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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Properties of Some Aminothiols of Phenylethane Series

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Abstract—Based on styrene, a method of synthesis of 1-phenyl-1,2-epithioethane, the key compound for the synthesis of ethane-1,2-aminothiols, is developed. Antimicrobial activity of the synthesized compounds is investigated

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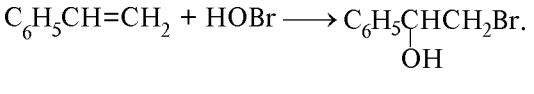
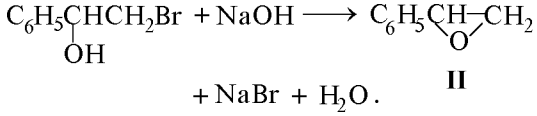
Aminothiols and their derivatives have a wide range of physiological activity and can be used to create adrenoblocators, autoimmunomodulators, antiseptics, and hypoglikemic means [1, 2]. They can serve as key compounds for the synthesis of various nitrogen- and sulfur-containing heterocycles with desirable properties. The interest to aminothiols extents due to their different functional properties, in particular, physiological activity which gives rise to their wide application in pharmaceutical practice as drug. As is known, the drugs tiphen diprophen are aminothiol esters and are widely used currently in medical practice [3].

Earlier [4–6] has been shown that aminothiols are effective antimicrobial additives to lubricating oils. In continuation of our studies in the field of synthesis of aminothiols and examining the relationship between their structure and antimicrobial activity, in this article are investigated the synthesis of 1-phenyl-1,2-epithioethane and its nucleophilic addition reactions with various amines. The synthesis was carried out as follows: at the first stage styrene was transformed into 1-bromo-2-hydroxy-2-phenylethane (**I**) by the reaction of hydrobromination with a bromide–bromate solution:



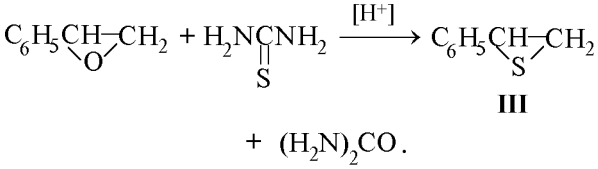
I

At the second stage, 1-bromo-2-hydroxy-2-phenylethane (**I**) under the action of 20% aqueous solution of sodium hydroxide was subjected to cyclization and transformed into corresponding oxirane (**II**):



II

1-Phenyl-1,2-epithioethane (**III**) was prepared on the basis of anionotropic substitution of oxygen atoms in the molecule of 1-phenyl-1,2-epoxyethane (**II**) by the sulfur atom in the reaction with thiocarbamide in the presence of a catalytic amount of sulfuric acid, with subsequent neutralization by a solution of sodium carbonate:



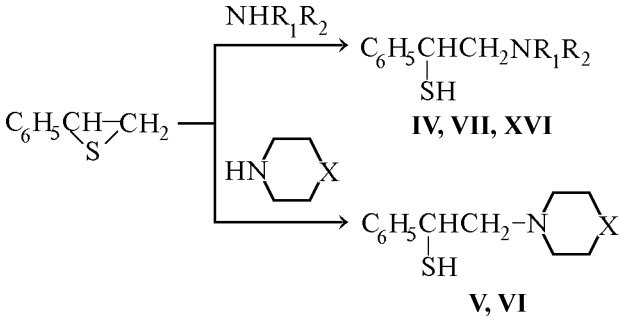
III

Nucleophilic addition reactions with 1-phenyl-1,2-epithioethane to various amines were carried out in sealed ampoule at a ratio of reacting components thiirane : amine = 1 : 2. It was found that the yield of target product increases at the use an excess amine, which in this case plays a role the solvent. Synthesis of 1,2-

Table 1. Physicochemical characteristics of the synthesized 1,2 -aminoethanethiols **IV**–**XVI**

