Synthesis of mono- and bis(aminomethyl)dioxanes from *N*-[3-(2-chloroethoxy)-2-hydroxypropyl]sulfamates

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N-Substituted aminomethyl- and 2,5-bis(aminomethyl)-1,4-dioxanes were prepared by cyclization of the corresponding potassium *N*-[3-(2-chloroethoxy)-2-hydroxypropyl]sulfamates under the action of an alkaline agent followed by alcoholysis of the resulting sulfamic acids.

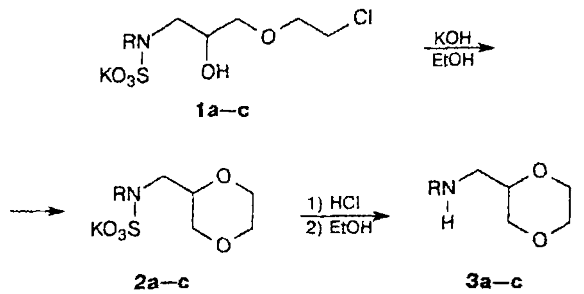
Key words: aminomethyl-1,4-dioxanes, 2,5-bis(aminomethyl)-1,4-dioxanes, *N*-[3-(2-chloroalkoxy)-2-hydroxypropyl]-*N*-alkylsulfamates, etherification, alcoholysis.

Dioxanes often represent structural fragments of various natural biologically active compounds and have been investigated thoroughly,[1] whereas aminomethyl-1,4-dioxanes are poorly studied. It is known[2] that the drugs prosympal, dibozane, and piperoxan containing *N*-substituted aminomethyl-1,4-benzodioxanes are α-adrenoblocking agents with a broad spectrum of action. Aminomethyl-1,4-dioxanes are also structural components of azo dyes.[3] 2,5-Bis(aminomethyl)-1,4-dioxane serves as a monomer in the synthesis of polyamides.[4]

Several procedures for the synthesis of *N*-substituted aminomethyl-1,4-dioxanes are known. However, all these procedures afford target products in low yields. The synthesis of aminomethyl-1,4-dioxanes by condensation of epichlorohydrin with ethylene glycol in sulfuric acid followed by the replacement of the halogen atom by amines was reported.[5] Another procedure is based on the use of hydroxymethyl-1,4-dioxane prepared by cyclization of 2-chloroethyl glycidyl ether.[6] The synthesis of aminomethyl-1,4-dioxanes by homolytic addition of dioxane to Schiff's bases was also described.[7] The preparation of 2,5-bis(dialkylaminomethyl)-1,4-dioxanes is based on the use of epichlorohydrin and secondary amine as the starting compounds.[8] In this case, the maximum yield was ~65%.

In the present work, we propose a method for the synthesis of *N*-substituted aminomethyl-1,4-dioxanes from potassium *N*-[3-(2-chloroethoxy)-2-hydroxypropyl]sulfamates (**1**), which we have prepared previously[9] (Scheme 1).

Scheme 1



R = H (**a**), Me (**b**), Et (**c**)

Cyclization in ethanol under the action of an alkaline agent afforded *N*-sulfo-2-aminomethyl-1,4-dioxanes (**2**) in virtually quantitative yields. Subsequent conversions of sulfamates **2** into *N*-substituted aminomethyl-1,4-dioxanes (**3**) were performed by alcoholysis of the corresponding acids[10] with the aim of decreasing losses in the course of their isolation. The total yields were 70—80%. However, we failed to extend this method to other cyclic diethers, for example, to 1,4-dioxepanes. Attempts to perform cyclization of the corresponding chloroalcohols under the action of alcoholic KOH led to the replacement of the Cl atom by the alkoxy group. The use of an inert solvent (DMF) resulted in the replacement of the Cl atom by the hydroxy group. When alkaline agents which do not possess intrinsic nucleophilicity (K_2CO_3 or $KHCO_3$) were used, the corresponding allyl ethers were formed.[10]

Treatment of potassium *N*-[3-(2,3-dichloropropoxy)-2-hydroxypropyl]-*N*-methylsulfamate with a solution of KOH in EtOH afforded potassium *N*-[3-(2-chloroallyloxy)-2-hydroxypropyl]-*N*-methylsulfamate (**5**) in virtually quantitative yield rather than the expected potassium *N*-(6-chloromethyl-1,4-dioxan-2-yl)methyl-*N*-methylsulfamate (**6**) (Scheme 2).

