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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

A Study of 2-Piperidino-1-ethanol and Its Derivatives as Antimicrobial Additives to Oils

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Abstract—Some derivatives of 1-hydroxy-2-pyperidinoethane were studied as antimicrobial additives to lubricant oils.

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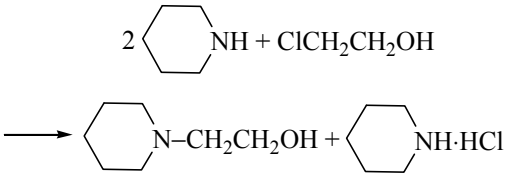
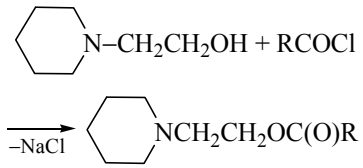
Piperidine fragments contained in various organic compounds exhibit a high physiological activity and are used in medical practice as analgesics and anesthetics [1]. They are also contained in various alkaloids, such as anabasine, morphine, bobeline, and tropine [2]. Piperidine derivatives containing hydroxy groups in their molecule are used in pharmacology of neuroleptics and analgesics.

In continuation of studies on the synthesis and examination of some amino alcohol derivatives in order to analyze the relationship between their structure and functional properties [3–8], we synthesized 2-piperidino-1-ethanol by reacting piperidine with 2-chloro-1-ethanol at 100°C within of 6 h at a reagent ratio of 2 : 1:



I

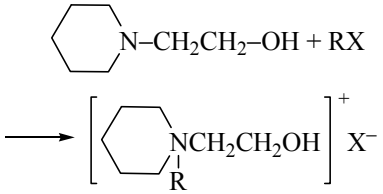
In acylation of 2-piperidino-1-ethanol with acetyl and benzyl chlorides in the presence of sodium hydroxide in a solution of carbon tetrachloride, the corresponding amino esters **II** and **III** were synthesized:



II, III

R = CH_3 (**II**), C_6H_5 (**III**).

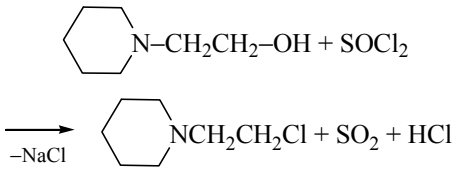
To expand the assortment of biocide additives to oils and to examine the dependence of their functional properties on their structure, we reacted 2-piperidino-1-ethanol with various alkyl halides to obtain quaternary salts **IV**–**VI**:



IV–VI

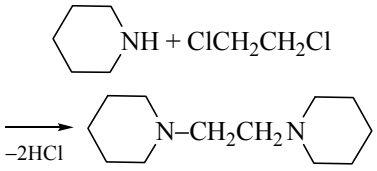
R = $(CH_3)_2CH$, X = I (**IV**); R = *n*-C_4H_9, X = Br (**V**); R = *n*-C_5H_{11}, X = Br (**VI**).

Chlorination of 2-piperidino-1-ethanol **I** with thionyl chloride yields 2-piperidinoethyl chloride **VII**:



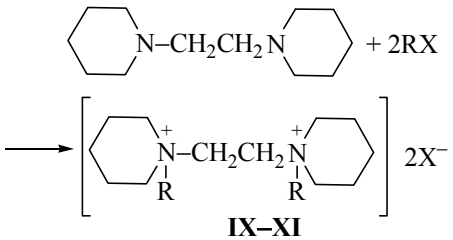
VII

An attempt to synthesize 2-piperidinoethyl chloride **VII** by reacting piperidine with 1,2-dichloroethane failed. The reaction product formed in this case was 1,2-bispiperidinoethane **VIII**:



VIII

The reactions of 1,2-bispiperidinoethane **VIII** with various alkyl halides yield bisquaternary salts:



IX–XI

R = $(CH_3)_2CH$, X = Br (**IX**); R = C_4H_9, X = Br (**X**); R = C_5H_{11}, X = Br (**XI**).

The physicochemical constants of the compounds synthesized are listed in Table 1. The composition and structure of the compounds were confirmed by IR and ^1H and ^{13}C NMR spectroscopy and by elemental analysis (Table 1).

