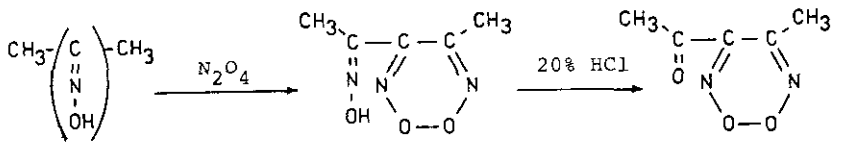
UNSYMMETRICALLY SUBSTITUTED FUROXANS. 10[1]. ACETYL-METHYL-FUROXANS

Rosella Calvino, Bruno Ferrarotti, Anna Serafino, and Alberto Gasco†

†Istituto di Chimica Farmaceutica e Tossicologica della Università di Torino, Corso Raffaello 31 - 10125 Torino, Italy

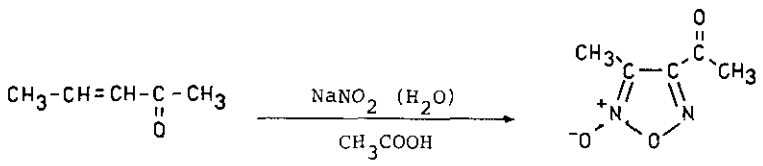
Abstract - The two isomeric acetyl-methyl-furoxans have been prepared. Discussion of their structures and thermal equilibration and kinetics of thermal conversion from 3-methyl to 4-methyl isomer are also reported.

In the development of our chemical and pharmaceutical research on unsymmetrically substituted furoxans, our present interest is addressed to acetyl-methyl derivatives of this ring system. An early work by Tappi[2] reports that the oxidation of dinitrogen tetroxide on 2,3,4-pentanetrione trioxime[3] 1 affords an oxime derivative of acetyl-methyl-furoxan. By effect of 20% hydrochloric acid on this product, the corresponding ketone can be obtained (mp 32-33°C). According to Ponzio's reports[4] the peroxide structures 2 and 3 were assigned to these compounds shown in the scheme.



1 2 3

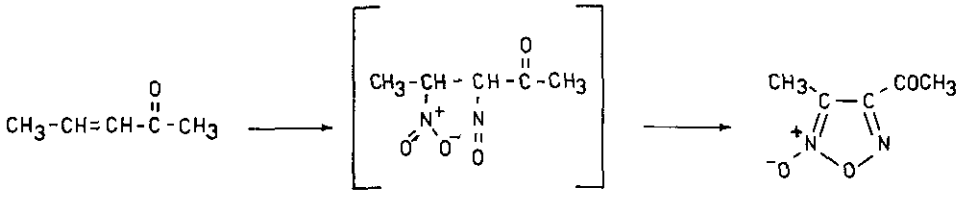
Since the above synthesis is a lengthy procedure, we explored an alternative route to this class of compounds. As it is known that furoxan systems can be obtained from dinitrogen trioxide and alkene derivatives[5], we tried to use this reagent on 3-penten-2-one 4 in acetic acid.



4 5a

From the reaction mixture, a white product, mp 31°C was isolated by flash chromatography (ca. 25% yield). It was identical (mixed mp, ir spectra) to the derivative 3 prepared by the procedure reported by Tappi. The 4-acetyl-3-methyl-furoxan structure 5a was assigned to the product on the base of its ^{13}C and ^{1}H nmr spectra (^{13}C-nmr (DMSO-d_6/TMS) δ_{ppm}= 190.7, 154.6, 111.8, 26.9, 8.4. ^{1}H-nmr (DMSO-d_6/TMS) δ_{ppm}= 2.61, 2.25).