Variations of the basic agents ($KHCO_3$, K_2CO_3, or Et_3N) led only to a change in the reaction rate but did not affect the composition of the products obtained. The structure of product **5** is confirmed by the presence of two singlet signals in the ^{1}H NMR spectrum at δ 5.42 and 5.50, which are typical of protons of the terminal methylene group of the 2-chloroallylic residue.[11]

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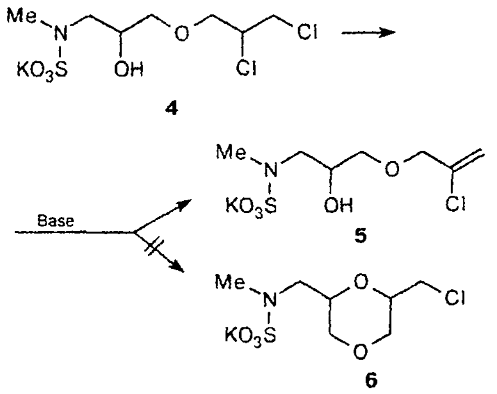
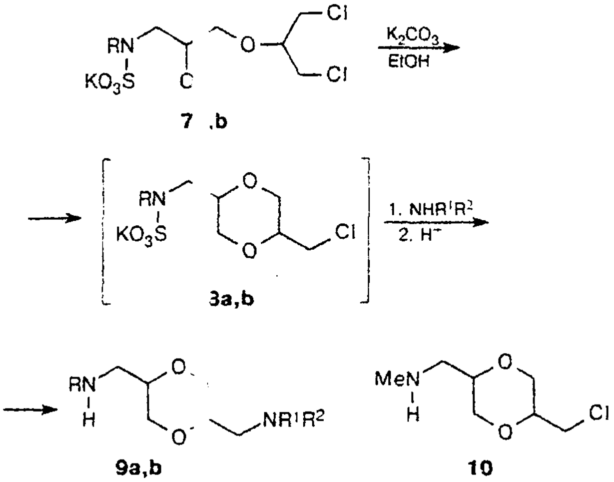
Scheme 2



Scheme 3



R = H (**a**), Me (**b**); ^{1} = H, R^2 = Me (**9a**);
R^1—R^2 = $(CH_2)_5$ (**9** ,

The synthesis of *N,N'*-substituted 2,5-bis(aminomethyl)-1,4-dioxanes proceeded in a more predictable manner. In the first stage, the closure of the dioxane ring in compounds **7a,b** occurred under the action of an alkaline agent (Scheme 3). However, further replacement of the Cl atom by the methylamine or piperidine residue in the resulting chloromethyldioxanes **8** was

Table 1. Physicochemical properties of the synthesized compounds

Compound	Yield (%)	B.p./°C (p/Torr) [M.p./°C]	n_D^{20}	Found/Calculated (%) C	H	N	Molecular formula	^{1}H NMR, δ (J/Hz)
2a	97*	[183—186]	—	25.60 25.52	4.37 4.28	6.13 5.95	$C_5H_{10}KNO_5S$	2.90—3.05 (m, 2 H, CH_2N); 3.28—3.90 (m, 7 H, 3 CH_2O, CHO)
2b	97*	[147—149]	—	—	—	5.86 5.62	$C_6H_{12}KNO_5S$	2.64 (s, 3 H, CH_3N); 2.79—3.05 (m, 2 H, CH_2N); 3.3—3.89 (m, 7 H, 3 CH_2O, CHO)
2c	97*	[244—247]	—	31.29 31.93	5.82 5.36	5.48 5.32	$C_7H_{14}KNO_5S$	0.98 (t, 3 H, CH_3, J = 16.0); 2.78—3.06 (m, 4 H, 2 CH_2N); 3.20—3.80 (m, 7 H, 3 CH_2O, CHO)
3a	80	78—80 (14)	1.4602	51.30 51.26	9.72 9.46	12.05 11.96	$C_5H_{11}NO_2$	2.68—2.79 (m, 2 H, CH_2N); 3.38—4.00 (m, 7 H, 3 CH_2O, CHO)
3b	75	75—76 (13)	1.4521	54.93 54.94	10.22 9.99	9.99 10.68	$C_6H_{13}NO_2$	2.42 (d, 3 H, CH_3N, J = 7.5); 2.58—2.78 (m, 2 H, 2 CH_2N); 3.42—4.03 (m, 7 H, 3 CH_2O, CHO)
3c	70	83—85 (13)	1.4524	—	—	9.82 9.65	$C_7H_{15}NO_2$	1.15 (t, 3 H, CH_3, J = 16.0); 2.61—2.75 (m, 4 H, 2 CH_2N); 3.40—4.00 (m, 7 H, 3 CH_2O, CHO)
9a	37	130—132 (11)	1.4828	51.61 52.48	9.82 10.07	17.98 17.48	$C_7H_{16}N_2O_2$	2.30 (d, 3 H, CH_3N, J = 5.3); 2.49—2.96 (m, 4 H, 2 CH_2N); 3.30—3.90 (m, 6 H, 2 CH_2O, CHO)
9b	34	125—126 (2)	1.4840	—	—	12.71 12.27	$C_{12}H_{24}N_2O_2$	.42—1.70 (m, 6 H, $CH_2CH_2CH_2$); 2.38 (d, 3 H, CH_3N, J = 5.3); 2.45—2.65 (m, 8 H, CH_2N); 3.40—4.00 (m, 6 H, 2 CH_2O, CHO)

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* According to the ^{1}H NMR spectral data.

incomplete. Thus the reaction with piperidine afforded bis(aminomethyl)dioxane **9b** and 5-chloromethyl-2-methylaminomethyl-1,4-dioxane (**10**) as the reaction products.

