Synthesis of furoxan derivatives based on 4-aminofuroxan-3-carboxylic acid azide

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A convenient preparative method was developed for the synthesis of 4-amino-3-furoxancarboxylic acid azide, which is a universal synthon for the preparation of functional furoxan derivatives. This method was used for preparing new azo-, azoxy-, azido-, cyano-, nitro-, carbonylamino-, and hydroxylamino-substituted furoxan derivatives, which have earlier been difficultly accessible.

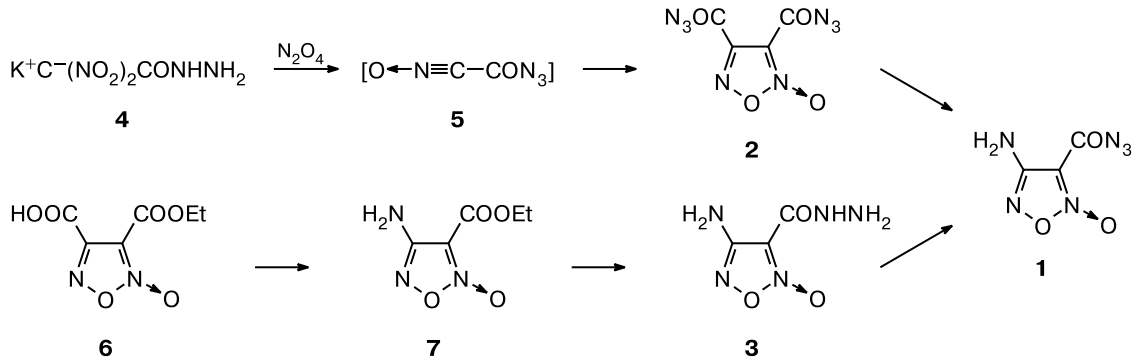
Key words: furoxans, azides, hydroxamic acids, azo and azoxy derivatives, oxidation, nucleophilic substitution, dehydration, nitriles.

In recent years, the synthesis of new derivatives of 1,2,5-oxadiazole (furoxan) has attracted considerable attention. This interest stems largely from the fact that many furoxan derivatives exhibit biological activities and, particularly, from the ability of some of these derivatives to serve as donors of nitrogen oxide.[1—5] In addition, N- and O-containing derivatives of this heterocycle may be of interest as potential components of gas-generating compositions.[6,7] 4-Aminofuroxan-3-carboxylic acid azide (**1**) (and in some cases, its synthetic precursor, *viz.*, furoxan-3,4-dicarboxylic acid diazide (**2**)) is one of the most convenient and universal synthons for the synthesis of many functional furoxan derivatives.

Compound **1** contains two highly reactive functional groups, *viz.*, the amino and azidocarbonyl groups. The amino group can be subjected to oxidation (to form nitro, azo, and azoxy derivatives), alkylation, and acylation. The azidocarbonyl group can serve as a precursor of the amino group (Curtius rearrangement). In fact, compound **1** serves as a convenient substitute of extremely unstable 3,4-diaminofuroxan,[8] and each of the substituents in the ring of **1** can be selectively transformed. In addition, the azido group can be replaced by different nucleophilic fragments (OH, OAlk, NH_2, *etc.*), which makes it possible to substantially extend the range of accessible compounds.

There are two approaches to the synthesis of compound **1**, *viz.*, the Curtius rearrangement of one of two azidocarbonyl groups in diazide **2** and nitrosation of 4-aminofuroxan-3-carboxylic acid hydrazide[8,9] (**3**) (Scheme 1). However, both methods cannot be considered as satisfactory. The first approach to the generation of **1** is based on the difficultly accessible and explosive potassium salt of dinitroacetic acid hydrazide (**4**), which gives diazide **2** in low yield under the action of N_2O_4 through the intermediate formation of azidocarbonylformonitrile oxide (**5**). Subsequently, diazide **2** is rather smoothly transformed into the target compound **1** in

Scheme 1



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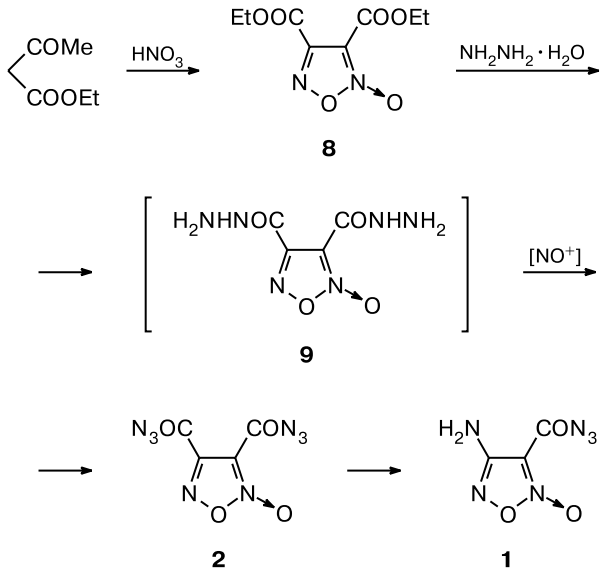
73% yield. The second approach is based on the use of monoethyl furoxan-3,4-dicarboxylate (**6**), which is transformed into the corresponding acyl azide followed by the Curtius rearrangement of the latter. In the latter process, ethyl 4-aminofuroxan-3-carboxylate[10] (**7**) is formed in a yield of no higher than 6%. Compound **7** is successively transformed into hydrazide **3** and then azide **1**. Both methods afford the final product **1** in a total yield of no higher than 2%.

