Flash chromatography [9] was performed on Merck silica gel (0.040-0.063 mm). Light petroleum refers to that fraction boiling in the range 40-60°. Methanol was purified as reported [10] and was used freshly prepared.

Compounds **5** [11], mp 140°; **7** [12], mp 81-83°; **8** [13] [14], mp 59°, **9** [13] [14], mp 202°; **30** [15], mp 154°; **31** [16], mp 128°; **32** [16], mp 62°; and **43** [17], mp 118-120°, employed in the irradiation, were prepared as reported. Compound **6** was prepared by adopting the procedure reported [11] for compound **5**, making use of *N*-methylaniline in the place of aniline. For analytical and spectroscopic data see tables 3 and 4.

The following compounds were also prepared: **14** [18], mp 212°; **18** [19], mp 135-138°; **24** [20], mp 235-240°; **25** [21], mp 157-158°; **26** [22], mp 250°; **27** [23], mp 230-232°; and **44** [24], mp 101°.

Structures of the irradiation products were assigned by a comparison with authentic samples (mp, ir, uv), or on the basis of analytical (Table 3) and spectroscopic data (ir, nmr, ms, Table 4) as well as on the basis of chemical evidences.

Table 1 reports significant uv data of compounds under irradiation, **5-9**, **30-32**, and **43**.

Table 3

Analytical Data

Compound	Mp (°C)	Solvent [a]	Formula	Found/(Calcd.) C	H	N
6	55-57	A	$C_{15}H_{13}N_3O$	71.60 (71.69)	5.20 (5.21)	16.65 (16.72)
21	110	A	$C_{16}H_{17}N_3O_2$	67.80 (67.82)	6.00 (6.05)	14.80 (14.83)
22	63-65	A	$C_{16}H_{16}N_2O_2$	71.55 (71.62)	5.95 (6.01)	10.35 (10.44)
23	35-38	A	$C_{10}H_{10}N_2O_3$	57.70 (57.68)	5.80 (5.81)	13.40 (13.44)
28	96-98	A	$C_{16}H_{16}N_2O_2$	71.60 (71.62)	5.95 (6.01)	10.40 (10.44)
33	185	B	$C_9H_{11}N_3O_2$	55.85 (55.95)	5.70 (5.74)	21.70 (21.75)
34	152-156	B	$C_{10}H_{13}N_3O_2$	58.00 (57.96)	6.30 (6.83)	20.30 (20.28)
35	110-115	B	$C_{11}H_{15}N_3O_2$	59.65 (59.71)	6.85 (6.83)	18.95 (18.99)
36	118	B	$C_9H_{11}N_3O_2$	55.90 (55.95)	5.70 (5.74)	21.80 (21.75)

[a] A = Light petroleum, B = Ethanol.

Photochemical Reactions. General Procedure.

A solution of the sample (500 mg) in freshly prepared anhydrous methanol (100 ml), in a quartz tube was degassed by bubbling in nitrogen (20 minutes), and then irradiated at 254 nm in an immersion well apparatus by means of a low-pressure mercury lamp (Helios Italquarz 17 W). The solvent was removed under reduced pressure and the residue was chromatographed on a flash silica gel column by using a mixture of light petroleum-ethyl acetate at various ratios as eluent. Minor components were discarded. Irradiation times and products isolated were reported in Table 2. For analytical and spectroscopic data see Tables 3 and 4, respectively.

Hydrolysis of Compounds **33**, **28**, and **36**.

A sample of **33** (0.3 g) in ethanol (10 ml) containing concentrated hydrochloric acid (1 ml) was gently refluxed for 15 minutes. After removing the solvent, the residue was taken up with water and filtered affording quantitative yield of benzoylurea, mp 215-218°, compared with an authentic sample.

Acid hydrolysis of **28** in ethanol and concentrated hydrochloric acid, on gentle refluxing (10 minutes), and after working as usual, gave compound **29** (90%), mp 165-166° (from ethanol), lit [25], mp 165-166°; ir: 3350, 3300 cm^{-1} (NH), 1690, 1660 cm^{-1} (CO); nmr (DMSO-d_6): δ 4.50 (d, CH_2, 2H, singlet after exchange with deuterium oxide), 7.30-8.10 (m, aromatic, NH, 11H), 9.05 (t, NH, 1H).

By the same procedure, compound **36** gave **37** (90%), mp 166-168° (from water), lit [26], mp 169°; ir: 3420, 3380, 3320, 3200 cm^{-1} (NH), 1750, 1700 cm^{-1} (CO); ms: m/z 179 (M^+), 160, 119, 93, 71, 44.

A sample of **33** (0.15 g) in ethanol (5 ml) containing aqueous 10% sodium hydroxide (0.5 ml) was refluxed for 4 hours. After removing the solvent, the residue was taken up with water and extracted with chloroform, which gave *O*-methylbenzamidoxime (90%), mp 55-57°, lit [27], mp 55-56°.

Table 4

Spectroscopic Data

Compound	ν max (cm^{-1})	^1H nmr (δ) [a]	m/z
6		3.50 (s, CH_3, 3H), 7.00-8.10 (m, aromatic, 10H). (Deuteriochloroform)	2.51 (M^+), 174, 105, 77
21	3250 (NH) 1620 (CO)	3.30 (s, CH_3, 3H), 3.90 (s, CH_3, 3H), 6.60-8.40 (m, aromatic, 10H), 10.80 (br s, NH, 1H)	283 (M^+), 105, 77
22	3200 (NH) 1655 (CO)	3.85 (s, CH_3, 3H), 4.05 (s, CH_2, 2H), 7.15-7.90 (m, aromatic, 10H), 9.55 (s, NH, 1H)	268 (M^+), 237, 131, 105, 77
23	3260, 3120 (NH) 1680 (CO)	3.60 (s, CH_3, 3H), 3.65 (s, CH_3, 3H), 7.30-7.95 (m, aromatic, 5H), 10.05 (s, NH, 1H)	208 (M^+), 174, 149, 131, 118, 105, 91
28	3380 (NH) 1625 (CO)	3.95 (s, CH_3, 3H), 4.40 (d, CH_2, 2H) [b], 7.20-8.30 (m, aromatic, 10H), 10.20 (t, NH, 1H)	268 (M^+), 253, 163, 105, 91, 77
33	3420, 3340, 3200 NH, NH_2) 1670 (CO)	3.70 (s, CH_3, 3H), 6.25 (s, NH_2, 2H), 7.25 (s, aromatic, 5H), 8.45 (s, NH, 1H)	193 (M^+), 150, 119, 104, 77
34	3340, 3280 (NH) 1650 (CO)	2.55 (d, CH_3, 3H) [b], 3.75 (s, CH_3, 3H), 6.70 (br signal, NH, 1H), 7.30 (s, aromatic, 5H), 8.50 (s, NH, 1H)	207 (M^+), 177, 162, 150, 119, 104, 91
35	3395 (NH) 1680 (CO)	2.80 (s, 2 × CH_3, 6H), 3.80 (s, CH_3, 3H), 7.30 (s, aromatic, 5H), 8.00 (s, NH, 1H)	221 (M^+), 189, 174, 158, 118, 104
36	3385, 3215 (NH, NH_2) 1680 (CO)	3.80 (s, CH_3, 3H), 6.50 (br s, NH_2, 2H), 6.85-7.10 (m, aromatic, 5H), 11.35 (s, NH, 1H)	193 (M^+), 176, 118, 77

[a] Unless otherwise specified the solvent was dimethylsulphoxide-d_6. [b] Singlet after exchange with deuterium oxide.

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