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THE DI-(2-ALKYL-2-NITROETHYL)-METHYLAMINES FROM REACTIONS OF NITROALKANES WITH FORMALDEHYDE AND METHYLAMINE

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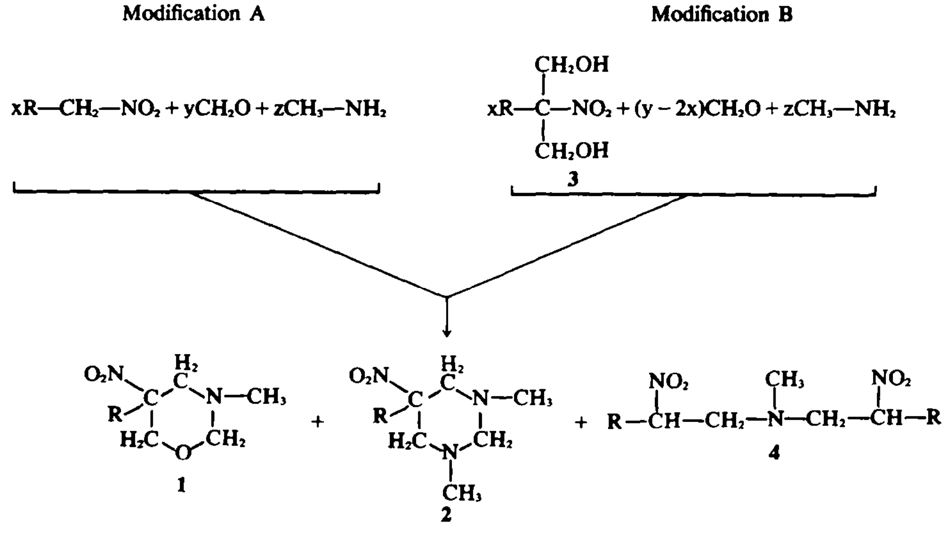
Abstract—Di-(2-alkyl-2-nitroethyl)-methylamines obtained from reactions of nitroalkanes with formaldehyde and methylamine were separated in diastereoisomers. NMR assignments of meso and racemic forms, and conformations are discussed. Partial separation of racemates into enantiomers was carried out by liquid-solid chromatography, on an optically-active adsorbent.

The reactions of nitroparaffins with formaldehyde and ammonia[1] or amines[2] were extensively investigated by Urbański *et al.* Primary nitroalkanes react with formaldehyde and methylamine to yield a mixture of 3 - methyl - 5 - alkyl - 5 - nitrotetrahydro - 1,3 - oxazines **1**[3] and 1,3 - dimethyl - 5 - alkyl - 5 - nitrohexahydropyrimidines **2**.[4] Changes in the molar ratios of the substrates result in shifting the reaction towards one or another of these products.[5] The reactions were carried out in an aqueous medium, and 2 - alkyl - 2 - nitropropane - 1,3 - diols **3** (products of the reaction of 1 mole of the nitroalkane with 2 moles of formaldehyde) were used rather than nitroparaffins to obtain higher yields and a higher purity of products.[2]

The reactions of nitroethane and 1-nitropropane were reinvestigated with the application of chromatographic techniques for analysis of product mixtures. No differences have been found in the results of the reaction in both the modifications (A and B, Scheme), if the temperature of the exothermic reaction of nitroalkanes with formaldehyde and methylamine was carefully controlled.

Two active protons of nitroparaffins are engaged in the formation of cyclic products, but under mild conditions only one active proton of primary ni-



x,y,z,—moles of substrates. In the B modification y ≥ 2x.
R = CH_3: meso **4a**, rac **4a**;
R = C_2H_5: meso **4b**, rac **4b**

SCHEME

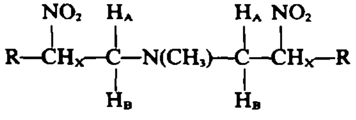
troparaffins can be engaged in the reaction to yield di-(2-alkyl-2-nitroethyl)-methylamines **4**. Similar compounds were obtained from secondary nitroparaffins with only one active proton, e.g. from 2-nitropropane.[6]

The formation of new compounds **4** was established by thin layer chromatography (TLC). Due to the presence of two asymmetric centers in molecules **4**, the substances were mixtures of diastereomers. The pairs of diastereomers meso **4a** and rac **4a**, from the reaction with nitroethane, and meso **4b** and rac **4b**, from the reaction with 1-nitropropane, were separated from the mixtures of products by chromatography on silica gel. The structures of the compounds are inferred from their NMR spectra. Each spectrum shows a multiplet with the chemical shift value of about $\tau = 5{\cdot}5$ ppm, characteristic of protons in the methine group bonded to the nitro group[7] and intensities corresponding to two protons. The pattern of eight signals characteristic of the AB part of an ABX system in the range $\tau = 6{\cdot}7$–$7{\cdot}5$ ppm has an integral intensity corresponding to two methylene groups. There are singlets of the N-methyl groups at 7·6 ppm in the spectra. The spectra of diastereomers meso **4a** and rac **4a** also show the doublet of two methyl groups; those of diastereomers meso **4b** and rac **4b** show signals of two ethyl groups bonded to methine groups.

