REARRANGEMENTS OF 1-OXA-2-AZOLES.

4.* SYNTHESIS AND REARRANGEMENT OF ISOXAZOLE- AND 4,5-DIHYDROISOXAZOLE-3-CARBOXYLIC ACID AMIDOXIMES

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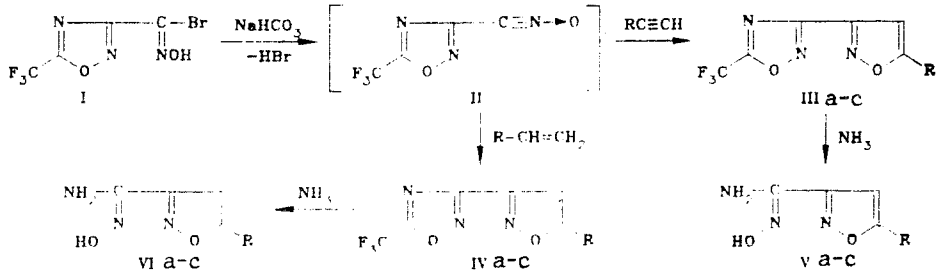
UDC 547.793.2'3

Isoxazole- and 4,5-dihydroisoxazole-3-carboxylic acid amidoximes were obtained in the reaction of 5-trifluoromethyl-1,2,4-oxadiazole-3-carbohydroximic acid bromide in the presence of sodium bicarbonate with monosubstituted ethylenes and acetylenes with subsequent opening of the oxadiazole ring. Amidoximes of the isoxazole series undergo rearrangement to aminofurazans under the influence of alkalis.

In our study of the rearrangement of furazan-3-carboxylic acid and 1,2,4-oxadiazole-3-carboxylic acid amidoximes we established that in the first case the reaction proceeds under severe conditions and is catalyzed by alkalis [2], whereas in the second case the reaction proceeds under mild conditions and, depending on the structure of the amidoximo group, may be catalyzed by either alkalis or acids [1]. The present research is devoted to a study of the conditions for the rearrangement of isoxazole-3-carboxylic acid amidoximes.

5-Trifluoromethyl-1,2,4-oxadiazole derivatives are convenient starting compounds in the synthesis of heterocyclic acid amidoximes, since they are readily formed in the reaction of amidoximes with trifluoroacetic anhydride and are smoothly cleaved by an aqueous or alcohol solution of ammonia to give the starting amidoximes [3]. We have established that 5-trifluoromethyl-1,2,4-oxadiazole-3-carbohydroximic acid bromide (I) in the presence of sodium bicarbonate is easily dehydrobrominated and undergoes cycloaddition with monosubstituted ethylenes and acetylenes. The reaction probably proceeds through a step involving the intermediate formation of nitrile oxide II. Its addition to acetylenes gives 3-(3-isoxazolyl)-5-trifluoromethyl-1,2,4-oxadiazoles III, and the reaction with olefins leads to the corresponding 4,5-dihydroisoxazole derivatives. The addition is highly regiospecific, and in all cases substituent R is located in the 5 position of the resulting heterocycle:



III, V a R=C_6H_5, b R=CH_2OH; III c R=$COOC_2H_5$; IV, VI a R=CN, b R=OC_2H_5; IV c R=$COOCH_3$; V, VI c R=$CONH_2$

In the case of IIIa-c evidence for this is provided by the chemical shift of the proton of the isoxazole ring (7.3-7.8 ppm), which is characteristic precisely for the 4 position, whereas the signals of the protons in the 5 position would be found at considerably weaker field (9-10 ppm [4]. Similarly, the PMR spectra of the compounds of the 4,5-dihydroisoxazole series (IVa-c) contain signals of two protons at 3.1-4.0 ppm, which is characteristic for the 4 position, whereas signals of only one proton are found at weaker field at 5.6-6.0 ppm, which is typical for the 5 position [5].

