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BRIEF COMMUNICATIONS

Synthesis of *N,N'*-Bis(alkyloxymethyl)piperazines and Examination of Their Antimicrobial Properties

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Abstract—Three-component condensation of piperazine with formaldehyde and aliphatic alcohols was employed for elucidating the possibility to synthesize *N,N'*-bis(alkyloxymethyl)piperazines. The structure of the resulting compounds was identified by 1H NMR spectroscopy. The antimicrobial properties of these compounds were examined with respect to microorganisms that infect cooling lubricants and lubricant oils.

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A promising line in modern petrochemistry and microbiology is synthesis of bacteria-resistant compounds whose action is underlain by the "in statu nascendi" principle. Meant by these agents are those having the basic active substance in a certain "depot" (in the bound state) which gradually releases the active toxophore part which exhibits prolonged action.

Today, extensive application as such "depots" is found by compounds containing "bound" formaldehyde [1, 2]. Some researchers [3] believe that these agents owe their antimicrobial action to the capability for hydrolytic decomposition with formation of formaldehyde. In turn, formaldehyde which possesses alkylating property can irreversibly react with various nucleophilic centers of the substrate (hydroxy, sulfohydryl, and carboxy, as well as amino groups). This blocks one of the cell cycle phases, thereby suppressing the growth of microorganisms.

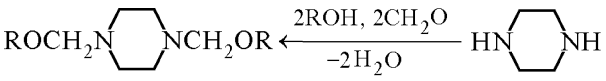
At the same time, the antimicrobial activity of these compounds can be associated not only with direct toxic action of the active part of the molecule on cells, but also with the nature of the carrier of the toxophore group. This may offer prospects of directed variation of the antimicrobial properties via using organic radicals of different nature as carrier of the toxophore group.

Earlier [4, 5] we employed three-component condensation–heterocyclization of alkanolamines (or alkylenediamines) with formaldehyde and hydroxy-containing compounds for synthesizing alkyloxy-methyl derivatives of 1,3-diheterocycloalkanes (1,3-oxaza- and 1,3-diazacycloalkanes) containing bound formaldehyde.

The results of those tests, along with a high antimicrobial activity of these compounds, suggest that this activity varies with the nature of the toxophore group carrier: the nature of the heterocycle (heterocycles containing diaza group perform better than do those containing oxaza group, and 6-membered heterocycles, better than do 5-membered heterocycles) and the length of the alkyl radical in the alkyloxymethyl group.

To continue those studies, we carried out here condensation of piperazine with formaldehyde and aliphatic alcohols into *N,N'*-bis(alkyloxymethyl)pipera

Scheme.



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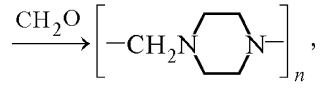

II

where R = (**a**) $-CH_3$; (**b**) $-C_2H_5$; (**c**) $-C_3H_7$; (**d**) iso-C_3H_7; (**e**) *n*–C_4H_9; (**f**) *iso*-C_4H_9; (**g**) n-C_7H_{15}; and (**h**) *n*-$C_{10}H_{21}$.

zines, alkyloxymethyl derivatives of 1,4-diazacyclanes, which are of interest in terms of comparison with similar derivatives of 1,3-diazacycloalkanes (see the scheme).

As the source of formaldehyde we used paraformaldehyde, to whose solution in the appropriate alcohol we added piperazine, whereupon the reaction water was distilled off as a water–benzene azeotrope. Under these conditions, we obtained a polymeric substance **II**, along with *N,N'*-bis(alkyloxymethyl)piperazine(I) in 45–75% yield. To prevent formation of substance **II**, we preliminary prepared hemiformal of the initial alcohol, which was entered into the reaction with piperazine at a temperature of 0–5°C.

We found that the yield of compound I is affected by the length of the radical in the initial alcohol, specifically, tends to increase with its lengthening.

The resulting products were identified by thin-layer and gas-liquid chromatography, and their composition and structure were established by elemental and ^{1}H NMR spectroscopic analyses.

The signals from protons of the NCH_2CH_2N group in the ^{1}H NMR spectra are represented by a triplet near 2.95–3.15 ppm, and those of from protons of the N–CH_2–O group, by a singlet in a weaker region at 3.95–4.16 ppm.