A broad absorption band at 3370–3380 cm^{-1}, characteristic of stretching vibrations of the primary hydroxy group, was found in the IR spectrum of the synthesized 2-piperidinoethanol **I**. The IR spectra of amino esters **II** and **III** contain no absorption bands at 3370–3380 cm^{-1}, associated with stretching vibrations of the hydroxy group of the starting amino alcohol, but there appears a strong absorption band at 1735 cm^{-1}, characteristic of the C=O bond. The absorption band at 1225 cm^{-1} corresponds to stretching vibrations of the C–O bond.

In the ^1H NMR spectrum of 2-piperidinoethanol **I**, two protons of a methylene group in the piperidine ring appear in a strong field as a triplet with a chemical shift centered at 1.4–1.6 ppm. Signals of four protons of two methylene groups in the piperidine ring were also observed as a triplet at 1.6–1.7 ppm. Signals of six protons in the $N(CH_2)_3$ moiety appear as a triplet at 2.4–2.6 ppm. Two protons bound to oxygen in the OCH_2 moiety were observed in a comparatively weak field as a triplet at 3.6–3.8 ppm. The proton of the hydroxy group appears as a singlet in a weak field at 4.95 ppm.

Table 1. Physicochemical constants of compounds **I–XI**

Compound no.	mp, °C or bp, °C (*p*, mm Hg)	n_D^{20}	Yield, %	Found, %		
				C	H	N
I	64 (1)	1.3725	75	66.01	11.78	11.01
II	69–70 (1)	1.4650	80	63.18	9.98	8.27
III	200–202	–	78	72.37	8.39	6.38
IV	fluid	1.4785	66	40.28	73.77	4.70
V	190–191	–	70	49.59	9.11	5.38
VI	80	–	73	51.49	9.32	5.09
VII	76 (10)	1.4115	75	57.01	9.50	9.51
VIII	100–102 (1)	1.4863	85	73.53	12.38	14.42
IX	200		67	40.45	7.29	5.38
X	180		69	51.13	8.96	6.00
XI	150		73	53.12	9.32	5.78

Table 1. (Contd.)

Compound no.	Formula	Calculated, %			R_f
		C	H	N	
I	$C_7H_{15}NO$	65.07	11.70	10.84	0.69
II	$C_9H_{17}NO_2$	63.13	10.01	8.18	0.55
III	$C_{14}H_{19}NO_2$	72.07	8.21	6.00	0.67
IV	$C_{10}H_{22}INO$	40.11	7.35	4.67	0.42
V	$C_{11}H_{24}BrNO$	49.63	9.09	5.26	0.33
VI	$C_{12}H_{26}BrNO$	51.43	9.35	5.00	0.34
VII	$C_7H_{14}ClN$	56.94	9.56	9.49	0.71
VIII	$C_{12}H_{24}N_2$	73.41	12.32	14.27	0.63
IX	$C_{18}H_{38}N_2I_2$	40.31	7.09	5.22	0.44
X	$C_{20}H_{42}Br_2N_2$	51.07	9.00	5.96	0.30
XI	$C_{22}H_{46}Br_2N_2$	53.02	9.30	5.62	0.46

The following peaks were found in the ^{13}C NMR spectrum of 2-piperidinoethanol **I** in accordance with the electronic structure of carbon: 24, 26.54, and 58.61 ppm. In the ^1H NMR spectrum of 1-acetoxy-2-piperidinoethyl acetate **II** there appears, in contrast to the spectrum of the starting amino alcohol **I**, a strong singlet at 1.85 ppm, which corresponds to three protons in the acetyl radical. In the case of amino benzoate **III**, protons of the phenyl ring appear as a multiplet at 7.2–7.8 ppm.

The broad absorption band at 3370–3380 cm^{-1}, characteristic of the hydroxy group, was not observed in the IR spectrum of 1,2-bispiperidinoethane. The signal of the proton of the hydroxy group at 4.95 ppm was not observed in the ^1H NMR spectrum, either. However, four protons of two methylene groups appear as a triplet at 1.5 ppm. Signals of eight protons belonging to four methylene groups in the piperidine ring were observed at 1.65 ppm. Signals of eight protons of two $N(CH_2)_2$ moieties were observed as a multiplet at 2.45 ppm. Signals of four protons of two methylene groups belonging to a piperidine ring were observed as a singlet at 2.52 ppm. The assignment of the signals is confirmed by the integral curve.

