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Effect of Structure of Nucleophile and Substrate on the Quaternization of Heterocyclic Amines

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Abstract—The influence of the nature of the quaternizing agent and substrate on the quaternization of heterocyclic amines, derivatives of pyridine, β-picoline, nicotinamide, pyridoxine, was studied. The synthesized compounds were characterized by IR spectroscopy and elemental analysis. The conclusions were made about the effect of the structure of nucleophile and substrate on the process of quaternization reaction.

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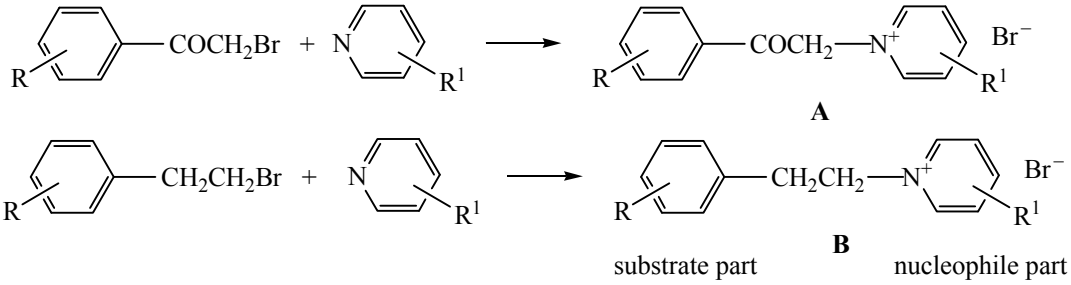
Quaternary salts of heterocyclic amines like pyridine and its homologues have a wide range of therapeutic effects and since nineteen forties have been used as antibacterial and anticarcinogenic agents [1]. Since the reaction of formation of such salts (exhaustive alkylation of amines) belongs to the reaction of nucleophilic substitution (S_N2), the yield of the target product and the reaction rate in general are affected by the structure of both reagents.

We investigated the influence of the nature of the nucleophiles and substrates of different structure on the quaternization reaction rate. The reaction rate was measured by the yield of the product and by comparing the data with the theoretical analysis of the molecular structure.

As the nucleophiles we selected pyridine (**I**), β-picoline [3-methylpyridine (**II**)], nicotinamide (**III**), and pyridoxine (**IV**), and as the substrates were taken haloketones and haloalkyls: phenacyl bromide (**V**), *n*-methoxyphenacyl bromide (**VI**), and β-phenylethyl bromide (**VII**). All the synthesized salts have a similar structure: two aromatic rings separated by two carbon atoms, but differing in the nature of substituents in both rings (structures **A** and **B**). The reaction proceeds according to the following scheme:



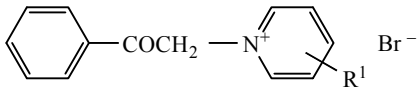
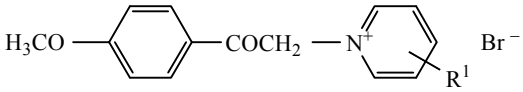
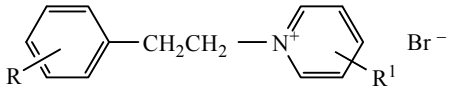
Nucleophiles: pyridine (**I**), 3-methylpyridine (**II**), pyridine-3-carboxamide (**III**), pyridoxine [4,5-bis-(hydroxymethyl)-2-methylpyridine-3-ol] (**IV**).

Substrates: phenacyl bromide (**V**), *n*-metoxy-phenacyl bromide (**VI**), and β-phenylethyl bromide (**VII**).

Quaternary salts were obtained by the reaction of an amine and a quaternizing agent in anhydrous alcohol for 0.5–15 h (depending on the activity of the reagents). Yields and constants of the salts are given in Table 1.

Our experimental data on the synthesis of quaternary salts of heterocyclic amines are consistent with

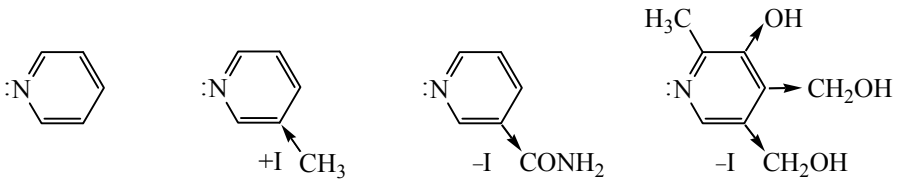
Table 1. Yields and constants of quaternary salts of heterocyclic amines

Run no.	Amine	Substrate	Yield, %	mp, °C	Formula	Elemental analysis, calculated/found, %	
						C	H
							
