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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Aminomethoxy Derivatives of Benzylsulfanylheptane

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Abstract—Synthesis and structure of new aminomethoxy derivatives of 1-benzylsulfanylheptane by the Mannich condensation of 1-benzylsulfanylheptan-2-ol, formaldehyde, and secondary amines were studied.

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Organic compounds containing various functional groups and heteroatoms, such as sulfur and nitrogen (or both together), are widely used as effective biologically active substances and pharmaceutical preparations, as well as additives improving the quality of oils and fuels [1–3]. A directed synthesis of these compounds used in various chemical industries is a rather topical task not only for development of synthetic organic chemistry, but also for applied research. In this context, syntheses of new compounds of this kind from accessible raw materials by improved methods continue to attract researchers' attention [4–6]. The Mannich reaction is an important and promising way to obtain sulfur- and nitrogen-containing compounds [7–9].

In continuation of previous studies concerned with nitrogen-containing alkyl(aryl) sulfanyl alkanes [10–14], we report here results obtained in synthesis of aminomethoxy derivatives of 1-benzyl sulfanyl heptane and analysis of their properties. For this purpose, we first synthesized the previously unknown sulfur-containing secondary alcohol, 1-benzyl sulfanyl heptan-2-ol (**III**) by reacting benzylthiol (**I**) with 1-bromoheptan-2-ol (**II**) by Scheme 1.

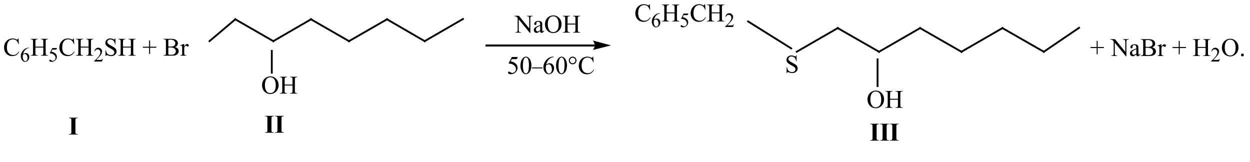
The secondary thioalcohol (**III**) was synthesized by reacting equimolar amounts of the starting components **I** and **II** in an alkaline medium (40% aqueous solution of NaOH) at a temperature of 50–60°C in the course of 3–4 h. The yield of the target product was 72%.

Further, we used the Mannich condensation of 1-benzyl sulfanyl heptan-2-ol (**III**) with formaldehyde in the presence of secondary amines (**IV**)–(**VIII**) to obtain amino derivatives of 1-benzyl sulfanyl heptane, (**IX**)–(**XIII**), by Scheme 2.

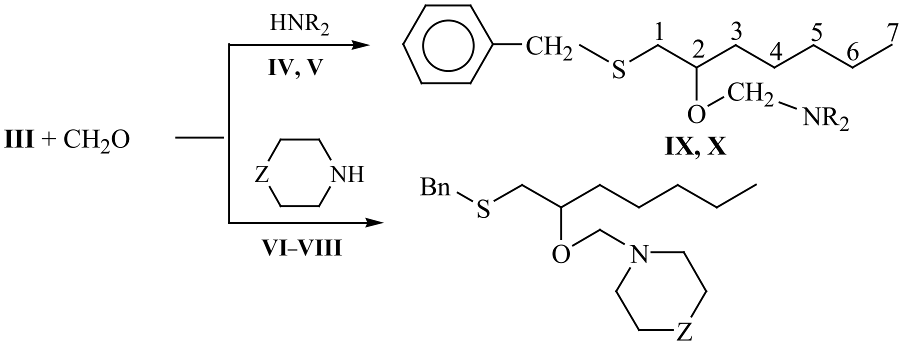
Aminomethoxy derivatives of 1-benzyl sulfanyl heptane, (**IX**)–(**XIII**), were synthesized at 50–60°C in the course of 3–4 h at the equimolar ratio between the starting components. In this case, the yield of the reaction products was 72–78%.

