# Unsymmetrically Substituted Furoxans. VIII (1). Chloromethylfuroxans



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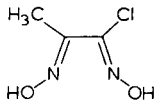
Received July 22, 1982

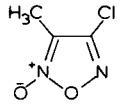
The two isomeric chloromethylfuroxans have been prepared. Their structures, thermal equilibration and reaction toward thiophenoxide ion are discussed. Kinetics of the 4-methyl → 3-methyl isomer thermal conversion are also reported.

*J. Heterocyclic Chem.*, **20**, 783 (1983).

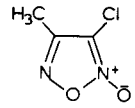
It has been reported (2,3) that chloromethylfuroxan can be obtained by oxidation of chloromethylglyoxime I (*anti*-configuration) with dinitrogen tetroxide in ether solution. The 3-methyl structure IIa was assigned to this compound on the basis of its ir spectrum and its low reactivity in the oxidation of iodide ion (3).



I



IIa

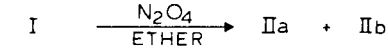


IIb

In the present paper we demonstrate that chloromethylfuroxan, obtained from the above route, is a mixture of the two possible isomers 4-chloro-3-methylfuroxan (IIa) and 3-chloro-4-methylfuroxan (IIb). The synthesis of the two isomers, their thermal equilibration, the kinetics of the IIb → IIa thermal conversion, and their reactivity towards thiophenoxide ion are also discussed.

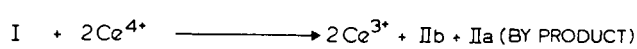
Chloromethylglyoxime I (4) (*anti*-configuration (5)) was dehydrogenated with dinitrogen tetroxide in ether according to the reported method (2,3) (see Scheme 1).

Scheme 1




After solvent removal the product was purified by silica gel column chromatography (see experimental section). The mass spectrum of the colourless oil so obtained was in keeping with a chloromethylfuroxan structure: 136, 134 ($M^+$), 106, 104 ($M^+ - NO$), 76, 74 ($M^+ - N_2O_2$), 30 ($NO^+$). Two absorptions in the methyl region of the nmr spectrum ($\delta$ 2.20, $\delta$ 2.38) showed that it was composed of a mixture of the two isomeric chloromethylfuroxans IIa and IIb in which IIa was predominant (IIa/IIb = 2.4) (6). In contrast, the 3-chloro-4-methyl isomer IIb, contaminated by *ca.* 5% of IIa (nmr analysis), was prepared by oxidation of I with ceric ion (see Scheme 2).

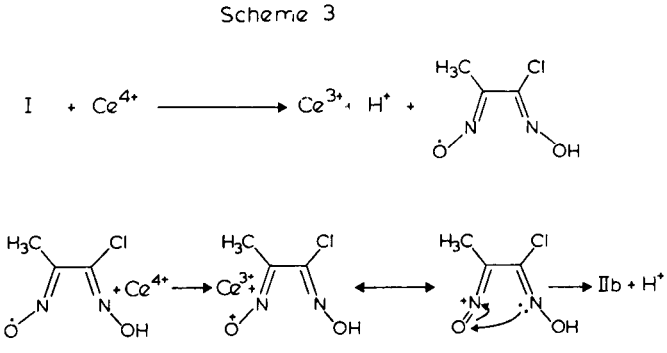
Scheme 2




Repeated recrystallisations (petroleum ether 40-60°) at low temperature of the oil obtained in this reaction gave white crystals of IIb (mp 21-22°) free from isomeric IIa (nmr analysis).

The oxidation of I by ceric ion is worthy of comment. The strong preference for the isomer IIb could be explained by the following two one-electron oxidation mechanism (see Scheme 3).

