Unsymmetrically Substituted Furoxans. III. Methylnitrofuroxan: Its Structure and Behavior Toward Nucleophilic Substitution

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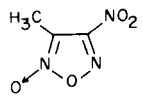
A series of unsymmetrically substituted furoxans have been prepared from methylnitrofuroxan and a variety of nucleophilic reagents. The nmr study of these compounds and of their parent furazans suggested the structure of 3-methyl derivatives for all the furoxans synthesized: on this ground the 3-methyl structure for methylnitrofuroxan was proposed. On heating some 3-methylfuroxan derivatives, a partial isomerization into the corresponding 4-methyl isomers occurred.

Introduction.

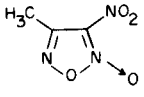
While the chemical behavior and the pharmacological activity of many nitro derivatives of heterocyclic *N*-oxides are well known (1,2,3), only very few data are reported in the literature on the nitrofuroxans. These compounds are very interesting for the study we have recently begun on the chemical and pharmacological properties of unsymmetrical substituted furoxans (4,5). In this paper the structure of methylnitrofuroxan is deduced from a structural study of nucleophilic substitution products which can easily be obtained from this molecule.

Results and Discussion.

Methylnitrofuroxan was synthesized by Beherend's method (6). In later papers (7,8,9) other methods of synthesis were reported, but no structural evidence was put forward. In Boyer's review (10) the structure of this compound is considered doubtful: no decision was made between formulae **1a** and **1b**.



1a

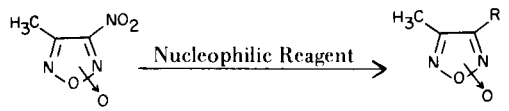


1b

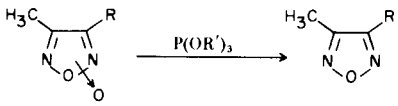
Methylnitrofuroxan, as expected, undergoes nucleophilic substitution reactions very easily. By allowing it to stand at room temperature with a variety of nucleophilic reagents, it is possible to displace the nitro group (see Table I).

In the reaction with sodium thiophenoxide significant amounts of diphenyl disulfide were also isolated. All the substitution products obtained were reduced by alkyl phosphites to the parent furazans **2-6** (see Table II).

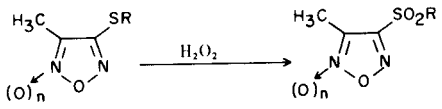
TABLE I



Reagents	Solvent	Compound:R	No.
C_2H_5OH+NaOH	ethanol	OC_2H_5	**2a**
C_6H_5OH+NaOH	aq. acetone	OC_6H_5	**3a**
	ether		**4a**
C_2H_5SH+NaOH	aq. acetone	SC_2H_5	**5a**
C_6H_5SH+NaOH	aq. acetone	SC_6H_5	**6a**



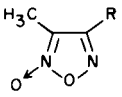
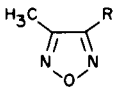
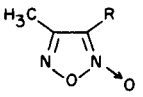
Furthermore, the sulfide derivatives were transformed at room temperature by 30% hydrogen peroxide into the corresponding sulfones.



n = 0 or 1
R = C_2H_5, C_6H_5

Since the resonance signals of the methyl groups in the furoxans (**a**) and in the parent furazans are different, (see Table II), it is possible, according to previously reported criteria (4,5), to assign to all the above methylfuroxans, prepared directly from the nitro compound, a 3-methyl structure.

TABLE II

R	No.	(CH_3)	No.	(CH_3)	No.	(CH_3)
OC_2H_5	**2a**	2.07	**2**	2.22	-----	-----
OC_6H_5	**3a**	2.17	**3**	2.32	-----	-----
	**4a**	2.28	**4**	2.45	-----	-----
SC_2H_5	**5a**	2.06	**5**	2.23	**5b**(a)	2.30 (b)
SC_6H_5	**6a**	1.97	**6**	2.17	**6b**(a)	2.21
$SO_2C_2H_5$	**7a**	2.33	**7**	2.56	**7b**(a)	2.50 (b)
$SO_2C_6H_5$	**8a**	2.32	**8**	2.57	**8b**(a)	2.57

(a) Obtained by thermal isomerization from the corresponding 3-methyl isomers. (b) The methyl resonance position is taken from the spectrum of the isomer mixture (see Experimental).

As all the nucleophilic substitutions were achieved under reaction conditions (see Experimental) in which thermal isomerization of the unsymmetrically substituted furoxans does not take place (11), the 3-methyl structures assigned to these products suggest a 3-methyl-4-nitro structure **1a** for the starting methylnitrofuroxan.

