Amine oxides of some alkyl derivatives of oxazolidine, their surface-active and antimicrobial properties

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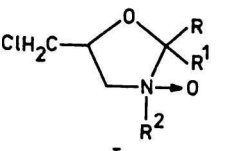
Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday

Corresponding amine oxides were prepared by the oxidation of 3-alkyl-, 2,3-dialkyl-, and 2,2,3-trialkyl-5-chloromethyloxazolidine using hydrogen peroxide. The structure of these compounds was confirmed by infrared and mass spectra. Surface-active properties and antimicrobial efficiency were also determined.

Окислением 3-алкил-, 2,3-диалкил-, и 2,2,3-триалкил-5-хлорметил-оксазолидина перекисью водорода были получены соответствующие аминоокиси. Строение этих соединений было подтверждено на основании инфракрасных и масс-спектров. Определялась также эффективность поверхностно-активного и антимикробного действия этих соединений.

Derivatives of oxazolidines are known to possess antimicrobial properties. This fact was confirmed in our papers [1—4]. Facile hydrolyzability of the oxazolidine ring in acidic and also in basic medium [5—8] limits practical utilization of these compounds in disinfection. This fact has to be taken into account while we want to prepare water-soluble derivatives from oxazolidines by introducing of hydrophilic group. Nonionic groups are the most suitable for this purpose. We have succeeded with amine oxide group, on the other hand, quaternary ammonium salts are not satisfactory [1]. We prepared a series of amine oxides of general formula *I* by the oxidation of 2,2,3-trialkyl-5--chloromethyloxazolidines with hydrogen peroxide in aqueous ethanolic solution. Their survey is given in Table 1.



I

These amine oxides are colourless or pale yellow viscous liquids unlimitedly soluble in water. Their aqueous solutions foam strongly. They are fairly soluble in ethanol, insoluble in acetone and in nonpolar solvents. Aqueous solutions of these compounds are stable but they decompose rapidly when dried, therefore

we do not give the data of elemental analysis. The best method for identification in this case seems to be the analysis of infrared spectra. In agreement with the literature [9, 10], a strong absorption band in the region of $\tilde{\nu} = 950$—$970\ cm^{-1}$ corresponding to the stretching vibration of N—O bond was found. However, no triplet was observed as mentioned *Hummel* in his work [11]. The starting oxazolidines showed in infrared spectra absorption bands of skeletal vibrations of oxazolidine ring in the regions of $\tilde{\nu} = 1150$—$1170\ cm^{-1}$, 1125—$1135\ cm^{-1}$, and 1088—$1100\ cm^{-1}$ [2, 12]. Amine oxides of oxazolidines exhibited in the region of $\tilde{\nu} = 1070$—$1100\ cm^{-1}$ only one significant absorption band. In the region of $\tilde{\nu} = 1660\ cm^{-1}$, formerly described [10] absorption bands of bonding water were observed, so this kind of amine oxides also forms hydrates.

In the mass spectra, the molecular ion $M^{+\bullet}$ was not registered in any case. In all the prepared derivatives, the peaks which we attributed to the following fragmentations (the maximum relative intensities I_r/% are given in brackets) were observed: A = $[M - O^{\bullet}]^+$ (29), B = $[M - H_3C{-}CH{=}CH_2]^{+\bullet}$ (6), C = = $[A - CH_3(CH_2)_9\dot{C}H_2]^{+\bullet}$ (11), D = $[A - CH_3(CH_2)_{10}\dot{C}H_2]^{+\bullet}$ (22), E = = $[M - CH_2ClCHO]^{+\bullet}$ (72), F = $[E - H_2C{=}CRR^1]^{+\bullet}$ (100), G = $[A - R^{\bullet}]^{+\bullet}$, resp. $[A - R^{1\bullet}]^{+\bullet}$ (14). In the mass spectrum [2], nonoxidized oxazolidine ring is splitted otherwise than corresponding amine oxide (fragmentation E and F). Fragmentations C and D occurred both in oxazolidines and in their amine oxides.