Scheme 3




The preferential attack of $Ce^{4+}$ on the oxime group adjacent to the methyl could be explained by the greater ability of this latter function, compared with the chlorine atom, to delocalize both radical and positive ionic sites (7). An attempt to oxidise I in alkaline medium with potassium ferricyanide, another one-electron oxidiser, did not work since decomposition of I occurred under these conditions. The mixture of two isomers obtained in the reaction of Scheme 1, was heated at 80° for 3 hours; an nmr of the final oil showed a strong preference for the 3-methyl derivative

Table 1 (a)

Isomerization Rate Constants and Activation Parameters

| Temperature °C (b) | $10^5$k (sec$^{-1}$) | Ea (kcal/mole) | log A | ΔH* (kcal/mole) | ΔS* (u.e.) |
|---|---|---|---|---|---|
| 60.0 | 3.69 ±0.08 | | | | |
| 65.0 | 7.29 ±0.04 | 29.5 ±0.3 | 15.0 ±0.2 | 29.0 ±0.3 | 8 |
| 70.0 | 14.0 ±0.1 | | | | |
| 75.0 | 25.6 ±0.2 | | | | |

(a) The specified uncertainties are standard errors as determined by least squares calculations. (b) Temperatures were maintained within ±0.1°C.

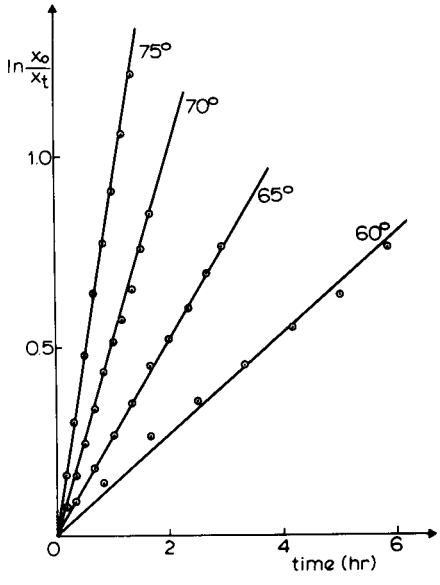
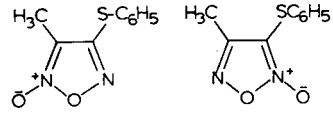



Figure 1. Plots of ln $X_0/X_t$ *vs* time for the conversion of Ib into Ia, at four temperatures in symmetrical tetrachloroethane solution; $X_0$ = initial mole fraction of Ib, $X_t$ = mole fraction of Ib at time t.

($K_{eq}$ = IIb/IIa < 0.03). Additional heating did not change the ratio between the isomers. Recrystallisation (petroleum ether 40-60°) at low temperature of the oil, previously filtered on a short silica gel column, gave white crystals of IIa (mp 20.5-21.5°) free from isomeric IIb (nmr analysis). The rates of IIb → IIa conversion (the reaction was considered irreversible) were determined at four temperatures in symmetrical tetrachloroethane (see Figures 1, 2 and Table 1). From these figures the Arrhenius and Eyring parameters for the reaction were derived (see Table 1). The activation energy value is the lowest yet found in the series of methylfuroxans for the conversion between isomers (8-10). The activation entropy, small and positive in sign, is in accordance with a probable intermediate dinitroso compound, as in other cases (8,9). Both the strong preference for the 3-methyl isomer at equilibrium and the low energy activation for IIb → IIa conversion, associate chloromethylfuroxans with the methylfuroxans substituted with electron-releasing groups.

In order to obtain additional information on the chemical behaviour of the two isomers, we studied their reaction with sodium thiophenoxide in a mixed acetone-water solvent. From IIb we obtained, in good yield, the expected 4-methyl-3-phenylthiofuroxan (IIIb). Small amounts of diphenyl disulfide were also isolated. A chlorine atom in the 3-position is therefore a good leaving group in this nucleophilic substitution.




IIIa IIIb

Under similar conditions, we isolated from IIa large amounts of diphenyl disulfide and IIIa as a by-product. Other compounds, present in the final reaction mixture, were not separated or identified. Obviously other reactions competitive with the nucleophilic substitution play a predominant role in this case.

