Unsymmetrically Substituted Furoxans. Part 16 [1]. Reaction of Benzenesulfonyl Substituted Furoxans with Ethanol and Ethanethiol in Basic Medium

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The use of benzenesulfonyl substituted furoxans as flexible intermediates for the synthesis of new functionalized furoxans interesting for their potential biological properties is discussed. Reaction of benzenesulfonylphenylsulfonylfuroxan isomers **7a** and **7b** with ethanol and ethanethiol in basic medium affords the expected ethers and sulphides respectively. Reaction of bis(benzenesulfonyl)furoxan (**1**) with ethanol in basic medium gives 3-benzenesulfonyl-4-ethoxyfuroxan (**2**) or diethoxyfuroxan (**3**), according to the experimental procedure. In contrast the reaction of **1** with ethanethiol gives a mixture of substitution compounds and the 4-benzenesulfonyl-3-ethylthiofurazan (**11**). The structure of the compounds has been assigned by nmr spectroscopy and, in the case of 3-benzenesulfonyl-4-ethylthiofuroxan (**9b**), confirmed by X-ray analysis.

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In previous papers we have discussed the nucleophilic substitution of the nitro group at the furoxan ring and we showed nitrofuroxans to be interesting intermediates for the preparation of many new functionalized derivatives of this heterocyclic system [2,3].

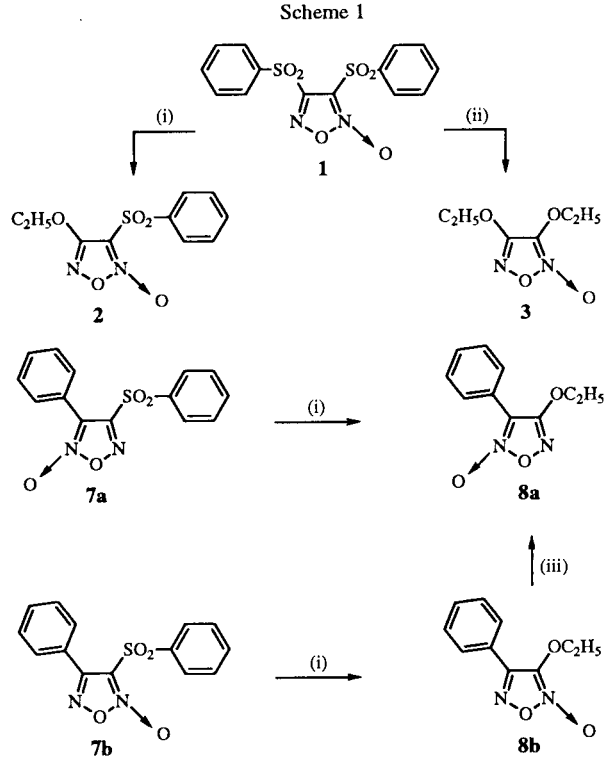
More recently, 3,4-dinitrofuroxan has been synthesized and used to prepare 4-functionally-substituted 3-nitrofuroxans by nucleophilic substitutions [4]. This last derivative suffers, as a synthetic intermediate, from its unstable and explosive nature [4].

In this paper we show that benzenesulfonyl substituted furoxans, stable compounds, easy to prepare, are prone to substitution by classical nucleophiles and therefore they can be used to obtain new furoxans so far not easily accessible. This is of interest in view of the potential biological significance of the furoxan system [5,6].

Bis(arenesulfonyl)furoxans can easily be prepared by a number of routes [7]. In ethanol containing alkali one (which one is not known) of the sulfonyl groups is replaced by ethoxide [8]. We repeated the preparation of the ethoxy derivative starting from bis(benzenesulfonyl)-furoxan **1** following a procedure slightly modified from that described in lit [8] (Scheme 1, route i). In particular we ran the reaction at room temperature in order to avoid possible furoxan isomerization. We isolated in good yield a single benzenesulfonylethoxyfuroxan isomer. No trace of the other possible isomer was detected by nmr.

The ^1H decoupled ^{13}C-nmr spectrum of the product (see Figure 1, F2 domain projection and Table 1), shows two low-intensity signals at 158.6 and 110.2 ppm attributable to the C-4 and C-3 respectively of the heterocyclic ring [9,10]. The other four resonances in the aromatic region (140-135 ppm) are assigned to the benzene ring, while the signals observed at 67.5 and 14.0 ppm respectively, are due to the carbons of the ethyl

Scheme 1



i) **1**, **7a,b**/NaOH/EtOH, 1/3/2 mole/mole; THF, room temperature, 2 hours (**1**), 4 hours (**7a**), 7 hours (**7b**)

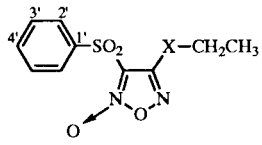
ii) **1**/NaOH/EtOH, 1/9/6 mole/mole; THF, room temperature, 7 hours

iii) *sym*-tetrachloroethane, 95°C, 1.5 hours

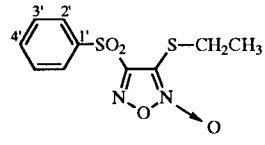
function. In order to ascertain the connectivity relative to the C-4 and C-3 of the furoxan ring and therefore to give the exact structure to compound **2**, an INEPT experiment has been performed [11]. The delay in the INEPT sequence was optimized with 30 ms according to a $^3J_{C-H}$ coupling constant value in the range of 3-10

Table 1

^1H- and ^{13}C-NMR Data of Compounds **2, 9a, 9b** δ, ppm from TMS, Solvent Deuteriochloroform



