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SYNTHESIS OF NEW PYRIDINES AND PYRAZOLO[1,5-a]PYRIMIDINES CONTAINING BIOGENIC AND PHARMACOPHORE FRAGMENTS BY RECYCLIZATION OF THE PYRIMIDINE RING

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The review is devoted to two rearrangements of iodoalkylates of pyrimidinylacetic acid derivatives proceeding under the action of biogenic and pharmacophore-containing primary amines and carboxylic acid hydrazides. The reactions result in almost inaccessible by other ways nicotinic acid and pyrazolo[1,5-a]pyrimidine derivatives.

Figs. 3, references 76.

Introduction

Pyridine and pyrimidine derivatives are known to form the basis of many medications. Therefore, obtaining new derivatives of these heterocycles to a great extent is a guarantee for revealing biological activity in synthesized compounds. The probability of biological activity manifestation significantly increases upon introduction of pharmacophore groups or fragments of natural biogenic compounds into a molecule of a compound being synthesized.

It is known that the reactions used in medical chemistry, as a rule, are based on well-proven and simple transformations, such as the reactions of substitution, condensation, cyclization.

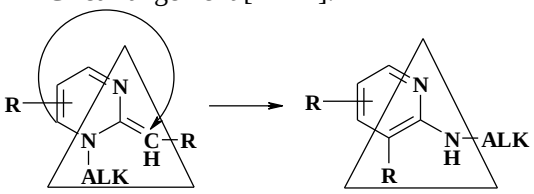
The presented review is devoted to novel, original methods of introducing pharmacophore and biogenic groups into molecules of nicotinic acid derivatives and those of condensed system of a series of pyrazolo[1,5-a]pyrimidine. Elaboration of these methods is connected with study and revealing in our laboratory novel nucleophilic recyclizations of 1,4,6-trimethyl-2-(ethoxycarbonyl)methylpyrimi-

dinium iodides proceeding under the action of such nucleophiles as various amines and hydrazine derivatives. The suggested presentation focuses on rearrangements of pyrimidinium iodide under the influence of different nitrogen-containing nucleophilic reagents proceeding through heterocycle recyclization. The described transformations result in derivatives of pyridine, 1,2,4-triazole and fused systems containing biogenic and pharmacophore fragments of the initial amine reagent.

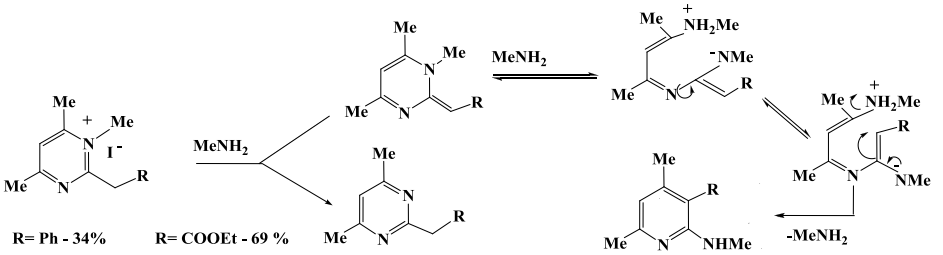
I.1.The background of work

Within the last several years the Laboratory of Nitrogenous Heterocycles of the Institute of Organic Chemistry of the Scientific Technological Centre of Organic and Pharmaceutical Chemistry NAS RA together with the Laboratory of Biologically Active Heterocycles of the Russian-Armenian University have been involved in the research of nucleophilic rearrangements of pyrimidine systems. The research is aimed at study of isomerizational recyclizations, in particular, of the so-called "enamine rearrangements" [1-8] or "Kost-Sagitullin rearrangements". These studies continue and develop the investigations started in the seventies, when was discovered the rearrangement of 1,4,6-trimethyl-2(ethoxycarbonyl)methylpyrimidinium iodide into 2-aminonicotinic acid derivatives proceeding under the action of amines, as well as recyclization of condensed pyrimidines into condensed pyridines [9-11].

Formally the recyclization proceeds with substitution of endocyclic nitrogen atom by exocyclic carbon atom. That is why to mark such recyclizations we have introduced the term N-C-rearrangement [12-14].

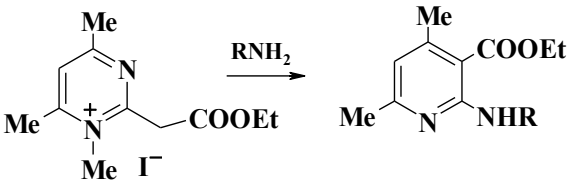


By analogy with the known Dimroth rearrangements in a series of pyrimidinium salts [15-19], where the initial nucleophilic attack is at position 6, we have proposed the scheme of the given transformation [2, 9] with the attack at position 6.

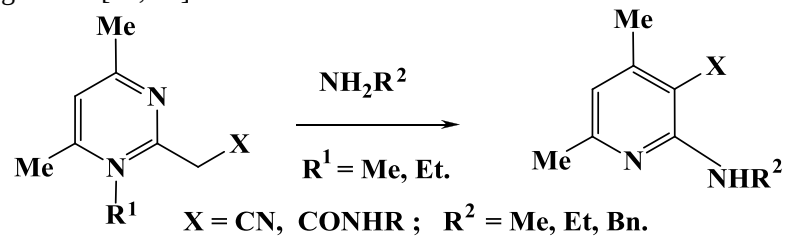


It has been shown in our laboratory that similar rearrangement of 1,2-dialkylpyrimidinium salts could also proceed under the action of various amines containing a radical other than that at a quaternized nitrogen atom of the

pyrimidinium salt [20-23]. This leads to recyclization of the pyrimidine derivative into pyridine derivative with simultaneous incorporation of the alkyl amine group of the amine reagent into the molecule of the reaction product. As a result almost inaccessible 2-alkylaminopyridines are formed that contain a fragment of the amine introduced into the reaction.



Iodomethylates of pyrimidinylacetic amides and nitriles also enter into similar rearrangements [14, 24].



X = CN, CONHR ; R^2 = Me, Et, Bn.

Experimental prove of the possibility of nucleophilic attack on the 2nd position was obtained in the process of the reaction (in cold) of pyrimidinium salt 1 with an alcoholic solution of potassium hydroxide. Intermediate product 2 was isolated, the structure of which was proved by the methods of NMR- and IR-spectroscopy and mass-spectrometry [25].

We have shown in subsequent studies that brief heating of pseudo base 2a in chloroform leads to anhydro base 3a in quantitative yield, while the complete accord of the mass spectrum of 3a with the mass spectrum previously recorded in the study of 2a (discrepancies only in the peak intensities) supports our previous proposal [25] of the loss of water upon electron impact during the recording of the mass spectrum of 2a.