The antimicrobial properties of the synthesized compounds were examined in the composition of Azerol-1 cooling lubricant in accordance with GOST (State Standard) 9.085–78 [6] and in the composition of M-10 lubricant oil in accordance with GOST 9.052–75 and GOST 9.082–87. For comparison we used 1,3-bis(methoxymethyl)imidazolidine. As known, Pseudomonas bacteria, Aspergillus fungi, and Candida yeast are the most aggressive with respect to oil products. The tests were carried out with these individual microorganisms and showed (see the table) that the compounds synthesized efficiently inhibit microbiological contamination of oil products, and when in concentration of 0.5 % exhibit destructive action both on bacteria and fungi that infect cooling lubricants and lubricant oils. However, analogous derivatives of 1,3-diazacycloalkanes [1,3-bis(methoxymethyl)imidazolidine] exhibit better performance characteristics than similar derivatives of 1,4-diazacycloalkanes [1,4-bis(methoxymethyl)piperazine].

Antimicrobial activity of N, N'-alkyloxymethylpiperazines

Compd.	Concentration, %	Diameter of the growth suppression zone for indicated microorganism, mm		
		Pseudomonas aeruginosa	*Aspergillus niger*	*Candida tropicalis*
Ia	0.5	1.8–1.9[a]	1.6–1.8	1.6–1.8
	1.0	2.5–2.6	2.8–3.0	2.3–2.5
Ib	0.5	1.9–2.0	1.8–2.0	2.1–2.4
	1.0	2.5–2.9	2.2–30	1.2–1.4
Ic	0.5	2.2–2.2	2.0–2.2	2.0–2.3
	1.0	3.0–3.2	3.0–2.8	2.4–2.5
Id	0.5	1.6–1.7	1.9–2.0	2.6–2.8
	1.0	0.8–1.0	0.6–0.8	0.6–0.7
Ie	0.5 1.0	2.5–2.7	2.2–2.4	2.8–3.2
		3.2–3.3	3.0–3.1	2.5–2.6
If	0.5	–	–	–
	1.0	1.8–1.9	1.3–1.4	1.3–1.4
Ig	0.5	2.9–3.0	2.5–2.7	2.9–3.0
	1.0	3.2–3.5	3.0–3.1	2.5–2.7
Ih	0.5	3.0–3.1	2.6–2.7	3.1–3.2
	1.0	3.5–3.6	3.0–3.2	2.6–2.7
II	0.03	3.5–3.7	2.5–2.6	3.1–3.2
	0.06	3.2–3.5	2.7–2.8	2.8
Cooling lubricant and M-10 oil without additives		Confluent growth of microorganisms		

[a] Numerator represents the data for microorganisms in the composition of Azerol-1 cooling lubricant, and denominator, those for M-10 oil.

EXPERIMENTAL

***N,N'*-Bis(methoxymethyl)piperazine Ia.** Paraformaldehyde [20 g (6 mol)], methanol (60 ml), and 1/2 granule of potassium hydroxide were placed into a three-necked flask supplied with a mechanical stirrer, a thermometer, a dropping funnel, a Dean–Stark trap, and a reflux condenser. The reaction mixture was heated on a boiling water bath till exhaustive depolymerization of paraformaldehyde, and cooled to 0°C. Next, a solution of piperazine [17 g (0.2 mol)] was added dropwise into 20 ml of methanol at a rate at which the temperature of the reaction mixture did not exceed 0–5°C. The resulting mass was left overnight. Next, 100 ml of benzene was added, and the excess of alcohol and the reaction water were removed. The residue was distilled in a vacuum, which yielded 15.60 g (44.8%) of a liquid product, bp 128–130°C/1 mm Hg; n_D^{20} =1.4462. ^{1}H NMR spectrum, δ, ppm: 2.95 t (NCH_2CH_2N), 3.26 s (OCH_3), 4.06 s (NCH_2O). Found, %: N 16.3. $C_8H_{18}N_2O_2$. Calculated, %: N 16.09.

***N,N'*-Bis(ethyloxymethyl)piperazine (Ib).** In a sim-ilar way, 20 g (0.6 mole) of paraformaldehyde, 60 ml of ethanol, 1/2 granule of KOH, and 17 g (0.2 mole) of piperazine in 20 ml of ethanol after vacuum distillation of the reaction mixture yielded 19.3 g (48%) of a liquid product, bp 130–132°C/1.5 mm Hg; n_D^{20} =1.4488. ^{1}H NMR spectrum, δ, ppm: 1.2 t (CH_3), 2.96 t (NCH_2CH_2N), 3.30 m (OCH_2), 4.08 s (NCH_2O). Found, %: N 14.06. $C_{10}H_{22}N_2O_2$. Calculated, %: N 13.86.