2, X = O; **9a**, X = S



9b

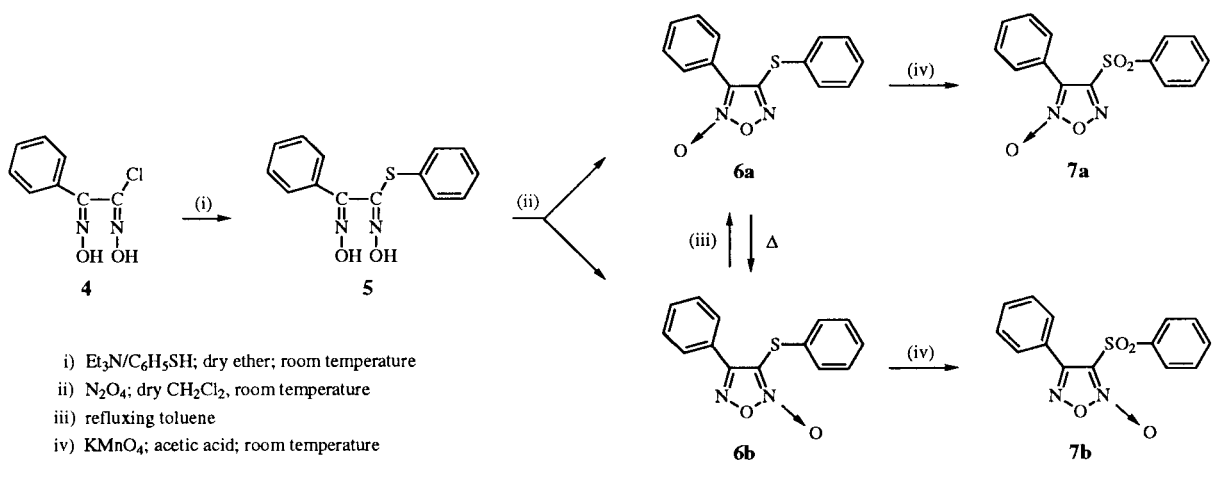
Compound	δ	C3	C4	CH_2	CH_3	C1'	C2'/C3'	C4'
2	^1H			4.51 (q, 2H)	1.51 (t, 3H)		8.1-7.6 (m, 5H)	
	^{13}C	110.2	158.6	67.5	14.0	137.7	128.2/129.3	135.3
9a	^1H			3.19 (q, 2H)	1.47 (t, 3H)		8.1-7.6 (m, 5H)	
	^{13}C	116.7	153.4	24.8	13.6	137.3	126.5/129.6	135.6
9b	^1H			2.99 (q, 2H)	1.15 (t, 3H)		8.1-7.6 (m, 5H)	
	^{13}C	108.3	159.8	25.8	14.7	136.5	129.3/129.5	135.6

Hz. In such a spectrum, the signal at 158.6 ppm, appeared as a typical INEPT modified triplet ($^3J_{C\text{-}H}$ = 2.8 Hz), while the signal at 110.2 ppm, was not detected. Since $J_{C\text{-}H}$ couplings through more than three bonds are usually very small [12], we proposed for the compound the structure 3-benzenesulfonyl-4-ethoxyfuroxan **2**. This proposal was confirmed by heteronuclear two-dimensional ^1H, ^{13}C chemical shift correlation spectrum *via* long range couplings (2D-HETCOR) which showed a cross peak with the coordinated δ-(C-$^1H_2$), δ-(^{13}C 4) (see Figure 1).

is confirmed by the behaviour of the two phenylbenzenesulfonylfuroxan isomers **7a** and **7b**.

We prepared these two compounds by the pathway reported in Scheme 2. The action of thiophenol in ether solution in the presence of triethylamine afforded the glyoxime **5**. This derivative was transformed into a mixture of the two phenylthiofuroxan isomers **6a** and **6b** (**6a/6b**~1/6) by the action of dinitrogen tetroxide in methylene chloride solution. The equilibrium thermodynamic concentrations of thermal interconversion **6a**⇌**6b** were reached by refluxing the mixture in toluene for 2

Scheme 2



When the reaction was repeated in the presence of a large excess of ethanol and sodium hydroxide (Scheme 1, route ii) after 7 hours diethoxyfuroxan (**3**) (yield 32%) was isolated. Running the reaction under the conditions described by Farrar [8], **2** (mp 105-106°; lit [8], mp 94-95°) and unreacted **1** were isolated by column chromatography.

That the phenylsulfonyl group is a good leaving group in this kind of reaction both at the 3- and the 4-positions,

hours (**6a/6b**~1, hplc detection). Column chromatography separation of the two derivatives and their oxidation with potassium permanganate in acetic acid solution gave the expected isomers **7a** and **7b**. The route above described to obtain derivatives **6a,b** and **7a,b** is more convenient than that we previously reported [13].

When **7a** was left to react with ethanol and sodium hydroxide, in the conditions similar to those under which