Further evidence for the above assignments was obtained from thermal modifications. On heating the compounds with sulfur-containing groups for several hours at temperatures between 80° and 120°, a partial isomerization into the corresponding 4-methyl isomers was obtained. In some cases the mixture was resolved by chromatography. The 4-methyl isomers, heated under the same conditions, gave the identical equilibrium mixture obtained from the corresponding 3-methyl compounds.

6a, R = SC_6H_5
8a, R = $SO_2C_6H_5$

6b, R = SC_6H_5
8b, R = $SO_2C_6H_5$

TABLE III

Analytical and Spectral Data

Compound	Molecular formula	M^+ (m/e)	Analytical data calcd./found C	H	N	Ir (cm^{-1}) furoxan	Nmr (δ) (a)
1a	$C_3H_3N_3O_4$	145	-----	-----	-----	1642, 1510 (b)	-----
2a	$C_5H_8N_2O_3$	144	41.7/41.4	5.6/5.5	19.4/19.7	1640 (c)	1.45 t (e) (3H) 4.41 q (e) (2H)
2	$C_5H_8N_2O_2$	128	46.9/46.7	6.3/6.1	21.9/21.7	-----	1.45 t (e) (3H) 4.37 q (e) (2H)
3a	$C_9H_8N_2O_3$	192	56.25/56.2	4.2/4.3	14.6/14.65	1642 (d)	7.33 m (5H)
3	$C_9H_8N_2O_2$	176	61.4/61.4	4.6/4.65	15.9/15.9	-----	7.30 m (5H)
4a	$C_7H_{11}N_3O_2$	169	49.7/49.9	6.55/6.6	24.8/24.9	1612 (b)	2.00 m (4H) 3.47 m (4H)
4	$C_7H_{11}N_3O$	153	54.9/54.6	7.2/7.2	27.4/27.55	-----	2.00 m (4H) 3.47 m (4H)
5a	$C_5H_8N_2O_2S$	160	37.5/37.5	5.0/5.2	17.5/17.6	1618 (b)	1.43 t (f) (3H) 3.18 q (f) (2H)
5	$C_5H_8N_2OS$	144	41.7/41.4	5.6/5.75	19.4/19.1	-----	1.43 t (f) (3H) 3.14 q (f) (2H)
5b	$C_5H_8N_2O_2S$	-----	-----	-----	-----	-----	1.23 t (f) (3H) 2.94 q (f) (2H) (g)
6a	$C_9H_8N_2O_2S$	208	51.9/52.1	3.9/4.0	13.5/13.4	1618 (b)	7.40 m (5H)
6	$C_9H_8N_2OS$	192	56.25/56.0	4.2/4.0	14.6/14.4	-----	7.37 m (5H)
6b	$C_9H_8N_2O_2S$	208	51.9/52.1	3.9/3.9	13.5/13.45	1595 (b)	7.24 m (5H)
7a	$C_5H_8N_2O_4S$	192	31.3/31.3	4.2/4.3	14.6/14.7	1625 (d)	1.46 t (e) (3H) 3.45 q (e) (2H)
7	$C_5H_8N_2O_3S$	176	34.1/33.9	4.6/4.6	15.9/15.7	-----	1.40 t (f) (3H) 3.47 q (f) (2H)
7b	$C_5H_8N_2O_4S$	-----	-----	-----	-----	-----	1.35 t (e) (3H) 3.35 q (e) (2H) (g)
8a	$C_9H_8N_2O_4S$	240	45.0/45.3	3.4/3.5	11.7/11.4	1625 (d)	7.80 m (5H)
8	$C_9H_8N_2O_3S$	224	48.2/48.3	3.6/3.7	12.5/12.4	-----	7.80 m (5H)
8b	$C_9H_8N_2O_4S$	240	45.0/45.0	3.4/3.5	11.7/11.6	1608 (d)	7.80 m (5H)

(a) The resonance signals of the ring methyl groups in the furoxans and in the parent furazans are reported in Table II: t = triplet. q = quartet; m = multiplet. (b) In carbon tetrachloride. (c) Liquid film. (d) Potassium bromide pellet. (e) J = 7 Hz. (f) J = 7.5 Hz. (g) The quoted values are taken from the nmr spectra of the isomer mixture.

TABLE IV

Preparation of Sulfones

Compound Oxidized	Acetic Acid	Hydrogen Peroxide (30%)	Reaction Time	Product (Yield)	M.p.	Recrystallizing Solvent
5a (1.6 g.)	8 ml.	3.0 ml.	7 days	**7a** (80%)	38-40°	methanol-water
5 (0.5 g.)	3 ml.	1.1 ml.	7 days	**7** (90%)	28°	petr. ether 100-140°
6a (1.5 g.)	25 ml.	2.3 ml.	11 days	**8a** (90%)	83-85°	methanol-water
6 (0.5 g.)	5 ml.	0.9 ml.	10 days	**8** (90%)	30-31°	methanol-water

The resonance signals of the methyl groups in this new series of compounds were close to those in the parent furazans (see Table II).