To make compound **1** more accessible and simplify the conditions for its preparation, we developed a new scheme for the synthesis of diazide **2** followed by its transformation into azide **1** according to a known reaction. We demonstrated that the target azide **1** can be synthesized in a total yield of 16% according to a rather short and simple scheme by destructive nitration of readily available acetoacetic ester[11] giving rise to diethyl furoxan-3,4-dicarboxylate (**8**). The reaction of the latter with hydrazine hydrate affords furoxan-3,4-dicarboxylic acid dihydrazide (**9**), which is nitrosated to form **2** and then transformed into the target azide **1** according to a known procedure.[8] It should be noted that the final azide **1** is synthesized from ester **8** without isolation of intermediates, including explosive diazide **2**, which is generated and used in the syntheses as a safe solution in CCl_4 (Scheme 2).

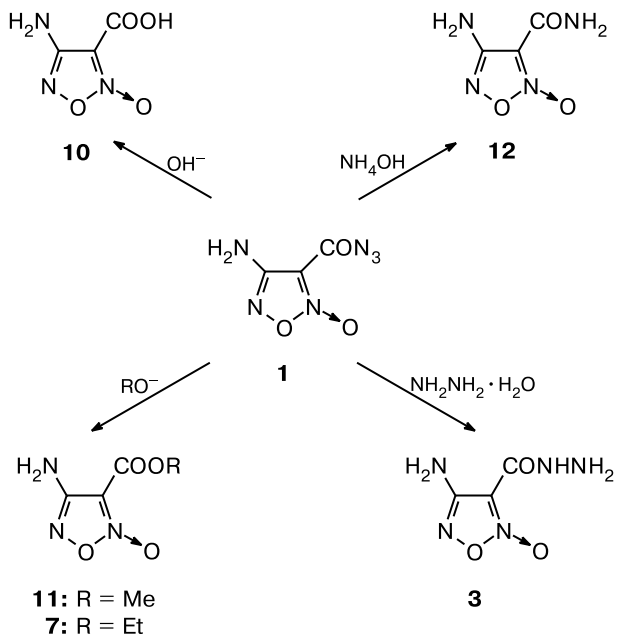
Scheme 2



The more convenient procedure for the preparation of azide **1** allowed us to make some furoxan derivatives, which have been synthesized earlier, much more readily accessible, study chemical transformations of both functional groups in this compound in more detail, and synthesize a series of new derivatives.

Thus, the azido group in **1** is readily subjected to the nucleophilic substitution under the action of various nucleophilic reagents. In particular, this enabled us to prepare both free 4-aminofuroxan-3-carboxylic acid (**10**) and its methyl (**11**) and ethyl (**7**) esters in high yields (~90%) by the reactions with O-nucleophiles. The reactions of **1** with ammonia or hydrazine hydrate as nucleophiles readily afforded amide **12** (in 92% yield) and hydrazide **3** (in quantitative yield), respectively. Earlier, amide **12** has been synthesized in low yield, but its characteristics, except for the melting point, have not been reported.[12] Hydrazide **3** was also prepared (see Scheme 1) but in very low yield. Since these compounds were difficultly accessible, investigations of their reactivities presented problems (Scheme 3).