The signals at 111.8 ppm and at 8.4 ppm can be assigned to C-3 of the furoxan system and to $-CH_3$ bound to the ring respectively[6] and they appear, in the undecoupled spectrum, as quartets ($^{1}J_{C-H}$= 133.3 Hz; $^{2}J_{C-C-H}$= 7.7 Hz). These two quartets are converted to two singlets when the decoupler is set at the resonance of the methyl protons at 2.25 ppm. The resonance at 190.7 ppm and at 26.9 ppm can be assigned to C=O and to $\underline{CH_3}$-C=O, respectively.Also these two signals appear in the undecoupled spectra as quartets ($^{1}J_{C-H}$= 130.0 Hz, $^{2}J_{C-C-H}$= 6.6 Hz) and they collapse to two singlets when the decoupler is centered at the resonance of the methyl protons at 2.61 ppm. Finally the resonance at 154.6 ppm can be assigned to C-4 of the ring system. The regiospecific formation of 5a is consistent with a mechanism in which dinitrogen trioxide behaves as a nucleophilic nitrating agent ($NO^{+}NO_2^{-}$) on the double bond activated to nucleophilic addition by the conjugation with the carbonyl group.



4 5a

Heating of 5a at 145°C for 48 h afforded a mixture of the two isomers 5a and 5b: 5a, 56%; 5b, 44%; the ratio was determined by nmr.

A similar result was obtained on heating 5a in sym-tetrachloroethane ($K_{145°}$= 0.78; this value is constant over the temperature range 135-145°C, within experimental error).

5a ⟷ 5b

Flash chromatography gave the pure isomer 5b. The structure of this compound was confirmed by ^{13}C nmr, *undecoupled and decoupled, and by* ^{1}H*-nmr (see experimental* part).

The rates of the conversion 5a ⟶ 5b were determined at five different temperatures in sym-tetrachloroethane. The activation parameters were calculated from these data.

Table 1 [(a)]

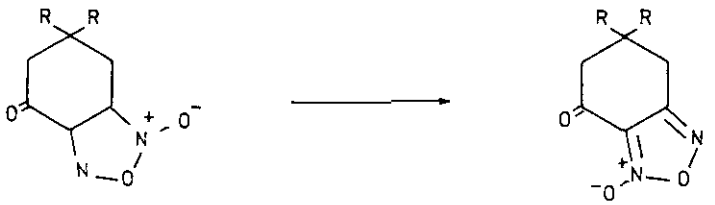
Isomerization Rate Constants and Activation Parameters

Temperature °C[(b)]	$10^5 k$ (s^{-1})	E_a (kJ mol^{-1})	log A (s^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (u.e.)
140.3	2.62 ± 0.03				
144.4	3.78 ± 0.06				
146.2	5.15 ± 0.07	166 ± 7	16.5 ± 0.8	163 ± 7	14
149.5	7.08 ± 0.09				
153.4	11.4 ± 0.1				

(a) The specified uncertainties are standard errors.

(b) Temperatures were maintained within ± 0.1°C.

The activation energy value is the highest yet found in the series of methylfuroxans for the conversion between isomers.[6] By comparing these data with those of Boulton et al.[7] on dihydrobenzofurazan4-one 1-oxides (6a, 7a) and 3-oxides (6b, 7b) some considerations on the factors which influence the equilibrium of thermal isomerisation in acylfuroxans are possible.



6a R = Me 6b

7a R = H 7b

The above authors found an activation energy for the reactions 6a ⟶ 6b and 7a ⟶ 7b (134 and 132 kJ/mole respectively) lower than that which we find for the reaction 5a ⟶ 5b. This could be explained by the effect of fused ring.[8] They showed also that in the thermal isomerisation 6a ⟷ 6b and 7a ⟷ 7b the b isomers are strongly favoured. The conjugation of the keto group with the adjacent N-oxide moiety was suggested to explain this result. The presence of this mesomeric interaction was also noticeable in the frequency of the ir carbonyl absorption.[7] In the case of 5a and 5b described in the present work the equilibrium constant of isomerisation is close to unity in spite of the fact that the ir carbonyl absorption of 3-methyl isomer occurs at higher frequency than that of 4-methyl isomer (5a, $CHCl_3$: $\nu_{C=O}$ = 1715 cm^{-1}; 5b, $CHCl_3$: $\nu_{C=O}$ = 1698 cm^{-1}).
If this difference is due to the conjugation of the N-oxide moiety with the acetyl group linked to the 3-position, we are forced to conclude that the other factors (e.g. steric factors) play an important role in determining the ratio of the 5a ⟷ 5b equilibrium.

