Reactions of derivatives of sulfamic acid with epoxides.
3.* Reactions of 3-chloro-2-hydroxypropylsulfamates with amines and synthesis of 1,3-diamino-2-propanols

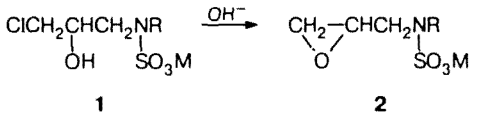
A. S. Ermakov, E. Yu. Kulikova, P. V. Bulatov, and V. A. Tartakovsky*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 117913 Moscow, Russian Federation.
Fax: 007 (095) 135 5328

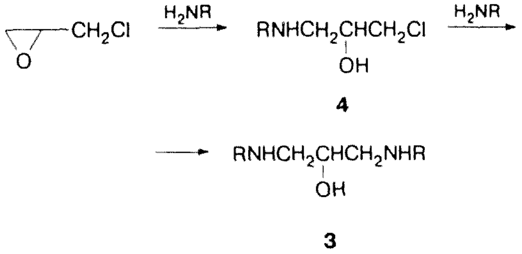
1,3-Diamino-2-propanols were prepared in high yields by reactions of potassium or sodium 3-chloro-2-hydroxypropylsulfamates with amines followed by acid hydrolysis of the 3-amino-2-hydroxypropylsulfamates that formed.

Key words: 3-chloro-2-hydroxypropylsulfamates, 2,3-epoxypropylsulfamates, 1,3-diamino-2-propanols.

Previously,[1,2] it was demonstrated that derivatives of sulfamic acid give 3-chloro-2-hydroxypropylsulfamates (**1**) under the action of epichlorohydrin. Compounds **1** readily form epoxysulfamates under the action of alkaline reagents, which we demonstrated using 2,3-epoxysulfamates (**2**). However, the high reactivities of these derivatives made it impossible to isolate them in an analytically pure form. Because of this, compounds **2** were reacted further without being isolated.



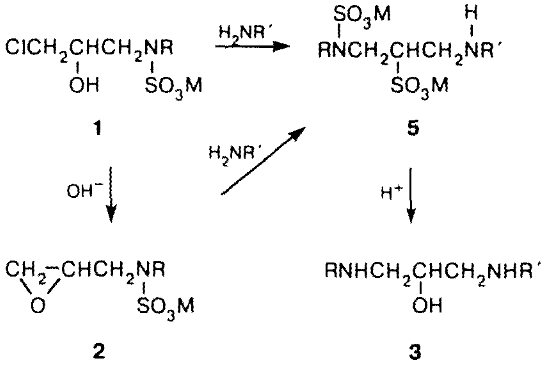
In this work, we studied reactions of sulfamates **1** with amines with the aim of preparing 1,3-diamino-2-propanols (**3**). The methods for the preparation of compounds **3** by reactions of amines with epichlorohydrin have been fairly well studied.[3–5]



In the case of NH_3 and primary amines, a number of by-products form, and resinification occurs. Therefore, products **3** were obtained in low yields. We succeeded in obtaining intermediate compounds **4** in reasonable yields only for higher primary amines ($R = C_6—C_{10}$).

It could be proposed that the yields of 1,3-diamino-2-propanols (**3**) could be increased by preparing these compounds from sulfamates **1** (Scheme 1).

Scheme 1



R = H, Me, Et;
R′= H, Me, Et, Pr^i, Bu^t, $(CH_2)_nOH$;
M = K, Na

Reactions of compounds **1** with amines were carried out in aqueous or aqueous-alcoholic solutions in the presence of alkali (KOH or NaOH). It was demonstrated by particular experiments that the formation of epoxide **2** from chlorohydrin **1** is virtually completed at 20—30 °C in 2—3 h, whereas reactions of amines with epoxides **2** proceed at 20—30 °C for 4—12 h. The yield of aminosulfamate (**5**) increases somewhat when alkali and amine are added to the reaction mixture simultaneously.

To prevent the formation of products of the dialkylation of primary amine, we used a twofold or threefold excess of amine. Under these conditions, the yield of the disubstituted product was no more than 5%.

