Synthesis of 3-amino-5-nitrobenzaldehyde oxime and its conversion into 3,4-bis(3-amino-5-nitrophenyl)furoxan and isomeric 3(4)-(3-amino-5-nitrophenyl)-4(3)-nitrofuroxans

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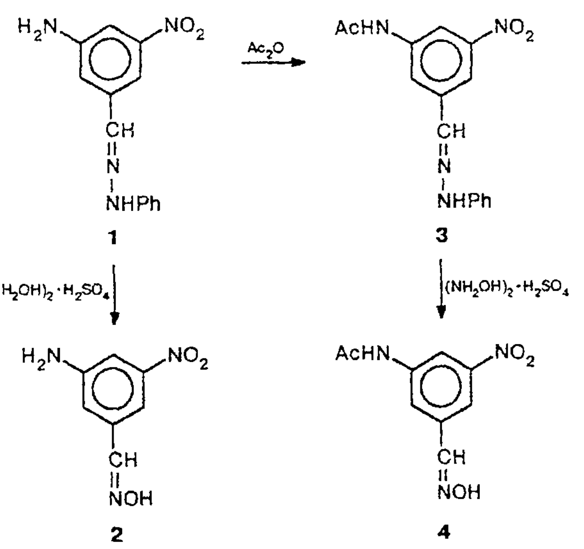
The oxime of the hitherto unknown 3-amino-5-nitrobenzaldehyde was synthesized by the reaction of 3-amino-5-nitrobenzaldehyde phenylhydrazone with excess of $(NH_2OH)_2 \cdot H_2SO_4$. The oxime obtained was used as the starting compound for the synthesis of novel diaryl- and arylnitrofuroxans.

Key words: 3-amino-5-nitrobenzaldehyde, oxime, phenylhydrazone, furoxans, exchange of imine fragment.

The present work is one of the steps in our studies into the series of the derivatives of nitrofuroxan[1–3] and polynitroarylfuroxans.[4,5] Previously,[6] we have proposed a method for the synthesis of 3-amino-5-nitrobenzaldehyde phenylhydrazone (**1**) by selective reduction of one aliphatic and one of the aromatic nitro groups in 3,5-dinitrophenylnitromethane under the action of $PhNHNH_2$. It should be noted that neither 3-amino-5-nitrobenzaldehyde nor derivatives of this carbonyl compound, other than compound **1**, have been reported so far. Meanwhile, isomeric aminonitrobenzaldehydes are widely used in the syntheses of heterocycles, including biologically active ones.[7,8] Furoxans with this kind of substituents have not been hitherto known.

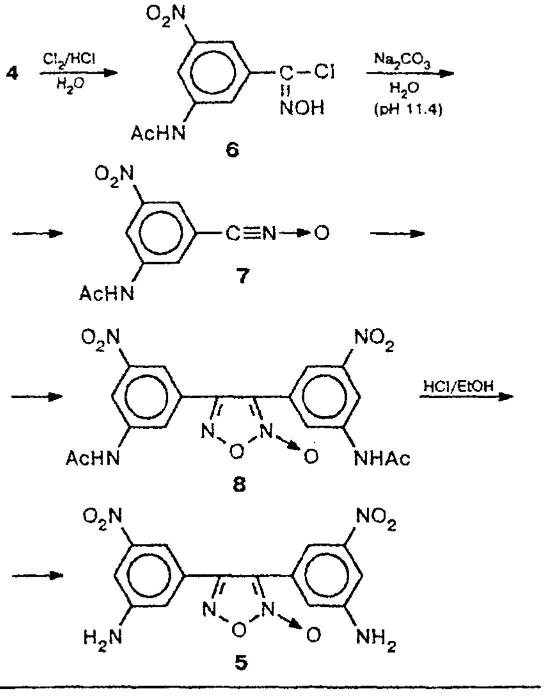
Scheme 1



In this work we offer a preparative method for obtaining 3-amino-5-nitrobenzaldehyde oxime (**2**) (Scheme 1) and a synthesis of 3,4-bis(3-amino-5-nitrophenyl)furoxan (**5**) (Scheme 2) and isomeric 3(4)-(3-amino-5-nitrophenyl)-4(3)-nitrofuroxans (**9** and **10**) (Scheme 3) from compound **2**.

