An Intermediate in the Isomerization from Nitrones to Amides

L. Baiocchi and G. Picconi*

Department of Chemistry, F. Angelini Research Institute, Viale Amelia 70, 00181 Rome, Italy

G. Palazzo

Institute of Pharmaceutical Chemistry, University of Turin, 10141 Turin, Italy

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This paper is dedicated to Professor L. Panizzi on the occassion of his 70th birthday.

Certain 1,2,4-oxadiazolyl-aryl nitrones isomerize to the corresponding amides by heating in ethanol *via* stable intermediates, for which the structure of 1,2,4-oxadiazolium inner salts was recognized.

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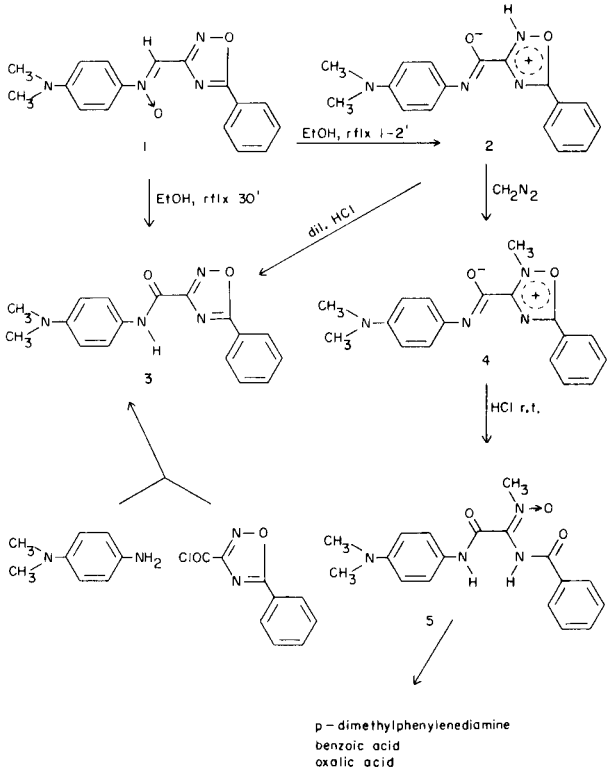
As part of a synthetic study on 1,2,4-oxadiazole-carboxaldehydes (1), 3-(5-phenyl-1,2,4-oxadiazolyl)-*N*-(4-dimethylaminophenyl) nitrone **1** was prepared in our laboratory. In an effort to recrystallize this yellow compound, it was dissolved in warm ethnanol, but after a few minutes of heating, a highly insoluble red precipitate separated from the boiling alcohol. This red compound **2**, which is isomeric with the starting nitrone, showed a higher m.p. and gave, when treated with dilute hydrochloric acid, the hydrochloride of the *p*-dimethylaminoanilide of 5-phenyl-1,2,4-oxadiazole-3-carboxylic acid **3**, instead of the expected 5-phenyl-1,2,4-oxadiazole-3-carboxaldehyde. When **1** was heated in ethanol for a longer time the same amide was isolated as the free base. The structure of **3** was confirmed by an independent synthesis from *p*-dimethyl-aminophenylenediamine and the known 5-phenyl-1,2,4-oxadiazole-3-carboxylic acid chloride (2).

Since this is the first time that an intermediate of the rearrangement of nitrones to amides has been isolated, we investigated the structure of **2**. In the nmr spectrum of the yellow nitrone **1**, a signal due to the vinyl proton falls between δ 7.25 and 8.25. This signal is no longer present in the spectrum of the red compound **2** which possesses a signal at δ 13.21. This position suggests the presence of an acidic proton, and indeed **2**, when treated with diazomethane, gave a red methyl derivative **4**, which was easily dissolved in cold dilute hydrochloric acid losing its colour. Upon basification of the solution, a white solid was obtained. The elemental analysis of this latter compound showed it to be a product of the hydration of **4**. The nmr spectrum of this compound shows a methyl group as a singlet at δ 3.90, whereas in the ir spectrum, only a C=O band at 1660 cm^{-1} is present. When **4** was refluxed for 1 hour in dilute hydrochloric acid, oxalic acid and *p*-dimethylamino phenylenediamine were obtained.

