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Synthesis and Antimicrobial Activity of Aminomethoxy-Substituted 1-(Ethylthio)heptanes

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Abstract—The Mannich condensation of 1-(ethylthio)heptane-2-ol, formaldehyde and secondary amines taken in equimolar amounts gives rise to new aminomethoxy-substituted 1-(ethylthio)heptanes in a yield of 70–77%. The structure of the synthesized compounds was proved by the elemental analysis, IR and ^{1}H NMR spectroscopy, and mass spectrometry. The compounds were tested as antimicrobial additives to lubricating oils. They were found to suppress effectively the activity of microorganisms.

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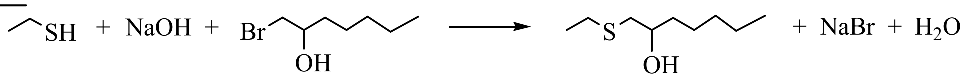
Organic compounds containing as heteroatoms both nitrogen and sulfur atoms have a high and diverse biological activity. Among such compounds were found effective drugs possessing the antiviral, antitumor, neurotropic and antibacterial action [1–3]. Also some compounds of this type are used as the antioxidant, anticorrosion and antimicrobial additives to fuels and oils [4]. An actual task is to search for new *N*- and *S*-containing compounds and to improve general methods of their synthesis.

In continuation of our research in the field of the nitrogen- and sulfur-containing organic compounds [5–8], in this work we synthesized and studied the new aminomethoxy-substituted 1-(ethylthio)heptanes.

For this purpose we at first obtained the previously unknown 1-(ethylthio)heptan-2-ol **III** via the reaction of 1-ethanethiol **I** with 1-bromoheptan-2-ol **II**.

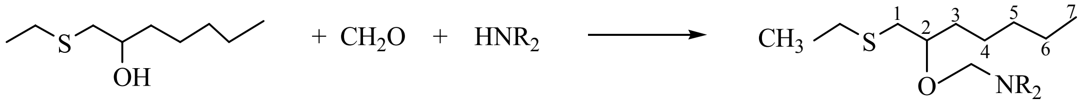
The reaction was performed at 45–50°C in an alkaline medium (40% NaOH aqueous solution) for 3–4 h using an equimolar ratio of the reactants to obtain the sulfur-containing alcohol **III** in a 68% yield.



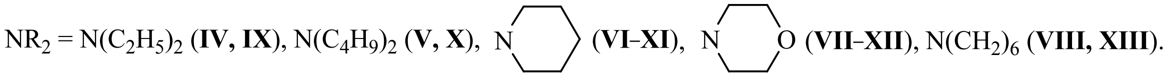
I **II** **III**

Further the three-component Mannich condensation of 1-ethylthioheptan-2-ol **III** with formaldehyde in the presence of secondary amines **IV–VIII** results in new 1-(ethylthio)-2-aminomethoxyheptanes **IX–XIII**. The reaction was carried out at 45–55°C for 4–5 h using an equimolar ratio of the starting substances to afford the target products in 70–77% yield.

The synthesized 1-ethylthioheptan-2-ol **III** and its aminometoxy derivatives **IX–XIII** are transparent



III **IV–VIII** **IX–XIII**



$NR_2 = N(C_2H_5)_2$ (**IV, IX**), $N(C_4H_9)_2$ (**V, X**), (**VI–XI**), (**VII–XII**), $N(CH_2)_6$ (**VIII, XIII**).

liquids having a characteristic odor. They are insoluble in water, but well soluble in organic solvents (ethanol, acetone, benzene, CCl_4, $CHCl_3$, etc.).

The structure and composition of the synthesized compounds **III**, **IX**–**XIII** were confirmed by the elemental analysis data, IR and ^{1}H NMR spectroscopy, and mass spectrometry. The purity of initial and synthesized compounds and the composition of the reaction mixtures were monitored by GLC.