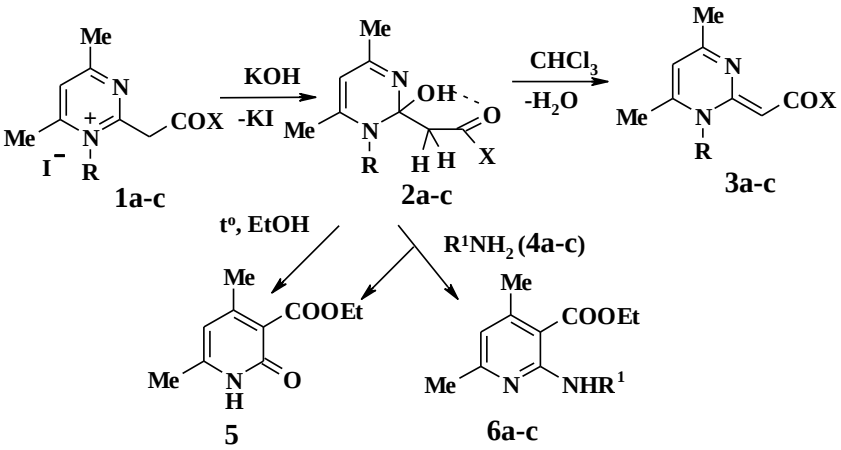
The similar attack of the hydroxide ion at C-2 in the pyrimidine ring was also noted in the reaction of 2-(ethoxycarbonyl)methyl-1-ethyl-4,6-dimethylpyrimidinium iodide (1b) with KOH, leading to pseudo base 2b, which also lost a water molecule upon heating in chloroform.

We noted that the elimination of water from pseudo base 2b upon heating in chloroform proceeded very rapidly. Thus, only anhydro base 3b was recorded in the mass spectrum and also in the ^{1}H NMR spectrum in $CDCl_3$. Products 2b and 3b differed in their physicochemical characteristics and IR spectral data, which caused to establish the structure of pseudo base 2b [26].

Heating 2-(carbamoyl)methyl-1,4,6-trimethylpyrimidinium iodide (1c) with an equivalent of KOH in absolute ethanol for 1 min led to anhydro base 3c, probably also through the intermediate formation of pseudo base 2c. Anhydro base 3c was isolated by chloroform extraction. By analogy with the previous examples, this

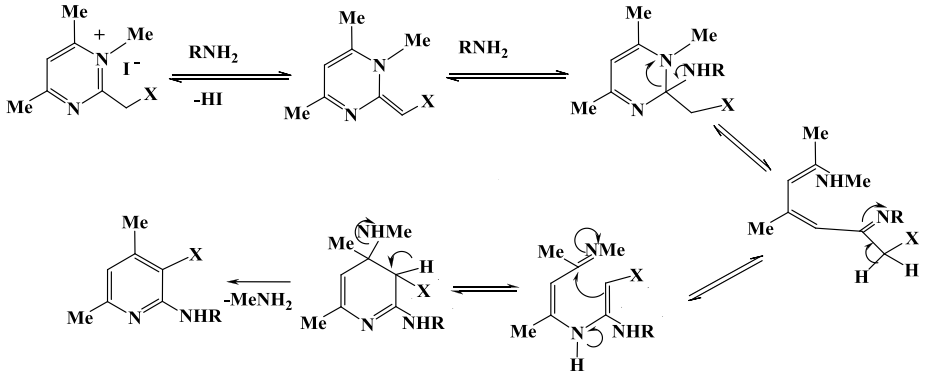
transformation also involved water elimination. The chloroform extraction was carried out to avoid side reactions occurring when using polar solvents since the intermediates of the transformation of iodide 1c do not dissolve in nonpolar solvents.

Pseudo base 2a rearranged upon heating in absolute ethanol as well as in the presence of primary amines 4a-c to give mainly pyridone 5, which was also formed in the rearrangement of 1a by the action of primary amines in an aqueous medium. The product of the normal rearrangement, 2-methylamino derivative 6a, and in the reaction with amines 4b and 4c the "product of the rearrangement with transamination" 6b and 6c were formed in small amounts. Partial demethylation also occurred, leading to pyrimidines.

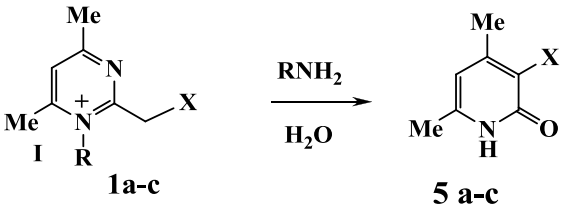


1, 2, 3: a X = OEt, R = Me; b X = OEt, R = Et; c X = NH_2, R = Me.

The assumed Scheme of the rearrangement is given below.

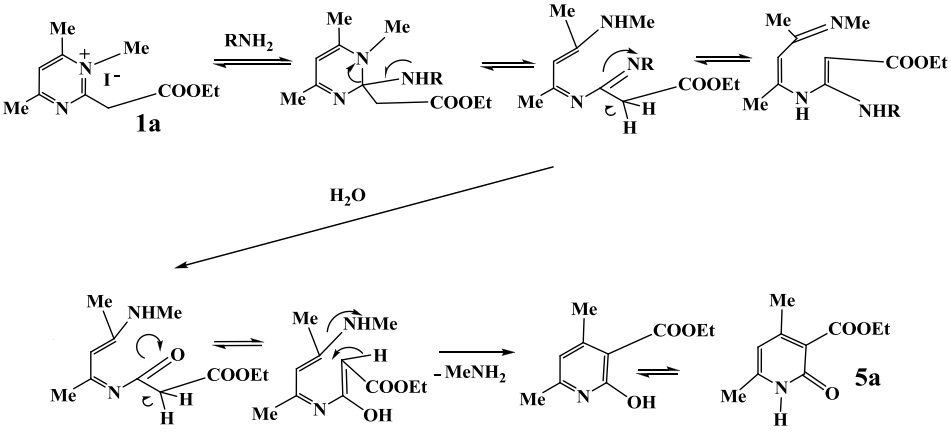


It was also shown that with recyclization of pyrimidinium salts under the action of different amines, the direction of transformation could vary depending on the presence of moisture. Thus, by interaction of salt 1 with different amines in the presence of even small amounts of water, in addition to the recyclization product with transamination substituted pyridone was also isolated [22, 27].



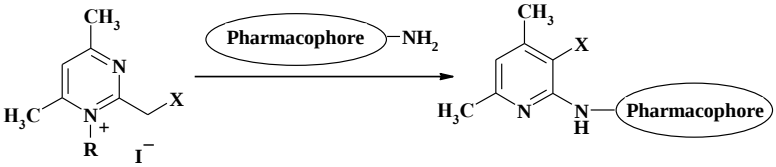
X = COOEt , $CONH_2$, CONHR .

The assumed Scheme of the rearrangement is given below.

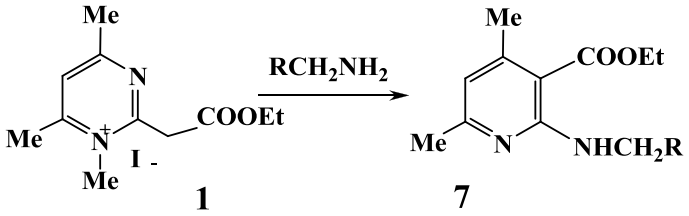


I.2. Pyrimidinium salts rearrangements under the action of biogenic amines

We have assumed that similar rearrangement with substitution of the amine moiety could also proceed by the action of various biogenic amines on the pyrimidinium salt. Such the amine moieties exchange should make this reaction suitable for the synthesis of novel biologically active pyridines. In particular, it was expected that by selection of the appropriate amines, including also biologically active ones, pharmacophore groups could be incorporated into the pyridine ring. In this case it could be possible to form easily, in one stage, almost inaccessible by other ways derivatives of biogenic nicotinic acid that also contained another biogenic moiety in the molecule, namely, moiety of the amine used in the reaction [28].