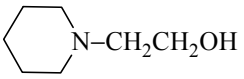
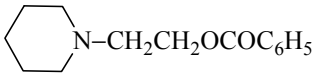
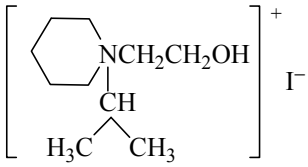
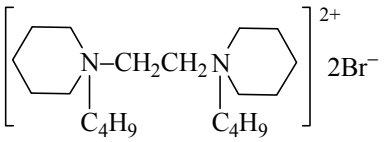
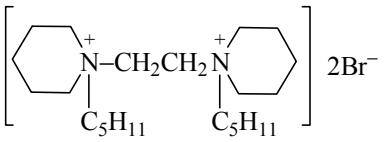
The NMR spectra of other quaternary salts, **IX**–**XI**, of the starting amino alcohol **I** and 1,2-bispiperidinoethane **VIII** are similar to the spectra considered above and differ only in signals characteristic of alkyl groups present in the molecule.

A study of the antimicrobial properties of compounds **I**–**XI** in an M-10 lubricant oil demonstrated (Table 2) that, taken in concentrations of 0.5–1 wt %, they effectively suppress the growth of microorganisms (bacteria and fungi) attacking this oil. All the compounds except **IV** exhibit effective fungicide properties. Apparently, this property is imparted by a piperidine ring present in their molecules. Introduction of an ester group into the molecule of amino alcohol **I** (compound **III**) enhances its biocide activity. It should be noted that quaternary salts of 2-piperidinoethanol with alkyl halides exhibit effective bactericide properties, whereas the bisquaternary salts of 1,2-bispiperidinoethane, **IX** and **X** possess only fungicide properties. The data on the antimicrobial properties of the compounds synthesized make it possible to recommend use of these compounds as biocide additives to lubricant oils to preclude their biodegradation.

EXPERIMENTAL

The course of the reactions was monitored and the individual nature of the products was verified by thin-layer chromatography on a fixed silica gel layer (Silufol). ^1H NMR spectra were recorded with a Bruker-300 MHz instrument of AVANCE type. Deuterated water (D_2O) and methanol-d4 served as solvents. The chemical shifts are given in ppm on the δ scale relative to hexamethyldisiloxane as internal

Table 2. Antimicrobial properties of the compounds synthesized as additives to M-10 oil

Compound no.	Compound	*c*, %	Microorganism suppression zone, cm[a]	
			mixture of bacteria in BEA	mixture of fungi in WA
I		1.0	+	2.5
		0.5	+	1.2
III		1.0	+	3.2
		0.5	+	1.6
IV		1.0	3.6	+
		0.5	1.5	+
IX		1.0	+	2.0
		0.5	+	1.0
XI		1.0	+	2.4
		0.5	+	1.2
	8-Oxyquinoline	1.0	1.8–2.0	1.6–2.0
		0.5	0.9–1.0	0.8–1.1
	M-10 oil without additives	–	+ +	

[a] (+) denotes abundant growth of microorganisms around a well in a Petri dish.

reference. The IR spectra were recorded with a Specord-75 instrument in liquid films or in mineral oil. The antimicrobial properties of the compounds were examined by the well method in an agar medium in conformity with GOST (State Standard) 9.052–88 and GOST 9.082–77. Tests were performed with pure strains of the fungi (*Asperigillus niger, Cladosporium resinae, Penicillium chrosegenum, Chaltonium globosum*) and bacteria (*Mycobacterium lacticola, Pseudomonas aeriginosa*), which widely occur in petroleum products and are their aggressive destructors. The microorganisms were grown at a temperature of 28±2°C in a specially mounted thermostat with a 90–100% humidity in the course of 5–7 days. Wort agar (WA) and beef-extract agar (BEA) served as nutrition media for fungi and bacteria, respectively.

2-Piperidino-1-ethanol (I). To 17 g (0.2 mol) of piperidine heated to 70°C was slowly added under agitation 8 g (0.01 mol) of 2-chloro-1-ethanol. The reaction mixture was heated at the same temperature on a water bath for 5 h. After that, the reaction product was cooled and the precipitate was several times extracted with dry ether. The solvent was evaporated and the residue was subjected to vacuum distillation. Yield 9.7 g (75%), bp 64–65°C (1 mm Hg), n_D^{20} 1.4712, R_f 0.69.