The IR spectrum of 1-(ethylthio)heptan-2-ol **III** contains a broad absorption band at 3550 cm^{-1}, which is characteristic of the hydroxy group [9]. In the IR spectra of aminomethoxy derivatives **IX–XIII** this band is absent. For all of synthesized compounds **III**, **IX–XIII** the absorption band of the C–S bond vibrations was detected at 735 cm^{-1}. The absorption bands in the range of 1350–1250 cm^{-1} are characteristic of the stretching vibrations of the C–N bond. In addition, the absorption bands observed at 2910–2885 and 2850–2830 cm^{-1} belong to the C–H bond vibrations in the CH_3 and CH_2 moieties, respectively. The stretching vibrations of the S–O bond give rise to a strong band at 1100–1050 cm^{-1}.

The ^{1}H NMR spectra of the synthesized compounds **III**, **IX**–**XIII** confirm the assumed structure. In the ^{1}H NMR spectrum of sulfur-containing secondary alcohol **III** the OCH-proton at the C^2 carbon atom is observed as a multiplet at 3.7 ppm. The doublets at 2.75 ppm correspond to the methylene protons of C^1SCH_2CH group. A singlet at 2.7 ppm belongs to the hydroxyl proton. The protons of the CH_3CH_2S fragment appear as a triplet at 2.50 ppm. A multiplet at 1.5–1.7 ppm corresponds to the methylene protons of C^3H_2–C^7H_2 groups. The methyl protons of CH_3CH_2S and C^7H_3 fragments are observed as a triplet at 1.2 ppm and a singlet at 0.9 ppm, respectively.

The proton spectra of **IX–XIII** are similar to that of **III**. The singlet of a hydroxy group is absent. The proton signals of $OCH_2N<$ fragment in the spectra of **IX**–**XIII** are observed in the range of 4.2–4.3 ppm as a doublet of doublets. A multiplet at 3.25–3.45 ppm corresponds to the OCH protons. The methyl protons of CH_3CH_2 fragment of compound **IX** appear as a triplet at 1.2 ppm. In the spectrum of **X** there are a triplet at 0.9 ppm of the methyl groups of the $CH_3(CH_2)_3N(CH_2)_3CH_3$ moiety. The proton signals of the CH_2NCH_2 methylene groups in the spectra of **IX**–**XIII** are observed in the range of 2.45–2.6 ppm as a multiplet. The multiplet signals at 2.7 ppm belong to the methylene protons of morpholine moiety.

The EI mass spectra of compounds **III**, **IX**–**XIII** contain the corresponding peaks of the molecular ions and their fragmentation products. In the mass spectrum of the secondary alcohol **III** there is a characteristic set of the signals, *m/z* (%): 177 (49) $[M + H]^+$, 176 (27) $[M^+]$, 159 (100) $[M^+ - OH]$, 145 (11) $[M^+ - OH - CH_2]$, 107(6), 104(38), 82(15). In the mass spectra of compounds **IX**–**XIII** are detected the signals of the corresponding molecular ions, *m/z*: 261 $[M^+]$ (**IX**), 317 $[M^+]$ (**X**), 274 $[M + H^+]$ (**XI**), 275 $[M^+]$ (**XII**), 287 $[M^+]$ (**XIII**).

The obtained compounds **IX**–**XIII** were tested as the antimicrobial additives in the Institute of Chemistry of Additives of the National Academy of Sciences of Azerbaijan. The oil of M-11 (GOST-9-052-75) grade was used as a test sample. The fungal and bacterial cultures were used as the test cultures. The results of this study are given in the Table.

As can be seen, the tested compounds **IX**–**XIII** have bactericidal and fungicidal properties and inhibit effectively the growth of microorganisms in the M-11 oil at a concentration of 0.5–0.25%. In this case, compounds **IX**–**XIII** have a relatively higher efficiency compared with other compounds and industrial additive 8-oxyquinoline taken as a reference. The other compounds show results similar to the reference.