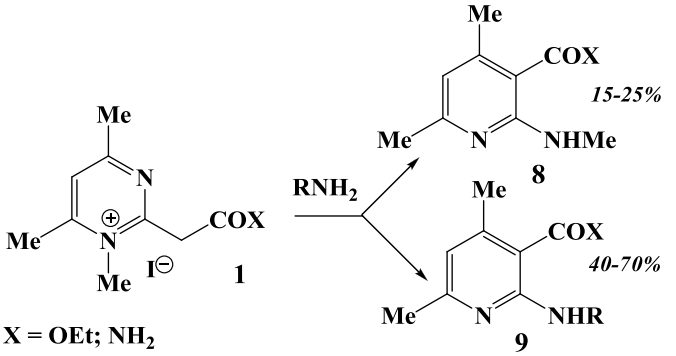
To verify this assumption, we have studied reactions of iodomethylates of some pyrimidinyl-2-acetic acid derivatives with amines containing various pharmacophore groups. In particular, we studied reactions with amino alcohols (aminoethanol, 3-aminopropanol and isomeric to it 1-amino-2-propanol). As a result 2-hydroxyethyl derivatives of substituted nicotinic ester 7 and isomeric hydroxypropyl derivatives of the same ester were obtained [29, 30].



R = CH_2OH;$CH(OH)CH_3$;CH_2CH_2OH.

The reactions with amines (ethylamine, benzylamine, *para*-isopropoxybenzylamine and cyclohexylamine) as well as with aminoether – ethoxyethylamine were carried out. As a result of the proceeding rearrangements, accompanied with amine exchange, different novel nicotinic acid derivatives were synthesized. In position 2 of the pyridine ring they contained fragments (moieties) of the amine reagent brought into the reaction [20, 21, 31, 32].

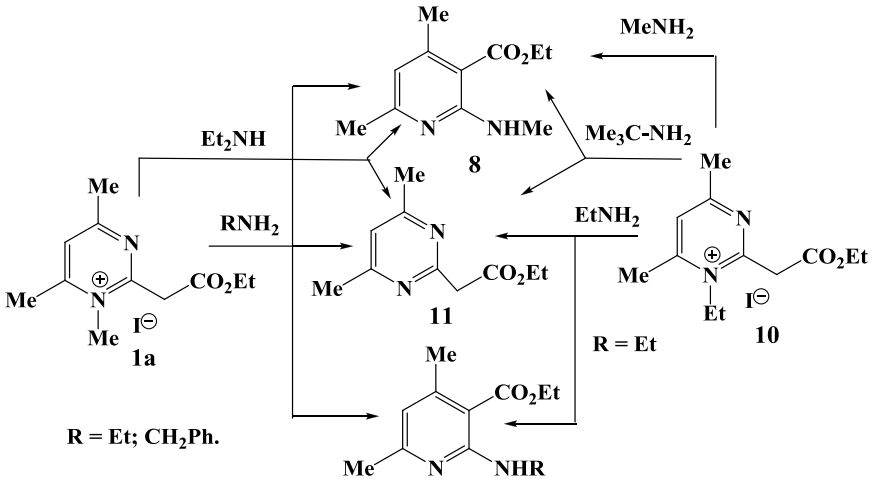
Of attention is the fact that, as a rule, the reaction of iodides 1 with amines proceeds in two directions resulting in affording the product of normal recyclization (8) and the product of "rearrangement with incorporation" into the molecule of amine reagent fragment (9). Noteworthy is also the fact that the yield of the product of "rearrangement with exchange amination" 9, as a rule, is much more than the yield of the product of normal rearrangement 8.



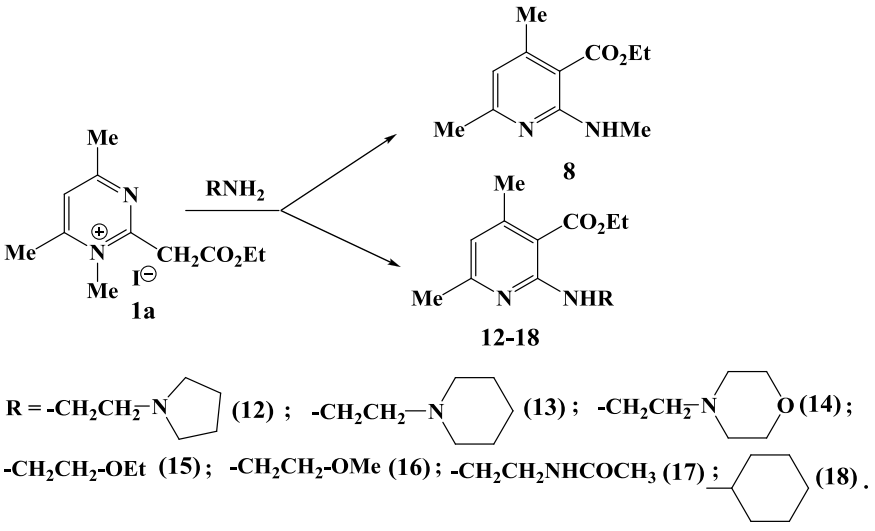
X = OEt; NH_2

R = C_2H_5, CH_2Ph, $CH_2C_6H_4$-p-$OCH(CH_3)_2$, $CH_2CH_2OC_2H_5$

The steric factor is likely to be significant in this reaction, as indicated by the high yield and formation of only the rearrangement–transamination product in the reaction of salt 10 containing an ethyl group with methylamine. In contrast, when the substituting group is bulkier than the leaving group, both possible enamine rearrangement products are formed. Furthermore, in a number of cases, the steric factor may completely prevent formation of the rearrangement–transamination product. Thus, the results of the reaction of salt 1a with diethylamine and that of iodoethylate 10 with tert-butylamine, in which rearrangement–dealkylation products are formed without rearrangement–transamination products, may be attributed to steric factors [22].