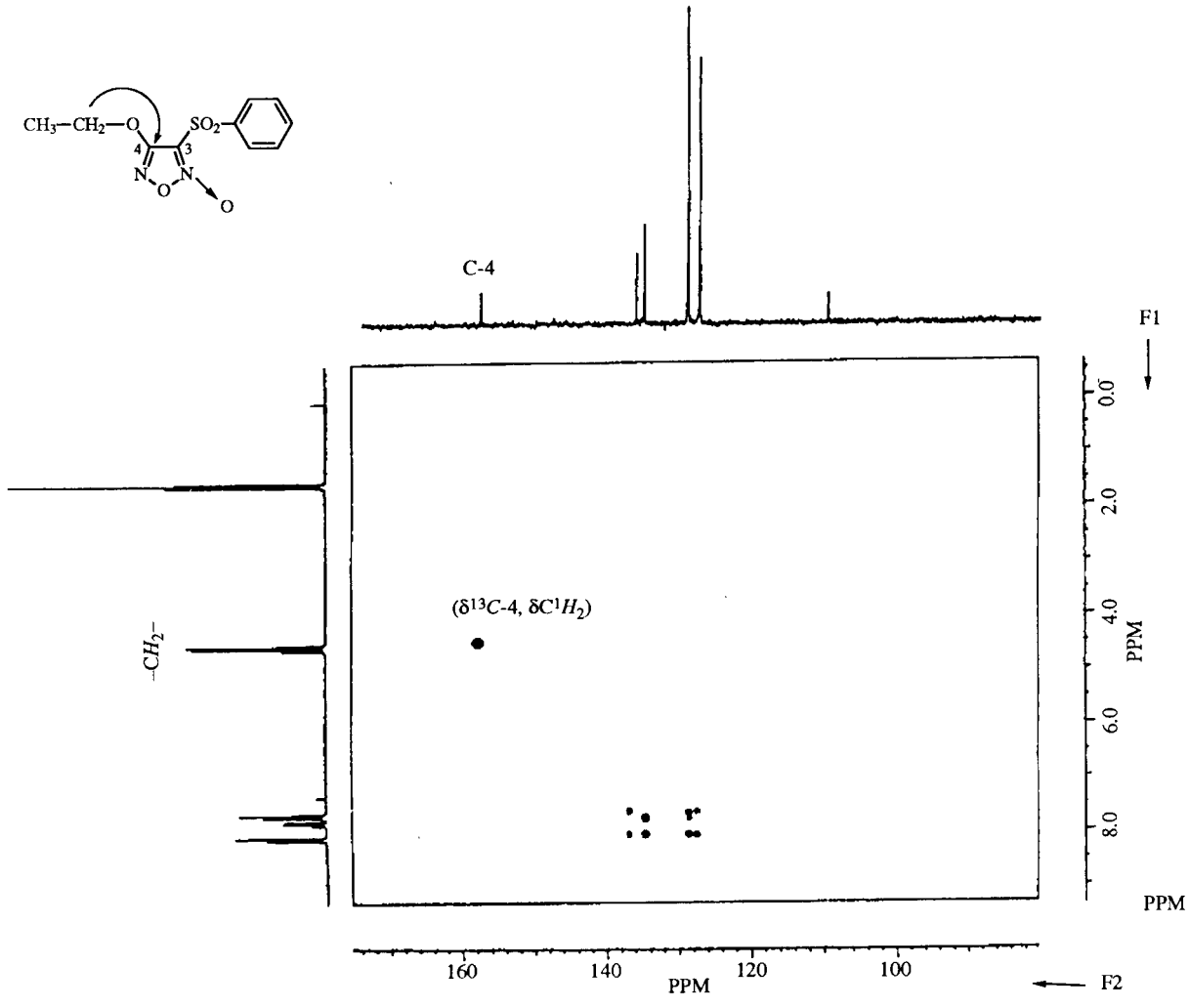


Figure 1. 2D Heteronuclear ^1H, ^{13}C chemical shift correlation spectrum for **2** (2D-HETCOR), *via* long range couplings; F1, ^1H frequencies domain, F2, ^{13}C frequencies domain.

1 afforded **2** (Scheme 1, route iii), 4-ethoxy-3-phenylfuroxan (**8a**) was obtained in quantitative yield.

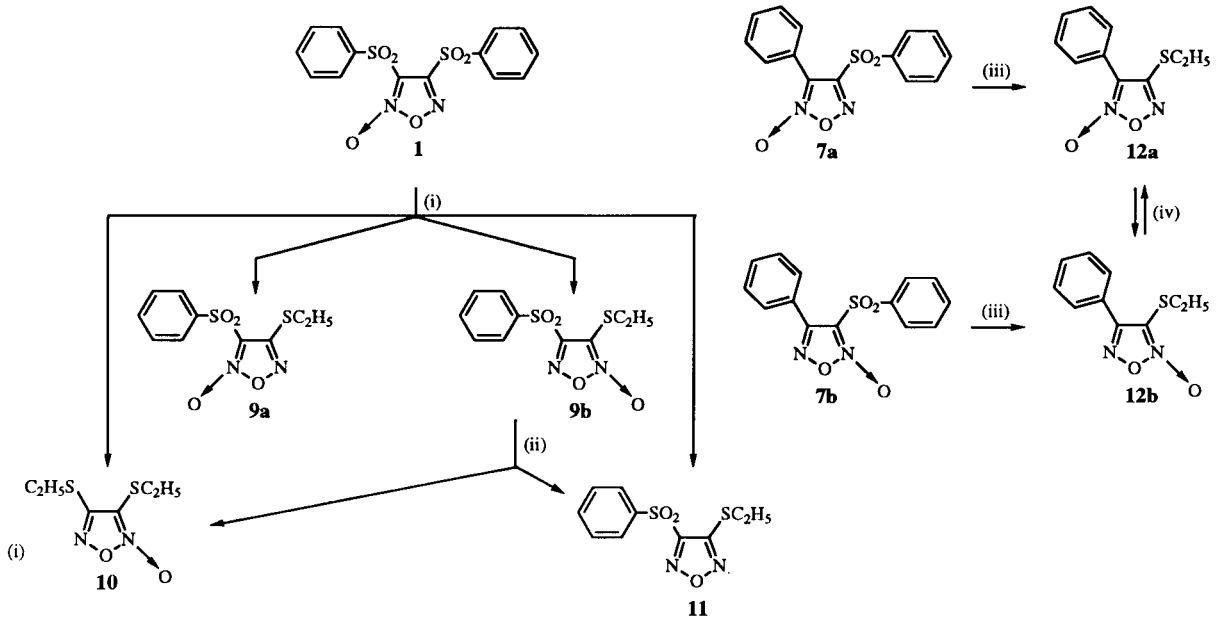
Similar results were obtained starting from **7b** and running the reaction for 7 hours, with the only exception that **8b** was obtained in capricious yields.

