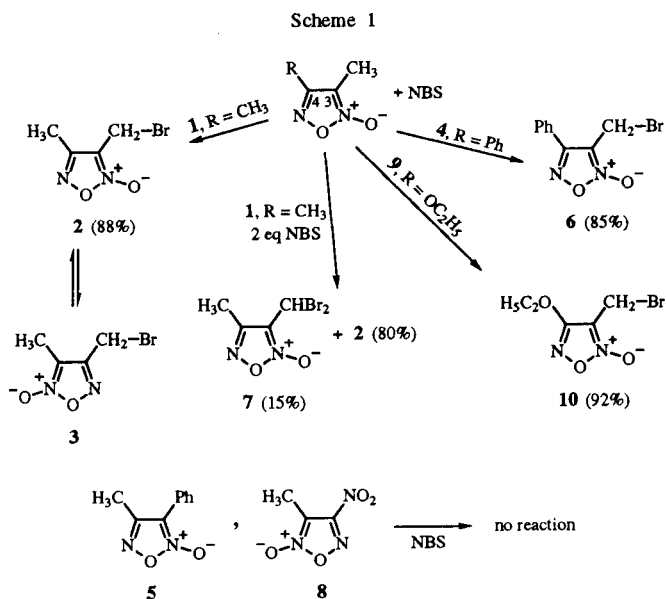


Dipartimento di Scienza e Tecnologia del Farmaco, Università di Torino,
 Via P. Giuria 9, 10125 Torino, Italy
 Received December 14, 1994

Treatment of the dimethylfuroxan **1** and of the two methylphenylfuroxan isomers **4**, **5** with *N*-bromosuccinimide (NBS) shows that the methyl group linked at the 3-position of the furoxan ring is selectively brominated. The same reaction run with the 3-methyl-4-nitrofuroxan **8** and with the 4-ethoxy-3-methylfuroxan **9** bears evidence that the reactivity of the 3-methyl group is dependent on the nature of the substituent at the 4-position. 3-Bromomethylfuroxan derivatives easily undergo nucleophilic substitutions to afford a variety of unsymmetrically substituted furoxans.

J. Heterocyclic Chem., **32**, 811 (1995).

Recent results have shown that furoxan derivatives are able to activate the soluble guanylate cyclase [2,3] by releasing nitric oxide (NO), under the action of thiol cofactors [3]. Since nitric oxide is an important messenger implicated in a wide range of biological functions [4], the furoxan system can be useful in the design of NO-releasing new drugs. In view of this interest we have examined new routes to obtain functionally substituted furoxans. In the present work we investigated the bromination, by *N*-bromosuccinimide (NBS), of the methyl group linked to the furoxan system (Scheme 1).

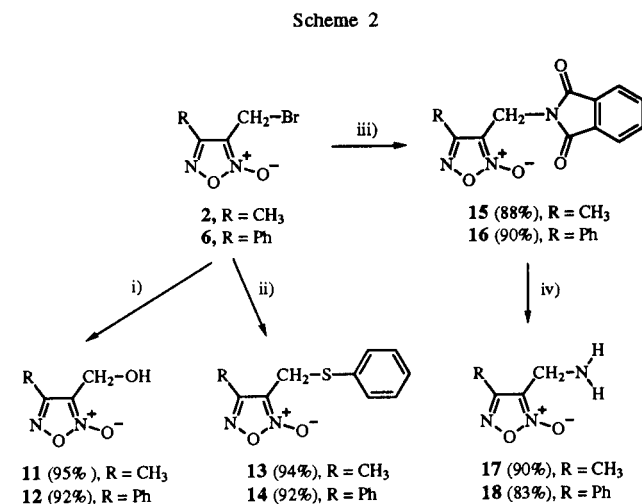


basis that the *N*-oxide group exerts a shielding influence both on ¹H and on ¹³C resonances of the 3-methyl and 3-methylene groups as compared to the resonances of the same groups at 4-position [5].

