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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 4-AMINOFUROXAN-3-CARBOXYLIC ACID

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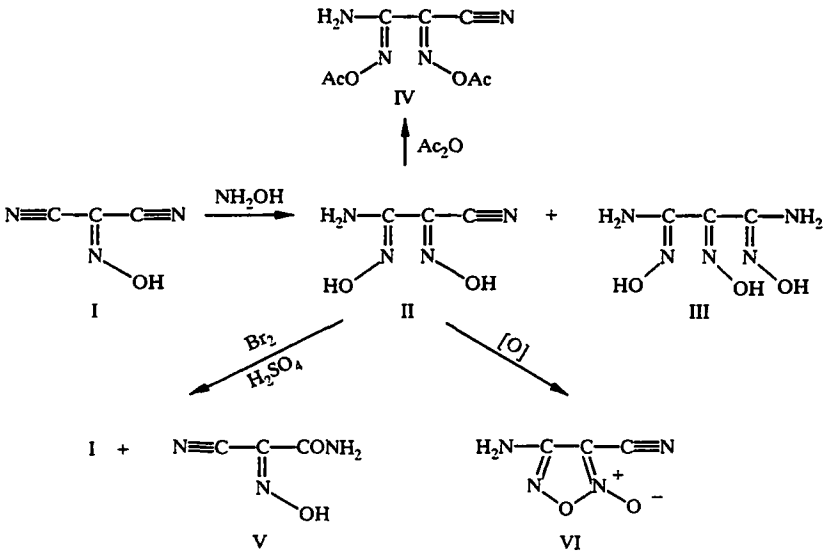
4-Amino-3-cyanofuroxan, obtained by the oxidation of aminocyanoglyoxime, reacts with hydrazine and hydroxylamine to form the amidrazone and amidoxime respectively of 4-aminofuroxan-3-carboxylic acid. The reaction of the amidoxime with triethyl orthoformate can lead to closure of both the pyrimidine and the 1,2,4-oxadiazole ring.

At the present time, aminofuroxans are some of the least studied compounds among furoxan derivatives. The aminofuroxans described in the literature mostly do not contain other functional groups in the molecule [1]. Of the functionally substituted furoxans, only 4-aminofuroxan-3-carboxamide is known [2], but its properties were not studied.

As starting material in the synthesis of derivatives of aminofuroxancarboxylic acid we used malononitrile, which was used earlier in the synthesis of aminofurazancarboxylic acid [3]. Its nitrosation gives hydroxyiminomalononitrile (I). This product is fairly unstable, since one of the nitrile groups is easily hydrolyzed to an amide group. Therefore, freshly prepared hydroxyiminomalononitrile was used at the next stage. Its reaction with hydroxylamine in an aqueous medium gives aminocyanoglyoxime (II) with diaminotrioxime (III) as impurity:



The aminocyanoglyoxime (II) is very soluble in water. It is therefore difficult to isolate the product from the solution and to purify it from the simultaneously formed trioxime (III). The aminocyanoglyoxime obtained in this way is unstable and soon darkens, being converted after 2-3 days into a dark insoluble product. We established that if the reaction is conducted in acetic acid solution, the dioxime (II) is obtained in the form of a complex with one molecule of acetic acid. The complex is readily soluble in water, ether, and alcohol but is little soluble in cold acetic acid and is precipitated during the reaction. The simultaneously formed diaminotrioxime (III) is readily soluble in acetic acid and remains in the solution. In the form of the complex with acetic acid, aminocyanoglyoxime is a stable product. It can be recrystallized from acetic acid and does not change when kept for several months.

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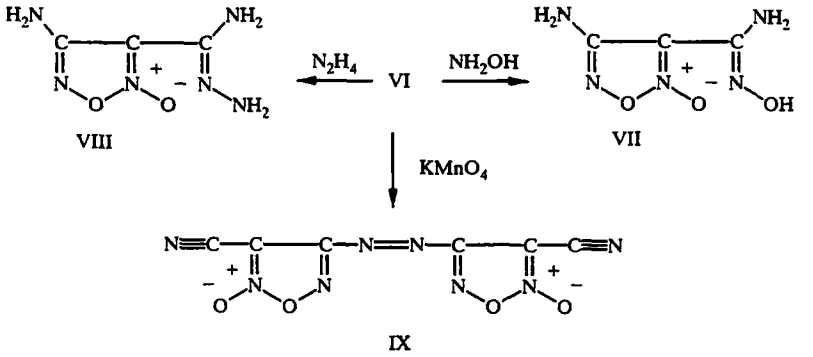
If the dioxime (II) is heated above the melting point, rapid decomposition occurs. Dehydration to a furazan derivative does not occur in reaction with acetic anhydride, but the diacetate (IV) is formed.

