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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Antimicrobial Properties of 3-(β-Hydroxyethyl)-1,3-oxazolidins

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Abstract—The possibility of synthesis of 3-(β-hydroxyethyl)-1,3-oxazolidin and its substituted derivatives at position *2* by the condensation-heterocyclization of diethanolamine with certain aldehydes and ketones was examined. The structure of the compounds was identified by NMR spectroscopy. We investigated antimicrobial properties of the synthesized compounds against microorganisms that affect the lube oil M-11 and found a dependence of the antimicrobial properties on the nature of the substituent at position *2* of oxazolidin heterocycle.

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It is known that most of the currently used petroleum products during storage, transportation, and operation is affected by microorganisms. Microbial processes occurring lead to a deterioration of physical-chemical, operational, and hygienic properties of petroleum products, resulting in reduced service life, and materials and constructions being in contact with petroleum products are subjected to corrosion [1].

The most efficient way to protect the petroleum products from microbial destruction is chemical method: introduction in their composition of special antimicrobial additives, biocides.

Since many biologically active compounds contain structural fragments of N–C–O, N–C–N, and N–C–S, compounds with these fragments in their structure were obtained prior to synthesize new substances which are promising as antimicrobial additives for mineral oils. Thus, the condensation-heterocyclization of alkanol amines [2] (or alkylene diamines [3]) was developed with formaldehyde and hydroxyl-containing compounds derived from N-alkoxymethyl derivatives of 1,3-diheterocycloalkanes (1,3-oxazines, 1,3-oxazolidins, 1,3-perhydropyrimidines, 1,3-imidazolidines). Microbiological tests have shown high efficiency and broad spectrum of antimicrobial action of these compounds to the microorganisms which affect petroleum products.

Therefore, synthesis of novel 1,3-diheterocycloalkane derivatives deserved attention as possible antimicrobial agent with respect to petroleum products.

In the study we considered diethanolamine condensation with certain aldehydes and ketones which resulted in 1,3-oxazolidin derivatives substituted at position *3* by β-hydroxyl group and at position *2* by alkyl or aryl group.

Formaldehyde (in the form of paraform), benzaldehyde, and its F, Cl, OH-substituted derivatives were used as aldehydes. Methylpropyl- and methylhexylketones were applied as ketones.

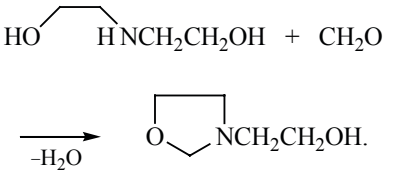
Diethanolamine condensation with aldehydes and ketones was carried out according to the known technique [4] at a molar ratio of initials reagents 1 : 1 by heating in benzene or toluene which was taken according to boiling point of the initial aldehyde or ketone, with azeotropic distillation of a reaction water into Dean–Stark trap. The reaction end was determined by completion of water release. Physical chemical constants and data of ^{1}H NMR spectra of the products are listed in the table. In addition, for clarity we recorded ^{13}C NMR spectra of compounds **II** and **III.**

Diethanolamine condensation with formaldehyde (in the form of paraform) at the 1 : 1 ratio of the initial reagents proceeds readily. 3-(β-Hydroxyethyl)-1,3-oxazolidin with 90% yield was obtained after distilling

Physicochemical constants of 3-(β-hydroxyethyl)-1,3-oxazolidin and its derivatives

