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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Antioxidative Activity of *N,N*-Diethylthiocarbamate-containing 1,2-Aminopropanethiols

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Abstract—Method for synthesis of *S*-(1,2-epithiopropyl)-*N,N*-diethylthiocarbamate, which is a key compound for production of various aryl-substituted 1,2-aminopropanethiols, was developed. The antioxidative activity of the compounds synthesized was studied.

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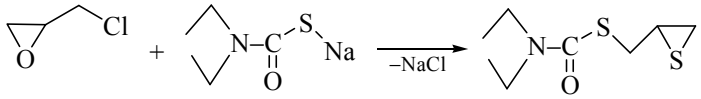
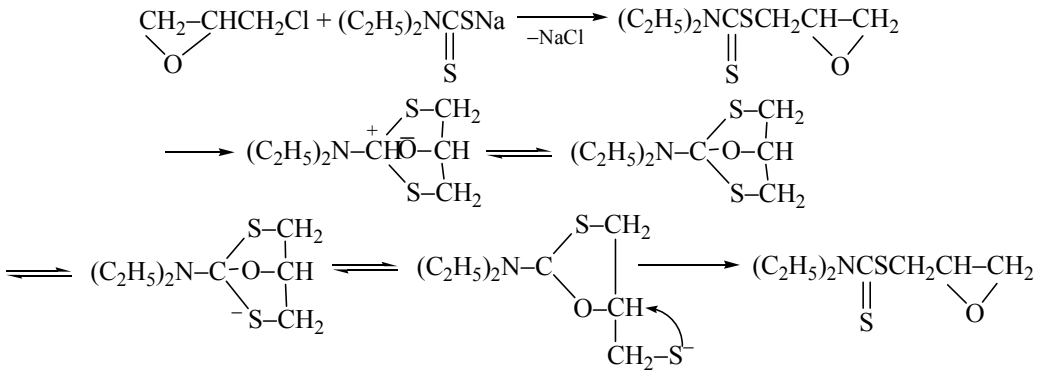
It is known [1, 2] that, similarly to thiocarbamide and thiocyanates of alkali metals [3], salts of thio- and dithiophosphoric acids are convenient thioepoxydizing agents and are successfully and widely used to convert oxiranes to thiiranes. However, as noted in the monograph [4], the applicability limits of the method developed in [1, 2] have not been determined so far. In view of the aforesaid, the reaction of the sodium diethyldithiocarbamate with 1,2-epoxy-3-chloropropane was studied. It was found that the sodium diethyldithiocarbamate can also serve as a thioepoxydizing agent for synthesis of thiiranes [5]. For this purpose, the reaction of 1,2-epoxy-3-chloropropane with anhydrous sodium diethyldithiocarbamate in a solution in benzene under mild conditions (60°C) was studied and thiirane **I** was synthesized in a 50–60% yield:



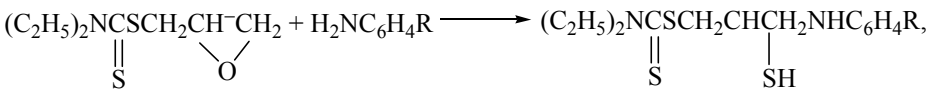
(1)

It should be noted that, in the reaction of 1,2-epoxy-3-chloropropane with undehydrated sodium diethyldithiocarbamate, the yield of thiirane decreases to 30%, because the molecule of sodium diethyldi-thiocarbamate contains three molecules of crystallization water. The mechanism of the reaction in which thiirane **I** is formed somewhat resembles that suggested by C. Calvenor [6]. Presumably, 1,2-epoxypropyl group first undergoes a nucleophilic substitution to give the corresponding oxirane, which is then converted via intramolecular cyclization to a bicyclic oxathiolane. Further, there occurs a Smiles rearrangement and, in the end, closure of the three-membered ring yields *S*-(2,3-epithiopropyl)-*N,N*-diethylthiocarbamate (**I**):



It is known that 1,2-amino thiols are of key practical importance among products of thiirane transformations in reactions with various nucleophilic reagents (amines, alcohols, etc.), which proceed via opening of the thiirane ring. This is due to the following factors: (1) among amino thiols, only the aminoethanethiol moiety contains coenzyme A, which plays an important part in the vital activity of organisms; (2) aminothiols and their derivatives are physiologically active compounds exhibiting radioprotective, hypotensive, muscle relaxant, and ganglion-blocking capacities and find wide use in medicine; and (3) these compounds become increasingly important in technology as effective components in polymerization processes, improve the radiation hardness of polymers, suppress oxidation and corrosion, and possess complexing properties.

