

Synthesis and Structure of Some Asymmetrically Substituted Furoxans. I.

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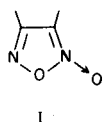
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From the mixture of isomeric esters obtained by heating 3-methyl-4-furoxancarboxylic acid ethyl ester, some furoxan derivatives have been prepared; their structures were assigned on the basis of nmr spectroscopy.

Introduction.

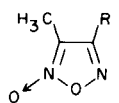
We have recently synthesized some furoxan derivatives in order to study their possible pharmacological activity. This paper describes the synthesis, structure and properties of some of these compounds that have been prepared from the ethyl esters of 3-methyl and 4-methyl-furoxancarboxylic acid (Va and Vb). The problem of the structure of the furoxan ring has been investigated by many authors and several formulas have been proposed to represent this heterocycle (1). Today structure I is commonly accepted for the furoxan ring; it has been confirmed by means of X-ray analysis in many cases, see for example (2,3,4,5,6,7).



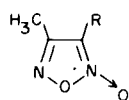
According to the usual convention (8), the "penta-valent" nitrogen is regarded as the 2-position of the furoxan ring.

Structure Assignments.

By analogy with the results of previous work on azoxy compounds and on benzofurazanoxide, Mallory and Cammarata (9) suggested that, in the nmr spectra of the methyl-ethylfuroxans IIa and IIb, and methylphenylfuroxans IIIa and IIIb, the chemical shift of the ring methyl group adjacent to the *N*-oxide oxygen (at C₃) occurs at higher fields than the methyl group remote from it (at C₄).



IIa, R = C₂H₅
IIIa, R = Ph



IIb, R = C₂H₅
IIIb, R = Ph

Since all the compounds described in the present work are R-substituted methylfuroxans, where R ≠ CH₃, and as we have at our disposal, in any case, the two possible isomers, we have assigned to the isomer with the higher field methyl resonance the 3-methyl structure and to the other isomer the 4-methyl structure. Such assignments are confirmed by the fact that the resonance positions of the methyl group in the furoxans to which the 4-methyl structure is attributed and in the corresponding furazans are nearly identical (see Table I).

Results and Discussion.

The starting material for the synthesis of all the furoxans described was a methylfuroxancarboxylic acid ethyl ester. This compound was prepared according to a previously described procedure (12), where it was considered to have the peroxidic structure IV. The yellow oil obtained from nitric acid (d. 1.2) oxidation of α,β-dioximinobutyric acid ethyl ester was distilled at 0.2 mm Hg rather than at atmospheric pressure. In this way we obtained a practically colorless oil whose analytical data and molecular weight were in agreement with the formula C₆H₈N₂O₄, and whose nmr spectrum is given in Figure 1.

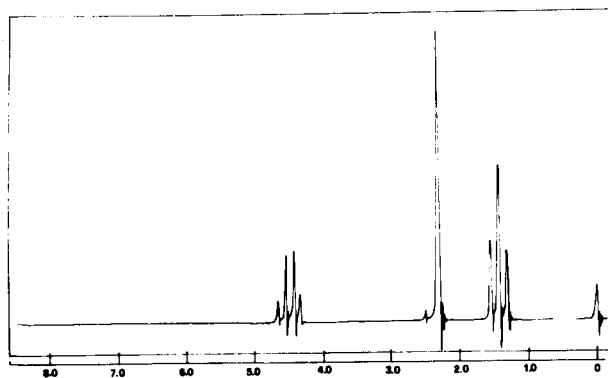
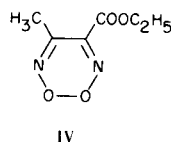


Figure 1

TABLE I

R	δ (CH ₃)	Solvent	δ (CH ₃)	Solvent	δ (CH ₃)	Solvent
COOC ₂ H ₅	2.31	CDCl ₃	2.50	neat (a)	2.50	CDCl ₃
CONH ₂	2.33	CD ₃ COCD ₃	2.50	CD ₃ COCD ₃ (a)	2.51	CD ₃ COCD ₃
CONHNH ₂ (b)	2.31	CD ₃ SOCD ₃	2.50	CD ₃ SOCD ₃	2.50	CD ₃ SOCD ₃
COOH (c)	2.33	CD ₃ COCD ₃	2.55	CD ₃ COCD ₃	2.53	CD ₃ COCD ₃

(a) From reference (10). (b) The furazan derivative has been prepared in accordance with reference (10). (c) The furazan derivative has been prepared in accordance with reference (11).