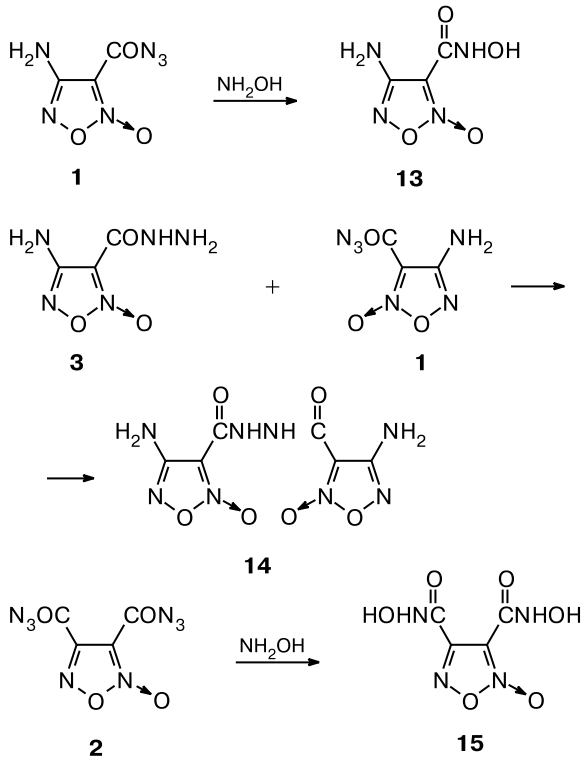
Scheme 3



The ease of replacement of the azide group in 4-amino-3-azidocarbonylfuroxan (**1**) is manifested also in the reactions with such N-nucleophiles as hydroxylamine and 4-aminofuroxan-3-carboxylic acid hydrazide (**3**), which give rise to 4-aminofuroxan-3-hydroxamic acid (**13**) and 1,2-bis(4-amino-3-furoxanoyl)hydrazine (**14**), respectively, under mild conditions. The synthetic precursor of azide **1**, *viz.*, diazide **2**, reacts with hydroxylamine in a similar way. In the latter case, both azido groups are replaced to give furoxan-3,4-dihydroxamic acid (**15**) in high yield. The latter synthesis was carried out with the use of explosive diazide **2** as its safe solution in CCl_4 (Scheme 4).

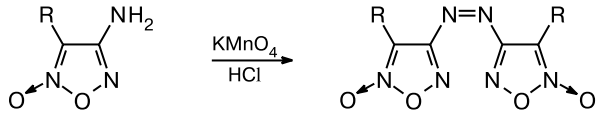
Since 4-aminofuroxan-3-carboxylic acid azide (**1**) is easily accessible, we studied its reactions proceeding at the amino group. Thus, the reactions of methoxycarbonyl derivative **11** and 4-amino-3-hydroxymethylfuroxan (**16**), which has been synthesized earlier,[14] with a solution of $KMnO_4$ under the conditions generally used for the prepa-

Scheme 4



ration of azo derivatives of furoxan[13] led to smooth oxidation of the amino group giving rise to the corresponding azo derivatives **17** and **18** (Scheme 5).

Scheme 5

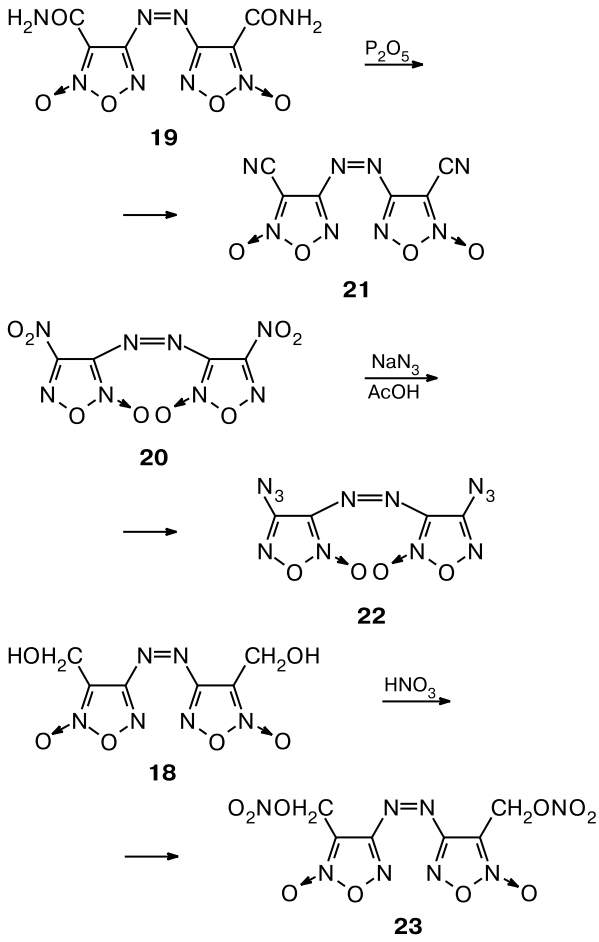


11: R = COOMe
16: R = CH_2OH

17: R = COOMe
18: R = CH_2OH

For azo derivatives **19** [13] and **20**,[15] which became much more readily accessible, and new azofuroxan **18**, selected directions of their further transformations were also examined. For example, heating of 3,3′-dicarbamoyl-4,4′-azofuroxan (**19**) with phosphoric anhydride led to dehydration of both amide groups to form the corresponding dinitrile **21**, while in low yield. Earlier,[16] compound **21** has been synthesized by oxidation to the azo derivative of 4-amino-3-cyanofuroxan. Diazido derivative **22** was synthesized by the reaction of 3,3′-dinitro-4,4′-azofuroxan (**20**) with sodium azide through the nucleophilic displacement of the nitro groups by the azido groups. The reaction of azo derivative **18** with fuming nitric acid in acetic anhydride afforded the corresponding bis(nitroxymethyl) derivative **23** (Scheme 6).