Oxime **2** was synthesized from hydrazone **1** by the replacement of the =NNHPh fragment by =NOH. It should be noted that the exchange of one imino group

Scheme 2



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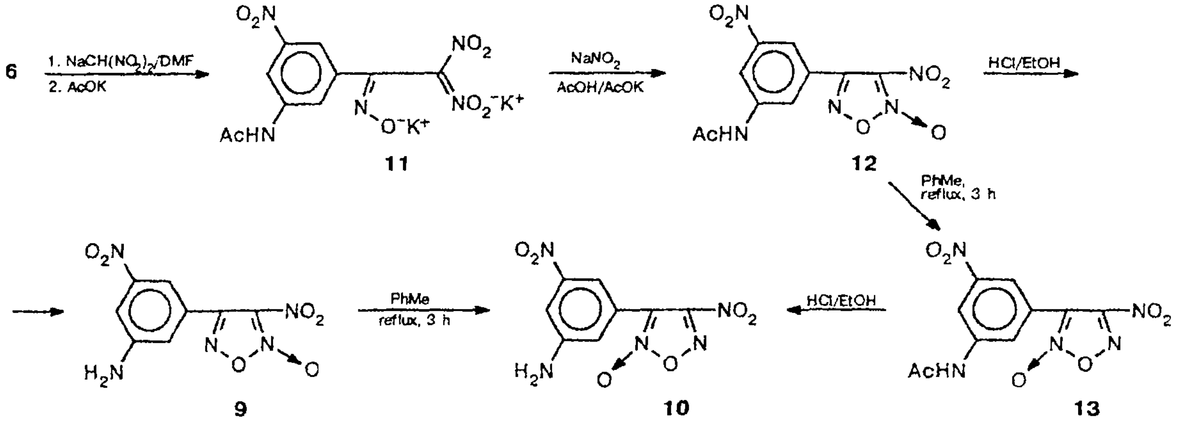
Scheme 3



for another by reactions of imines with other amines is rather common.[9] One can shift the equilibrium by various ways, in particular by using a considerable excess of an amine,[10] by removal of the amine being displaced,[11] or by performing the synthesis leading to the poorly soluble compounds.[12] Acid catalysis is required in many cases.[13,14]

The synthesis of oxime **2** was performed by heating phenylhydrazone **1** with a 10-fold molar excess of hydroxylamine sulfate in a DMSO—H_2O mixture. The yield of the product was 70%. In a similar way, 3-acetylamino-5-nitrobenzaldehyde oxime (**4**) was obtained in 81% yield from hydrazone **3** (see Scheme 1).

The chlorination of oxime **4** with gaseous chlorine in dilute HCl at 0 °C gave 3-acetylamino-5-nitrobenzhydroximoyl chloride (**6**), the starting compound for the syntheses of furoxans. In particular, the treatment of compound **6** with 0.1 *N* aqueous Na_2CO_3 gave 3,4-bis(3-acetylamino-5-nitrophenyl)furoxan (**8**) resulting from the cyclodimerization of the nitrile oxide **7** that formed initially. The reaction was carried out under conditions typically used for obtaining furoxans from hydroximoyl chlorides.[15] 3,4-Bis(3-amino-5-nitrophenyl)furoxan **5** was synthesized from furoxan **8** by removal of the acetyl protection (HCl in EtOH) (see Scheme 2).