The furoxan tautomerism [5] of **2** was studied heating this compound for 24 hours in *sym*-tetrachloroethane: partial isomerization into **3** occurred ($2 \rightleftharpoons 3$, $K_{125^\circ} = 1.07$). Thus we can conclude that NBS selectively attacks the 3-methyl group on the furoxan ring.

This finding is confirmed by the results we obtained, working under the same conditions, with the 3-methyl-4-phenylfuroxan **4** and with its 4-methyl isomer **5**. 3-Bromomethyl-4-phenylfuroxan **6** was obtained from **4** in very good yield (85%), while no 4-bromomethyl derivative was afforded by **5** (nmr detection). When **1** was treated with two equivalents of NBS a mixture of 3-bromomethyl **2** (80%) and of 3-dibromomethyl **7** (15%) was produced.

The ease of bromination of the 3-methyl group is



i) CaCO₃, dioxane/H₂O, Δ. ii) PhSH, *t*-BuOK, abs. EtOH, -10°. iii) K Phthalimide, benzyltriethylammonium chloride, CHCl₃. iv) CH₃NH₂, MeOH.

When we treated dimethylfuroxan **1** with an equivalent of NBS in boiling carbon tetrachloride for 24 hours in the presence of a catalytic amount of benzoyl peroxide, 3-bromomethyl-4-methylfuroxan **2** was obtained in a very good yield (88%). The compound was accompanied only by traces of the 3-methyl isomer **3** (<2%, nmr detection). The structure of the two isomers was assigned on the

Table 1

¹H and ¹³C NMR Data of the New Furoxan Derivatives. Chemical Shifts (δ_H, δ_C in ppm, solvent CDCl₃)

Compound	¹ H NMR	¹³ C NMR
2	2.43 (s, 3H, CH ₃), 4.30 (s, 2H, CH ₂)	153.4 (C4), 113.6 (C3), 15.6 (CH ₂), 10.8 (CH ₃)
3	2.21 (s, 3H, CH ₃), 4.38 (s, 2H, CH ₂)	154.3 (C4), 112.0 (C3), 18.5 (CH ₂), 7.5 (CH ₃)
6	4.41 (s, 2H, CH ₂), 7.5-7.8 (m, 5H, Ph)	155.8 (C4), 113.2 (C3), 131.4, 129.4, 127.4, 125.6 (Ph), 17.2 (CH ₂)
7	2.64 (s, 3H, CH ₃), 6.50 (s, 1H, CH)	153.4 (C4), 116.1 (C3), 19.7 (CH), 11.8 (CH ₃)
10	1.46 (t, 3H, J = 7 Hz, CH ₃), 4.22 (s, 2H, CH ₂), 4.46 (q, 2H, J = 7 Hz, OCH ₂)	161.4 (C4), 106.9 (C3), 66.7 (OCH ₂), 14.6, 14.0 (CH ₂ , CH ₃)
11	2.39 (s, 3H, CH ₃), 3.55 (br, 1H, OH), 4.56 (s, 2H, CH ₂)	154.45 (C4), 115.9 (C3), 52.5 (CH ₂), 10.7 (CH ₃)
12	3.15 (t, 1H, J = 6.6 Hz, OH), 4.73 (d, 2H, J = 6.6 Hz, CH ₂), 7.5-7.9 (m, 5H, Ph)	156.8 (C4), 114.9 (C3), 131.2, 129.2, 127.6, 125.9 (Ph), 53.0 (CH ₂)
13	2.06 (s, 3H, CH ₃), 3.89 (s, 2H, CH ₂), 7.3-7.4 (m, 5H, Ph)	153.9 (C4), 113.8 (C3), 132.4, 132.1, 129.2, 128.3 (SPh), 26.95 (CH ₂), 10.5 (CH ₃)
14	4.10 (s, 2H, CH ₂), 7.2-7.6 (m, 10H, Ph)	156.3 (C4), 113.2 (C3), 130.9, 129.15, 127.5, 126.1 (Ph), 132.7, 132.1, 129.05, 128.4 (SPh), 27.9 (CH ₂)
15	2.47 (s, 3H, CH ₃), 4.75 (s, 2H, CH ₂), 7.7-7.9 (m, 4H, Ph)	154.1 (C4), 111.7 (C3), 166.9, 134.4, 131.3, 123.7 (Phthal), 29.4 (CH ₂), 11.0 (CH ₃)
16	4.94 (s, 2H, CH ₂), 7.4-7.8 (m, 9H, Ph)	156.4 (C4), 110.75 (C3), 166.8, 134.3, 131.2, 123.5 (Phthal), 130.9, 129.05, 128.0, 125.7 (Ph), 30.75 (CH ₂)
17 [a]	2.42 (s, 3H, CH ₃), 4.06 (s, 2H, CH ₂), 8.62 s, 8.31 br (picric acid, active hydrogens)	156.1 (C4), 112.4 (C3), 161.0, 142.0, 125.4, 124.5 (picric acid), 30.5 (CH ₂), 10.8 (CH ₃)
18 [a]	4.19 (s, 2H, CH ₂), 7.65-7.85 (m, 5H, Ph), 8.61 s, 8.36 br (picric acid, active hydrogens)	157.2 (C4), 112.0 (C3), 131.6, 129.3, 128.1, 125.4 (Ph), 161.1, 142.0, 125.3, 124.3 (picric acid), 31.3 (CH ₂)