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* For Part 2, see Ref. 1.

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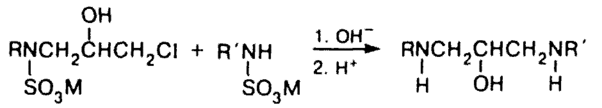
Table 1. Characteristics of 1,3-diamino-2-propanols (**3**)

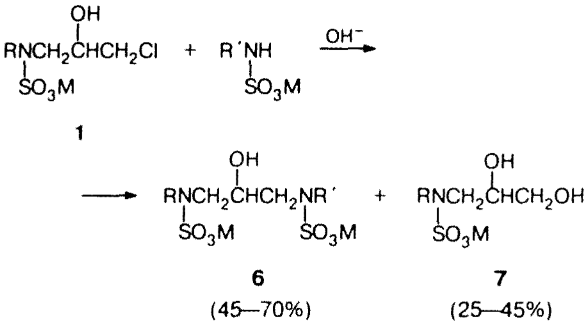


$R\underset{SO_3M}{N}CH_2\overset{OH}{C}HCH_2Cl + R'\underset{SO_3M}{NH} \xrightarrow[2.\ H^+]{1.\ OH^-} R\underset{H}{N}CH_2\underset{OH}{C}HCH_2\underset{H}{N}R'$

R	R′	Yield (%)	B.p./°C (*p*/Torr)* [M.p./°C]	
			This work	Literature data
Me	H	45	94—98 (0.3—0.4)	93—95 (0.3)[8]
Me	Me	70	80—85 (0.1—0.15)	80—90 (0.11)[9]
H	Et	60	118—121 (18—20)	117—119 (18)[10]
Et	Et	58	[39—41]	[40—42][5]

When sulfamates **1** were reacted with NH_3 and $MeNH_2$, intermediate product **5** was not isolated, and the reaction mixture was immediately subjected to acid hydrolysis. As shown in Scheme 1, aminosulfamate **5** can be prepared directly from sulfamate **1** under the action of amine. This reaction actually proceeds. However, a high temperature (~100 °C) is necessary for the formation of compound **5**. Therefore, in our case, the contribution of this reaction is insignificant.

As reported previously,[2] epichlorohydrin reacts with derivatives of sulfamic acid to form disubstituted byproducts (**6**) in addition to sulfamates **1**. In the presence of an alkaline reagent and excess sulfamate, this is the main reaction, and proceeds with a yield of 45—70% (Table 1) producing 1,2-dihydroxypropylsulfamates (**7**) as impurities (25—45%).



$$R\underset{SO_3M}{N}CH_2\overset{OH}{C}HCH_2Cl + R'\underset{SO_3M}{NH} \xrightarrow{OH^-} R\underset{SO_3M}{N}CH_2\overset{OH}{C}HCH_2\underset{SO_3M}{N}R' + R\underset{SO_3M}{N}CH_2\overset{OH}{C}HCH_2OH$$

1

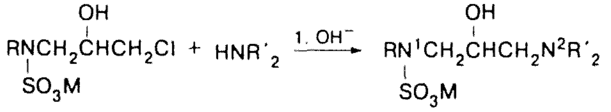
6 (45—70%)

7 (25—45%)

R = R′;
R ≠ R′;
R, R′ = H, Me, Et

Acid hydrolysis of the derivatives of sulfamic acid has been studied extensively. In the case of the simplest sulfamates (*N*-methyl- and *N*-ethylsulfamates), it is possible to obtain the corresponding salts of amines in high yields using this reaction (*ca.* 95%). However, according to the study reported in Ref. 7, only hydrochloric acid

Table 2. Characteristics of 3-amino-2-hydroxypropylsulfamates (**5**)



$R\underset{SO_3M}{N}CH_2\overset{OH}{C}HCH_2Cl + HNR'_2 \xrightarrow{1.\ OH^-} R\underset{SO_3M}{N^1}CH_2\overset{OH}{C}HCH_2N^2R'_2$