1	Pyridine	**V**	89	220–222 colorless prism	$C_{13}H_{12}BrNO$	56.1/56.9	4.3/4.0
2	β-Picoline		96	193–195 pale-yellow prism	$C_{14}H_{14}BrNO$	57.6/56.1	4.8/4.6
3	Nicotinamide		44	234–237 pale yellow needles	$C_{14}H_{13}BrN_2O_2$	52.3/53.1	4.1/4.8
4	Pyridoxine		40	206–208 (decomp.), pale yellow needles	$C_{16}H_{18}BrNO_4$	52.2/53.1	4.9/5.3
							
5	Pyridine	**VI**	66	223–225 (decomp.), pale yellow needles	$C_{14}H_{14}BrNO_2$	47.3/48.1	4.1/4.3
6	β-Picoline		78	216–218 pale-yellow prism	$C_{15}H_{16}BrNO_2$	48.6/48.7	4.4/4.6
7	Nicotinamide		21	238–240 white needles	$C_{15}H_{15}BrN_2O_3$	51.2/50.1	4.2/4.4
8	Pyridoxine		Следы	–	–	–	–
							
9	Pyridine	**VII**	49	125–129 colorless prism	$C_{13}H_{14}BrN$	59.0/58.4	5.3/5.8
10	β-Picoline		62	123–127 white needles	$C_{14}H_{16}BrN$	60.4/58.9	5.8/5.4
11	Nicotinamide		8	218–223 white needles	–	–	–

the theoretical notions on the structure of the nucleophile and substrate in these nucleophilic substitution reactions. Pyridine and its derivatives, in contrast to benzene, contain a nitrogen atom retaining its lone electron pair that defines the basic properties of these compounds and the possibility of formation of pyridinium ion.

Pyridine and related compounds despite their weak basic properties [K_{dis} (Py) = 1.8×10^{-9}] quite easily (as compared with aliphatic amines) enter the nucleophilic substitution reactions with the formation of quaternary salts due to greater steric accessibility of the unshared electron pair of the nitrogen atom rigidly fixed in the ring.

Since the reaction of formation of quaternary pyridinium salts is the reaction of nucleophilic substitution proceeding by S_N2 mechanism, then its rate depends on the structure of both the nucleophile and the substrate. In these reactions, heterocyclic amine acts as a nucleophile and reactivity of the amines is defined by the electron density on the nitrogen atom.

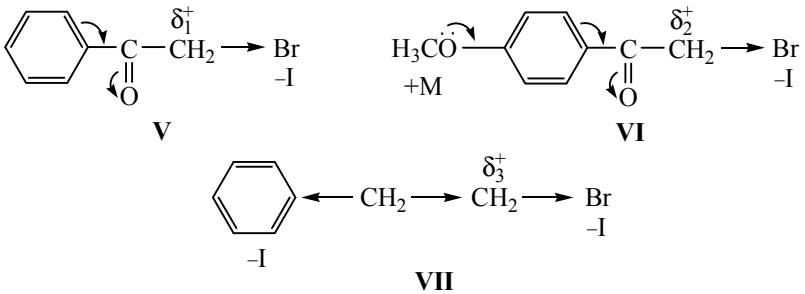


I **II** **III** **IV**

Electron-donor groups such as methyl (picoline) reinforce the basicity of pyridine: (pK_a: pyridine 5.17, β-picoline 5.68, γ-picoline 6.02) [2]. In the case of γ-picoline the substituent is in *para*-position and its influence is transmitted both by inductive and mesomeric effect, while in β-picoline only induction effect is operative [$\sigma_m(CH_3) = -0.07$). In β-picoline the electron density at the nitrogen is increased due to +*I*-effect of CH_3 [2], in nicotinamide the substituent decreases the nucleophilicity of nitrogen due to its negative inductive –*I*-effect [$\sigma_m(CONH_2) = +0.28$] [3]. All the investigated compounds by the nucleophilicity of nitrogen can be arranged in the series: **II** > **I** > **II** > **IV**. In the molecule of pyridoxine the nitrogen basicity is decreased by –*I*-effect of substituents; in addition, its reactivity is diminished by the lesser steric accessibility of the loan electron pair on the nitrogen.

The structure of the substrates also vary, which affects the ease of carbocation formation at cleavage of the C–Br bond.

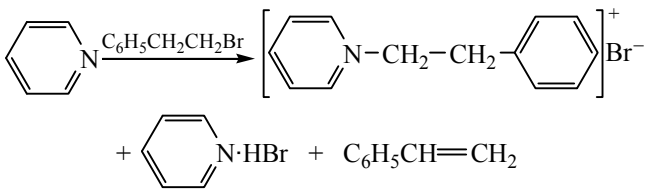
The nucleophilic substitution of halogen in the α-halo-ketones is considerably easier than in alkyl halides with the same number of carbon atoms because of the greater electrophilicity of the carbocation adjacent to the acceptor carbonyl group.



V **VI** **VII**

Depending on the value and the type of effect of substituents, all the investigated substrates by the reactivity (in terms of the carbocation charge δ^+) can be arranged in the following series: **V** > **VI** > **VII**.