The thus synthesized 1-benzyl sulfanyl heptan-2-ol (**III**) and its amino derivatives (**IX**)–(**XIII**) are transparent liquids with characteristic odors. They are insoluble in water, but can be well dissolved in ethanol,

Scheme 1.



Scheme 2.



XI–XIII

R = C_2H_5 (**IV**), (**IX**); C_4H_9 (**V**), (**X**); Z = CH_2 (**VI**), (**XI**); O (**VII**), (**XII**); $(CH_2)_2$ (**VIII**), (**XIII**).

acetone, benzene, and chloroform. The physicochemical characteristics of **III**, **IX–XIII** are listed in Tables 1 and 2, together with the elemental analysis data for these compounds.

The purity of the starting and synthesized compounds and the composition of the reaction mixtures was monitored by GLC. The structure of the target products was determined by elemental analysis, IR and ^{1}H NMR spectroscopies, and mass spectrometry. The IR spectrum of compound **III** shows an absorption band at 3500 cm^{-1}, which is characteristic of the hydroxy group and is not observed in the corresponding spectra of compounds **IX–XIII**. For all the compounds, we observed absorption bands at 795–730 cm^{-1} (characteristic of the C–S bond), 1220–1200 cm^{-1} (C–N bond), and 2940–2930 and 2880–2850 cm^{-1} (stretching vibrations of the C–H bond and CH_3 and CH_2 groups, respectively). The vibrations νCH of the benzene ring appear at 3030–3080 cm^{-1} as a medium-intensity band. The spectra of compounds **IX–XIII** contain strong absorption bands associated with out-of-plane deformation vibrations of the C–H band at 750–730 cm^{-1}.

The ^{1}H NMR spectra of the compounds synthesized are typical and also confirm the above structure. In the ^{1}H NMR spectrum of secondary alcohol **III**, the proton of the hydroxy group appears as a multiplet at 2.7 ppm. In the spectra of compounds **III** and **IX–XIII**, protons of methyl groups (CH_3) appear as a multiplet at 0.90–1.0 ppm. Protons of methylene groups (CH_2) give signals at 1.5–1.7 ppm in the form of a multiplet. To protons of SCH_2 (C^1) groups belong signals observed at 2.5 ppm as a triplet. Protons of the OCH moiety (C^2) appear at 3.4–3.7 ppm as a triplet, and protons of the OCH_2N moiety, at 4.2–4.3 ppm as a doublet of doublets. The signals observed at 3.9 ppm as a singlet are characteristic of protons of CH_2 groups in the benzyl moiety ($PhCH_2$). Protons of the phenyl moiety give downfield signals: protons in the *para*-position at 7.30 ppm, two protons in the *meta*-position at 7.34 ppm, and two protons in the *ortho*-position at 7.36 ppm as a multiplet.

The mass spectra (electron impact ionization) of compounds **III** and **IX–XIII** show signals of the

Table 1. Physicochemical characteristics of compounds **III** and **IX**–**XIII**

Compound	bp, °C (1–3 mm Hg)	n_D^{20}	d_4^{20}	Yield, %
1-Benzyl sulfanyl heptan-2-ol (**III**)	160–162	1.5360	1.0205	72
1-Benzyl sulfanyl-2-(*N,N*-diethylaminomethoxy)heptane (**IX**)	175–177	1.5210	0.9711	75
1-Benzyl sulfanyl-2-(*N,N*-dibutylaminomethoxy)heptane (**X**)	188–190	1.4984	0.9392	78
1-Benzyl sulfanyl-2-piperidinomethoxyheptane (**XI**)	182–184	1.5250	1.0014	73
1-Benzyl sulfanyl-2-morpholinomethoxyheptane (**XII**)	188–190	1.5246	1.0322	74
2-Benzyl sulfanyl-2-(*N*-hexamethyleniminomethoxy)heptane (**XIII**)	190–192	1.5246	0.9965	75