R	R'_2N	Yield of sulfamates **5** (%)	M.p. /°C	Molecular formula	Found/Calculated (%)			^1H NMR (D_2O, δ)
					C	H	N	
H	$O(CH_2CH_2)_2N$	90	78—83	$C_7H_{15}KN_2O_5S$	29.65 30.20	5.35 5.44	—	2.52—2.65 (m, 6 H, 3 CH_2N^2), 3.04 (m, 2 H, CH_2N^1), 3.78 (t, 4 H, 2 CH_2O), 4.04 (m, 1 H, $\underline{CH}CH_2$)
Me	$O(CH_2CH_2)_2N$	90	74—76	$C_8H_{17}KN_2O_5S$	—	—	9.54 9.58	2.5—2.7 (m, 6 H, 3 CH_2N^2), 2.74 (s, 3 H, Me), 2.99 (m, 2 H, N^1CH_2), 3.78 (t, 4 H, 2 CH_2O), 4.05 (m, 1 H, $\underline{CH}CH_2$)
Et	$O(CH_2CH_2)_2N$	85	68—72	$C_9H_{19}KN_2O_5S$	—	—	8.53 9.14	1.1 (t, 3 H, $\underline{CH_3}CH_2$), 2.35—2.58 (m, 6 H, 3 CH_2N^2), 2.85—3.2 (m, 4 H, 2 CH_2N^1), 3.72 (t, 4 H, 2 CH_2O), 4.04 (m, 1 H, $\underline{CH}CH_2$)
H	$HN(CH_2CH_2)_2N$	85	48—53	$C_7H_{16}KN_3O_4S$	—	—	15.03 15.15	2.4—2.75 (m, 6 H, 3 CH_2N^2, 4 H, 2 CH_2NH), 3.02 (m, 2 H, CH_2N^1) 4.03 (m, 1 H, $\underline{CH}CH_2$)

(to be continued)

can be used for sulfamates containing hydroxyl groups in the β and γ positions. When sulfuric acid was used for hydrolysis, it reacted with the hydroxyl group to yield sulfates. Our studies demonstrated that the formation of sulfuric esters can be almost completely excluded when hydrolysis is carried out with 20—30% sulfuric acid at 90—110 °C. In this case, yields were 70—90%.

The physical properties, yields, and NMR data for the compounds are given in Tables 1, 2, and 3, respectively.

Table 2. (*continued*)

