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RECYCLIZATION OF SUBSTITUTED FUROXANS INTO 1,2,3-TRIAZOL-1-OXIDE DERIVATIVES

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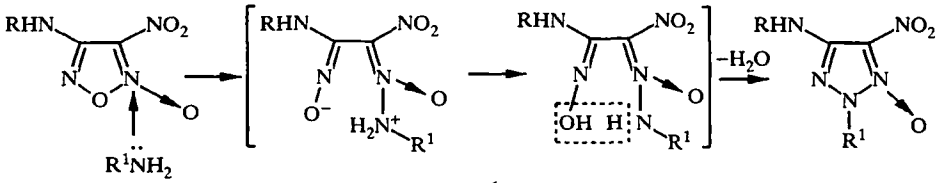
The effect of the position and nature of substituents on the recyclization of substituted furoxans has been established.

Previously we reported the conversion of 4-amino(alkylamino)-3-nitrofuroxans into the corresponding 5-nitro-1,2,3-triazol-1-oxides under the action of primary aliphatic amines [1,2].

To explain the results obtained we proposed a mechanism for forming the 1-oxidotriazole ring in which the first step of the reaction of furoxan with alkylamine is attack at the nitrogen atom of the N-oxide fragment by this nucleophile.



R = H, Alk; R^1 = Alk

It is known [3] that the N(O)—O bond is the weakest endocyclic bond of the furoxan ring. We propose that the furoxan ring is broken at precisely this bond by the action of the primary amine. A molecule of water is then eliminated and cyclization occurs with the formation of a 1,2,3-triazol-1-oxide derivative.

In the present work results obtained by us previously [1,2] on the effect on cyclization of the position and nature of substituents for a series of substituted furoxans (Ia-n) have been generalized and analyzed. In addition, new experimental data on this conversion are given involving primary amines of various structure.

Information on the ability of furoxans (Ia-n) to recyclize under the action of primary amines is given in Table 1. As is seen from Table 1 the necessary condition for the conversion of furoxanes (I) into 1,2,3-triazol-1-oxides is the presence in the initial compound of an electronegative substituent at position 3 and only an amino or alkylamino group [compounds (Ia-g)] at position 4.

The negative results of experiments with furoxans (Ik) and (Il) show the importance for recyclization of the presence of a hydrogen atom linked to the nitrogen of the amino group.

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TABLE 1. Behavior of Disubstituted Furoxans (Ia-n) Under Recyclization Reaction Conditions

Recyclized			Not recyclized		
furoxan	substituent		furoxan	substituent	
	3-	4-		3-	4-
Ia	NO_2	NH_2	Ih	NH_2	NO_2
Ib	NO_2	CH_3NH	Ii	CH_3	NH_2
Ic	NO_2	C_2H_5NH	Ij	NH_2	C_6H_5
Id	NO_2	C_3H_7NH	Ik	NO_2	$(CH_3)_2N$
Ie	NO_2	$NCCH_2CH_2NH$	Il	NO_2	$C_5H_{10}N$
If	NO_2	$H—OCH_2CH_2NH$	Im	NO_2	N_3
Ig	C_6H_5	NH_2	In	NO_2	CH_3O

The hypothesis also states that the rate and direction of the reaction being considered depend significantly on the charge on the nitrogen atom in position 2. To confirm this, quantum chemical calculations were carried out by the CNDO/2 method (Complete Neglect of Differential Overlap) for the structures of some furoxans, and also for the reactivity indexes, such as charges on atoms and bond resonance energies, correlating with the covalent component of bond strength.

The initial approximations for the calculations were the mean geometric parameters [3, p. 21]. As an example, molecular diagrams are given in Fig. 1 illustrating the results of calculations on 4-amino-3-nitro- and 3-amino-4-nitrofuroxans (Ia) and (Ih), and also on 4-amino-3-phenyl- and 3-amino-4-phenylfuroxans (Ig) and (Ij). It follows from the data obtained that the resonance energy of the endocyclic N(O)—O bond in compound (Ih)

