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SYNTHESIS AND NUCLEOPHILIC SUBSTITUTION REACTIONS OF 3,4-DINITROFUROXAN

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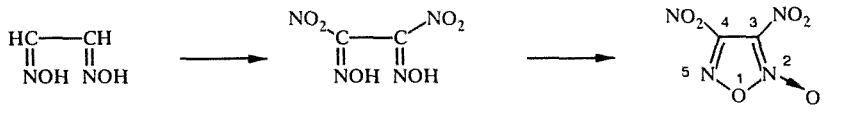
3,4-Dinitrofuroxan and 3-nitrofuroxans derived from it by functional group substitution at position 4 have been synthesized for the first time.

Fully nitrated heterocyclic compounds have previously been unknown and the question of their existence, or more accurately, their stability, remains unanswered. These compounds could, however, prove to be of interest not just from the theoretical standpoint, but from the point of view of possible applications in synthesis. One of the nitro groups in their structure should readily undergo nucleophilic substitution through activation by the other nitro groups to yield a whole range of substances. The subject of this report, 3,4-dinitrofuroxan (I), falls into just this category of compounds.

Since amino group oxidation, one of the commonest methods of incorporating nitro groups into aromatic and heterocyclic systems, cannot be used to obtain furoxan I (as the corresponding amino derivatives do not exist), we decided to construct its ring from a compound containing 2 nitro groups, namely nitroglyoxime II. We obtained the latter by nitrating glyoxime with 25% nitric acid in ether, then converting the intermediate product into dinitrofuroxan I by oxidizing with dinitrogen tetroxide in carbon tetrachloride (see Scheme 1 below).

Scheme 1



II I

Brief details of the synthesis and properties of I were reported by the present authors in a previous communication [1].

Furoxan I is a labile liquid with a slight yellowish hue and a pungent odor. It gradually decomposes at room temperature, but can be stored for long periods unchanged at −15 to −20°C. This compound is explosive and requires a good deal of care in handling. It is relatively stable in acidic media and sensitive to bases; it dissolves readily in most organic solvents, but decomposes in acetone, dimethylformamide, and dimethylsulfoxide.

It is well known that in mononitrofuroxans the nitro group at both position 3 [2] and position 4 [2-6] can be replaced by a nucleophile, but the relative capacity of these groups for substitution has remained an unanswered question. To this end dinitrofuroxan I was considered the most suitable compound with which to investigate the problem. We demonstrated that in dinitrofuroxan the nitro group located at position 4 is the first to react, the second nitro group being substituted only when acted upon by strong nucleophiles. Thus, furoxan I constitutes a convenient starting compound for synthesizing previously inaccessible 3-nitrofuroxans with functional groups at position 4 (see Scheme 2 at top of the following page).

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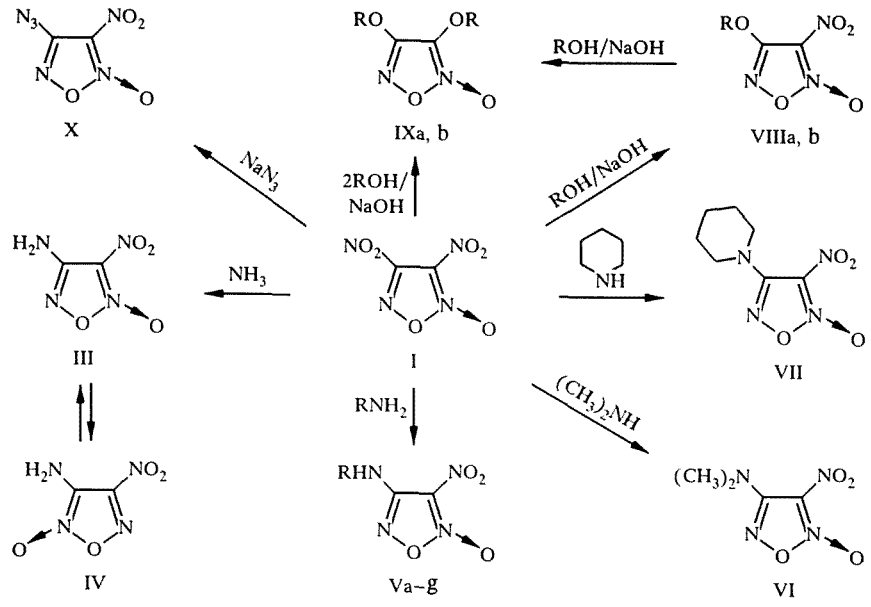
Scheme 2