While studying the oxidation of aminocyanoglyoxime (II) we found that the action of bromine in sulfuric acid solution leads to deoximation with the formation of a mixture of hydroxyiminomalononitrile (I) and hydroxyiminocyanoacetamide (V). 4-Amino-3-cyanofuroxan (IV) was obtained with a yield of about 30% during the oxidation of aminocyanoglyoxime (II) with lead tetraacetate. The best results were obtained with lead dioxide in an ether–acetic acid mixture. In this case, the yield of the aminocyanofuroxan (VI) amounted to 60-70%.

Comparison of the ^{13}C NMR spectrum of the furoxan (VI) with the spectrum of 4-amino-3-cyanofurazan confirms that the exocyclic oxygen atom is adjacent to the cyano group and not the amino group:

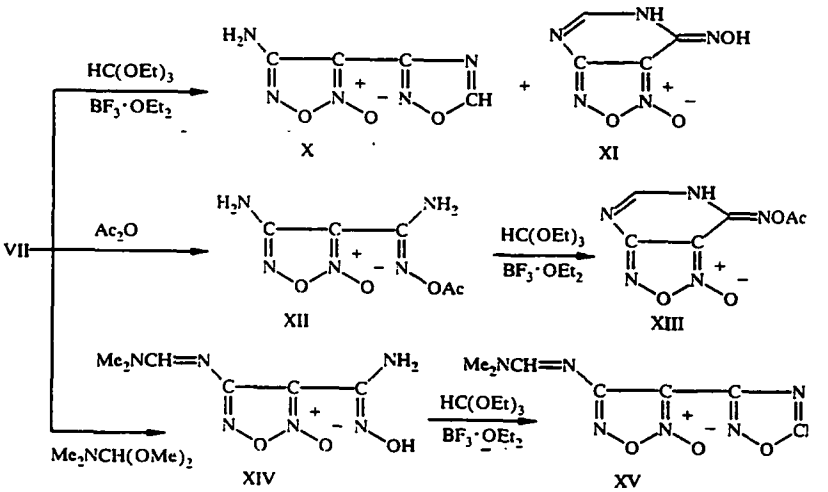
The large upfield shift of the signal of the carbon atom attached to the cyano group compared with other derivatives of furazan and furoxan is due to the anisotropic effect of the cyano group.

The electron-accepting furoxan ring strongly activates the cyano group, due to which the cyanofuroxan (VI) readily adds hydroxylamine and hydrazine with the formation of the amidoxime (VII) and the amidrazone (VIII):



The aminofuroxan (VI) is oxidized by potassium permanganate in an acidic medium to the azo derivative (IX).

Earlier we established that 4-aminofurazan-3-carboxamidoxime undergoes cyclization in reaction with triethyl orthoformate with the formation of 3-(4-amino-3-furazanyl)-1,2,4-oxadiazole [4]. In contrast, the reaction of the aminofuroxan (VI) with orthoformic ester takes place in two directions and leads to the formation of a mixture of the derivatives (X) and (XI) in a ratio of 2:1. The cyclization of the amidoxime (XII) with a protected oxime group leads to the formation of only the pyrimidine derivative (XIII), while the cyclization of the derivative (XIV) protected at the amino group leads only to the oxadiazole derivative (XV).



EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90 spectrometer in DMSO-d_6 with TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 580B instrument in Nujol.

The elemental analyses for C, H, and N agreed with the calculated data.

Aminocyanoglyoxime (II) ($C_3H_4N_4O_2 \cdot CH_3COOH$). To a solution of 33 g (0.5 mole) of malononitrile in 86 ml of concentrated hydrochloric acid and 250 ml of water, we added dropwise over 2 h at 15-20°C a solution of 69 g (1 mole) of sodium nitrite in 100 ml of water. The next day the hydroxyiminomalononitrile was extracted with ether (2 × 150 ml). The extract was dried over sodium sulfate, and the ether was distilled under vacuum.