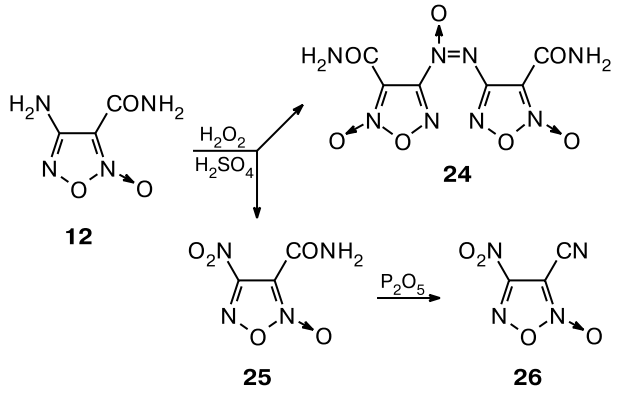
Scheme 6



In addition to one-electron oxidation, we examined the possibility of oxidation of 4-aminofuroxan-3-carboxamide (**12**) by a two-electron oxidizing agent, *viz.*, hydrogen peroxide in sulfuric acid. It was found that under the conditions used, oxidation of the amino group followed two pathways to give a mixture of two products, *viz.*, azoxy derivative **24** and nitro compound **25**, in a ratio of 1 : 4. 4-Nitrofuroxan-3-carboxamide (**25**), like 3,3′-dicarbamoyl-4,4′-azofuroxan (**19**), was also subjected to dehydration by phosphoric anhydride to produce 4-nitrofuroxan-3-carboxylic acid nitrile (**26**) in 60% yield. Earlier, the latter compound has been prepared[17] in 28% yield from the corresponding nitrolic acid (Scheme 7). The yields of the newly synthesized compounds and their physicochemical and spectroscopic characteristics are given in Tables 1 and 2.

To summarize, we developed a rather simple preparative procedure for the synthesis of 4-aminofuroxan-3-

Scheme 7



carboxylic acid azide (**1**), which is a universal synthon for the preparation of functional furoxan derivatives. Based on oxidative transformations of the amino group and the reactions of the azidocarbonyl group with O- and N-nucleophiles, we synthesized a broad spectrum of new furoxan derivatives containing the azo, azoxy, azido, cyano, nitro, carbonylamino, hydroxylamino, and other substituents. Earlier, these compounds, which are potential biologically active compounds or components of gas-generating compositions, have been difficultly accessible.

Experimental

The IR spectra were recorded on a UR-20 spectrometer in KBr pellets. The UV spectra were measured on a Specord UV-VIS spectrometer in MeOH. The NMR spectra were recorded on Bruker WM-250 (^{1}H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz; ^{14}N, 21.5 MHz) spectrometers in the δ scale. The ^{1}H and ^{13}C NMR chemical shifts were measured relative to Me_4Si as the internal standard and the ^{14}N NMR chemical shifts were measured relative to $MeNO_2$ as the external standard. The mass spectra were obtained on a Varian MAT CH-6 instrument. Thin-layer chromatography was carried out on Silufol UV-254 plates.

Table 1. Selected physicochemical characteristics of the compounds synthesized

Compound	Yield (%)	M.p./°C	R_f (eluent)	Found / Calculated (%)			Molecular formula
				C	H	N	
1	16	129—130 (lit. data[8]: 129—130)	0.25 ($CHCl_3$)				
3*	100	260 (with decomp.)	0.28 (PhH—MeOH, 10 : 1)	22.23 22.65	3.31 3.17	44.20 44.02	$C_3H_5N_5O_3$
10	90	130—131 (flash p.)	0.50 (EtOAc)	24.29 24.84	2.22 2.08	28.72 28.98	$C_3H_3N_3O_4$
11	91	147—148	0.40 ($CHCl_3$—EtOAc, 4 : 1)	29.82 30.20	3.55 3.17	26.17 26.41	$C_4H_5N_3O_4$
12**	93	190—191	0.15 ($CHCl_3$—EtOAc, 4 : 1)	25.47 25.01	2.90 2.80	38.35 38.88	$C_3H_4N_4O_3$
13	75	206—208	0.31 ($CHCl_3$—MeOH, 9 : 1)	25.22 25.51	2.22 2.52	35.49 35.00	$C_3H_4N_4O_4$
14	40	225—228	—	25.53 25.18	2.23 2.11	39.02 39.16	$C_6H_6N_8O_6$
15	78	100—101 (t.expl.)	0.31 ($CHCl_3$—MeOH, 9 : 1)	—	—	—	$C_4H_4N_4O_6$
17	62	139—141	0.47 ($CHCl_3$)	31.03 30.58	2.21 1.92	26.43 26.75	$C_8H_6N_6O_8$
18	79	111—112	0.33 ($CHCl_3$—Pr^iOH, 9 : 1)	22.03 22.37	2.00 1.88	26.33 26.09	$C_6H_6N_6O_{10}$
22	90	121—123 (t.expl.)	0.43 ($CHCl_3$)	17.32 17.15	— 	60.24 60.00	$C_4N_{12}O_4$
23	12	136—138	0.26 ($CHCl_3$)	21.02 20.70	1.12 1.16	32.28 32.19	$C_6H_4N_8O_{10}$
24	12	196—198 (t.decomp.)	0.19 ($CHCl_3$—EtOAc, 1 : 1)	23.64 24.01	1.70 1.34	37.11 37.33	$C_6H_4N_8O_7$
25	46	113—114	0.25 ($CHCl_3$—EtOAc, 4 : 1)	20.53 20.70	1.31 1.16	32.44 32.19	$C_3H_2N_4O_5$

