Preparation and antimicrobial properties of 2-alkyl-3-dodecyl--5-chloromethyloxazolidines

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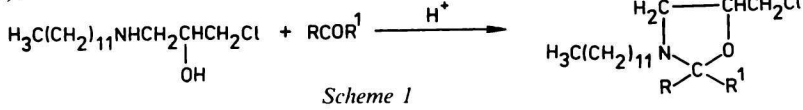
Ten new 2-alkyl-3-dodecyl-5-chloromethyloxazolidines were prepared by the cyclocondensation of a carbonyl compound with 1-dodecylamino-3--chloro-2-propanol. The structure of the synthesized compounds was determined on the basis of IR and mass spectral data. Antimicrobial activity of these compounds was studied.

Циклоконденсацией карбонильного соединения с 1-додециламино--3-хлор-2-пропанолом было приготовлено десять новых 2-алкил-3-додецил-5-хлорметилоксазолидинов. Структура полученных соединений была определена с помощью инфракрасных и масс-спектров. Была изучена антибактериальная активность этих соединений.

Lately, several papers have been published dealing with the antimicrobial activity of oxazolidines. *E.g.*, for disinfection, also in a larger scale, derivatives of 4,4-dimethyloxazolidines are used. They are mainly derivatives having different substituents in the position 3 of oxazolidine ring [1—3]. Also, 2,2,4,4--tetramethyl-3-chlorooxazolidine shows bactericidal activity [4]. Effect of ethyl ester of 2,2-dimethyl-3-(4,4-dimethyloxazolidin-3-yl)propionic acid on some species of cancer caused by viruses, is interesting [5]. Underivated 4,4-dimethyloxazolidine is industrially manufactured as Oxadine-A and it is used against virulent species of influenza Newcastle and Boney-1 [6]. Bactericidal, virucidal, and fungicidal properties of 3-acyloxazolidines [7—9] are utilized, some of these compounds are used as herbicides [10, 11]. 3-Alkyloxazolidines [12—15] have been published as easily available and antimicrobially active. 3-(1-Naphthyl)-oxazolidine showed antifungal properties [16]. It is evident that oxazolidines exhibit remarkable antimicrobial activity against broad spectrum of microorganisms.

In the present work we focused our attention to the preparation of antimicrobially active 2-alkyl-3-dodecyl-5-chloromethyloxazolidines. Cyclic condensation of 1-dodecylamino-3-chloro-2-propanol with aliphatic aldehydes or ketones was applied. The reaction was catalyzed by 4-toluenesulfonic acid (Scheme 1).



Scheme 1

The results of elemental analysis and yields of the prepared compounds (all undistillable oils) are given in Table 1. The best yields were obtained from the condensation of 1-dodecylamino-3-chloro-2-propanol with methyl ethyl ketone and with acetone (compounds *III* and *IV*). Derivative *X* was prepared from chloral hydrate. When chloral was used, the yield decreased to 38 %. Compound *I* was prepared using basically catalyzed cyclocondensation of 1-dodecylamino-3-chloro-2-propanol with formaldehyde in ethanol. Potassium hydroxide was used as catalyst. Similar cyclocondensations have already been published [17, 18].

In the mass spectra (12 eV) of all prepared 2-alkyl-3-dodecyl-5-chloromethyloxazolidines the peaks were observed, which we attributed to the following fragmentations: $A = [M - R^{\bullet}]^+$, $B = [M - R^{1\bullet}]^+$, $C = [M - H_3C(CH_2)_{10}^{\bullet}]^+$, $D = [C - RCOR^1]^+$, $E = [H_3C(CH_2)_{11}N{=}CH_2]^{+\bullet}$. All derivatives showed the peak of molecular ion. Compound *III* exhibited the highest relative intensity ($I_r = 9.7\,\%$), compound *V* exhibited the lowest one ($I_r = 4.2\,\%$). Fragmentations A and B showed the higher I_r, the larger substituent was splitted off from the position 2 of the oxazolidine ring. The peak corresponding to the fragmentation $[M - CCl_3^{\bullet}]^+$ in the compound *X* exhibited the highest I_r (26.3 %). Among the others, the peaks corresponding to the fragmentation C showed the highest I_r. Fragmentation D showed I_r of peaks in the range of 14.3 to 19.5 %. The highest I_r of this peak was observed in the case of compound *VII*, the lowest in *I*. The I_r of peaks of the fragmentation E was approximately the same (about 25 %) in all studied compounds.

