REARRANGEMENTS OF 1-OXA-2-AZOLES.

3.* REARRANGEMENT OF 1,2,4-OXADIAZOLE-3-CARBOXYLIC ACID AMIDOXIMES

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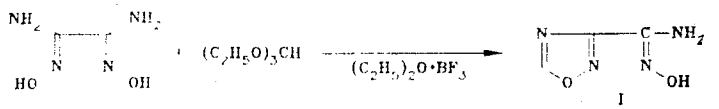
The rearrangement of unsubstituted 1,2,4-oxadiazole-3-carboxylic acid amidoxime and its N-isopropyl derivative to an aminofurazan is catalyzed by ammonia, while in the case of the amidoxime containing a piperidino substituent the rearrangement is catalyzed by acids. In ammonium hydroxide the piperidino and imidazolyl derivatives are converted to cyano amidoximes as a result of opening of the oxadiazole ring.

We have previously shown that 5-trifluoromethyl-1,2,4-oxadiazole-3-carboxylic acid amidoxime is readily converted to a diaminofurazan by the action of ammonia [2]. To ascertain the effect of the structure of the amidoximo group on the course of this reaction we studied the transformations of N-substituted 1,2,4-oxadiazole-3-carboxylic acid amidoximes in acidic and basic media.

From purely geometrical considerations it is apparent that the direct formation of a furazan ring is possible only for the E isomers of 1,2,4-oxadiazole-3-carboxylic acid amidoximes, whereas the substituents attached to the nitrogen atom of the amidoximo group have a significant effect on both the relative stabilities of the Z and E isomers and on the magnitude of the barrier to E—Z isomerization. Unsubstituted amidoximes are known only in the form of the thermodynamically more stable Z isomers. The Z isomers are also more favorable for N-alkyl-substituted amidoximes. However, in a number of cases the E form is observed in the PMR spectra of solutions of them [3, 4]; the barrier to Z—E isomerization here is 19.9-21.5 kcal/mole [3]. In the case of the N,N-dialkyl derivatives the E isomers are even more stable, and the barrier to isomerization is 21-25 kcal/mole [3, 5]. In addition, the Z forms are more favorable for amidoximes that contain a heteroaromatic ring as the amino function [6, 7], and the barrier to isomerization is extremely high [6]. To study the rearrangement we therefore selected derivatives I and III-V, for which substantial differences in the rate and equilibrium constants of the Z—E isomerization of the amidoxime group were expected.

1,2,4-Oxadiazole-3-carboxamidoxime (I) was previously obtained in low yield as a side product in the reaction of diaminoglyoxime with formic acid [8] or via a multistep route through 1,2,4-oxadiazole-3-carbonitrile [9]. We have developed a more convenient method for the synthesis of this compound from diaminoglyoxime and ethyl orthoformate in the presence of boron trifluoride etherate:



I

N-Substituted amidoximes III-V were obtained from 1,2,4-oxadiazole-3-carbohydroximic acid chloride (II) and the corresponding amines (see scheme below).

Triethylamine was used as a hydrogen-chloride acceptor in the reaction with imidazole, while an excess of the amine was used in the remaining reactions.

The reaction of the hydroximic acid halides with the amines proceeds through a step involving the formation of a nitrile oxide, to which the amine always adds to give the Z-amidoxime [10]. The rearrangement of amidoximes I and III-V should therefore be preceded by Z—E isomerization of the oxime group. This isomerization is reversible, although in many cases the equilibrium is shifted virtually completely to favor one of the isomers. The following

*See [1] for Communication 2.

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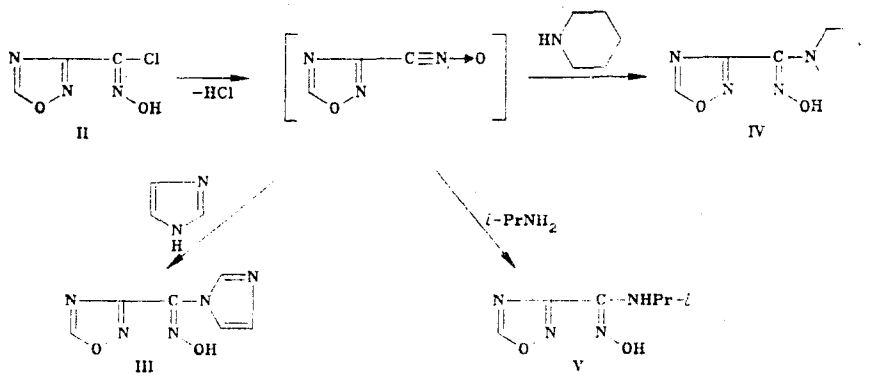
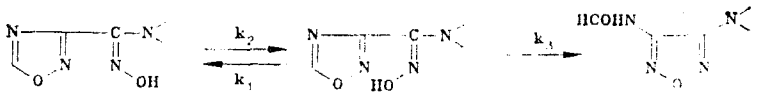


