Preparation and characteristics of some 2,5- and 2,3,5-substituted oxazolidines

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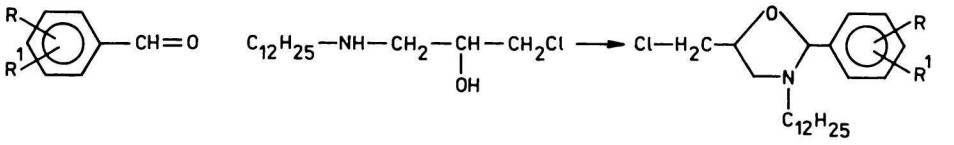
Fifteen new 2,5-disubstituted and 2,3,5-trisubstituted oxazolidines were prepared using the reaction of an aldehyde, ammonia and chloromethyloxirane, or of aldehyde and 1-amino-2-alkanol in the presence of an acidic catalyst. The structure of the synthesized compounds was determined from the IR and mass spectra.

Было приготовлено 15 новых 2,5-дизамещенных или 2,3,5-тризамещенных оксазолидинов реакцией альдегида, аммиака и хлорметилоксирана или альдегида и 1-амино-2-алканола в присутствии кислого катализатора. Структура полученных соединений была определена с помощью инфракрасных и масс-спектров и элементарного анализа.

Oxazolidines represent a group of heterocyclic compounds relatively frequently discussed in the literature from the point of view both of their structure and biological activities. The unstable heterocyclic ring of the oxazolidines and the possibility of tautomeric Schiff base formation during their preparation is the cause of difficulties at purification, study, and characterization of synthesized products [1, 2]. The oxazolidines are interesting also in relation to the antibacterial activity of some of their derivatives [3—5]. This was the main cause why we have synthesized them.

In this paper, the preparation and the characterization of some new 2,5-disubstituted and 2,3,5-trisubstituted oxazolidines is described. Two most frequently used methods were applied for their preparation [6—13]: the reaction of chloromethyloxirane with an aldehyde and ammonia, or the reaction of 1-amino-2-alkanol (in this case 1-dodecylamino-3-chloro-2-propanol) with the aldehyde in the presence of an acidic catalyst (Scheme 1). Chloromethyloxirane was used as one starting component because its oxirane group enables to synthesize oxazolidines in the known way. A further cause was its reactive —CH_2Cl group,



Scheme 1

Reaction of substituted benzaldehydes with 1-dodecylamino-3-chloro-2-propanol to substituted 2-phenyl-3-dodecyl-5-chloromethyl oxazolidine

suitable for substitutions, transforming it into a hydrophilic group. The scope of this work was the preparation of water-soluble, preferably surface- and antimicrobial-active compounds. Therefore, the 1-(*N*-dodecylamino) derivative was also used, giving with its alkyl group a hydrophobic chain in the final molecule.

The results of elemental analyses, yields, and melting points of the synthesized compounds are summarized in Table 1. Spectral data are given in Table 2.

As can be seen from the results, the substituted benzaldehydes give lower yields of oxazolidines when using the first method of synthesis (reaction of chloromethyloxirane with ammonia) than unsubstituted benzaldehyde, giving an 80 % yield [6]. In the case of substituted benzaldehydes, the yields were depending on the nature and position of the substituent. While the yield with 2-hydroxybenzaldehyde was relatively good (*ca.* 70 %), no corresponding oxazolidines could be prepared using 4-hydroxy- or 4-hydroxy-3-methoxybenzaldehyde. Only high-molecular resins were formed and these were not further investigated. Trials to prepare oxazolidines from an aliphatic amine or from aniline instead of ammonia were not successful. Similarly, when an aliphatic aldehyde was used instead of benzaldehyde, no oxazolidine was formed.

According to the second method, a catalytic amount of 4-toluenesulfonic acid was used for cyclization of 1-amino-2-alkanol with the carbonyl compound. Reaction water was distilled off as an azeotropic mixture. The yields of product were higher than with the first method. Also in this case, the yields of oxazolidines, prepared using 4-OH-substituted benzaldehydes were lower. All synthesized oxazolidines but the compound *IX* were viscous, not distillable oils, which were purified chromatographically on an alumina column (elution solvent benzene—methanol (volume ratio = 20:1)). We tried to prepare the oxazolidines *VII—XV* by refluxing not-alkylated oxazolidines *I—VI* with dodecyliodide in ethanol. Irrespective of the refluxing time, only the starting, unreacted oxazolidines were obtained from the reaction mixtures.

