

Amine Oxides of Substituted 2-Phenyl-3-dodecyl-5-chloromethyloxazolidines and Their Antimicrobial and Surface-Active Properties

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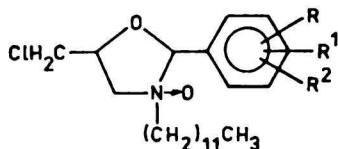
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Received 14 September 1990

Dedicated to Dr. Ing. Š. Bauer, DrSc., in honour of his 70th birthday

Thirty corresponding amine oxides were prepared by the oxidation of substituted 2-phenyl-3-dodecyl-5-chloromethyloxazolidines with hydrogen peroxide. Antimicrobial efficiency against selected microorganisms and surface tension of aqueous solutions of these compounds were determined.

Amine oxides have gained a broad range of application due to their surface-active and disinfectant properties. In cosmetic, they replace partly classical ionic and nonionic tensides, e.g. in shampoos, bath foams, shaving and depilatory creams [1]. They can be prepared by the oxidation of tertiary amines with hydrogen peroxide at temperatures of 60–80 °C. This reaction is strongly exothermic. At higher temperatures, elimination reactions occur and derivatives of hydroxylamine and olefins are formed [2]. Aqueous solutions of amine oxides are stable at temperatures up to 80 °C and at pH from 4 to 9 [3].



In our previous paper [4], preparation of substituted 2-phenyl-3-dodecyl-5-chloromethyloxazolidines was described. These oxazolidines exhibited relatively good antimicrobial efficiency especially against gram-positive bacteria [5]. However, application of these compounds was restricted by their insolubility in water, therefore antimicrobial activity testing was also necessary to perform in ethanol. On account of that, it was necessary to prepare water-soluble derivatives of these oxazolidines. The salts formed from oxazolidines and mineral acids appeared to be unsuitable because they decomposed to corresponding aldehyde and alkanol amine already by air moisture. By the oxidation of prepared oxazolidines with hydrogen

peroxide in aqueous ethanolic solution, amine oxides of substituted 2-phenyl-3-dodecyl-5-chloromethyloxazolidines I–XXX were prepared. These showed satisfactory properties as regards the solubility in water and stability. Their survey

Table 1. C_k and γ_k Values of Aqueous Solutions of the Prepared Amine Oxides I–XXX

| Compound | R | R ¹ | R ² | C_k | γ_k |
|----------|--------------------|----------------------------------|--------------------|--------------------|--------------------|
| | | | | g dm ⁻³ | mN m ⁻¹ |
| I | H | H | H | 0.52 | 32.56 |
| II | 4-CH ₃ | H | H | 0.63 | 39.03 |
| III | 2-OH | H | H | 0.60 | 36.96 |
| IV | 3-OH | H | H | 0.57 | 35.60 |
| V | 4-OH | H | H | 0.56 | 35.06 |
| VI | 2-OCH ₃ | H | H | 0.85 | 43.11 |
| VII | 3-OCH ₃ | H | H | 0.89 | 44.71 |
| VIII | 4-OCH ₃ | H | H | 0.86 | 43.84 |
| IX | 2-Cl | H | H | 1.05 | 45.73 |
| X | 3-Cl | H | H | 1.11 | 49.49 |
| XI | 4-Cl | H | H | 1.15 | 50.11 |
| XII | 2-Br | H | H | 1.30 | 49.78 |
| XIII | 3-Br | H | H | 1.38 | 50.39 |
| XIV | 4-Br | H | H | 1.36 | 50.44 |
| XV | 2-NO ₂ | H | H | 1.55 | 51.03 |
| XVI | 3-NO ₂ | H | H | 1.57 | 51.28 |
| XVII | 4-NO ₂ | H | H | 1.58 | 51.21 |
| XVIII | 2-Cl | 4-Cl | H | 1.90 | 53.14 |
| XIX | 2-Cl | 6-Cl | H | 1.89 | 52.45 |
| XX | 3-Cl | 4-Cl | H | 1.93 | 53.81 |
| XXI | 2-OH | 3-OCH ₃ | H | 1.38 | 40.39 |
| XXII | 3-OH | 4-OCH ₃ | H | 1.34 | 39.89 |
| XXIII | 4-OH | 3-OCH ₃ | H | 1.33 | 38.26 |
| XXIV | 3-OCH ₃ | 4-OCH ₃ | H | 1.40 | 47.64 |
| XXV | 4-OH | 5-OH | 3-OCH ₃ | 1.34 | 39.86 |
| XXVI | 4-OH | 3-OCH ₃ | 5-OCH ₃ | 1.42 | 48.89 |
| XXVII | 3-OCH ₃ | 4-OCH ₃ | 5-OCH ₃ | 1.76 | 51.55 |
| XXVIII | 2-OH | 3-OC ₂ H ₅ | H | 1.70 | 50.09 |
| XXIX | 4-OH | 3-OC ₂ H ₅ | H | 1.64 | 49.53 |
| XXX | 3,4-methylenedioxy | H | H | 1.78 | 51.42 |

is summarized in Table 1. These compounds are colourless viscous oils unlimitedly soluble in water, ethanol, and chloroform. They are insoluble in nonpolar solvents and acetone.