The structure of the couple of isomers **8a,b** was confirmed by nmr (see Table 3) on the basis of the knowledge that $N^+–O^-$ moiety exerts a shielding influence both on the C'-1 and, in a less extent, on the C'-4 of the 3-phenyl ring compared with the corresponding resonances of the 4-phenyl isomer [9,10]. The unusual down field resonance of the C-3 furoxan carbon (130.9 ppm) joined to the ethoxy group and adjacent to the C-4 bearing a substituent with a negligible β effect (phenyl moiety), is in keeping with the high deshielding action of an ethoxy function on a directly linked carbon [12].

Fairly different results were obtained when a THF solution of **1** was treated, under nitrogen, with an aqueous sodium hydroxide solution and ethanethiol, under the same conditions used to prepare **12a** or **12b** (Scheme 3, route iii). After an hour of reaction at room temperature a complex mixture of compounds was detected by combined column chromatograpy and hplc analysis (yields, **1**, 13%; **10**, 9%; **9a** and **11**, 21%; **9b**, 23%). With a stechiometric amount of the attacking nucleophile (Scheme 3, route i) the entire starting material was consumed. By column chromatography we isolated three fractions. The one eluted first was formed by **10** (yield 21%), while the one eluted last by **9b** (yield 11%).

Compound **9a** was obtained as pure compound (yield 13%) by crystallization of the intermediate fraction, a mixture of **9a** and of minor amount of the furazan derivative **11**. This latter compound could be formed by reduc-

Scheme 3



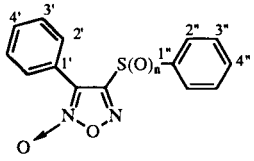
i) **1**/EtSH/NaOH, 1/2/3; THF, room temperature, 1 hour
ii) **9b**/EtSH/NaOH, 1/2/3; THF, room temperature, 5 hours
iii) **7a,7b**/EtSH/NaOH, 1/1/2; THF, room temperature, 1 hour
iv) *sym*-tetrachloroethane, 110°C, 24 hours

tion of the furoxans **9a,b** to the corresponding glyoximes followed by immediate dehydration. Also the bis-(phenylsulfonyl)glyoxime, a possible reduction product of **1**, could undergo nucleophilic substitution to afford the glyoxime intermediate enroute to **11**.

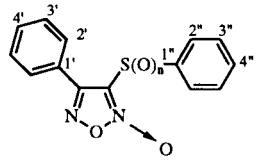
Dioximes are known reduction products, formed by the action of thiols, of benzofuroxans [9] and furoxans [5, 6]. We tested this hypothesis treating derivative **9b** with an excess of thiolate anion (route ii). We obtained a mixture of **10** and **11** and unreacted **9b**, which was resolved by flash chromatography (**10**, 13%; **11**, 33%; **9b**, 54%). However, we were unable to isolate any glyoxime derivative.

Probably such an intermediate is unstable and when formed immediately dehydrates to **11**. The isomer **9a**

Table 2
^{1}H- and ^{13}C-NMR Data of Compounds **6a,b** and **7a,b** δ ppm from TMS, Solvent Deuteriochloroform



6a, n = 0; **7a**, n = 2

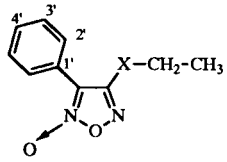


6b, n = 0; **7b**, n = 2

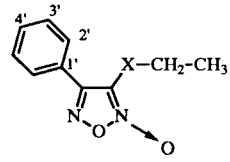
Compound	δ	C3	C4	C1'	C2'/3'-C2"/C3"	C4'	C1"	C2"/C3"-C2'/C3'	C4"
6a	^{1}H				7.4-7.9 (m, 10H)				
	^{13}C	114.3	154.1	122.0	128.8/133.9 127.5/129.6	130.6	126.1	127.5/129.6 128.8/133.9	129.8
6b	^{1}H				7.3-8.0 (m, 10H)				
	^{13}C	110.2	157.3	126.0	128.8/130.5 127.6/129.5	131.2	128.9	127.6/129.5 128.8/130.5	128.6
7a	^{1}H				7.5-7.9 (m, 10H)				
	^{13}C	112.2	158.7	120.3	128.9/129.0 129.4/129.5	131.4	136.0	129.4/129.5 128.9/129.0	135.5
7b	^{1}H				7.6-8.0 (m, 10H)				
	^{13}C	117.6	154.5	124.8	128.5/128.8 129.5/129.4	131.5	137.0	129.5/129.4 128.5/128.8	135.5

Table 3

^{1}H- and ^{13}C-NMR Data of Compounds **8a,b** and **12a,b**. δ, ppm from TMS, Solvent Deuteriochloroform



8a, X = O; **12a**, X = S



8b, X = O; **12b**, X = S

Compound	δ	C3	C4	CH_2	CH_3	C1'	C2'/C3'	C4'
8a	^{1}H			4.57 (q, 2H)	1.56 (t, 3H)		7.5-8.2 (m, 5H)	
	^{13}C	107.4	162.1	66.7	14.2	122.4	126.0/128.6	130.2
8b	^{1}H			4.58 (q, 2H)	1.44 (t, 3H)		7.5-8.0 (m, 5H)	
	^{13}C	130.9	150.3	68.4	15.1	125.5	126.3/128.9	131.1
12a	^{1}H			3.27 (q, 2H)	1.48 (t, 3H)		7.4-7.9 (m, 5H)	
	^{13}C	114.1	154.2	25.4	13.9	122.3	127.1/128.8	130.4
12b	^{1}H			3.01 (q, 2H)	1.22 (t, 3H)		7.4-8.0 (m, 5H)	
	^{13}C	110.3	157.1	25.2	14.7	126.1	127.5/128.7	131.0