The oxazolidinium chlorides of *VII—XV* prepared by introducing of dry HCl into the oxazolidine solution in ether, represented very hygroscopic deliquescent compounds. We could not determine the melting point of these compounds,

Table 1
Characterization of the prepared oxazolidines

Compound	R	R^1	R^2	Formula	M_r	w_i(calc.)/% / w_i(found)/%			Yield %	M.p. °C
						C	H	N		
I	2-OH	H	H	$C_{10}H_{12}ClNO_2$	213.55	56.21	5.62	6.56	70	52—53
						56.02	5.81	6.38		
II	3-NO_2	H	H	$C_{10}H_{11}ClN_2O_3$	242.55	49.48	4.54	11.55	74	151—152
						49.37	4.70	11.58		
III	4-NO_2	H	H	$C_{10}H_{11}ClN_2O_3$	242.55	49.48	4.54	11.55	57	83—84
						49.31	4.65	11.49		
IV	4-OCH_3	H	H	$C_{11}H_{14}ClNO_2$	227.56	58.02	6.15	6.15	70	63—64
						57.98	6.39	6.05		
V	4-$N(CH_3)_2$	H	H	$C_{12}H_{17}ClN_2O$	240.57	59.91	7.07	11.64	62	111—112
						59.80	7.16	11.61		
VI	4-$N(CH_3)_2$	3-NO_2	H	$C_{12}H_{16}ClN_3O_3$	285.57	50.47	5.60	14.71	66	80—81
						50.38	5.68	14.66		
VII	H	H	X[a]	$C_{22}H_{36}ClNO$	365.67	72.26	9.84	3.83	81	*b*
						72.11	9.92	3.80		
VIII	2-OH	H	X	$C_{22}H_{36}ClNO_2$	381.67	69.23	9.43	3.67	76	*b*
						69.19	9.54	3.61		
IX	3-NO_2	H	X	$C_{22}H_{35}ClN_2O_3$	410.67	64.34	8.52	6.82	85	47—48
						64.30	8.59	6.79		
X	4-OH	H	X	$C_{22}H_{36}ClNO_2$	381.67	69.23	9.43	3.67	65	*b*
						69.12	9.55	3.60		
XI	4-NO_2	H	X	$C_{22}H_{35}ClN_2O_3$	410.67	64.34	8.52	6.82	77	*b*
						64.24	8.63	6.80		
XII	4-OCH_3	H	X	$C_{23}H_{38}ClNO_2$	395.68	69.81	9.60	3.54	85	*b*
						69.78	9.67	3.51		
XIII	4-$N(CH_3)_2$	H	X	$C_{24}H_{41}ClN_2O$	408.69	70.53	10.03	6.85	81	*b*
						70.39	10.14	6.81		

Table 1 (Continued)

Compound	R	R^1	R^2	Formula	M_r	w_i(calc.)/% / w_i(found)/% C	H	N	Yield %	M.p. °C
XIV	4-$N(CH_3)_2$	3-NO_2	X	$C_{24}H_{40}ClN_3O_3$	453.69	63.53 63.42	8.82 8,89	9.26 9.18	83	*b*
XV	4-OH	3-OCH_3	X	$C_{23}H_{38}ClNO_3$	411.68	67.10 66.93	9.23 9.31	3.40 3.43	60	*b*

a) Dodecyl; *b*) viscous undistillable oil.

