REARRANGEMENTS OF 1-OXA-2-AZOLES

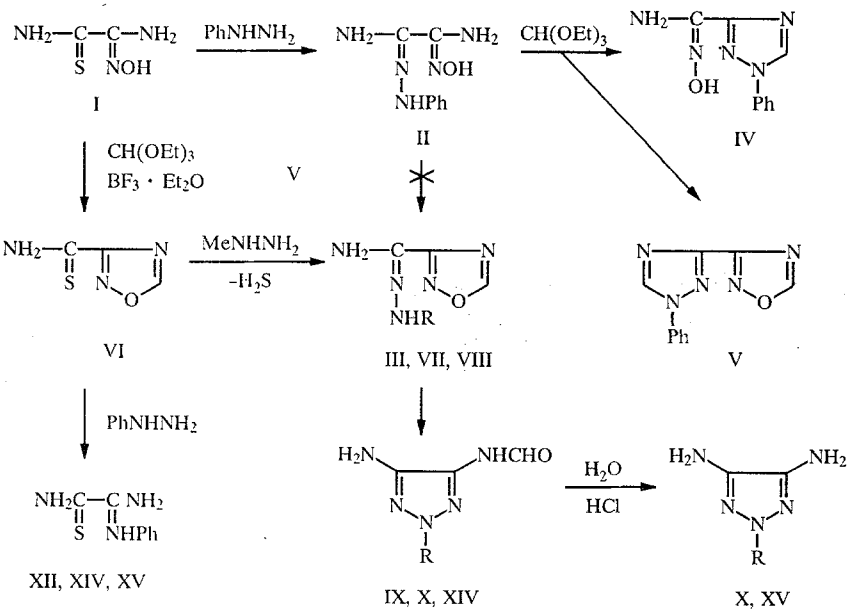
8.* SYNTHESIS AND REARRANGEMENT OF AMIDRAZONES OF 1,2,4-OXADIAZOLE-3-CARBOXYLIC ACID

V. G. Andrianov, V. G. Semenikhina, and A. V. Eremeev

The possible isolation of amidrazones of 1,2,4-oxadiazole-3-carboxylic acid by three reaction schemes was studied. It was established that the given amidrazones are unstable and undergo rearrangement to derivatives of 4,5-diaminotriazole.

We previously showed that the rearrangements of amidoximes of 1,2,4-oxadiazole-3-carboxylic acid provides a convenient method for the synthesis of derivatives of diaminofurazan [2]. The present work is dedicated to studying the possible utilization of the given method to synthesize the not readily available, and therefore little-studied, diamino derivatives of another heterocycle — 1,2,3-triazole — on the basis of the rearrangement of amidrazones of 1,2,4-oxadiazole-3-carboxylic acid.

In the search for methods of synthesis for these derivatives, we started from thiocarbamoylformamidoxime (I), obtained by the method of [3]. The amidrazone (II) was obtained by its reaction with phenylhydrazine. The amidrazone (II) was previously obtained by a much less convenient method — the sequential addition of one molecule of phenylhydrazine and one molecule of hydroxylamine to dicyan [4].



III, XIV, XV R = Ph; VII, IX R = H; VIII, X, XI R = Me

However, it was established in the attempt to synthesize the N-phenylamidrazone of 1,2,4-oxadiazole-3-carboxylic acid (III) that the amidrazone group and not the amidoxime group first enters into the reaction with orthoformic ester; the 1,2,4-triazole (IV), and not the 1,2,4-oxadiazole (III), is formed as a result. Both functional groups react with excess orthoformic ester; this leads to the isolation of the oxadiazolyltriazole (V).

*For Communication 7, see [1].

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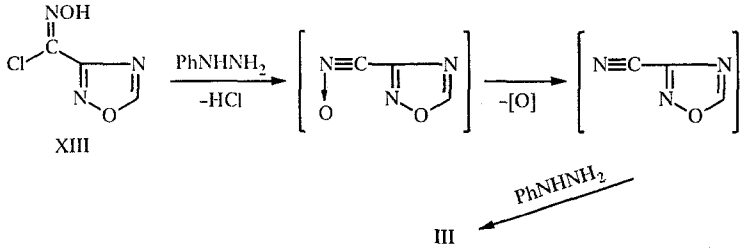
Therefore, it was necessary to change the order of the stages in the synthesis of the oxadiazole (III) due to the higher reactivity of the amidrazone group by comparison with the amidoxime group. However, according to the data of [3], the reaction of the amidoxime (I) with orthoformic ester does not lead to the formation of the thioamide of 1,2,4-oxadiazole-3-carboxylic acid (VI). Nevertheless, we established that when this reaction is performed in the presence of a catalyst — boron trifluoride etherate — the closing of the oxadiazole ring already proceeds at room temperature.