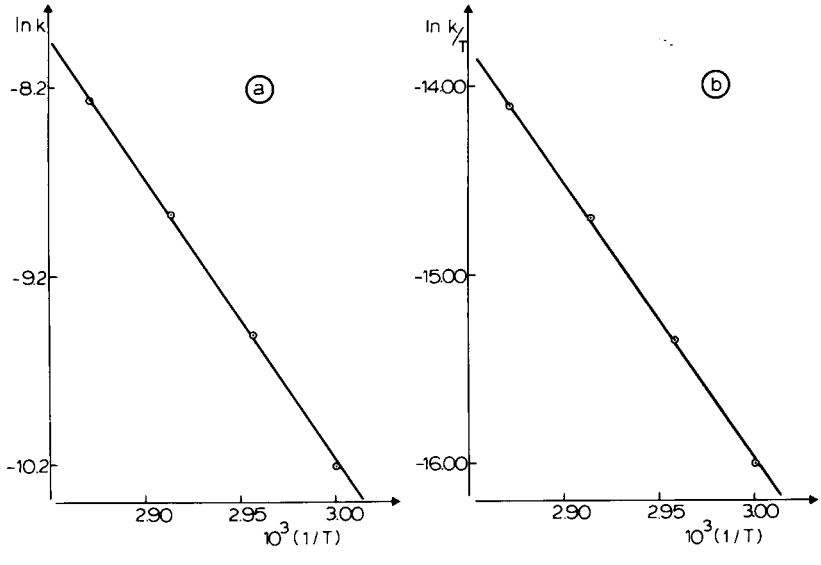



Figure 2. a) Plot of ln k *vs* (1/T). $10^3$. b) Plot of ln (k/T) *vs* (1/T). $10^3$; k = $sec^{-1}$, T is in °K.

## EXPERIMENTAL

All melting points were taken on a capillary melting point apparatus and are uncorrected. The nmr spectra were taken on a Varian A-60 spectrophotometer, in deuteriochloroform solution, using TMS as the internal standard. The ir spectra were determined using a Perkin Elmer 257 spectrophotometer. Mass measurements were carried out on a Varian CH/ mass spectrometer.

The equilibrium constant and equilibrium rates were determined by the method reported in reference (9).

### Action of Dinitrogen Tetroxide on Chloromethylglyoxime.

Compound I (5.0 g, 37 mmoles) was dehydrogenated by stirring with dinitrogen tetroxide distilled from phosphorus pentoxide, 3.5 g (38 mmoles), in 125 ml of anhydrous ether at 0-5°. After 19 hours the solution was worked up as reported in reference (3). The residual oil obtained, after removing dichloromethane at room temperature *in vacuo*, was purified on a chromatographic column (silica gel 60, E. Merck, eluent: petroleum ether 40-60° containing chloroform 0-30%). A mixture of the two isomeric chloromethylfuroxans IIa and IIb was obtained as a nearly colourless oil (40%) (IIa/IIb = 2.4); nmr: $\delta$ 2.20 (s, IIa, $CH_3$), 2.38 (s, IIb, $CH_3$); ms: 136, 134 ($M^+$), 106, 104 ($M^+$—NO), 76, 74 ($M^+$—$N_2O_2$), 30 ($NO^+$).

### 4-Chloro-3-methylfuroxan (IIa).

The mixture of IIa and IIb obtained as previously reported was heated in a closed flask for 3 hours at 80°. The nmr showed that IIb was converted nearly quantitatively into IIa under these conditions. The resulting oil was filtered on a short silica gel column, eluent: petroleum ether 40-60°-chloroform (70:30). Evaporation of the solvent followed by recrystallisation (petroleum ether 40-60°) at low temperature of the resulting oil gave white crystals, mp 20.5-21.5°; nmr: $\delta$ 2.20 (s, $CH_3$); ir (carbon tetrachloride): 1625 $cm^{-1}$ (furoxan); ms: 136, 134 ($M^+$).

*Anal.* Calcd. for $C_3H_3ClN_2O_2$: C, 26.8; H, 2.2; N, 20.8. Found: C, 26.8; H, 2.2; N, 20.75.

