Nitrosation of salts of 1-hydroxyimino-2,2-dinitro-1-R-ethanes, a novel method for the preparation of isomeric 3(4)-nitro-4(3)-R-furoxans

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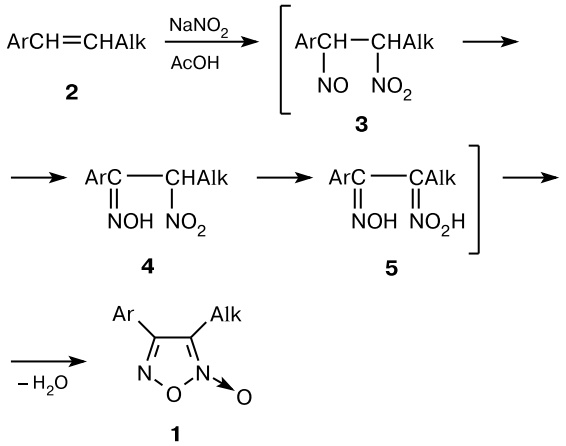
A novel general method for the synthesis of isomeric 3(4)-nitro-4(3)-R-furoxans is developed. 3-Nitro isomers were obtained by reaction of hydroximoyl chlorides with dinitromethane sodium salt followed by conversion of the resulting 1-substituted 1-hydroxyimino-2,2-dinitroethanes into dipotassium (or disodium salts) and their subsequent nitrosation with $NaNO_2$ in AcOH or with N_2O_4. Thermal isomerization of 3-nitro isomers afforded 4-nitro isomers were prepared in high yields.

Key words: isomeric 3(4)-nitrofuroxans, bis[3(4)-nitrofuroxan-4(3)-yl]arenes, α-nitro oximes, hydroximoyl chlorides, *aci*-nitro compounds, dinitromethane sodium salt, nitrosation, thermal isomerization, regiospecific synthesis.

The furoxan ring has a special place among various azoles, as it contains two atoms of active oxygen, which are not bonded to the carbon or hydrogen atoms being involved in the "hidden" nitro group.[1,2] The furoxan derivatives possess high density together with positive enthalpy of formation, which enables synthesis of high-energetic compounds on their basis. Nitrofuroxans are of particular importance among functional furoxan derivatives that, on the one hand, possess biological activity as nitrogen oxide donors,[3,4] and, on the other hand, are attractive as promising components for high-energy compositions. However, general synthetic methods furnishing 3(4)-nitrofuroxans in satisfactory yields have not been described. Oxidation of aminofuroxans is one of the well-known approaches toward nitrofuroxans, but only 4-aminofuroxans could be involved in this reaction[5]. The aim of the present work was the quest for novel general methods for the synthesis of 3(4)-nitrofuroxans bearing diverse substituents at the C(4) (or C(3)) atom of the ring.*

To solve this problem, we used the well-known method for the furoxan ring construction based on dehydration of α-nitro oximes. This method was developed[7,8] more than 100 years ago for the synthesis of alkylarylfuroxans **1** by the reaction of the corresponding 1-alkyl-2-arylethylenes **2** with sodium nitrite in acetic acid. It has been assumed that in the initial step N_2O_3 adds to the double bond of the starting ethylene **2** to give pseudonitrosite **3**, which successively isomerized *in situ* into α-nitro oxime **4** and its *aci*-form **5**, dehydration of which furnished furoxan **1**. Regiospecifity of this reaction is determined by the location of the nitro group in α-nitro oxime **4**; it is from this side that the oxygen atom of the *N*-oxide appears in the resulting furoxan **1** (Scheme 1).

Scheme 1



Later[9—11] this method has been extended to other olefins. Pseudonitrosites **3′** in the form of the nitroso dimers were obtained by passing a mixture of gaseous NO and oxygen or air through a solution of the starting 1,2-dialkylethylene **6** in diethyl ether or benzene. Heating of pseudonitrosites **3′** in dipolar aprotic solvents (DMF, DMSO, HMPA) is a facile and convenient method for the isomerization of pseudonitrosites **3′** into α-nitro oximes **4′**. Transformation of α-nitro oximes **4′** into *aci*-nitro compounds **5′** as well as its dehydration into dialkylfuroxans **7**

* Brief communication, see Ref. 6.

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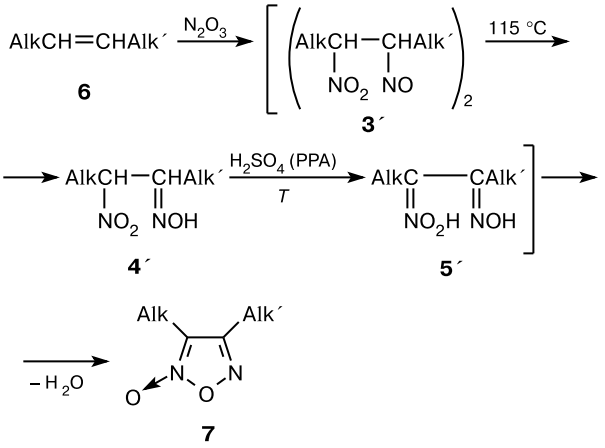
was carried out by short heating in concentrated sulfuric or polyphosphoric acid. (Scheme 2).

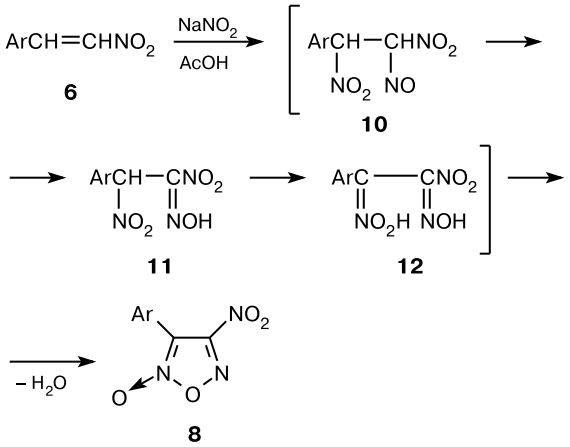
Scheme 2



PPA is polyphosphoric acid

The use of this approach for an access to nitrofuroxans required synthesis of α-nitro oximes bearing the nitro group as one of the substituents. Previously,[12] we have developed a similar pathway toward 3-aryl-4-nitrofuroxans **8**, which was based on the reaction of β-nitrostyrenes **9** with $NaNO_2$ in AcOH. In this case, the addition of the N_2O_3 fragments to the double bond followed another pattern than that shown in Scheme 1. The NO_2 fragment adds to the carbon atom adjacent to the Ar-substituent, while the NO fragment adds to the carbon atom of the $CHNO_2$ group to give isomeric pseudonitrosites **10**, which, apparently, were converted in 4-nitrofuroxans **8** *via* α-nitro oximes **11** and their *aci*-nitro form **12** by the pattern similar to that shown in Scheme 1 (Scheme 3). This method has significant disadvantages: the reaction is very slow (several days), portion-

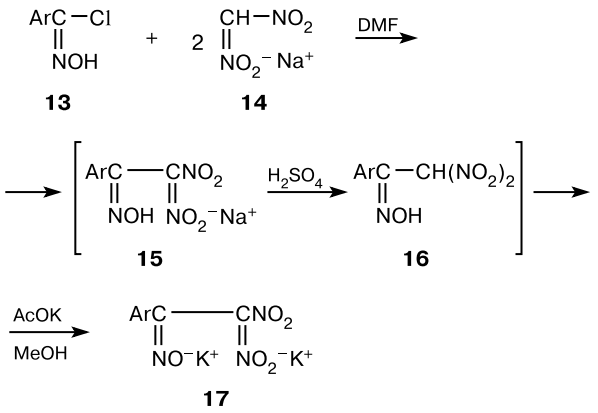
Scheme 3



wise addition of a large excess of $NaNO_2$ (10—15 mol) is required, and the yields of the resulting furoxan are low (21—26%). The lengthy reaction and low yield of furoxan are probably due to the difficulty of converting the nitro group in the *aci*-form under the reaction conditions.