The meso forms, meso **4a** and meso **4b**, were assigned to the diastereomers with smaller retention volumes on chromatography and slightly higher R_f values on TLC under the conditions described in the experimental section. This assignment was given on basis of the formation of crystalline R(+)-camphorsulphonates of meso **4a** and meso **4b**. The free bases of these salts show no rotation of the plane of polarization and are identical with the appropriate bases obtained by chromatography. An attempt at obtaining crystalline camphorsulphonates of rac **4a** and rac **4b** which are mixtures of optically active RR and SS forms was not successful. The assignment given above was proved by a chromatographic attempt to resolve rac **4a** and rac **4b** into the optically active RR and SS forms directly on the column packed with silica gel chemically treated to contain optical activity. Unfortunately, only poor resolution of chromatographic peaks was observed. However, the collected fractions showed small but clearly opposite optical activities.

The NMR analysis of the ABX systems of the two methylene protons and the methine proton leads to further conclusions about the stereochemistry of the compounds. The experimental values of chemical shifts and coupling constants for the ABX patterns are given in Table 1.

Table 1.



$$R\text{—}\overset{NO_2}{C}H_X\text{—}\underset{H_B}{\overset{H_A}{C}}\text{—}N(CH_3)\text{—}\underset{H_B}{\overset{H_A}{C}}\text{—}\overset{NO_2}{C}H_X\text{—}R$$

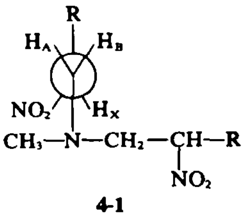
	meso **4a**	rac **4a**	meso **4b**	rac **4b**
τ_A	6·95	6·90	7·02	6·94
τ_B	7·35	7·34	7·36	7·36
τ_X	5·36	5·37	5·58	5·56
J_{AB}	13·5	14·0	13·5	14·0
J_{AX}	10·1	11·4	8·6	9·8
J_{BX}	3·8	2·6	5·4	5·5

There is only one ABX system in the spectrum of each diastereomer. This shows that the two 2-nitroalkyl moieties in the molecule have identical conformations. The magnetic nonequivalence of the two geminal protons is due to the existence of asymmetric centres in the molecule. Most probably, hindered rotation does not contribute to this nonequivalence, because in the NMR spectrum of a very similar molecule di - (2 - methyl - 2 - nitropropyl) - methylamine,[6] which has no centers of asymmetry, the protons of the methylene groups give a singlet in the temperature range from room to − 52°C.

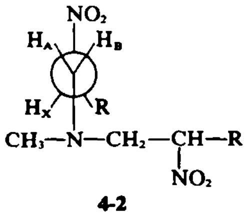
Conformation **4-3** does not agree with the coupling of the methine proton with the two geminal protons where J_{AX} is large and J_{BX} small. Relatively high chemical shift differences for the two geminal protons are due to different effects of the nitro group on these protons. The more strongly deshielded proton should be nearer the nitro group.[8] Thus conformation **4-1** is favoured, and should be the most populated in the conformer equilibrium of each diastereomer **4**.

EXPERIMENTAL

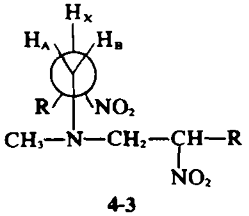
Thin Layer Chromatography (TLC) was carried out on 75 × 25 mm glass plates coated with silica gel G (Merck). A mixture of n-hexane–ethyl ether 3 : 7 (v/v) was used as the developing solvent. The developed plates were air-dried and sprayed with Dragendorff reagent.



4-1



4-2



4-3

Liquid–solid chromatography separations of diastereomers were performed on the glass column measured 8·6 × 950 mm dry packed with *ca* 33 g of silica gel less than 0·08 mm Merck for column chromatography. For resolution of optically active forms the gel was treated with 1% (by weight of silica gel) sodium R(+)-camphorsulphonate in aqueous solution. Then water was evaporated under reduced pressure and the gel was activated by heating at 100°C for 4 h. A pump with a maximum pumping capacity of 5 ml/min and pressure up to 25 atm was used with pulse-dampening to deliver the eluent. The sample, an ether solution (1 : 2 by weight), was injected to the pipe connecting the pumping system with the column, after stopping the flow and releasing the pressure. The UV detector operating at 254 nm was equipped with a microflow cell, having an internal volume of 8 μl and a path length of 10 mm, without a reference beam. As the eluent, a mixture of hexane and ethyl ether was used— with continuously changing the ratio of the components. The solvents were purified by routine methods to show no absorption in the UV detector employed. The columns were prepared for chromatography by passing ca. 10 column volumes of a degassed mixture of hexane and ethyl ether with the initial concentration of hexane. The degassing of the eluent was performed by refluxing it in the flask from which it was simultaneously supplied to the pump through a heat exchanger. The flask served also for mixing the components of the eluent. After injecting the sample, the concentration of hexane in the eluent was changed according to the equation:

$$C = C_0 e^{-v/V_m}$$

where C is the concentration of hexane in the eluent after passing volume v (ml) of the eluent, C_0 is the initial concentration of hexane and V_m is the volume of the eluent in the mixer. This change of mobile phase composition was performed by adding ethyl ether to the mixer with the same flow rate as that of the eluent in the column. The flow rate was *ca* 1 ml/min, pressure 20–22 atm, C_0 = 20%, and V_m = 150 ml.