This oil, after being heated at 170-180° for 30 minutes, gave the nmr spectrum shown in Figure 2. Since the possibility of interconversion by the heating of some methylalkyl, methylaryl and aminoaryl isomeric furoxans is well known (9,13,14,15), we conclude that heating caused a partial conversion of the starting ester into its furoxan isomer.

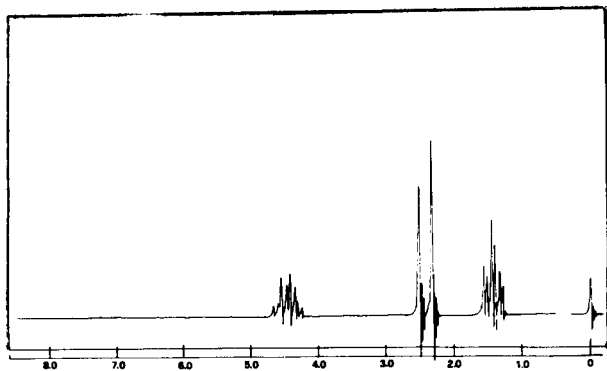


Figure 2

In agreement with the criteria given above, the ester distilled at 0.2 mm Hg is considered to have structure Va, while the ester obtained from Va by thermal isomerization is assigned the structure Vb. The presence, in the spectrum given in Figure 1, of a peak at 2.50 ppm, whose area is ~ 5% of the peak at 2.31 ppm relative to the 3-methyl group, shows that the ester distilled at 0.2 mm Hg is impure, with minor amounts of its isomer.

From the mixture of the two esters Va and Vb, mix-

tures of the isomeric amides VIa and VIb and of the isomeric hydrazides VIIa and VIIb were prepared in the usual way.

The mixture of amides was resolved into its components due to the fact that the 3-methyl derivative is more soluble than the 4-methyl in ethanol, and less so in benzene. Nmr spectral data were used to assign structure VIa to the isomer with m.p. 145°, and VIb to the isomer with m.p. 135°. Analogously, the mixture of hydrazides was resolved into its components; the isomer with m.p. 124-126° is assigned the structure VIIa, while the isomer with m.p. 129-131° is assigned the structure VIIb.

Both VIa and VIb, when refluxed over a period of 7 and 22 hours, respectively, in trimethylphosphite, gave 3-methyl-4-furazancarboxylic acid amide (VIII) in good yields.

The result of the above reduction seems to confirm the suggested furoxan nature of the starting esters.