Generally, it is known that oxazolidines are easily hydrolyzable. For example, the half-time of hydrolysis of 2-pentamethyleneoxazolidine in water at pH 7 and at temperature of 37 °C is 4 s [6], in the case of 2,3-dimethyl-5-phenyloxazolidine it is 5 s at the same conditions [7]. On the other hand, amine oxides prepared by us are not hydrolyzable either during a long standing in aqueous solutions. On the contrary, when water is distilled off, these amine oxides are subjected to a fast decomposition. Polarographic measurements showed that about 50 % of amine oxide was decomposed in the course of 5 d at 25 °C.

The presence of amine oxide in the reaction mixture can be well monitored by infrared spectroscopy. Stretching vibrations of N—O bond are demonstrated by a strong absorption band at $\bar{\nu} = 960 \text{ cm}^{-1}$ [8]. In the case of oxazolidines, the bands of skeletal vibrations in the region of $\bar{\nu} = 1086\text{—}1185 \text{ cm}^{-1}$ were found [4, 9]. After oxidation to amine oxides, absorption bands were observed only in the region of $\bar{\nu} = 1070\text{—}1110 \text{ cm}^{-1}$, where mostly, it was only one absorption band, while in the case of starting oxazolidines, three characteristic bands were observed.

Mass spectra of amine oxides of oxazolidines were similar to those of starting oxazolidines. Molecular ion M^{+} was registered neither in one case. Of the whole series of the prepared amine oxides, following fragmentations were characteristic (the maximum relative intensities of peaks $I_r/\%$ are given in brackets): A = $[M - \dot{O}]^{+}$ (29), B = $[A - \dot{C}H_2Cl]^{+}$ (20), C = $[A - CH_3(CH_2)_2\dot{C}H_2]^{+}$ (16), D = $[A - CH_3(CH_2)_{10}\dot{C}H_2]^{+}$ (57), E = $[A - \dot{C}_6H_2RR^1R^2]^{+}$ (100), F = $[A - C_6H_2RR^1R^2\dot{C}H]^{+}$ (42) and mostly, the peaks corresponding to the fragmentation G = $[A - \dot{X}]^{+}$ (18) occurred, where X represented one of R, R¹, and R² substituents.

Measuring of dependence of surface tension γ on concentration of tenside in aqueous solution was used for characterization of tenside properties of the prepared amine oxides. In the region of critical micellar concentration (C_k), graphical dependence $\gamma = f(\log c)$ exhibits an expressive change and C_k can be ascertained from the point of intersection of extrapolated linear parts of the curve. The C_k and γ_k values (γ_k is the value of surface tension at concentration C_k) are given in Table 1. As it is shown, the best surface-active properties were exhibited by unsubstituted amine oxide of 2-phenyl-3-dodecyl-5-chloromethyloxazolidine (I), followed by monosubstituted hydroxy

Table 2. Antimicrobial Activity (MIC/ $\mu\text{g cm}^{-3}$) of the Prepared Amine Oxides I—XXX

| Compound | <i>Staphylococcus aureus</i> | <i>Escherichia coli</i> | <i>Candida albicans</i> |
|----------|------------------------------|-------------------------|-------------------------|
| I | 20 | 60 | 300 |
| II | 90 | 200 | 400 |
| III | 70 | 90 | 100 |
| IV | 50 | 100 | 200 |
| V | 80 | 300 | 300 |
| VI | 70 | 400 | 300 |
| VII | 60 | 300 | 400 |
| VIII | 10 | 500 | 600 |
| IX | 200 | 800 | 500 |
| X | 100 | 600 | 400 |
| XI | 7 | 200 | 100 |
| XII | 300 | 800 | 500 |
| XIII | 200 | 800 | 400 |
| XIV | 200 | 700 | 400 |
| XV | 90 | 700 | 100 |
| XVI | 50 | 400 | 100 |
| XVII | 60 | 300 | 200 |
| XVIII | 100 | 500 | 300 |
| XIX | 100 | 500 | 400 |
| XX | 300 | 900 | 800 |
| XXI | 90 | 800 | 500 |
| XXII | 8 | 400 | 500 |
| XXIII | 80 | 500 | 600 |
| XXIV | 10 | 300 | 200 |
| XXV | 30 | 600 | 800 |
| XXVI | 50 | 500 | 600 |
| XXVII | 6 | 300 | 100 |
| XXVIII | 40 | 700 | 500 |
| XXIX | 30 | 500 | 200 |
| XXX | 60 | 500 | 200 |
| Septonex | 2 | 20 | 0.8 |