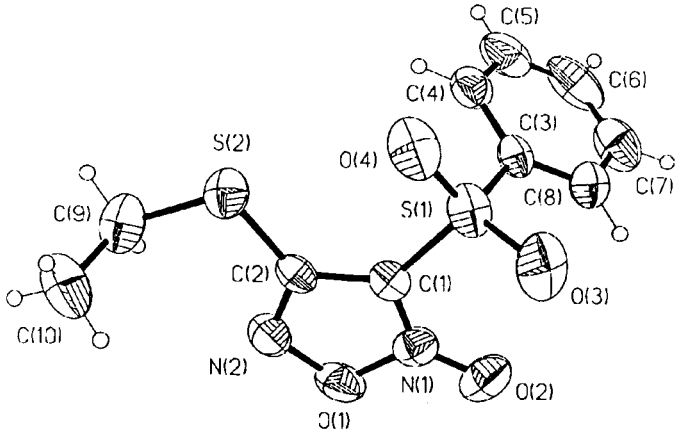


Figure 2. ORTEP Diagram of **9a**.

behaves similarly, but affords the furazan analogue in minor amount (**11**, 8%, hplc detection).

The high reactivity of the phenylsulfonyl function linked either at the 3- or at the 4-position of the furoxan ring toward the thiolate anion is confirmed by the formation of the isomers **12a** and **12b** by the action of this reagent on **7a** and **7b** respectively.

The structure of the couple of isomers **9a,b** was assigned by nmr (see Table 1) on the basis of the known larger deshielding effect of the SO_2R group than that of S-R moiety [10] and on the basis of INEPT ^{13}C-nmr experiments. In fact, compound **9a** shows the typical INEPT modified triplet ($^3J_{C-H}$ = 4.5 Hz) relative to the signal at 153.4 ppm, while **9b** displays the same pattern at 108.3 ppm ($^3J_{C-H}$ = 5.5 Hz).

Our structural assignment was confirmed for the derivative **9a** by X-ray analysis. Figure 2 shows the thermal ellipsoids and atom numbering scheme. The bond lengths and angles in the furoxan ring are in keeping with the available data on

Table 4

Crystal Data and Structure Refinement for **9a**

Crystal Data

C10 H10 N2 04 S2	Z = 4
Monoclin	FW= 286.3
P21/n	D(calc.) = 1.515 Mg/m^3
a = 4.924(2) Å	μ = 0.432 mm^{-1}
b = 16.502(8) Å	F(000) = 592
c = 15.522(5) Å	white prism
β = 95.65(2)°	0.36 x 0.36 x 0.40 (mm)
V = 1255.1(9) Å^3	

Data Collection

Siemens P4 Diffractometer	2 standard reflections measured
MoK$_\alpha$ (λ = 0.71069 Å)	every 50 reflections
T = 298 K	-5 < H < 5
Highly oriented graphite	0 < K < 19
monochromator	0 < L < 18
2θ Range from 2.0 to 50.0°	2276 Reflections Collected
ω scans	2197 (Rint = 4.26%)
	Independent
Scan Speed Variable	Reflections
(3.00 to 50.00°/min. in ω)	1477 (F > 4.0σ(F)) Observed
Scan Range (ω) = 1.00°	Reflections
Background Measurement	Absorption Correction: empirical
Stationary crystal and stationary	
counter at beginning and end of	
scan, each for 0.7%	
of total scan time	

Solution and Refinement

Solved by Direct Methods with SIR92	Data-to-Parameter Ratio = 9.1:1
Refined by Full-Matrix Least-Squares	R = 5.26 %, wR = 5.26 % (obs. data)
with Siemens SHELXTL IRIS	GooF = 1.02
Minimized Σw(F$_o$-F$_c$)^2	Largest Δ/σ = 0.046
Riding model and fixed isotropic U	Mean Δ/σ = 0.003
for Hydrogens	Largest Difference Peak = 0.59 eÅ^{-3}
Unit weights	Largest Difference Hole = -0.36 eÅ^{-3}
Refined 163 Parameters	

Table 5

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients [a] (Å^2 x 10^3) for **9a**

Atom	x	y	z	U(eq)
C(1)	3042(9)	3941(3)	2691(3)	56(2)
C(2)	1984(9)	3747(3)	3486(3)	60(2)
C(3)	3129(9)	5427(3)	1879(3)	59(2)
C(4)	1727(12)	5973(4)	2350(4)	80(2)
C(5)	11(15)	6499(4)	1894(6)	108(4)
C(6)	-294(16)	6497(5)	1014(7)	123(4)
C(7)	1132(16)	5977(5)	569(5)	108(3)
C(8)	2834(12)	5425(4)	997(4)	78(2)
C(9)	557(13)	3706(5)	5139(4)	106(3)
C(10)	1665(17)	2998(5)	5532(5)	141(5)
N(1)	1988(10)	3449(3)	2093(3)	74(2)
N(2)	333(10)	3136(3)	3375(3)	83(2)
O(1)	235(9)	2913(2)	2512(3)	94(2)
O(2)	2137(9)	3370(3)	1319(3)	103(2)
O(3)	7059(7)	4408(3)	1858(3)	113(2)
O(4)	6285(8)	5038(3)	3263(3)	103(2)
S(1)	5268(2)	4727(1)	2442(1)	74(1)
S(2)	2702(3)	4233(1)	4459(1)	81(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 6

Bond Lengths (Å) and Bond Angles (°) for **9a**.