In the present work, with the aim at synthesizing an isomeric α-nitro oxime with the oxime moiety located near the aryl substituent and the nitro group at the neighboring carbon atom, we carried out the reaction of arylhydroximoyl chlorides **13** with 2 mol. equiv. of dinitromethane sodium salt **14**. The reaction was conducted in DMF at −10—0 °C with subsequent keeping at 0 °C for 15—24 h and at room temperature for 3—4 h. The excess of dinitromethane sodium salt **14** was used to achieve more complete conversion of the starting chloride **13** into α-nitro oxime **16**, which in turn gave monosodium salt **15**, since the acidity of nitro oxime **16** is higher than that of dinitromethane. After aqueous work-up of the reaction mixture, dinitromethane that formed was extracted with chloroform, the aqueous layer was carefully acidified with 15—20% H_2SO_4, and α-nitro oxime **16** was extracted with diethyl ether, then methanol was added to the etheral extract. Removal of diethyl ether *in vacuo* and treatment of the residue with a solution of anhydrous AcOK in methanol furnished dipotassium salt **17** (Scheme 4). All operations were performed quickly at temperature no higher than 10 °C. In all cases, the yields of salts **17** were higher than 80%.

Scheme 4



Ar = 4-MeO-3,5-$(NO_2)_2C_6H_2$ (**a**), Ph (**b**), 2-$NO_2C_6H_4$ (**c**), 3-$NO_2C_6H_4$ (**d**), 4-$NO_2C_6H_4$ (**e**), 4-BrC_6H_4 (**f**)

Structures of dipotassium salts **17** were established based on the data from IR spectroscopy and elemental analysis (Table 1). It is of note that no absorption bands of the OH groups in the range of 3200—3400 cm^{-1} were found in IR spectra indicating the absence of the free oxime units. Besides, the ionization constants of dinitromethyl and oxime fragments were determined by UV spectrosco-

Table 1. Yields, IR spectroscopic data, and elemental analysis data of synthesized dipotassium salts of 1-aryl-1-hydroxyimino-2,2-dinitroethane **17a—f** and tetrapotassium salt of 1,4-bis(2,2-dinitroethyl-1-hydroxyimino)benzene **25b**

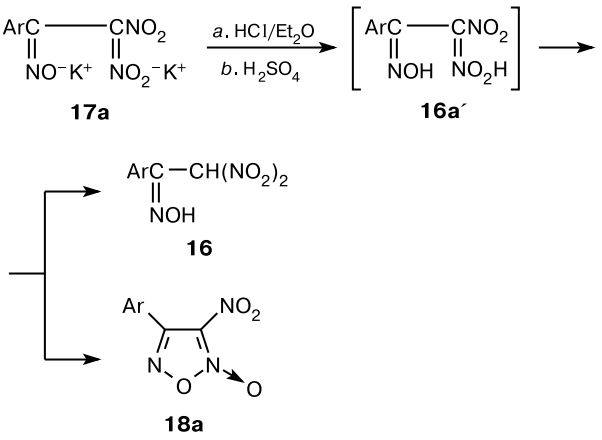
Compound	Ar	Yield (%)	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}
			C	H	N		
17a	4-MeO-3,5-$(NO_2)_2C_6H_2$	87	25.47 25.65	1.31 1.20	16.50 16.62	$C_9H_5K_2N_5O_{10}$	3170, 1550, 1540, 1500, 1470, 1440, 1410, 1350, 1300, 1210, 1200, 1115, 1090, 1020, 1005, 990
17b	Ph	82	31.78 31.89	1.72 1.67	13.81 13.94	$C_8H_5K_2N_3O_5$	3160, 2850, 1500, 1480, 1440, 1440, 1410, 1370, 1300, 1270, 1215, 1180, 1150, 1120, 1090, 1010, 990, 930
17c	2-$NO_2C_6H_4$	86	27.61 27.74	1.09 1.16	16.03 16.18	$C_8H_4K_2N_4O_7$	3160, 1550, 1540, 1485, 1450, 1410, 1380, 1305, 1240, 1210, 1125, 1010, 940
17d	3-$NO_2C_6H_4$	83	27.56 27.74	1.11 1.16	16.30 16.18	$C_8H_4K_2N_4O_7$	3160, 1500, 1480, 1440, 1410, 1380, 1300, 1190, 1130, 1090, 1005
17e	4-$NO_2C_6H_4$	85	27.70 27.74	1.04 1.16	16.33 16.18	$C_8H_4K_2N_4O_7$	3170, 1500, 1480, 1410, 1350, 1340, 1300, 1280, 1220, 1180, 1120, 1090, 1000, 940
17f	4-BrC_6H_4	87	26.40 26.24	1.08 1.10	7.71 7.65	$C_8H_4BrK_2N_2O_5$	3150, 1490, 1420, 1340, 1300, 1285, 1205, 1140, 1030, 1005, 980, 920, 890
25b*	*p*-Phenylene	90	22.71 22.90	0.58 0.76	16.20 16.03	$C_{10}H_4K_4N_6O_{10}$	3140, 1552, 1492, 1384, 1368, 1236, 1188, 1132, 996, 936, 848, 828, 808, 752, 700

* ^{1}H NMR of compound **25b** in DMSO-d_6: δ 7.38 (s, 4 H, Ar).

py by an example of compound **17a**. It was found that pK_a of the dinitromethyl group is 2.23 and pK_a of the oxime group is 4.43 (pK_a of AcOH is 4.76). The ionization constants were calculated by the standard equations.[13]

Thus, we synthesized α-nitro oximes **16** as stable dipotassium salts **17** that could be used for the development of the synthetic method toward furoxans. If α-nitro oximes **16** are prone to ring closure, they should be isolated from the salts, and conditions for the cyclization could be found. Initially, we tried to acidify salt **17a** with dry HCl in diethyl ether in the hope that the resulting α-nitro oxime **16a** would not immediately transform from *aci*-form **16a´** into nitro compound but will undergo ring closure to 4-aryl-3-nitrofuroxan **18a** (Scheme 5). Nitrofuroxan **18a** was isolated, but in the yield of only 4%. Apparently, under selected conditions, the isomerization of *aci*-form **16a´** into nitro compound **16** occurred much faster than the ring closure to give furoxan **18a**. The existence of the *gem*-dinitromethyl group in the *aci*-form in the equilibrium with the nitro form have previously been shown by IR spectroscopy by the example of the solution of dinitromethane salt in concentrated sulfuric acid.[14] However, the replacement of HCl by H_2SO_4 resulted in the increase in the yield of furoxan **18a** up only to 14% (see Scheme 5).

