Base-catalysed Rearrangement of 2-Phenylamino-1,3,4-oxadiazole into 4-Phenyl-1,2,4-triazolin-5-one

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The behaviour in alkaline media (water, water–dioxane, or water–dimethyl sulphoxide) of 2-phenylamino-1,3,4-oxadiazole (I*H*) has been studied, together with the title reaction. Chemical and kinetic evidence support the occurrence of a ring conversion through an intermediate cyclic compound (IV$^-$), followed by the formation of an open-chain anion (V$^-$) that cyclizes fast to the triazole derivative (III$^-$).

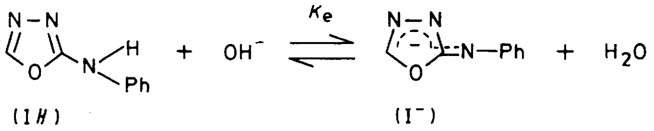
5-Substituted 2-amino-1,3,4-oxadiazoles rearrange with bases, under forcing conditions, into 5-substituted 1,2,4-triazol-3-ones.[1] An analogous rearrangement can be achieved by treating 2,5-dialkyl- or 2,5-diaryl-1,3,4-oxadiazoles with primary alkyl- or aryl-amines.[2] Moreover, 2-amino-5-alkyl- or 2-amino-5-aryl-1,3,4-oxadiazoles, when treated with potassium alkoxide, yield 3-alkoxy-5-alkyl- and 3-alkoxy-5-aryl-1,2,4-triazoles, respectively.[3] In some instances the acylsemicarbazides suggested as reaction intermediates have been isolated, and thereafter converted into 1,2,4-triazol-3-ones by further action of a base.[4] The nature of the reaction products and of the isolated intermediates indicates that in the rearrangements investigated the ring opening occurs at the O–C(2) bond.

Only scanty data have been reported for the reactions of 5-unsubstituted 2-amino-1,3,4-oxadiazoles and no corresponding kinetic data are available.[5]

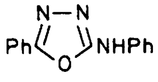
In order to gain information about the kinetic course of the rearrangement and to contribute to the understanding of the reaction mechanism we have studied the smooth rearrangement of 2-phenylamino-1,3,4-oxadiazole (I*H*) in the presence of sodium hydroxide in water and in mixed solvents [dioxane–water and dimethyl sulphoxide (DMSO)–water]. For comparison we have also collected some kinetic data for the rearrangement of 2-phenylamino-5-phenyl-1,3,4-oxadiazole (II) in DMSO–H_2O.

Results and Discussion

The u.v. spectrum of 2-phenylamino-1,3,4-oxadiazole (I*H*) in water is strongly affected by the pH of the solution. The spectral changes are reversible and can be related to the ionization shown in Scheme 1.† The equilibrium constant, K_e, measured at 298.2 K in different solvents (Table 1), increases as expected on going from a protic to an aprotic dipolar solvent.



Scheme 1.



(II)

Table 1. Equilibrium constants for the reaction (I*H*) ⇌ (I$^-$) in various solvents at 298.2 K

Solvent	$K_e \pm s$ [a]/ l mol^{-1}	λ [b]/ nm	log ε [b]
H_2O [c]	59.5 ± 3.2	280	4.20
H_2O [d]	75.7 ± 2.7	280	4.20
Dioxane–H_2O (20 : 80 v/v) [c]	160 ± 5	286	4.23
Dioxane–H_2O (40 : 60 v/v) [c]	214 ± 7	286	4.27
DMSO–H_2O (20 : 80 v/v) [c]	171 ± 2	285	4.26
DMSO–H_2O (40 : 60 v/v) [c]	778 ± 16	288	4.31
DMSO–H_2O (50 : 50 v/v) [c]	1 550 ± 70	292	4.33
DMSO–H_2O (60 : 40 v/v) [c]	4 500 ± 500	295	4.35
DMSO–H_2O (75 : 25 v/v) [c]	19 000 ± 3 000	300	4.40
DMSO–H_2O (90 : 10 v/v) [c]	>30 000	305	4.42

[a] *s* is the standard deviation of K_e. [b] Values at the absorption maximum of (I$^-$) used for the spectrophotometric determination of K_e values. [c] At ionic strength 0.2M. [d] At ionic strength 1M.