Compounds **IX**–**XIII** were also tested for the antimicrobial activity in Azerbaijan Medical University (Department of Medical Microbiology and Immunology). The study of antimicrobial properties of these compounds was carried out in comparison with the substances used in practice: ethanol, carbolic acid (phenol), chloramine, rivanol, nitrofungin. The antimicrobial activity was studied by the serial dilutions method. The Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*), Gram-positive (*Staphylococcus aureus*), the spore-bearing (anthracoid) bacteria and yeast-like fungi (*Candida*) were used as the test cultures. The results obtained show that the test compounds **IX**–**XIII** possess a more pronounced antimicrobial activity than those used in practice, alcohol, phenol, rivanol, nitrofungin and furacillin. These compounds can be recommended as the antimicrobial agents.

Thus, the new aminomethoxy-substituted 1-(ethylthio)heptanes were synthesized and characterized. They are effective biologically active compounds.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in the range of 4000–400 cm^{-1}. The ^{1}H NMR spectra were recorded on a Bruker WP-400 spectrometer (400 MHz) using $CDCl_3$ as a solvent and TMS as a reference. The mass spectra were obtained on a G-7070E mass spectrometer (70 eV). The GLC-analysis was performed on a LKhM-8MD chromatograph using a steel column (3000×3 mm) filled with 5% PEGS (polyethyleneglycolsuccinate) on Dinochrome-P, helium as a carrier gas (40 cm^3/min) and katharometer as a detector (column and evaporator temperatures were 150 and 220°C, respectively).

The effect of compounds **IX**–**XIII** on the antimicrobial properties of the M-11 oil was studied using their 0.5–1% solutions in this oil. The antimicrobial properties were determined in a thermal chamber. The experiments were carried out a temperature of 28–30°C for 2–3 days. Fungal and bacterial cultures were used as test-microorganisms.

1-(Ethylthio)heptane-2-ol (III). To a mixture of 15.5 g of 1-ethanethiol **I** and 25 g of 40% aqueous solution of NaOH (prepared from 10 g of NaOH in 15 ml of water) was added dropwise 48.75 g of 1-bromoheptan-2-ol **II** at 45–50°C. The reaction mixture was stirred for 3–4 h at the same temperature. After cooling, to the mixture was added benzene, the organic layer was separated and washed subsequently with 5% NaOH solution and water until the neutral reaction, and dried over $MgSO_4$. After the solvent removal, the residue was distilled in a vacuum. Yield 30 g (68%), bp 93–94 (2 mm Hg), n_D^{20} 1.4728, d_4^{20} 0.9342, MR_D 52.92 (calculated 53.32). IR spectrum, ν, cm^{-1}: 3550 (OH), 2910 (CH_3), 2840 (CH_2), 735 (C–S). ^{1}H NMR spectrum, δ_H, ppm: 0.9 t (3H, CH_3), 1.2 t (3H, $\underline{CH_3}CH_2S$), 1.5–1.7 m (8H, $4CH_2$), 2.5 m (2H, SCH_2), 2.7 d. d (2H, SCH_2CH), 3.7 m (OCH). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 177 (49) $[M + H]^+$, 176 (27) $[M^+]$, 159 (100) $[M – OH]$, 145 (11) $[M – OHCH_2]$, 107 (6), 104 (38), 82 (15), $[M^+]$ 176.3. Found, %: C 61.18; H 11.34; S 18.08. $C_9H_{20}OS$. Calculated, %: C 61.31; H 11.43; S 18.19.

2-Aminomethoxy derivatives of 1-(ethylthio)heptane (IX–XIII) *(general procedure).* To a mixture of 0.03 mol of 1-(ethylthio)heptan-2-ol **III** and 0.03 mol of formaldehyde in 30 ml of benzene was added dropwise 0.03 mol of secondary amines **IV**–**VIII** at 20–22°C with stirring. The stirring was continued for 4–5 h at 45–55°C. Then the solvent was removed, and the residue was distilled in a vacuum.