The reactions of the thioamide (VI) with hydrazine hydrate and methylhydrazine proceed at room temperature, are accompanied by the isolation of hydrogen sulfide, and lead to products which, according to the data of the PMR and IR spectra, are 1,2,3-triazole derivatives. It follows from this that the intermediate amidrazones (VII) and (VIII), which should be formed in the first stage, are unstable and undergo rearrangement in the course of the reaction. When the compound (X) is boiled in a solution of hydrochloric acid, the formamide group is hydrolyzed with the formation of 4,5-diamino-2-methyl-1,2,3-triazole (IX). The PMR spectrum of this compound indicates the equivalence of the amino groups; this excludes the alternative unsymmetrical structure – 4,5-diamino-1-methyltriazole.

In contrast to hydrazine hydrate and methylhydrazine, the weaker nucleophile phenylhydrazine does not react with the thioamide (VI) at room temperature; the heating of the mixture gives a complex mixture of products from which the thiocarbamoyl-N-phenylformamidrazone (XII) was isolated. The amidrazone (III) was obtained by another method — the reaction of 1,2,4-oxadiazole-3-carbohydroxamic chloride (XIII) with phenylhydrazine. It is known that, in a series of cases, the reaction of halogenooximes with phenylhydrazine leads not to hydrazidoximes, but to amidrazones [5, 6]. It is proposed that the reaction proceeds via the stage of the reduction of the intermediate nitrile oxide by phenylhydrazine and the subsequent addition of a second phenylhydrazine molecule at the nitrile group. The resulting amidrazone (III) is unstable and gradually undergoes rearrangement to the triazole (XIV), the formamide group of which is readily hydrolyzed by the dilute acid to form 4,5-diamino-2-phenyl-1,2,3-triazole (XV).



The PMR spectra of the formamide derivatives (IX), (X), and (XIV) show the doubling of the signals of the protons of the CH–NH and NH_2 groups. A similar picture was already noted previously taking the example of one of the analogs of the given compounds [7]. The slowed rotation about the nitrogen–ring bond, determined by the conjugation of the amino group with the ring, was thereby presented as the cause of such a phenomenon.

The spin–spin interaction of the protons in the CH–NH fragment appears in the amides (IX), (X), and (XIV), which we obtained. The SSCC of the conformers thereby varies strongly. It is equal to 11.0 and 1.5 Hz for the derivatives (IX) and (X) respectively; and the second constant is close to zero for the derivative (XIV). The large variation in the SSCC indicates that the protons of the CH–NH fragment have different mutual disposition in the conformers. It follows from this that the conformational isomerism is engaged from its onset in the delayed rotation about the amide bond, and not the nitrogen–ring bond. The assignment of the structures of the conformers was performed on the basis of the SSCC values. High SSCC values are known to be characteristic of the conformers with the antidisposition of the interacting protons. The ratio of the syn- and anti-conformers is approximately 2:1.