In order to synthesize 4-(3-acetylamino-5-nitrophenyl)-3-nitrofuroxan (**12**), we employed the cyclization of di-K salts of the type **11** into 3-nitrofuroxans under the action of nitrosating reagents recently discovered by us.[1] Nitrofuroxan **12** was obtained by the reaction of chloride **6** with Na-salt of dinitromethane followed by treatment of the resulting dipotassium salt of 2-hydroxyimino-2-(3-acetylamino-5-nitrophenyl)-1,1-dinitroethane (**11**) with $NaNO_2$ in AcOH in the presence of AcOK. The isomerization of compound **12** into the 4-nitro isomer (**13**) occurred on its boiling in toluene in almost quantitative yield. Removal of the acetyl protection from furoxans **12** and **13** gave high yields of isomeric 4(3)-(3-amino-5-nitrophenyl)-3(4)-nitrofuroxans (**9** and **10**). 4-Nitrofuroxan **10** was also synthesized by the thermal isomerization of 3-nitrofuroxan **9** (see Scheme 3).

Experimental

IR spectra were recorded on a UR-20 spectrometer (KBr pellets), and UV spectra were obtained on a Specord UV-VIS instrument (MeOH). ^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 instrument (300, 75.5, and 21.5 MHz, respectively). Chemical shifts were measured relative to Me_4Si as the internal standard (^1H and ^{13}C) and $MeNO_2$ as the external standard (^{14}N). Mass spectra were recorded on a Varian MAT CH-6 instrument (70 eV). TLC was performed on Silufol UV-254 plates (the eluents used are listed below). The spots were visualized in UV light and by spraying with a 1% solution of diphenylamine in EtOH followed by heating. The basic characteristics of the compounds synthesized are presented in Tables 1 and 2.

Synthesis of 3-amino(3-acetylamino)-5-nitrobenzaldehyde oximes (2 and 4) (general procedure). A hot solution of

Table 1. ^1H NMR spectra (DMCO-d_6) of the derivatives of 3-amino-5-nitrobenzaldehyde and furoxans

Com-	δ^a				
pound	NOH	C(NOH)<u>H</u>	NH	NH<u>R</u>	H in Ar
2	11.11	8.11	5.91	5.91 (H)	7.15, 7.28, 7.32
4	11.75	8.65	10.53	2.25 (Ac)	8.10, 8.25, 8.31
5			6.10	6.10 (H)	7.12, 7.15, 7.40, 7.45, 7.50, 7.55
6	12.72		10.41	2.14 (Ac)	8.15, 8.31, 8.52
8			10.56	2.13 (Ac)	7.91, 7.95, 7.98, 8.22, 8.68, 8.73
9			6.15	6.15 (H)	7.28, 7.62, 7.68
10			6.08	6.08 (H)	7.25, 7.45, 7.50
12			9.63	2.11 (Ac)	8.40, 8.65, 8.72
13			9.30	2.12 (Ac)	8.31, 8.50, 8.61

[a] The signals of all protons are displayed as singlets.