Diphenylacetylene could not be made to undergo this reaction; this is in agreement with the low reactivity of nitrile oxides with respect to disubstituted acetylenes [6].

*See [1] for Communication 3.

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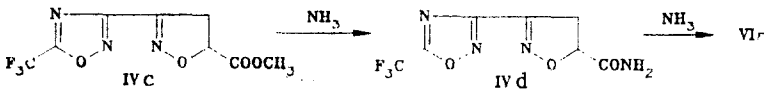
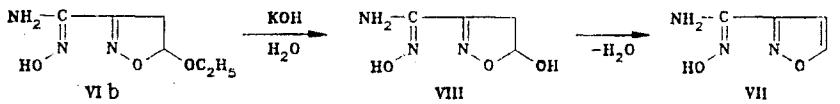
As in the case of the previously investigated 5-trifluoromethyloxadiazoles [3], under the influence of an aqueous or alcohol solution of ammonia the oxadiazole ring in derivatives IIIa-c and IVa-c is readily cleaved to give an amidoximo grouping; in the case of esters IIIc and IVc the ester group is converted to an amido group simultaneously with opening of the oxadiazole ring. However, in the brief reaction of ester IVc with ammonia one can isolate intermediate amide IVd, which is converted to the corresponding amidoxime VIc by the prolonged action of ammonia.

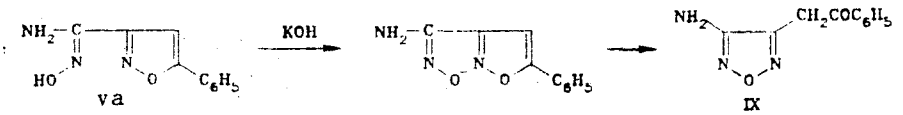


The cleavage of the oxadiazole ring has usually been carried out with an alcohol solution of ammonia at room temperature. The use of an aqueous or aqueous alcohol solution makes it possible to significantly accelerate the process. In addition to 4,5-dihydroisoxazole VIb, isoxazole-3-carboxamidoxime (VII) is formed in very small amounts in the opening of the oxadiazole ring in ethoxy derivative IVb. The same product was obtained in good yield by the alkaline hydrolysis of ester VIb:



The reaction probably proceeds through a step involving the formation of unstable 5-hydroxy-4,5-dihydroisoxazole VIII, which is readily dehydrated to give isoxazole VII.

In contrast to 1,2,4-oxadiazole-3-carboxylic acid amidoximes [1, 3], the analogous derivatives in the isoxazole series do not undergo rearrangement to aminofurazans under the influence of ammonia or when they are refluxed in alcohol solution in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. However, under more severe conditions — by refluxing in an alcohol solution of an alkali — amidoxime Va is, nevertheless, converted to aminofurazan IX:



The rearrangement of isoxazoles Vc and VII under the influence of alkalis ultimately leads to 3-amino-4-methylfurazan (XI). The reaction probably proceeds via a scheme that includes hydrolysis of amide Vc to the corresponding acid, its decarboxylation to isoxazole VII, rearrangement of the latter to furazan X, and its deformylation.

A reaction similar to deformylation, viz., debenzoylation, was previously observed when 3-phenacyl-4-phenylfurazan was treated with alkali [7]; however, it proceeds under more severe conditions.