In view of the aforesaid, the goal of this study was to synthesize and examine diethylcarbamate-substituted 1,2-aminopropanethiols **II**–**XI** produced by reactions of *S*-(2,3-epithiopropyl)-*N,N*-diethylthiocarbamates with various ring-substituted aromatic amines:



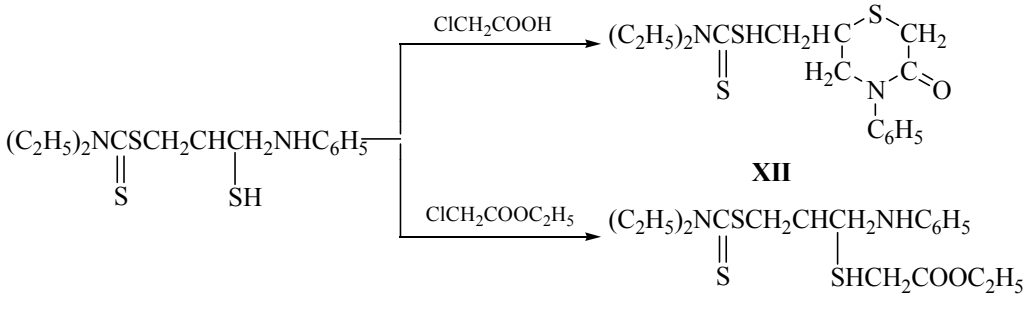
II–XI

R = H (**II**), 2-CH_3 (**III**), 3-CH_3 (**IV**), 4-CH_3 (**V**), 2-CH_3O (**VI**) 3-CH_3O (**VII**), 4-CH_3O (**VIII**), 2-Cl (**IX**), 3-Cl (**X**), 4-Cl (**XI**).

Systematic studies in synthesis of 1,2-aminopropanethiols and analysis of their antioxidative properties have shown [6–8] that the yield of the target product increases if the reaction is performed with an excess of an amine, which serves as a solvent in this case. When the reaction is carried out in air, the amount of by-products increases via oxidation of 1,2-aminopropanethiols and polymerization of thiiranes. All these undesirable factors lead to a pronounced decrease in the yield of the target product.

Therefore, the reaction of the thiirane **I** under study with various substituted aromatic amines was performed in a sealed ampule at a thiirane : amine ratio of 1 : 2.

The reactivity of the 1,2-aminopropanethiols synthesized is due to the presence of two reaction centers, which may be involved in reactions both separately and together, depending on the nature of the reagents used. In this context, it is of interest to study the reaction of 1,2-aminopropanethiol **II** with bifunctional reagents, namely, with α-chloroacetic acid and its ethyl ester:



XII

XIII

It was found that the intramolecular lactonization of the primary product formed in the interaction of 1,2-aminopropanethiol (**II**) with chloroacetic acid yields tetrahydro-1,4-thiazin-3-one (**XII**). A similar reaction with chloroacetic acid ethyl ester proceeds to give an acyclic product, aminothioester **XIII**.

1,2-Aminopropanethiols **II**–**XI** are colorless fluids with a characteristic odor. Upon prolonged storage, the fluids turn yellow. They are well soluble in all organic solvents, but insoluble in water. The physicochemical constants of the compounds are listed in Table 1.

Table 1. Yield, constants, and elemental analysis data for the compounds synthesized