Since it is well known that 3,5-disubstituted-1,2,4-oxadiazoles are unaffected by aqueous acids (3) and, on the other hand, that the 1,2,4-oxadiazolium salts are easily hydrolysed by diluted acids (4,5), the structure of an oxadiazolium salt was assigned to **4**. The structure **5** was assigned to the corresponding hydrolysis product. Thus, the following sequence may be written.



From the ir spectrum the structure of *o*-benzoylhydroxylamine (hydrolysis of the 4-5 bond) may be excluded for **5** (6). From the nmr spectrum it is possible to exclude the alternative structure **6**, since the methyl signal in *N*-methylbenzamides falls near δ 3.0 (7). Compound **6**

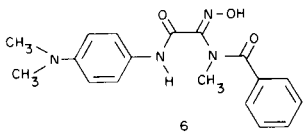


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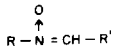
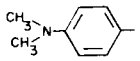
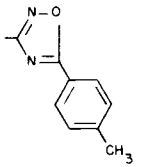
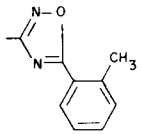
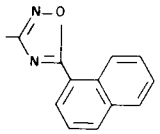
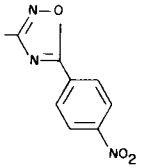
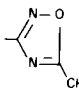
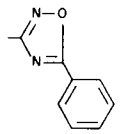
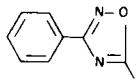
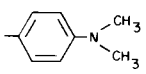
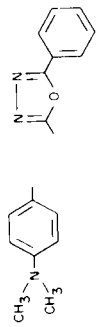
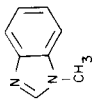
Table I

Characteristics and Transformations of some Nitrones 

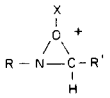
Compound No.	R	R′	Nitrone M.p. °C	Formula		Analysis C	H	N	Effect (a)	Action of Boiling Ethanol M.p. °C		Analysis C	H	N
8			149° dec	$C_{18}H_{18}N_4O_2$			(1)		I	165° dec	Calcd.	67.06	5.63	17.38
											Found	67.12	5.77	17.48
9			88-90°	$C_{18}H_{18}N_4O_2$			(1)		I	152-154°	Calcd.	67.06	5.63	17.38
											Found	67.08	5.94	17.08
10			110-112°	$C_{21}H_{18}N_4O_2$	Calcd.	70.37	5.06	15.63	I	153-155°	Calcd.	70.37	5.06	15.63
					Found	70.48	5.25	15.42			Found	70.33	5.25	15.83
11			208-210°	$C_{17}H_{15}N_5O_4$			(1)		U					
12			102° dec	$C_{12}H_{14}N_4O_2$	Calcd.	58.52	5.73	22.75	A	162-164°	Calcd.	58.52	5.73	22.75
					Found	58.63	5.73	22.74			Found	58.22	5.93	22.48
13			104-108°	$C_{15}H_{11}N_3O_2$	Calcd.	67.91	4.18	15.84	A	153-157°	Calcd.	67.91	4.18	15.84
					Found	67.80	4.25	15.70			Found	68.39	4.50	15.68
14			146-148°	$C_{17}H_{16}N_4O_2$			(1)		U					

15		165-166°	$C_{17}H_{16}N_4O_2$	Calcd.	66.22	5.23	18.17	U
				Found	66.28	5.46	18.39	
16		149-152°	$C_{16}H_{18}N_4O$	Calcd.	68.06	6.43	19.85	U
				Found	67.73	6.58	18.61	
17		144°	$C_{15}H_{16}N_2O$			(12)		U
18		118-121°	$C_{15}H_{15}N_3O_3$			(13)		U

(a) I, The compound gave an intermediate analogous to **2**; A, the compound gave the amide analogous to **3**; U, the compound was recovered unaltered.

would be obtained from hydrolysis of the 4-methyloxadiazolium salt which is isomeric with **4**.

The behaviour of this particular nitrone can be of help to better understand the mechanism of rearrangement of nitrones to amides in general. This rearrangement can be achieved with alcoholates, acid chlorides or anhydrides, but not with ethanol alone (8). It has been the subject of several discussions (9,10,11). Lamchen pointed out that the mechanism previously proposed by Kröhnke (9) (*i.e.*, 1-3 dipolar addition followed by 1-2 elimination) does not explain the action of agents such as phosphorus pentachloride, and proposed an oxaziridinium cation (**7**) as a key intermediate in this rearrangement. Our observations



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are in agreement with Lamchen's interpretation: the driving force of the reaction seems to be the abstraction of the group X^+ from **7**. This abstraction may be prompted in general by ethoxide, carboxylate or chloride anion, and particularly in our specific case in which X = H, by the oxadiazole 2-N.