Compd.	Yield, %	mp, °C (*P*, mm Hg)	n_D^{20}	R_f	Found, %				Formula	Calculated, %			
					C	H	N	S		C	H	N	S
IV	30	77–78 (0.5)	.5398	0.46	68.78	8.92	6.56	15.16	$C_{12}H_{19}NS$	68.89	9.09	6.69	15.31
V	60	121–127 (0.3)	.5599	0.57	70.44	8.44	6.16	14.33	$C_{13}H_{19}NS$	70.58	8.59	6.33	14.47
VI	71	126–127 (0.4)	.5624	0.68	64.28	7.54	6.15	14.13	$C_{12}H_{17}NSO$	64.54	7.67	6.27	14.36
VII	63	118–120 (0.1)	.5555	0.51	73.13	6.42	6.29	13.76	$C_{14}H_{15}NS$	73.32	6.59	6.11	13.97
VIII	71	130–131(0.1)	.5421	0.58	73.84	6.91	5.63	13.03	$C_{15}H_{17}NS$	74.03	7.04	5.76	13.18
IX	75	134–135 (0.1)	.5475	0.42	73.87	6.88	5.62	13.02	$C_{15}H_{17}NS$	74.03	7.04	5.76	13.18
X	67	131–132 (0.1)	.5432	0.49	73.89	0.14	5.60	13.04	$C_{15}H_{17}NS$	74.03	7.04	5.76	13.18
XI	78	139v140 (0.1)	.5475	0.71	69.21	6.79	5.17	13.51	$C_{15}H_{17}NOS$	6.46	6.56	5.40	13.16
XII	69	142–143 (0.1)	.5432	0.63	69.29	6.43	5.27	13.04	$C_{15}H_{17}NOS$	6.46	6.56	5.40	13.16
XIII	74	140–141(0.1)	.5483	0.52	69.29	6.41	5.27	13.05	$C_{15}H_{17}NOS$	69.46	6.56	5.40	13.16
XIV	65	134–135 (0.1)	.5565	0.41	63.62	5.21	5.14	13.28	$C_{15}H_{17}NSC1$	63.75	5.35	5.31	13.44
XV	74	136–137 (0.1)	.5530	0.53	63.57	5.22	5.15	13.27	$C_{15}H_{17}NSC1$	63.75	5.35	5.31	13.44
XVI	69	133–134 (0.1)	.5585	0.61	63.58	5.17	5.12	13.18	$C_{15}H_{17}NSC1$	63.75	5.35	5.31	13.44

aminoethanethiols **IV**–**XVI** carried out as follows:



$R^1 = R^2 = C_2H_5$ (**IV**); X = CH_2 (**V**); X = O (**VI**); R^1 = H, $R^2 = C_6H_5$ (**VII**); R^1 = H, R^2 = 2-$CH_3C_6H_4$ (**VIII**); R^1 = H, R^2 = 3-$CH_3C_6H_4$ (**IX**); R^1 = H, R^2 = 4-$CH_3C_6H_4$ (**X**); R^1 = H, R^2 = 2-$CH_3OC_6H_4$ (**XI**); R^1 = H, R^2 = 3-$CH_3OC_6H_4$ (**XII**); R^1 = H, R^2 = 4-$CH_3OC_6H_4$ (**XIII**); R^1 = H, R^2 = 2-ClC_6H_4 (**XIV**); R^1 = H, R^2 = 3-ClC_6H_4 (**XV**); R^1 = H, R^2 = 4-ClC_6H_4 (**XVI**).

Synthesized 1-amino-2-phenyl-2-ethanethiols (1,2-aminoethanethiols) **IV**–**XVI** are a colorless liquid with a characteristic odor. If long-term storage the liquid yellows. Compounds **IV**–**XVI** are well soluble in organic solvents but insoluble in water.

Physico-chemical constants of the synthesized compounds are given in Table. 1.