A suspension of 41 g (0.5 mole) of sodium acetate and 35 g (0.5 mole) of hydroxylamine hydrochloride in 130 ml of acetic acid was stirred for 5 h. The precipitate was filtered off, and the hydroxyiminomalononitrile obtained at the previous stage was added to the filtrate dropwise at 20-25°C with stirring. The next day the precipitate was filtered off, and 58 g (62%) of aminocyanoglyoxime (II) was obtained; mp 150-152°C (from acetic acid). PMR spectrum (δ, ppm): 1.91 (3H, s, CH_3); 5.76 (2H, s, NH_2); 11.63 (1H, s, NOH); 11.73 (1H, s, NOH); 11.82 (1H, s, COOH). IR spectrum, cm^{-1}: 3495 and 3390 (NH_2), 3150 and 3210 (OH), 2246 (C≡N), 1681 (C=N).

Aminocyanoglyoxime Diacetate (IV) ($C_7H_8N_4O_4$). We dissolved 1.0 g (5.3 mmole) of aminocyanoglyoxime (II) in 5 ml of acetic anhydride at 100°C. After 3 min the solution was cooled and poured into water. The precipitate was filtered off, and 0.6 g (85%) of the diacetate (IV) was obtained; mp 154-156°C (from acetic acid). PMR spectrum (δ, ppm): 2.18 (3H, s, CH_3); 2.38 (3H, s, CH_3); 7.24 (2H, s, NH_2). IR spectrum, cm^{-1}: 3610 and 3513 (NH_2), 1800-1700 (C=O).

4-Amino-3-cyanofuroxan (VI) ($C_3H_2N_4O_2$). To a solution of 15 g (0.08 mole) of aminocyanoglyoxime in a mixture of 350 ml of ether and 10 ml of acetic acid we added 38 g (0.16 mmole) of lead dioxide. The mixture was stirred vigorously for 5 h. The ether layer was removed, washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and evaporated, and 6.2 g (62%) of 4-amino-3-cyanofuroxan was obtained; mp 118-120°C (from acetic acid). IR spectrum, cm^{-1}: 3395 and 3309 (NH_2), 1600 (furoxan), 2255 (C≡N).

4-Aminofuroxan-3-carboxamide Oxime (VII) ($C_3H_5N_5O_3$). To a solution of 1.04 g (15 mmole) of hydroxylamine hydrochloride and 0.6 g (15 mmole) of sodium hydroxide in 20 ml of water we added 1.26 g (10 mmole) of cyanofuroxan (VI). The mixture was stirred for 15 min, the precipitate was filtered off, and 1.22 g (77%) of the amidoxime (VII) was obtained; mp 158-160°C (from water). PMR spectrum (δ, ppm): 5.52 (2H, s, NH_2); 5.80 (2H, s, NH_2); 6.30 (2H, s, NH_2). IR spectrum, cm^{-1}: 3440 and 3305 (NH_2), 1600 (C=N), 1629 (furoxan).

4-Aminofuroxan-3-carboxamidrazone (VIII) ($C_3H_6N_6O_2$). To a solution of 2.0 g (16 mmole) of cyanofuroxan (VI) in 20 ml of ethanol we added dropwise at room temperature 2.4 ml of hydrazine hydrate. After 2 h the precipitate was filtered off, and 1.5 g (60%) of the amidrazone (VIII) was obtained. PMR spectrum (δ, ppm): 6.30 (2H, s, NH_2); 10.3 (1H, s, OH).

3,3′-Dicyanoazofuroxan (IX) ($C_6N_8O_4$). To a suspension of 1.26 g (10 mmole) of cyanofuroxan (VI) in a mixture of 25 ml of water and 25 ml of hydrochloric acid we added dropwise over 10 min at 20°C a solution of 1.61 g of potassium permanganate in 50 ml of water. The mixture was stirred for 15 min, and oxalic acid was added to decolorize the solution. The precipitate was filtered off and washed with water, and 0.62 g (50%) of azofuroxan (IX) was obtained; mp 175°C. ^{13}C NMR spectrum, ppm: 92.04 (C−C≡N), 107.05 (C≡N), 162.88 (C−N=N). IR spectrum, cm^{-1}: 2255 (C≡N), 1651 (furoxan).