To summarize, we studied a new approach to the synthesis of mono- and bis(aminomethyl)-1,4-dioxanes based on *N*-[3-(2-chloroethoxy)-2-hydroxypropyl]sulfamates.

Experimental

The ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments (250 and 300 MHz, respectively) in D_2O with HMDS as the external standard.

Potassium *N*-(1,4-dioxanyl)methyl-*N*-methylsulfamate (2b). A solution of KOH (1.3 g, 20 mmol) in EtOH (10 mL) was added dropwise with stirring to a solution of potassium *N*-[3-(2-chloroethoxy)-2-hydroxypropyl]-*N*-methylsulfamate (**1b**) (5.6 g, 20 mmol) in EtOH (15 ml). The reaction mixture was refluxed for 30 min and the solution was concentrated. The product was separated from KCl (the content of **2b** was >97%, ^{1}H NMR spectral data) by extraction with acetone and the extract was concentrated.

Compounds **2a,c** were prepared analogously; their physicochemical characteristics are given in Table 1.

2-Methylaminomethyl-1,4-dioxane (3b). A solution of *N*-methyl-*N*-(1,4-dioxanyl)methylsulfamic acid[10] (2.1 g, 10 mmol) in EtOH (10 mL) was kept in a sealed tube at 110 °C for 1 h. After cooling, the reaction mixture was poured into a solution of KOH (1 g) in EtOH (10 mL). Then ether (15 mL) was added and the mixture was filtered. The filtrate was concentrated and the residue was extracted with ether (2×10 mL). The extracts were combined and concentrated. Compound **3b** was obtained in a yield of 1 g.

Compounds **3a,c** were prepared analogously; their physicochemical characteristics are given in Table 1.

Potassium *N*-[3-(2-chloroallyloxy)-2-hydroxypropyl]-*N*-methylsulfamate (5). A solution of KOH (1 g, 15 mmol) in MeOH (5 mL) was added to a solution of potassium *N*-[3-(2,3-dichloropropoxy)-2-hydroxypropyl]-*N*-methylsulfamate **4** [9] (5.05 g, 15 mmol) in MeOH (5 mL). The reaction mixture was refluxed for 20 min and cooled. Then ether (1 mL) was added and the KCl that precipitated was filtered off. The filtrate was concentrated and potassium *N*-[3-(3-chloroallyloxy)-2-hydroxypropyl]-*N*-methylsulfamate **5** was obtained in a yield of 4.2 g. ^{1}H NMR, δ: 2.84 (s, 3 H, MeN); 3.02—3.23 (m, 2 H, CH_2N); 3.58—3.80 (m, 2 H, CH_2O); 4.08—4.23 (m, 1 H, CHOH); 4.32 (s, 2 H. $\underline{CH}_2CCl{=}CH_2$); 5.63 (s, 1 H, HC=CCl); 5.71 (s, 1 H, $\underline{H}C{=}C{-}CH_2O{-}$). Found (%): N, 4.79. $C_7H_{13}ClKNO_5S$. Calculated (%): N, 4.97.

2-Methylaminomethyl-5-piperidinomethyl-1,4-dioxane (9b). Finely dispersed K_2CO_3 (4.2 g, 30 mmol) was added to a solution of potassium *N*-[3-(1,3-dichloropropan-2-yloxy)-2-hydroxypropyl]-*N*-methylsulfamate[9] (**7b**) (6.3 g, 18 mmol) in EtOH (15 mL). The reaction mixture was refluxed for 20 h and piperidine (3 g, 35 mmol) was added to the suspension. The reaction mixture was refluxed for 25 h and diluted with water (~10 mL). Then concentrated HCl was added to pH ≈ 0.5. The precipitate that formed was filtered off, the filtrate was concentrated, the residue was dissolved in EtOH (15 mL), and the resulting solution was kept at 110 °C for 5 h. After cooling, the reaction mixture was treated with a solution of KOH (2.6 g) in EtOH (15 mL) and ether (30 mL) was added. The precipitate that formed was filtered off, the filtrate was concentrated, and the residue was extracted with ether (2×15 mL). The ethereal extracts were combined and concentrated and the residue (2.6 g, a mixture of dioxanes) was separated by distillation. 5-Chloromethyl-2-methylaminomethyl-1,4-dioxane (**10**) was obtained in a yield of 0.85 g, b.p. 99—101 °C (2 Torr). ^{1}H NMR, δ: 2.41 (d, 3 H, MeN, J = 5.3 Hz); 2.66 (d, 2 H, CH_2N, J = 5.3 Hz); 3.0 (m, 1 H, $NCH_2\underline{CH}CH_2O$); 3.52—4.10 (m, 7 H, CH_2Cl, CH_2O, CHO). Compound **10** was converted into hydrochloride, m.p. 129—131 °C. Found (%): N, 6.51. $C_7H_{14}ClNO_2 \cdot HCl$. Calculated (%): N, 6.48. The second fraction with b.p. 125—126 °C (2 Torr) was 2-methylaminomethyl-5-piperidinomethyl-1,4-dioxane (**9b**); the yield was 1.02 g (34%). The properties of **9b** are given in Table 1. Compound **9a** was prepared analogously.

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