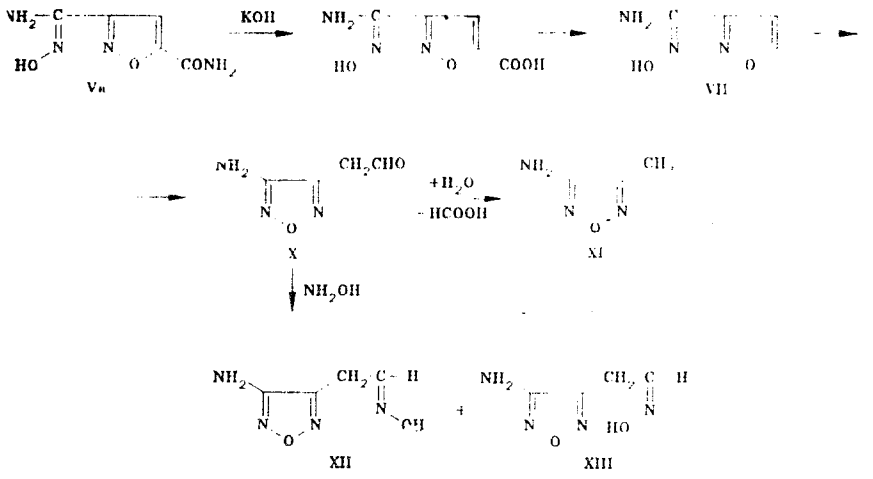
Carrying out the rearrangement in the presence of hydroxylamine made it possible to detect aldehyde X in the form of a mixture of syn- and anti-aldoximes XII and XIII in a ratio of 1:3. The preponderant anti isomer was obtained in individual form by recrystallization from water. The assignment of the isomers was made on the basis of PMR spectroscopic data, since it is known that the signal of the OH proton in the spectra of syn-aldoximes is located at stronger field [8]. In addition, in the spectra of aldoximes the signal of a substituent that is anti-oriented with respect to the hydroxy group is shifted to stronger field as compared with the signal of the same syn-oriented substituent [9] (see scheme below).

Amidoximes Vb and VIa, c decompose when they are refluxed with alcoholic alkali, and the corresponding furazans cannot be isolated. This is probably associated with the fact that the functional substituents in both the starting and final compounds are unstable under the reaction conditions.

Thus the rearrangement of isoxazole derivatives proceeds under more severe conditions as compared with 1,2,4-oxadiazoles, which undergo rearrangement at room temperature [1, 3], but under milder conditions as compared with furazans, for which heating at 120-130°C is necessary [2].

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 in Nujol were obtained with a Perkin—Elmer spectrometer. The progress of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates in ethyl acetate—hexane (2:1) and ether—hexane (2:1) systems with development in UV light.



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

General Method for Obtaining IIIa-c and IVa-c. A solution of 0.59 g (7 mmole) of sodium bicarbonate in 10 ml of water was added dropwise with stirring at room temperature to a mixture of 1.3 g (5 mmole) of bromo oxime I and 7 mmole of the corresponding acetylene or olefin in 35 ml of ether. If a precipitate formed, it was removed by filtration after 1 h and recrystallized. In other cases the organic layer was separated, and the aqueous layer was extracted twice with water. The organic layer and the extracts were combined, washed with water, dried with Na_2SO_4, and evaporated. The products obtained, except for ester IIIc, which was an oil, were recrystallized. The characteristics of IIIa-c and IVa-c are presented in Table 1.

General Method for Obtaining IVd, Va-c, and VIa-c. Dry ammonia was passed through a solution of 7 mmole of IIIa-c and IVa-c in 50-100 ml of absolute ethanol for 30-60 min, after which the mixture was allowed to stand for 1-2 days (when water was added, the reaction time was shortened to 6-8 h). The alcohol was evaporated, and the products were recrystallized.

In the preparation of IVd ammonia was passed through the solution for 10 min, and the reaction mixture was allowed to stand for 30 min. The characteristics of the compounds obtained are given in Tables 1 and 2.

Isoxazole-3-carboxamidoxime (VII). A 15-ml sample of 10% aqueous potassium hydroxide solution was added to 0.73 g (4.2 mmole) of amidoxime VIb. After 20 min, the reaction mixture was neutralized, extracted with ethyl acetate, and dried with Na_2SO_4. After removal of the solvent, the residue was recrystallized from water.