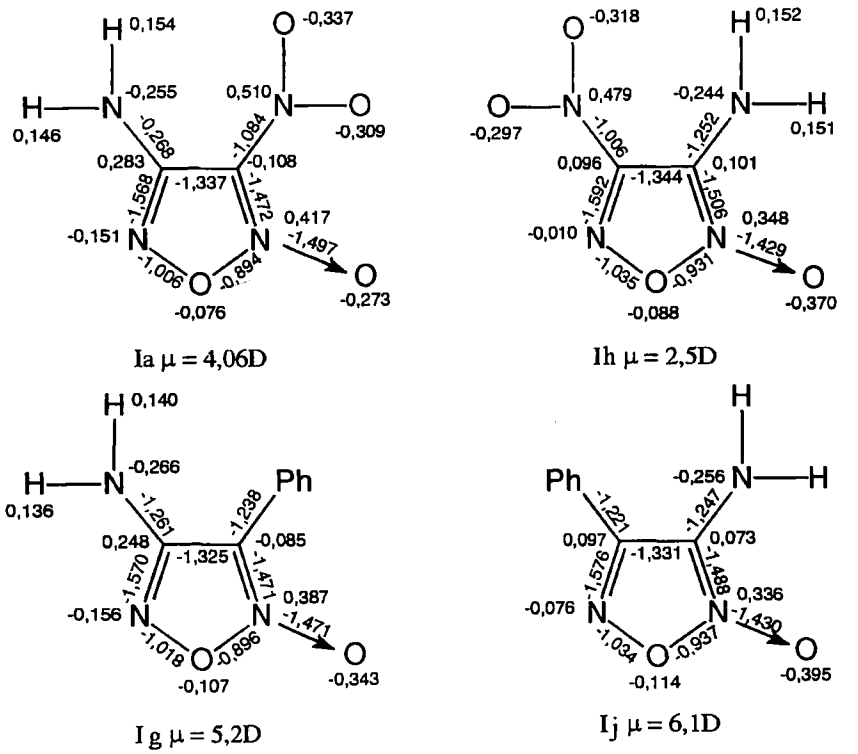


Fig. 1. Molecular diagrams for furoxan compounds. Values of the resonance energy in arbitrary units are given below bonds; values of charges in electron charge units (-e) are given at atoms; μ is dipole moment.

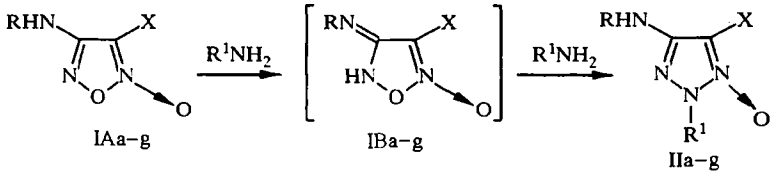
(-0.931) is less than the energy of the analogous bond in compound (Ia) (-0.894). The same is characteristic of the amino and phenyl substituted furoxans. The N(O)—O bond is stronger in compound (Ij) (-0.937) than in compound (Ig) (-0.896). These data are in agreement with the experimental results. Recyclization is a characteristic of furoxans (Ia) and (Ig), but this reaction does not take place for furoxans (Ih) and (Ij).

An analogous tendency was observed for the charge values on the nitrogen oxide atoms, being somewhat greater in the case of compounds (Ia) and (Ig) than for compounds (Ih) and (Ij). However the differences between the resonance energy and charge values are very small and it is not possible to confirm that these parameters determine the ability of the compounds to cyclize.

We also attempted to explain the conversion of substituted 4-aminofuroxans into 1,2,3-triazol-1-oxides by the presence of an intramolecular hydrogen bond in the initial compounds, since it is known [4] that the formation of such bonds leads to delocalization of electron density, a reduction in bond population and, as a result, to a weakening of their strength. In reality a hydrogen bond may occur in compounds (Ia-f) (Table 1) between a hydrogen atom of the amino group and an oxygen atom of the nitro group assisting recyclization. However in furoxan (Ig), which undergoes the same conversion, this bond is absent.

On the other hand compound (Ih) is not recyclized although intramolecular hydrogen bonds may be present between a hydrogen atom of the amino group and an oxygen atom of the nitro group, or the N-oxide fragment.

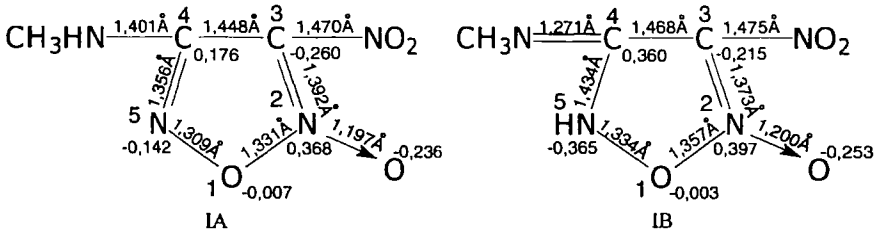
Consequently analyzing the above results we concluded that the recyclization of amino-furoxans (I) containing an electronegative substituent in position 3 into 1,2,3-triazol-1-oxides (II) is probably caused in the first place by the presence of a hydrogen atom on the exocyclic nitrogen atom at position 4 of the furoxan ring (structure IA). We suggest that under the action of primary amine this hydrogen atom migrates to the nitrogen atom at position 5 (structure IB) and then the product (IB) formed is converted into the corresponding triazoloxide (II).