Table 2. Elemental analysis and molecular refraction data for compounds **III** and **IX**–**XIII**

Compound	Found Calculated MR_D	Found, % Calculated, % C	H	N	S	Formula	Found Calculated M
III	72.84 72.97	70.38 70.56	9.26 9.31	–	13.38 13.45	$C_{14}H_{22}OS$	239 238.39
IX	99.97 100.21	70.10 70.28	10.22 10.28	4.30 4.33	9.85 9.91	$C_{19}H_{33}NOS$	324 323.54
X	118.57 118.75	72.54 72.76	10.82 10.88	3.66 3.69	8.39 8.44	$C_{23}H_{41}NOS$	380 379.61
XI	102.69 102.81	71.26 71.59	9.85 9.91	4.14 4.17	9.49 9.55	$C_{20}H_{33}NOS$	336 335.55
XII	100.15 100.03	67.38 67.61	9.20 9.26	4.12 4.15	9.44 9.50	$C_{19}H_{31}NO_2S$	338 337.53
XIII	107.44 107.46	71.82 72.15	10.03 10.09	3.98 4.01	9.12 9.17	$C_{21}H_{35}NOS$	350 349.58

corresponding molecular ions and products of their fragmentation. The mass spectrum of the starting sulfur-containing alcohol (**III**) is characterized by the following set of fragments: 238 (27%) $[M^+]$, 221 (100%) M–OH, 207 (9%) / M–OH–CH_2, 138 (72%) /$C_8H_{10}S$, and 122 (6%) / C_7H_6S.

The mass spectra of compounds **IX–XIII** show signals of the corresponding molecular ions and products of their fragmentation.

Aminomethoxy derivatives of benzyl sulfanyl heptane, **IX**–**XIII**, were tested as antimicrobial additives. The tests were made in an M-11 oil [GOST (State Standard) 9-052–75].

As test cultures served fungal (*Aspergillus niger, Candida tropicalis*) and bacterial (*Pseudomonas aeruginosa*) cultures. The results obtained are presented in Table 3.

The test results demonstrated that, under certain

Table 3. Results of tests of compounds **IX–XIII** as antimicrobial additives to lubricant oils for the example of M-11 oil

Compound	Concentration, %	Diameter of the microorganism growth suppression zone, mm fungi *Aspergillus niger*	 *Candida tropicalis*	 *Pseudomonas aeruginosa* bacteria
Additive to M-11 oil:				
IX	0.5	22	20	18
	1	42	38	34
X	0.5	22	18	20
	1	42	31	38
XI	0.5	16	18	18
	1	30	34	34
XII	0.5	16	18	18
	1	30	34	34
XIII	0.5	18	18	20
	1	34	34	36
8-Oxyquinoline (reference)	0.5	14	12	14
	1	34	26	32
M-11 oil (without additives)[a]	+	+	+	+

[a] (+) stands for heavy growth of microorganism around a lunula in a Petri dish.

conditions (0.5–1.0 wt %), the compounds suppress growth of microorganisms. It can be seen in Table 3 that compounds **IX** and **XIII** show the highest efficiency. Their antimicrobial activity exceeds that of the industrial additive 8-oxyquinoline, taken as a reference. The rest of the compounds show results close to that of the reference. It was found that, at a content of 0.5–1.0 wt % of these compounds, there are no negative changes in the service parameters of oils, and their antiseptic effect is long preserved at higher humidities and temperatures. Compounds **IX–XIII** exert no adverse influence on the physicochemical properties of oils. These compounds were also tested as antimicrobial preparations in medicine.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrophotometer in the range 4000–400 cm^{-1}, and the ^{1}H NMR spectra, with a Bruker WP-400 instrument (400 MHz, $CDCl_3$ as solvent), with the chemical shifts given relative to TMS. The mass spectra were obtained on a G-7070E mass spectrometer at an ionizing voltage of 70 eV.

