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Synthesis and Antimicrobial Activity of Some 3-(N-Arylcarboxamido)-N-benzyl halides

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Abstract Some 3-(N-arylcarboxamido)-N-benzylchlorides, bromides and iodides were synthesized by quaternization of N-arylnicotinamides with benzyl halides. N-Arylnicotinamides were obtained by acylation of aniline, 1- and 2-naphthylamines with chloride of nicotinic acid. The synthesized salts were employed in antimicrobial tests against both Gram- negative, Gram-positive bacteria and fungus using the microdilution method. Antimicrobial tests indicated that all salts have reasonable activity but the salts containing iodine anions are more active than others in the series against majority of tested bacteria and fungi strains: *Staphylococcus aureus, Escherichia coli, Shigella flexneri, Proteus vulgaris, Pseudomonas aeruginosa, Bacterium antracoides, Bacterium subtilis, S. sonnei, E. aerogenes and Candida albicans.*

Keywords 3-(N-Arylcarboxamido)-N-benzylchlorides, bromides and iodides, synthesis, antibacterial and antifungal activity

1. Introduction

Increasing resistance of bacteria to antimicrobial agents is important issue in drug development studies. The solution of this problem is to expand the variety of antimicrobial agents. Quaternary ammonium salts were previously reported to exert antimicrobial properties [1-4] and they have found applications as biocides or disinfectants [5]. Such salts belong to cationic surfactants containing quaternary nitrogen atom and anionic halogen. The mechanism of these salts action against bacterial cells is known to involve destruction bacterial lipid bilayer membranes, which constitute the bacterial cytoplastic membrane and outer membrane of bacteria. Pyridinium salts like quaternary nitrogen salts have also antimicrobial properties and adsorption properties on negatively charged solids [6]. Factors controlling their antimicrobial activity are the different aryls attached to pyridinium ring, electron density of the ammonium nitrogen atom and nature of the anionic halogen [7- 14]. The compounds with a lone electron pair on the additional nitrogen atom and oxo group displayed remarkable activity, among them the compounds having a naphthalene ring had the lowest MIC values, in other words the highest antimicrobial activity [4].

The aim of this study was to prepare a series of 3-(N-arylcarboxamido)-N-benzyl halides and to investigate the effects of structural modifications of quaternary pyridinium salts on the antimicrobial activity against Gram-positive, Gram-negative bacteria, spore, bacteria capsular and yeasts.

2. Experimental

General

^{1}H-NMR spectra were recorded on a JEOL spectrometer (90MHz) in DMSO-d_6 or $CDCl_3$ with TMS as internal reference, chemical shifts were measured in the δ scale. IR spectra of compounds were recorded as potassium bromide pellets on a Specord 75-IR instrument.

General Procedure for Synthesis of N-Arylnicotinamides **1-3**.

A mixture 0,011 mol of aniline, 1- or 2-naphthylamines, 0,011 mol nicotinic acid chloride were stirred in $CHCl_3$ (50 ml) by cooling, then the reaction mixture was refluxed for 8h, washed with 10% NaOH. The obtained precipitate was filtered and washed with cool ethanol. The crude products were crystallized from benzene to give compounds **1-3** [15]**.**

Amide **1:** Yield 58,6%; mp. 127^{o}C; IR(cm^{-1}): 3365(NH), 1705(C=O). ^{1}H-NMR($CDCl_3$): 8.43(1H,NH), 9.05(1H,d, j=1.0 Hz), 8.70(1H,d, j=4.0 Hz), 8.16(1H,dd, j=6.0 Hz), 7.14-7.62(6H,m).

Amide **2:** Yield 51.0%; mp. 136^{o}C; IR(cm^{-1}): 3310(NH), 1635(C=O). ^{1}H-NMR($CDCl_3$): 8.26(1H,NH), 9.20(1H,d, j=1.0 Hz), 8.79(1H,dd,j=1.0 Hz, j=4.0 Hz), 8.26-7.51(9H,m).

Amide **3:** Yield 44.0%; mp. 161^{o}C; IR(cm^{-1}): 3250(NH), 1625(C=O). ^{1}H-NMR($CDCl_3$): 8.43(1H,NH), 9.12(1H,d, j=1.0 Hz), 8.73(1H,dd,j=1.0 Hz, j=4.0 Hz), 8.28-7.31(9H,m).

