Unsymmetrically Substituted Furoxans. VII (1).
A ^{13}C NMR Study of a Series of Isomeric Pairs of Furoxans and the Structure of the Two Isomeric Chloro-phenyl-furoxans

R. Calvino, R. Fruttero, A. Gasco* and V. Mortarini

Istituto di Chimica Farmaceutica e Tossicologica dell'Università, Torino, Italy

S. Aime

Istituto di Chimica Generale ed Inorganica dell'Università, Torino, Italy

The structure of two isomeric chloro(phenyl)furoxans is proposed by comparison of their ^{13}C nmr spectra with those of several unsymmetrically substituted furoxans and related furazans.

Introduction.

In the development of our research on unsymmetrically substituted furoxans, we were recently interested in halogeno-phenyl-furoxans. Early work by Ponzio (2) showed that, in the reaction between dinitrogen tetroxide and chlorophenylglyoxime (*anti*-configuration) (I) in ether a chloro-phenyl-furoxan (mp 66-67°) can be obtained. The peroxide structure II was then suggested. We re-examined
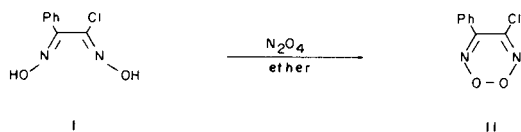
this work and we obtained a mixture of two isomeric compounds. Column chromatography gave the pure isomers: one of them had mp 66-67°, identical to that of the compound isolated by Ponzio. We believed the two derivatives to have structure IIIa (X = Cl) and IIIb (X = Cl), but an unambiguous characterisation was not straightforward since routine spectral measurements (uv, ir, ^{1}H nmr, ms) failed to distinguish the two isomers.

As ^{13}C nmr spectroscopy has been shown to be a powerful tool in assigning the structures of organic compounds, we recorded the ^{13}C spectra of the two derivatives. Unfortunately, although a great deal of results concerning organic compounds have been obtained (3,4), we were confronted with a lack of ^{13}C nmr data on simple furoxans since only the spectrum of dimethylfuroxan has been reported (5).

In order to get an unambiguous structural assignment
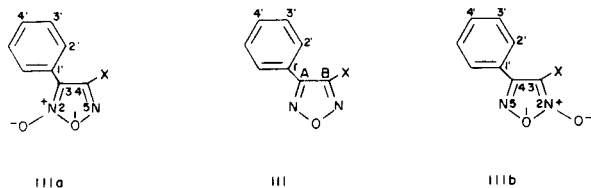

X = H, Me, Ph, NH$_2$, N(Me)$_2$, NO$_2$, SPh, SO$_2$Ph, Cl

to the isomeric chloro-phenyl-furoxans, we have undertaken a detailed ^{13}C nmr study of related series of furazans (III) and furoxans (IIIa) and (IIIb).

Preparation of Derivatives.

Details on the preparation of derivatives are reported in the Experimental. The formation and structure of IIIa (X = H) are worthy of comment. We prepared IIIa (X = H) according to Ponzio (6), by the action of dilute nitric acid on β-phenylglyoxime (*anti*-configuration) (IV). Ponzio
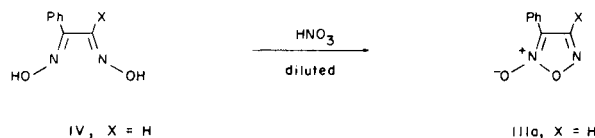
named this compound generically "β-phenylglyoxime peroxide" and was reluctant to assign a precise structure to it, although its chemical behaviour (6,7) strongly suggested it to be the 3-phenylfuroxan (IIIa) (X = H). The ^{13}C nmr is in full accord with this, as is its behaviour on heating. At 140° in 1,1,1,2-tetrachloroethane the product partially isomerizes, with decomposition, to 4-phenylfuroxan (IIIb) (X = H) (8).
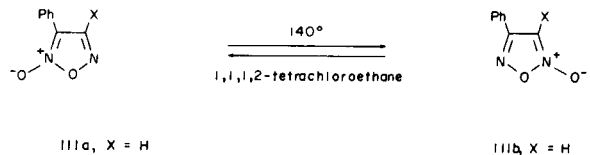
Results and Discussion.