[a] Picrate, solvent: DMSO-d₆.

strongly dependent on the nature of the other substituent at the 4-position of the furoxan ring. In fact while 3-methyl-4-nitrofuroxan **8** does not react with NBS, the 4-ethoxy-3-methylfuroxan **9** gives, after 12 hours of reaction, the corresponding 3-bromomethyl derivative **10** in an excellent yield (92%).

The 3-bromomethyl moiety easily reacts with nucleophiles (Scheme 2). Thus when **2** or **6** were treated with calcium carbonate in a mixture of dioxane/water, the corresponding 3-hydroxymethyl derivatives **11** and **12** were obtained. Likewise the reactions with thiophenol and potassium phthalimide afforded the expected substitution derivatives **13-16**. From the phthalimido derivatives the 3-aminomethylfuroxans **17** and **18** were easily prepared.

In conclusion 3-bromomethyl functionalized furoxans are excellent starting materials to obtain a variety of new unsymmetrically substituted furoxans.

EXPERIMENTAL

All melting points were taken on a capillary melting point apparatus and are uncorrected. The ¹H and ¹³C nmr spectra were measured on a Bruker AC-200. The nmr data are reported in Table 1. All compounds were routinely checked by ir (Shimadzu FTIR-9101M) and mass spectrometry (Finningam-Mat TSQ-700). The equilibrium constant for the **2** ⇌ **3** isomerization was determined by integration of the methyl peaks in the ¹H nmr spectrum, after heating of **2** for 24 hours in *sym*-tetrachloroethane at 125° (±1°). Silica gel (Merck Kieselgel 100),

70-230 mesh ASTM was employed for column chromatography. Petroleum ether (bp 40-60°) was used for the chromatographic purifications and crystallizations. Anhydrous magnesium sulphate was used as drying agent. Derivatives **1** [6], **8** [7], **9** [8] were synthesized according to the methods reported in the literature. Derivatives **4** and **5** were prepared according to the literature [9]; the isomeric mixture obtained by sodium hypochlorite oxidation and heating to reach thermodynamic equilibrium concentrations was resolved by flash chromatography, using petroleum ether:diisopropyl ether (75:25, v/v) as the eluent.

3-Bromomethyl-4-methylfuroxan (**2**).