Scheme 5

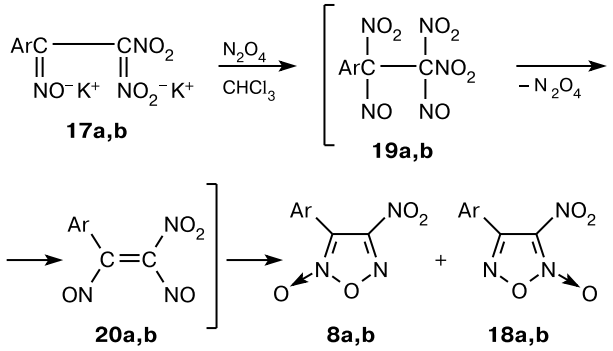


Ar = 4-MeO-3,5-$(NO_2)_2C_6H_2$

For the development of the synthetic pathways toward 4-aryl-3-nitrofuroxans **18**, nitrosation of salts **17** was studied. At first, N_2O_4 was used for nitrosation. The reaction was carried out in chloroform at 20 °C using salts **17a,b** as model compounds. In comparison with the reaction of salt **17a** with acids, this approach is more efficient, however, this reaction yielded a mixture of arylnitrofuroxan

isomers (**8a,b** and **18a,b**) in 30% total yield. Apparently, under these conditions nitration of the oxime moiety to give nitrosomethyl fragment as well as nitrosation of the dinitromethyl group to give dinitronitrosomethyl fragment take place. Intermediates **19** were converted into furoxans by elimination of N_2O_4 *via* dinitroethylenes **20** in non-regiospecific reaction, which furnished a mixture of isomeric furoxans **8a,b** and **18a,b** in the ratio 1 : 1 (Scheme 6).

Scheme 6

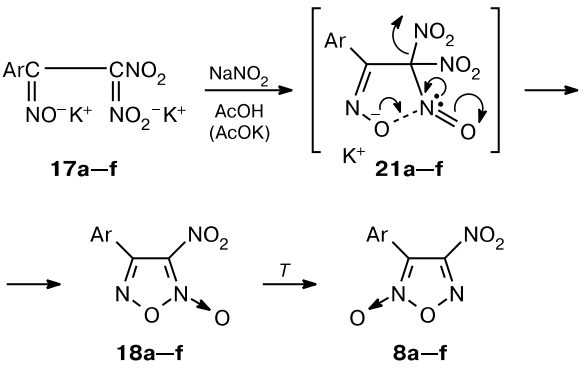


Ar = 4-MeO-3,5-$(NO_2)_2C_6H_2$ (**a**), Ph (**b**)

The use of $NaNO_2$ in glacial AcOH instead of N_2O_4 resulted in regiospecific nitrosation of salts **17**. Under these conditions, 4-aryl-3-nitrofuroxans **18** were exclusively obtained in significantly increased yields of 50—55%. Probably, under these conditions, the oxime group exists as the anion and the initial step of the reaction is nitrosation of the dinitromethyl anion to give intermediate **21**. Later, the anion of the oxime group attacks the nitroso group of the intermediate to result in furoxan ring closure with elimination of the NO_2 anion. The mechanistic pattern was refined by the use in the reaction of an additional amount of AcOK, which maintained the anionic form of the oxime fragment. Indeed, under these conditions the yield of furoxan **18a** increased to 80%; the yields of 3-nitrofuroxans **18b—f** also markedly increased. The resulting 3-nitrofuroxans **18a—f** underwent thermal isomerization into 4-nitrofuroxans **8a—f** in nearly quantitative yields (Scheme 7, Table 2).

The methoxy group of isomeric nitrofuroxans **8a** and **18a** with 4-MeO-3,5-$(NO_2)_2C_6H_2$ substituent was converted into NO_2 group. At first, the MeO group was replaced by the amino group to give the corresponding amino derivatives **18g** and **8g** (in the case of 3-nitro isomer **18a** ammonium hydrogencarbonate in a DMF—MeOH mixture was used, while 4-nitro isomer **8a** was treated with dry ammonia in chloroform, because the above-mentioned conditions resulted in partial replacement of the 4-nitro group with the MeO-group). The aromatic amino groups in isomers **18g** and **8g** were oxidized with perfluoroacetic acid or 85% H_2O_2 in conc. H_2SO_4 to give isomeric 3(4)-nitro-4(3)-(3,4,5-trinitrophenyl)furoxans **18h** and **8h**. The best yields (76—82%) were obtained using the latter oxidizing reagent (Scheme 8, see Table 2).

Scheme 7



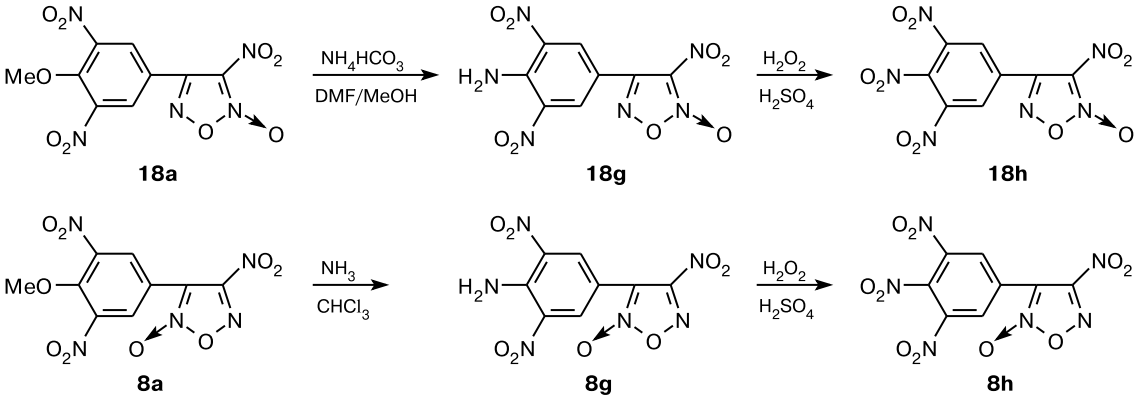
Ar = 4-MeO-3,5-$(NO_2)_2C_6H_2$ (**a**), Ph (**b**), 2-$NO_2C_6H_4$ (**c**), 3-$NO_2C_6H_4$ (**d**), 4-$NO_2C_6H_4$ (**e**), 4-BrC_6H_4 (**f**)

Synthesis of 3-nitorfuroxans **18** by nitrosation of dipotassium salts **17** is a hitherto unknown approach to the construction of the furoxan ring. The ^{15}N-labeled chloride **13f′** was synthesized using $^{15}NH_2OH \cdot HCl$; the corresponding 3- and 4-nitrofuroxans **18f′** and **8f′** were derived to confirm the involvement in the cyclization of the oxime group that formed in the reaction of arylhydroximoyl chloride **13** with dinitromethane sodium salt **14**. Data from ^{15}N and ^{13}C NMR spectroscopy using the $^{13}C—^{15}N$ coupling constant showed that the ^{15}N-label was incorporated completely in the resulting furoxans. (This part of the research will be presented as a separate publication.)