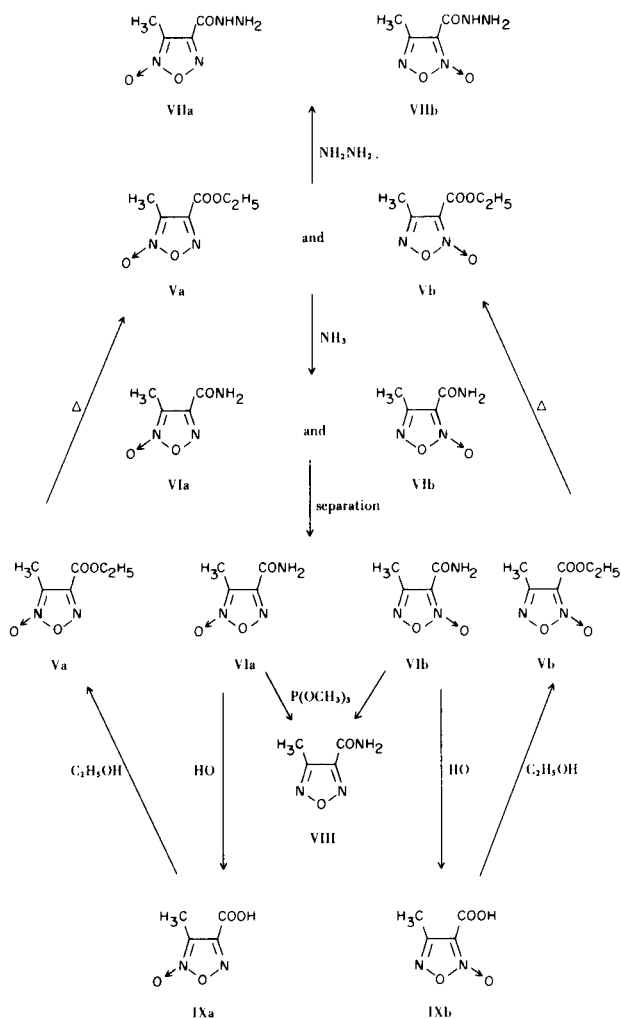
Both VIa and VIb hydrolyzed readily in base. The acid compound obtained by hydrolyzing VIb melts at 87-89° while the one obtained from VIa melts at 92° (crystallized from benzene). A sample of the latter compound was identical (mixed m.p., ir spectra) to the methyl-furoxancarboxylic acid prepared according to the procedure described by Angeli (16); to this compound, the author had assigned the peroxidic structure analogous to IV.

On the basis of nmr spectroscopy, the isomer with m.p. 92° is assigned the structure IXa, while the isomer with m.p. 87-89° is assigned the structure IXb. These acids and the parent 3-methyl-4-furazancarboxylic acid were found to have high values for the acidity constants (3-methyl-4-furazancarboxylic acid, $pK_a = 1.6$, 3-methyl-4-furoxancarboxylic acid (IXa) $pK_a = 1.3$ and 4-methyl-3-furoxancarboxylic acid (IXb) $pK_a = 1.3$).

The esters Va and Vb were synthesized by esterification of IXa and IXb, respectively. Both crude products after heating for half an hour at 170° gave a mixture of isomeric esters; their nmr spectrum was essentially superimposable upon the spectrum shown in Figure 2.

The general synthetic outline of the furoxans studied in the present work is given in Scheme 1.

SCHEME 1



EXPERIMENTAL

Melting points and boiling points are uncorrected. Mass measurements were carried out on the Varian CH7 MAT mass spectrometer. Ir spectra were recorded in potassium bromide pellets using a Perkin Elmer 257 spectrophotometer. Nmr were recorded on a Varian A-60 spectrophotometer using TMS as internal standard. Abbreviations: s = singlet; t = triplet; qu = quartet. The purity of the analytical samples was checked by tlc (silica gel). The potentiometric titrations were performed at 25° with a Metrohm compensator E/388.

3-Methyl-4-furoxancarboxylic Acid Ethyl Ester (Va).

This compound was prepared as described by Jovitschitsch by nitric acid oxidation of α,β -dioximinobutyric acid ethyl ester (12). The crude oily ester was purified by distillation at 82° (0.2 mm Hg); nmr (neat) Figure 1: δ 1.43 (t, 3H, $J = 7$ Hz, CH_2CH_3), 2.31 (s, 3H, CH_3 -Furox), 4.43 (qu, 2H, $J = 7$ Hz, CH_2CH_3). $M^+ m/e$ 172.

Anal. Calcd. for $\text{C}_6\text{H}_8\text{N}_2\text{O}_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.79; H, 4.63; N, 16.23.

Mixture of 3-Methyl-4-furoxancarboxylic Acid Ethyl Ester (Va) and 4-Methyl-3-furoxancarboxylic Acid Ethyl Ester (Vb).

The ester Va, heated for 30 minutes at 170-180° gave the equilibrium mixture of Va and Vb in a ratio of 1.1:1; nmr (neat) Figure 2: δ 1.43 (t, 3H, $J = 7$ Hz, CH_2CH_3 of Va); 1.40 (t, 3H, $J = 7$ Hz, CH_2CH_3 of Vb); 2.31 (s, 3H, CH_3 -Furox of Va); 2.50 (s, 3H, CH_3 -Furox of Vb); 4.36 (qu, 2H, $J = 7$ Hz, CH_2CH_3 of Vb); 4.43 (qu, 2H, $J = 7$ Hz, CH_2CH_3 of Va).