Classical DC polarography [13] was used for determination of the analytical concentrations of amine oxides of oxazolidines in aqueous solutions. This method is suitable for observation of thermal and acid-base stability of these compounds and more details will be published elsewhere. On the basis of polarographic measurements we can state that aqueous solutions of amine oxides of 2,2,3-trialkyl-5-chloromethyloxazolidines are stable in the region of pH 2 to 8 and at the temperatures up to 50 °C. For example, amine oxide of 2,2-dimethyl-3-dodecyl-5-chloromethyloxazolidine loses at 50 °C about 8 % of polarographic activity in the course of 30 min.

At measurement of critical micellar concentrations C_k of aqueous solutions of amine oxides of oxazolidines, we took into account the fact that arising micelles cause changes of physical properties of solution in the narrow concentration range near C_k. The C_k values we obtained from the graphical dependence of surface tension on concentration $\varkappa = f(\log c)$ or from the measurement of concentration changes of absorbance of amine oxide aqueous solutions using benzopurpurine 4B as a dyestuff [14]. The results of both these methods coincided in order, however the second method is applied only for orientation. The C_k and $\varkappa_k$ values ($\varkappa_k$ is the value of surface tension at concentration C_k) of the prepared amine oxides are given in Table 1. The best results (the lowest values of C_k and $\varkappa_k$) were measured in the case of aqueous solution of amine oxide of

Table 1

C_k and $\varkappa_k$ values of aqueous solutions of the prepared amine oxides *I*

Compound	R	R^1	R^2	C_k		$\varkappa_k$
				ϱ/(g dm^{-3})	c/(mmol dm^{-3})	mN m^{-1}
Ia	H	H	Dodecyl	0.42	1.31	31.6
Ib	CH_3	H	Dodecyl	0.40	1.25	30.1
Ic	CH_3	CH_3	Hexyl	—	—	—
Id	CH_3	CH_3	Octyl	1.30	4.68	44.9
Ie	CH_3	CH_3	Decyl	0.42	1.37	26.3
If	CH_3	CH_3	Dodecyl	0.35	1.05	23.4
Ig	CH_3	CH_3	Tetradecyl	0.38	1.05	24.2
Ih	CH_3	CH_3	Hexadecyl	0.42	1.08	29.1
Ii	CH_3	CH_3	Octadecyl	0.48	1.15	33.2
Ij	CH_2CH_3	CH_3	Dodecyl	0.38	1.09	27.0
Ik	$COCH_3$	CH_3	Dodecyl	1.08	2.98	40.3
Il	CH_2COCH_3	CH_3	Dodecyl	1.21	3.22	44.2
Im	$CH(OCH_3)_2$	CH_3	Dodecyl	1.15	2.92	41.8
In	CH_2OH	CH_3	Dodecyl	0.45	1.29	32.9
Io	CH_2OH	CH_2OH	Dodecyl	0.43	1.17	32.0
Ip	CCl_4	H	Dodecyl	1.05	2.48	40.6

Table 2

Antimicrobial activity (MIC/(μg cm^{-3})) of the prepared amine oxides *I*

Compound	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*
Ia	9	80	500
Ib	9	60	300
Ic	290	> 1000	> 1000
Id	50	70	70
Ie	7	30	30
If	7	30	20
Ig	4	40	20
Ih	20	590	100
Ii	50	> 1000	200
Ij	20	100	80
Ik	50	150	300
Il	80	400	550
Im	40	300	500
In	8	250	90
Io	2	150	60
Ip	30	300	300
Septonex	2	20	0.8

2,2-dimethyl-3-dodecyl-5-chloromethyloxazolidine. Therefore, the series of amine oxides of 2,2-dimethyl-3-alkyl-5-chloromethyloxazolidines *Ic—Ii* was prepared and the dependence of C_k and $\varkappa_k$ upon the length of alkyl chain in the position 3 was studied. The best results were found in the case of dodecyl derivative *If*. Decyl derivative *Ie* and tetradecyl derivative *Ig* have still excellent surface-active properties but the values of C_k and $\varkappa_k$ increase considerably in the case of derivatives with longer and shorter alkyls. It was impossible to find out the C_k value of hexyl derivative *Ic* from the graph $\varkappa = f(\log c)$.