Purity of the synthesized 1-amino-2-phenyl-2-ethanethiols **IV**–**XVI** is confirmed by data of elemental analysis, thin layer and gas-liquid chromatography; the structure of the compounds is proved with the use of IR and NMR spectroscopy.

In the IR spectra of 1-amino-2-phenyl-2-ethanethiols there are characteristic absorption band at 3340–3360 cm^{-1}, corresponding to stretching vibrations of secondary amine NH groups. Stretching vibrations of SH groups are revealed by a band at 2545–2550 cm^{-1}. This band has a weak intensity, and not always could be identified [7, 8]. In addition, all the synthesized 1,2-aminoethanethiols **IV**–**XVI** have absorption bands at 1060–1070 cm^{-1}, relevant to CN bonds. In the areas of 1420–1440, 1500–1510, 1610–1620 cm^{-1} are found the absorption bands characteristic of stretching C=C vibrations in aromatic ring.

In the ^{1}H NMR spectrum of 1-(*N*-diethylamino)-2-phenyl-2-ethanethiol **IV** a triplet signal of six protons of two methyl groups occurs at 1.15 ppm. In the region of 2.40 ppm there is a multiplet signals of protons in the $CHCH_2$ fragment. The signal of proton of SH groups occurs at 2.15 ppm; it was identified on the basis of changes in the spectrum upon the addition of D_2O.

Nonequivalent protons of aromatic rings give a signal in the form of two triplets, at 6.40 and 6.75 ppm.

The ^{1}H NMR spectrum of remaining 1-amino-2-phenyl-2-ethanethiols **V**–**XVI** are similar to the spectrum of compounds **IV**, but differs by the position the signals of respective substituents (pentamethylenimino-, morpholino-, various substituted phenyl radicals, etc.).

The synthesized compounds were tested in accordance with GOST 9.052-75 and 9.085-75 as antimicrobial additives for lubricating oil M-11. For the examination are used bacteria *Prendomanas aeruginosa* and fungi *Aspergillus-niger* and *Canadida-tragicalic*.

The results of testing the synthesized compounds as antimicrobial additives to oil M-11 are shown in Table 2. The oil M-11 does is not biologically stable and is destructed by these organisms.

The synthesized compounds have a pronounced antimicrobial action at low concentrations (0.5–1.0%), well soluble in the oil M-11 and do not stimulate corrosion. The synthesized 1,2-aminoethanethiols **IV**–**XVI** are more effective than industrial antimicrobial additive 2-mercaptobenzthiazol taken as a reference.

As can be seen from the Table 2, at adding 0.5–1.0% of 1-diethylamino-2-phenyl-2-ethanethiol **IV** the width of the zone for bacteria is 0.5–1.2, and for the fungi 0.8–1.5. Similar picture is observed at the testing the antimicrobial effectiveness of 1-(*N*-phenylamino)-2-phenyl-2-ethanethiol **VII**, where the width of the zone of inhibition by bacteria is 0.9–1.9, by fungi 1.2–2.3 cm. In the case of 2-mercaptobenzthiazol at concentrations 0.5–1.0% the area of oppression by bacteria is 0.4–1.0, and by fungi, 0.8–1.5 Other synthesized 1-amino-2-phenyl-2-ethanethiols **V**–**XVI** also exhibit high antimicrobial activity, and their effect on fungi is much stronger than on the bacterial culture.

As can be seen from Table 2, 1,2-aminoethanethiols **V** and **VI** containing heterocyclic amine fragments have a lower antimicrobial activity compared to 1,2-aminoethanethiols with aryl-substituted fragments. Methyl and methoxy substituents in arylamine fragments of 1,2-aminoethanethiols do not significantly affect their antimicrobial activity. However, in going from the methyl and methoxy substituents to chlorine the antimicrobial activity increases significantly. Thus, as a result of the research is found the relationship between the structure of the synthesized compounds and their antimicrobial activity.

