Synthesis of 1-mono- and 1,4-disulfoalkylpiperazines

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The optimal conditions of the formation of 1-sulfopropyl- and 1-sulfobutylpiperazines, without preliminary blocking of piperazine aminegroup, were analysed. By alkylation of 1-sulfoalkylpiperazines with alkyl-or alkylarylhalides, using the phase trasfer catalysis method, unsymmetrical 1,4-disubstituted piperazines were formed. On the reaction of alkanesultones with piperazine (in the ratio 2:1) 1,4-disulfoalkylpiperazines were isolated.

Key words: piperazine, 1,3-propane- and 1,4-butanesultones, alkylhalides

INTRODUCTION

Piperazine is one of the most widely used and thoroughly explored heterocyclic compounds. The piperazine nucleus is a structural fragment of many analgesics, psychotropic and antitumour drugs [1–3]. 1,4-Disulfoalkylpiperazines are used as buffering agents [4]. Frequently, mono-N-substituted piperazines are synthesized by the substitution of hydrogen atom of piperazine amine group with various substitutes [5]. By alkylation of piperazine with alkylhalides (in the presence of equivalent amounts of reactants) a mixture of 1-mono- and 1,4-disubstituted piperazines is formed [6], which are difficult to separate (except the cases when the reaction products can be separated by distillation). Therefore one of piperazine amine groups is blocked with easily removable groups, such as acyl-, formyl- or nitrosogroup [7–9]. In rare occasions, without preliminary blocking of piperazine NH-group, 1-monosubstituted piperazine in high yield (~90%; with 2–3% of 1,4-disubstituted piperazine) is obtained [10]. In this paper, we explored the possibility to synthesise 1-monosulfoalkylpiperazines by using 1,3-propane- and 1,4-butanesultones.

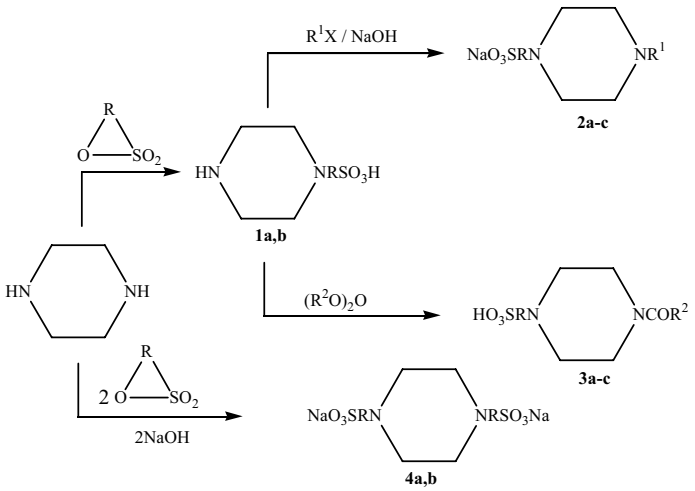
RESULTS AND DISCUSSION

On the interaction of piperazine with 1,3-propane- and 1,4-butanesultones, without preliminary blocking of piperazine NH-group, 1-sulfopropyl- and 1-sulfobutylpiperazines (**1a, b**) were received. The optimal conditions of the reactions (the ratio of sultone : piperazine 1:3.5 in dioxane or tetrahydrofurane as a solvent) were determined, whereas by using benzene or toluene as a solvent lower yields of the products were obtained. According of the data ^{1}H NMR spectra 1,4-disulfoalkylpiperazines did not form under such conditions. When this reaction was performed in ethanol or 2-propanol, the mixtures of 1-mono- and 1,4-disulfoalkylpiperazines were received.

The obtained **1a** can be alkylated with alkyl- and alkylarylhalides using the phase transfer catalysis (PTC) method by applying triethylbenzylammonium chloride (TEBA) in the presence of NaOH. The reactions were performed in a toluene/water mixture as a solvent, and 1,4-disubstituted piperazines (**2 a–c**) were synthesized. By using this method, **1a** (a substance that was hard to isolate from the product) was fully converted.

The corresponding 1,4-substituted alkanesulfonic acids (**3 a–c**) were obtained when **1a** or **1b** reacted with acetic or benzoic anhydrides in 1-methoxy-2-(2-methoxyethoxy)-etane as a solvent.