V, VIII, IX a R = CH_3, b R = C_2H_5, c R = C_3H_7, d R = C_6H_5, e R = $C_6H_4CH_2$, f R = CH_2CH_2OH, g R = $NCCH_2CH_2$

Compound I reacted with ammonia gas to afford 4-amino-3-nitrofuroxan (III). When solutions of the latter in organic solvents were kept at 18-20°C, an equilibrium system of isomers was produced which did not change its composition with time and contained, according to ^{14}N NMR spectroscopy, up to 30% of 3-amino-4-nitrofuroxan (IV).

The action of primary and secondary amines of various structures on I yielded the corresponding 3-nitro substituted products: 3-nitro-4(R-amino)furoxans (Va-g), 4-dimethylamino-3-nitrofuroxan (VI) and 3-nitro-4-piperidylfuroxan (VII).

In the reactions outlined above dinitrofuroxan I was not isolated from organic solvent solution on synthesis, but was reacted immediately with ammonia or amines at a temperature below 0°C. The second component was added until compound I was no longer present in the reaction mixture, this point being ascertained by TLC monitoring.

Temperature and nucleophilic reagent quantity play a significant role in these reactions: decomposition of the initial furoxan was observed if the temperature was raised or an excess of nucleophile was employed.

When compound I was reacted with alcohols in the presence of alkali with a 1:1 molar ratio of (I):alkali, 4-alkoxy-3-nitrofuroxans (VII) resulted. Using a twofold excess of alkali produced dialkoxyfuroxans IX, which can also be obtained from VIII.

Furoxan I reacted with sodium azide both in glacial acetic acid and methanol, but in the latter case the yield of 4-azido-3-nitrofuroxan (X) was almost halved.

Despite numerous attempts it proved impossible to replace the nitro group in furoxan I with a nucleophile when the compound was reacted with either p-nitroaniline or dinitromethane sodium salt. This can be explained by the weak nucleophilic capacity of these compounds.

One of the factors that affects the nucleophilic substitution reaction rate is the size of the positive charge on the carbon atom under attack. Quantum chemical computations of the electronic structure of compound I made using the CNDO/2 method showed that there is a marked difference in the full charges on the carbon atoms of the furoxan ring: the charge on the $C_{(3)}$ atom is negative (−0.069), while that on the $C_{(4)}$ atom is positive (0.170), i.e., the nitro group at position 3 is less active than that at position 4, which was borne out by the results of the nucleophilic substitution reaction study.

The structure of the newly synthesized compounds was substantiated using elemental analysis, IR, NMR, and mass-spectrum data. Signals in ^{13}C NMR spectra were assigned in a similar way to those for isomeric nitrophenylfuroxans [7].