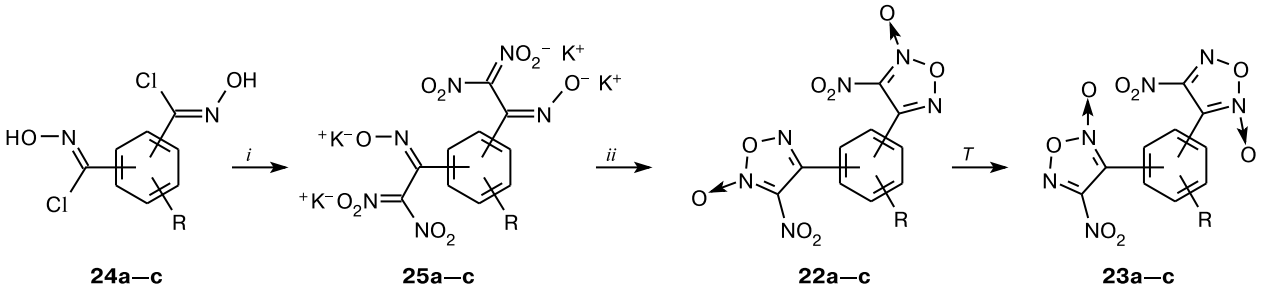
Synthetic approach toward arylnitrofuroxans **8** and **18** with one nitrofuroxan ring was extended to the synthesis of compounds bearing two nitrofuroxanyl moieties in the aromatic ring, 1,3- (**22a,c**) and 1,4-bis(3-nitrofuroxanyl)arenes (**22b**), and isomeric 1,3- (**23a,c**) and 1,4-bis-(4-nitrofuroxanyl)arenes **23b***. 3-Nitro isomers **22a—c** were obtained under conditions similar to those employed for the synthesis of 4-aryl-3-nitrofuroxans **18**. Reaction of bis(chlorides) of 1,3- and 1,4-aryl(bishydroximic)acids **24a—c** with dinitromethane sodium salt resulted in tetrapotassium salts **25a—c**. The structure of salt **25b** was confirmed by the data from IR and ^1H NMR spectroscopy. Due to sensitivity to the mechanical manipulations, no spectroscopic study of tetrapotassium salts **25a** and **25c** was carried out. Their formation was proved by the isolation of their 3-nitrofuroxan derivatives, which were obtained by *in situ* nitrosation of salts **25a** and **25c** with sodium nitrite in acetic acid. The yields of 1,3- and 1,4-bis-(3-nitrofuroxanyl)arenes **22a—c** are 42—56%. 3-Nitro isomers **22a—c** were thermally isomerized into 4-nitro isomers **23a—c** in high yields (Scheme 9, Tables 1—3).

* Brief communication, see Ref. 15.

Scheme 8



Scheme 9



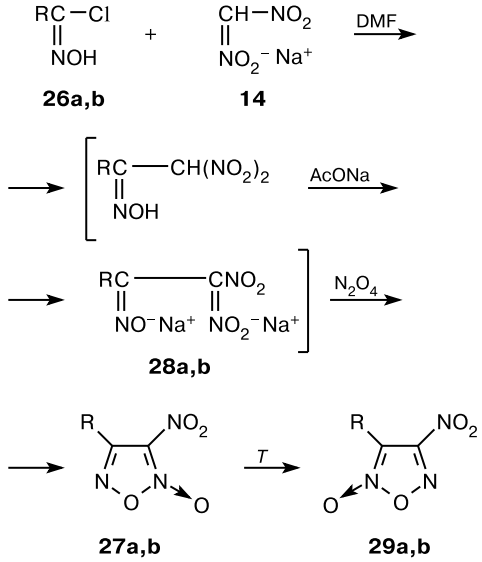
a: R = H, 1,3-isomer; **b:** R = H, 1,4-isomer; **c:** R = Me, 1,3-isomer

Reagent and conditions: *i*. 1) $NaCH(NO_2)_2$/DMF, 2) H_2SO_4/H_2O, 3) AcOK/MeOH; *ii*. $NaNO_2$, AcOH (AcOK).

The method developed for the synthesis of the isomeric 3(4)-aryl-4(3)-nitrofuroxans **8** and **18** is suitable for the preparation of isomeric nitrofuroxans with non-aromatic substituents, namely, COMe and CO_2Et. However, the procedure for the conversion of the hydroximoyl chlorides **26a,b** into 3-nitrofuroxans **27a,b** significantly differed from that for 4-aryl-3-nitrofuroxans **18**. It was found that dipotassium salts, similar to salts **17**, cannot be isolated from the reaction mixture of chlorides **26a,b** with 2 mol. equiv. of dinitromethane sodium salt **14**. Therefore, an excess of AcONa was added to the reaction mixture of compounds **26** and **14** yielding disodium salts **28a,b**, which underwent *in situ* nitrosation with N_2O_4. The yields of the resulting 3-nitrofuroxans **27a,b** (28—44%) were lower as compared with 4-aryl-3-nitrofuroxans **18**. However, the reaction proceeded regiospecifically furnishing exclusively 3-nitro isomers **27a,b**, which were thermally isomerized into 4-nitro isomers **29a,b** in nearly quantitative yields (Scheme 10, see Tables 2 and 3).

In summary, a convenient general method for the synthesis of isomeric 3- and 4-nitorfuroxans bearing aromatic or functional substituents at the C(4) (C(3)) atom of the

Scheme 10



R = COMe (**a**), CO_2Et (**b**)

Table 2. Yields and selected physicochemical parameters of synthesized 3- (**18a—h**, **22a—c**, **27a,b**) and 4-nitrofuroxans (**8a—h**, **23a—c**, **29a,b**)