The reaction mixtures were subjected to an chromatographic analysis and the purity of the compounds synthesized with an LKhM-80 MD chromatograph [300 × 3 mm steel column; 5% polyethylene glycol succinate on Dynachrom P phase; carrier-gas helium (40 $\mathrm{cm}^3\ \mathrm{min}^{-1}$); catharometer as detector; column and evaporator temperatures 155 and 230°C, respectively].

The effect of compounds **IX–XIII** on the antimicrobial properties of M-11 oil were studied with their solutions in this oil used in concentrations of 0.5–1.0%. The antimicrobial properties were determined in a hygrothermal chamber by the lunula method. Experiments were carried out at a temperature of 28–30°C in the course of 2 to 3 days. Fungal and bacterial cultures were used as test organisms.

1-Benzyl sulfanyl heptan-2-ol (III). To a mixture of 31 g (0.25 mol) of benzylthiol (**I**) and 25 g of a 40% solution of an alkali [solution of 10 g (0.25 mol) of NaOH in 15 g of water] was added dropwise under agitation 48.75 g of 1-bromopentan-2-ol (**II**) at 50–60°C. The agitation was continued for 3–4 h at the same temperature. After the mixture cooled, 15 ml of a 5% NaOH solution was added. The organic layer was separated, 30 ml of benzene was added, the mixture was washed with water to a neutral reaction and dried over $MgSO_4$. After the solvent was evaporated, the residue was distilled in a vacuum. A 43-g portion (72%) of 1-benzyl sulfanyl heptan-2-ol (**III**) was obtained: bp 160–162°C (1 mm Hg), n_D^{20} 1.5360, d_4^{20} 1.025; MR_D 72.84, calculated 72.97. IR spectrum, ν, cm^{-1}: 3500 (OH), 2930 (CH_3), 2850 (CH_2), 735 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.9 t (3H, CH3), 2.75 s (1H, OH), 2.4 m (2H, SCH2), 3.4 t (1H, OCH), 3.8 s (2H, $PhCH_2$), 7.30–7.36 t (5H, C_6H_5). Found (%): C 70.38, H 9.26, S 13.38. $C_{14}H_{22}OS$. Calculated (%): C 70.56, H 9.31, S 13.45.

General procedure for synthesis of aminomethoxy derivatives of 1-benzyl sulfanyl heptane, (IX)–(XIII). To a solution of 4.76 g (0.02 mol) of 1-benzyl sulfanyl heptan-2-ol (**III**) in 30 ml of benzene was added under agitation a solution of 0.6 g (0.02 mol) of formaldehyde in 10 ml of benzene. Then, a solution of 0.02 mol of a freshly distilled amine, (**IV**)–(**VII**) in 10 ml of benzene was added dropwise to this mixture at room temperature. The agitation was continued for 1 h at the same temperature, and then for 3–4 h at 50–60°C. After the mixture cooled, the solvent was evaporated and the residue was distilled in a vacuum. The physicochemical parameters, yield, and spectral characteristics of the compounds thus synthesized are listed in Tables 1 and 2.

CONCLUSIONS

(1) 1-Benzyl sulfanyl heptan-2-ol was synthesized in 72% yield by reacting benzylthiol with 1-bromoheptan-2-ol in an alkaline medium at a temperature of 50–60°C.

(2) The Mannich condensation of 1-benzyl sulfanyl heptan-2-ol, formaldehyde, and secondary amines at 50–60°C in the course of 3–4 h gives previously unknown aminomethoxy derivatives of 1-benzyl sulfanyl heptane in 73–78% yield.

(3) Aminomethoxy derivatives of 1-benzyl sulfanyl heptane effectively suppress growth of microorganisms in M-11 oil in concentrations of 0.5–1.0%.

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