In the IR spectra of compounds prepared, absorption bands corresponding to the skeletal vibrations of oxazolidine ring in the region $\tilde{\nu} = 1150$—$1170\,cm^{-1}$, 1125—$1135\,cm^{-1}$, and 1088—$1100\,cm^{-1}$ were observed. In the case of compound *I*, absorption band at $\tilde{\nu} = 1073\,cm^{-1}$ was observed, which would also belong to this type of vibration. Stretching vibration of the C—Cl bond in the chloromethyl group was observed in the region of about $\tilde{\nu} = 740\,cm^{-1}$. Alkyl chain showed intensive bands at about $\tilde{\nu} = 2930\,cm^{-1}$ (stretching antisymmetric vibrations of CH_2 groups) and in the region of $\tilde{\nu} = 2855\,cm^{-1}$ (stretching symmetric vibrations of CH_2 groups). Rocking vibrations of the same groups were demonstrated by a weak band in the region of $\tilde{\nu} = 720\,cm^{-1}$. Terminal methyl group of the dodecyl chain showed most expressively one band in the region of $\tilde{\nu} = 1380\,cm^{-1}$. In the case of compound *III*, a doublet was observed in this region. The band belonging to the methyl of $COCH_3$ group of compound *V* and *VI*, was shifted up to $\tilde{\nu} = 1355\,cm^{-1}$.

The results of antimicrobial activity tests, given by the values of minimum inhibitory concentration (MIC), are summarized in Tables 2 and 3. Compounds *III*, *IV*, and *IX* are the most effective against gram-positive bacteria. Their activity is comparable with Septonex and better than the activity of Ajatin,

Table 1

Characterization of the prepared 2-alkyl-3-dodecyl-5-chloromethyloxazolidines

Compound	R	R[1]	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield[a]
					C	H	N	%
I	H	H	$C_{16}H_{32}ClNO$	289.90	66.29	11.13	4.83	78
					66.20	11.21	4.79	
II	CH_3	H	$C_{17}H_{34}ClNO$	303.92	67.19	11.28	4.61	57
					67.07	11.35	4.55	
III	CH_3	CH_3	$C_{18}H_{36}ClNO$	317.95	68.00	11.41	4.41	82
					67.94	11.48	4.36	
IV	CH_2CH_3	CH_3	$C_{19}H_{38}ClNO$	331.97	68.74	11.54	4.22	80
					68.65	11.61	4.18	
V	$COCH_3$	CH_3	$C_{19}H_{36}ClNO_2$	345.96	65.96	10.49	4.05	53
					65.82	10.59	3.98	
VI	CH_2COCH_3	CH_3	$C_{20}H_{38}ClNO_2$	359.98	66.73	10.64	3.89	49
					66.64	10.71	3.82	
VII	$CH(OCH_3)_2$	CH_3	$C_{20}H_{40}ClNO_3$	378.00	63.55	10.67	3.71	56
					63.50	10.74	3.67	
VIII	CH_2OH	CH_3	$C_{18}H_{36}ClNO_2$	333.95	64.74	10.87	4.19	43
					64.68	10.92	4.15	
IX	CH_2OH	CH_2OH	$C_{18}H_{36}ClNO_3$	349.95	61.78	10.37	4.00	40
					61.71	10.44	3.90	
X	CCl_3	H	$C_{17}H_{31}Cl_4NO$	407.26	50.14	7.67	3.44	57
					50.06	7.76	3.41	

a) After column chromatography.