According to the literature [4], the reaction of piperazine with two equivalents of 1,3-propane- or 1,4-butanesultones using water as a solvent resulted in 1,4-disulfoalkylpiperazines; however, the structure of the reaction products was confirmed only by the microanalysis data. The sultones are sensitive to hydrolysis, thus hydroxyalkanesulfoacids are formed easily in water [11, 12], therefore we synthesized 1,4-disulfoalkylpiperazines (**5 a, b**) using the PTC method. This method is suitable for synthesis of 1,4-disulfoakylsubstituted piperazine derivatives, since the contact of sultones with water is avoided.



1a, 2a-c, 3a,b, 4a R = $(CH_2)_3$, **1b, 3c, 4b** R = $(CH_2)_4$, **2a** $R^1 = C_2H_5$, X = Br, **2b** $R^1 = CH_2CH{=}CHC_6H_5$, X = Cl, **2c** $R^1 = CH(C_6H_5)_2$, X = Cl, **3a** $R^2 = CH_3$, **3b,c** $R^2 = C_6H_5$.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H NMR spectra were recorded on a Tesla BS-567A NMR spectrometer at 80 MHz with *DSS* as internal standard in D_2O.

Synthesis of 1-monosulfoalkylpiperazines (1a,b). To the solution of 40 mmol of 1,3-propane- or 1,4-butanesultone in 10 ml of dioxane (at 70–80 °C in the case of 1,3-propanesultone and to a boiled solution of 1,4-butanesultone) was added dropwise the solution of 12.06 g (140 mmol) of piperazine dissolved in 25 ml of dioxane. After refluxing for 0.5 h, the reaction mixture was cooled to 60 °C, dioxane was poured off and the oil-like mass left in a refrigerator. The formed crystalls were filtered off, throughly washed with hot (~80 °C) dioxane (4 × 20 ml) and recrystallized from ethanol. Information on compounds **1 a, b** is provided in Table.

Synthesis of 1-alkyl- and 1-alkylaryl-4-sulfopropylpiperazines (2 a–c). 1.6 g (40 mmol) of NaOH, 0.2 g of TEBA and 4.16 g (20 mmol) of 3-(1-piperazinyl)-1-propanesulfonic acid (**1a**) were added to 30 ml of water while stirring and then 20 mmol of bromoethane (or 3-chloro-1-phenyl-1-propene, chlorodiphenylmethane) dissolved in 30 ml of toluene was added. The mixture was

Table. **Data of 1-mono- and 1,4-disubstituted piperazines 1 a, b, 2 a–c, 3 a–c, 4 a, b**

Cpd. No	Yield, %	Mp,* °C	Found / requires, % C	H	S	Formula	^{1}H NMR spectra data (δ, ppm)
1a	79.4	266	40.28 40.38	7.82 7.74	15.20 15.39	$C_7H_{16}N_2O_3S$	1.87 (m, 2H, CCH_2C). 2.50 (t, 2H, CH_2S), 2.67–3.11 (m, 10H, CH_2N)
1b	66.4	228	43.18 43.22	8.23 8.16	14.28 14.42	$C_8H_{18}N_2O_3S$	1.71 (m, 4H CH_2N), 2.60 (t, 2H, CH_2S), 2.87–3.10 (m, 10H, CH_2N)
2a	81.4	273	41.84 41.85	7.49 7.41	12.47 12.41	$C_9H_{19}N_2NaO_3S$	1.47 (t, 3H, CH_3), 2.02 (m, 2H, CCH_2C), 2.76 (t, 2H, CH_2S), 2.88–3.15 (m, 12H, CH_2N)
2b	61.3	308	55.41 55.47	6.74 6.69	9.33 9.25	$C_{16}H_{23}N_2NaO_3S$	1.92 (m, 2H, CCH_2C), 2.42 (t, 2H, CH_2S), 2.64–2.90 (m, 12H, CH_2N), 6.01–6.53 (m, 2H, CH=CH), 7.29 (m, 5H, C_6H_5)
2c	76.4	273	60.51 60.59	6.43 6.35	8.12 8.19	$C_{20}H_{25}N_2NaO_3S$	2.04 (m, 2H, CCH_2C), 2.58 (t, 2H, CH_2S), 3.01 (m, 10H, CH_2N), 3.64 (s, 1H, CH), 6.46–7.92 (m, 10H, C_6H_5)
3a	77.8	234	43.28 43.18	7.49 7.25	12.76 12.81	$C_9H_{18}N_2O_4S$	2.05 (s, 3H, CH_3), 2.32 (m, 2H, CCH_2C), 3.04 (t, 2H, CH_2S), 3.38 (m, 6H, CH_2N), 3.89 (m, 4H, CH_2NCO)
3b	71.6	226	53.71 53.83	6.51 6.45	10.21 10.26	$C_{14}H_{20}N_2O_4S$	2.08 (m, 2H, CCH_2C), 2.52 (t, 2H, CH_2S), 2.63 (m, 6H, CH_2N), 3.05 (m, 4H, CH_2NCO), 7.32–8.20 (m, 5H, C_6H_5)
3c	57.4	269	55.24 55.19	6.74 6.79	9.87 9.82	$C_{15}H_{22}N_2O_4S$	1.84 (m, 4H, CCH_2C), 2.94 (t, 2H, CH_2S), 3.41 (m, 6H, CH_2N), 3.81 (m, 4H, CH_2NCO), 7.60 (m, 5H, C_6H_5)
4a	86.4	289	32.11 32.08	5.32 5.38	17.21 17.13	$C_{10}H_{20}N_2Na_2O_6S_2$	2.07 (m, 4H, CCH_2C), 2.96 (t, 4H, CH_2S), 3.37–3.44 (m, 12H, CH_2N)
4b	82.7	314	35.87 35.81	6.09 6.01	16.02 15.93	$C_{12}H_{24}N_2Na_2O_6S_2$	1.78 (m, 8H, CCH_2C), 2.50 (t, 4H, CH_2S), 2.64–3.00 (m, 12H, CH_2N)