* The characteristics of compound **3** were not reported in the study.[8]

** For compound **12**, only the melting point (205 °C) was given in the study.[12]

Table 2. Spectroscopic characteristics of the compounds synthesized

Compound	IR, ν/cm^{-1} (UV, λ_{max}/nm)	^{1}H, [^{13}C], {^{14}N} NMR		MS, *m/z* (I_{rel} (%))
		Solvent	δ	
3	3428, 3316, 1676, 1648, 1596, 1524, 1480, 1348, 1308, 1228, 1196, 1104, 1016, 972, 940, 876, 848, 812, 760, 728, 656	—	—	—
10	3425, 3330, 3250, 3178, 1750, 1732, 1638, 1610, 1560, 1500, 1385, 1375, 1230 (210, 267, 367)	Acetone-d_6	6.45 (s, 2 H, NH_2)	145 [M^+] (35), 115 [$M^+ - NO$] (81), 101 [$M^+ - CO_2$] (100), 85 [$M^+ - 2$ NO] (71), 71 [$M^+ - NO - CO_2$] (80)
11	3440, 3330, 3165, 3025, 2970, 2862, 1711, 1615, 1525, 1442, 1368, 1238 (211, 259, 367)	DMSO-d_6	3.90 (s, 3 H, Me); 6.35 (s, 2 H, NH_2)	—
12	3423, 3405, 3320, 3210, 3180, 1684, 1665, 1612, 1580, 1520, 1410, 1260 (210, 254, 367)	DMSO-d_6	6.50 (s, 2 H, NH_2); 7.10 (s, 1 H, CONH); 8.47 (s, 1 H, CONH)	—
13	3408, 3308, 3092, 1668, 1640, 1624, 1592, 1552, 1496, 1472, 1456, 1352, 1216, 1108, 1040, 1008, 884, 860, 788, 768, 744, 684, 656	DMSO-d_6	3.30 (br.s, 1 H, OH); 6.55 (s, 2 H, NH_2); 10.50 (br.s, 1 H, NH)	160 [M^+] (8), 130 [$M^+ - NO$] (24), 68 [furoxan ring] (100)
14	3468, 3428, 3320, 3176, 1692, 1660, 1620, 1592, 1536, 1488, 1348, 1256, 1204, 1120, 1012, 912, 856, 768, 708, 656	DMSO-d_6	6.65 (s, 4 H, 2 NH_2); 10.50 (br.s, 2 H, 2 NH)	257 [$M^+ + 1 - NO$] (7), 209 [$M^+ - 1 - 2$ NO $- NH_2$] (25), 187 [$M^+ + 1$ – aminofuroxan] (16), 144 [$M^+/2 + 1$] (17), 68 [furoxan ring] (100)
15	3572, 3412, 1708, 1558, 1476, 1424, 1328, 1284, 1204, 1096, 1052, 1024, 948, 892, 860, 792, 748, 700, 628	DMSO-d_6	3.40 (br.s, 2 H, 2 OH); 10.30 (br.s, 2 H, 2 NH)	—
		DMSO-d_6	[109.88 (C(3) of the ring); 151.78 and 151.90 (2 CO); 153.81 (C(4) of the ring)]	
17	2960, 1720, 1630, 1620, 1320, 1480 (206, 256, 350)	Acetone-d_6	3.91 (s, 6 H, 2 Me)	—
18	3392, 2948, 2884, 1632, 1620, 1460, 1404, 1372, 1292, 1240, 1136, 1052, 1032, 944, 844,760, 728, 692, 616	DMSO-d_6	4.10 (s, 2 H, 2 OH); 4.60 (s, 4 H, 2 CH_2)	—
22	2205, 2135, 1580, 1510, 1460, 1345, 1225, 1090, 1055, 1030, 860, 805, 760	Acetone-d_6	[125.65 (C(3) of the ring); 150.20 (C(4) of the ring)]	280 [M^+] (4), 224 [$M^+ - 2\ N_2$] (7), 192 [$M^+ - 2$ NO $- N_2$] (100)
23	3020, 2908, 1640, 1620, 1496, 1468, 1448, 1420, 1380, 1312, 1280, 1156, 1056, 1008, 944, 848, 768, 756, 744, 680, 612	$CDCl_3$	5.65 (s, 4 H, 2 CH_2)	—
		$CDCl_3$	{−50.6 ($CONO_2$)}	
24	3440, 3412, 3284, 3224, 3180, 1712, 1692, 1620, 1600, 1520, 1496, 1464, 1376, 1316, 1256, 1156, 1072, 1036, 1012, 924, 828, 800, 752, 736, 720	DMSO-d_6	7.88 (s, 1 H, CONH); 8.33 (s, 1 H, CONH); 8.39 (s, 1 H, CONH); 8.53 (s, 1 H, CONH)	300 [M^+] (2), 270 [$M^+ - NO$] (7), 257 [$M^+ - H_2NCO + 1$] (19), 227 [$M^+ - H_2NCO - NO$] (2), 184 [$M^+ - 2\ H_2NCO - NO + 2$] (8), 159 [H_2NCO – ring – NO + 1] (3), 129 [H_2NCO – ring + 1] (10), 113 [H_2NCO – ring – O + 1] (22), 84 [furoxan ring.] (24), 44 [N_2O] (100)
		DMSO-d_6	[105.9 (C(4) of the ring); 106.1 (C(4) of the ring); 153.1 (CO); 154.4 (C(4) of the ring); 155.6 (C(4) of the ring)]	
		DMSO-d_6	{66.1 (NNO)}	
25	3448, 3304, 3284, 3184, 1700, 1640, 1564, 1512, 1452, 1400, 1340, 1028 (213, 245)	DMSO-d_6	8.23 (s, 1 H, CONH); 8.54 (s, 1 H, CONH)	—
		Acetone-d_6	{−277 (N_{ring}, $\Delta\nu_{1/2}$ = 150 Hz); −36.1 (NO_2, $\Delta\nu_{1/2}$ = 11.5 Hz)}	