Test results of antimicrobial properties of aminomethoxy-substituted 1-(ethylthio)heptanes **IX**–**XIII** in the M-11 oil

Comp. no.	Concentration of additives, %	Inhibition zone, mm		
		Aspergillus niger	*Candida tropicalis*	*Pseudomonas aeruginosi*
IX	1.0	41	37	33
	0.50	19	18	17
	0.25	15	14	14
X	1.0	40	35	34
	0.50	20	16	18
	0.25	16	14	14
XI	1.0	42	36	35
	0.50	21	17	16
	0.25	16	13	14
XII	1.0	45	42	37
	0.50	22	21	18
	0.25	18	19	14
XIII	1.0	41	36	35
	0.50	21	17	16
	0.25	17	15	14
8-Oxy-quinoline	1.0	25	26	28
	0.50	14	13	14
	0.25	9	9	10
Without any additives[a]	0	+	+	+

[a] + abundant microorganisms growth around the hole in the Petri dish.

1-(Ethylthio)-2-(*N*,*N*-diethylaminomethoxy)heptane (IX) was prepared from 5.3 g of 1-(ethylthio) heptan-2-ol **III**, 0.9 g of formaldehyde, and 2.2 g of diethylamine **IV**. Yield 5.5 g (70%), bp 115–117°C (1 mm Hg), n_D^{20} 1.4630, d_4^{20} 0.8982, MR_D 80.18 (calculated 80.49). IR spectrum, ν, cm^{-1}: 2910 (CH_3), 2850 (CH_2), 1240 (CN), 735 (CS). ^{1}H NMR spectrum, δ_H, ppm: 0.9 t (3H, CH_3), 1.2 t (9H, $\underline{CH_3}CH_2S$, $\underline{CH_3}CH_2\cdot NCH_2\underline{CH_3}$), 2.45–2.7 m (8H, CH_2NCH_2, CH_2SCH_2), 3.4 m (OCH), 4.2 d. d (OCH_2N). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 261 (8) [M^+], 200 (5) [$M^+ - C_2H_5S$], 199 (13) [$C_{10}H_{21}OS$], 135 (13) [$M^+ - C_7H_{12}NO$], 86 (100) [$M^+ - C_9H_{19}OS$], 82 (33). Found, %: C 64.14; H 11.88; N 5; S 12.18. $C_{14}H_{31}NOS$. Calculated, %: C 64.31; H 11.95; N 5.36; S 12.26.

1-(Ethylthio)-2-(*N*,*N*-dibutylaminomethoxy)heptane (X) was prepared from 5.3 g of 1-(ethylthio) heptan-2-ol **III**, 0.9 g of formaldehyde, and 3.87 g dibutylamine **V**. Yield 7.3 g (76.6%), bp 158–160°C (1 mm Hg), n_D^{20} 1.4602, d_4^{20} 0.8804, MR_D 98.84 (calculated 99.06). IR spectrum, ν, cm^{-1}: 2900 (CH_3), 2840 (CH_2), 1220 (C–N), 725 (C–S). ^{1}H NMR spectrum, δ_H, ppm: 0.9 t (9H, $3CH_3$), 1.2 t (3H, $\underline{CH_3}CH_2S$), 1.5–1.7 m (16H, CH_2), 2.4–2.7 m (8H, NCH_2, SCH_2), 3.7 m (OCH), 4.3 d.d (2H, OCH_2N). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 317 (9) [M^+], 256 (13) [$M^+ - C_2H_5S$], 176 (13) [$C_9H_{20}OS$], 159 (15) [$M^+ - C_9H_{20}NO$], 140 (100) [$M^+ - C_9H_{21}OS$], 82 (33). Found, %: C 67.82; H 12.31; N 4.35; S 10.89. $C_{18}H_{39}NOS$. Calculated, %: C 68.08; H 12.39; N 4.41; S 10.96.