*With decomposition.

refluxed for 4 h, the aqueous layer was separated, water partially evaporated until the appearance of the first crystalls. 50 ml of acetone was added and the reaction mixture left in a refrigerator. The formed crystalls were filtered off and recrystallized from water. Information on compounds **2 a–c** is provided in Table.

Synthesis of 1-acetyl- and 1-benzoylpiperazine alkanesulfonic acids (3 a–c). 10 mmol of the corresponding piperazinylsulfonic acids (**1 a, b**) and 10 mmol of acetic or benzoic anhydrides in 30 ml of 1-methoxy-2-(2-methoxyethoxy)-etane were refluxed for 3 h. The formed crystalls were filtered off, throughly washed with hot (~70 °C) ethanol and recrystallized from water. Information on compound **3 a–c** is provided in Table.

Synthesis of 1,4-disulfoalkylpiperazines (4 a, b). To a solution of 2.0 g (50 mmol) of NaOH in 30 ml of water 2.15 g (25 mmol) of piperazine and 0.2 g of TEBA were added while stirring. Then 50 mmol of 1,3-propanesultone (or 1,4-butanesultone) dissolved in 30 ml of benzene was added and the mixture was refluxed for 1 h (in the case of 1,4-butanesultone for 2 h). The separation was performed as in the case of compounds **2 a–c**. Information on compounds **4 a, b** is provided in Table.

CONCLUSIONS

3-(1-Piperazinyl)-1-propane- and 4-(1-piperazinyl)-1-butanesulfonic acids were synthesized from piperazine and 1,3-propane- or 1,4-butanesultones, without the preliminary blocking of the aminegroup of piperazine. Unsymmetrical 1,4-disubstituted piperazines were formed by alkylation of 1-piperazinylalkanesulfonic acids with alkyl-, alkylarylhalides, or acetylation with acetic or benzoic anhydrides. Symmetrical 1,4-disulfoalkylpiperazines were received by the interaction of piperazine and alkanesultones (ratio 1:2) under phase transfer catalysis conditions.

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1-MONO- IR 1,4-DISULFOALKILPIPERAZINŲ SINTEZĖ

S a n t r a u k a

3-(1-Piperazinil)-1-propan- and 4-(1-piperazinil)-1-butansulfonrūgštys gaunamos, be išankstinio piperazino NH-grupės blokavimo, reaguojant piperazinui su 1,3-propan- arba 1,4-butansultonais. Susintetintos 1-piperazinilalkansulfonrūgštys su alkil-, alkilarilhalogenidais bei acto ir benzoiniu anhidridais sudaro nesimetrinius 1,4-dipavaduotus piperazinus. Reaguojant piperazinui su alkansultonais (1:2) tarpfazinės katalizės sąlygomis, susidaro simetriniai 1,4-disulfoalkilpiperazinai.