In alkaline solution (*e.g.* at pH *ca.* 12) and at higher temperatures (*e.g.* at 333.2 K) (I*H*) rearranges into (III$^-$), *i.e.* the anion of 4-phenyl-1,2,4-triazolin-5-one (III*H*). Studying this rearrangement at various sodium hydroxide concentrations, at constant ionic strength, we have observed a hyperbolic dependence of the apparent kinetic constant, k_A, on the pH (Table 2 and Figure). This kind of functional dependence agrees with a complex reaction pattern, such as that indicated in Scheme 2, where an acid–base equilibrium competes with a base-catalysed rearrangement. The kinetic law appropriate to the reaction mechanism of Scheme 2 is equation (1), which can be rearranged into equation (2). Therefore from measurements of k_A and K_e it is possible to calculate k_R at any hydroxide concentration.

$$k_A = \frac{k_R[OH^-]}{1 + K_e[OH^-]} \qquad (1)$$

$$k_R = \frac{k_A\{1 + K_e[OH^-]\}}{[OH^-]} \qquad (2)$$

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† The spectral changes of (I*H*) could also be accounted for by the formation of an adduct such as (IV$^-$) (see later). This hypothesis has been rejected on the basis of n.m.r. spectral evidence. In fact, the chemical shift of the proton at C-5 in (I*H*) in DMSO [δ 8.72 (1 H, s)] is unaffected by addition of 1 equiv. of sodium hydroxide, at variance with what one would have expected for the formation of the adduct (IV$^-$) (see M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667). Instead, the addition of sodium hydroxide causes the disappearance of the N*H* signal according to the equilibrium of Scheme 1.

Table 2. Apparent rate constants,[a] k_A, and rearrangement rate constants, k_R, for the conversion of (I^-) into (III^-) at 333.2 K

10^2[NaOH]/M	H_2O [b]		H_2O [c]		Dioxane–H_2O (40 : 60 v/v) [b]	
	$10^6 k_A$/ s^{-1}	$10^6 k_R$/ l $mol^{-1} s^{-1}$	$10^6 k_A$/ s^{-1}	$10^6 k_R$/ l $mol^{-1} s^{-1}$	$10^6 k_A$/ s^{-1}	$10^6 k_R$/ l $mol^{-1} s^{-1}$
1.0	1.51	241				
1.6	1.93	235				
2.0			2.35	295	3.53	932
2.8	2.70	257	2.76	308	3.84	959
4.0	3.13	264	3.38	340	4.23	1 010
6.0	3.35	255	3.66	338	4.57	1 050
8.0					4.61	1 040
15.0	4.25	281	4.53	373	4.81	1 060
20.0	4.34	280	4.72	381	4.87	1 070
50.0			5.13	399		
100.0			5.39	413		

[a] Rate constants are accurate to within ±3%. The wavelengths and the logarithms of the molar extinction coefficients used for the kinetic measurements are reported in Table 1. [b] At ionic strength 0.2M. [c] At ionic strength 1.0M.

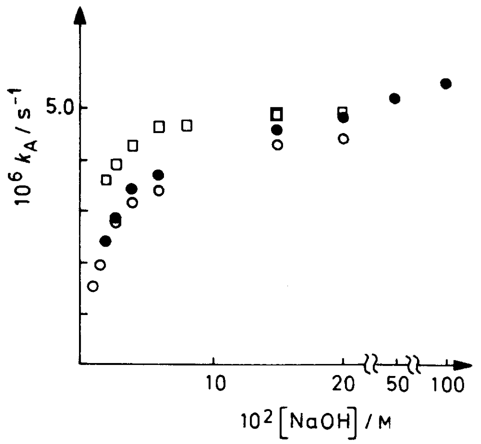
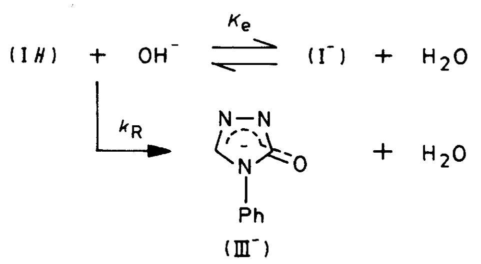


Figure. Plot of apparent rate constants, k_A, *versus* [NaOH] in water (ionic strength ○ 0.2, ● 1.0) and in dioxane-water (40 : 60 v/v) (□)



Scheme 2.