Furoxan-3,4-dicarboxylic acid diazide (2) and 4-aminofuroxan-3-carboxylic acid azide (1). A solution of diethyl furoxan-3,4-dicarboxylate[11] (23 g, 0.1 mol) in MeOH (80 mL) was added dropwise to a mixture of 85% hydrazine hydrate (25 mL, 0.42 mol), MeOH (80 mL), and water (50 mL) at −20 °C for 45 min. The reaction mixture was stirred at the same temperature for 1 h, after which concentrated HCl (80 mL) was added dropwise for 30 min and then a solution of $NaNO_2$ (32 g) in water (160 mL) was added for 30 min. The reaction mixture was kept at −20 °C for 1 h, extracted with CCl_4 (3×40 mL), washed with water (3×40 mL), dried with $MgSO_4$, and concentrated on a rotary evaporator at a temperature of no higher than 30 °C **to a volume of no less than 40 mL**. Dioxane (40 mL) and water (1.5 mL) were added to the resulting solution (containing ~4.9 g of diazide **2**). The reaction mixture was rapidly heated to 80 °C, stirred for 10 min, and cooled. Then water (60 mL) was added dropwise. The precipitate that formed was filtered off, washed with water, and dried in air. Compound **1**, which was identical with the product prepared earlier,[8] was obtained in a yield of 2.72 g.

4-Aminofuroxan-3-carboxylic acid hydrazide (3). Water (80 mL) and hydrazine hydrate (6.5 g, 0.13 mol) were added to azide **1** (10.2 g, 0.06 mol) wetted with dioxane. The reaction mixture was stirred at ~20 °C for 1 h. The precipitate that formed was filtered off, washed three times with water, and dried in air. Compound **3** was prepared in a yield of 9.5 g.

Methyl 4-aminofuroxan-3-carboxylate (11). A solution of NaOH (2.36 g, 0.059 mol) in MeOH (20 mL) was added dropwise to a suspension of azide **1** (10 g, 0.059 mol) in MeOH (50 mL) at ~20 °C for 10 min and the reaction mixture was stirred for 10 min. The product was filtered off and washed three times with water. An additional amount of the product was obtained from the mother liquor by distilling off the methanol. The latter portion of the product was washed with water and combined with the main portion, after which the product was dried in air.