3-(4-Amino-3-furoxanyl)-1,2,4-oxadiazole (X) ($C_4H_3N_5O_3$) and 7-Hydroxyimino-6,7-dihydrofuroxano[3,4-*d*]pyrimidine (XI) ($C_4H_3N_5O_3$). A suspension of 1.59 g (10 mmole) of the amidoxime (VII) in 4.0 ml of triethyl orthoformate and 0.02 g of boron trifluoride etherate was heated at 70-80°C for 10 min. The mixture was cooled, and the precipitate was filtered off. According to PMR spectroscopy, the product was a mixture of the oxadiazole (X) and pyrimidine (XI) in a ratio of 2:1. The precipitate was treated with 20 ml of a 5% solution of sodium bicarbonate, and the hydroxyimino derivative (XI) passed into solution. The insoluble product was filtered off, and 0.94 g (56%) of the oxadiazole (X) was obtained; mp 195-196°C (from a 1:1 mixture of acetonitrile and water). PMR spectrum (δ, ppm): 6.62 (2H, s, NH_2); 9.98 (1H, s, CH). IR spectrum, cm^{-1}: 3460 and 3320 (NH_2), 31.40 (CH of ring), 1643 (NH_2), 1613 (furoxan).

The bicarbonate solution was neutralized with hydrochloric acid, and the product was extracted with ethyl acetate. The ethyl acetate was distilled under vacuum, and 0.4 g (24%) of furoxanopyrimidine (XI) was obtained; mp 196-197°C (from water). PMR spectrum (δ, ppm): 7.62 (1H, d, J = 3.5 Hz, CH); 11.6 (1H, nd, NH); 11.8 (1H, s, OH). IR spectrum, cm^{-1}: 3240 (NH), 3190 (OH), 1650 (furoxan).

4-Aminofuroxan-3-carboxamide O-Acetyl Oxime (XII) ($C_5H_7N_5O_4$). A suspension of 4.77 g (30 mmole) of the amidoxime (VII) in 25 ml of acetic anhydride was stirred at room temperature for 2 h, and 60 ml of water was added. The mixture was stirred for 20 min, and the precipitate was filtered off. We obtained 5.4 g (90%) of the product (XII); 191-193°C (from ethanol). PMR spectrum (δ, ppm): 2.16 (3H, s, CH_3), 6.56 (2H, s, NH_2), 7.13 (2H, s, NH_2). IR spectrum, cm^{-1}: 3460, 3411, 3330, 3295 (NH_2), 1760 (C=O), 1654 (furoxan).

7-Acetoxyimino-6,7-dihydrofuroxano[3,4-*d*]pyrimidine (XIII) ($C_6H_5N_5O_4$). A suspension of 2.01 g (10 mmole) of acetamide oxime (XII) in 10 ml of triethyl orthoformate and 0.02 g of boron trifluoride etherate was heated at 70-80°C for 10 min. The mixture was cooled, and the precipitate was filtered off. We obtained 1.45 g (69%) of the furoxanopyrimidine (XII); mp 228-230°C (from ethanol). PMR spectrum (δ, ppm): 2.22 (3H, s, CH_3); 7.82 (1H, s, CH); 12.0 (1H, s, NH). IR spectrum, cm^{-1}: 3245 (NH), 1750 (C=O), 1645 (furoxan).

4-Dimethylaminomethyleneaminofuroxan-3-carboxamide Oxime (XIV) ($C_6H_{10}N_6O_3$). To a suspension of 1.0 g (6 mmole) of the amidoxime (VII) in 8 ml of acetonitrile we added 1.1 g (9 mmole) of dimethylformamide dimethyl acetal. The initial product dissolved, and after a short time a precipitate began to separate. After 30 min the precipitate was filtered off, and 1.04 g (77%) of the product (XIV) was obtained; mp 214-215°C (from a 1:1 mixture of ethanol and acetonitrile). PMR spectrum (δ, ppm): 2.98 and 3.13 [3H each, s, s, $(CH_3)_2N$]; 6.04 (2H, c, NH_2); 8.24 (1H, s, CH); 10.2 (1H, s, OH). IR spectrum, cm^{-1}: 3455 and 3318 (NH_2), 3200 (OH), 1640 (C=N), 1605 (furoxan).

3-(4-Dimethylaminomethyleneamino-3-furoxanyl)-1,2,4-oxadiazole (XV) ($C_7H_8N_6O_3$). A solution of 1.0 g (5 mmole) of the amidoxime (XIV) in 3.0 ml of triethyl orthoformate and 0.02 g of boron trifluoride etherate was heated at 70-80°C for 5 min. The mixture was cooled and diluted with ether, and the precipitate was filtered off. We obtained 0.64 g (61%) of the product (XV); mp 134-136°C (from ethanol). PMR spectrum (δ, ppm): 3.07 and 3.13 [3H each, s, s, $(CH_3)_2N$]; 8.24 (1H, s, CH); 9.87 (1H, s, CH of ring). IR spectrum, cm^{-1}: 3130 (CH of ring), 1643 (C=N), 1620 (furoxan).

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