Table 3. Apparent rate constants,[a] k_A, and rearrangement kinetic constants, k_R, for the conversion of (I^-) into (III^-) at 333.2 K and at [NaOH] 0.2M

Solvent	$10^6 k_A/s^{-1}$	$10^6 k_R$/l $mol^{-1} s^{-1}$
H_2O [b]	4.34	280
H_2O [c]	4.72	381
Dioxane–H_2O (20 : 80 v/v) [b]	4.51	744
Dioxane–H_2O (40 : 60 v/v) [b]	4.87	1 070
DMSO–H_2O (20 : 80 v/v) [b]	4.60	810
DMSO–H_2O (40 : 60 v/v) [b]	5.44	4 260
DMSO–H_2O (50 : 50 v/v) [b]	7.04	10 900
DMSO–H_2O (60 : 40 v/v) [b]	10.4	46 900
DMSO–H_2O (75 : 25 v/v) [b]	19.2	365 000
DMSO–H_2O (90 : 10 v/v) [b]	42.5	>1 280 000

[a–c] As in Table 2.

The k_R values calculated (Table 2) vary little with changing pH, showing only a small increase with increasing concentration of sodium hydroxide; this represents the best evidence in favour of a mechanism requiring such a functional dependence of k_A on [OH^-] as given by equation (2).*

In order to clarify the nature of the transition state involved in the conversion of (I*H*) into (III^-) we have measured the rearrangement rate also in mixed solvents (dioxane–H_2O and DMSO–H_2O); the relevant kinetic data are shown in Table 3. The k_R values, calculated for each solvent mixture according to equation (2), show the same trend as K_e with changing solvent, *i.e.* a large increase on going from a protic to an aprotic dipolar solvent. This indicates that the ionic transition state is less solvated than the starting materials [6] and allows us to take into account only mechanisms which imply the slow formation of a species that rapidly gives the final product.

A model for the reaction course could be that shown in Scheme 3, where the first formed ionic intermediate (IV^-) gives an open-chain anion (V^-) that cyclises rapidly to the ion (III^-).

The following experimental evidence proves that attack of hydroxide ion occurs at C-5, as indicated in (IV^-).

(*a*) (I*H*) reacts with sodium methoxide in methanol, but the product is not 3-methoxy-4-phenyl-1,2,4-triazole (VI) as one might have expected on the basis of an attack of methoxide at C-2 followed by fission of the C(2)–O bond. Instead, by acidification of the reaction mixture, a 1 : 3 mixture of (III*H*) and (VII) is obtained; this indicates attack of methoxide ion at C-5 followed by rupture of the C(5)–O bond.

(*b*) 5-Phenyl-2-phenylamino-1,3,4-oxadiazole (II), in which attack at C-5 is sterically hindered, does not react when boiled with 0.2M-sodium hydroxide in DMSO–H_2O (90 : 10)

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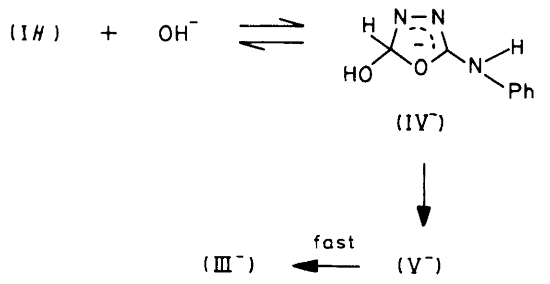
* The observed dependence of k_A on pH agrees also with a spontaneous slow rearrangement of (I^-) into (III^-):

$$\begin{tikzcd}
(IH) + OH^- \arrow[r, shift left, "\text{fast}"] & (I^-) + H_2O \arrow[l, shift left, "K_e"] \arrow[dr, "\text{slow}", "k_R"'] & \\
& & (III^-)
\end{tikzcd}$$

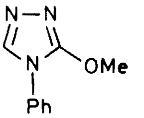
in which case the kinetic law should be:

$$k_A = \frac{K_e k_R [OH^-]}{1 + K_e [OH^-]}$$

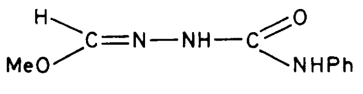
The following experimental results permit us to exclude this interpretation. First, if (I^-) gave (III^-) the rearrangement (I^-) ⟶ (III^-) would be independent of the nature of the base; indeed, the same results should be (but are not) obtained by action of either sodium hydroxide or methoxide (see later). Secondly, in DMSO–H_2O mixtures with a high DMSO content, owing to the high value of K_e, the previous kinetic law should turn into $k_A = k_R$, and this does not occur (see Table 3). Finally, the rearrangement rates measured in mixed solvents (*e.g.* in DMSO–H_2O; see later) do not agree with the solvent effect observed (see E. Buncel and H. Wilson, *Adv. Phys. Org. Chem.*, 1977, **14**, 133).