To a stirred solution of **1** (1.14 g, 10 mmoles) in dry carbon tetrachloride (50 ml), *N*-bromosuccinimide (1.96 g, 11 mmoles) and a catalytic amount of benzoyl peroxide were added. The suspension was refluxed under stirring for 24 hours and then filtered. The residue obtained after *in vacuo* solvent removal was purified on a short silica gel column eluted with petroleum ether:methylene chloride (1:1, v/v) to give 1.70 g (88%) of pure **2** as a white solid. The product was recrystallized from petroleum ether, mp 45-46°.

Anal. Calcd. for C₄H₅BrN₂O₂: C, 24.89; H, 2.61; N, 14.51. Found: C, 24.78; H, 2.61; N, 14.42.

3-Dibromomethyl-4-methylfuroxan (**7**).

The title compound was prepared and purified following the procedure reported for the synthesis of **2**, using two equivalents of *N*-bromosuccinimide (3.29 g, 22 mmoles). After solvent removal the mixture of **2** and **7** obtained was resolved by column chromatography to give 0.41 g (15%) of **7** as a pure oil and 1.54 g (80%) of **2**.

Anal. Calcd. for C₄H₄Br₂N₂O₂: C, 17.67; H, 1.48; N, 10.30. Found: C, 17.82; H, 1.49; N, 10.33.

3-Bromomethyl-4-phenylfuroxan (6).

The title compound was prepared and purified according to the procedure reported for the synthesis of **2**. Column chromatography gave 2.16 g (85%) of **6** as a pure white solid. The product was recrystallized from petroleum ether/chloroform, mp 65-66°.

Anal. Calcd. for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.26; H, 2.76; N, 10.94.

3-Bromomethyl-4-ethoxyfuroxan (10).

The title compound was prepared and purified according to the procedure reported for the synthesis of **2** (reaction time, 12 hours). Column chromatography gave 2.05 g (92%) of **10** as a pure oil.

Anal. Calcd. for $C_5H_7BrN_2O_3$: C, 26.93; H, 3.16; N, 12.56. Found: C, 27.01; H, 3.20; N, 12.55.

3-Hydroxymethyl-4-methylfuroxan (11).

To a solution of **2** (0.77 g, 4 mmoles) in dioxane (10 ml) calcium carbonate (2.00 g, 20 mmoles) and water (10 ml) were added. The mixture was refluxed for 8 hours under stirring and then evaporated *in vacuo*. The residue was treated with methylene chloride (30 ml) and then with 2*N* hydrochloric acid until dissolution of the white precipitate occurred. The separated aqueous phase, saturated with sodium chloride, was extracted several times with methylene chloride. The combined organic layers were dried and evaporated *in vacuo* and the residue obtained was purified on a short silica gel column eluted with petroleum ether:ethyl acetate (75:25, v/v) to give 0.50 g (95%) of the pure title compound as an oil.

Anal. Calcd. for $C_4H_6N_2O_3$: C, 36.93; H, 4.65; N, 21.53. Found: C, 36.84; H, 4.78; N, 21.38.

3-Hydroxymethyl-4-phenylfuroxan (12).

The title compound was prepared according to the procedure reported for the synthesis of **11**. Solvent removal gave 0.71 g (92%) of pure **12** as a white solid. The product was recrystallized from benzene/petroleum ether, mp 66-67° (lit [10], mp 66-67°).

4-Methyl-3-phenylthiomethylfuroxan (13).

To a stirred and ice-salt cooled solution of **2** (0.58 g, 3 mmoles) in absolute ethanol (10 ml) a solution of thiophenol (0.34 ml, 3.3 mmoles) and potassium *t*-butoxide (0.37 g, 3.3 mmoles) in absolute ethanol (10 ml) was added dropwise. The reaction mixture was stirred at -10° for 10 minutes, poured into water and then extracted with ether. The combined organic layers, washed with 1*N* sodium hydroxide and then with a sodium chloride saturated solution, were dried and evaporated *in vacuo* to give 0.63 g (94%) of pure **13** as a white solid. The product was recrystallized from a mixture chloroform/petroleum ether, mp 50°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.79; H, 4.54; N, 12.49.