EXPERIMENTAL

The PMR spectra were taken on the Bruker WH-90 spectrometer using DMSO-D_6 and the internal standard of TMS. The IR spectra were recorded on the Perkin-Elmer 580B instrument using Nujol. The monitoring of the course of the reaction and the purity of the products obtained was accomplished by the method of TLC on plates of Silufol UV-254 in the 2:1 system of ethyl acetate–hexane or ethyl acetate; development was effected in UV light.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C*	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	
II	$C_8H_{11}N_5O$	164...165**	3474, 3365 (NH_2); 3180 (OH), 1650 (C=N)	5,32 (2H, s, NH_2), 5,41 (2H, s, NH_2), 6,51...7,25 (5H, m, C_6H_5), 8,27 (1H, s, NH), 9,61 (1H, s, OH)	57
III	$C_9H_9N_5O$	114...115	3375, 3245 (NH_2), 3200 (NH), 3135 (CH of rings); 1604 (phenyl)	6,11 (2H, s, NH_2), 6,60...7,30 (5H, m, C_6H_5), 8,71 (1H, s, NH), 9,59 (1H, s, CH)	50
IV	$C_9H_9N_5O$	171...173	3418, 3290 (NH_2), 3170 (OH), 3135 (CH of rings), 1664 (C=N)	5,71 (2H, s, NH_2), 7,39...7,97 (5H, m C_6H_5), 9,29 (1H, s CH), 9,86 (1H, s, OH)	38
V	$C_{10}H_7N_5O$	167...169	3112, 3100 (CH of rings, 1593 (phenyl)	7,46...8,01 (5H, m, C_6H_5), 9,52 (1H, s, CH)	81
VI	$C_3H_3N_3O$	172...177	3360, 3265 (NH_2), 3124 (CH of ring) 1624 (C=H)	9,71 (1H, s, CH), 9,97 & 10,48 (each 1H, broad s, NH_2)	81
IX	$C_3H_5N_5O$	97...98	3410, 3365 (NH_2), 3200 (NH), 1664 (C=O)	Syn-isomer 4,73 (2H, s, NH_2), 8,04 (1H, d, J = 1,5, CH), 10,24 (1H, unres. d, NH), 12,04 (1H, c, NH). Anti-isomer 4,84 (2H, s, NH), 8,31 (1H, d, J = 11,0, CH), 9,53 (1H, d, J = 11,0, NH), 12,04 (1H, s, NH)	67
X	$C_4H_7N_5O$	83...84	3382, 3310 (NH_2), 3240, 3130 (NH), 1688 (C=O)	Syn-isomer 3,81 (3H, s, CH_3), 4,77 (2H, s, NH_2), 8,09 (1H, d, J = 1,5, CH), 10,25 (1H, unres. NH). Anti-isomer 3,81 (3H, s, CH_3), 4,88 (2H, s, NH_2), 8,33 (1H, d, J = 11,0, CH), 9,59 (1H, d, J = 11,0, NH)	49
XI	$C_3H_7N_5$	124...126		3,55 (3H, s, CH_3), 4,47 (4H, s, NH_2)	43
XII	$C_8H_{10}N_4O_5$	139...141		5,99 (2H, s, NH_2), 6,59...7,20 (5H, m, C_6H_5), 8,46 (1H, s, NH), 9,20 9,51 (broad 1H, s, s, NH_2)	20
XIV	$C_9H_9N_5O$	143...146	3340, 3260 (NH_2), 3200 (NH), 1664 (C=O)	Syn-isomer 5,38 (2H, s, NH_2), 7,19...7,82 (5H, m, C_6H_5), 8,21 (1H, s, CH), 10,67 (1H, s, NH). Anti-isomer: 5,48 (2H, s, NH_2), 7,19...7,82 (5H, m, C_6H_5), 8,61 (1H, d, J = 11,0, CH), 10,01 (1H, d, J = 11,0, NH)	93
XV	$C_8H_9N_5$	141...142**		5,20 (4H, s, NH_2), 6,85...7,57 (5H, m, C_6H_5)	50

*Compound (II) was crystallized from ethyl acetate. Compounds (III), (XIV), and (XV) were crystallized from water. The remaining compounds were crystallized from alcohol. **According to the literature data, the melting points of the compounds (II), (VI), and (XV) are 174°C [4], 174-175°C [3], and 143°C [4] respectively.

The data of the elemental analysis for C, H, and N correspond with the calculated data. The characteristics of the compounds obtained are presented in Table 1.

Phenylamidrazone of α-Hydroximinoglycine (II). The mixture of 2.98 g (25 mmole) of thiocarbamoylformamidoxime, and 2.70 g (25 mmole) of phenylhydrazine in 20 ml of water is boiled for 1.5 h. The reaction mixture is cooled, and the reaction product is filtered off and washed with water. The yield of 2.75 g of the crystalline product is obtained.