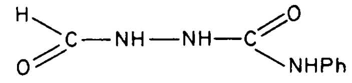
Scheme 3.



(VI)



(VII)



(VH)

for 52 h.* This gives an estimated value of k_A lower than 3.3×10^{-6} s^{-1} at 416.2 K for (II) as compared with 42.5×10^{-6} s^{-1} at 333.2 K for (I*H*).

In order to elucidate the nature of the intermediate (V^-) we have prepared the compound (V*H*), the anion of which could be the open-chain intermediate,† and treated it with sodium hydroxide in water at 333.2 K. A 60% yield of (III^-) is obtained as well as hydrolysis products of (V*H*): moreover, by following the progress of the reaction by t.l.c. analysis we have ascertained that under the foregoing experimental conditions (V*H*) gives both the 1,3,4-oxadiazole (I^-) and the 1,2,4-triazole (III^-) in addition to hydrolysis products. After a long time the concentration of (I^-) diminishes and those of (III^-) and hydrolysis products increase.

We have also followed by t.l.c. the course of the rearrangement (I^-) ⟶ (III^-): although in this case the presence of (V*H*) was not detectable, traces of aniline were observed after a long reaction time.‡

As a whole, the foregoing experimental results can be represented as in Scheme 4. Since the conversion (I*H*) ⟶ (III^-) is nearly quantitative, whereas (V*H*) ⟶ (III^-) is not so, we consider that the rate of salt formation of (V*H*) is similar to its hydrolysis rate. As a consequence of a supposedly high salt formation rate for (V*H*), its cyclization rate must also be high, and this excludes the possibility that cyclization of the open-chain intermediate could be the rate-determining step of the rearrangement (I*H*) ⟶ (III^-).

$$\begin{tikzcd}
(\mathrm{I}H) + \mathrm{OH}^- \arrow[r, shift left] & (\mathrm{IV}^-) \arrow[l, shift left] \arrow[r, shift left] & (\mathrm{V}^-) \arrow[l, shift left] \arrow[r] \arrow[d, shift left, "\mathrm{OH}^-"] & (\mathrm{III}^-) \\
 & & (\mathrm{V}H) \arrow[u, shift left] \arrow[d, "\mathrm{OH}^-"] & \\
 & & \text{hydrolysis products} &
\end{tikzcd}$$

Scheme 4.

The present work clearly indicates that the conversion follows a reaction pathway different from that of other 1,3,4-oxadiazole ⟶ 1,2,4-triazole rearrangements. For example, the rearrangement of 2-amino-1,3,4-oxadiazoles bearing no substituent on exocyclic nitrogen has been shown [1,4] to proceed through fast formation of an open-chain intermediate, sometimes isolable, which slowly cyclizes to a 1,2,4-triazole.

Clearly the reaction pathway can be affected by many factors; prominent among them are the nature of the nucleophile and the kind of substituents present in the starting heterocycle which determine the stability and reactivity pattern of the reaction intermediates.

Experimental

Materials.—Dioxane and dimethyl sulphoxide (reagent grade, Carlo Erba) and standard sodium hydroxide solutions (Normex, Carlo Erba) were used throughout. Water, 2-phenylamino-1,3,4-oxadiazole (I*H*),[7] 2-phenylamino-5-phenyl-1,3,4-oxadiazole (II),[8] 4-phenyl-1,2,4-triazolin-5-one (III*H*),[9] and 1-formyl-4-phenylsemicarbazide (V*H*)[9] were prepared and purified as described in the literature.

Reaction of the Oxadiazole (I*H*) *with Sodium Hydroxide.*—The oxadiazole (I*H*) (1 g) was refluxed (6 h) with 1M-sodium hydroxide (50 ml). After cooling, the mixture was acidified with concentrated hydrochloric acid and the product (III*H*) (0.7 g) was collected by filtration; extraction with chloroform gave more (III*H*) (0.25 g).

In order to test for the presence of (V*H*) during the rearrangement (I*H*) ⟶ (III^-) we repeated the experiment at 333.2 K and followed the progress of the reaction by t.l.c. analysis. Samples of the aqueous solution were taken after 1, 7, 24, 48, 72, and 120 h, extracted with chloroform, acidified with hydrochloric acid, and extracted again with chloroform. The chloroform layer from the basic solution contained unchanged (I*H*) and traces of aniline (after at least 48 h); that from the acid solution contained both (I*H*) and (III*H*): no (V*H*) was detectable.