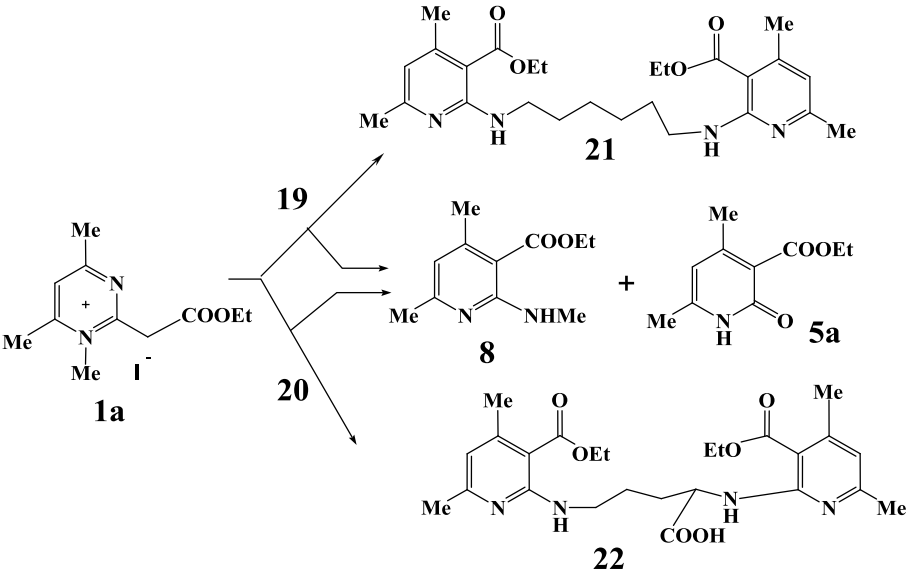
As reagents in the rearrangement were also used various derivatives of ethylamine, containing fragments of morpholine, piperidine, pyrrolidine and of other bioactive groups that are active moieties of many medications [32-34]. The rearrangement of iodide 1a under the action of indicated amines proceeded in two alternative reaction paths. This led to formation of the product of normal rearrangement 8 and the product of "rearrangement with exchange amination" 12-18. On the example of pyrrolidine, morpholine, and piperidine derivatives it was proved that, when carrying out the rearrangement of iodide 1a without a solvent at 90 ^{o}C in the excess of these primary amines, the yield of the product of "rearrangement with exchange amination" (12-14) increased, and the yield of the product of normal rearrangement 8 decreased [35].



Such increase in the yield of products of rearrangement-exchange amination was also noted upon interaction of iodide 1a with monoacetylethylenediamine and cyclohexylamine in ethanol and without a solvent [35]. Thus, if in ethanol the yield of compounds 17 and 18 made up 31% and 24%, carrying out the same reactions

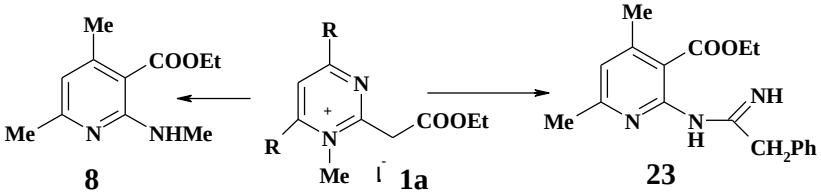
without a solvent in the excess of amine afforded products of exchange amination in the increased yield of 66% and 55%, correspondingly.

The reaction of pyrimidinium salts with such diamines as hydrazine and amidine derivatives leads to formation of pyrazole, triazole, or pyrimidine derivatives [36, 37]. We studied the reactions of 2-(ethoxycarbonyl)methyl-1,4,6-trimethylpyrimidinium iodide (1a) with hexamethylenediamine 19 and ornithine 20, which are compounds containing two primary amino groups. In both experiments, in addition to the rearrangements that are typical of these reactions (pyridine 8 and pyridine 5a, and also pyrimidine 11), compounds were isolated (21 and 22 respectively) for which the ^{1}H and ^{13}C NMR spectra and the elemental analysis data suggested participation of both amine groups in a "rearrangement with transamination." [38]. The latter was observed for the first time not only in Kost–Sagitullin rearrangements but also in the better studied Dimroth rearrangement.

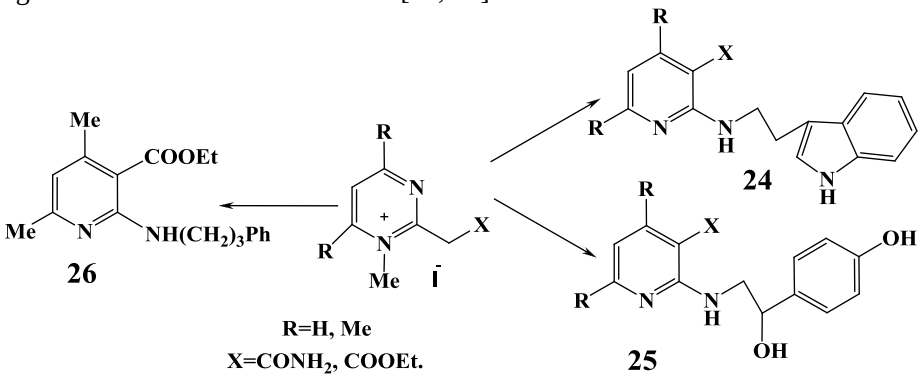


It is notable that, as it was mentioned above, in the reaction of pyrimidinium salt with monoacetylethylenediamine the recyclization proceeded at the expense of only the single nonacylated amine group (17). This can be explained by the reduced nucleophilicity of the atom of amide nitrogen.

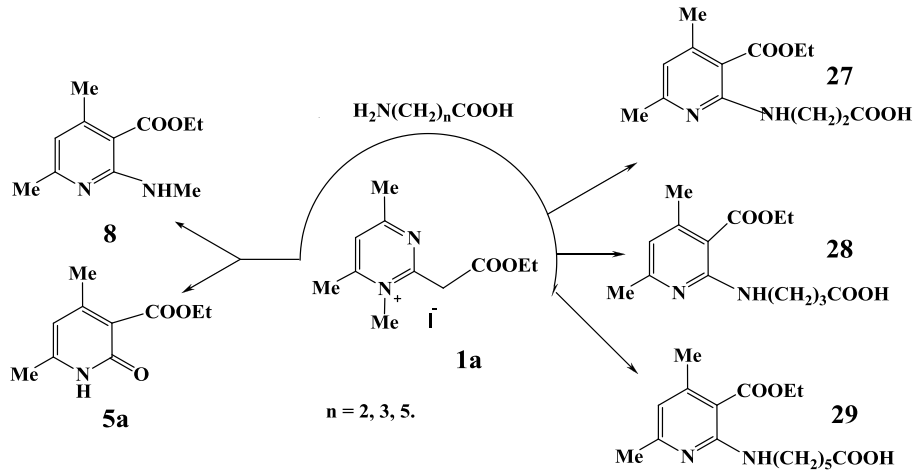
An interesting example of “rearrangement with exchange amination” is the observed transformation under the action of benzylamidine when the amidine moiety of the molecule is incorporated into the molecule of the nicotinic acid derivative and compound 23 is formed.



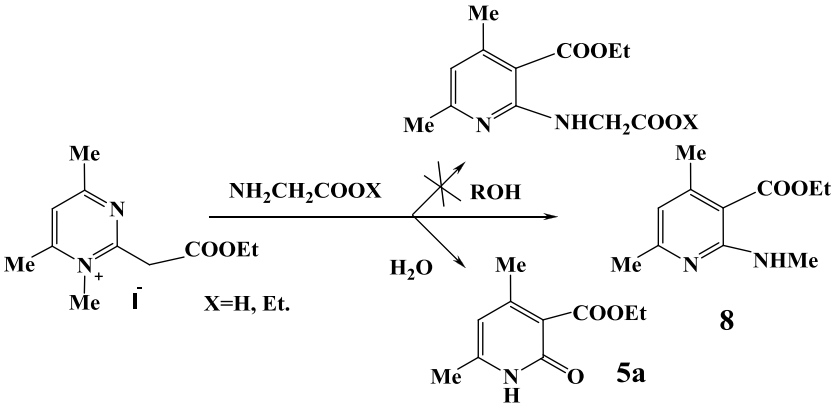
It is shown that similar “rearrangement with exchange amination” also proceeded with participation and by the action of various biogenic amines, namely, triptamine, octopamine (structural analog of noradrenaline), 3-phenylpropylamine. As a result were synthesized new derivatives of nicotinic acid 24-26 containing two active biogenic fragments in a molecule – fragment of the corresponding amine and fragment of nicotinic acid derivative [34, 39].