Comp. no.	Yield, %	bp, °C (p, mm Hg)	n_D^{20}	Formula	Calculated/Found, %				R_f
					C	H	N	S	
I	66	108	1.5402	$C_8H_{15}NOS_2$	46.83/46.71	7.32/7.17	6.83/6.65	31.22/31.08	0.49
II	63	119–120 (0.7)	1.5555	$C_{14}H_{22}N_2OS_2$	56.38/56.25	7.38/7.20	9.40/9.22	21.48/21.32	0.57
III	70	137–138 (0.1)	1.6935	$C_{15}H_{24}N_2OS_2$	57.69/57.56	7.69/7.58	8.97/8.19	20.51/20.35	0.68
IV	72	138–139 (0.1)	1.6912	$C_{15}H_{24}N_2OS_2$	57.69/57.56	7.69/7.54	8.97/8.41	20.51/20.34	0.47
V	71	140–141 (0.1)	1.6945	$C_{15}H_{24}N_2OS_2$	57.69/57.52	7.69/7.57	8.97/8.41	20.51/20.37	0.55
VI	55	155–156 (0.1)	1.6959	$C_{15}H_{24}N_2O_2S_2$	54.88/54.72	7.32/7.15	8.54/8.37	19.51/19.32	0.63
VII	69	161–162 (0.1)	1.6917	$C_{15}H_{24}N_2O_2S_2$	54.88/54.71	7.32/7.14	8.54/8.38	19.51/19.35	0.72
VIII	72	160–161 (0.1)	1.6890	$C_{15}H_{24}N_2O_2S_2$	54.88/54.69	7.32/7.18	8.54/8.39	19.51/19.34	0.58
IX	75	162–163 (0.1)	1.6975	$C_{14}H_{21}ClN_2OS_2$	50.53/50.39	6.32/6.17	8.42/8.26	19.25/19.09	0.53
X	81	160–161 (0.1)	1.6956	$C_{14}H_{21}ClN_2OS_2$	50.53/50.38	6.32/6.19	8.42/8.24	19.25/19.09	0.65
XI	76	172–173 (0.1)	1.5967	$C_{14}H_{21}ClN_2OS_2$	50.53/50.37	6.32/6.17	8.42/8.23	19.25/19.08	0.42
XII	60	188–189 (0.1)	1.5415	$C_{16}H_{22}N_2O_2S_2$	56.80/56.67	6.51/6.38	8.28/8.14	18.94/18.74	0.63
XIII	75	175–176 (0.1)	1.5729	$C_{18}H_{28}N_2O_3S_2$	56.25/56.10	7.29/7.18	7.29/7.17	16.67/16.53	0.46

The purity of 1,2-aminopropanethiols **I**–**XIII** was confirmed by thin-layer chromatography and elemental analysis, and their structure, by IR and ^{1}H NMR spectroscopies.

The IR spectrum of thiirane **I** contains a characteristic absorption band at around 675 cm^{-1}, related to the thiirane ring; to stretching vibrations of the C=O bond corresponds the band at 1650 cm^{-1}.

The IR spectra of the 1,2-aminopropanethiols **II**–**XI** show a characteristic absorption band in the range 3330–3350 cm^{-1}, which corresponds to stretching vibrations of the NH group of secondary amines. Stretching vibrations of the group appear as a weak band at 3540–3545 cm^{-1}. All the spectra contain strong absorption bands at 1440–1465, 1500–1510, and 1590–1600 cm^{-1}, characteristic of stretching vibrations of the C=C bond in the benzene ring.

In the ^{1}H NMR spectrum of thiirane **I**, protons of two methyl groups of the $(C_2H_5)_2N$ moiety appear as a triplet at 1.10–1.45 ppm. Protons of the CH_2 group, bound to the sulfur atom in the three-membered ring, appear as two doublets at 2.45 and 2.60 ppm. In a weak field at 3.60–4.75 ppm appear as a multiplet superimposed signals of a proton of the methine group, protons of the CH_2 group bound to the C(O)S group, and two methylene groups at the nitrogen atom.

In the ^{1}H NMR spectra of 1,2-aminopropanethiols **II**–**XI**, three protons of the methyl bound to the aromatic ring [compounds **III**–**V**] appear as a doublet at 2.1–2.2 ppm. Protons of the methoxy group in compounds **VI**–**VIII** appear in a weaker field at 3.6–3.7 ppm. Protons of the SH and NH groups and those of the $CHCH_2$ moiety appear as a multiplet at 2.9–3.7 ppm in all the spectra. Nonequivalent protons of the benzene ring appear as an unresolved group of multiplets at 6.0–7.27 ppm.

To elucidate the mechanism of the antioxidative effect of 1,2-aminopropanethiols **II**, **III**, **VI**, and **IX**, the activity of these compounds was studied in model reactions in which the oxidation of cumene is inhibited by cumyl peroxide radicals. The oxidation of cumene was initiated with azobisisobutyronitrile (AIBN) at 60°C in the presence of these compounds.

As can be seen in Table 2, 1,2-aminopropanethiols **II**, **III**, **VI**, and **IX** containing a substituted phenylamine moiety hinder the initiated oxidation of cumene. It is known that thiols do not exhibit any antioxidative activity by themselves. Only when a molecule combines ArNH and SH groups, a high antioxidative activity is manifested.

The duration τ of the induction period was used to calculate the stoichiometric coefficient equal to the

Table 2. Kinetic parameters of the reaction of 1,2-aminopropanethiols **II**, **III**, **VI**, and **IX** with cumene peroxide radicals (60°C, [AIBN] = 2×10^{-2} M, Wi = 2×10^{-7} M) and cumene hydroperoxide

R	Comp. no.	f	$k_7\times10^{-4}$	k	ν
			$M^{-1}\ s^{-1}$		
C_6H_5	**II**	1.70	1.67	8.12	18900
$C_6H_4CH_3$-2	**III**	2.15	1.85	3.95	21400
$C_6H_4OCH_3$-2	**VI**	2.17	2.00	4.12	23000
C_6H_4Cl-2	**IX**	1.05	0.85	2.15	10500

number of oxidation chains terminated on a molecule of an inhibitor and its conversion products.