The ^{13}C benzene ring resonances, both in the furazan and the furoxan series, were assigned on the basis of multiplicities in the ^{1}H coupled spectra (see Tables 1 and 2). When X is a phenyl-containing substituent it was not possible to distinguish clearly between two sets of phenyl groups. Furthermore some ambiguity still remains in the assignments of *ortho* and *meta* carbons, when overlaps, in

Table 1

¹³C Spectra of Furazan Derivatives III

X	C (A)	C (B)	C (1')	C (2')	C (3')	C (4')	C (others)	Lit
H	154.3	139.4 ($^1J = 195$ Hz)	125.1	127.2	129.2	130.9	-	-
Me	153.8	149.6	126.0	128.0	129.0	130.4	Me = 9.2	-
Ph	153.1	153.1	125.7	128.8	128.9	130.4	-	11
NH₂ (a)	148.2	156.5	126.8	128.9	130.3	131.4	-	12
N(Me)₂	147.6	159.8	126.8	128.2	128.8	130.1	Me = 41.2	-
NO₂	149.1	158.9	121.8	129.0	129.4	132.1	-	10
SPh	153.0	151.0	.	.	.	.	-	10
SO₂Ph	152.4	156.6	.	.	.	.	-	10

(a) Ref. DMSO-d₆.

Table 2

¹³C Spectra of Furoxan Derivatives IIIa, IIIb

X	C (3)	C (4)	C (1')	C (2')	C (3')	C (4')	C (others)	Lit
H	a) 114.0 ($^1J = 199$ Hz)	143.6	122.2	125.5	129.4	130.8	.	6
	b) 102.2 ($^1J = 208$ Hz)	156.5	126.0	126.5	129.4	131.6	.	13
Me	a) 115.0	153.6	123.0	127.4	129.2	130.5	Me = 12.5	14
	b) 112.1	156.9	126.7	127.3	129.2	131.1	Me = 8.6	14
Ph	a) 114.0	156.2	122.7 / 126.4	.	.	130.5 / 131.0	.	15
	b)							
NH₂(a)	a) 110.3	158.1	124.0	128.1	129.9	131.3	.	16
	b) 123.9	151.8	127.3	128.2	130.3	132.1	.	16
N(Me)₂	a) 110.1	160.4	123.8	128.1	128.8	130.2	Me = 39.9	16
	b) 124.7	153.2	126.7	126.9	129.1	131.0	Me = 39.5	16
NO₂	a) 109.2	158.1	119.4	128.8	129.3	132.0	.	10
	b) 126.0	151.2	123.9	129.1	129.2	132.4	.	10
SPh	a) 114.3	154.2	.	.	.	.	.	10
	b) 110.4	157.6	.	.	.	.	.	10
SO₂Ph	a) 112.3	158.8	.	.	.	.	.	10
	b) 117.7	154.7	.	.	.	.	.	10

(a) Ref. DMSO-d₆.

¹H coupled spectra, did not allow the expected patterns to be recognized. The heterocyclic carbon resonances were generally slightly broadened and of low intensity when the spectra were recorded in standard conditions, but their intensity increased when an inert relaxation reagent (Cr(acac)₃, 0.05 M) was added to the solution. In the case of compounds IIIa, III, IIIb (X = NO₂), the resonances of heterocyclic carbons bonded to the nitro group appear as triplets with ¹³C-¹⁴N coupling constants of about 17 Hz.

Furazans.

The ¹³C resonances of the furazan ring were assigned using the chemical shift parameters for the benzene series (3,4,9). In the compounds III (X = H, Me) these assignments were confirmed by the multiplicities observed in the ¹H coupled spectra (see Table 1). The trend of $\delta[C(B)]_X - \delta[C(B)]_{X = H}$ is similar to that of effects on C(1) positions in X-substituted benzenes. The C(A) resonances are less influenced by the nature of X and the behaviour of $\delta[C(A)]_X - \delta[C(A)]_{X = H}$ partially reflects that observed for effects on *ortho*-positions in the corresponding monosubstituted benzenes.

Furoxans.