TABLE 1. Physical Properties and Spectral Characteristics of Compounds III-VII*

Compound	Empirical formula	mp, °C	Mass-spectrum, m/z (%)	PMR spectrum in $CDCl_3$, δ, ppm	Yield, %
III+IV*[2]	$C_2H_2N_4O_4$	40...43	$M^{+\cdot}$ 146 (80), 130 (35), 100 (12), 70 (100)	5,30 (2H, broad s, NH_2)	75
Va*[3]	$C_3H_4N_4O_4$	89...90	$M^{+\cdot}$ 160(20), 114 (15), 84 (40), 69 (100)	3,10 (3H, d, CH_3), 5,70 (1H, m, NH)	61
Vb	$C_4H_6N_4O_4$	23,5...25,5	M^+ 174(2), 158 (1), 128 (24), 98 (26), 69 (100)	1,30 (3H, t, CH_3), 3,40 (2H, m, CH_2), 5,65 (1H, m, NH)	97
Vc	$C_5H_8N_4O_4$	33...35	$M^{+\cdot}$ 188 (12,5), 172 (12,5), 142 (88), 112 (41), 69 (100)	0,97 (3H, t, CH_3), 1,67 (2H, m, CH_2), 3,35 (2H, q, CH_2N), 5,75 (1H, m, NH)	51
Vd	$C_8H_6N_4O_4$	142...144 (dcomp.)	$M^{+\cdot}$ 222 (19), 206 (1), 192 (1), 176 (60), 146 (100)	7,19 (1H, m, p-H_{Ph}, 7,44 (2H, m, t-H_{Ph}), 7,49 (2H, m, o-H_{Ph}), 7,86 (1H, m, NH)	53
Ve	$C_9H_8N_4O_4$	100...101		7,27 (1H, m, p-H_{PH}, 7,39 (2H, m, t-H_{Ph}), 7,75 (2H, m, o-H_{Ph}), 6,00 (1H, m, NH), 3,90 (2H, m, CH_2)	25
Vf	$C_4H_6N_4O_5$	74,5...75,5	$M^{+\cdot}$ 190 (16), 174 (16), 144 (100), 114 (83), 83 (25)	3,40...3,86 (4H, m, $(CH_2)_2$), 6,35 (2H, m, NH и OH)*[5]	66
Vg*[4]	$C_5H_5N_5O_4$	117...118 (decomp.)		2,94 (2H, t, CH_2CN), 3,54 (2H, q CH_2), 7,57 (1H, m, NH)	20
VI	$C_4H_6N_4O_4$	71...73	M^+ 174 (20), 144 (32), 128 (40), 98 (100)	3,30 (6H, s, $2CH_3$)	73
VII	$C_7H_{10}N_4O_4$	26...27,5	$M^{+\cdot}$ 214 (30), 168 (25), 138 (40), 110 (36), 109(50)	3,32 (4H, m, $2CH_2$—N), 1,81 (6H, br s, $3CH_2$)	41

*Intense absorption bands were observed in the IR spectra of all compounds at 1640-1650 (C=N) and 1520, 1340, and 830 cm^{-1} (NO_2).

*[2] ^{13}C NMR spectrum: 128.0 (C−NO_2, III) and 152.3 (C−NH_2, III), 126.7 (C−NO_2, IV) and 158.0 ppm (C−NH_2, IV). ^{14}N NMR spectrum ($(CD_3)_2CO$): −34.30 (NO_2, III) and −31.38 ppm (CH_3−NH).

*[3] ^{13}C NMR spectrum ($CDCl_3$): 125.59 (C−NO_2), 159.16 (C−$NHCH_3$), 30.25 ppm (CH_3−NH).

*[4] ^{13}C NMR spectrum (DMSO): 122.90 (C−NO_2), 151.38 (C−NH), 119.29 (C≡N), 39.26 (CH_2NH), 18.65 ppm (CH_2CN). ^{14}N NMR spectrum: −33.80 ppm (NO_2).

*[5] In $(CD_3)_2CO$.

EXPERIMENTAL

IR spectra were obtained in KBr tablets on a Specord instrument. ^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 (300, 75.5, and 21.7 MHz, respectively), internal standard TMS. Mass spectra were obtained using a Varian CH-6 with ionizing voltage of 70 eV. Melting points were determined on a Boetius-type table at a heating rate of 4°C per minute. Silica gel L 100/60 μ was used for column chromatography. The reaction course and the purity of synthesized compounds was monitored using TLC on Silufol UV-254 plates with detection in UV light at 254 nm, and by developing the spots after spraying with a 1% alcoholic solution of diphenylamine.

Elemental analysis data for the synthesized compounds with respect to C, H, and N were in line with calculated values.