I, II a — f X = NO_2, g X = C_6H_5; a R = H, R^1 = CH_3; b R = R^1 = CH_3; c R = R^1 = C_2H_5;
d R = R^1 = C_3H_7; e R = CH_2CH_2CN, R^1 = CH_3; f R = CH_2CH_2OH, R^1 = CH_3; g R = H, R^1 = CH_3

Examples of hydrogen atom migration from a substituent to the ring and vice versa in other five- and six-membered heterocycles with one, two, or more nitrogen atoms are known [5, 6].

Quantum chemical calculations were carried out to clarify the problems of the comparative stability of structures (IA) and (IB), viz. the charge values on atoms, bond lengths, and their stability to the action of primary amine. A theoretical investigation of the (IA) and (IB) structures was effected by the semi-empirical CNDO/2 quantum chemical method for 4-methylamino-3-nitrofuroxan (Ib). A schematic representation of structures (IA) and (IB) for compound (Ib) with charge values on atoms and bond lengths is as follows.



As is seen from the data the N(O)—O bond is somewhat longer and the charge on $N_{(2)}$ greater in structure (IB) than in structure (IA). The attack of a nucleophilic reagent is determined by the maximum positive charge. It therefore follows that structure B must be more readily converted into a triazol-N-oxide under the action of primary amines.

TABLE 2. Characteristics of the Products Obtained from the Reaction of Amines R^1NH_2 with 4-Amino-3-nitrofuroxan (Ia)

R^1	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum in $CDCl_3$, δ, ppm	Yield, %
		C	H	N			
C_2H_5	$C_4H_7N_5O_3$	27,63 / 27,75	4,12 / 4,08	40,29 / 40,45	134...136	5,27 (2H, br. s, NH_2); 4,35 (2H, q, CH_2); 1,46 (3H, t, CH_3)	40
C_6H_{13}	$C_8H_{15}N_5O_3$	41,99 / 41,91	6,53 / 6,60	30,67 / 30,55	59...60	5,25 (2H, s, NH_2); 4,27 (2H, t, NCH_2); 1,60...1,32 (8H, m, $4CH_2$); 0,90 (3H, t, CH_3)	53
C_7H_{15}	$C_9H_{17}N_5O_3$	44,57 / 44,43	7,13 / 7,04	28,87 / 28,79	61...62	5,23 (2H, s, NH_2); 4,27 (2H, t, NCH_2); 1,58...1,32 (10H, m, $5CH_2$); 0,88 (3H, t, CH_3)	60
C_8H_{17}	$C_{10}H_{19}N_5O_3$	46,79 / 46,68	7,53 / 7,44	27,31 / 27,22	58...60	5,23 (2H, s, NH_2); 4,26 (2H, t, NCH_2); 1,32...1,27 (12H, m, $6CH_2$); 0,88 (3H, t, CH_3)	48
$C_{12}H_{25}$	$C_{14}H_{27}N_5O_3$	53,78 / 53,65	8,61 / 8,68	22,48 / 22,35	82...83	5,25 (2H, s, NH_2); 4,27 (2H, t, NCH_2); 1,33...1,25 (20H, m, $10CH_2$); 0,88 (3H, t, CH_3)	58
i-C_3H_7	$C_5H_9N_5O_3$	32,19 / 32,08	4,93 / 4,85	37,52 / 37,42	151...152	5,23 (2H, s, NH_2); 5,20 (1H, m, CH); 1,47 (6H, d, $2CH_3$)	41
i-C_4H_9	$C_6H_{11}N_5O_3$	35,95 / 35,82	5,59 / 5,51	34,97 / 34,81	72...73	5,23 (2H, s, NH_2); 5,06 (1H, m, CH); 1,87 (2H, m, CH_2); 1,43 (3H, d, $\underline{CH_3}CH$); 0,90 (3H, t, $\underline{CH_3}CH_2$)	35
CH_2CH_2OH	$C_4H_7N_5O_4$	25,59 / 25,40	3,80 / 3,73	37,13 / 37,03	145...149	5,23 (2H, br. s, NH_2); 3,82 (2H, t, CH_2N); 3,40 (2H, m, CH_2OH)	45
$CH_2CHOHCH_3$	$C_5H_9N_5O_4$	29,65 / 29,56	4,53 / 4,47	34,58 / 34,48	132...134	4,89 (3H, br. s, NH_2,OH); 4,33 (1H, m, CH); 4,23 (2H, d, CH_2); 1,27 (3H, d, CH_3)	51
CH_2CH_2CN	$C_5H_6N_6O_3$	30,28 / 30,31	3,15 / 3,05	42,61 / 42,42	183...184	6,39 (2H, s, NH_2); 3,14 (2H, t, CH_2N); 2,67 (2H, t, CH_2CN)	63
C_6H_{11} (cyclohexyl)	$C_8H_{13}N_5O_3$	42,34 / 42,29	5,87 / 5,77	30,91 / 30,82	123...124	5,22 (2H, s, NH_2); 4,85 (1H, m, CH); 2,04...1,42 (10H, m, $5CH_2$)	53
$C_6H_5CH_2$	$C_9H_9N_5O_3$	45,92 / 45,96	3,87 / 3,86	29,89 / 29,78	174,5...175	5,22 (2H, s, NH_2); 5,42 (2H, s, CH_2); 7,41...7,27 (5H, m, C_6H_5)	44