Compound	Yield (%)	M.p./°C [(b.p./°C)/*p*/Torr]	R_f (eluent)	Found / Calculated (%)			Molecular formula
				C	H	N	
18a	68	149—150	0.43 ($CHCl_3$)	33.10 / 33.04	1.51 / 1.54	21.47 / 21.41	$C_9H_5N_5O_9$
8a	80	126—127	0.43 ($CHCl_3$)	33.15 / 33.04	1.46 / 1.54	21.27 / 21.41	$C_9H_5N_5O_9$
18b	74	109—110 (106—107)[5]	0.66 (C_6H_{14}—CH_2Cl_2 (3 : 1))	—	—	—	—
8b	85	97—98 (97—97.5)[5]	0.63 ($CHCl_3$)	—	—	—	—
18c	78	127—128	0.48 ($CHCl_3$)	38.00 / 38.11	1.67 / 1.60	22.10 / 22.22	$C_8H_4N_4O_6$
8c	78	91—92	0.48 ($CHCl_3$)	38.02 / 38.11	1.71 / 1.60	22.05 / 22.22	$C_8H_4N_4O_6$
18d	79	117—118	0.45 ($CHCl_3$)	38.30 / 38.11	1.72 / 1.60	22.33 / 22.22	$C_8H_4N_4O_6$
8d	82	92—93	0.45 ($CHCl_3$)	38.20 / 38.11	1.63 / 1.60	22.07 / 22.22	$C_8H_4N_4O_6$
18e	80	132—133	0.50 ($CHCl_3$)	38.17 / 38.11	1.62 / 1.60	22.17 / 22.22	$C_8H_4N_4O_6$
8e	80	101—102	0.50 ($CHCl_3$)	38.27 / 38.11	1.70 / 1.60	22.20 / 22.22	$C_8H_4N_4O_6$
18f	83	80—81	0.46 ($CHCl_3$)	33.70 / 33.59	1.35 / 1.41	14.78 / 14.69	$C_8H_4BrN_3O_4$
8f	87	56—57	0.46 ($CHCl_3$)	33.77 / 33.59	1.40 / 1.41	14.66 / 14.69	$C_8H_4BrN_3O_4$
18g	76	194—195	0.27 ($CHCl_3$)	30.66 / 30.78	1.34 / 1.29	27.07 / 26.92	$C_8H_4N_6O_8$
8g	88	214—215	0.27 ($CHCl_3$)	30.70 / 30.78	1.21 / 1.29	26.95 / 26.92	$C_8H_4N_6O_8$
18h	76	163—164	0.25 ($CHCl_3$)	28.03 / 28.08	0.41 / 0.59	24.50 / 24.56	$C_8H_2N_6O_{10}$
8h	82	192	0.25 ($CHCl_3$)	27.83 / 28.08	0.43 / 0.59	24.41 / 24.56	$C_8H_2N_6O_{10}$
22a	56	139—140	0.27 (CCl_4—EtOAc (1 : 1))	35.61 / 35.73	1.21 / 1.20	24.85 / 25.00	$C_{10}H_4N_6O_8$
23a	91	142—144	0.21 (CCl_4—$CHCl_3$ (1 : 1))	35.64 / 35.73	1.28 / 1.20	24.97 / 25.00	$C_{10}H_4N_6O_8$
22b	45	180—203*	0.31 (CCl_4—EtOAc (1 : 1))	35.69 / 35.73	1.18 / 1.20	25.01 / 25.00	$C_{10}H_4N_6O_8$
23b	90	212—214	0.20 (CCl_4—$CHCl_3$ (1 : 1))	35.84 / 35.73	1.22 / 1.20	25.05 / 25.00	$C_{10}H_4N_6O_8$
22c	42	122—124	0.20 (CCl_4—$CHCl_3$ (1 : 1))	37.59 / 37.73	1.72 / 1.73	24.13 / 24.00	$C_{11}H_6N_6O_8$
23c	70	138—141	0.20 (CCl_4—$CHCl_3$ (1 : 1))	37.60 / 37.73	1.81 / 1.73	24.07 / 24.00	$C_{11}H_6N_6O_8$
27a	28	Oil	0.44 ($CHCl_3$)	27.67 / 27.75	1.76 / 1.71	24.32 / 24.40	$C_4H_3N_3O_5$
29a	94	[72—74/1]	0.71 (C_6H_{14}—EtOAc (3 : 1))	27.54 / 27.75	1.65 / 1.71	24.56 / 24.40	$C_4H_3N_3O_5$
27b	44	Heavy oil	0.60 ($CHCl_3$)	29.40 / 29.57	2.41 / 2.48	20.58 / 20.69	$C_5H_5N_3O_6$
29b	92	[58/0.3]	0.60 ($CHCl_3$)	29.72 / 29.57	2.43 / 2.48	20.89 / 20.69	$C_5H_5N_3O_6$

* Melting of 3-nitro isomer **22b** resulted in 4-nitro isomer **23b** with higher melting point.

Table 3. ^{1}H, ^{13}C, ^{14}N NMR, IR, and MS spectral data of synthesized 3- (**18a—h**, **22a—c**, **27a,b**) and 4-nitrofuroxans (**8a—h**, **23a—c**, **29a,b**)

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz) [MS, *m/z* (I_{rel} (%))]	^{3}C NMR, δ [^{14}N NMR, δ, $\Delta\nu_{1/2}$/Hz]
18a	3100, 1649, 1570, 1555, 1541, 1521, 1480, 1450, 1422, 1405, 1352, 1121, 1060, 1021, 978, 920, 860	4.08* (s, 3 H, MeO); 8.70 (s, 2 H, Ar) [327 $[M]^+$ (16), 311 (3), 297 (10), 281 (31), 267 (3), 251 (100), 222 (21)]	64.8* (MeO), 120.8 (C(1), Ar), 131.0 (C(2), C(6), Ar), 140.4 (C(4), Ar), 144.5 (C(3), C(5), Ar), 127.8 (C(3) in the furoxan ring), 149.4 (C(4) in the furoxan ring)
8a	3100, 1639, 1590, 1580, 1571, 1555, 1541, 1526, 1510, 1490, 1458, 1429, 1411, 1357, 1300, 1280, 1265, 1170, 1120, 1031, 980, 919, 890, 842	4.10* (s, 3 H, MeO); 8.73 (s, 2 H, Ar) [327 $[M]^+$ (9), 311 (2), 297 (8), 281 (20), 267 (3), 251 (100), 223 (88)]	—
18c	3120, 3080, 1655, 1640, 1622, 1539, 1527, 1510, 1458, 1428, 1355, 1150, 1018, 860, 853, 800	8.00* (m, 3 H, Ar); 8.45 (d, 1 H, Ar) [252 $[M]^+$ (13), 222 (68), 206 (100), 160 (15), 130 (17), 106 (34)]	119.6* (C(1), Ar), 146.9 (C(2), Ar), 125.2, 133.2, 133.4, 135.2 (C, Ar), 127.2 (C(3) in the furoxan ring), 150.1 (C(4) in the furoxan ring)
8c	3100, 1649, 1638, 1624, 1589, 1580, 1572, 1540, 1510, 1490, 1460, 1371, 1352, 1320, 1292, 1175, 1140, 1082, 1050, 1010, 991, 970, 860	7.96* (m, 3 H, Ar); 8.35 (d, 1 H, Ar) [176 (15), 148 (44), 134 (30), 102 (100)]	118.8* (C(1), Ar), 142.2 (C(2), Ar), 123.4, 135.3, 135.9, 136.2 (C, Ar), 109.2 (C(3) in the furoxan ring), 158.2 (C(4) in the furoxan ring)
18d	3120, 1590, 1520, 1460, 1410, 1355, 1209, 1110, 1030, 1018, 1005, 920, 875, 860, 820, 800	8.35* (m, 3 H, Ar); 8.50 (s, 1 H, Ar) [252 $[M]^+$ (24), 222 (63), 176 (90), 148 (59), 130 (36), 102 (100)]	—
8d	3110, 1630, 1572, 1490, 1378, 1360, 1315, 1278, 1150, 1100, 1018, 1020, 909, 880, 850, 812	8.35* (m, 3 H, Ar); 8.63 (s, 1 H, Ar) [252 $[M]^+$ (3), 222 (50), 176 (100), 148 (60), 130 (26), 118 (4), 102 (90)]	—
18e	3120, 1650, 1618, 1542, 1525, 1442, 1404, 1355, 1320, 1295, 1201, 1118, 1020, 990, 859	7.98*, 8.36 (both d, 4 H, Ar, ^{3}J = 9.6) [252 $[M]^+$ (39), 236 (5), 222 (100), 206 (14), 176 (100), 160 (12)]	130.9* (C(1), Ar), 123.9 (C(3), C(5), Ar), 131.3 (C(2), C(6), Ar), 149.6 (C(4), Ar), 128.2 (C(3) in the furoxan ring), 151.5 (C(4) in the furoxan ring)
8e	3130, 1630, 1580, 1540, 1520, 1498, 1410, 1305, 1280, 1079, 860,800	7.98*, 8.36 (both d, 4 H, Ar, ^{3}J = 9.6) [194 (28), 176 (3), 148 (60), 118 (70), 102 (100)]	—
18f	3090, 1624, 1540, 1508, 1472, 1428, 1388, 1332, 1276, 1256, 1192, 1072, 1016, 1008, 980, 964, 852, 824, 792, 752, 724, 712, 672	7.58****, 7.71 (both d, 4 H, Ar, ^{3}J = 8.2)	122.7**** (C(1), Ar), 127.2 (C(4), Ar), 130.5 (C(3), C(5), Ar), 131.7 (C(2), C(6), Ar), 126.5 (C(3) in the furoxan ring), 150.5 (C(4) in the furoxan ring) [−38.7 NO_2****, $\Delta\nu_{1/2}$ = 11]
8f	3088, 1612, 1572, 1504, 1480, 1396, 1360, 1304, 1284, 1124, 1072, 1012, 984, 828, 800, 756, 744, 708, 692	7.47****, 7.68 (both d, 4 H, Ar, ^{3}J = 8.4)	118.3**** (C(1), Ar), 126.7 (C(4), Ar), 130.4 (C(3), C(5), Ar), 132.4 (C(2), C(6), Ar), 108.8 (C(3) in the furoxan ring), 157.7 (C(4) in the furoxan ring) [−34.4 NO_2****, $\Delta\nu_{1/2}$ = 36]
18g	3475, 3370, 3090, 1650, 1641, 1589, 1555, 1542, 1510, 1454, 1410, 1371, 1360, 1349, 1278, 1225, 1120, 1060, 1022, 939, 910, 860	3.15** (s, 2 H, NH_2); 9.06 (s, 2 H, Ar) [312 $[M]^+$ (15), 296 (3), 266 (21), 236 (100), 208 (28), 194 (15), 190 (9), 174 (6)]	—
8g	3470, 3362, 3110, 1658, 1632, 1575, 1560, 1520, 1510, 1465, 1412, 1370, 1348, 1258, 1082, 1035, 921, 905, 850	3.15* (s, 2 H, NH_2); 8.90 (s, 2 H, Ar) [312 $[M]^+$ (6), 296 (2), 266 (7), 252 (9), 236 (42), 208 (100)]	—