Dinitroglyoxime (II, $C_2H_2N_4O_6$). A 25.5 ml sample (120 mmoles) of 25% HNO_3 was added dropwise over 15 min at 15-20°C to a suspension of 3.52 g (40 mmoles) of glyoxime and $NaNO_2$ (on the tip of a spatula) in 50 ml of ether. After 2.5 h the organic layer was separated off, washed with water, and dried over $MgSO_4$. When the drying agent had been filtered off, 20 ml CF_3COOH was added to the ether solution at 10°C and the bulk of the solvent was evaporated off. Rubbing the residue with a Teflon rod brought about the precipitation of product II, which was filtered off, washed with CF_3COOH and dried in air: mp 84-84.5°C (decomp.), ρ 1.837. Unstable when stored, especially in a sealed vessel. IR spectrum: 3340 (OH), 1665 (C=N), 1570, 1350, and 835 cm^{-1} (NO_2). PMR spectrum ($(CD_3)_2CO$): 6.8 ppm (OH). ^{13}C NMR spectrum: 148.27; ^{14}N NMR spectrum: −25.11 ppm (NO_2). Yield 3.92 g (55%).

3,4-Dinitrofuroxan (I, $C_2N_4O_6$). A solution of 1.5 ml (25 mmoles) of N_2O_4 in 10 ml of CCl_4 was added at 20-25°C to a solution of 0.89 g (5 mmoles) of glyoxime (II) in 20 ml of CCl_4. After 3.5 h the solvent was evaporated off and 20 ml of water and 50 ml of CCl_4 were added to the mixture. The organic layer was washed with water (3 × 25 ml) and dried over $MgSO_4$. (This solution was used for the reaction of I with ammonia and amines). After the solvent had been driven off, the residue was purified on a column using a 3:2 hexane−$CHCl_3$ elutriator. The purification process was monitored using TLC (CH_2Cl_2 elutriator); product I displayed an intense black spot, R_f 0.9; mp 8°C, decomp. temp. 50°C, n_D^{20} 1.5375, d_4^{20} 1.71, $MR_{Dcalc.}$ 30.14; MR_{Dfound} 32.27, Σ_R = +2.13. IR spectrum: 1680 (C=N), 1580, 1330, and 850 cm^{-1} (NO_2). ^{13}C NMR spectrum: 122.7 ($O_2NC{=}N{-}O$) and 153.6 ppm ($O_2NC{=}N$), ^{14}N NMR ($CDCl_3$): −42.57 (4-NO_2) and −47.72 ppm (3-NO_2). Yield 0.71 g (81%).

Reactions between −15 to −20°C. 3,4-Dinitrofuroxan I and Amines (A General Method). A solution of the appropriate nucleophile in CH_2Cl_2, $CHCl_3$, or CCl_4 (in the case of methyl- and ethylamines aqueous solutions can be used) was added dropwise with stirring to a solution of furoxan I in the same solvent. The reaction course was monitored using TLC, CH_2Cl_2 elutriator. When the starting compound I had disappeared from the reaction mixture (R_f 0.9), the precipitate was filtered off and washed with CCl_4; the combined filtrate was evaporated and the products were separated from the residue using column chromatography (CH_2Cl_2 elutriator). Physical properties and spectral characteristics of compounds III-VII are shown in Table 1.

4-Methoxy-3-nitrofuroxan (VIIIa, $C_3H_3N_3O_5$). A 0.16 g sample (4 mmoles) of NaOH in 10 ml CH_3OH was added over 1 h at −25 to −15°C to a solution of 0.7 g (4 mmoles) of I in 10 ml CH_3OH. After warming to room temperature the reaction mixture was kept until the starting compound I had disappeared (from TLC data, CH_2Cl_2 elutriator); the reaction mixture was then poured out into a twofold excess by volume of a water−ice mixture and extracted with ether (3 × 30 ml). The extract was washed with water and dried over $MgSO_4$. When the solvent had been driven off, the residue was purified on a column (CCl_4 elutriator); mp 94-94.5°C. IR spectrum: 2800 (CH_3), 1650 (C=N), 1590, 1350, and 820 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 4.3 ppm (3H, s, OCH_3). ^{13}C NMR spectrum: 123.10 (C−NO_2), 158.87 (C−OCH_3), 59.42 ppm (OCH_3). Mass spectrum, *m/z* (%): $M^{+\cdot}$ 161 (13), 115 (36), 85 (36), 70 (100). Yield 0.4 g (62%).