Reaction of the Oxadiazole (I*H*) *with Sodium Methoxide.*—The oxadiazole (I*H*) (2 g) was refluxed (6 h) with 1M-sodium methoxide (100 ml). The methanol was removed at reduced pressure and the residue treated with water (35 ml) and filtered off. The solid obtained (0.94 g) was crystallized from aqueous methanol (m.p. 156 °C) and identified as the phenylsemicarbazone (VII) of methyl formate on the basis of the following data: m/z 193 (M^+), 162, 120, 93, 74, 28; δ_H [$(CD_3)_2SO$] 3.78 (s, 3 H, OMe), 6.85 (s, 1 H, CH), 7.03—7.73 (m, 5 H, C_6H_5), 8.87 (s, 1 H, NH), and 9.26 (s, 1 H, NH).

The chloroform extract of the reaction mixture gave, after removal of the solvent, an unidentified tarry residue (0.26 g). The aqueous alkaline solution was acidified with hydrochloric acid and then extracted with chloroform. The chloroform layer was chromatographed on a column of silica gel 60 deactivated with H_2O (15%) using cyclohexane–ethyl acetate (3 : 2) as eluant and gave unchanged (I*H*) (0.28 g) and (III*H*) (0.34 g).

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* The steric hindrance of a phenyl group to cyclization has at least one precedent. In substituted imidoylsemicarbazides the presence of a bulky substituent, such as phenyl, strongly affects the course of the reaction (see K. M. Doyle and F. Kurzer, *Tetrahedron*, 1976, **32**, 2347).

† Indeed, many tautomers are possible for both (V*H*) and (V^-). However, we think that, as far as the nature of the reaction intermediate is concerned, a discussion on their stability is not essential. In fact, an anion occurring only in minute concentration could be the reactive intermediate.

‡ We have estimated by t.l.c. analysis the rates of the two reactions: (V*H*) $\xrightarrow{\mathrm{OH}^-}$ (III^-) and (I^-) ⟶ (III^-), the first reaction being at least ten times faster than the second.

Reaction of the Semicarbazide (V*H*) *with Sodium Hydroxide.*—The semicarbazide (V*H*) (2 g) was refluxed (6 h) with 1M-sodium hydroxide (100 ml). After cooling the solution was extracted with chloroform: the organic layer was separated and, after removal of the solvent, gave aniline (0.2 g).

On acidification of the alkaline solution with hydrochloric acid, (III*H*) (0.84 g) precipitated. More (III*H*) (0.26 g) was obtained from the acid solution concentrated at reduced pressure as well as more aniline, precipitated as benzaldehyde azine (0.3 g) by the action of benzaldehyde.

In order to investigate the intermediate formation of other compounds during the conversion (V*H*) $\longrightarrow$ (III*H*), we repeated the foregoing experiment at 333.2 K and followed the progress of the reaction by t.l.c. analysis. Samples of the aqueous solution were taken after 1, 3, 7, 24, 48, and 192 h, extracted with chloroform, acidified with hydrochloric acid, and extracted again with chloroform. The first extracts contained unchanged (V*H*), (I*H*), and traces of aniline (after 7 h); after 192 h significant amounts of aniline were present. The extracts from the acid solution contained both (I*H*) and (III*H*).

Determination of Equilibrium Constants.—The equilibrium constants (Table 1) were determined spectrophotometrically, at constant ionic strength, according to the general method described by Albert and Serjeant.[10]

Kinetic Measurements.—The kinetics of rearrangement were followed spectrophotometrically, at constant ionic strength, by measuring the disappearance of (I^-) [the fast-formed anion of (I*H*)], at the wavelength of its absorption maximum, in samples diluted with an excess of sodium hydroxide solution. The concentration range of (I*H*) was 2×10^{-4} to 1×10^{-3}M; the concentrations of sodium hydroxide are indicated in Tables 2 and 3. Owing to the exceedingly low reaction rates, no experiment was performed at [OH^-] values lower than 1×10^{-2}M.

Acknowledgements

We thank the C.N.R. for support.

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5 See *e.g.* H. C. van der Plas, ' Ring Transformations of Heterocycles,' Academic Press, New York, 1973, pp. 375 *et seq.*

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Received 3rd *May* 1983; *Paper* 3/693