***N,N'*-Bis(propyloxymethyl)piperazine (Ic).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 80 ml of *n*-propanol, 1/2 granule of KOH, and 17 g (0.2 mole) of piperazine in 20 ml of propanol yielded 23.9 g (52%) of a liquid product, bp 137–140°C/1 mm Hg; n_D^{20}=1.4525. ^{1}H NMR spectrum, δ, ppm: 0.9 t (CH_3), 1.3–1.5 m (CH_2CH_2), 2.95 t (NCH_2CH_2N), 3.30 t (OCH_2), 4.06 s (NCH_2O). Found, %: N 12.50. $C_{12}H_{26}N_2O_2$. Calculated, %: N 12.17.

***N,N'*-Bis(isopropyloxymethyl)piperazine (Id).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 80 ml of isopropanol, 1/2 granule of KOH, and 17 g (0.2 mole) of piperazine in 20 ml of isopropanol yielded 22.5 g (49%) of a liquid product, bp 142–143°C/1 mm Hg; n_D^{20} =1.4474. ^{1}H NMR spectrum, δ, ppm: 0.95 d ($2CH_3$), 3.1 t (NCH_2CH_2N), 3.38 t (OCH), 3.95 s (NCH_2O). Found, %: N 12.30. $C_{12}H_{26}N_2O_2$. Calculated, %: N 12.17.

***N,N'*-Bis(butyloxymethyl)piperazine (Ie).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 80 ml of *n*-butanol, 1/2 granule of KOH, and 17 g (0.2 mole) of piperazine yielded 31.0 g (60%) of a liquid product, bp 148–152°C/1 mm Hg; n_D^{20}=1.4522. ^{1}H NMR spectrum, δ, ppm: 0.83 t (CH_3), 1.33–1.66 (CH_2CH_2), 3.15 t (NCH_2CH_2N), 3.38 t (OCH_2), 4.95 s (NCH_2O). Found, %: N 10.97. $C_{14}H_{30}N_2O_2$. Calculated, %: N 10.85.

***N,N'*-Bis(isobutyloxymethyl)piperazine (If).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 80 ml of isobutanol, 1/2 granule of KOH, and 17 g (0.2 mole) of piperazine yielded 29.8 g (58 %) of a liquid product, bp 143–147°C/1 mm Hg; n_D^{20}=1.4482. ^{1}H NMR spectrum, δ, ppm: 0.9 d ($2CH_3$), 1.5 m (CH), 3.1 t (NCH_2CH_2N), 3.27 t (OCH), 4.15 s (NCH_2O). Found, %: N 11.20. $C_{14}H_{30}N_2O_2$. Calculated, %: N 10.85.

***N,N'*-Bis(heptyloxymethyl)piperazine (Ig).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 100 ml of *n*-heptane, and 17 g (0.2 mole) of piperazine yielded 44.5 g (65%) of a liquid product, bp 157–160°C/1 mm Hg; n_D^{20} =1.4522. ^{1}H NMR spectrum, δ, ppm: 0.9 t (CH_3), 1.130–1.150 m ($CH_2CH_2CH_2CH_2CH_2$), 3.05 t (NCH_2CH_2N), 3.30 t (OCH_2), 3.95 s (NCH_2O). Found, %: N 8.41. $C_{20}H_{42}N_2O_2$. Calculated, %: N 8.19.

***N,N'*-Bis(decyloxymethyl)piperazine (Ih).** In a similar way, 20 g (0.6 mole) of paraformaldehyde, 100 ml of *n*-decyl alcohol, and 17 g (0.2 mole) of piperazine yielded 64.4 g (75.5%) of a liquid product, bp 173°C/1 mm Hg; n_D^{20}=1.4568. ^{1}H NMR spectrum, δ, ppm: 0.85 t (CH_3), 1.33–1.68 [$(CH_2)_8$], 3.10 t (NCH_2CH_2N), 3.38 t (OCH_2), 3.95 s (NCH_2O). Found, %: N 6.95. $C_{26}H_{54}N_2O_2$. Calculated, %: N 6.57.

CONCLUSIONS

(1) Three-component condensation of piperazine with formaldehyde and aliphatic alcohols yielded *N,N'*-bis(alkyloxymethyl)piperazines.

(2) The yield of the target product tends to increase with lengthening of the hydrocarbon radical in the initial alcohol.

(3) The compounds synthesized exhibit antimicrobial properties with respect to microorganisms that infect cooling lubricants and lubricant oils, but are superseded in performance characteristics by similar derivatives of 1,3-diazacycloalkanes (imidazolidines).

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