Ethyl 4-aminofuroxan-3-carboxylate (7) was prepared analogously to compound **11** in 91% yield. Its characteristics are identical with those of the product prepared earlier.[10]

4-Aminofuroxan-3-carboxylic acid (10). A solution of NaOH (7.71 g, 0.118 mol) in water (40 mL) was added dropwise to a suspension of azide **1** (10 g, 0.059 mol) in water (107 mL) at ~20 °C. The reaction mixture was stirred for 5 min, after which dilute H_2SO_4 was added dropwise to pH 7. Then the reaction mixture was stirred for 5 min and a solution of $NaNO_2$ (4.07 g) in water (10 mL) was added dropwise. After 5 min, anhydrous Na_2SO_4 (13.5 g) was added and the reaction mixture was stirred for 20 min. The product was filtered off, washed two times with cold water, and dried in a vacuum desiccator over P_2O_5. **Caution:** *The compound is sensitive to mechanical treatment; it explodes upon grinding with a porcelain pestle in a porcelain mortar.*

4-Aminofuroxan-3-carboxamide (12). A concentrated NH_4OH solution (20 mL) was added in one portion to a suspension of azide **1** (10.2 g, 0.06 mol) in water (100 mL) at ~20 °C and the reaction mixture was stirred for 40 min. The precipitate that formed was filtered off, washed with water, and dried in air.

4-Aminofuroxan-3-carbohydroxamic acid (13). Azide **1** (1.70 g, 0.01 mol) was added to a solution of $NH_2OH \cdot HCl$ (1.05 g, 0.015 mol) neutralized with $NaHCO_3$ (1.26 g, 0.015 mol) in water (15 mL). The reaction mixture was stirred until the azide was consumed (according to the TLC data). The color of the suspension gradually changed from yellow to white. The precipitate that formed was filtered off, washed with water, and dried in air.

1,2-Bis(4-aminofuroxan-3-carbonyl)hydrazine (14). Azide **1** (1.70 g, 0.01 mol) was added to a solution of hydrazide **3** (1.59 g, 0.01 mol) in a minimum amount of DMSO. The reaction mixture was stirred until the starting azide **1** was consumed (according to the TLC data). The white precipitate that formed was filtered off, washed with water and acetone, and dried in air. Since the compound is virtually insoluble in organic solvents, its ^{13}C NMR spectrum was not measured and a satisfactory chromatogram was not obtained.

Furoxan-3,4-dicarbohydroxamic acid (15). A solution of $NH_2OH \cdot HCl$ (2.8 g, 0.04 mol) neutralized with $NaHCO_3$ (3.36 g, 0.04 mol) in a minimum amount of water was added to a solution containing diazide **2** (~2.24 g, ~0.01 mol) in CCl_4. The reaction mixture was stirred for ~3—4 h until the starting diazide was consumed (according to the TLC data, R_f 0.67, $CHCl_3$ as the eluent) and then cooled to ~0 °C. The precipitate that formed was filtered off, washed with a small amount of ice water and CCl_4, and dried in air.

3,3′-Bis(methoxycarbonyl)-4,4′-azofuroxan (17). Methyl ester **11** (8.48 g, 0.053 mol) was dissolved in acetone (207 mL) at 35 °C. Concentrated HCl (310 mL) was rapidly added with cooling and vigorous stirring. Then a solution of $KMnO_4$ (72 g) in water (1100 mL) was added dropwise at 20 °C (cooling), the reaction mixture was stirred at 20 °C for 2.5 h, and MnO_2 that precipitated was dissolved by adding oxalic acid. The product was filtered off and dissolved in AcOH (200 mL) at 55 °C. After cooling to 20 °C, the reaction mixture was diluted with water (200 mL) for 20 min. The precipitate was filtered off, washed with 40% AcOH and water, and dried in air.

3,3′-Bis(hydroxymethyl)-4,4′-azofuroxan (18). A solution of $KMnO_4$ (2.91 g, 0.0184 mol) in water (50 mL) was added dropwise to a solution of 4-amino-3-hydroxymethylfuroxan **16** [14] (2.41 g, 0.0184 mol) in concentrated HCl (24 mL) and CH_2Cl_2 (10 mL) at a temperature of no higher than 20 °C. The reaction mixture was stirred for 15 min. Then oxalic acid was added until MnO_2 was consumed. The solution was saturated with NaCl (35 g) and extracted with EtOAc (3×20 mL). The extracts were dried with $MgSO_4$ and the solvent was distilled off. After drying in a vacuum desiccator over P_2O_5, a resinous product was obtained. An analytically pure sample was prepared by flash chromatography on 5/40 μm silica gel (Pr^iOH—$CHCl_3$, 1 : 9, as the eluent).