R	R'$_2$N	Yield of sulfamates 5 (%)	M.p. /°C	Molecular formula	Found/Calculated (%)			^{1}H NMR (D$_2$O, δ)
					C	H	N	
Me	$HN(CH_2CH_2)_2N$	85	178—183	$C_8H_{18}KN_3O_4S$	—	—	14.52 14.42	2.3—2.75 (m, 6 H, 3 CH_2N^2, 4 H, 2 CH_2NH), 2.65 (s, 3 H, Me), 2.88 (m, 2 H, CH_2N^1), 4.01 (m, 1 H, $\underline{CH}CH_2$)
Et	$HN(CH_2CH_2)_2N$	90	Resin	$C_9H_{20}KN_3O_4S$	—	—	14.07 13.78	1.03 (t, 3 H, $\underline{CH_3}CH_2$), 2.3—2.69 (m, 6 H, 3 CH_2N^2, 4 H, 2 CH_2NH), 2.8—3.1 (m, 4 H, 2 CH_2N^1), 3.98 (m, 1 H, $\underline{CH}CH_2$)
H	Bu^{t}NH	75	115—118	$C_7H_{17}KN_2O_4S$	—	—	—	1.09 (s, 9 H, Bu^t), 2.5—2.62 (m, 2 H, CH_2N^2), 3.00 (m, 2 H, CH_2N^1), 3.78 (m, 1 H, $\underline{CH}CH_2$)
Me	Bu^{t}NH	75	196—202	$C_8H_{19}KN_2O_4S$	—	—	9.60 10.06	1.09 (s, 9 H, Bu^t), 2.56—2.61 (m, 2 H, CH_2N^2), 2.69 (s, 3 H, Me), 2.98 (m, 2 H, CH_2N^1), 3.85 (m, 1 H, $\underline{CH}CH_2$)
Et	Bu^{t}NH	80*	—	$C_9H_{21}KN_2O_4S$	—	—	—	1.1 (s, 9 H, Bu^t, 3 H, Et), 2.5—2.8 (m, 2 H, CH_2N^2), 2.9—3.2 (m, 4 H, CH_2N^1), 3.88 (m, 1 H, $\underline{CH}CH_2$)
H	Pr^{i}NH	75*	Resin	$C_6H_{15}KN_2O_4S$	—	—	—	1.11 (d, 6 H, Pr^i), 2.61—2.84 (m, 2 H, CH_2N^2), 2.92 (q, H, $\underline{CH}Me$), 3.02 (m, 2 H, CH_2N^1), 3.92 (m, 1 H, $\underline{CH}CH_2$)
Me	Pr^{i}NH	85	119—120	$C_7H_{17}KN_2O_4S$	—	—	10.64 10.60	1.1 (d, 6 H, Pr^i), 2.5—2.7 (m, 2 H, CH_2N^2), 2.7 (s, 3 H, Me), 2.78 (q, 1 H, $\underline{CH}Me$), 2.95 (m, 2 H, CH_2N^1), 3.88 (m, 1 H, $\underline{CH}CH_2$)
Et	Pr^{i}NH	70	Resin	$C_8H_{19}KN_2O_4S$	34.94 34.51	7.02 6.88	—	1.10—1.20 (m, 6 H, Pr^i, 3 H, Et), 2.70—2.84 (m, 2 H, CH_2N^2), 2.90—3.20 (m, 4 H, 2 CH_2N^1, 1 H, $\underline{CH}CH_3$), 3.96 (m, 1 H, $\underline{CH}CH_2$)
H	$HOCH_2CH_2NH$	92	Resin	$C_5H_{13}KN_2O_5S$	—	—	11.57 11.10	2.56—2.84 (m, 4 H, 2 CH_2N^2), 3.04 (m, 2 H, CH_2N^1), 3.74 (t, 2 H, CH_2OH), 3.91 (m, 1 H, $\underline{CH}CH_2$)
Me	$HOCH_2CH_2NH$	85	Resin	$C_6H_{15}KN_2O_5S$	26.31 27.06	5.32 5.68	—	2.55—2.80 (m, 4 H, 2 CH_2N^2), 2.7 (s, 3 H, Me), 3.00 (m, 2 H, CH_2N^1), 3.68 (t, 2 H, CH_2OH), 3.95 (m, 1 H, $\underline{CH}CH_2$)

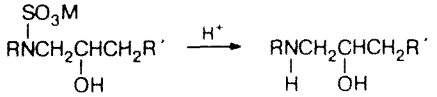
(*to be continued*)

Table 2. (*continued*)

R	R'_2N	Yield of sulfamates 5 (%)	M.p. /°C	Molecular formula	Found / Calculated (%) C	H	N	^1H NMR (D_2O, δ)
Me	$HO(CH_2)_3NH$	83	Resin	$C_7H_{17}KN_2O_5S$	—	—	$\underline{10.03}$ 10.06	1.74 (m, 2 H, $\underline{CH_2}CH_2$), 2.55—2.78 (m, 4 H, $2CH_2N^2$), 2.73 (s, 3 H, Me), 3.00 (m, 2 H, CH_2N^1), 3.63 (t, 2 H, CH_2OH), 3.98 (m, 1 H, $\underline{CH}CH_2$)
H	$4-MeC_6H_4NH$	90	178—180	$C_{10}H_{15}KN_2O_4S$	—	—	$\underline{10.02}$ 9.39	2.06 (s, 3 H, Me), 2.84—3.04 (m, 4 H, CH_2N^1, CH_2N^2), 3.81 (m, 1 H, $\underline{CH}CH_2$), 6.58 (d, 2 H, Ph—H), 6.91 (d, 2 H, Ph—H)
H	Et_2N	86	Resin	$C_7H_{17}KN_2O_4S$	—	—	$\underline{10.33}$ 10.60	1.1 (t, 6 H, 2 Et), 2.58—2.83 (m, 6 H, 3 CH_2N^2), 3.03 (m, 2 H, CH_2N^1), 4.01 (m, 1 H, $\underline{CH}CH_2$)

* The compounds obtained were transformed to the corresponding amines without additional purification.