The scheme proposed by us previously [1, 2] for the recyclization of a furoxan ring into a 1,2,3-triazol-1-oxide, included as the first step cleavage of the endocyclic N(O)—O bond, as being the weakest and close to a single bond [3]. We have found no unequivocal confirmation of this in the literature for uncondensed compounds of this class. Examples for and against cleavage of this bond are known only for fused furoxans. For example, on reaction of benzofuroxan with potassium or sodium salts of formanilides of various structure the N(O)—O bond is the first broken in the opinion of the authors of [7].

However cleavage of the other N—O bond in the ring is also possible when the unoxidized nitrogen atom of the furoxan ring is the subject of the initial attack. This occurs, for example, on reaction of benzofuroxan with secondary amines [8, 9], sulfites, and aryl- or alkylsulfinates of the alkali metals [10].

Substituted pyridofuroxans react analogously with dimethyl sulfoxide [11], with alkali, metal alcoholates, and amines [12]. The reaction mechanism of the furoxans indicated with nucleophilic reagents is not well established at present. Either of the nitrogen atoms of the furoxan ring may be subject to attack [13].

Our repeated attempts to confirm the formation of compound B in the course of the reaction using thin layer chromatography were unsuccessful. It may be suggested that either reaction of the initial furoxan with primary amine proceeds very rapidly or the intermediate product is unstable.

We confirmed the presence of the new intermediate compound in the recyclization reaction using spectral methods (UV, PMR) when studying the reaction of 4-methyl-amino-3-nitrofuroxan (Ib) with methylamine. It was first proved strictly on the basis of data of ^{13}C and $^{14/15}N$ NMR spectra that the initial furoxan was in form A and contained no admixture of form B. The UV spectra of the initial furoxan (Ib) and methylamine and also of product (IIb) each contain their own characteristic absorption band at 395, 305, and 222 nm respectively. After mixing the reactants a band appeared in the UV spectrum of the reaction mixture at 298 nm, the intensity of which gradually fell together with growth in the intensity of the band at 222 nm for the final product.

Convincing confirmation of the formation of the intermediate compound in the reaction process was also obtained with the aid of PMR spectra taken in a mixture of CD_2Cl_2 and $CDCl_3$ at 10°C. A new singlet appeared in the spectrum of the reaction mixture at 3.04 ppm 5 min after mixing the reactants in addition to the methyl group proton signals characteristic of the initial compounds, viz. a doublet at 3.07 (Ib) and a triplet at 2.41 ppm (methylamine). The new singlet was appreciably reduced after 8 min and had disappeared completely after 45 min. Concurrently the intensity of the signals for the two methyl groups of the final product (IIb) gradually grew, being a singlet at 3.88 and a doublet at 2.78 ppm.

The spectral data presented therefore point in favor of the formation of an intermediate compound of type B, thereby explaining why only amino- and monoalkylaminofuroxans react with primary amines.