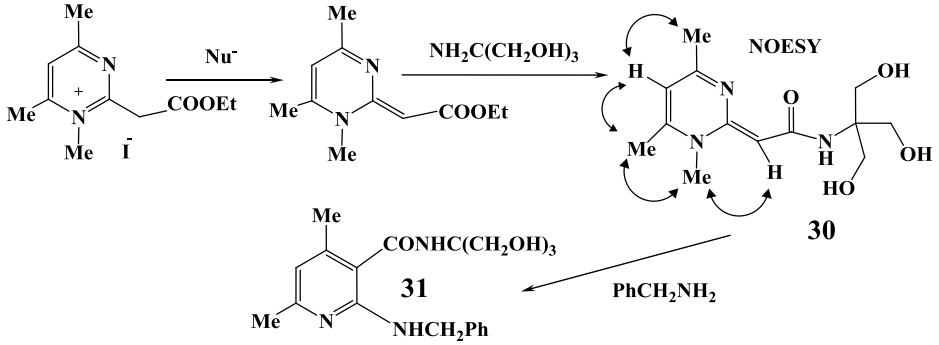
Such amphoteric amines, as aminoacids (β-alanine, γ-aminobutyric acid, and ω-aminocaproic acids) and their esters turned out to be able to undergo the reactions of “rearrangement with exchange amination” with iodide 1a. This allowed to obtain new compounds 27-29 – N-substituted amino acid derivatives containing two biogenic fragments in a molecule – fragment of the corresponding amino acid and fragment of the nicotinic acid derivative [40]. It should be mentioned that besides the nicotinic acid derivative, which contained amino acid moiety, pyridine 8 and pyridone 5a were also formed.



It is interesting that with glycine and its ester we failed to carry out rearrangement with exchange amination and the product of normal rearrangement 8 was isolated (in case of carrying out the reaction in ethanol or isobutanol), and when the reaction was carried out in water, pyridone 5a was formed in 55% yield [40].

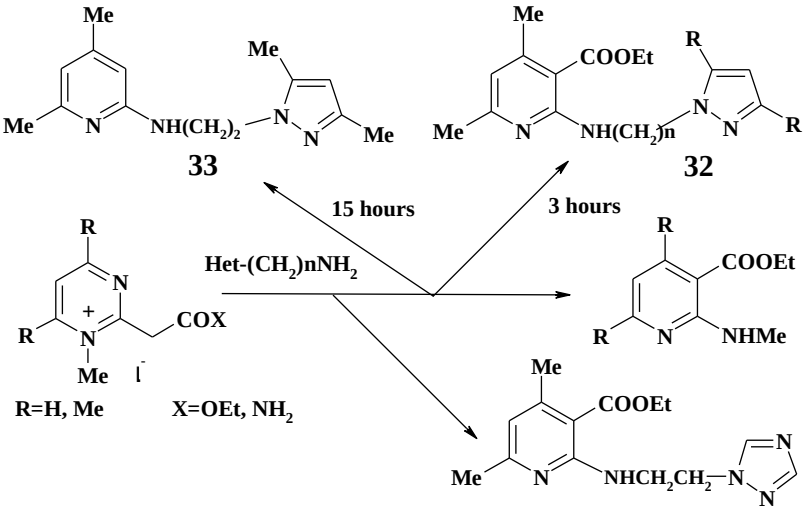


Upon interaction of salt 1a with tri(hydroxymethyl)aminomethane the volumetric substituent of the latter, connected with the amine group, created hindrances for the amine attack on the pyrimidine ring. Therefore the amine attack was delivered on the esterial group, which resulted in affording amide 30. The latter readily rearranged when reacted with benzylamine having a less volumetric substituent. This resulted in obtaining pyridine 31 [26].



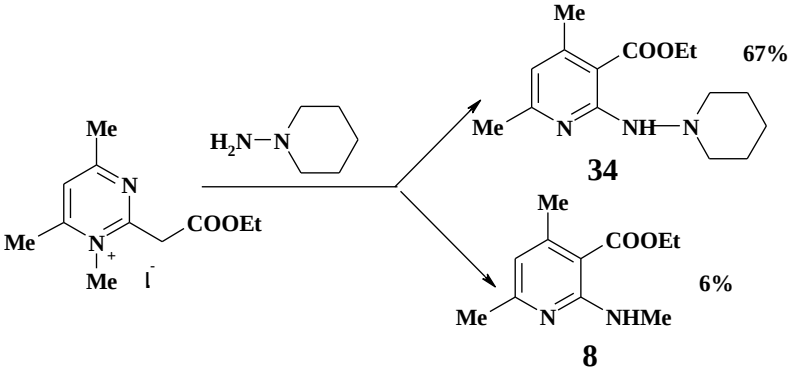
Rearrangement of iodomethylates of some pyrimidinyl-2-acetic acid derivatives under the action of amines containing biologically active heterocycles – pyrazole and 1,2,4-triazole ring was also studied [41, 42]. The direction of the reaction was revealed to depend on the duration of heating and reaction conditions. Thus, 3-hour boiling of iodide 1 with 2-(3`,5`-dimethylpyrazolyl-1`)ethylamine yielded the product of "rearrangement with exchange amination" – derivative of nicotinic acid 32. But on longer boiling together with rearrangement, elimination of the esterial group also occurred and pyridine substituted derivative 33 was formed.

The yield of the product of "rearrangement with exchange amination" was also found to increase when the reaction was carried at room temperature, i.e. without heating.



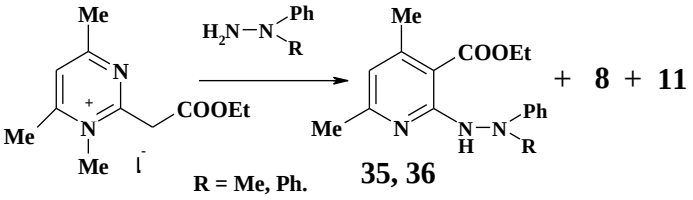
R = H; X = OEt; $R_1 = R_2$ = Me; n = 2.
R = Me; X = OEt; $R_1 = R_2$ = Me; n = 2.
R = Me; X = NH_2; $R_1 = R_2$ = Me; n = 2.
R = Me; X = NH_2; R_1 = Me; R_2 = H; n = 2.
R = Me; X = OEt; R_1 = Me; R_2 = H; n = 2.
R = Me; X = OEt; R_1 = H; R_2 = Me; n = 2.
R = Me; X = OEt; $R_1 = R_2$ = H; n = 2.
R = Me; X = OEt; $R_1 = R_2$ = Me; n = 3.

The interaction between iodide 1a and 1-aminopiperidine, which may be considered as 1,1-disubstituted hydrazine derivative, resulted in products of normal rearrangement 8 and of "rearrangement with exchange amination" 34. Actually such a hydrazine derivative reacted as a primary amine. Similarly to other amines, the reaction between salt 1a and 1-aminopiperidine without a solvent, in the excess of 1-aminopiperidine led to the yield increase of the product of "rearrangement with exchange amination" – pyridine 34 up to 67% [35].