(*to be continued*)

Table 3 (*continued*)

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz) [MS, *m*/*z* (*I*$_{rel}$ (%))]	^{3}C NMR, δ [^{14}N NMR, δ, Δν$_{1/2}$/Hz]
18h	3110, 1649, 1629, 1590, 1571, 1555, 1510, 1465, 1430, 1408, 1364, 1350, 1290, 1270, 1160, 1094, 1060, 1020, 933, 914, 859, 849	8.92** (s, 2 H, Ar) [342 $[M]^+$ (12), 326 (2), 312 (61), 296 (26), 266 (100), 174 (5)]	—
8h	3110, 1648, 1590, 1580, 1570, 1560, 1530, 1485, 1445, 1410, 1365, 1350, 1311, 1295, 1185, 1152, 1090, 1080, 1030, 935, 912, 848	9.42* (s, 2 H, Ar) [342 $[M]^+$ (31), 326 (3), 312 (61), 296 (36), 266 (100), 174 (5)]	—
22a	3096, 1632, 1544, 1468, 1448, 1392, 1264, 1220, 1172, 1040, 1000, 984, 856, 808, 756, 720	7.92*** (t, 1 H, C(5), Ar, ^3J = 7.9); 8.15 (d, 2 H, C(4),(6), Ar, ^3J = 7.9); 8.28 (s, 1 H, C(2), Ar)	125.4*** (C(1), C(3), Ar), 129.0, 129.8 (C(2), C(5), Ar), 132.2 (C(4), C(6), Ar), 127.3 (C(3) in the furoxan ring), 151.4 (C(4) in the furoxan ring) [−38.4 NO_2****, Δν$_{1/2}$ = 18]
23a	1632, 1568, 1512, 1484, 1372, 1296, 1268, 1144, 1116, 1072, 1028, 1000, 988, 896, 828, 796, 792, 704	7.92*** (t, 1 H, C(5), Ar, ^3J = 7.9); 8.09 (d, 2 H, C(4),(6), Ar), ^3J = 7.9; 8.22 (s, 1 H, C(2), Ar)	121.9*** (C(1), C(3), Ar), 129.5, 131.04 (C(2), C(5), Ar), 132.8 (C(4), C(6), Ar), 110.0 (C(3) in the furoxan ring), 158.9 (C(4) in the furoxan ring) [−34.9 NO_2****, Δν$_{1/2}$ = 37]
22b	3112, 2800, 2332, 1632, 1548, 1436, 1340, 1200, 1012, 984, 844, 792, 712	8.13*** (s, 4 H, Ar)	129.8*** (C(1), C(4), Ar), 129.8 (C(2), C(3), C(5), C(6), Ar), 128.2 (C(3) in the furoxan ring), 151.8 (C(4) in the furoxan ring) [−38.3 NO_2***, Δν$_{1/2}$ = 15]
23b	1624, 1612, 1536, 1488, 1408, 1364, 1292, 1268, 1132, 1076, 992, 840, 792	8.09*** (s, 4 H, Ar)	123.9*** (C(1), C(4), Ar), 130.2 (C(2), C(3),C(5), C(6), Ar), 110.1 (C(3) in the furoxan ring), 158.9 (C(4) in the furoxan ring) [−34.9 NO_2***, Δν$_{1/2}$ = 38]
22c	2932, 2876, 1648, 1628, 1536, 1468, 1412, 1348, 1260, 1172, 1076, 880, 844, 776	2.60*** (s, 3 H, Me); 7.97 (s, 2 H, Ar); 8.08 (s, 1 H, Ar)	20.3*** (Me), 127.4 (C(5), Ar), 132.9 (C(4), C(6), Ar), 139.7 (C(2), Ar), 125.7 (C(3) in the furoxan ring), 151.8 (C(4) in the furoxan ring) [−38.4 NO_2***, Δν$_{1/2}$ = 18]
23c	2920, 1624, 1560, 1504, 1356, 1304, 1272, 1136, 1076, 1048, 1016, 1000, 872, 832, 776, 744, 704	2.56*** (s, 3 H, Me); 7.88 (s, 2 H, Ar); 7.99 (s, 1 H, Ar)	20.3*** (Me), 121.8 (C(1), C(3), Ar), 128.2 (C(2), Ar), 133.1 (C(4), C(6), Ar), 110.0 (C(3) in the furoxan ring), 158.9 (C(4) in the furoxan ring) [−35.1 NO_2***, Δν$_{1/2}$ = 40]
27a	2930, 2820, 1725, 1640, 1540, 1360	2.77**** (s, 3 H, Me)	26.6**** (Me), 167.2 (CO), 126.3 (C(3) in the furoxan ring), 149.9 (C(4) in the furoxan ring) [−40.6 NO_2****, Δν$_{1/2}$ = 17]
29a	2940, 1730, 1640, 1520,1350	2.63**** (s, 3 H, Me)	27.0**** (Me), 108.8 (C(3) in the furoxan ring), 158.1 (C(4) in the furoxan ring), 186.8 (CO)
27b	2990, 2940, 2915, 2845, 1755, 1650, 1575, 1550, 1350	1.42**** (t, 3 H, Me); 4.48 (q, 2 H, CH_2)	14.3**** (Me), 65.20 (CH_2), 156.2 (CO), 127.0 (C(3) in the furoxan ring), 145.8 (C(4) in the furoxan ring) [−40.3 NO_2****, Δν$_{1/2}$ = 18]
29b	3000, 2955, 2925, 1765, 1665, 1580, 1325	1.36**** (t, 3 H, Me); 4.51 (q, 2 H, CH_2)	14.0**** (Me), 64.9 (CH_2), 154.4 (CO), 103.8 (C(3) in the furoxan ring), 157.9 (C(4) in the furoxan ring) [−35.3 NO_2****, Δν$_{1/2}$ = 35]