3-Nitro-4-ethoxyfuroxan (VIIIb, $C_4H_5N_3O_5$). Obtained in a similar way to furoxan VIIIa from I and C_2H_5OH; mp 42-44°C. IR spectrum: 1650 (C=N), 1580, 1360, and 820 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 1.8 (3H, t, CH_3), 4.97 ppm (2H, q, CH_2). Mass spectrum, *m/z* (%): $M^{+\cdot}$ 175 (20), 174 (40), 129 (45), 115 (45), 99 (100). Yield 40%.

3,4-Dimethoxyfuroxan (IXa, $C_4H_6N_2O_4$). A. A solution of 0.15 g (3.75 mmoles) of NaOH in 20 ml CH_3OH was added at −20 to −10°C to a solution of 0.65 g (3.7 mmoles) of furoxan I in 10 ml CH_3OH. The reaction mixture was kept at this temperature until all the starting compound I had disappeared (TLC, CH_2Cl_2); it was then warmed to room temperature and a solution of 0.15 g (3.75 mmoles) of NaOH in 20 ml CH_3OH was added to it. The reaction course was monitored using TLC until the VIIIa spot had completely disappeared. The flask contents were poured out onto ice and extracted with CH_2Cl_2 (3 × 50 ml), then the combined extract was washed with cold water (50 ml) and dried over $MgSO_4$. When the solvent had been driven off, the residue was purified on a column (1:1 $C_2H_4Cl_2$:CCl_4 elutriator), yielding an oily substance that crystallized on cooling; mp 30.5-32.5°C. IR spectrum: 1664 (C=N), 1570, 1335, and 863 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 4.1 ppm (6H, s, OCH_3). ^{13}C NMR spectrum: 125.59 (O−N=C−OCH_3), 159.40 (N=C−OCH_3), 60.02 and 57.41 ppm (2-OCH_3). Mass spectrum, *m/z* (%): $M^{+\cdot}$ 146 (35), 130 (4.7), 116 (14), 86 (100), 70 (23). Yield 0.4 g (74%).

B. A solution of 0.1 g (2.5 mmoles) of NaOH in 10 ml CH_3OH was added over 15 min at −5 to 0°C to a solution of 0.4 g (2.5 mmoles) of furoxan VIIIa in 20 ml CH_3OH. Then the mixture was raised to room temperature and when the reaction was complete (from TLC), it was poured out onto ice. The method then followed that described in A. Yield 0.3 g (83%).

3,4-Diethoxyfuroxan (IXb, $C_6H_{10}N_2O_4$). Compound IXb was obtained in a similar way to IXa (method A) from furoxan and ethanol, yielding an oily liquid, n_D^{20} 1.4683. IR spectrum: 1664 (C=N), 1572, 1326, and 820 cm^{-1} (NO_2). PMR spectrum ($CDCl_3$): 1.38 (6H, m, CH_3), 4.38 ppm (4H, q, CH_2). Mass spectrum, *m/z* (%): $M^{+\cdot}$ 174 (100), 158 (15), 146 (73), 144 (12), 114 (25), 118 (36). Yield 71%.

4-Azido-3-nitrofuroxan (X, $C_2N_6O_4$). A 2.9 g sample (45 mmoles) of finely divided NaN_3 was added to a solution of 2.3 g (13 mmoles) of furoxan I in 40 ml of glacial acetic acid. When the reaction was complete (from TLC), the mixture was poured out into 10 ml of water and extracted with CCl_4 (4 × 30 ml). The combined extract was washed with water (2 × 40 ml) and dried over $MgSO_4$. When the solvent had been driven off, the residue was recrystallized from pentane; mp 40-43°C, ρ 1.83. IR spectrum: 2190 (N_3), 1580, 1360, and 830 cm^{-1} (NO_2). ^{13}C NMR spectrum ($(CD_3)_2CO$): 128.3 (C−NO_2), 148.1 ppm (C−N_3). Caution! The product is explosive. Yield 1.8 g (86%).

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