EXPERIMENTAL

Melting points were measured in capillary apparatus and are uncorr; ir spectra were determined using a Perkin Elmer Model 781 spectrophotometer. Mass measurements were carried out on a Varian CH7 MAT mass spectrometer. ^{1}H-nmr spectra were taken both

on a Varian T-60 spectrometer and on a Jeol GX270/89 spectrometer. ^{13}C-nmr spectra were taken on a Jeol GX270/89 spectrometer (δ_{DMSO-d_6} = 39.6 ppm). The equilibrium constants and equilibrium rates were determined by the method reported in ref.[9] For the flash chromatography silica gel Merck Kieselgel 60, 230-400 mesh ASTM was used, eluent petroleum ether at bp 40-60°C: tetrahydrofuran 9:1.

4-Acetyl-3-methylfuroxan 5a

To a stirred solution of 1.0 g (11.8 mmol) of 3-penten-2-one 4 (supplied by Janssen Chimica, 90%) in 2.0 ml of glacial acetic acid, saturated aqueous sodium nitrite (41.0 mmol) was added dropwise. The reaction was exothermic and the highest temperature reached was ca. 55°C. The mixture was stirred at room temperature for 1 h after the addition, then diluted with water and extracted with ether. The combined organic layer was washed with water and dried on magnesium sulphate. Flash chromatography of the residue obtained after removal of ether gave 5a in 25% yield, recrystallized from petroleum ether (40-60°C), mp 31°C (lit.[2] 32-33°C). ^{1}H-nmr (DMSO-d_6/TMS) δ_{ppm} = 2.25 (3H,s, CH_3-furox), 2.61 (3H,s, CH_3-C=O); ^{13}C-nmr (DMSO-d_6/TMS) δ_{ppm} = 190.7 (q, J=6.6 Hz, C=O), 154.6 (m, C-4), 111.8 (q, J=7.7 Hz, C-3), 26.9 (q, J=130.0 Hz, $\underline{C}H_3$-C=O), 8.4 (q, J=133.3 Hz, $\underline{C}H_3$-furox); ir ($CHCl_3$): 1715 (C=O), 1618 (Furox) cm^{-1}; ms (70 eV): m/e = 142 (M^+), 127 (M^+-CH_3), 112 (M^+-NO), 82 ($M^+-N_2O_2$), 30 (NO^+). Anal.Calcd. for $C_5H_6N_2O_3$: C, 42.25; H, 4.25; N, 19.7; Found: C, 41.9; H, 4.2; N, 19.55.

Compound 5a was also prepared according to the procedure described by Tappi.[2]

3-Acetyl-4-methylfuroxan 5b

The compound 5a obtained as above was heated in a closed flask for 48 h at 145°C. The ^{1}H-nmr spectrum showed that a mixture of 5a (4-acetyl-3-methylfuroxan) and 5b (3-acetyl-4-methylfuroxan) was formed. 5b was separated from 5a by flash chromatography; recrystallized from petroleum ether (40-60°C), mp 69-70°C; ^{1}H-nmr (DMSO/d_6/TMS) δ_{ppm} = 2.44 (3H,s, CH_3-Furox), 2.51 (3H,s, CH_3-C=O). ^{13}C-nmr (DMSO-d_6/TMS) δ_{ppm} = 187.4 (q, J=6.6 Hz, C=O), 155.0 (q, J=7.7 Hz, C-4), 114.9 (m, C-3), 28.8 (q, J=130.0 Hz, $\underline{C}H_3$-C=O), 12.6 (q, J=132.2 Hz, $\underline{C}H_3$-Furox); ir ($CHCl_3$): 1698 (C=O), 1595 (Furox) cm^{-1}; ms (70 eV): m/e = 142 (M^+), 127 (M^+-CH_3), 112 (M^+-NO), 82 ($M^+-N_2O_2$), 30 (NO^+). Anal.Calcd. for $C_5H_6N_2O_3$: C, 42.25; H, 4.25; N, 19.7; Found: C, 42.1; H, 4.2; N, 19.6.

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