Heating the phenoxy, ethoxy and pyrrolidine derivatives under similar conditions, no isomerization was obtained. The situation for methylnitrofuroxan was more complex, with a little isomerization and decomposition. The quantitative study of these equilibria and the discussion of the structural factors which influence the equilibrium positions will be reported in a future paper (11).

In a preliminary pharmacological screening, the methylnitrofuroxan was found to have a strong antibacterical and antifungal activity and some sulfones were found to be antituberculosis agents (12).

EXPERIMENTAL

All melting points were taken on a capillary melting point apparatus and are uncorrected. Infrared spectra were determined using a Perkin Elmer 257 spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrophotometer, in deuteriochloroform solution, using TMS as internal standard. Nmr of furoxans were taken on both crude and purified samples to ascertain that no isomerization had occurred during the purification. Mass measurements were carried out on a Varian CH7 MAT mass spectrometer. Analytical and spectral data of all the compounds are reported in Table III.

3-Methyl-4-nitrofuroxan (**1a**).

This compound was prepared by Beherend's method. The purity of the compound was checked by tlc and nmr, m.p. 65-66° (lit. (6) 66-67°).

4-Ethoxy-3-methylfuroxan (**2a**).

To a stirred solution of **1a** (4.35 g.) in a little ethanol, sodium hydroxide (1.30 g.) in ethanol (32 ml.) was added dropwise at 15-20°. The reaction mixture was then maintained at room temperature for an additional 60 minutes. The residue was diluted with water and the mixture was extracted with ether. The ether extracts were dried (magnesium sulfate) and the solvent evaporated at reduced pressure to leave an oil (85%) which was purified by distillation at 94-95° (5 mm Hg).

3-Ethoxy-4-methylfurazan (**2**).

The furoxan **2a** (3.00 g.) was deoxygenated by refluxing for 27 hours with trimethyl phosphite (20 ml.). Pouring into cold water (40 ml.) containing 10 *N* hydrochloric acid (*ca.* 4 ml.) gave an oil which was purified by steam distillation (90%). An analytical sample was prepared by microdistillation *in vacuo*; $n_D^{25} = 1.4267$.

3-Methyl-4-phenoxyfuroxan (**3a**).

To the nitrofuroxan **1a** (1.45 g.) in acetone (5 ml.), a solution of phenol (1.00 g.) and of sodium hydroxide (0.48 g.) in a mixture of acetone (10 ml.) and water (3 ml.) was added dropwise with stirring at 15-20°. After a further 90 minutes at 20°, the solvent was partly removed *in vacuo* at room temperature. The residue was diluted with water and the resulting solid was collected by filtration and dried (60%). An analytical sample was recrystallized from ethanol-water, as plates, m.p. 120-121°.

3-Methyl-4-phenoxyfurazan (**3**).

The furoxan **3a** (1.50 g.) was deoxygenated with refluxing trimethyl phosphite (15 ml.) for 20 hours. The reaction solution was treated in the usual manner giving **3** (95%) which, after recrystallization from ethanol, gave needles, m.p. 46-47°.

3-Methyl-4-pyrrolidinofuroxan (**4a**).

To a stirred solution of **1a** (1.45 g.) in dry ether, pyrrolidine (2 ml.) was added dropwise at 15-20°. The stirred reaction mixture was maintained at room temperature for 120 minutes and the ether was then removed *in vacuo*. The residue was diluted with water and the resulting solid was collected by filtration and dried (75%). Recrystallization from ethanol-water gave small plates, m.p. 101°.

3-Methyl-4-pyrrolidinofurazan (**4**).

A sample of **4a** (0.50 g.) was deoxygenated by refluxing in triethyl phosphite (5 ml.) for 10 hours. The deoxygenation was accompanied by a considerable decomposition. The reaction solution was treated in the usual way, giving **4** (45%). Recrystallization from ethanol-water gave needles, m.p. 44-46°.

4-Ethylthio-3-methylfuroxan (**5a**).

To a stirred mixture of ethyl mercaptan (3 ml.) and sodium hydroxide (1.60 g. in 5 ml. of water) in acetone (30 ml.) a solution of **1a** (4.35 g.) in acetone (15 ml.) was added at 15-20°. The reaction mixture was maintained at room temperature for 60 minutes. Solvent was partially removed *in vacuo* at room temperature and the residue was worked up as in the preparation of **2a**. The product **5a** was obtained as an oil (85%). An analytical sample was purified by distillation *in vacuo* at 61-63° (0.15 mm Hg). During the purification a little isomerization can occur.