Table 2. Yields and characteristics of the compounds synthesized

Compound	Yield (%)	M.p./°C	R_f	$\frac{\text{Found}}{\text{Calculated}}$ (%)			Molecular formula	IR, ν/cm^{-1} (I_{rel} (%))	MS, *m/z* [UV, λ_{max}/nm]
				C	H	N			
2	70	198—200	0.26^a	46.35 46.40	3.90 3.87	22.98 23.18	$C_7H_7N_3O_3$	930, 980, 1350, 1470, 1530, 1590, 1650, 3080, 3230, 3430	181 [M]$^+$ (100), 164 (9), 149 (14), 135 (14), 118 (38)
4	81	240—243	0.20^a	48.30 48.43	4.12 4.03	18.72 18.82	$C_9H_9N_3O_4$	890, 950, 980, 1010, 1100, 1160, 1250, 1280, 1300, 1350, 1360, 1370, 1420, 1540, 1600, 1620, 1680, 3100, 3330, 3400	223 [M]$^+$ (50), 181 (100), 165 (15), 149 (18), 135 (18)
5	74	243—245	0.37^a	46.90 46.92	2.60 2.79	23.30 23.44	$C_{14}H_{10}N_6O_6$	880, 970, 1000, 1030, 1100, 1170, 1270, 1350, 1430, 1500, 1550, 1600, 1650, 3100, 3250, 3400	358 [M]$^+$ (78), 342 (58), 298 (100), 252 (42), 204 (49), 179 (73), 133 (55)
6	89	210—212	0.25^a	45.00 45.14	3.61 3.50	16.48 16.34	$C_9H_8ClN_3O_4$	900, 970, 1020, 1070, 1100, 1190, 1300, 1350, 1380, 1410, 1480, 1540, 1560, 1580, 1600, 1615, 1640, 1690, 2890, 3040, 3180, 3250, 3370	257 [M]$^+$ (2), 222 (7), 221 (49), 215 (9), 179 (100), 163 (21), 133 (25)
7		141—143	0.45^a		—^{b}		$C_9H_7N_3O_4$	890, 1020, 1125, 1230, 1270, 1340, 1370, 1460, 1530, 1610, 1640, 2300, 3070, 3250	[230, 255, 335]
8	71	158—160	0.15^a	48.91 48.81	3.18 3.16	18.69 18.98	$C_{18}H_{14}N_6O_8$	880, 1000, 1040, 1090, 1250, 1260, 1340, 1400, 1420, 1480, 1500, 1530, 1590, 1620, 1670, 3090, 3300	442 [M]$^+$ (45), 426 (19), 401 (36), 383 (54), 341 (94), 298 (98), 221 (43), 205 (54), 179 (100)
9	91	120—122	0.49^c	35.90 35.96	1.99 1.87	26.30 26.25	$C_8H_5N_5O_6$	930, 1000, 1030, 1050, 1100, 1180, 1260, 1350, 1430, 1480, 1520, 1550, 1590, 1650, 1680, 3120, 3400, 3490	267 [M]$^+$ (73), 251 (7), 221 (56), 207 (100), 191 (56), 175 (77), 163 (33), 145 (90)
10	91	155—157	0.49^c	35.82 35.96	1.90 1.87	26.30 26.25	$C_8H_5N_5O_6$	880, 960, 1000, 1040, 1250, 1290, 1310, 1350, 1380, 1490, 1510, 1550, 1580, 1630, 3120, 3410, 3510	267 [M]$^+$ (78), 251 (4), 221 (52), 207 (100), 191 (52), 175 (87), 163 (39), 145 (83)
11	76	>300	—		—		$C_{10}H_7K_2N_4O_8$	870, 1000, 1110, 1200, 1350, 1480, 1530, 1620, 1660, 2850, 3350	[230, 365]
12	71	90—92	0.34^c	38.73 38.83	2.35 2.27	22.72 22.68	$C_{10}H_7N_5O_7$	800, 860, 900, 1020, 1100, 1250, 1270, 1350, 1390, 1460, 1550, 1640, 1670, 1710, 3120, 3380	309 [M]$^+$ (55), 293 (19), 267 (79), 251 (43), 241 (40), 233 (36), 221 (60), 203 (62),163 (100)
13	93	183—185	0.34^c	38.85 38.83	2.30 2.27	22.80 22.68	$C_{10}H_7N_5O_7$	900, 1020, 1050, 1080, 1130, 1250, 1280, 1350, 1380, 1420, 1460, 1520, 1550, 1580, 1600, 1650, 1680, 3100, 3290	309 [M]$^+$ (41), 293 (2), 267 (100), 251 (1), 249 (1), 233 (1), 221 (55), 207 (77), 191 (52), 175 (43), 163 (65)

[a] $CHCl_3$—acetone (4 : 1). [b] The compound could not be isolated in an analytically pure form. [c] $CHCl_3$—acetone (3 : 1).

