Antimicrobial Activity of Quaternary Ammonium Salts of Some Saturated Heterocycloalkyl Amines [1]

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N,N-Dialkyl Ammonium Salts of Saturated Heterocyclic Amines, Antimicrobial Activity

Antimicrobial activity of N-alkyl-N-dodecylpiperidinium bromides and N-ethyl-N-dodecylheterocycloalkyl ammonium bromides (pyrrolidine, morpholine, perhydroazepine) determined on grampositive and gramnegative bacteria, yeasts and moulds, presented as minimum inhibition concentration (MIC). Comparison of the effect of change of structure: lenghtening of alkyl chain, change of heterocyclic ring. Change in the lenght of alkyl chain markedly affects the antimicrobial activity, change of heterocyclic ring has no substantial effect. The most active compounds were N-heptyl- and N-hexyl-N-dodecylpiperidinium bromides.

Organic ammonium salts are known for their marked antimicrobial effect. Their use at a large scale started after Domagk [2] published his work in 1935. Different types of such compounds are known but for the display of antimicrobial effect it is utmost necessary that at least one of the substituents on nitrogen is a long alkyl chain having from 8 – 18 carbon atoms [3], whereas the optimum efficiency is attained in the range of 12 – 16 carbon atoms. A good review of antimicrobial properties of quaternary ammonium salts and the mechanism of the action is provided by Petrocci [4]. Preparation and chemical properties are described in [5].

In connection with a study of solubilization [6 – 9] we prepared a series of organic ammonium salts derived from saturated heterocyclic amines: pyrrolidine, piperidine, morpholine and perhydroazepine by nucleophilic reaction of tertiary amines with respective 1-bromoalkane [10].

In this work we studied the dependence of antimicrobial effect on change of molecular structure and specifically the effect of change in the length of the alkyl chain (Table I) and the effect of change in the structure of heterocyclic ring (Table II).

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Table I. Antimicrobial activity of 1-alkyl-1-dodecylpiperidinium bromides (MIC in μg/ml).

No.	R	A	B	C	D	E	F	G
1	methyl	10	1	30	30	2	10	20
2	ethyl	10	2	30	20	1	10	50
3	propyl	10	5	50	20	1	1	20
4	butyl	5	2	50	10	1	1	10
5	pentyl	3	1	30	6	5	7	10
6	hexyl	2	1	30	3	0.5	1	1
7	heptyl	1	1	40	4	1	1	1
8	oktyl	6	7	40	9	9	6	2
9	decyl	0.9	0.9	200	90	4	0.6	0.6
10	allyl	10	1	20	10	1	10	20
11	cyclo-hexyl	>1000	30	300	200	80	80	>1000

Table II. Antimicrobial activity of N-dodecyl-N-ethylheterocycloalkyl ammonium bromides (MIC in μg/ml).

No.	R	A	B	C	D	E	F	G
12	pyrrolidine	3	1	20	9	1	10	10
13	morpholine	3	1	30	10	0.5	20	10
14	perhydroazepine	3	2	20	10	1	10	30

Experimental

For testing we used microorganisms: *Bacillus subtilis* Bs 8/58 (A); *Staphylococcus aureus* Oxford Mau 1/45 (B); *Escherichia coli* Eck 61/59 (C); *Salmonella minnesota* SK 99 (D); *Candida albicans* 45/53 (E); *Trichophyton terrestre* 61/62 (F) and *Microsporum gypseum* 109/56 (G). The tests were carried out by dilution method described in our preceding paper [11]. Results are presented as minimum inhibition concentration (MIC) in μg/ml.

Results and Discussion

As it is evident from the results (Table I) lengthening of the alkyl chain markedly affects the antimicrobial activity of the studied compounds while change in the structure of the heterocycle (Table II) has no considerable effect on the activity even though the derivates of pyrrolidine seem to be the most active among this group of compounds. We found that from among the series of microorganisms which were tested, the gramnegative bacteria are the least sensitive towards ammonium salts. This finding is in agreement with those of other authors [12].

We found that the most effective compounds are those which in addition to a relatively long chain (dodecyl) have an alkyl substituent of medium length (hexyl, heptyl). The decrease in the activity of compound No. 9 against *E. coli* and *S. minnesota* is, however, surprising. It is probably related to the more liphophilic character of this compound, though the possibility of steric effects also may not be ruled out.

Manifestation of steric hindrance is very prominent at substitution by cyclohexyl group which leads to a marked decrease or in some cases *(B. subtilis, M. gypseum)* to disappearance of antimicrobial activity.

Introduction of alkylene chain (allyl) into the molecule as compared to its saturated analogue (propyl) has no substantial effect on the activity.

On the basic of these results it is possible to agree with the assumption that for mono ammonium salts having alkyl (not cycloalkyl) substituent at nitrogen atom to have antimicrobial activity it is necessary that the total number of carbon atoms in molecule varied between a range of nearly 18 – 25 [13].

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