On going from the furazan to the furoxan series the main spectral feature is a drastic upfield shift of one of heterocyclic carbons. By comparison with ring carbon resonances in the parent furazans, the upfield shift has been assigned to the C(3) directly bonded to Ñ—Ō moiety (see Table 2). These assignments were confirmed in the compounds IIIa (X = H, Me) and IIIb (X = H, Me) by ¹H coupled spectra and agree with those earlier made (5) for

Table 3

^{13}C Data of Two Isomeric Chlorophenylfuroxans and of the 3-Chloro-4-phenylfurazan

Compounds	benzene carbons				heterocyclic carbons			
	C (1')	C (2')	C (3')	C (4')	C (3)	C (4)	C (A)	C (B)
Chlorophenylfuroxan mp 66-67°	120.9	127.4	129.0	131.1	112.8	146.0	-	-
Chlorophenylfuroxan mp 74-75°	124.9	127.2	129.2	131.8	110.0	154.1	-	-
3-Chloro-4-phenylfurazan	123.8	128.1	129.1	131.3			152.1	144.9

C(3) and C(4) in dimethylfuroxan.

$\delta[C(3)]_{Furox} - \delta[C(A)]_{Furaz}$ is almost constant (-39 ± 1 ppm) in series (IIIa) but $\delta[C(3)]_{Furox} - \delta[C(B)]_{Furaz}$ is markedly influenced by the nature of the substituents in series IIIb. The observed behaviour can be explained in terms of an important contribution of structure IIIc to the resonance hybrid describing the furoxan ring. Furthermore the furazan to furoxan transformation


IIIc
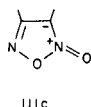
is always accompanied (except when X = NO$_2$) by a small downfield of the C(4) resonances in the furoxan ring compared with the corresponding resonances in the parent furazans. The trend of $\delta[C(4)]_b - \delta[C(4)]_a$ in correlated members of b and a furoxan series is similar to $\delta[C(A)] - \delta[C(B)]$ in the parent furazans. It confirms our assignments of heterocyclic carbons in series III. A comparison among C(1') resonances (and to a less extent C(4')) in benzene rings of furoxan derivatives is also useful to our purpose: in fact the high field effect related to the Ñ—Ō moiety is significantly transmitted to these resonances. This same situation occurs for the chemical shifts of ^{13}CH$_3$ groups in derivative IIIa (X = Me) and IIIb (X = Me) and in dimethylfuroxan (5).

The Structures of the Two Isomeric Chloro-phenyl-furoxans.

In Table 3 are reported ^{13}C nmr data of two isomeric chloro-phenyl-furoxans and of the parent 3-chloro-4-phenylfurazan III (X = Cl). On the basis of C(1') and C(4') chemical shifts we suggest for the chlorofuroxan with mp 66-67° a 3-phenyl structure IIIa (X = Cl) and for its isomer with mp 74-75° a 4-phenyl structure IIIb (X = Cl). From this statement the reported assignments for C(3) and C(4) follow. Chemical shift parameters of chloro and phenyl groups in the benzene series suggest the assignments of Table 3 for the parent furazan. For this last compound identical C(A) and C(B) chemical shifts can be proposed making use of $\delta[(C(4)]_b - \delta[C(4)]_a$ value derived from chloro-phenyl-furoxans.

The chloro-phenyl-furoxan obtained by Ponzio is thus the 4-chloro derivative. Apparently this same structure could have been suggested on the basis of its chemistry. In fact Ponzio (2) was able to obtain from his derivative, by action of sodium hydroxide in boiling alcohol, an ethoxy-phenyl-furoxan identical to the ethoxy derivative obtained by Wieland (17) from nitro-phenyl-furoxan under similar conditions. Since Wieland's nitrofuroxan has the 4-nitro structure IIIa (X = NO$_2$) (10) a 3-phenyl structure IIIa (X = Cl, OEt) for Ponzio's chloro and ethoxy derivatives follows. These considerations however can't be definitive
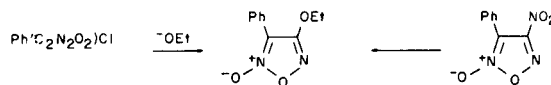
because the preparation and purification conditions of Ponzio's ethoxy derivatives were not sufficiently mild to avoid eventual thermal isomerization (1).