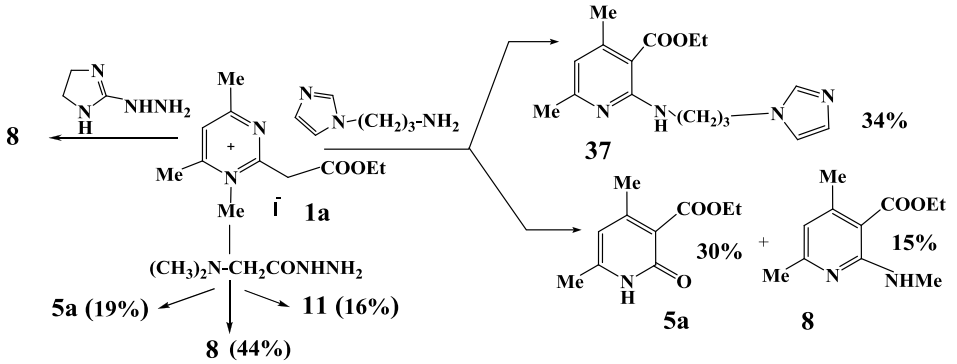


In continuation of this work, the possibility of rearrangement of 1,4,6-trimethyl-2-(ethoxycarbonyl)methylpyrimidinium ethyl ester iodide (31) into pyridine derivatives under the action of other 1,1-disubstituted hydrazines was studied. It

turned out that salt 31 with 1-methyl-1-phenyl and 1,1-diphenylhydrazines transformed into 4,6-dimethylnicotinic ethyl esters (compounds 34 and 35, correspondingly) containing the appropriate hydrazine fragments in position 2 of pyridine. Ethyl esters of 2-methylamino-4,6-dimethylnicotinic acid (8) and (4,6-dimethylpyrimidin-2-yl)acetic acid (11) were also isolated from the reaction mixtures. That is, besides recyclization, which proceeded with the inclusion of the nucleophilic moiety into the reaction product, concurrently proceeded isomerizational recyclization without inclusion of the reagent (pyridine 8) [43].

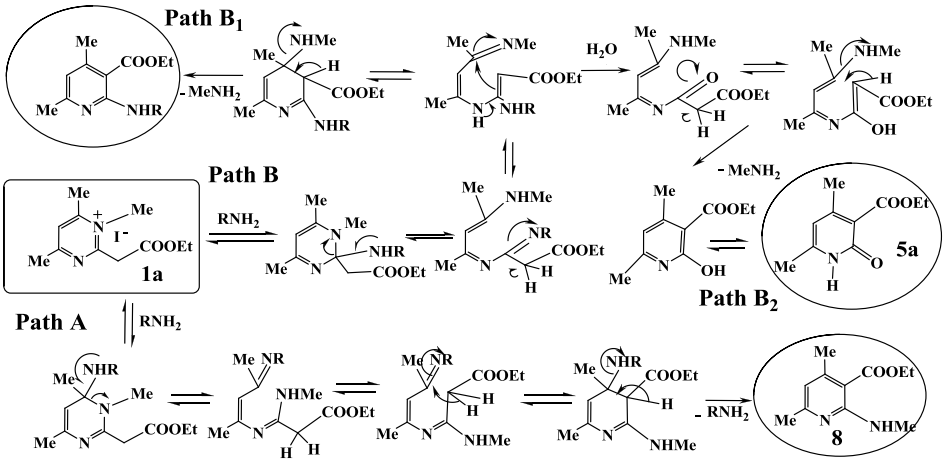


The rearrangement with the inclusion of the reagent into the final reaction product was observed when salt 1a reacted with 1-(3-aminopropyl)imidazole. It resulted in isolation of 2-[3-(1*H*-imidazol-1-yl)propylamino]-4,6-dimethylnicotinic ethyl ester (37) as well as of derivatives of pyridine 8 and pyridone 5a formed in the process of recyclization and hydrolysis of the amine group. Under the influence of 2-hydrazino-4,5-dihydroimidazole the transformation proceeded in the direction of recyclization of the classical enamine rearrangement, and under the influence of dimethylaminoacetic acid hydrazides – pyridone 5a, pyridine 8 and pyrimidine 11 [43].



Summarizing, it can be concluded that when interacting salts of pydimidinylacetic acid derivatives with various primary amines the rearrangements can proceed in three directions:

- with the attack of the nucleophilic particle at position 6 (path A) affording the product of classical rearrangement (compound 8);
- with the attack at position 2 of the pyrimidine ring (path B) affording the product of rearrangement with inclusion of the amine reagent into the forming pyridine (path B_1) or, affording pyridone 5 in case of the presence of water in the solution (path B_2).



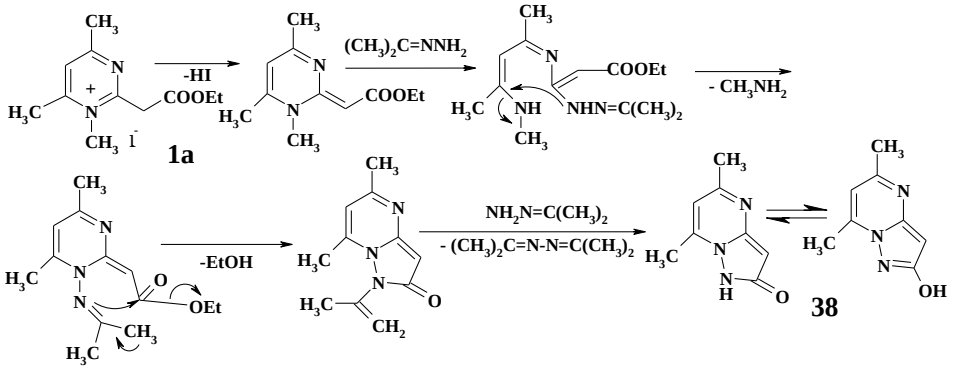
Thus, a novel, non-conventional approach to obtaining potentially biologically active derivatives of nicotinic acid and of nicotinamide that contain in position 2 of the pyridine ring biogenic and pharmacophore groups has been developed. It has been proved that by selection of the appropriate amine it is possible to incorporate into the pyridine various groups including also pharmacophore ones, i.e. to model compounds with a pre-set biological activity. It is necessary to underline that it is difficult to obtain similar polysubstituted pyridine derivatives by other routes. Therefore the reaction under investigation may become a tool in obtaining novel, potentially biologically active compounds.