$(NH_2OH)_2 \cdot H_2SO_4$ (6.9 g, 42 mmol) in H_2O (15 mL) was added to a solution of the corresponding phenylhydrazone (**1** or **3**) (4.2 mmol) in DMSO (20 mL) at ~100 °C, and the reaction mixture was stirred for ~20 min at ~100 °C until the starting compound disappeared (TLC). Water (50 mL) was added, and the mixture was kept for 16 h at ~20 °C. The resulting precipitate was filtered off, washed with water, and dried in air.

3-Acetylamino-5-nitrobenzhydroximoyl chloride (6). Oxime **4** (2.2 g, 0.1 mmol) was added with cooling (~0 °C) and stirring to an HCl—water mixture (1 : 1, 400 mL). Then Cl_2 was passed for 30 min through the mixture, which was kept at 5 °C until the starting compound disappeared (TLC). The precipitate was filtered off, washed with cold water, and dried in a vacuum desiccator with P_2O_5.

3-Acetylamino-5-nitrobenzonitrile oxide (7) and 3,4-bis(3-acetylamino-5-nitrophenyl)furoxan (8). Aqueous Na_2CO_3 (0.1 *N*, 15 mL, pH 11.4) and then water (75 mL) were added with stirring at ~20 °C to a solution of chloride **6** (1.5 g, 5.83 mmol) in ethyl acetate (200 mL), and the reaction mixture was stirred until the starting compound disappeared (TLC). The organic layer was separated, washed with water, and dried with $MgSO_4$. The resulting nitrile oxide **7** dimerizes into furoxan **8** in ~20 days at ~20 °C. ^{13}C NMR for furoxan **8** (acetone-d_6), δ: 24.26 (Me); 114.03 (C_{cycl}-3); 116.08, 116.44, 118.22, 118.51, 124.92, 125.19, 125.50, 128.98 (Ar); 141.99, 142.18 (Ar—NH); 149.63, 149.77 (Ar—NO_2); 155.62 (C_{cycl}-4); 170.19 (CO).

4-(3-Acetylamino-5-nitrophenyl)-3-nitrofuroxan (12). Dipotassium salt **11** obtained by the known procedure[1] (0.1 g, 0.25 mmol) and $NaNO_2$ (0.12 g, 1.87 mmol) were added alternately to a mixture of AcOH (2 mL) and AcONa (0.14 g, 1.7 mmol). The reaction mixture was stirred for 0.5 h at 60 °C and cooled, and then water (10 mL) was added. The precipitate of compound **12** was filtered off and washed with water. ^{13}C NMR for furoxan **12** (acetone-d_6), δ: 24.25 (Me); 116.69, 119.37, 125.78, 127.64 (Ar); 127.68 (C_{cycl}-3); 141.86 (Ar—NH); 149.45 (Ar—NO_2); 151.76 (C_{cycl}-4); 170.13 (CO).

3-(3-Acetylamino-5-nitrophenyl)-4-nitrofuroxan (13). Furoxan **12** (0.15 g, 0.48 mmol) was refluxed for ~3 h in toluene. The solvent was evaporated, and the residue was washed with hexane and dried in air.

Synthesis of 3,4-bis(3-amino-5-nitrophenyl)furoxan (5), 4-(3-amino-5-nitrophenyl)-3-nitrofuroxan (9), and 3-(3-amino-5-nitrophenyl)-4-nitrofuroxan (10) (general procedure). Concentrated HCl (5 drops) was added to a solution of furoxan **8**, **12**, or **13** in EtOH (5 mL), and the mixture was kept for 2—7 days at ~20 °C until the starting compound disappeared (TLC). The reaction mixture was poured into water, and the precipitate was filtered off, washed with water, and dried in air.

Furoxan **10** was also obtained by refluxing furoxan **9** (0.15 g, 0.56 mmol) in toluene for 3 h, yield 81%.

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