EXPERIMENTAL

Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Varian T-60 in deuteriochloroform with TMS as internal standard. The ir spectra were measured on a Perkin Elmer 257 spectrometer. Mass spectral measurements were carried out on a Varian CH7 MAT mass spectrometer. The ^{13}C nmr spectra were recorded on a Jeol-PFT-100 operating at 25.1 MHz in the Fourier Transform mode. The deuteriochloroform or DMSO-d$_6$ absorptions were used as internal references; chemical shifts were corrected at δ_{TMS} with $\delta_{TMS} = \delta_{CDCl_3} + 77.0$ and $\delta_{TMS} = \delta_{DMSO-d_6} + 40.4$ ppm. Accumulations of 2000-10,000 transients were performed at 22° with a spectral width of 4000 Hz. Concentrations in the range of 0.3-1 M were used.

Preparation of Derivatives.

Most of the compounds have been prepared according to literature methods (see Tables 1 and 2). Derivatives III (X = H, Me) were synthetized by action of succinic anhydride on β-methylphenylglyoxime (anti-configuration) (18) and on anti-phenyl-amphi-glyoxime (19), respectively, according to the procedure reported for the preparation of dimethyl-furazan (20). They were separated from the reaction mixture by steam distillation; the physical properties agreed with those reported (21,22).

4-Chloro-3-phenylfuroxan (IIIa) (X = Cl) and 3-Chloro-4-phenylfuroxan (IIIb) (X = Cl).

Anti-chlorophenylglyoxime (23,24) (5.0 g) was dehydrogenated by stirring with dinitrogen tetroxide (2.5 g) in anhydrous ether (50 ml) at 0-5°. After 6 hours the ether solution was washed with 2% sodium hydroxide and then with water. Removal of solvent and steam distillation gave a mixture of products in which the two isomeric chloro-phenyl-furoxans were present. Column chromatography (silicagel 60, E. Merck, eluent petroleum ether (40-60°) containing chloroform 0-30%) gave 4-chloro-3-phenylfuroxan (first compound) and 3-chloro-4-phenylfuroxan (second compound eluted). In our hands the combined yield of chloro-phenyl-furoxans was *ca.* 20%. The ratio of products IIIb/IIIa was *ca.* 0.8, being somewhat dependent on the speed of steam distillation, as at 100° thermal isomerisation between two isomers occurs.

Compound IIIa.

This compound had mp 66-67° from petroleum ether (40-60°); ¹H nmr: δ 7.45-8.10 (m, C₆H₅); ir (potassium bromide) 1592 cm⁻¹ (furox); ms: m/e 198, 196 (M)⁺, 168, 166 (M-NO)⁺, 138, 136 (M-N₂O₂)⁺.

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.9; H, 2.6; N, 14.2. Found: C, 49.2; H, 2.4; N, 14.2.

Compound IIIb.

This compound had mp 74-75° from petroleum ether (40-60°); ¹H nmr: δ 7.43-8.08 (m, C₆H₅); ir: 1608 cm⁻¹ (furox); ms: m/e 198, 196 (M)⁺; 168, 166 (M-NO)⁺; 138, 136 (M-N₂O₂)⁺.

Anal. Calcd. for $C_8H_5ClN_2O_2$: C, 48.9; H, 2.6; N, 14.2. Found: C, 48.8; H, 2.3; N, 14.05.

3-Chloro-4-phenylfurazan (III) (X = Cl).

4-Chloro-3-phenylfuroxan (1.0 g) was deoxygenated by refluxing in trimethyl phosphite (10 ml) for 4 hours. After this period the reaction solution was poured into cold water (10 ml) containing 6*N* hydrochloric acid (6 ml). The mixture was extracted with ether. The organic layers, washed several times with water, were dried (magnesium sulfate) and distilled *in vacuo*. The residue was filtered on a short column of silica gel (eluent:petroleum ether 40-60°) to give 3-chloro-4-phenylfurazan as a colourless oil, yield 80%, mp 8° (lit (25), mp 5°); ¹H nmr: δ 7.43-8.10 (m, C₆H₅); ms: m/e 182, 180 (M)⁺.