2,2-Dialkyl-3-dodecyl-5-chloromethyloxazolidines exhibited relatively good antimicrobial activity [2] which even increased after transformation to amine oxides. For antimicrobial activity testing, three characteristic species of microorganisms were used — Gram-positive bacterium *Staphylococcus aureus*, Gram-negative bacterium *Escherichia coli* and the yeast *Candida albicans*. The results, expressed as minimal inhibitory concentration (MIC) are given in Table 2. The efficiency of currently used disinfectant Septonex — [1-(ethoxycarbonyl)pentadecyl]trimethylammonium bromide is given for comparison.

When we compare the C_k and $\varkappa_k$ values and the values of MIC on the other hand, we can state that amine oxides having the best surface-active properties exhibit also the highest antimicrobial efficiency. Decyl, dodecyl, and tetradecyl derivatives were the most effective. Amine oxides with longer or shorter alkyl chain exhibited essentially lower values of MIC.

As it follows from the mentioned results, amine oxide of 2,2-dimethyl-3-dodecyl-5-chloromethyloxazolidine (*If*) could find application in liquid detergent compositions (*e.g.* for washing and simultaneous disinfection of floors, dishes, and instruments, respectively for washing of textiles) because of suitable combination of tenside and disinfecting properties. Stability of the aqueous solution of this derivative would also suit to these purposes.

Experimental

Infrared spectra of the prepared compounds were measured (liquid film) on a Perkin—Elmer 983 instrument. Mass spectra ($U = 70$ eV) were obtained on a Jeol JMS-100D spectrometer at an emission current of 300 μA, applying direct sample-introduction technique. The values of surface tension were measured on a tensiometer (Lauda). Polarographic measurements were performed on an OH-105 Radelkis polarograph. Absorbances of aqueous solutions of amine oxides were determined on a Spekol 23-G315 instrument at the wavelength $\lambda = 500$ nm.

MIC was determined by using qualitative suspension method, where selected microorganisms were suspended into aqueous solutions of tested compounds and, after the

required period (for bacteria 1—2 days, for fungi 3—4 days), a part of the suspension was inoculated on solid cultivation media (cultivation medium No. 2 for bacteria and Sabouraud's medium for fungi). After incubation, the growth of microorganisms was evaluated at different concentrations of the tested compound.

The starting oxazolidines were prepared according to the known method [2]. The other used chemicals were commercial products (Lachema, Fluka, Merck).

Amine oxides of 3-alkyl-, 2,3-dialkyl-, 2,2,3-trialkyl-5-chloromethyloxazolidines Ia—Ip

Starting oxazolidine (0.1 mol) is dissolved in ethanol (20 cm^3) and, under stirring, the solution is heated to 60 °C. Hydrogen peroxide (0.12 mol, 20 mass % aqueous solution) is added during 30 min. At this temperature, reaction mixture is stirred for next 2 h, then it is allowed to stand overnight at room temperature. Excessive peroxide is decomposed by the use of platinum black and undesirable products are extracted to ethyl acetate (20 cm^3). 1-Butanol (20 cm^3) is added to the aqueous solution of amine oxide and the mixture of solvents is removed by azeotropic distillation under diminished pressure at 40 °C. In this manner prepared amine oxide need not be purified any more [10, 15]. The yields of the reaction reach up to 90 %. For the sake of stability, it is necessary to keep these compounds in aqueous solutions, because a rapid decomposition occurs in dry conditions.

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