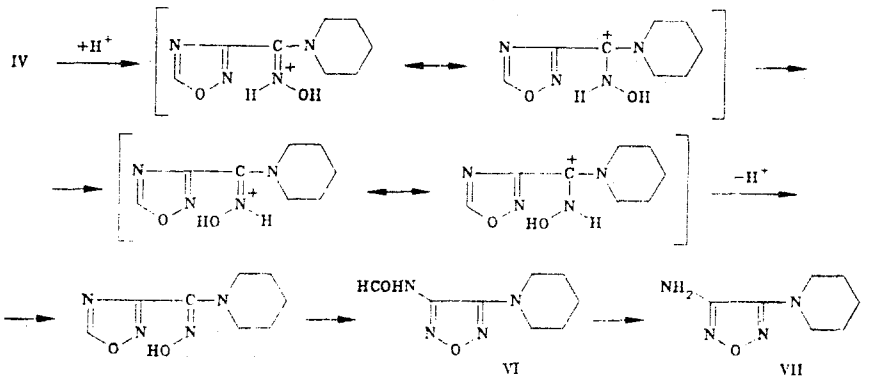
recyclization step is irreversible. It is extremely important that the first step requires acid catalysis, while base catalysis is necessary for the second step:



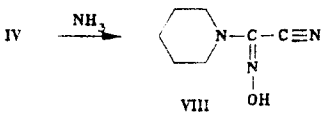
The observed rate constant (k) of this reaction is expressed by [11]

$$k = \frac{k_2 k_3}{k_1 + k_3} = \frac{k_2}{k_1/k_3 + 1}.$$

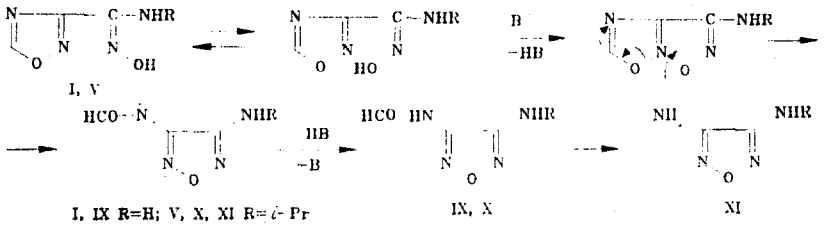
The spontaneous rearrangement of piperidino Z-oxime IV to diaminofurazan VII at room temperature proceeds slowly. However, under the influence of an acid, which catalyzes Z—E isomerization, piperidino oxime IV is rapidly converted to furazan VI:



Since in the case of N,N-dialkylamidoximes the Z—E equilibrium is shifted virtually completely to favor the E isomer [5, 10] (i.e., $k_2 >> k_1$), while an intermediate E-oxime is not detected in the reaction mixture (the rate of its conversion to a furazan is much higher than the rate of conversion to the starting Z-oxime, i.e., $k_3 >> k_1$), then $k \approx k_2$. Consequently, the rate-determining step in the rearrangement of piperidino Z-oxime IV is Z—E isomerization. In conformity with this, under the influence of a base (an aqueous or alcohol solution of ammonia), which decreases the barrier to recyclization but increases the barrier to Z—E isomerization, piperidino oxime IV does not undergo rearrangement to a furazan, and the oxadiazole ring undergoes complete cleavage:

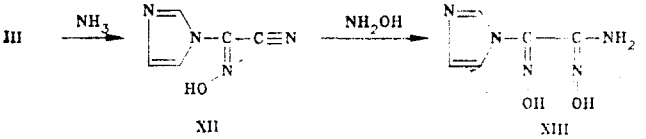


A different pattern is observed in the case of unsubstituted amidoxime I and its N-isopropyl derivative V. The Z—E isomerization of these amidoximes proceed very rapidly even at room temperature, although the equilibrium is also shifted to favor the Z isomer. In this case rate constant k_1 is much larger than k_3, while the observed rate constant $k \approx (k_2/k_1) \cdot k_3 = K \cdot k_3$. Consequently, the rate of rearrangement in this case is determined by the constant of the Z—E equilibrium and the rate of recyclization. As a result, since the slow second step requires base catalysis, amidoximes I and V do not undergo rearrangement under the influence of acids, but their conversion to furazans proceeds rapidly in the presence of a base — ammonia:



Equilibrium constants K are considerably smaller for unsubstituted amidoximes than for the monosubstituted compounds. Therefore, although isopropyl amidoxime V undergoes spontaneous rearrangement to a furazan on standing for a few days, amidoxime I remains unchanged on standing. Its rearrangement under the influence of an alcohol solution of ammonia proceeds more slowly than that of isopropyl amidoxime V, while a side reaction involving opening of the oxadiazole ring to give diaminoglyoxime is observed when the reaction is carried out in an aqueous solution.

As we have already pointed out, the Z isomers are more stable for amidoximes that contain a heteroaromatic ring as an amino group, but, in contrast to unsubstituted and monosubstituted amidoximes, in this case the barrier to Z—E isomerization is high, and it does not occur in an alkaline medium [5]. Only cleavage of the oxadiazole ring to give cyano amidoxime XII occurs in the action of ammonia on imidazole derivative III. Aminoglyoxime XIII was obtained when the reaction was carried out in the presence of hydroxylamine.



The rearrangement also does not take place in an acidic medium, since the amount of the E isomer in the equilibrium mixture is small, and the recyclization reaction, as in the case of amidoximes I and V, can take place only in the case of base catalysis.

TABLE 1. Characteristics of I and III-XIII

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm			Yield, %
			NH_2; NH	OH	others	
I	$C_3H_4N_4O_2$	137...138	5,91	10,29	9,56 (OCH)	82
III	$C_6H_5N_5O_2$	146...148	—	13,00	7,03; 7,50; 8,07; 9,73 (OCH)	72
IV	$C_8H_{12}N_4O_2$	112...114	—	10,53	1,51; 3,13; 9,60 (OCH)	91
V	$C_6H_{10}H_4O_2$	84...86	5,64	10,33	1,05 (CH_3); 3,46 (CH); 9,62 (OCH)	83
VI	$C_8H_{12}N_4O_2$	122...124	10,63	—	1,56 3,13 (CH_2); 8,46 (CHO)	78
VII	$C_7H_{12}N_4O$	93...94	5,73	—	1,56; 3,04	75
VIII	$C_7H_{11}N_3O$	52...53	—	10,96	1,51; 3,11	61
IX	$C_3H_4N_4O_2$	168...169	6,04; 10,47	—	8,33 8,66 (CHO)*	77
X	$C_6H_{10}N_4O_2$	139...141	5,96; 10,47	—	1,16 (CH_3); 3,53 (CH); 8,36 8,64 (CHO)*	91
XI	$C_5H_{10}N_4O$	96...98	5,71**	—	1,16 (CH_3); 3,49 (CH)	82
XII	$C_5H_4N_4O$	175...177	—	14,10	7,07; 7,62; 8,29	64
XIII	$C_5H_7N_5O_2$	164...166	5,53	10,27; 12,09	6,89; 7,22; 7,71	74

*The signal is split into a doublet because of impaired rotation about the amide C—N bond.

**The signals of the NH and NH_2 groups are overlapped.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker WH-90 spectrometer with tetramethylsilane (TMS) as the internal standard. The IR spectra of suspensions of the compounds in Nujol were obtained with a Perkin—Elmer 508B spectrometer.

The characteristics of the compounds obtained are presented in Table 1.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

1,2,4-Oxadiazole-3-carboxamidoxime (I). A suspension of 1.18 g (10 mmole) of diaminoglyoxime in 2.2 g (15 mmole) of ethyl orthoformate containing 0.01 ml of boron trifluoride etherate was heated at 75-80°C for 5 min, after which the reaction mixture was cooled, and the resulting precipitate was removed by filtration and recrystallized from water. IR spectrum: 3468 and 3370 (NH_2); 3118 (CH); 3070 (OH); 1656 cm^{-1} (C=N).

3-(1-Imidazolylcarbonyl)-1,2,4-oxadiazole Z-Oxime (III). A solution of 0.8 g (5.4 mmole) of chloro oxime II in 40 ml of acetone was added dropwise at 5-10°C to a solution of 0.4 g (5.8 mmole) of imidazole and 0.8 g (7.9 mmole) of triethylamine in 10 ml of acetone. After 1 h, the salt was removed by filtration, the filtrate was evaporated, and the residue was recrystallized from water.