It can be seen in Table 2 that the stoichiometric coefficient varies from 1.05 to 2.17 for 1,2-aminopropanethiols. The inhibition rate constant k_7 varies from 0.85×10^{-4} to 2.0×10^{-4} $M^{-1}\ s^{-1}$.

Introduction of electron-donor substituents into the molecule of 1,2-aminopropanethiols **III** and **VI** makes higher their inhibiting activity (f = 2.17, $k_7 = 2.00\times10^{-4}$). However, introduction of electron-acceptor substituents (Cl) impairs the inhibiting activity (f = 1.05, $k_7 = 0.85\times10^{-4}$).

At $f \geq 1$, inhibitors commonly terminate a single oxidation chain. Because the molecule of 1,2-aminopropanethiols contains a sulfhydryl group, f somewhat exceeds unity.

The reaction of 1,2-aminopropanethiols **II**, **III**, **VI**, and **IX** with cumene hydroperoxide (CHP) was carried out in the atmosphere of nitrogen at 110°C. It was found that all the compounds under study actively decompose CHP. It was shown that one molecules of 1,2-aminopropanethiols can decompose up to several tens of thousands of CHP molecules. The values of the parameters characterizing the catalytic decomposition of CHP under the action of compounds **I**, **III**, **VI**, and **IX** under study are listed in Table 2. It can be seen that the catalytic factor ν is the largest for 1,2-aminopropanethiol **VI**, which contains an *ortho*-anisidine moiety in its molecule (k = 4.12, ν = 2.3 104). In this case, electron-donor substituents also make larger the catalytic factor; by contrast, electronegative substituents (Cl) make it smaller.

The value of the catalytic factor ν characterizing the number of CHP molecules decomposing a single inhibitor molecule was calculated using the formula

$$\nu = \frac{[ROOH]_0 - [ROOH]_\infty}{[In]_0},$$

where $[ROOH]_0$ and $[ROOH]_\infty$ are, respectively, the initial and final concentrations of CHP; $[In]_0$, initial concentration of an inhibitor; and k, rate constant of the catalytic factor ν.

Thus, the compounds under study are oxidation inhibitors of combined action: they catalytically decompose hydroperoxides to give molecular products and thereby terminate oxidation chains in a reaction with peroxide radicals.

EXPERIMENTAL

The IR spectra were measured with a Specord75-IR spectrophotometer, and ^{1}H NMR spectra, with a Bruker-300 MHz instrument.

The reaction was monitored by means of thin-layer chromatography on Silufol-254 plates. Hexane and ethanol taken in a 1 : 5 ratio served as the eluent. Only a single spot was present on a chromatogram developed with an iodine vapor.

***S*-(2,3-Epithiopropyl)-*N*,*N*-diethylthiocarbamate (I).** A three-necked flask equipped with a mechanical stirrer, reflux, thermometer, and dropping funnel was charged with 17.1 g (0.11 mol) of dry sodium diethyldithiocarbamate in 50 ml of benzene and 9.3 g (0.1 mol) of 1,2-epoxy-3-chloropropane was added dropwise under vigorous stirring, with the temperature of the reaction mixture increasing to 50°C. Then the temperature of the reaction mixture was raised to 60°C and it was agitated at this temperature for 3 h. The resulting precipitate was filtered off and benzene was evaporated. The reaction product was subjected to vacuum distillation to give 12 g (60%) of compound **I**, bp 105°C (0.7 mm Hg), n_D^{20} 1.5402, n_4^{20} 1.1271. Found, %: C 46.71, H 7.17, N 6.65, S 31.08. $C_8H_{15}NOS_2$. Calculated, %: C 46.83, H 7.32, N 6.83, S 31.22.

***S*-(1-Diethylcarbamato)-3-*N*-phenylamino-2-propanethiol (II).** A 9.32-g portion of aniline and 10.3 g (0.05 mol) of *S*-(2,3-epithiopropyl)-*N*,*N*-diethylthiocarbamate (**I**) were heated in a sealed ampule on a boiling water bath for 6 h. Then the reaction mixture was cooled and the ampule was opened. First the excess amount of aniline and then the target reaction product were subjected to vacuum distillation to give 9.5 g of compound **II**, bp 119–120°C (0.1 mm Hg), n_D^{20} 1.5555, R_f 0.72. Found, % : C 56.25, H 7.20, N

9.24, S 21.32. $C_{14}H_{22}N_2OS_2$. Calculated, % : C 56.38, H 7.38, N 9.40, S 21.48.