II. 1. Rearrangements of pyrimidinium salts under the action of carboxylic acids hydrazides

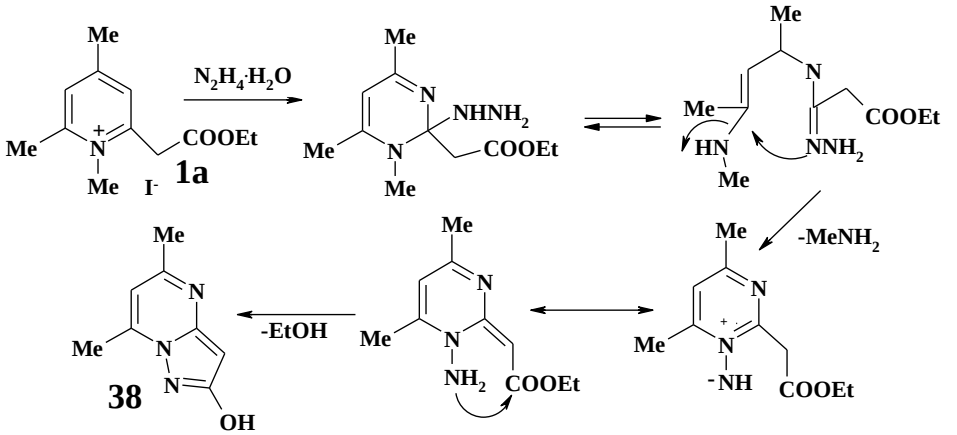
The other direction of our work in the last years became study of the effect of carboxylic acid hydrazides on pyrimidinium salt 1. Pyrimidines and N-alkyl derivatives – pyrimidinium salts are known to readily react with hydrazine and its substituted derivatives forming, as a rule, azoles derivatives - pyrazole and 1,2,4-triazole [44-48].

We showed above that in the reaction with 1-aminopiperidine, iodide 1a unusually rearranged into pyridine derivative 34. This is explained by the fact that the second – disubstituted nitrogen atom is unable to participate in the process of the azole ring formation.

In the reaction of iodide 1a with acetone hydrazone we did not exclude similar obtaining of the compound with hydrazone fragment incorporation into the product of the Kost-Sagitullin rearrangement. However, the product of one more recyclization was isolated – 2-hydroxy-5,7-dimethylpyrazolo[1,5-a]pyrimidine (38) [30]. The structure of compound 38 has been confirmed by mass- and NMR spectra, as well as by comparison with samples obtained by an independent route.



The like recyclization to 2-hydroxy-5,7-dimethylpyrazolo[1,5-a]pyrimidine (38) was also observed when hydrazine hydrate reacted with iodide 1a [39]. The possible Scheme of the transformation is given below:

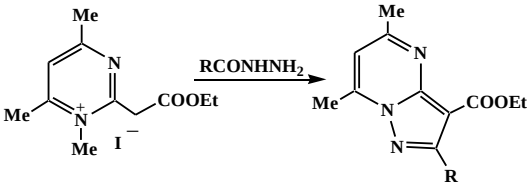


Until recently, two synthetic strategies for the preparation of pyrazolo[1,5-*a*]pyrimidines, as well as other azolopyrimidines, had been known: starting either from the pyrimidine ring or from the five-membered ring, and constructing the other heterocycle [49, 50]. Thus, syntheses of similar fused systems from 5-aminopyrazoles and other α-aminoazoles, where reactions with β-dicarbonyl compounds and their derivatives were used [49, 50], have been described. For example, synthesis of azolopyrimidines from a pyrimidine derivative was achieved by reacting 2-hydrazinopyrimidines with orthoformate and some other carboxylic acid derivatives [51, 52].

Compounds containing condensed pyrimidine systems and a bridged nitrogen atom are known to present interest as potential analgetics, antitumor drugs, broncholiths and breathing stimulants [53-57]. In patents and articles there are many indications on possibility of their practical application. Antituberculous [58], antiviral [59, 60], psychotropic [61, 62], antimicrobic [63, 64], anticonvulsive effects of compounds close by the structure have been reported. They form the composition of some drugs [65, 66]. Therefore, study of a new reaction, which gives an opportunity in one stage to obtain novel, potentially biologically active

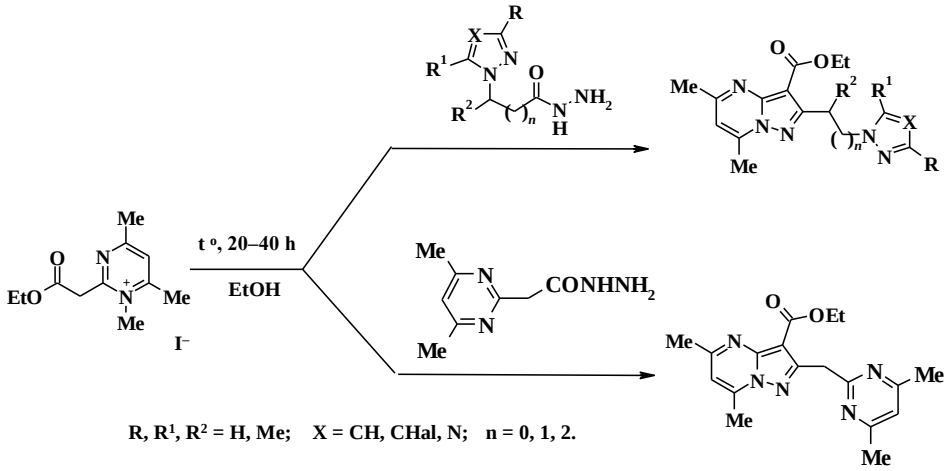
condensed pyrimidines, containing a bridged nitrogen atom, could not be ignored by us.

During study of recyclization reactions between pyrimidine derivatives and nitrogen-containing nucleophilic agents, we identified an unusual transformation of 2-(ethoxycarbonyl)methyl-1,4,6-trimethylpyrimidinium iodide (1a) in the presence of certain acyl hydrazides [67, 68]. We discovered that in the reaction of this salt with carboxylic acids hydrazides one more unusual and earlier not described rearrangement took place. As a result of such transformation pyrazolo [1,5-a]pyrimidine derivatives that contained a fragment of carboxylic acid hydrazide were also formed.



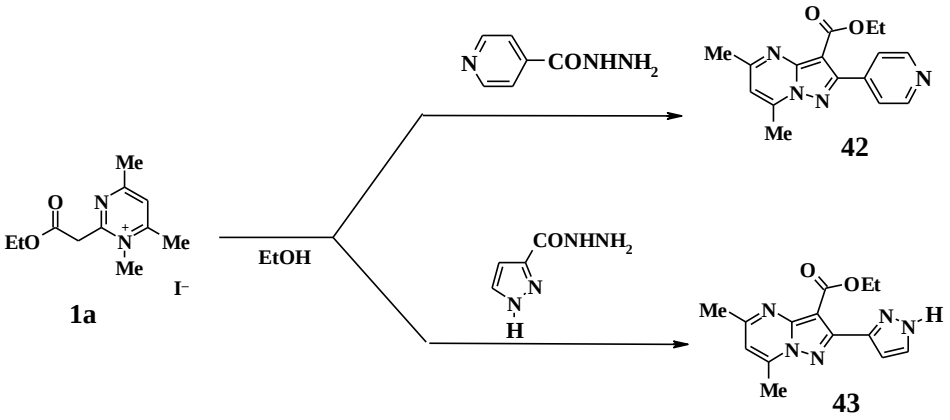
This previously unknown transformation was performed in a single step by substituting the N(1)–CH_3 fragment in the starting salt with the terminal nitrogen atom of hydrazide group, with subsequent intramolecular cyclization, leading to the formation of pyrazole ring condensed with a pyrimidine ring.