3-(Piperidinocarbonyl)-1,2,4-oxadiazole Z-Oxime (IV). A solution of 0.5 g (3.4 mmole) of chloro oxime II in 30 ml of acetone was added dropwise at 5-10°C to a solution of 0.7 g (8.2 mmole) of piperidine in 10 ml of acetone. After 1 h, the salt was removed by filtration, and the filtrate was evaporated. Benzene was added to the residue, and the product was removed by filtration and recrystallized from benzene.

N-Isopropyl-1,2,4-oxadiazole-3-carboxamidoxime (V). A solution of 0.5 g (3.4 mmole) of chloro oxime II in 40 ml of alcohol was added dropwise at 0-5°C to a solution of 0.5 g (8.5 mmole) of isopropylamine in 10 ml of alcohol. After 1 h, the solvent was removed by distillation, and the product was extracted with ether. The ether was removed by distillation, petroleum ether was added to the residue, and the product was removed by distillation.

3-Piperidino-4-formamidofurazan (VI). A 0.2-g (1.0 mmole) sample of piperidino oxime IV was dissolved in a mixture of 0.3 ml of concentrated HCl and 0.6 ml of water. After 4 h, the acid was neutralized with a saturated solution of sodium bicarbonate, and the precipitate was removed by filtration and recrystallized from water.

2-Hydroxyimino-2-piperidinoacetonitrile (VIII). A suspension of 0.2 g (1.0 mmole) of oxadiazole IV in 5 ml of ammonium hydroxide was stirred for 8 h, after which the product was extracted with ether. The ether was dried with sodium sulfate, and the ether was removed by distillation to give an oil, which began to crystallize on standing. IR spectrum: 3422 (OH), 2241 (C≡N), 1590 cm^{-1} (C=N).

The reaction proceeded similarly with an alcohol solution of ammonia; however, 2 days were necessary for its completion.

3-Isopropylamino-4-formamidofurazan (IX). A 0.1-g (0.6 mmole) sample of amidoxime V was dissolved in 5 ml of concentrated ammonium hydroxide. After 10 min, the solvent was removed by distillation in vacuo, and the product was recrystallized from water.

Hydrolysis of Amides VI and IX. A suspension of 1.0 mmole of amide VI or IX in 1 ml of 5% HCl was heated to the boiling point, after which it was cooled, and the precipitate was removed by filtration and recrystallized from water.

3-Amino-4-formamidofurazan (XI). Dry ammonia was passed through a suspension of 0.3 g (2.3 mmole) of amidoxime I in 3 ml of absolute ethanol for 20 min. After 24 h, the alcohol was removed by distillation in vacuo, and the product was recrystallized from water. The characteristics of the furazan XI obtained were in agreement with the characteristics of the product obtained by alternative synthesis [11].

Isomerization of 1,2,4-Oxadiazole-3-carboxamidoxime (I) in Ammonium Hydroxide. A 0.5-g (3.9 mmole) sample of amidoxime I was dissolved in 4 ml of ammonium hydroxide. After 3 h, the solvent was removed by distillation in vacuo until a precipitate began to form. The precipitate, which was identified as formamidofurazan XI, was removed by filtration, and the filtrate was evaporated to dryness. Isopropyl alcohol was added to the residue, and the precipitated diaminoglyoxime was removed by filtration. Both products were recrystallized from water. Furazan XI was obtained in 40% yield, and diaminoglyoxime was obtained in 22% yield.

2-Hydroxyimino-2-(1-imidazolyl)acetonitrile (XII). A 0.18-g (1.0 mmole) sample of oxadiazole V was dissolved in 4 ml of ammonium hydroxide. After 24 h, the solvent was removed by distillation, and the product was recrystallized from water. IR spectrum: 3198 and 3118 (ring CH); 2245 cm^{-1} (C≡N).

1-Amino-2-(1-imidazolyl)glyoxime (XIII). A 0.14-g (2.0 mmole) sample of hydroxylamine hydrochloride and 0.18 g (1.0 mmole) of oxadiazole were dissolved in 4 ml of ammonium hydroxide. The next day, the reaction mixture was evaporated to dryness, water was added to the residue, and the precipitate was removed by filtration and recrystallized from water.

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