Phenylamidrazone of 1,2,4-Oxadiazole-3-carboxylic Acid (III). To the mixture of 1.5 g (14 mmole) of phenylhydrazine in 40 ml of ether and 0.67 g (8.0 mmole) of sodium bicarbonate in 10 ml of water are added, in portions, 1.03 g (7.0 mmole) of the oxime (XIII). The mixture is held for 1 h. The ether layer is separated, and the aqueous layer is extracted with 2 × 30 ml of ether. The extracts are combined, washed with water, dried with Na_2SO_4, and concentrated.

Amidoxime of 1-Phenyl-1,2,4-triazole-3-carboxylic Acid (IV). The mixture of 0.30 g (1.55 mmole) of the amidrazone (II), 0.23 g (1.55 mmole) of orthoformic ester, and 0.05 ml of boron trifluoride etherate in 1.5 ml of abs. alcohol is boiled for 30 min. The reaction mixture is concentrated in vacuo. Ether is added to the residue, and the residue is filtered off and washed with water.

3-(1,2,4-Oxadiazolyl-3)-1-phenyl-1,2,4-triazole (V). The mixture of 0.38 g (2.0 mmole) of the amidrazone (II), 1.18 g (8.0 mmole) of orthoformic ester, and 0.1 ml of boron trifluoride etherate is heated to boiling. After 10 min, a residue comes down from the reaction mixture. It is filtered off and washed with water.

3-Thiocarbamoyl-1,2,4-oxadiazole (VI). The mixture of 0.6 g (5.0 mmole) of thiocarbamoylformamidoxime, 1.1 g (7.5 mmole) of orthoformic ester, and 0.1 ml of boron trifluoride etherate is mixed at room temperature for 20 min. In the course of the reaction, the color of the residue changes from brown to light yellow. Ether is added to the reaction mixture, and the product is filtered off.

4-Amino-5-formamido-1,2,3-triazole (IX). To the solution of 0.52 g (4.8 mmole) of the oxadiazole (VI) in 15 ml of abs. tetrahydrofuran is added, dropwise at room temperature, the solution of 0.24 g (4.8 mmole) of hydrazine hydrate in 5 ml of tetrahydrofuran. The product is filtered off after 2 h and washed with ether.

4-Amino-2-methyl-5-formamido-1,2,3-triazole (X). To the solution of 0.5 g (3.9 mmole) of the oxadiazole (VI) in 15 ml of abs. tetrahydrofuran at room temperature are added 0.27 g (5.8 mmole) of methylhydrazine in 5 ml of tetrahydrofuran. After 24 h, the reaction mixture is concentrated. The residue is dissolved in acetonitrile and chromatographed on silica gel with the eluent of the 2:1 mixture of ethyl acetate–hexane.

4,5-Diamino-2-methyl-1,2,3-triazole (XI). The solution of 0.18 g (1.27 mmole) of the triazole (X) in 2.5 ml of 10% HCl is boiled for 30 min. The reaction mixture is cooled, neutralized with a saturated solution of $NaHCO_3$, and concentrated to dryness. Abs. ethanol is added to the residue, and the sodium chloride is filtered off. The filtrate is evaporated. Ether is added, and the product is filtered off.

Thiocarbamoyl-N-phenylformamidrazone (XII). The solution of 0.20 g (1.55 mmole) of the oxadiazole (VI) and 0.17 g (1.55 mmole) of phenylhydrazine in 6 ml of abs. alcohol is boiled for 30 min. The reaction mixture is concentrated in vacuo. The residue is chromatographed on silica gel with the eluent of the 2:1 mixture of ethyl acetate–hexane.

4-Amino-2-phenyl-5-formamido-1,2,3-triazole (XIV). The phenylamidrazone (III) (0.15 g, 0.73 mmole) is dissolved in 3 ml of ethyl acetate; the mixture is left overnight at room temperature. The ethyl acetate is distilled off. Ether is added to the residue, and the product is filtered off.

4,5-Diamino-2-phenyl-1,2,3-triazole (XV). The solution of 0.10 g (0.49 mmole) of the triazole (XIV) in 2.5 ml of 10% HCl is boiled for 20-30 min. The reaction mixture is cooled, neutralized with a saturated solution of $NaHCO_3$, and concentrated to dryness. The product is extracted with abs. alcohol. The alcohol is distilled off. Ether is added to the residue, and the triazole (XV) is filtered off.

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