C(1)-C(2)	1.423 (7)	N(2)-C(2)-S(2)	123.6 (4)
C(1)-N(1)	1.303 (7)	C(4)-C(3)-C(8)	121.5 (5)
C(1)-S(1)	1.764 (5)	C(4)-C(3)-S(1)	118.3 (4)
C(2)-N(2)	1.296 (7)	C(8)-C(3)-S(1)	120.2 (4)
C(2)-S(2)	1.715 (5)	C(3)-C(4)-C(5)	117.1 (7)
C(3)-C(4)	1.386 (8)	C(4)-C(5)-C(6)	121.5 (7)
C(3)-C(8)	1.362 (8)	C(5)-C(6)-C(7)	120.4 (8)
C(3)-S(1)	1.740 (5)	C(6)-C(7)-C(8)	120.2 (7)
C(4)-C(5)	1.360 (10)	C(3)-C(8)-C(7)	119.1 (6)
C(5)-C(6)	1.359 (15)	C(10)-C(9)-S(2)	115.7 (6)
C(6)-C(7)	1.343 (12)	C(1)-N(1)-O(1)	106.1 (5)
C(7)-C(8)	1.365 (10)	C(1)-N(1)-O(2)	135.3 (5)
C(9)-C(10)	1.403 (11)	O(1)-N(1)-O(2)	118.6 (5)
C(9)-S(2)	1.790 (8)	C(2)-N(2)-O(1)	107.3 (5)
N(1)-O(1)	1.434 (7)	N(1)-O(1)-N(2)	108.0 (4)
N(1)-O(2)	1.219 (7)	C(1)-S(1)-C(3)	103.9 (2)
N(2)-O(1)	1.386 (7)	C(1)-S(1)-O(3)	107.7 (3)
O(3)-S(1)	1.426 (5)	C(3)-S(1)-O(3)	107.9 (3)
O(4)-S(1)	1.419 (4)	C(1)-S(1)-O(4)	103.9 (3)
C(2)-C(1)-N(1)	108.8 (4)	C(3)-S(1)-O(4)	110.7 (3)
C(2)-C(1)-S(1)	130.1 (4)	O(3)-S(1)-O(4)	121.2 (2)
N(1)-C(1)-S(1)	121.0 (4)	C(2)-S(2)-C(9)	102.1 (3)
C(1)-C(2)-N(2)	109.8 (5)	C(1)-C(2)-S(2)	126.6 (4)

Table 7

Anisotropic Displacement Coefficients [a] (Å^{2}x10^3) for **9a**

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	38(3)	61(3)	66(3)	7(2)	-6(2)	7(3)
C(2)	49(3)	53(3)	75(4)	0(2)	-5(2)	14(3)
C(3)	39(2)	72(4)	67(3)	-12(2)	5(2)	12(3)
C(4)	76(4)	74(4)	93(4)	-13(3)	20(3)	6(4)
C(5)	96(5)	65(5)	168(8)	12(4)	36(5)	22(5)

Table 7 (Continued)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(6)	84(5)	92(6)	185(10)	0(4)	-27(6)	67(7)
C(7)	111(6)	111(6)	94(5)	-14(5)	-22(5)	38(5)
C(8)	72(4)	92(5)	71(4)	-1(3)	7(3)	9(3)
C(9)	83(5)	153(7)	82(4)	0(5)	10(4)	7(5)
C(10)	154(8)	133(8)	139(7)	-22(6)	25(6)	50(6)
N(1)	74(3)	72(3)	74(3)	18(3)	-4(3)	-2(3)
N(2)	97(4)	71(3)	76(3)	-13(3)	-6(3)	9(3)
O(1)	115(3)	60(3)	104(3)	-20(2)	-10(3)	-3(3)
O(2)	114(4)	114(4)	79(3)	26(3)	0(3)	-21(3)
O(3)	47(2)	159(5)	136(4)	26(3)	34(2)	31(3)
O(4)	73(3)	137(4)	90(3)	-42(3)	-30(2)	22(3)
S(1)	34(1)	105(1)	82(1)	4(1)	-2(1)	21(1)
S(2)	70(1)	103(1)	67(1)	-7(1)	-8(1)	3(1)

[a] The anisotropic displacement factor exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$.

Table 8

H-Atom Coordinates (x10^4) and Isotropic Displacement Coefficients (Å^2 x 10^3) for **9a**

Atom	x	y	z	U
H(4A)	1982	5980	2971	80
H(5A)	-1037	6877	2195	80
H(6A)	-1533	6870	0705	80
H(7A)	0958	5998	-0052	80
H(8A)	3815	5037	0687	80
H(9A)	0134	4064	5595	80
H(9B)	-1123	3570	4804	80
H(10A)	0423	2744	5888	80
H(10B)	2057	2632	5079	80
H(10C)	3327	3132	5879	80

X-ray diffraction studies on this heterocyclic system. In particular the N(1)-O(2) bond is unusually short (1.219 Å) and the N(1)-O(1) bond rather long (1.434 Å) [14].

The structures of the isomers **12a** and **12b** were proposed on the basis of the same rule applied in the case of derivatives **8a** and **8b**. The thermal furoxan tautomerism was studied for all the new derivatives by ^{1}H-nmr in 1,1,2,2-tetrachloroethane solution.

The thermal equilibration of the ethoxy derivatives, at 95°, gave only 4-ethoxy isomers, no 3-ethoxy form being detectable. The complete transformation of **8b** into **8a** required about 1.5 hours. As far as the thermal equilibration between the ethylthio derivatives **9a**⇌**9b** is concerned, it could not be measured directly because the compounds decomposed rapidly on heating (100°) with only a slight degree of concurrent isomerization. The K value for the isomerization **12a** ⇌ **12b** was 0.41 (110°, equilibrium approached from both sides).

EXPERIMENTAL

All melting points were taken on a capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were

measured on a Bruker AC-200. The nmr data are reported in Table 1-3. ^{13}C assignments were made on the basis of coupled, undecoupled and INEPT spectra.

Long range INEPT spectral conditions were optimized with 16K time domain data points, 10000-Hz spectral width, $\Delta_1 = 0.25/J_{C-H} = 30$ ms, relaxation delay 2 s. 2D-HETCOR spectral conditions were optimized with 10000-Hz spectral width, 1K F2 time domain data points (^{13}C frequencies) and 2000-Hz spectral width, 512 W F1 time domain data points (^1H frequencies), $\Delta_1 = \Delta_2 = 0.5/J_{C-H} = 100$ ms, relaxation delay 2 s.