Found, %			Calculated, %		
C	H	N	C	H	N
66.01	11.78	11.01	65.07	11.70	10.84

Formula: $C_7H_{15}NO$

1-(2-Phenylcarbonyloxyethyl)piperidine (III). To a solution of 6.5 g (0.05 mol) of 1-hydroxy-2-piperidinoethane **I** in 30 ml of carbon tetrachloride was added 2 g (0.05 mol) of sodium hydroxide and the mixture was vigorously agitated. The reaction course was monitored by thin-layer chromatography. To

separate the target product from sodium chloride, the reaction mixture was treated with distilled water. The organic layer was dried over calcium chloride. After the solvent was evaporated, the reaction product was recrystallized in a 1 : 1 mixture of isopropanol and hexane. Yield 9 g (78%), mp 200–201°C, R_f 0.67.

Found, %			Calculated, %		
C	H	N	C	H	N
72.37	8.39	6.38	72.07	8.21	6.00

Formula: $C_{14}H_{19}NO_2$

Similarly, 2-piperidinoethyl acetate **II**, whose physicochemical constants are listed in Table 1, was synthesized from 2-piperidinoethanol **I** and acetyl chloride.

To obtain quaternary salt **V** by the reaction of 2-piperidinoethanol **I** with butyl bromide, a mixture of 1.29 g (0.01 mol) of 1-hydroxy-2-piperidinoethane **I** and 1.37 g (0.01 mol) of n-butyl bromide was heated on a water bath at 80°C for 5 h. White crystals were precipitated. The reaction product was dissolved in dry ethyl ether. Yield 1.86 g (70%), mp 190°C, R_f 0.47.

Found, %			Calculated, %		
C	H	N	C	H	N
49.59	9.11	5.38	49.62	9.02	5.26

Formula: $C_{16}H_{24}BrNO$

The other quaternary salts **IV**, **VI**, and **IX**–**XI** were synthesized similarly. Their physicochemical constants are listed in Table 1.

2-Piperidinoethyl chloride (VII). A three-necked flask equipped with a stirrer, dropping funnel, and thermometer was charged of 12.9 g (0.1 mol) of 2-piperidinoethanol **I** in 50 ml of dry benzene and the solution was vigorously agitated. Then, 12.9 g (0.01 mol) of thionyl chloride was added dropwise to the reaction mixture. An exothermic reaction occurred and the temperature increased to 50–60°C. The reaction mixture was agitated at this temperature on a water bath for 5 h and benzene was evaporated. The reaction product was distilled in a vacuum. Yield 10 g 75%), bp 72–73°C (1 mm Hg), n_D^{20} 1.4115, R_f 0.47.

Found, %			Calculated, %		
C	H	N	C	H	N
57.01	9.50	9.51	56.94	9.56	9.49

Formula: $C_{17}H_{14}ClN$

1,2-Bispiperidinoethane (VIII). To a mixture of 17 g (0.2 mol) of piperidine, heated to 100°C, was added 4.9 g (0.05 mol) of 1,2-dichloroethane. The reaction mixture was heated at the same temperature on an oil bath for 5 h. After that, the reaction product was cooled and the precipitate was several times washed with dry ethyl ether. The solvent was evaporated and the reaction product was subjected to vacuum distillation. Yield 8.3 g (85%), mp 100–101°C (1 mm Hg), n_D^{20} 1.4863, R_f 0.63.

Found, %			Calculated, %		
C	H	N	C	H	N
73.53	12.38	14.42	73.41	12.32	14.27

Formula: $C_{14}H_{24}N_2$

CONCLUSIONS

(1) A purposeful synthesis of some 2-piperidinoethanol derivatives was performed in order to determine how the structure of these compounds affects their antimicrobial properties.

(2) A study of the compounds in an M-10 lubricant oil (0.5–1%) demonstrated that the presence of the piperidine moiety in molecules of the compounds imparts to them effective biocide and, in particular, fungicide properties. The presence of an ester group in the molecules enhances their biocide activity.

(3) It was shown that quaternary salts of 2-piperidinoethanol with isopropyl iodide exhibit only bactericidal properties, and bisquaternary salts of 1,2-bispiperidinoethane with alkyl bromides, only fungicidal properties.

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