Table 2. Antimicrobial activity of 1,2-aminoethanthiols **IV**–**XI** in oil M-11

Compd. no.	*c*, %	Diameter of the inhibition zone of growth of microorganisms, cm	
		by bacterias in beef-extract gar	by fungi in wort agar medium
IV	0.5	0.5	0.8
	1.0	1.2	1.5
V	0.5	0.7	0.8
	1.0	1.3	1.5
VI	0.5	0.7	0.9
	1.0	1.5	1.7
VII	0.5	0,9	1.2
	1.0	1.9	2.3
VIII	0.5	0.8	1.1
	1.0	1.8	2.1
IX	0.5	0.90	1.2
	1.0	1.5	2.2
X	0.5	1.0	1.3
	1.0	2.0	2.3
XI	0.5	1.0	1.4
	1.0	2.0	2.4
XII	0.5	1.0	1.3
	1.0	1.9	2.2
XIII	0.5	1.2	1.4
	1.0	2.1	2.3
XIV	0.5	1.1	1.3
	1.0	1.8	2.3
XV	0.5	1.2	1.4
	1.0	1.8	2.3
XVI	0.5	1.3	1.5
	1.0	1.9	2.5
2-Mercapto-benzthiazol	0.5	0.4	0.8
	1.0	1.0	1.5
M-11		+	+

EXPERIMENTAL

The IR spectra were registered on a Specord 75-IR instrument, the ^{1}H NMR spectra on a VXR-400S device (400 MHz) for the solutions of substances in DMSO-d_6, internal reference TMS. Purity raw materials and the analysis of reaction products were carried out by TLC (Silufol, eluent hexane–isopropyl alcohol 1 : 3, development in iodine vapor).

Bromide–bromate solution is prepared as follows. In the flask of 3 liter was poured 1.25 l of distilled water and dissolved 125 g of KBr. Then, with stirring was added dropwise 40 ml of bromine and stirring was continued till complete bromine dissolving.

1-Bromo-2-hydroxy-2-phenylethane (I). A three-neck 2 l flask equipped with two dropping funnel, one of which is 100 ml, and the other 1000 ml (for the bromide–bromate solution), was placed in a water bath. The temperature in the bath was maintained at 90–100°C. The reaction was carried out by adding alternately

portions 52 g (0.5 mol) of styrene, followed by bromide-bromate solution. Initially was added 250 ml of distilled water, then was poured 10–15 g styrene, followed by 50 ml of bromide-bromate solution. The next portion of styrene was added after the solution bleaching. The reaction was carried out for 3 h. Then the reaction mixture was stired for 30 min at 90–100°C. Then the bottom layer (containing organic bromide) was separated from the water, dried over sodium sulfate and subjected to vacuum distillation. 19 g (20%) of compound **I** was obtained, bp 114°C (4 mm Hg), n_D^{20} 1.5782.

1-Phenyl-1,2-epoxyethane (II). To a mixture of 20.1 g (0.1 mol) of 1-bromo-2-hydroxy-2-phenylethane **I** and 50 ml of hexane at vigorous stirring was added dropwise g 20% solution of sodium hydroxide. Then the flask content was heated at 60°C for 2 h, the reaction mixture was then cooled, washed several times with water to neutral reaction and dried over anhydrous sodium sulfate. After distilling the solvent off, the reaction products were distilled with a 20-cm Vigre column. Compound **II** of 9 g (80%) was obtained, n_D^{20} 1.5368 (published [9] n_D^{20} 1.5342).