General Procedure for Synthesis of quaternary salts **4-9**.

A mixture of the corresponding amides (0.012mol) and benzyl halides (0.012mol) were refluxed in benzene (50ml) for 8h. The mixture was cooled to room temperature and the obtained precipitate was filtered and washed with benzene to give salts **4-9.**

Salt **4:** Yield 74.0%; mp.119^{o}C; IR(cm^{-1}): 3340(NH), 1700(C=O). ^{1}H-NMR(DMSO-d_6): 3.28(2H, s,CH_2), 10.29(1H, NH), 9.17(1H,d, j=1.0 Hz), 8.74(1H, dd, j=4.0, j=1.0), 8,30(1H, dd, j=6.0 Hz, j=1.0 Hz), 7.73-7.08(11H,m).

Salt **5:** Yield 67.0%; mp.128^{o}C; IR(cm^{-1}): 3340(NH), 1680(C=O). ^{1}H-NMR(DMSO-d_6): 3.71(2H, s,CH_2), 10.61(1H, NH), 9.10(1H,d, j=1.0 Hz), 8.75(1H, dd, j=4.0, j=1.0), 8.49-7.48(14H,m).

Salt **6:** Yield 72.0%; mp.148^{o}C; IR(cm^{-1}): 3350(NH), 1670(C=O). ^{1}H-NMR(DMSO-d_6): 3.52(2H, s,CH_2), 10.80(1H, NH), 9.23(1H,d, j=1.0 Hz), 8.84(1H, dd, j=4.0, j=1.0), 8.54-7.41(14H,m).

Salt **7:** Yield 40%; mp.165^{o}C; IR(cm^{-1}): 3388 (NH), 1680 (C=O) . ^{1}H-NMR(DMSO-d_6): 3.62(2H, s,CH_2), 10.67(1H, NH), 9.13(1H,d, j=1.0 Hz), 8.64(1H, dd, j=4.0, j=1.0), 8.55-7.44(14H,m).

Salt 8**:** Yield 71,3%; mp.160^{o}C; IR(cm^{-1}); 3320(NH), 1660 (C=O) . ^{1}H-NMR(DMSO-d_6): 4,10(2H, s,CH_2), 10.65(1H, NH), 9.43(1H,d, j=1.0 Hz), 8.51(1H, dd, j=4.0, j=1.0), 8.44-7.49(14H,m).

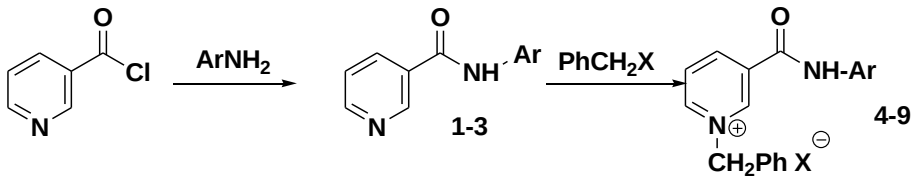
Salt **9:** Yield 76,8%; mp.232^{o}C; IR(cm^{-1}); 3360(NH), 1650 (C=O) . ^{1}H-NMR(DMSO-d_6): 4,16(2H, s,CH_2), 10.41(1H, NH), 9.32(1H,d, j=1.0 Hz), 8.48(1H, dd, j=4.0, j=1.0), 8.40-7.52(14H,m).

Antimicrobial Activity

The salts **4-9** were evaluated for antimicrobial activity toward the bacteria and fungus. The bacterial strains represent important Gram positive and Gram negative species, which are *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, fungus Candida albicans* and others. The antibacterial activities were assessed by measuring minimum inhibitory concentration (MIC) with standard broth dilution assay (Table 1). All the synthesized salts were weighed, dissolved in DMSO and diluted with water to prepare the stock solutions. The bacterial suspension was added to each probe with a final DMSO concentration. Each experiment was carried out in duplicate [16].