We also investigated the effect of the nature of the primary amine on the recyclization of furoxans into 1,2,3-triazol-1-oxides. It was shown using 4-amino-3-nitrofuroxan (Ia) as an example that in addition to alkylamine substituents of both normal (CH_3, C_2H_5, C_6H_{13}-C_8H_{17}, $C_{12}H_{25}$) and iso structure (i-C_3H_7, i-C_4H_9) such amines as allylamine, ethanolamine, isopropylamine, 3-aminopropionitrile, cyclohexylamine, and benzylamine may also take part in this reaction. In all cases the corresponding 5-nitro-1,2,3-triazol-1-oxide was formed (see Table 2).

The IR spectra of these products contain intense absorption bands characteristic of N-oxides of a triazole ring (1620-1625 cm^{-1}), nitro (1370-1390 and 1520-1534 cm^{-1}) and amino groups (3460-3470 cm^{-1}). Absorption at 221, 222, 310, and 400 nm was characteristic of the UV spectra. The mass spectra contained peaks for the molecular ions, the fragmentation of which confirmed the structure of the compounds synthesized.

The results obtained permit the hypothesis that 4-amino- or 4-alkylaminofuroxans containing an electron-withdrawing substituent at position 3 of the furoxan ring will undergo the conversion under the action of primary amines more basic than ammonia.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker AM 300 instrument, internal standard was TMS. The UV spectra were taken on a Specord UV instrument in absolute ethanol. Melting points were determined on a Boetius stage with a rate of heating of 4°C/min at the melting point.

The synthesis of 4-substituted 3-nitrofuroxans (Ia-f,h,k-n) has been described previously [14]. Furoxans (Ig) and (Ij) were obtained by the procedure of [15], and furoxan (Ii) was described in [16].

The conversion of compounds (Ia-c), (Ie), and (If) into the corresponding 1,2,3-triazol-1-oxides was reported in [1,2].

The reaction of furoxan (Ia) with methyl- and allylamines and the characteristics of the 1,2,3-triazol-1-oxides obtained were reported in [1,2].

The characteristics of the 2-substituted 4-amino-5-nitro-1,2,3-triazol-1-oxides synthesized by the known procedure of [2] by the action of the appropriate amine R^1NH_2 on furoxan (Ia) are given in Table 2.

Synthesis of triazoloxides (IId,g) by the reaction of furoxans (Id) and (Ig) with propylamine and methylamine respectively was carried out by the known procedure of [2].

5-Nitro-2-propyl-4-propylamino-1,2,3-triazol-1-oxide (IId). Yield was 23%, mp 55-56°C. IR spectrum: 3515, 2980, 2950, 2885, 1620, 1527, 1510, 1480, 1450, 1410, 1393, 1383, 1345, 1319, 1275, 1238, 1185, 1169, 1133, 1104, 1065, 1045, 905, 826, 770, 750, 716, 685 cm^{-1}. UV spectrum, λ: 310, 400 nm. Mass spectrum, *m/z*: 229 $[M]^{+\cdot}$; 213 $[M-O]^{+\cdot}$; 183 $[M-NO_2]^{+\cdot}$; 113 $[M-NO_2-C_3H_6N_2]^{+\cdot}$; 97 $[M-NO_2-C_3H_6N_2-O]^{+\cdot}$; 96 $[M-NO_2-C_3H_6N_2-OH]^{+\cdot}$; 95 $[M-NO_2-C_3H_6N_2-H_2O]^{+\cdot}$. Found, %: C 41.99; H 6.53; N 30.67. C8H15N5O3. Calculated, %: C 41.91; H 6.60; N 30.55.

4-Amino-2-methyl-5-phenyl-1,2,3-triazol-1-oxide (IIg). Yield was 25%, mp 148-150°C. IR spectrum: 3345, 3220, 2935, 2865, 1655, 1615, 1590, 1545, 1495, 1460, 1435, 1365, 1335, 1315, 1285, 1170, 1145, 1080, 1065, 1035, 970, 930, 915, 855, 820, 765, 740, 715, 695 cm^{-1}. UV spectrum, λ: 215 and 265 nm. PMR spectrum $[(CD_3)_2CO]$: 8.02-7.96 (2H, br. s, NH_2); 7,47-7.43 (5H, m, C_6H_5); 3.76 ppm (3H, s, CH_3). Mass spectrum, *m/z*: 190 $[M]^{+\cdot}$; 174 $[M-O]^{+\cdot}$; 97 $[M-O-Ph]^{+\cdot}$; 144 $[M-O-NO]^{+\cdot}$.

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