Unsymmetrically Substituted Furoxans. Part 11 [1]. Methylfuroxancarbaldehydes

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The two isomeric 3-methyl-4-furoxancarbaldehydes (**2a**) and 4-methyl-3-furoxancarbaldehyde (**2b**) have been prepared. Discussion of their structures, thermal equilibration and kinetic of thermal conversion from the 3-methyl to the 4-methyl isomer are also reported. (Phenylsulfonyl)hydrazones **3a** and **3b** have been prepared as derivatives in view of their potential antitumoral properties.

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Up to now no asymmetrically substituted furoxan containing an aldehyde group directly joined to the heterocyclic system has been described. To our knowledge furoxandicarbaldehyde is the sole furoxan compound reported in the literature bearing this function. It was obtained by hydrolysis of isocyanilic acid [2].

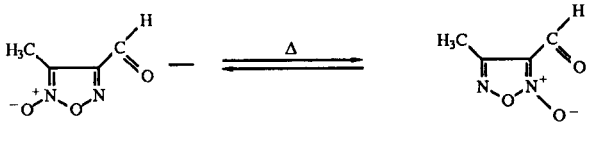
In this paper we describe the synthesis, structure, thermal equilibrium and the kinetic of thermal conversion of the two isomeric methylfuroxancarbaldehydes **2a** and **2b**.

By the action of dinitrogen trioxide on crotonaldehyde (**1**) dissolved in acetic acid, a white product, mp 46-47°, was obtained.

1 **2a**

The analytical data and mass spectrum, m/e 128 (M^+), were in keeping with the molecular formula $C_4H_4N_2O_3$. The ir and ^1H nmr spectroscopies showed that it was one of the two isomeric methylfuroxancarbaldehydes.

The product was partially transformed into the other isomer by heating over 98 hours in boiling toluene. The mixture was resolved by flash chromatography (30% of the isomer **2a** eluted second, 70% of the isomer **2b** eluted first). The new isomer **2b** melted at 51-52°.



2a **2b**

The structure of the two isomers was assigned on the basis of the knowledge that the *N*-oxide group exerts a shielding influence both on ^1H and on ^{13}C resonances of the 3-methyl group [3]. So we attributed the structure **2a** (3-methyl-4-furoxancarbaldehyde) to the isomer obtained by action of dinitrogen trioxide on **1** and the structure **2b** (4-methyl-3-furoxancarbaldehyde) to the isomer obtained by thermal isomerization (see Table I). Therefore the attack of dinitrogen trioxide is regiospecific and affords the 3-methyl isomer **2a**.

Table I

NMR Data of 2a and 2b (Deuterioacetone, δ ppm from Tetramethylsilane)

		^{13}C NMR		^1H NMR	
2a	C=O	184.0	CHO	10.10
	C-4	155.2	CH_3	2.33
	C-3	110.0		
	CH_3	7.7		
2b	C=O	179.7	CHO	9.92
	C-4	153.8	CH_3	2.53
	C-3	114.6		
	CH_3	11.0		

The regiospecific formation of **2a** is consistent with an ionic mechanism in which dinitrogen trioxide behaves as a nucleophilic nitrating agent ($NO^+NO_2^-$) on the activated double bond by the conjugation with the carbonyl group.

1 **2a**

It is interesting to point out that, contrary to what we found for the aliphatic analogues, in the aromatic α,β-unsaturated ketones and aldehydes the orientation of the dinitrogen trioxide addition is reversed. In fact these compounds give pseudonitrosites which easily cyclize to form an isoxazole [4,5]. Perhaps this is due to a radical reaction mechanism operating in the latter case. In this hypothesis the $NO_2^{\cdot}$ attack is expected to occur at the α-position to carbonyl group.

Table II

Isomerization Rate Constants and Activation Parameters [a]

Temperature [b] °C	$10^5 k$ (s^{-1})	E_a (0 kJ mol^{-1})	$\log_{10} A$ (s^{-1})	ΔH^* (0 kJ mol^{-1})	ΔS^* [c] (u.e.)
136.2	8.08 ±0.02				
138.0	10.0 ±0.1				
140.2	12.6 ±0.1	153 ±2	15.5 ±0.2	152 ±2	9.4 ±0.2
141.8	14.9 ±0.1				
143.2	17.3 ±0.1				

[a] The specified uncertainties are standard errors. [b] Temperatures were maintained within ± 0.1°. [c] 1 u.e. (cal deg^{-1} mol^{-1}) = H.18H JK^{-1} mol^{-1}.

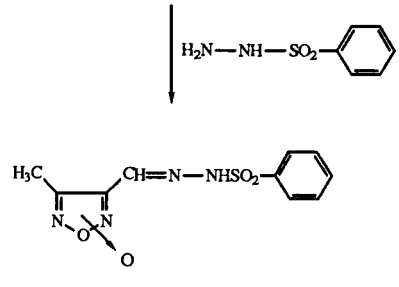
The equilibrium constant K = 2.26 of the **2a** ⇄ **2b** isomerization was obtained on heating either **2a** or **2b** in *sym*-tetrachloroethane at 142°. This value was constant over the temperature range 136-143°, within experimental error.

The rates for the **2a** → **2b** convertion were determined at five different temperatures in *sym*-tetrachloroethane. The activation parameters were calculated from these data (see Table II).

It is interesting to observe that the equilibrium concentration of the 4-methyl isomer **2b** is higher than that found for the corresponding 4-methyl-3-acetylfuroxan derivative [1]. This could be due to a better conjugation of the 3-positioned formyl group with the N^+-O^- function compared with the 3-acetyl group. Steric considerations might justify this hypothesis. The activation energy for the **2a** → **2b** isomerization is just a little lower than that found for the corresponding convertion of the acetyl isomers. However it is in agreement with the values found for other isomerizations in methylfuroxan isomers bearing on the ring electron withdrawing functions. The small and positive ΔS^* value is in line with a probable intermediate dinitroso compound as found in other furoxan tautomerizations [3,6].