All compounds were routinely checked by ir (Shimadzu FTIR-9101M) and mass spectrometry (Finnigan-Mat TSQ-700).

The equilibrium constant for the thermal isomerization **12a** ⇌ **12b** was determined by integration of the methyl and methylene peaks in ^1H nmr spectrum, after heating the compounds in *sym*-tetrachloroethane at 110° for 24 hours.

The hplc analyses were performed on a Shimadzu system equipped with two LC100A pumps, a SPD-M10A diode array detector and class LC10 software, using a RP-18 column (250 x 4.6 mm, 5 μm particles, Bio-Rad) with eluent methanol/water, 70/30 flow rate 1 ml/minutes for the separation between **9a** and **11** and a silica gel column (250 x 4.6 Techsil) with eluent chloroform/hexane 60/40, flow rate 1 ml/minute.

Silica gel (Merck Kieselgel 60), 70-230 mesh ASTM was employed for column chromatography. Petroleum ether (bp 40-60°) was used for the chromatographic purification and crystallizations.

Anhydrous magnesium sulfate was used as drying agent for the organic layers. Microanalyses were performed by REDOX (Cologno M.).

Compounds **1** [8] and **4** [15] were prepared by literature methods.

3-Benzenesulfonyl-4-ethoxyfuroxan (**2**).

To a stirred solution of THF (20 ml) containing absolute ethanol (0.25 g, 5.4 mmoles) and **1** (1.00 g, 2.7 mmoles), 0.65 g (8.1 mmoles) of 50% w/w sodium hydroxide solution were added portionwise at room temperature. The reaction mixture was allowed to stir for 2 hours. The residue obtained after solvent removal was extracted with methylene chloride. The combined organic layers were evaporated *in vacuo* and the residue was purified on a short silica gel column eluting with petroleum ether:methylene chloride (70:30, v/v) to give the pure title compound as white crystals, mp 105-106° (methanol) (lit [8], mp 94-95°).

Anal. Calcd. for $C_{10}H_{10}N_2O_5S$: C, 44.44; H, 3.73; N, 10.37. Found: C, 44.53; H, 3.74; N, 10.33.

3,4-Diethoxyfuroxan (**3**).

To a stirred solution of THF (40 ml) containing absolute ethanol (1.50 g, 32.6 mmoles) and **1** (2.00 g, 5.47 mmoles), 3.59 g (49.4 mmoles) of 50% w/w sodium hydroxide solution was added portionwise at 25°. The reaction mixture was stirred at room temperature until firstly all the starting material **1** and then derivative **2** had disappeared (7 hours tlc detection). Solvent removal left a residue which was extracted with methylene chloride. The oil obtained after solvent removal was purified as reported for **2** (eluent petroleum ether:ethyl acetate 95:5 v/v). The title compound was obtained (32%) according to the literature [4] as an oily liquid; ^1H nmr (deuteriochloroform): δ 4.39 (2 x q, 2 x 2H, 3-OCH_2CH$_3$, 4-OCH_2CH$_3$),1.45, 1.38 (2 x t, 2 x 3H, 3-OCH$_2$CH_3, 4-OCH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 157.9 (C-4), 124.0 (C-3), 69.0, 66.4 (3-OCH_2CH$_3$, 4-OCH_2CH$_3$), 14.8, 13.9 (3-OCH$_2$CH_3, 4-OCH$_2$CH_3).

1-Phenyl-2-phenylthioglyoxime (**5**).

To a stirred suspension of **4** (10 g, 50 mmoles) in a solution of thiophenol (5.50 g, 50 mmoles) in dry ether (200 ml) triethylamine (7.6 ml, 55 mmoles) in dry ether (20 ml) was added dropwise. The reaction mixture was stirred for 1 hour at room temperature and then washed first with dilute hydrochloric acid, and then with water. The organic layer was evaporated *in vacuo* to give the title compound, which was crystallized from ethyl acetate, mp 190°. An additional crop of material was obtained by adding petroleum ether to the ethyl acetate, combined yield 90%; ^1H nmr (deuteriochloroform): δ 12.10 (s, 1H, OH), 11.67 (s, 1H, OH), 7.5-7.3 (m, 10H, C_6H_5); ^{13}C nmr (deuteriochloroform): δ 148.9, 148.7 (*C*=N-OH), 134.7, 131.1, 129.0, 128.9, 128.8, 128.7, 128.5, 127.7 (2 x C_6H_5).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.88; H, 4.45; N, 10.26.

3-Phenyl-4-phenylthiofuroxan (**6a**) and 4-Phenyl-3-phenylthiofuroxan (**6b**).

To a stirred solution of **5** (5.00 g, 18 mmoles) in methylene chloride (50 ml), 10 ml of a solution 1.03 *M* of dinitrogen tetroxide in methylene chloride was added dropwise over 30 minutes. The mixture was stirred for 30 minutes at room temperature then was washed with water. Solvent removal gave a crude oily mixture of the title compounds. The mixture was resolved by column chromatography eluent petroleum ether:methylene chloride 2:1 v/v; **6b** first eluted (77%), mp 30-31° (petroleum ether) (lit [13], mp 31-32°); **6a** eluted second (13%), mp 67-68° (petroleum ether) (lit [13], mp 68-69°)

4-Benzenesulfonyl-3-phenylfuroxan (**7a**) and 3-Benzenesulfonyl-4-phenylfuroxan (**7b**).

To a stirred and water cooled solution of the appropriate phenylthio derivative (6.53 g, 24 mmoles) in acetic acid (65 ml) potassium permanganate (11.40 g, 74 mmoles) was added portionwise. The mixture was stirred at room temperature overnight and was then diluted with water. The excess of potassium permanganate and the manganese dioxide which formed were destroyed with sodium sulfite. The precipitate was filtered, partially dried, dissolved in methylene chloride and filtered on a bed of silica gel. Solvent removal afforded the title products **7a** (80%), mp 102-103° (methanol) (lit [13], mp 103-104°); **7b** (75%), mp 132-133° (methanol) (lit [13], mp 132-133.5°).