1-(Ethylthio)-2-piperidinomethoxyheptane (XI) was prepared from 5.3 g of 1-(ethylthio)heptan-2-ol **III**, 0.9 g of formaldehyde, and 2.55 g of piperidine **VI**. Yield 5.9 g (72%), bp 148–150°C (2 mm Hg), n_D^{20} 1.4782, d_4^{20} 0.9336, MR_D 82.94 (calculated 83.15). IR spectrum, ν, cm^{-1}: 2890 (CH_3), 2840 (CH_2), 1220 (C–N), 730 (C–S). ^{1}H NMR spectrum, δ_H, ppm: 0.9 t (3H, CH_3), 1.2 t (3H, $\underline{CH_3}CH_2S$), 1.5–1.7 m (14H, $7CH_2$), 2.45–2.7 m (8H, NCH_2, SCH_2), 3.45 m (OCH), 4.3 d.d (2H, OCH_2N). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 274 (6) [$M + H^+$], 273 (10) [M^+], 212 (8) [$M^+ - C_2H_5S$], 191 (7) [$M^+ - C_5H_9N$], 97 (100) [$M^+ - C_9H_{20}SO$], 75 (46). Found, %: C 65.62; H 11.34; N 5.06; S 11.63. $C_{15}H_{31}NOS$. Calculated, %: C 65.88; H 11.42; N 4.4; S 11.72.

1-(Ethylthio)-2-morpholinomethoxyheptane (XII) was prepared from 5.3 g of 1-(ethylthio)heptane-2-ol **III**, 0.9 g of paraformaldehyde, and 2.6 g of morpholine **VII**. Yield 6 g (72.5%), bp 139–141°C (1 mm Hg), n_D^{20} 1.4772, d_4^{20} 0.9758, MR_D 79.79 (calculated 80.28). IR spectrum, ν, cm^{-1}: 2885 (CH_3), 2830 (CH_2), 1250 (C–N), 1100 (C–O), 735 (C–S). ^{1}H NMR spectrum, δ_H, ppm: 0.9 t (3H, C^7H_3), 1.2 t (3H, $\underline{CH_3}CH_2S$), 1.6 m (8H, $4CH_2$), 1.56–1.6 m (8H, CH_2S, CH_2N), 2.45–2.6 m (8H, CH_2N, CH_2S), 2.7 m (4H, CH_2O_{morph}), 3.45 m (OCH), 4.30 d.d (2H, OCH_2N). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 275 (4) [M^+], 214 (18) [$M^+ - C_2H_5S$], 205 (2) [$M^+ - C_4H_8N$], 176 (15) [$M^+ - C_5H_9ON$], 156 (100) [$M^+ - C_7H_7NO$], 100 (25), 75 (C_3H_7S). Found, %: C 60.86; H 10.54; N 5.04; S 11.56. $C_{14}H_{29}NO_2S$. Calculated, %: C 61.04; H 10.61; N 5.08; S 11.64.

1-(Ethylthio)-2-(hexamethyleneiminomethoxy)heptane (XIII) was prepared from 5.3 g of 1-(ethylthio)-heptan-2-ol **III**, 0.9 g of formaldehyde, and 2.9 g of hexamethyleneimine **VIII**. Yield 6.4 g (74%), bp 156–158°C (1 mm Hg), n_D^{20} 1.4826, d_4^{20} 0.9368, MR_D 87.58 (calculated 87.73). IR spectrum, ν, cm^{-1}: 2890 (CH_3), 2880 (CH_2), 1200 (C–N), 1150 (C–O), 730 (C–S). ^{1}H NMR spectrum, δ_H, ppm: 0.95 t (3H, C^7H_3), 1.2 t (3H, $\underline{CH_3}CH_2S$), 1.35–1.65 m (8H, NCH_2, SCH_2), 3.45 m (OCH), 4.30 d.d (2H, OCH_2N). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 287 (5) [M^+], 196 (5) [$M^+ - C_6H_5N$], 179 (8) [$M^+ - C_6H_6NO$], 138 (27) [$C_8H_{10}S$], 122 (6) [C_7H_6S], 91 (100) [C_6H_5N]. Found, %: C 66.82; H 11.49; N 4.82; S 11.06. $C_{16}H_{33}NOS$. Calculated, %: C 66.84; H 11.57; N 4.87; S 11.15.

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