The extent of hydration varies for the two aldehyde compounds, when dissolved in water. The ^1H nmr spectrum of **2a**, recorded immediately after dissolving the product, shows the disappearance of the signal related to the aldehyde proton and the presence of only one absorption in the methyl region (δ 2.30 ppm relative to tetramethylsilane). This means that the hydration equilibrium is quantitatively shifted towards the hydrated form. On the contrary the spectrum of **2b** shows still a low intensity resonance related to the aldehyde group and two signals in the methyl region (δ 2.63, 2.55 ppm relative to tetramethylsilane) in a ratio of *ca.* 30%. The most intense signal occurs upfield and can be attributed to the hydrated form. This situation does not change on standing. The upfield shift trend of the methyl protons of the hydrated form resembles that found for α- and β-protons in aliphatic aldehydes [7]. We prepared the (phenylsulfonyl)hydrazones **3a** and **3b** as derivatives of **2a** and **2b**, in view of the potential antitumor activity of these compounds [8].

2a, 2b



3a, 3-CH_3

3b, 4-CH_3

Indeed preliminary tests show that **3a** inhibits the colony forming ability of cultured HeLa cells ($ID_{50\%}$, 4.3 μg/ml). On the contrary **3b** was inactive.

EXPERIMENTAL

Melting points were measured in capillary apparatus and are uncorrected; ir spectra were determined using a Perkin Elmer Model 781 spectrophotometer. The ^1H nmr spectra were recorded on a Varian T-60 spectrometer. The ^{13}C nmr spectra were taken on a JEOL GX270/89 spectrometer. The equilibrium constants and equilibrium rates were determined with the following method: tubes containing solutions (0.5 *M*) of the furoxan in 1,1,2,2-tetrachloroethane were immersed in a bath at the temperatures indicated in the Table II. At intervals they were withdrawn and the ^1H nmr spectra were measured. Isomerization was followed by electronic integration of the methyl peaks. For the determination of the equilibrium constants, the temperatures quoted in Table II were maintained to an accuracy of ± 1°. For

the rate constants, ± 0.2 was achieved. For the flash chromatography silica gel Merck Kieselgel 60, 230-400 mesh ASTM was used.

3-Methyl-4-furoxancarbaldehyde (**2a**).

To a stirred solution of 10.0 g (0.142 mole) of crotonaldehyde (supplied by Janssen Chimica, 85%) in 20 ml of glacial acetic acid, saturated aqueous sodium nitrite solution (0.497 mole) was added. During the addition the temperature of the reaction mixture was kept at about 14°. The stirring was continued at room temperature for 1 hour and then the solution, diluted with water, (200 ml) was extracted several times with dichloromethane. The organic layer was washed with water and dried on magnesium sulphate. The residue obtained after removal of dichloromethane, purified by flash chromatography [eluent petroleum ether (40-60°) containing dichloromethane 0-30%], gave **2a**, yield *ca.* 40%, mp 46-47° after crystallization from petroleum ether (40-60°); ir (potassium bromide): 2780, 1710 (CHO); 1600 (furox) cm^{-1}.

Anal. Calcd. for $C_4H_4N_2O_3$: C, 37.51; H, 3.15; N, 21.87. Found: C, 37.28; H, 3.18; N, 21.79.

4-Methyl-3-furoxancarbaldehyde (**2b**).

Four g of **2a** was dissolved in toluene (50 ml) and the solution was refluxed over 98 hours. Solvent removal left a mixture of **2a** and **2b**. The mixture was resolved by flash chromatography [eluent petroleum ether (40-60°) and, after separation of **2b**, petroleum ether (40-60°) containing dichloromethane 0-30%]: **2b** eluted first, 70%, mp 51-52° after recrystallization from petroleum ether (40-60°); **2a** (eluted second 30%).

Compound **2b** had ir (potassium bromide): 2740, 1700 (CHO), 1600 (furox).

Anal. Calcd. for $C_4H_4N_2O_3$: C, 37.51; H, 3.15; N, 21.87. Found: C, 37.40; H, 2.89; N, 21.75.

General procedure for preparation of (Phenylsulfonyl)hydrazones **3a** and **3b**.

To a solution of 0.40 g (2.3 mmoles) of (phenylsulfonyl)hydrazide in dry methanol (5 ml), 0.30 g (2.3 mmoles) of **2a** or **2b** were added. The stirring was continued for 2 hours and then the white precipitate was filtered, washed with cold methanol and dried.

Compound **3a** was obtained in 80% yield, mp 168-169° after recrystallization from a 1:1 mixture of methanol and water; ir (potassium bromide): 1350, 1170 split (SO_2) cm^{-1}; ^{13}C nmr (deuterioacetone/tetramethylsilane): δ ppm = 153.5, 139.0, 135.6, 133.7, 129.5, 127.8, 110.8, 8.85.

Anal. Calcd. for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85. Found: C, 42.35; H, 3.53; N, 20.08.

Compound **3b** was obtained in 75% yield, mp 182° after recrystallization from a 1:1 mixture of methanol and water; ir (potassium bromide): 1300, 1170 split (SO_2) cm^{-1}; ^{13}C nmr (deuterioacetone/-tetramethylsilane): δ ppm = 153.7, 139.0, 133.8, 132.9, 129.5, 128.0, 113.6, 12.23.

Anal. Calcd. for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85. Found: C, 42.37; H, 3.48; N, 20.01.

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