3-Ethylthio-4-methylfurazan (**5**).

A sample of **5a** (3.00 g.) was deoxygenated by refluxing for 21 hours with trimethyl phosphite (20 ml.). The reaction mixture was worked up as in the preparation of **2**. After removal of the ether, an oil was obtained (90%) which was purified by microdistillation *in vacuo*. $n_D^{25} = 1.4881$.

3-Methyl-4-phenylthiofuroxan (**6a**).

The furoxan **1a** (1.45 g.) in acetone (5 ml.) was added at 15-20° to a stirred mixture of thiophenol (1.2 ml.) and sodium hydroxide (0.48 g. in 5 ml. of water). The reaction mixture was maintained at room temperature for 90 minutes. Solvent was partially removed *in vacuo* at room temperature. The residue was diluted with water, and the resulting solid was collected by filtration and dried. From the crude material **6a** (53%) and diphenyl disulfide (21%) (m.p. 60-61° from methanol, lit. (13) m.p. 60-61°) were obtained by silica gel column chromatography (eluent benzene). The compound **6a** can also be obtained in good yield from the crude mixture by repeated crystallization from petroleum ether (40-60°). An analytical sample was recrystallized from petroleum ether (40-60°), giving hexagonal prisms, m.p. 84-86°.

3-Methyl-4-phenylthiofurazan (**6**).

Compound **6a** (1.00 g.) was deoxygenated with trimethyl phosphite (10 ml.) for 8 hours in the usual way, giving a crude material (90%) which was recrystallized from methanol-water, as microcrystalline product, m.p. 27-28°.

General Method of Preparation of Sulfone Derivatives.

To a solution of the sulfide in glacial acetic acid an excess of 30% hydrogen peroxide was added. The reaction flask was stoppered and kept at room temperature for several days. After this period, the reaction mixture was diluted with water and the separated solid was collected by filtration. In the case of **7a** the sulfone derivative was extracted from aqueous solution with ether. The ether layers were stirred with aqueous sodium hydrogen carbonate. The organic layer was separated, dried (magnesium sulfate) and distilled *in vacuo*. The reaction conditions of the preparation of sulfone derivatives are reported in Table IV.

Thermal Isomerization of Furoxan Sulfides and Sulfones.

On heating **5a** and **6a** for some hours at 100° and **7a** and **8a** at 120°, a partial thermal isomerization occurs. In the cases of the mixtures **6a-6b** and **8a-8b** the separation of isomers was performed on a silica gel column using as eluent light petroleum (40-60°) containing 0-30% benzene. In the equilibrium mixtures the 3-methyl isomers were slightly favored.

4-Methyl-3-phenylthiofuroxan (**6b**).

After heating this compound (an oil at room temperature) under the same conditions as **6a**, the identical equilibrium mixture was obtained.

4-Methyl-3-phenylsulfonylfuroxan (**8b**).

Recrystallized from chloroform-petroleum ether (40-60°), gave needles m.p. 97-98°. Heating this compound in the same conditions of **8a**, the identical equilibrium mixture was obtained.

Acknowledgment.

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REFERENCES

(1) M. H. Bichel, *Pharmacol. Rev.*, **21**, 325 (1969).

(2) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," Academic Press, London and New York, 1971.

(3) E. Ochiai, "Aromatic Amine Oxides," Elsevir Publishing Co., Amsterdam, 1967.

(4) A. Gasco, V. Mortarini, G. Ruà and E. Menziani, *J. Heterocyclic Chem.*, **9**, 837 (1972).

(5) A. Gasco, V. Mortarini, G. Ruà, G. M. Nano and E. Menziani, *ibid.*, **9**, 577 (1972).

(6) R. Beherend and J. Schmitz, *Ann. Chem.*, **277**, 310 (1893).

(7) N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1100 (1946).

(8) S. Fumasani, G. Giacobbe, R. Martinelli and G. Scippa, *Chim. Ind.* (Milan), **47**, 1064 (1965).

(9) A. D. Nikolaeva, Yu. N. Matyushin, V. I. Pepekin, V. S. Smelov, V. V. Bulidorov, T. I. Bulidorova, and A. Ya. Apin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **4**, 965 (1972); *Chem. Abstr.*, **77**, 75165g (1972).

(10) J. H. Boyer in "Heterocyclic Compounds," R. C. Elderfield, Ed., Vol. 7, John Wiley, New York, 1961, pp. 462-508.

(11) A. Gasco and A. J. Boulton, unpublished work.

(12) M. A. Bianco, private communication.

(13) "Beilstein Handbuch der Organischen Chemie" 4th Ed., Vol. VI, 3rd Suppl., Ed. Springer-Verlag, Berlin, 1965, p. 1028.