The NMR spectra were recorded in: * $(CD_3)_2SO$, ** CD_3CN, *** $(CD_3)_2CO$, **** $CDCl_3$.

furoxan ring, including the compounds with two furoxanyl rings in one aromatic core was developed. This method could be extended to the synthesis of other isomeric nitrofuroxans. The yields and physicochemical and spectral characteristics of the compounds synthesized are given in Tables 1—3. The chemical shifts of the signals for the $C(3)NO_2$ or $C(4)NO_2$ groups in the ^{13}C or ^{15}N NMR spectra are the characteristic parameters for the assignment of the compound to the $C(3)NO_2$ or $C(4)NO_2$ isomer. All signals for the $C(3)NO_2$ groups appeared in higher fields as compared with the corresponding signals for the $C(4)NO_2$ groups (see Table 2), while $\Delta\nu_{1/2}$ value of 3-nitro isomers is nearly twofold smaller than that of 4-nitro isomers. We have previously established similar patterns for phenylnitrofuroxans.[5]

Experimental

The IR spectra were measured on a UR-20 spectrometer in KBr pellets. The NMR spectra were obtained on Bruker WM-250 (^1H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz; ^{14}N, 21.5 MHz) instruments. Chemical shifts in the ^1H and ^{13}C NMR spectra are given relative to Me_4Si (internal standard), relative to $MeNO_2$ (external standard) in the ^{14}N NMR spectra. Mass spectra were recorded on a Varian MAT CH 6 (70 eV) spectrometer. TLC was carried out on Silufol UV-254 plates, visualization with UV light.

1-Aryl-1-hydroxyimino-2,2-dinitroethane dipotassium salts 17a—f and 1,3- and 1,4-bis(1-hydroxyimino-2,2-dinitroethyl)-arene tetrapotassium salts 25a—c (general procedure). A stirred solution of dinitromethane sodium salt **14** (10.5 g, 82 mmol) was cooled to 10 °C, and hydroximoyl chloride **13** (41 mmol) (or 1,3- or 1,4-dihydroximoyl chlorides **24a—c** (20.5 mmol)) was added. The reaction mixture was stirred for 2 h, kept at 0—5 °C for 15—24 h, and then stirred at 15—20 °C for 3—4 h. The mixture was poured into cold water (400 mL) and extracted with $CHCl_3$ (3×100 mL). The aqueous layer was cooled to 8—10 °C, carefully acidified to pH 1—2 with H_2SO_4, and extracted with diethyl ether (3×150 mL). The organic layer was dried with $MgSO_4$ and the solution was concentrated *in vacuo* at ≤20 °C to 60—80 mL, then MeOH (40 mL) was added and diethyl ether completely removed *in vacuo* (~10 min). The residue was cooled to 10 °C and a solution of anhydrous AcOK (20 g) in MeOH (50 mL) was added gradually with stirring. The resulting thick suspension was stirred for 1 h and cooled to 8—10 °C. The product was filtered off, washed on the filter with MeOH (3×5 mL) and diethyl ether (3×20 mL). The resulting potassium salts were dried in air.

4-(4-Methoxy-3,5-dinitrophenyl)-3-nitrofuroxan (18a). ***A.*** To a suspension of 1-hydroxyimino-1-(4-methoxy-3,5-dinitrophenyl)-2,2-dinitroethane dipotassium salt (**17a**) (3.99 g, 9.5 mmol, dried over P_2O_5 in a vacuum desiccator prior to use) in anhydrous diethyl ether (60 mL), a saturated solution of hydrogen chloride in diethyl ether (50 mL) was added. The reaction mixture was stirred for 10 min, then the solvent was decanted, and diethyl ether (50 mL) was added to the precipitate. This procedure was repeated three more times. The combined ethereal solution was washed with 5% aqueous $NaHCO_3$ (3×100 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Compound **18a** was obtained in the yield of 0.124 g (4%).

B. To a stirred 98% H_2SO_4 (40 mL), salt **17a** (1.00 g, 2.4 mmol) was carefully added portionwise at 0—5 °C (flashing could be observed). The resulting solution was heated to 60—70 °C and stirred for 30 min. After cooling to room temperature, the mixture was poured onto ice (100 g) and extracted with chloroform (3×20 mL); the combined organics was washed with 5% aqueous $NaHCO_3$ (3×50 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Compound **18a** was obtained in the yield of 0.11 g (14%).

Synthesis of 4-substituted 3-nitrofuroxans 18a,b and 3-substituted 4-nitrofuroxans 8a,b by reaction of 1-aryl-1-hydroxyimino-2,2-dinitroethane dipotassium salts 17a,b with N_2O_4 (general procedure). A suspension of dipotassium salts **17a,b** (4.75 mmol) in chloroform (80 mL) was cooled to 5—10 °C and N_2O_4 (0.46 g, 5 mmol) was added dropwise with stirring. After being stirred for 20 min, the reaction mixture was washed with 5% aqueous $NaHCO_3$ (3×50 mL), dried with $MgSO_4$, and concentrated *in vacuo* to 10—20 mL. The residue was passed through a silica gel pad (40/100 mesh, 2 cm), the sorbent was washed with chloroform. Removal of the solvent afforded mixture of compounds **18a,b** and **8a,b**.

Synthesis of 4-substituted 3-nitrofuroxans 18a—f and 1,3- and 1,4-bis(3-nitrofuroxanyl)arenes 22a—c by reaction of 1-aryl-1-hydroxyimino-2,2-dinitroethane dipotassium salts 17a—f and 1,3- and 1,4-bis(1-hydroxyimino-2,2-dinitro)arene tetrapotassium salts 25a—c with $NaNO_2$ in AcOH (general procedure). To a stirred mixture of glacial AcOH (60 mL) and AcOK (6.8 g, 70 mmol) at 15—20 °C (ice bath cooling), compound **17a—e** (23 mmol) (or compound **25a—c** (11.5 mmol) and $NaNO_2$ (4.0 g, 58 mmol) were added alternately in small portions. The reaction mixture was stirred for 15 min, heated to 50 °C, and stirred for 20—30 min with portionwise addition of water (150 mL). The white precipitate that formed was filtered off, washed with dilute AcOH, water, and hexane, and dried in air.

Isomerization of 4-substituted 3-nitrofuroxans 18a—f into 3-substituted 4-nitrofuroxans 8a—f, and of 1,3- and 1,4-bis-(3-nitrofuroxanyl)arenes 22a—c into bis(4-nitrofuroxanyl)arenes 23a—c (general procedure). A suspension of compounds **18a—f** (20 mmol) (or compounds **22a—c** (10 mmol)) in toluene (30 mL) was refluxed for 2.5—3 h. Toluene was removed *in vacuo*, the product was recrystallized from AcOH and dried in air.