4-Ethoxy-3-phenylfuroxan (**8a**) and 3-Ethoxy-4-phenylfuroxan (**8b**).

To a stirred solution of THF (10 ml) containing absolute ethanol (0.125 g, 2.72 mmoles) and the appropriate phenylsulfonyl derivative (1.36 mmoles), 0.33 g of 50% w/w sodium hydroxide solution (4.10 mmoles) was added portionwise keeping the temperature at 25°. The reaction mixture was stirred at 25° and when the starting compound had disappeared (**8a** 4 hours, **8b** 7 hours, tlc detection) it was evaporated *in vacuo*. The residue was extracted with methylene chloride and after solvent removal the title compounds were obtained as pure white solids; **8a** (92%), mp 81-82° (ethanol) (lit [10,16], mp 82-83°); **8b** (72%), mp 40-41° (petroleum ether).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.47; H, 4.95; N, 13.58.

Preparation of 3,4-Diethylthiofuroxan (**10**), 3-Benzenesulfonyl-4-ethylthiofuroxan (**9a**) and 4-Benzenesulfonyl-3-ethylthiofuroxan (**9b**).

To a stirred solution of **1** (2.00 g, 5.47 mmoles) in THF (20 ml) kept under nitrogen, first ethanethiol (0.81 ml, 10.9 mmoles) and then later 1.30 g (16.2 mmoles) of 50% w/w sodium hydroxide solution was added portionwise, keeping the temperature at 25-28°. The mixture was left under stirring at 25° for 1 hour and then it was evaporated *in vacuo*. The residue was extracted with methylene chloride. Solvent removal gave a mixture of the title compounds which was resolved by flash chromatography (eluent, petroleum ether:methylene chloride, 70:30%). The first eluted fraction (21%) was formed by pure **10** (oil); ^{1}H nmr (deuteriochloroform): δ 2.91, 3.14 (q, 4H, 3-SC*H*$_2$CH$_3$, 4-SC*H*$_2$CH$_3$), 1.22, 1.40 (t, 6H, 3-SCH$_2$C*H*$_3$, 4-SCH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 158.1 (C-4), 110.2 (C-3), 24.6, 25.81 (3-S*C*H$_2$CH$_3$, 4-S*C*H$_2$CH$_3$), 14.9, 13.9 (3-SCH$_2$*C*H$_3$, 4-SCH$_2$*C*H$_3$).

Anal. Calcd. for $C_6H_{10}N_2O_2S_2$: C, 34.95; H, 4.85; N, 13.59. Found: C, 35.00; H, 4.93; N, 13.61.

The second fraction (17%) was a mixture of **9a** (77%) and of its furazan analogue **11** (23%). The mixture was recrystallized from petroleum ether/ethyl acetate to give pure **9a**, mp 117-119°.

Anal. Calcd. for $C_{10}H_{10}N_2O_4S_2$: C, 41.96; H, 3.52; N, 9.79. Found: C, 41.97; H, 3.55; N, 9.76.

The third fraction was composed of pure **9b** (11%), mp 50-51° (petroleum ether/ethyl acetate).

Anal. Calcd. for $C_{10}H_{10}N_2O_4S_2$: C, 41.96; H, 3.52; N, 9.79. Found: C, 41.90; H, 3.53; N, 9.75.

4-Benzenesulfonyl-3-ethylthiofurazan (**11**).

The title compound was obtained starting from **9b** (0.52 mmole) ethanethiol (1.1 mmoles) and sodium hydroxide (1.6 mmoles) according to the procedure described for the preparation of the furoxan analogues (reaction time 5 hours). The reaction mixture was resolved by flash chromatography to give unreacted **9b** (54%), **10** (13%) and **11** (33%), mp 65-66° (petroleum ether); ^{1}H nmr (deuteriochloroform): δ 8.1-7.6 (m, 5H, C_6H_5), 3.20 (q, 2H, CH_2), 1.45 (t, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 155.2 (*C*-SO$_2$C$_6$H$_5$), 151.6 (*C*-SCH$_2$CH$_3$).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S_2$: C, 44.44; H, 3.73; N, 10.37. Found: C, 44.37; H, 3.76; N, 10.25.

4-Ethylthio-3-phenylfuroxan (**12a**) and 3-Ethylthio-4-phenylfuroxan (**12b**).

To a stirred solution of the appropriate sulfonyl derivative(1.00 g, 3.3 mmoles) in THF (10 ml) kept under nitrogen, first ethanethiol (0.27 ml, 3.6 mmoles) and after 0.53 g (6.6 mmoles) of 50% w/w sodium hydroxide solution was added portionwise, keeping the temperature at 25°. The mixture was left under stirring at 25° for 1 hour and then it was evaporated *in vacuo*. The residue was extracted with methylene chloride. Derivative **12a** was obtained as a pure white solid (95%) after solvent removal, mp 42-43° (petroleum ether).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.98; H, 4.54; N, 12.64.

Derivative **12b**, obtained as an oil, was purified on by flash chromatography (eluent petroleum ether:methylene chloride, 70:30 v/v) (90%).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.01; H, 4.72; N, 12.78.

Crystal Structure Analysis.

The Crystal Data and Structure Refinement are given in Table 4.

The structure was solved by direct method using SIR92 [17] program. All subsequent calculations were carried out by the SHELXTL IRIS [18] system. Unit weights were chosen because they gave the best least square solution.

The structure for the asymmetric unit is shown in Figure 2, the atomic coordinates are given in Table 5, selected bond and angles are given in Table 6, anisotropic displacement coefficients are given in Table 7 and hydrogen coordinates and isotropic displacement coefficients are given in Table 8.

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