In order to confirm the above findings we studied the behaviour of several other nitrones when heated in ethanol. The results are summarized in Table I.

Only the compounds bearing the nitrone function in position 3 of the 1,2,4-oxadiazole nucleus isomerize to amides by simple heating in ethanol. Depending on the substituent in position 5 of the oxadiazole nucleus, the isomerization occurs more or less readily. For example, a *p*-nitrophenyl substituent hinders the reaction, whereas when a methyl substituent is present in the same position, only the corresponding amide and not the intermediate is obtained. The same result was obtained starting from 5-phenyl-1,2,4-oxadiazole derivatives instead of the 5-*p*-dimethylaminophenyl analogues.

When the nitrone function is in position 5 of the 1,2,4-oxadiazole nucleus, the isomerization does not take place. This is in accordance with the proposed structure **2** of the intermediate, which is the result of a 1-3 hydrogen shift in **1** from the C=N carbon atom to the oxygen linked nitrogen atom. 1,3,4-Oxadiazole nitrones and other heterocyclic or non-heterocyclic nitrones are unaffected by boiling ethanol according to the literature.

EXPERIMENTAL

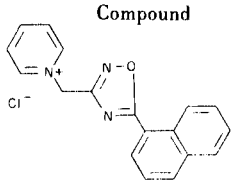
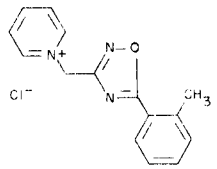
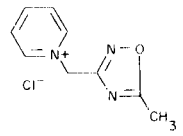
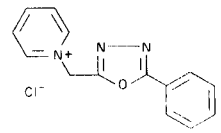
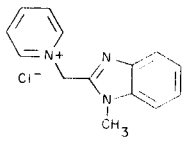
For generalities see the preceding paper (1).

3-(5-Phenyl-1,2,4-oxadiazolyl)-*N*-(4-dimethylaminophenyl) Nitrone (**1**).

The preparation of this compound is described in the preceding paper.

Table II

Pyridinium Salts

Compound	M.p. °C	Yield %	Formula		Analysis C	H	N	Cl
	229-231°	70	$C_{16}H_{14}ClN_3O$	Calcd.	66.77	4.36	12.98	10.95
				Found	66.52	4.42	13.04	11.06
	219° dec	65	$C_{15}H_{14}ClN_3O$	Calcd.	62.61	4.90	14.60	12.32
				Found	62.59	4.88	14.51	12.11
	197° dec	67	$C_9H_{10}ClN_3O$	Calcd.	51.07	4.76	19.85	16.75
				Found	51.00	4.63	20.02	16.89
	205-207°	64	$C_{14}H_{12}ClN_3O$	Calcd.	61.43	4.79	15.35	
				Found	61.34	4.80	15.33	
	227° dec	60	$C_{14}H_{14}ClN_3$	Calcd.	64.74	5.43	16.18	13.65
				Found	64.62	5.28	16.33	13.58

It shows uv (95% ethanol): λ max 400 nm (ε = 8,000), 256 (ε = 24,000); nmr (deuteriochloroform): 3.00 (s, 6H, CH_3-N), 6.65-6.75 (m, 2H, *o*-aromatics), 7.25-8.25 (m, 8H, aromatics and CH=).

N-(4-Dimethylaminophenyl)-3-(5-phenyl-2*H*-1,2,4-oxadiazolium)carboxamide Inner Salt (**2**).

Compound **1** (3 g., 0.01 mole) was dissolved in boiling ethanol (20 ml.). After 1-2 minutes of reflux, a red crystalline solid precipitated. The reflux was continued for a total of five minutes. The mixture was then cooled, and the solid was filtered, washed with ethanol and dried. Thus, 1.7 g. (57%) of **2** was obtained, m.p. 160°; uv: λ max 442 nm (ε = 13,000), 307 (ε = 17,700), 267 (ε = 17,200); nmr (deuteriochloroform): 2.90 (m, 6H, N-CH_3), 6.60-6.70 (m, 2H, *o*-aromatics), 7.20-8.15 (m, 7H, aromatics), 13.21 (s, 1H, acidic proton).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.00; H, 5.25; N, 18.51.