Table 2

Antimicrobial activity (MIC/(μg cm $^{-3}$)) of 2-alkyl-3-dodecyl-5-chloromethyloxazolidines against gram-positive and gram-negative bacteria

Compound	*Staphylococcus epidermidis*	*Staphylococcus aureus*	*Bacillus subtilis*	*Streptococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella typhimurium*	*Shigella flexneri*	*Enterobacter aerogenes*
I	10	10	10	10	1000	1000	1000	1000	1000
II	100	10	10	100	1000	1000	1000	1000	1000
III	1	1	10	10	100	1000	100	100	100
IV	1	1	10	10	100	1000	1000	100	100
V	10	10	10	10	1000	1000	100	1000	1000
VI	100	10	100	100	1000	1000	100	1000	1000
VII	10	10	10	100	1000	1000	100	1000	1000
VIII	10	10	10	100	1000	1000	10	1000	1000
IX	1	1	10	10	1000	1000	10	1000	1000
X	100	10	10	100	1000	1000	1000	1000	1000
Septonex	1	1	10	1	100	100	10	10	100
Ajatin	10	10	10	10	100	100	10	100	1000

Table 3

Antimicrobial activity (MIC/(μg cm^{-3})) of 2-alkyl-3-dodecyl-5-chloromethyloxazolidines against fungi .

Compound	*Candida albicans*	*Saccharomyces cerevisiae*	*Microsporum gypseum*	*Trichophyton terrestre*	*Aspergillus niger*
I	100	100	100	100	100
II	1000	100	100	100	1000
III	100	100	100	100	100
IV	100	100	10	1	100
V	100	100	100	100	1000
VI	1000	1000	100	100	1000
VII	100	100	100	1000	1000
VIII	100	1000	100	100	1000
IX	100	100	100	100	1000
X	100	100	100	100	1000
Septonex	1	10	1	1	10
Ajatin	10	100	10	10	100

which we used as standards. *Streptococcus faecalis* was found to be the most resistant against studied derivatives of oxazolidine. The activity of the prepared oxazolidines was lower against gram-negative bacteria, and *Pseudomonas aeruginosa* was found as the most resistant. Compound *III* showed the most universal effect. Compound *IV* exhibited the highest activity against fungi. Generally, compounds *III* and *IV* showed the best properties from the point of view of the antimicrobial activity. In the following, these compounds were used as intermediates for the preparation of antimicrobially active surfactants.

Experimental

1-Dodecylamino-3-chloro-2-propanol was prepared according to the known method [19—21]. All the used carbonyl compounds, like dodecylamine and chloromethyloxirane, were commercial products (Lachema, Brno; Fluka; Merck, Darmstadt.)

Mass spectra (12 eV) were measured on a Jeol JMS-100D mass spectrometer at an emission of 300 μA, applying direct sample-introduction technique. Infrared spectra were obtained on a Perkin—Elmer 983 instrument and elemental analyses were performed on a Perkin—Elmer 240 analyzer.

MIC was determined by using suspension method on solid cultivation media (cultivation medium No. 2 for bacteria and Sabouraud's medium for fungi and yeasts).

3-Dodecyl-5-chloromethyloxazolidine (I)

1-Dodecylamino-3-chloro-2-propanol (1 mol) was dissolved in ethanol (200 cm^3), and potassium hydroxide (0.1 mol) dissolved in water (100 cm^3) was added. The mixture was

stirred at room temperature and 36 % solution of formaldehyde in water (1.1 mol) was added in the course of 30 min. Stirring continued for 8 h, then ether (200 cm^3) was added. Ethereal solution was washed with water until pH = 7, dried over anhydrous sodium sulfate and solvent was distilled off under reduced pressure. Distillation residue was separated on a column of silica gel, using the mixture acetone—methanol (volume ratio = 50: 1) as eluent. The yield was 78 %.

2,2-Dimethyl-3-dodecyl-5-chloromethyloxazolidine (III)

1-Dodecylamino-3-chloro-2-propanol (1 mol) was dissolved in dry acetone (200 cm^3) and 4-toluenesulfonic acid (0.5 g) was added. After 5 h of refluxing, toluene (250 cm^3) was added into the reaction mixture. In the course of next 5 h, water arising during the reaction, was removed using adapter for azeotropic distillation. Then, the mixture was cooled, ether (200 cm^3) was added and the resulting solution was washed with 0.1 M-$NaHCO_3$ (50 cm^3) and with water until pH = 7. Solvents were distilled off *in vacuo*, and the residue was separated on the silica gel column as described above. The other 2-alkyl-3-dodecyl-5-chloromethyloxazolidines were prepared analogically.

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