3-Dimethylamino-4-phenylfurazan (III) (X = N(Me)₂).

3-Dimethylamino-4-phenylfuroxan (16) (2.0 g) was deoxygenated at 150° in triethyl phosphite (20 ml) for 24 hours. After this period the reaction solution was worked up as in the preparation of (III) (X = Cl) and extracted with ether. The organic layers were distilled *in vacuo* and the residue was washed several times with water. Column chromatography (silica gel, eluent: petroleum ether (40-60°) containing 0-30% chloroform) gave 3-dimethylamino-4-phenylfurazan as colourless crystals, yield 40%, mp 33.5-34.5° from pentane; ¹H nmr: 2.80 (s, N(Me)₂), 7.38-7.85 (m, C₆H₅); ms: m/e 189 (M)⁺.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.5; H, 5.9; N, 22.2. Found: C, 63.75; H, 5.9; N, 22.2.

REFERENCES AND NOTES

(1) Part VI: R. Calvino, A. Gasco, A. Serafino, and D. Viterbo, *J. Chem. Soc., Perkin Trans. II.*, 1240 (1981).

(2) G. Ponzio, *Gazz. Chim. Ital.*, **62**, 127 (1932).

(3) G. C. Levy and G. L. Nelson, "Carbon-13 Nmr For Organic Chemists", Wiley-Interscience, New York, 1972.

(4) F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden, London, 1978.

(5) F. A. L. Anet and I. Yavari, *Org. Magn. Reson.*, **8**, 158 (1976). When this work had been completed we ascertained that in the paper of L. I. Khmel'nitskii, T. I. Godovikova, N. A. Ruleva, B. N. Khasapov, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2295 (1979); *Chem. Abstr.*, **92**, 94317 (1980), the ¹³C spectra of compounds IIIa (X = H) and IIIb (X = H) were reported.

(6) G. Ponzio, *Gazz. Chim. Ital.*, **55**, 698 (1925); *ibid.*, **66**, 134 (1936).

(7) G. Ponzio and L. Avogadro, *ibid.*, **57**, 124 (1927).

(8) R. Calvino and B. Ferrarotti, unpublished results.

(9) M. Mishima, M. Fujio, R. Takeda, and Y. Tsuno, *Mem. Fac. Sci., Kyushu Univ., Ser. C*, **11**, 97 (1978); *Chem. Abstr.*, **90**, 120756 (1979).

(10) R. Calvino, V. Mortarini, A. Gasco, A. Sanfilippo, and M. L. Ricciardi, *Eur. J. Med. Chem.-Chim. Ther.*, **15**, 485 (1980).

(11) F. D. Dodge, *Ann. Chem.*, **264**, 178 (1891).

(12) F. Angelico and S. Cusmano, *Gazz. Chim. Ital.*, **66**, 3 (1936).

(13) H. Wieland, *Ann. Chem.*, **424**, 107 (1921).

(14) F. B. Mallory and A. Cammarata, *J. Am. Chem. Soc.*, **88**, 61 (1966).

(15) J. H. Boyer and U. Toggweiler, *ibid.*, **79**, 895 (1957).

(16) A. R. Gagneux and R. Meier, *Helv. Chim. Acta*, **53**, 1883 (1970).

(17) H. Wieland, *Ann. Chem.*, **328**, 154 (1903).

(18) G. Ponzio, *Gazz. Chim. Ital.*, **58**, 329 (1928).

(19) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.*, **36**, 1 (1971).

(20) L. C. Beher and J. T. Brent, *Org. Synth.*, **34**, 40 (1954).

(21) M. Milone, *Gazz. Chim. Ital.*, **62**, 432 (1932).

(22) R. A. Olofson and J. S. Michelman, *J. Org. Chem.*, **30**, 1854 (1965).

(23) G. Ponzio, *Gazz. Chim. Ital.*, **60**, 886 (1930), and reference (8) reported therein.

(24) C. Pigenet, J. Armand and H. Lumbroso, *Bull. Soc. Chim. France*, 2124 (1970), and reference (8) reported therein.

(25) B. W. Nash, R. A. Newberry, R. Pickles, and W. K. Warburton, *J. Chem. Soc. (C)*, 2794 (1969).