N-(4-Dimethylaminophenyl)-5-phenyl-1,2,4-oxadiazole-3-carboxamide (**3**).

Compound **2** (1.0 g., 0.003 mole) was dissolved in 3*N* hydrochloric acid (10 ml.) at room temperature. After standing for 30 minutes, the solid which separated was collected and recrystallized from ethanol to give 1.0 g. of **3**·HCl·H_2O, m.p. 212°; ir (potassium bromide): 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$·HCl·H_2O: Cl, 10.28. Found: Cl, 9.89.

The free base had m.p. 150° (ethanol); ir (potassium bromide): 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.38; H, 5.48; N, 18.46.

The same hydrochloride (mixed m.p.) was obtained by mixing together, at room temperature, two ethereal solutions of 5-phenyl-1,2,4-oxadiazole-3-carboxylic acid chloride (**2**) and *N,N*-dimethyl-*p*-phenylenediamine. The amide free base may also be obtained by recrystallization from ethanol of the gummy residue which is obtained on refluxing a solution of **1** in ethanol for 1 hour.

N-(4-Dimethylaminophenyl)-2-methyl-5-phenyl-1,2,4-oxadiazolium-3-carboxamide Inner Salt (**4**).

To a solution of **2** (3.2 g., 0.01 mole) in chloroform (150 ml.) a large excess of an ethereal solution of diazomethane (100 ml., 0.2*N*) was added at room temperature. After standing several hours the solvent was evaporated and the residue recrystallized twice from benzene to give **4** (0.9 g.), m.p. 162-164°; nmr (deuteriochloroform): 3.00 (s, 6H, CH_3-N), 4.18 (s, 3H, CH_3-N), 6.65 (m, 2H, aromatics), 7.50 (m, 5H, aromatics), 8.1 (m, 2H, aromatics).

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 66.62; H, 5.46; N, 17.38.

N-(4-Dimethylaminophenyl)-*N'*-methyl-*N''*-benzoyloxamic amidine *N'*-Oxide (**5**).

Compound **4** (0.37 g., 0.001 mole) was dissolved in 3*N* hydrochloric acid (2 ml.). The solution was brought to *p*H 10 with 10% sodium carbonate solution and the white precipitate was collected and recrystallized from benzene to give **5** (0.21 g.), m.p. 149-152°; ir (potassium bromide): 1660 cm^{-1} (C=O); nmr (deuteriochloroform): 2.9 (s, 6H, N-CH_3), 3.9 (s, 3H, N-CH_3), 6.65 (m, 2H, aromatics), 7.50 (m, 5H, aromatics), 7.9 (m, 2H, aromatics), 8.45 (m, 2H, NH protons).

Anal. Calcd. for $C_{16}H_{20}N_4O_3$: C, 63.51; H, 5.92; N, 16.46. Found: C, 63.52; H, 5.95; N, 16.15.

Hydrolysis of **5**.

Compound **5** (0.21 g., 0.0006 mole) was refluxed for 1 hour with 2*N* hydrochloric acid (6 ml.). After cooling the solution, a white solid separated and was recognized as benzoic acid. Oxalic acid and *p*-dimethylaminophenylenediamine were also detected with the usual techniques in the acidic solution.

Nitrones **8-18** (see Table I).

Compounds **8-9**, **11** and **14** have been described in the preceding paper. The other nitrones were obtained by the same procedure in yields ranging between 60 and 90%, starting from the appropriate pyridinium salt.

Pyridinium Salts.

These compounds were obtained by the procedure described in the preceding paper (1) by reacting pyridine with the appropriate chloromethyl derivative. The yields, analyses and m.p. of the new products are listed in Table II.

Chloromethyl Derivatives.

These compounds are all known products except for the following.

3-Chloromethyl-5-*o*-tolyl-1,2,4-oxadiazole.

This compound had b.p. 131°/0.2 torr, yield 74%.

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.35; N, 13.43. Found: C, 57.48; H, 4.38; N, 13.33.

3-Chloromethyl-5-naphthyl-1,2,4-oxadiazole.

This compound had m.p. 87-89°, yield 77%.

Anal. Calcd. for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 64.02; H, 3.82; N, 11.31.

Both products have been prepared according to the described procedure.

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