3-Methyl-4-furoxancarboxylic Acid Amide (Vla) and 4-Methyl-3-furoxancarboxylic Acid Amide (Vlb).

The mixture of esters Va and Vb (20 g.) was shaken vigorously with concentrated aqueous ammonia (50 ml.) for 45 minutes at room temperature. The solid was collected, washed with cold water and dried (yield 85%). The crude product (5 g.) was treated with warm benzene (30 ml.) until about half of the solid had dissolved in the solvent. The solid residue was filtered from the warm solution and recrystallized from benzene to obtain pure Vla. The mother liquor was evaporated *in vacuo* and the residue was recrystallized from ethanol to obtain pure Vlb. Compound Vla, m.p. 145°; nmr (deuterioacetone): δ 2.33 (s, 3H, CH_3 -Furox); 7.50 (broad, 2H, CONH_2); ir: cm^{-1} 3395, 3318, 3210 (NH_2) 1720 (C=O). $M^+ m/e$ 143.

Anal. Calcd. for $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$: C, 33.57; H, 3.52; N, 29.37. Found: C, 33.79; H, 3.54; N, 29.42.

Compound Vlb, m.p. 134-135°, nmr (deuterioacetone); δ 2.51 (s, 3H, CH_3 -Furox); 7.50 (broad, 2H, CONH_2); ir: cm^{-1} 3395, 3300, 3140 (NH_2), 1695 (C=O). $M^+ m/e$ 143.

Anal. Calcd. for $\text{C}_4\text{H}_5\text{N}_3\text{O}_3$: C, 33.57; H, 3.52; N, 29.37. Found: C, 33.77; H, 3.56; N, 29.38.

3-Methyl-4-furoxancarboxylic Acid Hydrazide (VIIa) and 4-Methyl-3-furoxancarboxylic Acid Hydrazide (VIIb).

The mixture of esters (30 g.) was shaken vigorously with 85% hydrazine hydrate (10.7 ml.) in water (10 ml.) for 60 minutes at 0°; the solid was collected, washed with cold water and dried (yield 86%). The crude product (5 g.) was treated with warm benzene (50 ml.) until about half of the solid had dissolved in the solvent. The solid residue was filtered from the warm solution and recrystallized from benzene to obtain pure VIIa. The mother liquor was evaporated *in vacuo* and the residue was recrystallized from methanol to obtain pure VIIb. Compound VIIa m.p. 124-126°; nmr (deuteriodimethylsulfoxide): δ 2.31 (s, CH_3 -Furox); 5.66 (broad, NH_2NH); ir: cm^{-1} 3325, 3210 (NH_2NH), 1695 (C=O). $M^+ m/e$ 158.

Anal. Calcd. for $\text{C}_4\text{H}_6\text{N}_4\text{O}_3$: C, 30.38; H, 3.82; N, 35.43. Found: C, 30.30; H, 3.87; N, 35.67.

Compound VIIb, m.p. 129-131°; nmr (deuteriodimethylsulfoxide): δ 2.50 (s, CH_3 -Furox); 5.08 (broad, NH_2NH); ir: cm^{-1} 3315, 3280 (NH_2NH); 1675 (C=O). $M^+ m/e$ 158.

Anal. Calcd. for $\text{C}_4\text{H}_6\text{N}_4\text{O}_3$: C, 30.38; H, 3.82; N, 35.43. Found: C, 30.46; H, 3.77; N, 35.71.

3-Methyl-4-furoxancarboxylic Acid Amide (VIII).

Compounds VIa (1 g.) and VIb (1 g.) were deoxygenated by refluxing for 7 hours and 22 hours, respectively, with trimethylphosphite (23 ml.). The reaction mixture was poured into cold water (150 ml.) containing 10 N hydrochloric acid (~ 5 ml.) to accelerate the hydrolysis of excess phosphite. The aqueous phase was extracted with ether and the ether phase was washed twice with a small amount of water, dried (magnesium sulfate), and evaporated under vacuum. Recrystallization from water gave the product (0.55 g. from VIa; 0.60 g. from VIb) as colorless needles, m.p. 123°, identical (m.p., mixed m.p., ir spectra) with an authentic sample prepared by the published method (10,17).