4-Phenyl-3-phenylthiomethylfuroxan (14).

The title compound was prepared according to the procedure reported for the synthesis of **13**. Solvent removal gave an oily residue which was purified on a short silica gel column eluted with petroleum ether:methylene chloride (1:1, v/v) to afford 0.78 g (92%) of pure **14** as a pale oil.

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.35; H, 4.26; N, 9.91.

4-Methyl-3-phthalimidomethylfuroxan (15).

To a stirred solution of **2** (0.58 g, 3 mmoles) in chloroform (15 ml) potassium phthalimide (0.67 g, 3.6 mmoles) and benzyltriethylammonium chloride (0.07 g, 0.3 mmole) were added. The reaction mixture was kept under stirring at room temperature for 24 hours. The solution was filtered on a short silica gel pad, washed with 2*N* sodium hydroxide, dried and evaporated *in vacuo* to give 0.69 g (88%) of pure **15** as a white solid. The product was crystallized from ethyl acetate/petroleum ether, mp 156°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.69; H, 3.49; N, 16.19.

4-Phenyl-3-phthalimidomethylfuroxan (16).

The title compound was prepared according to the procedure reported for the synthesis of **15**. Solvent removal afforded 0.87 g (90%) of pure **16** as a white solid. The product was crystallized from ethyl acetate/petroleum ether, mp 152-153°.

Anal. Calcd. for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.22; H, 3.44; N, 12.97.

3-Aminomethyl-4-methylfuroxan Picrate (17•C₆H₃N₃O₇).

To a 33% solution of methylamine in ethanol (10 ml) **15** (0.78 g, 3 mmoles) was added. The reaction mixture was stirred at room temperature overnight. Solvent removal *in vacuo* afforded a slurry which was extracted with ether several times. The combined organic layers, dried and evaporated *in vacuo*, gave a residue which was transformed into the corresponding picrate (0.86 g, 90%), yellow solid, mp 151-153° dec (water).

Anal. Calcd. for $C_{10}H_{10}N_6O_9$: C, 33.53; H, 2.81; N, 23.34. Found: C, 33.41; H, 2.76; N, 23.34.

3-Aminomethyl-4-phenylfuroxan Picrate (18•C₆H₃N₃O₇).

The title compound was prepared according to the procedure reported for the synthesis of **17**. The residue obtained after solvent removal was transformed into the corresponding picrate (1.07 g, 83%), mp 141-142° (water).

Anal. Calcd. for $C_{15}H_{12}N_6O_9$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.73; H, 2.84; N, 19.96.

REFERENCES AND NOTES

- [1] Part 14. A. M. Gasco, A. Di Stilo, R. Fruttero, G. Sorba, A. Gasco, and P. Sabatino, *Liebigs Ann. Chem.*, 441 (1993).
- [2] D. Ghigo, R. Heller, R. Calvino, P. Alessio, R. Fruttero, A. Gasco, A. Bosia, and G. Pescarmona, *Biochem. Pharmacol.*, **43**, 1281 (1992).
- [3] M. Feelish, S. Schonafinger, and E. Noack, *Biochem. Pharmacol.*, **44**, 1149 (1992).
- [4] J. K. Kerwin, Jr., and M. Heller, *Med. Res. Rev.*, **14**, 23 (1994).
- [5] A. Gasco and A. J. Boulton, *Adv. Heterocyclic Chem.*, **29**, 251 (1981).
- [6] R. Scholl, *Ber.*, **23**, 3490 (1890).
- [7] A. D. Nikolaeva, Yu. N. Matyushin, V. L. 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**, 75165f (1972).
- [8] A. Gasco, V. Mortarini, G. Ruà, and A. Serafino, *J. Heterocyclic Chem.*, **10**, 587 (1973).
- [9] G. Ponzio, *Ber.*, **61**, 1316 (1928).
- [10] A. M. Gasco, R. Fruttero, G. Sorba, and A. Gasco, *Liebigs Ann. Chem.*, 1211 (1991).