3-Amino-4-phenacylfurazan (IX, $C_{10}H_9N_3O_2$). A mixture of 0.25 g (1.2 mmole) of amidoxime Va, 0.5 g (8.9 mmole) of potassium hydroxide, and 10 ml of absolute ethanol was refluxed for 2 h, during which a precipitate formed. The reaction mixture was cooled, treated with 5 ml of water, neutralized with HCl, and evaporated to dryness. The resulting solid residue was washed with water and recrystallized from ethanol to give 0.14 g (56%) of furazan IX with mp 111.5-112.0°C. IR spectrum: 3338 and 3416 (NH_2); 1675 cm^{-1} (C=O). PMR spectrum: 4.62 (2H, s, CH_2); 6.09 (2H, s, NH_2); 7.58 and 8.01 ppm (5H, m, C_6H_5).

3-Amino-4-methylfurazan (XI, $C_3H_5N_3O$). A. This compound was obtained by means of the preceding method from amidoxime Vc in 46% yield and had mp 71-72°C (from water (mp 72-73°C [10]). PMR spectrum: 2.22 (3H, s, CH_3), 6.05 ppm (2H, s, NH_2).

B. A 5-ml sample of 10% aqueous potassium hydroxide solution was added to 0.2 g (1.5 mmole) of VII, and the mixture was maintained at room temperature for 6 days. It was then worked up as in the method indicated above to give 0.06 g (40%) of XI.

4-Amino-3-furazanylacetaldehyde syn- and anti-Oximes (XII and XIII, $C_4H_6N_4O_2$). A solution of 0.38 g (3 mmole) of VII, 0.24 g (3.5 mmole) of hydroxylamine hydrochloride, and 0.39 g (7.0 mmole) of potassium hydroxide in 5 ml of water was maintained at room temperature for 2 days, after which it was neutralized with HCl, and the product was extracted with ethyl acetate. The extract was dried with Na_2SO_4 and evaporated to give 0.23 g (54%) of a crystalline substance. According to the PMR spectral data, this product was a mixture of syn- and anti-oximes XII and XIII in a ratio of 1:3. Recrystallization from water gave anti isomer XIII with mp 116.8-118.0°C. IR spectrum: 3345 and 3427 (NH_2); 3230 cm^{-1} (OH). PMR spectrum: 3.65 (2H, d, J = 5.0 Hz, CH_2); 6.12 (2H, s, NH_2); 6.93 (1H, t, J = 5.0 Hz,

TABLE 1. Characteristics of IIIa-c and IVa-d

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Yield, %
IIIa	$C_{12}H_6F_3N_5O_2$	167,7 ... 167,9	1160 ... 1210 (CF_3), 3060 (C_6H_5), 3140 (CH)	7,56 and 7,99 (3H and 2H, m, C_6H_5); 7,79 (1H, s, CH)	62
IIIb	$C_7H_4F_3N_3O_3$	49,2 ... 49,5	1155 ... 1220 (CF_3), 3140 (CH), 3200 (OH)	5,03 (2H, s, CH_2); 5,81 (1H, br s, OH); 7,34 (1H, s, CH)	49
IIIc	$C_9H_6F_3N_3O_4$	—	1150 ... 1220 (CF_3), 1745 (C=O), 3150 (CH)	1,37 (3H, t, CH_3); 4,43 (2H, q, CH_2); 7,48 (1H, s, CH)	58
IVa	$C_7H_3F_3N_4O_2$	103 ... 104	1165 ... 1220 (CF_3), 2260 (C≡N)	3,87 (1H, dd, J=8,2 and 17,0, $C_{(4)}H$); 4,09 (1H, dd, J=9,2 and 17,0, $C_{(4)}H$); 6,03 (1H, dd, J=8,2 and 9,2, $C_{(5)}H$)	52
IVb	$C_8H_8F_3N_3O_3$	54,0 ... 54,6	1167 ... 1210 (CF_3)	1,16 (3H, t, J=7,0, CH_3); 3,16 (1H, dd, J=2,0 and 18,3, $C_{(4)}H$); 3,64 and 3,84 (ea. 1H, dq, dq, J=7,0 and 9,5, CH_2O); 3,69 (1H, dd, J=6,8 and 18,3, $C_{(4)}H$); 5,96 (1H, dd J=2,0 and 6,8, $C_{(5)}H$)	66
IVc	$C_8H_6F_3N_3O_4$	51,1 ... 51,7	1155 ... 1220 (CF_3), 1765 (C=O)	3,70 (3H, s, CH_3); 3,63 (1H, dd, J=8,0 and 17,0, $C_{(4)}H$); 3,89 (1H, dd, , J=11,0 and 17,0, $C_{(4)}H$); 5,56 (1H, dd, J=8,0 and 11,0, $C_{(5)}H$)	57
IVd	$C_7H_5F_3N_4O_3$	179 ... 182	1162 ... 1222 (CF_3), 3320 and 3418 (NH_2)	3,53 (1H, dd, J=8,0 and 17,0, $C_{(4)}H$); 3,80 (1H, dd, J=11,0 and 17,0, $C_{(4)}H$); 5,31 (1H, dd, J=8,0 and 11,0, $C_{(5)}H$); 7,51 and 7,79 (ea. 1H, brs, brs NH_2)	53