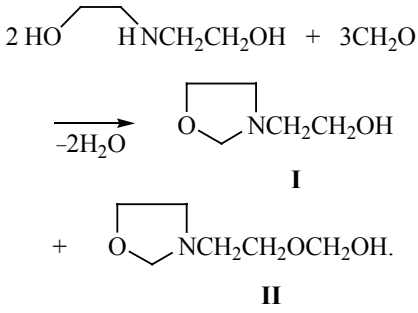
Compound	bp, °C/*P*, mm Hg	Yield, %	n_D^{20}	Content N, %		^{1}H NMR spectrum, chemical shift δ, ppm
				found	calculated	
3-(β-Hydroxyethyl)-1,3-oxazilidin (**I**)	85–87/3	90.0	1.4786	12.1	11.96	4.19 s (2H, OCH_2N); 3.68 t (2H, OCH_2C); 3.55 t (2H, CCH_2O); 2.92 t (2H, CCH_2N); 2.60 t (NCH_2C)
3-(1-Hydroxy-2-oxabutyl-4)-1,3-oxazilidin (**II**)	Decomposition occurs at high temperature	Quantitative	1.4720	11.5	10.69	4.23 s (2H, OCH_2O); 4.19 s (2H, OCH_2N); 3.67 t (2H, OCH_2C); 3.55 t (2H, CCH_2O); 2.90 t (2H, CCH_2N); 2.63 t (2H, NCH_2O)
2-Phenyl-3-(β-hydroxyethyl)-1,3-oxazilidin (**III**)	162–163/1	54.5	1.4436	7.25	6.98	6.7–7.3 m (5H, C_6H_5); 4.7 s (1H, OCHN); 3.6–3.7 t (2H, OCH_2C); 3.3–3.5 t (2H, CCH_2O); 2.8 t (2H, CCH_2N); 2.5 t (2H, NCH_2C)
2-*p*-Fluorophenyl-3-(β-hydroxyethyl)-1,3-oxazilidin (**IV**)	178–182/1	56.9	1.4464	6.98	6.63	6.7–7.3 m (4H, C_6H_4F); 4.75 s (1H, OCHN); 3.8–3.9 t (2H, OCH_2C); 3.3–3.5 t (2H, CCH_2O); 2.7–2.8 t (2H, CCH_2N); 2.4–2.5 t (2H, NCH_2C)
2-(*o*-Fluorophenyl)-3-(β- hydroxyethyl)-1,3-oxazilidin (**V**)	136–137/1	54.0	1.4460	6.63	5.59	Spectrum is analogous to that of **IV**
2-(*p*-Chlorophenyl)-3-(β- hydroxyethyl)-1,3-oxazilidin (**VI**)	155–156/1	66.1	1.5530	6.52	6.11	6.9–7.05 m (4H, C_6H_4Cl); 4.8 s (1H, OCHN); 3.8–3.95 t (2H, OCH_2C); 3.3–3.5 t (2H, CCH_2O); 2.2–2.8 m (4H, CCH_2N and NCH_2C)
2-(*o*-Chlorophenyl)-3-(β- hydroxyethyl)-1,3-oxazilidin (**VII**)	167–171/1	61.2	1.5534	6.47	6.11	6.9–7.1 m (4H, C_6H_4Cl); 4.8 s (1H, OCHN); 3.7–3.9 t (2H, ClH_2O); 3.3–3.4 t (2H, OCH_2C); 2.6–2.7 t (2H, NCH_2C); 2.3–2.5 t (2H, CCH_2N)
2-(*o*-Oxyphenyl)-3-(β-hydroxyethyl)-1,3-oxazilidin (**VIII**)	175–177/1	60.6	1.5530	6.74	6.7	6.7–7.0 m (4H, C_6H_4); 5.9–6.2 br.s (1H, C_6H_5OH); 4.9 s (1H, OCHN); 3.2–4.0 m (4H, CCH_2OH, CCH_2O); 2.0–3.0 m (4H, CCH_2N)
2-Methyl-2-propyl-3-(β- hydroxyethyl)-1,3-oxazilidin (**IX**)	108/0.4	50.0	1.4744	8.6	8.09	3.4–3.6 t (2H, CCH_2O); 3.05–3.15 t (2H, CCH_2OH); 2.7–2.8 t (2H, CCH_2N); 2.4–2.53 t (2H, NCH_2C); 1.45–1.53 m (4H, CCH_2CH_2); 1.08 s (3H, CH_3C); 0.85–0.95 t (3H, CH_3CH_2)
2-Methyl-2-hexyl-3-(β-hydroxyethyl)-1,3-oxazilidin (**X**)	130/0.5	75.7	1.4656	6.75	6.51	3.4–3.6 t (2H, CCH_2O); 2.6–2.8 t (2H, NCH_2C); 3.05 t (2H, CCH_2OH); 2.4–2.5 t (2H, CCH_2N); 1.2–1.5 m (10H, $CH_2CH_2CH_2CH_2CH_2$); 1.05 s (3H, CH_3C); 0.85–0.95 t (3H, CH_3CH_2)

off a solvent and distillation of residue under a vacuum:



I

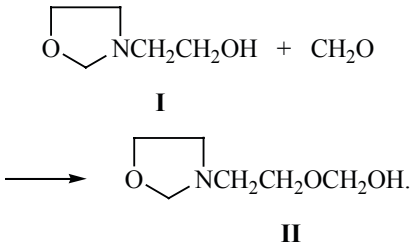
In the ^{13}C NMR spectrum of the product **I** a chemical shift of the signal of 86.90 ppm corresponds to the carbon atom at position *2* (that is an evidence of heterocycle formation). If the reaction is carried out at a 2 : 3 molar ratio of diethanolamine to formaldehyde, then an equimolar mixture of compounds **I** and **II** is formed:



I

II

The formation of mixture of products **I** and **II** was determined by TLC technique and ^1H NMR spectroscopy. A structure of product **II** was proved with the aid of a counter synthesis:

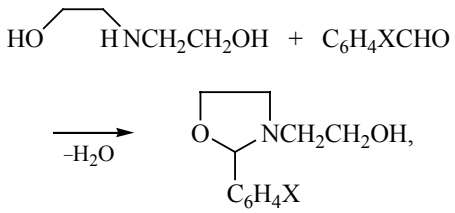


I

II

In the ^{13}C NMR spectrum of compound **II** unlike that of **I** an additional signal was found at 90.07 ppm corresponding to the chemical shift of C atom in OCH_2OH group, while the chemical shifts of other atoms C were identical with chemical shifts of compound **I**.

Diethanolamine condensation with benzaldehyde and its *ortho*- and *para*-F,Cl, *ortho*-OH-substituted derivatives resulted in 3-(β-hydroxyethyl)-1,3-oxazolidin derivatives substituted at position *2* by C_6H_4X:



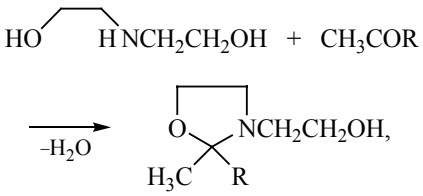
III–VIII

where X = H (**III**), *o*-F (**IV**), *p*-F (**V**), *o*-Cl (**VI**), *p*-Cl (**VII**), *o*-OH (**VIII**).

The examinations demonstrated that a yield of condensation products was 54–66% regardless of the ratio of initial reagents and depended on the substituent nature and position in the benzene ring and grew in an order H < F < OH < Cl therewith *o*-F < *p*-F, *o*-Cl < *p*-Cl.

In the ^1H NMR spectrum of compounds **III–VIII** a multiplet of 6.7–7.5 ppm field corresponds to the chemical shifts of protons of aromatic ring. In these compounds, similar to compounds **I**, **II**, in the field of 2.7–2.8 and 3.3–3.5 ppm the signals of protons of methylene groups of 1,3-oxazolidin heterocycle are observed at positions C_4 and C_5, respectively.

In contrast to the reaction of aldehydes that of ketones proceeds slowly however with 55 and 75.7% yield of 2-methyl-2-propyl- and 2-methyl-2-hexyl-3-(β-hydroxyethyl)-1,3-oxazolidin, respectively:



IX, X

where R = C_3H_7 (**IX**), C_6H_{13} (**X**).

In ^1H NMR spectra of products **IX, X** a triplet in 0.85–0.95 ppm field corresponds to terminal methyl groups of hydrocarbon radicals C_3H_7 and C_6H_{13}. Singlet in the field of 1.08 ppm (1.05 ppm) corresponds to protons of groups CH_3 at C_2. Signals in region 2.5–2.8 and 3.5–3.6 ppm corresponds to chemical shifts of protons at C_4 and C_5.

Antimicrobial properties of synthesized compounds were researched in a lubricating oil M-11 composition (State Standard: GOST 9.082–77 and 9.052–88). The resulting data show that 3-(β-hydroxyethyl)-1,3-oxazolidin and its methylol derivative possess high antimicrobial

properties. Substitution of hydrogen atom at position *2* of 3-(β-hydroxyethyl)-1,3-oxazolidin by phenyl group impairs its bactericide properties. Depending on the nature and position of substituent in the benzene ring we found the following order of lowering the fungicidal properties: *o*-F > *p*-F > *o*-Cl > *p*-Cl > OH > H.

The high antimicrobial activity of compounds **I**, **II** is presumably due to the fact that in these substances the bond between positions *1* and *3* of the oxazolidin ring is readily broken with formation of formaldehyde that leads to a death of microbial cells.

CONCLUSIONS

(1) We found that the diethanolamine condensation with certain aldehydes and ketones was accompanied by heterocyclization of diethanolamine with the formation of 3-(β-hydroxyethyl)-1,3-oxazolidin (at condensation with formaldehyde) or its substituted derivatives in position *2*.

(2) The synthesized compounds owing to their antimicrobial activity at a 0.25–1.0 wt % concentration protect lubricating oil against microbiological damage.

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