3,3′-Dicyano-4,4′-azofuroxan (21). A suspension of 3,3′-dicarbamoyl-4,4′-azofuroxan (**19**)[13] (1 g, 0.0035 mol) and P_2O_5 (2.8 g, 0.020 mol) in tetrachloroethane (10 mL) was heated with stirring to 100 °C and kept at this temperature for 1 h. Then $CHCl_3$ (20 mL) was added and the reaction mixture was refluxed for 5 min. The organic layer was decanted away. The residue was extracted with boiling $CHCl_3$ (2×20 mL). The extracts were combined and filtered through a layer of 40/100 μm silica gel (the diameter was 25 mm, the height of the layer was 15 mm). The solvent was concentrated until a dense suspension was obtained. The product was filtered off, washed on a filter with $CHCl_3$ (one time), and dried in air. Compound **21** was prepared in a yield of 15 mg (1.7%). Its characteristics are identical with those of the product synthesized earlier.[16]

4,4′-Diazido-3,3′-azofuroxan (22). Sodium azide (0.78 g, 0.012 mol) was added with stirring to a solution of 3,3′-dinitro-4,4′-azofuroxan (**20**)[15] (0.29 g, 0.001 mol) in AcOH (15 mL).

After 48 h, the precipitate that formed was filtered off and washed with water. An additional amount of the product was isolated from the mother liquor by adding water (10 mL). The total yield was 0.25 g.

3,3´-Bis(nitroxymethyl)-4,4´-azofuroxan (23). Nitric acid (d = 1.51 g cm^{-3}) (5.9 mL, 0.141 mol) was added dropwise to Ac_2O (20 mL) at 0—5 °C and then a solution of diol **18** (1.83 g) in AcOH (2 mL) was added. The reaction mixture was poured into an ice—water mixture (100 g), a resinous substance being formed on the walls of the beaker. The aqueous phase was decanted away and the resinous substance was dissolved in EtOAc (2×20 mL). The solvent was evaporated *in vacuo*. The residue was stirred with $CHCl_3$ (10 mL) for 5 min. The yellow precipitate that formed was filtered off and washed with $CHCl_3$ (5 mL). The product was purified by flash chromatography. For this purpose, the precipitate was dissolved in CH_2Cl_2 (60 mL), filtered through a layer of 5/40 μm silica gel (the diameter was 36 mm, the height of the layer was 26 mm) on a Schott funnel, and washed out with CH_2Cl_2 (40 mL). The solvent was concentrated *in vacuo*. The product was transferred to a filtering funnel, washed two times with $CHCl_3$, and dried in air. Pale-yellow crystals were obtained in a yield of 385 mg. An additional amount of the product (15 mg) was isolated from the mother liquor.

4-Nitrofuroxan-3-carboxamide (25) and 3,3´-dicarbamoyl-4,4´-azoxyfuroxan (24). Concentrated H_2SO_4 (45 mL) and then CCl_4 (45 mL) were added dropwise to 85% hydrogen peroxide (45 mL) at 15 °C. Then amide **12** (12.0 g, 0.083 mol) was added in one portion. The reaction mixture was stirred at 20 °C for 1 h, during which it turned green. After 30 min, the reaction mixture turned yellow. Then the reaction mixture was diluted with ice water (135 mL) and a layer of CCl_4 was separated. The aqueous layer was extracted with EtOAc (5×60 mL) and washed with water (2×45 mL). Ethyl acetate was evaporated *in vacuo*. The residue was diluted with water (50 mL) and stirred until the oil that formed solidified. The precipitate was filtered off and dried in a vacuum desiccator over P_2O_5. A mixture of compounds **24** and **25** was obtained in a yield of 10.35 g. To isolate compound **25**, the mixture of the compounds was dissolved in EtOAc (20 mL) at 40 °C, $CHCl_3$ (80 mL) was added, and the precipitate that remained undissolved was filtered off. This operations was repeated three times. The combined mother liquors were concentrated to dryness and dried in air to prepare compound **25**. The undissolved product was washed one time with the same mixture of the solvents and dried in air to prepare compound **24**.

3-Cyano-4-nitrofuroxan (26). A mixture of amide **25** (4.57 g, 0.036 mol) and P_2O_5 (3.89 g) was heated on an oil bath (the bath temperature was 140—160 °C) *in vacuo* (1—5 Torr). The product was distilled off into a trap cooled with an acetone—solid CO_2 mixture for 30 min. The crude product was sublimed *in vacuo* (20—30 Torr) using a water-aspirator pump at 75 °C to prepare the product in a yield of 3.37 g. Then the product was dissolved in CH_2Cl_2 (4 mL), CCl_4 (4 mL) was added, and the mixture was concentrated on a rotary evaporator at ~20 °C until a dense suspension was obtained. The precipitate was filtered off, washed on a filter with CCl_4 (1.5 mL), and dried in air to prepare compound **26** in a yield of 2.71 g (48%). The characteristics of **26** are identical with those of the product synthesized earlier.[17]

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