Table 3. Characteristics of 1,3-diamino-2-propanols



$$RN(SO_3M)CH_2CH(OH)CH_2R' \xrightarrow{H^+} RNHCH_2CH(OH)CH_2R'$$

R	R′	Yield of amine (%)	n_D^{20} M.p./°C	Molecular formula	Found / Calculated (%) C	H	N	^1H NMR (D_2O, δ)
H	$O(CH_2CH_2)_2N$	95	1.4828	$C_7H_{16}N_2O_2$	$\underline{52.90}$ 52.48	$\underline{10.40}$ 10.07	—	2.4—2.74 (m, 8 H, 3 CH_2N, CH_2NH), 3.73 (t, 4 H, 2 CH_2O), 3.88 (m, 1 H, $\underline{CH}CH_2$)
Me	$O(CH_2CH_2)_2N$	95	1.4828	$C_8H_{18}N_2O_2$	—	—	$\underline{15.50}$ 16.08	2.34 (s, 3 H, Me), 2.45—2.63 (m, 8 H, 3 CH_2N, CH_2NH), 3.74 (t, 4 H, 2 CH_2O), 3.99 (m, 1 H, $\underline{CH}CH_2$)
Et	$O(CH_2CH_2)_2N$	80	1.4808	$C_9H_{20}N_2O_2$	—	—	$\underline{14.67}$ 14.88	1.01 (t, 3 H, Et), 2.4—2.64 (m, 10 H, 3 CH_2N, 4 CH_2NH), 3.69 (t, 4 H, 2 CH_2O), 3.93 (m, 1 H, $\underline{CH}CH_2$)
H	$HN(CH_2CH_2)_2N$	90	36—38	$C_7H_{17}N_3O$	—	—	$\underline{26.81}$ 26.39	2.32—2.88 (m, 12 H, 3 CH_2N, 3 CH_2NH), 3.82 (m, 1 H, $\underline{CH}CH_2$)
Me	$HN(CH_2CH_2)_2N$	80	1.4730	$C_8H_{19}N_3O$				2.26 (s, 3 H, Me),
					$\underline{55.41}$ 55.46	$\underline{10.76}$ 11.06	—	2.3—2.75 (m, 12 H, 3 CH_2N, 3 CH_2NH), 3.94 (m, 1 H, $\underline{CH}CH_2$)
Et	$HN(CH_2CH_2)_2N$	90	32—34	$C_9H_{21}N_3O$	$\underline{58.09}$ 57.72	$\underline{11.48}$ 11.30	—	1.05 (t, 3 H, Et), 2.32—2.76 (m, 14 H, 3 CH_2N, 4 CH_2NH), 3.95 (m, 1 H, $\underline{CH}CH_2$)

(*to be continued*)