4-(4-Amino-3,5-dinitrophenyl)-3-nitrofuroxan (18g). A stirred solution of 4-(4-methoxy-3,5-dinitrophenyl)-3-nitrofuroxan **18a** (10 g, 30.6 mmol) in a mixture of DMF (30 mL) and MeOH (10 mL) was heated to 35—40 °C, and NH_4HCO_3 (3.16 g, 40 mmol) was added portionwise (by portions of 300—500 mg) over a period of 30 min. The mixture was stirred until full conversion of the starting compound was achieved (TLC monitoring), then a mixture of water (30 mL), MeOH (30 mL) and AcOH (5 mL) was added over a period of 30 min. The yellow precipitate that formed was filtered off, washed with MeOH (2×5 mL), water (2×5 mL), and hexane (3×10 mL), and dried in air.

3-(4-Amino-3,5-dinitrophenyl)-4-nitrofuroxan (8g). Dry ammonia was slowly passed through a solution of 3-(4-methoxy-3,5-dinitrophenyl)-4-nitrofuroxan (**8a**) (2.6 g, 8 mmol) in anhydrous MeOH (180 mL) at 25—30 °C. In the course of reaction, the mixture acquired yellow color and the precipitate formed. The reaction mixture was stirred until complete consumption of the starting compound (TLC monitoring), cooled to −5—0 °C, the precipitate that formed was filtered off, washed with chloroform (2×3 mL), and dried in air.

4-(3,4,5-Trinitrophenyl)-3-nitrofuroxan (18h) and 3-(3,4,5-trinitrophenyl)-4-nitrofuroxan (8h). A solution of 85% H_2O_2 (2 mL) in conc. H_2SO_4 (28 mL) was cooled to −5 °C, and 4-(4-amino-3,5-dinitrophenyl)-3-nitrofuroxan **18g** or 3-(4-amino-3,5-dinitrophenyl)-4-nitrofuroxan **8g** (1.25 g, 4 mmol) was added with stirring. The reaction mixture was stirred at 30—35 °C for 1 h (until gas evolution ceased and yellow color of the reaction mixture disappeared). The greenish precipitate that formed was filtered off, washed with 92%, 50%, and 20% aqueous H_2SO_4 (2×5 mL), water (2×3 mL), hexane (3×5 mL), and dried over P_2O_5 in a vacuum disiccator. The dry product was recrystallized from 100% HNO_3.

4-Acetyl-3-nitrofuroxan (27a) and ethyl 3-nitrofuroxan-4-carboxylate (27b). To a solution of dinitromethane sodium salt **14** (6.74 g, 52 mmol) in anhydrous DMF (50 mL) acethydroximoyl chloride **26a** (3.2 g, 26 mmol) or ethoxyhydroximoyl chloride **26b** (4.0 g, 26 mmol) was added at −5—0 °C. The reaction mixture was stirred for 30 min, kept at 2—5 °C for 48 h, anhydrous AcONa (8.6 g, 105 mmol) was added, and stirring was continued for 30 min; then a solution of N_2O_4 (12 g, 130 mmol) in CCl_4 (15 mL) was added dropwise at 0—5 °C. The reaction mixture was stirred at 10—15 °C for 1 h and poured into cold water (300 mL). The resulting mixture was extracted with CCl_4 (5×100 mL), the combined organics was washed with 0.5% aqueous $NaHCO_3$ 15 (mL), water (3×100 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo* at ≤30 °C.

Isomerization of 4-acetyl-3-nitrofuroxan (27a) and ethyl 3-nitrofuroxan-4-carboxylate (27b) into 3-acetyl-4-nitrofuroxan (29a) and ethyl 4-nitrofuroxan-3-carboxylate (29b) was achieved by heating compound **27a** (1 g, 5.8 mmol) or compound **27b** (1 g, 5 mmol) on a water bath for 30 min.

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References

1. L. I. Khmel´nitskii, S. S. Novikov, T. I. Godovikova, *Khimiya furoksanov: stroenie i sintez* [*Chemistry of furoxans: structure and synthesis*], 2nd ed., Nauka, Moscow, 1996, 383 pp. (in Russian).
2. N. N. Makhova, I. V. Ovchinnikov, A. S. Kulikov, S. I. Molotov, E. L. Baryshnikova, *Pure Appl. Chem.*, 2004, **76**, 1691.
3. A. Ya. Kots, M. A. Grafov, Yu. V. Khropov, V. L. Betin, N. N. Belushkina, O. G. Busygina, M. Yu. Yazykova, I. V. Ovchinnikov, A. S. Kulikov, N. N. Makhova, N. A. Medvedeva, T. V. Bulargina, I. S. Severina, *Brit. J. Pharm.*, 2000, **129**, 1163.
4. I. V. Ovchinnikov, A. S. Kulikov, N. N. Makhova, P. Tosco, A. Di-Stilo, R. Fruttero, A. Gasco, *Il Farmaco*, 2003, **58**, 677.
5. N. N. Makhova, I. V. Ovchinnikov, B. N. Khasapov, L. I. Khmel´nitskii, *Izv. Akad. Nauk SSSR*, *Ser. Khim.,* 1982, 646 [*Bull. Acad. Sci. USSR*, *Div. Chem. Sci.* (*Engl. Transl.*), 1982, **31**, 583].
6. V. G. Dubonos, I. V. Ovchinnikov, N. N. Makhova, L. I. Khmel´nitskii, *Mendeleev Commun.*, 2002, 120.
7. A. Angeli, *Gazz. Chim. Ital.*, 1892, **22**, 325.
8. H. Wieland, *Liebigs Ann. Chem.*, 1903, **329**, 225.
9. D. Klamann, W. Koser, P. Weyerstahl, M. Fligge, *Chem. Ber.*, 1965, **98**, 1831.
10. J. Crosby, R. M. Paton, R. A. C. Rennie, Pat. 1435894 (England), appl. 1972, publ. 1976; Pat. 2336403 (Bundesrepublik Deutschland), appl. 1972, publ. 1974; *Chem. Abstr.*, 1974, **81**, 49257a.
11. J. Crosby, R. M. Paton, R. A. C. Rennie, Pat. 1474692 (England), appl. 1973, publ. 1977; Pat. 2424700 (Bundesrepublik Deutschland), appl. 1973, publ. 1974; *Chem. Abstr.*, 1976, **84**, 44067r.
12. N. N. Makhova, V. G. Dubonos, A. N. Blinnikov, I. V. Ovchinnikov, L. I. Khmel´nitskii, *Zh. Org. Khim.*, 1997, **33**, 1216 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 1997, **33**].
13. L. P. Hammett, *Physical Organic Chemistry*, 2nd ed., McGraw Hill, New York, 1970, 505 pp.
14. G. I. Oleneva, A. I. Ivanov, V. A. Shlyapochnikov, S. S. Novikov, *Izv. Akad. Nauk SSSR*, *Ser. Khim.*, 1972, 638 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1972, **21**].
15. I. V. Ovchinnikov, A. O. Finogenov, M. A. Epishina, Yu. A. Strelenko, N. N. Makhova, *Mendeleev Commun.*, 2009, **19**, 217.

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