3-Methyl-4-furoxancarboxylic Acid (IXa).

A mixture of VIa (2.8 g.) and potassium hydroxide (1.4 g.) in water (16 ml.) was shaken vigorously at room temperature until the solid had dissolved. The resulting solution after being washed twice with ether, was diluted, acidified with concentrated hydrochloric acid (3.6 ml.) and extracted several times with ether. The organic phase was dried (magnesium sulfate), and the ether was removed under vacuum to leave a crude material (2.7 g.) which, after being recrystallized from benzene and dried *in vacuo*, melted at 92° and was identical (m.p., mixed m.p., ir spectra) with an authentic sample of 3-methyl-4-furoxancarboxylic acid prepared by the method reported in the literature (16); nmr (deuterioacetone): δ 2.33 (s, 3H, CH_3 -Furox); 10.25 (s, 1H, COOH); ir: cm^{-1} 3550, 3000-2200 (OH); 1737 (C=O). M^+ m/e 144. Potassium salt: m.p. 235° with decomposition.

Anal. Calcd. for $C_4H_3KN_2O_4$: C, 26.37; H, 1.66; N, 15.37. Found: C, 25.97; H, 1.91; N, 15.09.

4-Methyl-3-furoxancarboxylic Acid (IXb).

A mixture of VIb (2.8 g.) and potassium hydroxide (1.4 g.) in water (16 ml.) was shaken vigorously at 40° until the solid had dissolved. The solution was worked up as described above for the preparation of IXa. The residue (2.6 g.) obtained from evaporation of the ether phase was recrystallized from water and dried *in vacuo* over phosphorus pentoxide, m.p. 87-89° (with modification of crystalline structure at 82°); nmr (deuterioacetone): δ 2.53 (s, 3H, CH_3 -Furox); 10.56 (s, 1H, COOH); ir: cm^{-1} 3445, 3200-2400 (OH); 1725 (C=O). M^+ m/e 144.

Anal. Calcd. for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.44. Found: C, 33.05; H, 2.82; N, 19.21.

The potassium salt explodes if heated above 115°.

Anal. Calcd. for $C_4H_3KN_2O_4$: C, 26.37; H, 1.66; N, 15.37. Found: C, 26.16; H, 1.69; N, 15.26.

3-Methyl-4-furoxancarboxylic Acid Ethyl Ester (Va).

Compound IXa (3 g.) was dissolved in absolute alcohol (10 ml.) and a dry current of hydrogen chloride was passed for 1 hour through the solution which was kept cool in an ice bath. The mixture was allowed to stand at room temperature for two days with occasional swirling. The solvent was evaporated under vacuum at room temperature and the oily residue was poured into water. The aqueous phase was neutralized with sodium bicarbonate and extracted with ether.

The combined ether layers were dried (magnesium sulfate) and evaporated at room temperature to leave a crude oil (1.9 g.) which gave nmr spectrum identical with the spectrum reported in Figure 1; but free from the signal at 2.50 ppm. The crude oil heated for 30 minutes at 170° gave a spectrum identical with the spectrum reported in Figure 2; ir (carbon tetrachloride): cm^{-1} 1740 (C=O).

4-Methyl-3-furoxancarboxylic Acid Ethyl Ester (Vb).

Compound IXb (3 g.) was esterified following the procedure outlined above except that the solution was saturated with hydrogen chloride gas and allowed to stand at room temperature for three days, (yield 1.8 g.) nmr (deuteriochloroform): δ 1.40 (t, 3H, $J = 7$ Hz, CH_2CH_3); 2.50 (s, 3H, CH_3 -Furox); 4.45 (qu, 2H, $J = 7$ Hz, CH_2CH_2); ir (carbon tetrachloride): cm^{-1} 1730 (C=O). The crude oil heated for 30 minutes at 170° gave a spectrum identical with that reported in Figure 2.

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