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Letters to the Editor

Synthesis of 9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxides

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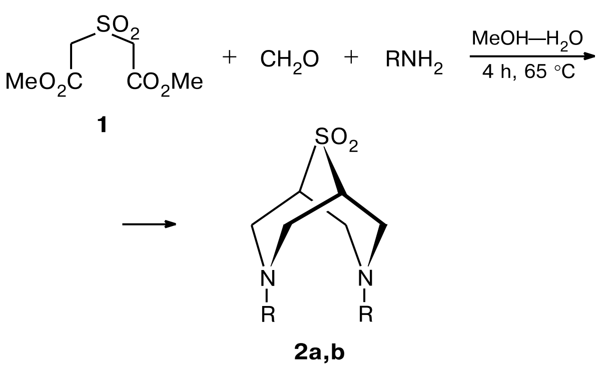
Reactions of aliphatic ketones,[1] piperidin-4-ones,[1] or nitro compounds[2—5] with primary amines and aldehydes under mild conditions are a convenient route to 3-aza- and 3,7-diazabicyclo[3.3.1]nonane derivatives. In a similar way, derivatives of 3-thia-7-azabicyclo[3.3.1]nonane have been obtained.[1,6—9]

In the present work, we applied this approach to the synthesis of earlier unknown 9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxides from bis(methoxycarbonylmethyl)sulfone (**1**). These dioxides are of interest as biologically active compounds, complexones, and model compounds for conformational analysis. It should be emphasized that previous attempts to obtain 9-thia-3,7-diazabicyclo[3.3.1]nonane derivatives by the Mannich reaction were unsuccessful.[10] Our choice of sulfone **1** was not accidental because the presence of reactive methylene groups, as in acetonedicarboxylic acid,[11—13] allows its transformation into 3,7-diazabicyclo[3.3.1]nonanes.

The reaction of sulfone **1** with formaldehyde and methylamine hydrochloride (molar ratio 1 : 10 : 5, respectively) in boiling aqueous methanol at pH 7.5—8 afforded 3,7-dimethyl-9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxide (**2a**) in 23% yield, the product being deprived of ester groups (Scheme 1). The necessary pH value of the solution was established by adding a solution of NaOH. Use of an aqueous solution of $MeNH_2$ reduced the yield of heterocycle **2a** to ~12%. Analogously, the condensation of sulfone **1** with formaldehyde and isopropylamine gave 3,7-diisopropyl-9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxide (**2b**) in 16% yield. Apparently, the for-

Scheme 1



R = Me (**a**), Pr^i (**b**)

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mation of sulfones **2a,b** is accompanied by hydrolysis of the methoxycarbonyl groups and by decarboxylation of the acid fragments.

The individuality of compounds **2a,b** was confirmed by GLC (column with 5% SE-30 on the N-AW DMCS Inerton) and TLC data (Silufol plates). The compositions of compounds **2a,b** were determined by elemental analysis and mass spectrometry. Their structures were proved by IR and ^{1}H and ^{13}C NMR spectroscopy.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. IR spectra were recorded on a Specord M-80 instrument (thin film or Nujol). Mass spectra were recorded on an MX-1300 spectrometer (ion source temperature 100 °C, ionizing voltage 12 and 70 eV).

3,7-Dialkyl-9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxides 2a,b (general procedure). A 33% aqueous solution of formaldehyde (4.32 g, 48 mmol) and sulfone **1** (1.01 g, 4.8 mmol) were added to a solution of methylamine hydrochloride (1.62 g, 24 mmol) or isopropylamine hydrochloride (1.42 g, 24 mmol) in a mixture of water (15 mL) and MeOH (30 mL). The reaction mixture was alkalified to pH 7.5—8 with a 20% aqueous solution of NaOH (~5 mL) and refluxed for 4 h. The mixture was concentrated *in vacuo*, acidified to pH 1 with 1 *M* HCl, and washed with $CHCl_3$ (3×25 mL). On being extracted, the acidic aqueous solution was neutralized with a 20% aqueous solution of NaOH and the product was extracted with $CHCl_3$ (3×25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, the solvent was removed *in vacuo*, and the residue was chromatographed on SiO_2 with $CHCl_3$—Pr^iOH (9 : 1) as the eluent.

3,7-Dimethyl-9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxide (2a). Yield 0.22 g (23%), colorless crystals, m.p. 201—204 °C. Found (%): C, 47.24; H, 7.72; N, 13.76; S, 15.32. $C_8H_{16}N_2O_2S$. Calculated (%): C, 47.04; H, 7.89; N, 13.71; S, 15.66. MS, *m/z*: 204 $[M]^+$. IR, ν/cm^{-1}: 1108, 1288 (SO_2). ^{1}H NMR, δ: 2.36 (s, 6 H, 2 Me); 2.84 (s, 2 H, H(1), H(5)); 3.21 (d, 4 H, H_{eq}(2), H_{eq}(4), H_{eq}(6), H_{eq}(8), ^2J = 11.7 Hz); 3.35 (d, 4 H, H_{ax}(2), H_{ax}(4), H_{ax}(6), H_{ax}(8), ^2J = 11.7 Hz). ^{13}C NMR, δ: 46.14 (2 MeN); 54.45 (C(3), C(7)); 57.28 (C(2), C(4), C(6), C(8)).

3,7-Diisopropyl-9-thia-3,7-diazabicyclo[3.3.1]nonane 9,9-dioxide (2b). Yield 0.20 g (16%), oil. Found (%): C, 55.05; H, 9.61; N, 10.65; S, 12.35. $C_{12}H_{24}N_2O_2S$. Calculated (%): C, 55.35; H, 9.29; N, 10.76; S, 12.31. MS, *m/z*: 260 $[M]^+$. IR, ν/cm^{-1}: 1108, 1292 (SO_2). ^{1}H NMR, δ: 1.01 (d, 12 H, 4 Me, ^3J = 6.6 Hz); 2.83—2.92 (m, 4 H, H(1), H(5), 2 CHN); 3.18 (d, 4 H, H_{eq}(2), H_{eq}(4), H_{eq}(6), H_{eq}(8), ^2J = 11.5 Hz); 3.44 (d, 4 H, H_{ax}(2), H_{ax}(4), H_{ax}(6), H_{ax}(8), ^2J = 11.5 Hz). ^{13}C NMR, δ: 17.86 (4 Me); 50.26 (C(2), C(4), C(6), C(8)); 50.37 (2 CHN); 53.37 (C(3), C(7)).

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