It should be taken into account at carrying out the quaternization reaction that at the formation of quaternary salts an alternative elimination reaction is possible in the substrate, which leads to the formation of a olefin and N-protonated amine salt, thereby reducing the yield of the product, as occurred in the case β-phenylethyl bromide.



Our studies showed that the most reactive pair of reagents is β-picoline and phenacyl bromide (Table 1). Among the investigated amines, pyridoxine was the least reactive, probably not only because of lower nucleophilicity of nitrogen, but also because of steric hindrances. In some cases we were unable to isaolate the product, even at prolonged reaction.

Among the investigated substrates, the less reactive was the β-phenylethyl bromide. Its quaternization reaction had to be performed in a more polar solvent nitromethane, and the reaction duration was by an order of magnitude longer than in the case of phenacyl bromide. Consequently, the presence in the substrate molecule of a highly acceptor carbonyl group, as in the case of phenacyl bromide, leads to redistribution of electron density in the molecule, and the weakening of C–Br bond resulted in easier removal of the leaving group. In β-phenylethyl bromide, the inductive effect

Table 2. Characteristics of the vibration spectra of the synthesized compounds

Run no.	Characteristic absorption bands, cm^{-1}
2	δ_{C-H} (mono) 710–670
3	$\nu_{C=O}$ (amide I) 1700, 1650; ν_{N-H} 3450–3400; δ_{N-H} 1610, 1580
4	ν_{O-H} 3560–3300
5	ν_{C-O-C} 1275–1250, $\nu_{C=O}$ 1710, 1680
6	ν_{C-Car} 1620, 1500, 1400, ν_{C-Har} 3080, ν_{C-H} 2980
7	$\nu_{C=O}$ (amide I) 1710, 1690; ν_{N-H} 3400, 3350
8	–
9	ν_{C-Car} 1610, 1450; ν_{C-Har} 3095, 3020; δ_{C-Har} 720, 696
10	ν_{C-Car} 1610, 1580, ν_{C-Har} 3085, ν_{C-H} 2980
11	–

of the phenyl group (*–I*-effect) is much weaker and C–Br bond is stronger, and that defines the lower reactivity of the latter compound. It is possible that the reaction is complicated also by the elimination of HBr and the formation of an olefin.

EXPERIMENTAL

Precursors. **Substrates**: phenacyl bromide (mp 51–52°C) and *p*-metoxyphenacyl bromide (mp 69–70°C) were prepared by bromination of respective ketones, acetophenone and *p*-methoxyacetophenone, using the general procedure [4]. β-Phenylethyl bromide (1-phenyl-2-bromoethane), bp 98°C (14 mm Hg) was obtained by reaction of phenethyl alcohol with 48% hydrobromic acid according to the general procedure [5].

Nucleophiles: Pyridine (bp 115°C), β-picoline (3-methylpyridine, bp 144°C), nicotinamide (mp 129–131°C, vitamin B3, the antipellagric vitamin that belongs to the enzyme systems involved in the processes of cellular respiration) were commercial products, purified by distillation or recrystallization. Pyridoxine [adermin, 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)pyridine] was obtained from the respective hydrochloride (drug) by heating its suspension in anhydrous alcohol with an excess of $NaHCO_3$ until the cease of CO_2 release. Insoluble salt NaCl was filtered off, and the mother liquor was evaporated to dryness in a vacuum. Crystalline pyridoxine was immediately used in the synthesis. Pyridoxine, a representative of vitamins of B_6 group, is a component of enzymes involved in protein metabolism.

General procedure for preparation of quaternary salts. 0.05 mol of amine and 0.075 mol of the quaternizing agent were dissolved separately in a double volume of anhydrous alcohol. The solutions were combined and left for 30 minutes, and then heated for 0.5–1 h in a water bath. The solvent was evaporated in a vacuum, the residue was treated twice with small portions of dry cold ether to remove unreacted substances and then the salt was recrystallized from a mixture of dry ethyl acetate and ethyl alcohol (1:1). For all the synthesized salts a general test for halogen was carried out (test with $AgNO_3$) which was positive. The quaternary salts are soluble in water, alcohol, acetone, insoluble in ether. Yields and constants are listed in Table 1.

The synthesis conditions were slightly changed in the case of difficultly forming salts at the quaternization of amines with β-phenylethyl bromide. In this case more polar solvent nitromethane was used and the reaction time was increased to 15–20 h. At the quaternization of pyridoxine with β-phenylethyl bromide only trace amounts of product were obtained, which were not analyzed.

In the spectra of all investigated compounds there were absorption bands of aromatic rings (ν_{CCar} 1650, 1580, 1400; ν_{CHar} 3030, 3010 cm^{-1}). In the spectra of the derivatives there were extra absorption bands of functional groups (Table 2).

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