1-Phenyl-1,2-epithioethane (III). To the three-neck flask was placed 7.6 g (0.1 mol) of thiourea and 3 ml of sulfuric acid (1 eq. of acid in 350 ml of water). At vigorous stirring the reaction mixture was cooled to 5–10°C and at that temperature was added dropwise 11 g (0.1 mol) of 1-phenyl-1,2-epoxyethane **II**. The mixture was maintained at room temperature for 1 h, and then was hydrolyzed with 10.6 g (0.1 mol) of sodium carbonate dissolved in 45 ml of water. The water layer was separated and extracted with ether (40 ml). The extract was combined with the organic layer and dried over anhydrous sodium sulfate. After distilling ether off, the residue was distilled in a vacuum. 11 g (87%) of 1-phenyl-1 ,2-epitioethane **III** was obtained, bp 87–88°C (4 mm Hg), n_D^{20} 1.6030 (published [10] bp 30°C at 0.01 mm Hg, n_D^{20} 1.6015).

1-(*N*-Phenylamino)-2-phenyl-2-ethanethiol (VII). A mixture of 9.3 g (0.1 mol) of aniline and 6.8 g (0.05 mol) of 1-phenyl-1,2-epithioethane **III** was heated in a sealed ampoule at a boiling water bath for 8 h. After cooling the ampoule was open and the reaction mixture was distilled under reduced pressure. First was distilled the excess of aniline, and then the target product of reaction. 7.9 g of 1-(*N*-phenylamino)-2-phenyl-2-ethanethiol **VII** was obtained, bp 118–120°C (0.1 mm Hg), n_D^{20} 1.5555, R_f 0.51. Found, %: C 73.07, H 6.86, N 6.43, S 13.76. $C_{14}N_{15}NS$. Calculated (%): C 73.32, H 6.59, N 6.11, S 13.97.

Similarly have been synthesized other 1-amino-2-phenyl-2-ethanethiols **IV**–**XVI**.

CONCLUSIONS

(1) The method of synthesis of 1-phenyl-1,2-epithioethane on the basis of styrene is developed.

(2) 1-Amino-2-phenyl-2-ethanethiols, synthesized in the interaction of 1-phenyl-1,2-epithioethane with various amines, have antimicrobial activity.

(3) A relationship between the structure of aminothiols and their antimicrobial activity is revealed.

REFERENCES

1. Magerramov, A.M., Allakhverdiev, M.A., Guseinova, A.T., and Kuliev, D.A. *Aminotioly i ikh proizvodnye* (Aminothiols and Their Derivatives), Baku: Bakin. Gos. Univ., 2007.
2. Magerramov, A.M. and Allakhverdiev, M.A., *Bifunktsional'nye aminnye soedineniya* (Bifunctional Amine Compounds), Baku: "Chashyoglu", 2005.
3. Rubtsov, M.V. and Baichikov, A.T., *Sinteticheskie khimikofarmatsevticheskie preparaty* (Synthetic Chemical Farmaceutic Chemicals), Moscow: Meditsina, 1971.
4. Guseinova, A.T., Magerramov, A.M., Nadim, Kh.A., and Allakhverdiev, M.A., *Zh. Prikl. Khim.,* 2002, vol. 75, no, 8, pp.1306–1308.
5. Allakhverdiev, M.A., Farzaliev, V.M., Guseinova, T.M. et al., *Zh. Prikl. Khim.,* 1994, vol. 67, no. 11, pp. 1872–1876.
6. Allakhverdiev, M.A., Farzaliev, V.M., and Guseinova, T.M., *Zh. Org. Khim.,* 1995, vol. 31, no. 1, pp. 532–534.
7. Atavin, A.S., Shostakovskii, M.F., Vyalykh, E.T., and Trofimov, B.A., *Zh. Org. Khim.,* 1970, vol. 6, no. 2, pp. 222–227.
8. Bellamy, L.J., *The Infra-red Spectra of Complex Molecules*, London: Methuen, 1958.
9. Malinovskii, M.S., *Okisi olefinov i ikh proizvodnykh* (Olefin Oxides and Their Derivatives), Moscow: Goskhimizdat, 1961.
10. Stewart, J.M., *J. Org. Chem.,* 1963, vol. 29, p.1655.