3. Results and Discussion

3-(N-Arylcarboxamido)-N-benzyl halides were prepared in two steps. In the first step aniline, 1- and 2-naphthylamines were refluxed with nicotinic acid chloride in $CHCl_3$ to obtained the corresponding amides **1-3**. In the last step the final compounds **4-9** were obtained by quaternization of amides **1-3** with benzyl halides in benzene under reflux. These transformations are shown in Scheme 1:



*Scheme 1: Synthesis of 3-(N-Arylcarboxamido)-N-benzyl halides **4-9***

The structures of all final compounds **4-9** were determined by spectral analyses and the spectroscopic properties were in accord with proposal structures. The IR spectra of the compounds 4-9 showed intense absorption band within 750-760, 1680-1715 and 3370-3380 cm^{-1} that were attributed to NH and C=O function vibrations respectively. Singlets of NH-group proton at 6.03-6.12 ppm and of the methylene protons of benzyl radical at 3.11-3.61 ppm are presented in ^{1}HNMR spectra of these salts.

The salts **4-9** were evaluated for antimicrobial activity toward the bacteria and fungus: *Staphylococcus aureus, Escherichia coli, Shigella flexneri, Proteus vulgaris, Pseudomonas aeruginosa, Bacterium antracoides, Bacterium subtilis, S.sonnei, E.aerogenes and Candida albicans.* The antibacterial activities were assessed by measuring minimum inhibitory concentration (MIC) with standard broth dilution assay (Table 1).

Table 1: Antibacterial activity of salts **4-9** (MIC) in μg/ mL

Salt No	***S. aureus***	***E. coli***	***P. aeruginosa***	***P. vulgaris***	***B. antracoides***	***B. subtilus***	***S. flexneri***	***S. sonnei***	***E. aerogenes***	***C. albicans***
4	125	125	125	125	62,5	125	62,5	125	125	125
5	31,25	125	125	125	31,25	62,5	62.5	31.25	250	125
6	62,5	62,5	62,5	125	125	62,5	62,5	15,6	125	62,5
7	62,5	125	125	62,5	125	62,5	125	62,5	125	52,5
8	15,6	15,6	31,25	31,25	31,25	31,25	15,6	15,6	15,6	31,25
9	15,6	15,6	31,25	31,25	15,6	31,25	15,6	15,6	15,6	15,6

As can be seen from Table 1, all synthesized salts **4-9** have sufficiently antimicrobial activity against tested bacteria and fungus. Although chloride and bromide are two different counter ions, their impact on antimicrobial properties seems to be minimal based on the results of tests. The salts **8-9** containing iodide atoms are the most active than the chloride and bromide containing salts **4-7** in the series against majority tested bacteria strains. The highest antimicrobial activity was achieved from the naphthoylamino derivate, the compound possessing the largest aromatic group. The benzoylamino derivate **4** showed similar but slightly weaker activity compared with that of naphthoylamino derivates **5-6**. It is known [6], that the ability of quaternary ammonium salts to interact with the hydrophobic cell membrane of a bacterium is determined by structure of hydrophobic alkyl- or aryl chain. The affinity between of such salts with the lipid bilayer of outer membrane lead to rapid interaction and therefore kill to bacteria. The naphthoyl or benzoyl may improve interaction and penetration of the pyridinium salts through the bacterial membranes and increase biocidal power of such salts. The above results confirmed that the structure of salts **4-9** could improve antimicrobial activity.

Conclusion

In summary, we have synthesized some 3-(N-arylcarboxamido)-N-benzyl halides by means of simply methods using accessible reagents. The structures of these compounds were determined by IR- and ^{1}H-NMR spectra. Synthesized salts were employed in antimicrobial tests against both Gram- negative, Gram-positive bacteria and fungus using the microdilution method. Antimicrobial tests indicated that all salts have reasonable activity but the salts containing iodine anions are more active than the salts containing chloride and bromide anions in the series against majority of tested bacteria and fungi strains: *Staphylococcus aureus, Escherichia coli, Shigella flexneri, Proteus vulgaris, Pseudomonas aeruginosa, Bacterium antracoides, Bacterium subtilis, S.sonnei, E.aerogenes and Candida albicans.*

The present study showed the relationship between antimicrobial activity and structure of 3-(N-arylcarboxamido)-N-benzyl halides.

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