derivatives III—V. These amine oxides strongly foam in aqueous solutions. For comparison of γ_k values given in Table 1, the surface tension of water is 71.8 mN m^{-1} .

As a measure of antimicrobial efficiency, minimum inhibitory concentration (MIC) was chosen. Its values for the prepared amine oxides and for [1-(ethoxycarbonyl)pentadecyl]trimethylammonium bromide (Septonex), which was tested as a standard, are given in Table 2. On the basis of the obtained results, it is evident that prepared amine oxides were the most effective against gram-positive bacteria *Staphylococcus aureus* where three derivatives (XI, XII, and XXVII) exhibited MIC lower than $10 \mu\text{g cm}^{-3}$ and further nineteen amine oxides showed MIC lower than $100 \mu\text{g cm}^{-3}$. With regard to the gram-negative bacteria *Escherichia coli* and fungi *Candida albicans*, the efficiency was essentially lower — in the first case, only three and in the second one only five amine oxides reached the value of MIC up to $100 \mu\text{g cm}^{-3}$.

In our previously published series of amine oxides of 2,2,3-trialkyl-5-chloromethyloxazolidines [10] we have found that amine oxides having the

best surface-active properties exhibited also the best antimicrobial efficiency. In the case of those amine oxides where variously substituted phenyl is in the position 2, such dependence was not observed. Surprisingly, incorporation of halogens and nitro group into phenyl did not increase antimicrobial efficiency. Only 4-chloro derivative *XI* exhibited good antimicrobial efficiency against all three species of the used microorganisms.

As seen from Table 2, Septonex exhibits much better disinfecting properties. However, its surface-active properties are not as good as in the case of our amine oxides of oxazolidines. Just the combination of surface-active and antimicrobial properties represents the greatest advantage of the described compounds. Therefore, it would be possible to apply them as additives into cosmetic products, where besides improvement of their tenside properties, they could have an effect on undesirable microorganisms. A possibility of their application in tenside mixtures suitable for detergency, fat-removal, and disinfection of strongly contaminated areas is also eligible.

EXPERIMENTAL

Infrared spectra were measured (liquid film) on a Perkin—Elmer G-983 instrument. Mass spectra ($U = 70$ eV) were obtained on a Jeol JMS-100D spectrometer at an emission current of 300 μ A, applying direct sample-introduction technique. The values of surface tension were obtained on a tensiometer (Lauda).

MIC was determined by using qualitative suspension method [10].

The starting 2-phenyl-3-dodecyl-5-chloromethyl-oxazolidines were prepared by the cyclic condensation of 1-dodecylamino-3-chloro-2-propanol with variously substituted benzaldehydes according to the known method [4, 11, 12]. The other used chemicals were commercial products (Lachema, Brno; Fluka, Buchs; Merck, Darmstadt).

Amine Oxides of Substituted 2-Phenyl-3-dodecyl-5-chloromethyloxazolidines I—XXX

To the corresponding oxazolidine (0.1 mol) dissolved in ethanol (20 cm³), hydrogen peroxide

(0.12 mol, 30 mass % aqueous solution) was added. Reaction mixture was preheated to 60 °C and during the reaction, owing to its exothermic character, temperature started to rise gradually. At about 75 °C, it is necessary to begin cooling so that temperature would not step over 80 °C. After 30 min, temperature began to fall and it was necessary to keep it at 60—70 °C for additional 90 min by means of external heating. Then the reaction mixture was left to stand for 10 h at room temperature. Excessive peroxide was destroyed by the use of platinum black and undesirable by-products were extracted by ethyl acetate (20 cm³). 1-Butanol (20 cm³) was added to the aqueous solution of amine oxide and the mixture of solvents was removed by azeotropic distillation under diminished pressure at 40 °C. The yields of products were about 80 %. Distillation residue, which represents pure amine oxide, must be kept in aqueous or ethanolic solution [13].

Acknowledgements. The authors thank Dr. M. Kačuráková and A. Gembická (Institute of Chemistry, Slovak Academy of Sciences, Bratislava) for measurements of IR and mass spectra.

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Translated by M. Kočš