NMR spectra were measured with a JEOL JNM 4H-100 spectrometer in 10% deuteriochloroform solutions with tetramethylsilane as internal standard, and optical activity measurements at room temperature on a Perkin–Elmer Model 141 Polarimeter with 1 ml capacity, 10 cm path length cell at 589 nm.

Di - (2 - nitropropyl) - methylamines, meso **4a** *and rac* **4b**

To 15 g (0·2 mole) of nitroethane, 8 g (0·1 mole + 10%) of 40% aqueous methylamine and then 17 g (0·2 mole) of 37% aqueous formaldehyde were added dropwise with homogenization of resulting mixture by a vibratory mixer. The temperature of the exothermic reaction was kept at 20°C by cooling on an acetone-dry ice bath when the substrates were added. The reacting mixture was then kept at this temperature for 4 h with continuous mixing. The products were extracted by ether, dried with molecular sieves 4A and then the solvent was evaporated to yield 17·6 g of a mixture of the products. 116 mg of the mixture was injected onto the column. After the chromatographic separation, 23 mg of meso **4a** and 22·4 mg of rac **4a** were obtained; the yields relative to the nitroethane used in the reaction are 17% and 16·5%, respectively. meso **4a**: m.p. 34–35°C (from ethanol); R_f = 0·44; Found: C, 41·08%; H, 7·58%; N, 20·56%; $C_7H_{15}N_3O_4$ requires: C, 40·97%; H, 7·37%; N, 20·48%. rac **4a**: m.p. 48–49°C (from ethanol); R_f = 0·40; Found: C, 40·93%; H, 7·57%; N, 20·50%; $C_7H_{15}N_3O_4$ requires: C, 40·97%; H, 7·37%; N, 20·48%.

17 g of the mixture of products were dissolved in 4 ml of ethanol and left overnight at 0°C. Separated crystals of rac **4a** were filtered off (3·2 g of crude product). After two recrystallizations from ethanol, 2·1 g of rac **4a** (m.p. 48–49°C) were obtained.

Di-(2-nitrobutyl)-methylamines, meso **4b** *and rac* **4b**

18 g (0·2 mole) of nitropropane was treated as described above, but the temperature of the reaction was kept at 40°C for 6 h. 18·7 g of mixture of the products was obtained. 14·2 mg of meso **4b** and 16·8 mg of rac **4b** were separated by chromatography from 125 mg of the mixture. The yields relative to the nitropropane used in the reaction are 9·1% and 10·7%, respectively. meso **4b**: m.p. 40–41°C (from ethanol); R_f = 0·51; Found: C, 46·08%; H, 8·39%; N, 17·91% $C_9H_{19}N_3O_4$ requires: C, 46·34%; H, 8·21%; N, 18·02%. rac **4b**: m.p. 30–31°C (from ethanol; R_f = 0·48; Found: C, 45·99%; H, 8·36%; N, 18·01%; $C_9H_{19}N_3O_4$ requires: C, 46·34%: H, 8·21%; N, 18·02%.

meso **4a** *R(+)-camphorsulphonate*

To 102 mg (0·5 mmole) of meso **4a** in ethanol, an ethanolic solution of 125 mg (0·5 mmole) of R(+))-camphorsulphonic acid monohydrate was added. After evaporation of excess solvent, the crystalline salt was filtered off. 194 mg of meso **4a** (R(+)-camphorsulphonate (yield 89%, m.p. 120–121°C) was obtained. Found: C, 46·78%; H, 7·15%; N, 9·37%; $C_{17}H_{31}N_3O_8S$ requires C, 46·08%; H, 7·09%; N, 9·61%.

meso **4b** *R(+)-camphorsulphonate*

From 116 mg (0·5 mmole) of meso **4b**, 211 mg of meso **4b** R(+)-camphorsulphonate (yield 91%, m.p. 125–126°C) was obtained, as described above. Found: C, 48·91% H, 7·61%; N, 8·84%; $C_{19}H_{35}N_3O_8S$ requires: C, 49·03%; H, 7·53%; N, 9·03%.

meso **4a** *and meso* **4b** *from their R(+)-camhorsulphonates*

The salt and an excess of sodium carbonate were suspended in ethyl ether and stirred with a magnetic stirrer for 4 h. The solid was filtered off and washed with ether. The solvent was removed from the solution and the free base was obtained.

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