Diethylcarbamate-substituted 1,2-aminopropanethiols **III**–**XI**, whose physicochemical constants are listed in Table 1, were synthesized similarly.

6-Diethylaminocarbamatothiomethyl-4-*N*-phenyltetrahydro-1,4-thiazin-3-one (XII). A three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel was charged with 15 g (0.05 mol) of *S*-(1-diethylcarbamato)-3-*N*-phenylamino-2-propanethiol (**II**), 2 g (0.05 mol) of caustic soda, and 10 ml of water. Then 0.05 mol of a sodium salts of chloroacetic acid (4.73 g $ClCH_2COOH$ + 2 g NaOH + 10 g H_2O) was added dropwise under vigorous agitation. After that the reaction mixture was acidified with hydrochloric acid and extracted with ether. The extract was dried over calcined sodium sulfate. The solvent was evaporated and the residue was subjected to vacuum distillation to give 10.3 g (60%) of compound **XII**, bp 188–189°C (0.1 mm Hg), n_D^{20} 1.5415, R_f 0.63. Found, % : C 56.67, H 6.38, N 8.14, S 18.74. $C_{16}H_{22}N_2O_2S_2$. Calculated, % : C 56.80, H 6.51, N 8.28, S 18.94.

1-(*N,N*-Diethylthiocarbamato-2-ethoxycarbonylmethylthio-3-*N*-phenylamino propane (XIII). A three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel was charged with 15 g (0.05 mol) of *S*-(1-*N,N*-diethylcarbamato)-3-*N*-phenylamino-2-propanethiol (**II**) and 2 g (0.05 mol) of NaOH in 15 ml of water, and the mixture was vigorously agitated. A 6.3-g portion (0.05 mol) of monochloroacetic acid ethyl ester was added dropwise and the mixture was heated at 30–40°C at 1 h. Then the organic layer was extracted with ether, and the extract was thrice washed with water and dried over calcined sodium sulfate. The solvent was evaporated and the residue was subjected to vacuum distillation to give 17 g (75%) of compound **XIII**, bp 175–176°C (0.1 mm Hg), n_D^{20} 1.5729, R_f 0.46. Found, % : C 56.10, H 7.18, N 7.17, S 16.53. $C_{18}H_{28}N_2O_3S_2$. Calculated C 56.25, H 7.29, N 7.29, S 16.67.

CONCLUSIONS

(1) Diethylcarbamate-substituted 1,2-aminopropanethiols with various ring-substituted aromatic amines were synthesized from *S*-(1,2-epithiopropyl)-*N,N*-diethylthiocarbamate and their properties were studied.

(2) Fundamental aspects of the influence exerted by substituents in the molecule of 1,2-aminopropanethiols on their reactivity as inhibitors in elementary reactions of inhibition of cumene oxidation were revealed.

REFERENCES

1. Nuretdinova, O.N. and Arbuzov, B.A., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1971, no. 2, pp. 353–358.
2. Nuretdinova, O.N. and Arbuzov, B.A., *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1970, no. 1, p. 145.
3. Fokin, A.V., Allakhverdiev, M.A., and Kolomiets, A.F., *Usp. Khim*., 1990, vol. 59, no. 5, pp. 705–737.
4. Fokin, A.V. and Kolomiets, A.F., *Khimiya tiiranov* (Chemistry of Thiiranes), Moscow: Nauka, 1978.
5. Allakhverdiev, M.A., Farzaliev, V.M., and Khalilova, A.Z., *Zh. Org. Khim*., 1984, vol. 20, no. 6, pp. 1350–1351.
6. Magerramov, A.M., Allakhverdiev, M.A., Guseinova, A.T., and Kuliev, S.A., *Aminotioly i ikh proizvodnye* (Amino Thiols and Their Derivatives), Baku: Baku Univ., 2007.
7. Magerramov, A.M., Rzaeva, I.A., Farzaliev, V.M., et al., Abstracts of Papers, *XVIII Mendeleevskii s''ezda po obshchei i prikladnoi khimii* (XVIII Mendeleev Congr. on General and Applied Chemistry, 2007, p. 321.
8. Magerramov, A.M., Huseynova, A.T., Rzayeva, I.A., et al., Abstracts of Papers, *XX Ulusal Kimya kongresi*, Türkiyə, Kayseri, 2006. Ok-141, p. 162.