Table 3. *(continued)*

R	R′	Yield of amine (%)	n_D^{20} M.p./°C	Molecular formula	Found/Calculated (%) C	H	N	^{1}H NMR (D_2O, δ)
H	Bu^{t}NH	80	1.4596	$C_7H_{18}N_2O$	—	—	19.08 19.17	1.08 (s, 9 H, Bu^t), 2.48—2.74 (m, 4 H, 2 CH_2NH), 3.61 (m, 1 H, $\underline{CH}CH_2$)
Me	Bu^{t}NH	80	223—226*	$C_8H_{20}N_2O \cdot 2HCl$	—	—	12.33 12.01	1.36 (s, 9 H, Bu^t), 2.77 (s, 3 H, Me), 2.99—3.29 (m, 4 H, 2 CH_2NH), 4.22 (m, 1 H, $\underline{CH}CH_2$)
Et	Bu^{t}NH	90	249—253* (with decomposition)	$C_9H_{22}N_2O \cdot 2HCl$	43.22 43.73	9.61 9.78	—	1.22—1.38 (m, 12 H, Bu^{t}Et), 2.95—3.32 (m, 6 H, 3 CH_2NH), 4.18 (m, 1 H, $\underline{CH}CH_2$)
H	Pr^{i}NH	70	1.4729	$C_6H_{16}N_2O$	—	—	21.57 21.19	1.02 (d, 6 H, Pr^i), 2.43—2.77 (m, 5 H, 2 CH_2NH, CHNH), 3.64 (m, 1 H, $\underline{CH}CH_2$)
Me	Pr^{i}NH	70	300—302 (with decomposition)	$C_7H_{18}N_2O \cdot 2HCl$	—	—	12.20 12.78	1.11 (d, 6 H, Pr^i), 2.56 (s, 3 H, Me), 2.86—3.26 (m, 5 H, 2 CH_2NH, CHNH), 4.08 (m, 1 H, $\underline{CH}CH_2$)
Et	Pr^{i}NH	65	1.435	$C_8H_{20}N_2O$	—	—	17.11 17.48	1.0—1.1 (m, 9 H, Pr^i, Et), 2.44—2.85 (m, 7 H, 3 CH_2NH, CHNH), 3.80 (m, 1 H, $\underline{CH}CH_2$)
H	$HOCH_2CH_2NH$	90	153—155*	$C_5H_{14}N_2O_2 \cdot 2HCl$	—	—	13.11 13.52	2.98—3.33 (m, 6 H, CH_2NH), 3.78 (t, 2 H, CH_2OH), 4.28 (m, 1 H, $\underline{CH}CH_2$)
Me	$HOCH_2CH_2NH$	87	133—135*	$C_6H_{16}N_2O_2 \cdot 2HCl$	32.58 32.62	8.29 8.20	—	2.75 (s, 3 H, Me), 3.02—3.29 (m, 6 H, 3 CH_2NH), 3.83 (t, 2 H, CH_2OH), 4.29 (m, 1 H, $\underline{CH}CH_2$)
Me	$HO(CH_2)_3NH$	90	—		—	—	16.90 17.26	1.67 (m, 2 H, $\underline{CH_2}CH_2$), 2.25 (s, 3 H, Me), 2.47—2.66 (m, 6 H, 3 CH_2NH), 3.58 (t, 2 H, CH_2OH), 3.82 (m, 1 H, $\underline{CH}CH_2$)
H	4-MeC_6H_4NH	85	190—192*	$C_{10}H_{16}N_2O \cdot 2HCl$	48.04 47.44	7.40 7.17	—	2.39 (s, 3 H, Me), 3.05—3.5 (m, 4 H, 2 CH_2NH), 4.25 (m, 1 H, $\underline{CH}CH_2$), 7.32 (m, 4 H, Ph—H)
H	MeNH	74						
Me	MeNH	83						

* The data are given for hydrochlorides of the corresponding amines.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250 MHz.

General procedure for the preparation of 3-amino-2-hydroxypropylsulfamates (5). 3-Chloro-2-hydroxypropylsulfamates **1** (0.015 mol) were dissolved in water (5 mL). Then the amine (0.03 mol) and KOH (0.015 mol) dissolved in water (1 mL) were added, and the mixture was stirred and kept at ~20 °C for 12 h. The solution was evaporated to dryness. The residue was dissolved in ethyl alcohol (15 mL). The precipitate was filtered off, and the filtrate was evaporated to dryness. The excess high-boiling amines (ethanolamine and morpholine) were removed by refluxing in a bath at 120—140 °C (7 Torr) or by extraction with ether (propanolamine and piperazine). Sulfamate **5** was recrystallized from a minimum amount of hot ethyl alcohol.

General procedure for the preparation of 1,3-diamino-2-propanols (3). Compound **5** (0.015 mol) was dissolved in water (14 mL), and then concentrated sulfuric acid (0.06 mol) was added. The reaction mixture was kept at 100 °C for 5—8 h. Then the solution was cooled to ~20 °C, alkalized to pH ~12.0, and evaporated on a rotary evaporator. The precipitate that formed was filtered off, and the filtrate was evaporated. To additionally purify 1,3-diamino-2-propanols, they were extracted repeatedly from the residue with ether or transformed to hydrochloride.

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