*The compounds were recrystallized: IIIa and IVa from ethanol—water (1:1), IIIb and IVc from hexane—ether, IVb from hexane, and IVd from water.

TABLE 2. Characteristics of Amidoximes Va-c, VIa-c, and VII

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm⁻¹				PMR spectrum, δ, ppm (J, Hz)	Yield, %
			OH	NH_2	C=N	CH		
Va	$C_{10}H_9N_3O_2$	178,8 . . . 179,2	3150	3363, 3443	1615	3138	5,82 (2H, s, NH_2); 7.08 (1H, s, CH); 7,51 and 7,98 (3H and 2H, m C_6H_5); 10,12 (1H, s, OH)	82
Vb	$C_5H_7N_3O_3$	185,4 . . . 186,5	3157, 3303	3344, 3450	1603	3138	4,56 (2H, d, CH_2); 5,64 (1H, t, COH); 5,76 (2H, s, NH_2); 6,43 (1H, s, CH); 10,09 (1H, s, NOH)	60
Vc	$C_5H_6N_4O_3$	240,2 . . . 240,5	3185, 3300	3344, 3390, 3450	1625	3124	5,91 (2H, s, NH_2); 7,11 (1H, s, CH); 7,93 and 8,30 (ea. 1H, brs, brs, $CONH_2$); 10,23 (1H, s, OH)	64
VIa	$C_5H_6N_4O_2$	190 . . . 190,5	3328	3195, 3248, 3440	1618	—	3,43 (1H, dd, J=7,0 and 17,0, $C_{(4)}H$); 3,66 (1H, dd, J=10,0 and 17,0, $C_{(4)}H$); 5,67 (2H, s, NH_2); 5,71 (1H, dd, J=7,0 and 10,0, $C_{(5)}H$); 10,5 (1H, s, OH)	71
VIb	$C_6H_{11}N_3O_3$	154,1 . . . 154,5	3226	3344, 3450	1617	—	1,10 (3H, t, J=7,0, CH_3); 2,80 (1H, dd, J=2,0 and 18,0, $C_{(4)}H$); 3,24 (1H, dd, J=6,0 and 18,0, $C_{(4)}H$); 3,52 and 3,68 (ea. 1H, dq, dq J=7,0 and 9,5, CH_2O); 5,53 (2H, s, NH_2); 5,61 (1H, dd, J=2,0 and 6,0, $C_{(5)}H$); 10,2 (1H, s, OH)	63
VIc	$C_5H_8N_4O_3$	223 . . . 224	3314	3340, 3437	1610	—	2,98 (1H, dd, J=8,0 and 17,0, $C_{(4)}H$); 3,42 (1H, dd, J=11,0 and 17,0, $C_{(4)}H$); 4,98 (1H, dd, J=8,0 and 11,0, $C_{(5)}H$); 5,56 (2H, s, NH_2); 7,39 and 7,55 (ea. 1H, brs, brs, $CONH_2$); 10,3 (1H, s, OH)	74
VII	$C_4H_5N_3O_2$	136,5 . . . 138,0	3050	3475, 3328	1600	3128, 3164	5,81 (2H, s, NH_2); 6,65 (1H, d, J=2,0, $C_{(4)}H$); 8,87 (1H, d, J=2,0, $C_{(5)}H$); 10,1 (1H, s, OH)	85