Table 2

Infrared and mass spectral data of the prepared oxazolidines

Compound	$\tilde{\nu}$/cm^{-1} — Significant bands	m/z (I_r/%) — Significant peaks
I	1198, 1150, 1090, 1058	216, 214 (2.5, 7.5), 215, 213 ($M^{+\cdot}$, 19, 55), 164 (27.5), 135 (16), 134 (100), 107 (37.5)
II	1526, 1355, 1097, 1056	244, 242 ($M^{+\cdot}$, 2.75, 8), 193 (6.5), 164 (14.7), 163 (100), 136 (5)
III	1514, 1346, 1104, 1047	244, 242 ($M^{+\cdot}$, 3.3, 11), 193 (5.8), 164 (17.3), 163 (100), 136 (6.6)
IV	1260, 1178, 1108, 1065, 1049	229, 227 ($M^{+\cdot}$, 2.6, 10.5), 178 (5), 149 (16), 148 (100), 121 (40)
V	1360, 1172, 1140, 1070	243, 241 (0.7, 2.1), 242, 240 ($M^{+\cdot}$, 4.8, 14.5), 191 (3.5), 162 (9), 161 (100), 134 (12)
VI	1538, 1347, 1170, 1130, 1070	287, 285 ($M^{+\cdot}$, 9, 37), 270, 268 (5, 19), 242, 240 (2.5, 11.5), 236 (9), 206 (100), 160 (23), 145 (10)
VII	1175, 1126, 1061	367, 365 ($M^{+\cdot}$, 2, 5.8), 290, 288 (9, 26), 212, 210 (32, 100), 198, 196 (4, 12), 106, 104 (2.8, 8)
VIII	1200, 1154, 1060	384, 382 (7.3, 23), 383, 381 ($M^{+\cdot}$, 19.8, 58), 290, 288 (13.6, 36), 228, 226 (31.7, 100), 106, 104 (15, 44)
IX	1523, 1355, 1172, 1095, 1058	412, 410 ($M^{+\cdot}$, 2.2, 6), 290, 288 (9.3, 26.6), 257, 255 (34, 100), 243, 241 (3.6, 11), 224 (8), 196 (6), 106, 104 (9.3, 26.7)
X	1218, 1158, 1104, 1060	384, 382 (2.4, 6.3), 383, 381 ($M^{+\cdot}$, 4.3, 12.5), 290, 288 (6.6, 20), 228, 226 (34.3, 100), 106, 104 (31, 96)
XI	1518, 1346, 1107, 1046	412, 410 ($M^{+\cdot}$, 1.2, 3), 290, 288 (7.3, 18), 257, 255 (32.5, 100), 243, 241 (2.8, 8), 106, 104 (8.4, 27)
XII	1254, 1170, 1111, 1065, 1043	398, 396 (3.6, 11), 397, 395 ($M^{+\cdot}$, 10, 28), 290, 288 (9, 25.7), 242, 240 (34, 100), 228, 226 (2.6, 6.5), 106, 104 (7.3, 23)
XIII	1360, 1170, 1138, 1067	411, 409 (18, 50), 410, 408 ($M^{+\cdot}$, 24.7, 62.6), 359 (33), 330 (99), 290, 288 (34.3, 100), 198 (81), 106, 104 (14.5, 44.3)
XIV	1530, 1356, 1170, 1138, 1070	456, 454 (8.3, 23.3), 455, 453 ($M^{+\cdot}$, 17.8, 49.4), 404 (21.7), 300, 298 (36, 100), 198 (35), 106, 104 (18.3, 55)
XV	1288, 1210, 1157, 1124, 1044	414, 412 (2.8, 8.7), 413, 411 ($M^{+\cdot}$, 6.3, 18), 290, 288 (9.6, 28.5), 258, 256 (33.8, 100), 106, 104 (21, 65)

because simultaneously with deliquescence also hydrolytic ring opening took place. Due to this ring opening, we did succeed under these conditions to isolate the oxazolidinium chlorides of *I—VI*.

The mass spectra ($U = 12$ eV) of all prepared oxazolidines showed peaks of molecular ions. In most cases, peaks of $[M+H]^+$ were also observed. These peaks were very strong for compounds containing OH groups in the positions 2 and 4 of the benzene ring (compounds *I*, *VIII*, and *X*). Further fragmentation depends upon the structure of the oxazolidines. In compounds not substituted on N (*I—VI*), opening of the oxazolidine ring took place. The fragment splitted off involved the group >CH— from position 5, an O atom, and the chloromethyl group. The ions $[RR^1C_6H_3CHNCH_2]^+$ formed by fragmentation represent the fundamental peaks of the mass spectra. These fundamental peaks relate oxazolidines substituted on N (*VII—XV*), except compound *XIII*, to the ions $[M - (CH_2)_{10}CH_3]^+$ formed by undecyl splitting off as a radical from the molecular ion. Relatively weak peaks prove also the fragmentation to $M^{+\cdot}—\dot{C}H_2(CH_2)_{10}CH_3$.