### 3-Chloro-4-methylfuroxan (IIb).

To a stirred solution of 5.0 g (37 mmoles) of I in 150 ml of aqueous acetic acid (acetic acid/water, 9/1), a solution of 40 g (73 mmoles) of ceric ammonium nitrate in 40 ml of water was added dropwise at 5°. The reaction solution was poured into 360 ml of ice and water. The mixture was extracted several times with 150 ml portions of petroleum ether 40-60°. The combined organic layers, washed three times, at first with 100 ml portions of a 3% solution of sodium bicarbonate, and then with 100 ml portions of water, were dried over anhydrous magnesium sulfate. The oil resulting after removal of solvent at room temperature *in vacuo* (30%), was repeatedly recrystallized at low temperature from petroleum ether 40-60° giving white crystals, mp 21-22°; nmr: $\delta$ 2.38 (s, $CH_3$); ir (carbon tetrachloride): 1620 $cm^{-1}$ (furoxan); ms: 136, 134 ($M^+$).

*Anal.* Calcd. for $C_3H_3ClN_2O_2$: C, 26.8; H, 2.2; N, 20.8. Found: C, 26.7; H, 2.2; N, 20.8.

### 4-Methyl-3-phenylthiofuroxan (IIIb).

A solution of 0.27 g (2 mmoles) of IIb in 1.5 ml of acetone was added dropwise at 24° to a stirred solution of 0.22 g (2 mmoles) of thiophenol and 0.090 g (2.2 mmoles) of sodium hydroxide in 1.0 ml of water. After half an hour acetone was removed *in vacuo* at room temperature. The residue was diluted with water and the resulting mixture extracted with chloroform. The collected organic layers, dried on magnesium sulfate, were evaporated *in vacuo* at room temperature. The residue was chromatographed on a silica gel column (silica gel 60 E. Merck, eluent: petroleum ether 40-60°-chloroform (60:40)). Compound IIIb was obtained as a nearly colourless oil (85%). Its ir spectrum was identical to the spectrum of 4-methyl-3-phenylthiofuroxan obtained as reported in reference (11).

*Anal.* Calcd. for $C_9H_8N_2O_2S$: C, 52.0; H, 3.9; N, 13.45. Found: C, 52.2; H,3.8; N, 13.6.

### 3-Methyl-4-phenylthiofuroxan (IIIa).

The reaction of IIa and sodium thiophenoxide was carried out at 27° by following the procedure outlined above in the preparation of IIIb. The reaction was protracted for 5 hours. By column chromatography [silica gel 60, E. Merck, eluent: petroleum ether 40-60°-chloroform (60:40)] a large amount of diphenyl disulfide (0.180 g) was obtained, and crude IIIa was also separated. This material was purified by preparative tlc on silica gel [eluent: petroleum ether 40-60°-chloroform (60:40)]. Pure IIIa (0.01 g) so obtained was identical (mp, mixed mp, ir spectra) to 3-methyl-4-phenylthiofuroxan obtained as reported in reference (11).

## REFERENCES AND NOTES

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(5) C. Pigenet, J. Armand and H. Lumbroso, *Bull. Soc. Chim. France*, 2124 (1970), and references 8 and 16 there reported.

(6) The up-field methyl signal has to be assigned to the 3-methyl group in IIa, the down-field methyl signal has to be assigned to the 4-methyl group in IIb. For a discussion of this point see: A. Gasco and A. J. Boulton, *Adv. Heterocyclic Chem.*, **29**, 251 (1981).

(7) Another possible mechanism not involving intermediate radicals is a two-electron oxidation with a polymeric cerium species or with the $Ce^{4+} \rightleftharpoons Ce^{2+}$ system; see, *e.g.* W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966).

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

(9) A. Gasco and A. J. Boulton, *J. Chem. Soc., Perkin Trans. II*, 1613 (1973).

(10) We found that IIb, in deuteriochloroform solution, at 32° isomerizes into IIa during 3 months.

(11) A. Gasco, V. Mortarini, G. Ruà and A. Serafino, *J. Heterocyclic Chem.*, **10**, 587 (1973).