*The compounds were recrystallized: VIc from isopropyl alcohol—water (1:1), Va from ethanol—water (1:1), and the remaining compounds from water.

CH); 11.29 ppm (1H, s, OH). PMR spectrum of syn-isomer XII: 3.55 (2H, d, J = 5.2 Hz, CH_2), 5.81 (2H, s, NH_2), 7.47 (1H, t, J = 5.2 Hz, CH), 10.82 ppm (1H, s, OH).

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NITRATION OF ACETYL DERIVATIVES OF 1-METHYLPYRAZOLE

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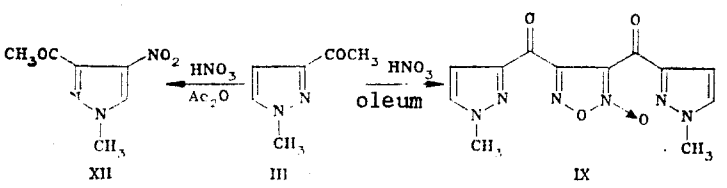
The nitration of acetyl-substituted 1-methylpyrazoles with nitric acid in 20% oleum and in acetic anhydride was studied. Dipyrazoloylfuroxans are formed in the case of nitration in oleum. 4-Nitro-3-acetyl-1-methylpyrazole was obtained by nitration of 3-acetyl-1-methylpyrazole in acetic anhydride.

We have previously studied the peculiarities of the nitration of 1-methylpyrazolecarboxylic acids and their 4-halo-substituted derivatives [1, 2]. In continuing our study of the peculiarities of the nitration of carbonyl derivatives of 1-methylpyrazole we have accomplished the nitration of a number of acetyl-1-methylpyrazoles: 4-acetyl-1,3- and -1,5-dimethylpyrazoles (I, II), 3-acetyl-1-methylpyrazole (III), and 5-acetyl-1-methylpyrazole (IV).

The starting acetylpyrazoles I and II were obtained by direct acetylation of the corresponding pyrazoles with acetic anhydride in the presence of sulfuric acid [3], while III and IV were synthesized by the reaction of 1-methylpyrazole-3- and -5-carboxylic acid nitriles (V, VI) with methylmagnesium iodide [4].

The nitration of acetylpyrazoles I-IV was accomplished with concentrated nitric acid in 20% oleum or in acetic anhydride. In the case of nitration of acetylpyrazoles I-IV in oleum none of the indicated compounds form products with a nitro group in the pyrazole ring; as in the nitration of acetophenone [5], the corresponding 3,4-dipyrazoloylfuroxans VII-X are obtained. The highest yields of VII-X are obtained when the reaction is carried out in the presence of acetic acid and at no higher than 70°C. The nitration of acetylpyrazole IV at higher temperatures leads to 1-methylpyrazole-5-carboxylic acid (XI) as a consequence of oxidative processes.

As demonstrated by our studies, I, III, and IV do not undergo nitration on treatment with concentrated nitric acid in acetic anhydride at 0°C. Under similar conditions II is converted to furoxan in 40% yield. However, 3-acetyl-4-nitro-1-methylpyrazole (XII) was isolated as the only product in the nitration of acetylpyrazole III in acetic anhydride under severe conditions (70°, 3 h).



XII III IX

An attempt to introduce a nitro group into the furoxan VIII molecule was unsuccessful. Compound VIII is not nitrated by an equimolar amount of nitric acid in 20% oleum at 70°C, while the use of a tenfold amount of nitric acid

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