The IR spectra of the prepared oxazolidines show two or three bands at $\tilde{\nu} = 1086—1185$ cm^{-1}, typical for vibrations of the O—C—N bonds in the oxazolidine ring [14—16].

Experimental

4-Dimethylamino-3-nitrobenzaldehyde has been prepared by nitration of 4-dimethylaminobenzaldehyde using the known procedure with nitric acid in concentrated H_2SO_4 [17]. The other substituted benzaldehydes used, as well as chloromethyloxirane and dodecylamine were of commercial quality (Lachema, Fluka).

The melting points were determined using a Kofler hot-stage (corrected values). IR spectra (in KBr pellets; 2.0—3.0 mg sample in 400 mg KBr; liquid samples as liquid film of indefinite thickness) were measured on a Perkin—Elmer 457 apparatus. Mass spectra ($U = 12$ eV) were registered using the JMS-100D spectrometer with 300 μA emission and using the direct sample-introduction technique.

1-Dodecylamino-3-chloro-2-propanol

This compound has been prepared from chloromethyloxirane and dodecylamine according to the procedure known for 1-octylamino-3-chloro-2-propanol [18] with one exception: Hexane was used as solvent instead of Skellysolve F. The yield of product was 91 %, m.p. = 39—40 °C.

For $C_{15}H_{32}ClNO$ ($M_r = 277.60$) w_i(calculated): 64.90 % C, 11.53 % H, 5.04 % N; w_i(found): 64.99 % C, 11.61 % H, 5.11 % N.

2-Phenyl-5-chloromethyloxazolidines (I—VI)

A 2-substituted benzaldehyde (0.02 mol), concentrated aqueous ammonia (26 % NH_3, 2 cm^3, for the compounds *II* and *III* 4 cm^3 were used), and ethanol (20 cm^3) were mixed and chloromethyloxirane (2.31 g; 0.025 mol) was added during 2 h. Stirring was continued during 8 h. Ammonia and ethanol were then removed *in vacuo*, cold water (30 cm^3) added and the mixture was stirred for 1 h. The oily layer had been diluted with ether, separated from water, and petroleum ether was added to the organic layer up to turbidity. The solution in petroleum ether was decanted from the precipitated oil and this oily product gradually solidified.

2-Phenyl-3-dodecyl-5-chloromethyloxazolidines (VII—XV)

1-Dodecylamino-3-chloro-2-propanol (0.01 mol) and substituted benzaldehyde (0.013 mol) in benzene (100 cm^3; toluene was used for the preparation of the compounds *IX, XI—XIV*) were stirred. 4-Toluenesulfonic acid (0.1 g) was added to this solution and the mixture was refluxed for 5—8 h using an adapter for azeotropic water removing. After cooling, ether (100 cm^3) was added and the mixture was shaken in a separating funnel with a diluted $NaHCO_3$ solution. The organic layer was then washed with cold water to neutral reaction on an indicator paper. The solvent was distilled off *in vacuo*, the product dissolved in acetone (25 cm^3), and the obtained solution was poured into cold water (30 cm^3). After evaporation of acetone at ambient temperature, the residual oily layer was separated from water and dissolved in ether (50 cm^3). This solution was dried over Na_2SO_4, purified by chromatography on a column filled with alumina (elution mixture benzene—methanol (volume ratio = 20:1)) and the pure components were obtained from the eluted zones.

The antimicrobial activity of the prepared oxazolidines was tested against a number of gram-positive and gram-negative bacteria. The compounds *VII—XV* had MIC values = 10 ppm against gram-positive bacteria, whilst the results against gram-negative microorganisms are less expressive (MIC = 1000 ppm).

Particulars about the antimicrobial activity will be published in another paper in cooperation with the Faculty of Pharmacy, Komenský University, Bratislava.

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