When alcoholic iodide 1a reacted with acetic, cyanoacetic, phenylacetic acids hydrazides, the corresponding 2-substituted-3-ethoxycarbonyl-5,7-dimethylpyrazolo[1,5-a]pyrimidines 39-41 containing in position 2 carboxylic acid radical (R = CH_3, CH_2CN, $CH_2C_6H_5$) [67, 69] were obtained. When carboxylic acids hydrazides, containing in the hydrocarbonaceous radical heterocyclic rings (pyrimidine, pyrazole and triazole), were incorporated into the reaction with pyrimidinium salts, we succeeded in obtaining pyrazolo[1,5-a]pyrimidine derivatives. The latter contained in position 2 biologically active (pharmacophore) heterocyclic groups [50, 70-74].

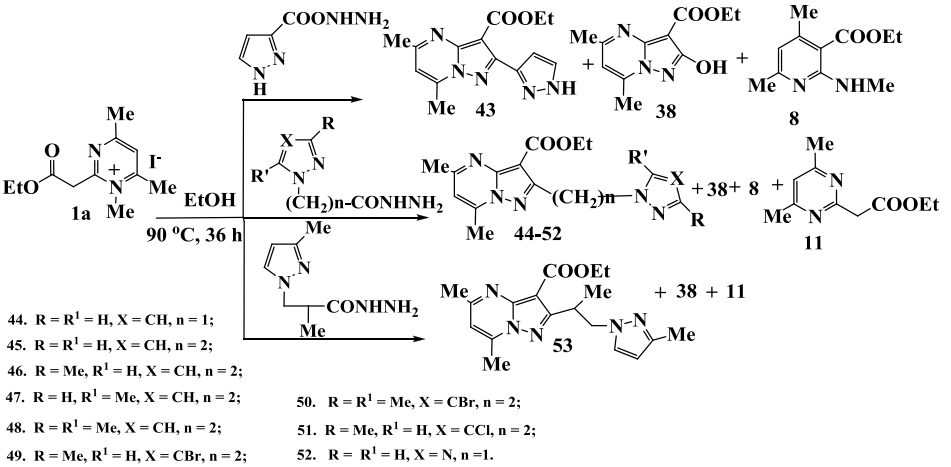


Heterocyclic acids hydrazides, in which a hydrazide fragment is immediately connected with a heterocyclic ring, also undergo a similar reaction. Thus by the

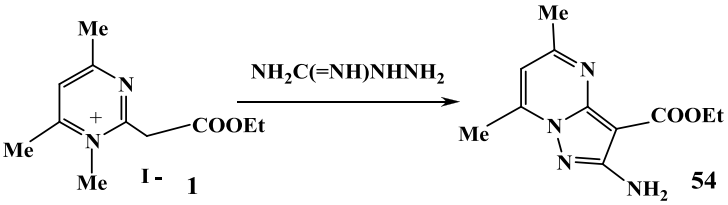
reactions of salt 1 with isonicotinic acid hydrazide (isoniazid) and pyrazol-3-carboxylic acid hydrazide we managed to obtain pyrazolo[1,5-a]pyrimidine derivatives 42 and 43 that contained in position 2 pyridine and pyrazole rings [67, 70].



We should note that, along with pyrazolopyrimidines 44–53, another recyclization product, 2-hydroxy-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (38), was isolated from the reaction mixtures in all cases. In some experiments, the starting salt 1a gave small amounts of enamine rearrangement product, ethyl 4,6-dimethyl-2-methylaminopyridine-3-carboxylate (8), and demethylation product, ethyl 4,6-dimethyl-pyrimidinyl-2-acetate (11), which were typically formed also in other nucleophilic recyclization reactions of pyrimidines by interaction of salt 1a with primary amines (Kost–Sagitullin enamine rearrangement and recyclization to 1,2,4-triazole derivatives) [2, 42, 48, 67].



Close to the mentioned reactions is an example of iodide 1 recyclization under the action of aminoguanidine. In this case a hydrazine fragment also participates in the process of rearrangement affording 2-amino-3-ethoxycarbonyl-5,7-dimethylpyrazolo[1,5-a] pyrimidine (54) [67].



The composition of compounds was proved by X-ray structural investigation as well as mass- and NMR spectra.

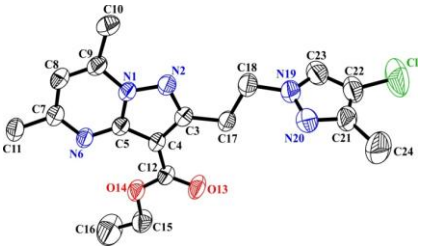


Fig. 1. Molecular structure of compound 51 according to X-ray structural analysis with atoms represented by thermal vibration ellipsoids of 50% probability.

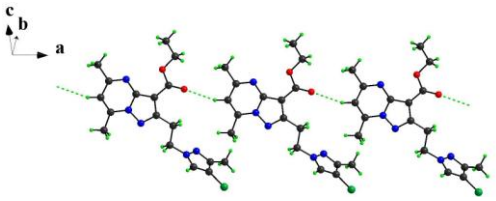
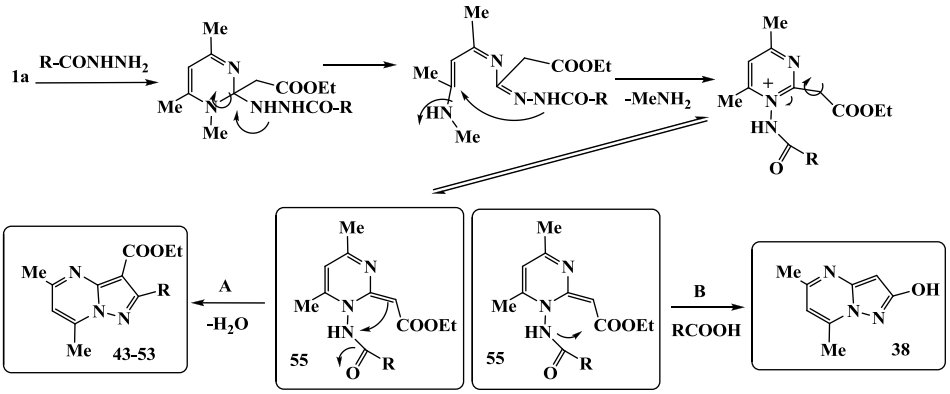


Fig. 2. Infinite molecular chain in the structure of compound 51 along the [100] direction.

The three-dimensional molecular packing in the crystal 51 featured an unusual C(8)–H(8)···O(13) hydrogen bond (the interatomic distances were the following: C–H 1.01(3) Å, H···O 2.46(3) Å, C···O 3.409(3) Å, while the C–H–O angle was 157(2)°). This hydrogen bond between pyrimidine H-5 proton of one molecule and carbonyl group oxygen of another molecule linked the molecules of this compound in an infinite chain in the [1 0 0] direction.

The rearrangements leading to pyrazolo[1,5-*a*]pyrimidine derivatives 44–53 can be apparently interpreted as involving an intermediate adduct, compound 55, with a mechanism consisting of attack by terminal nitrogen atom of hydrazide at position 2 of the salt 1a, opening of pyrimidine ring at the N(1)–C(2) bond, followed by a cyclization that includes hydrazine nitrogen atom into the pyrimidine ring. The last stage of recyclization, namely, the reaction of intermediate 55 leading to closure of five-membered ring, can occur in two different directions (I and II), leading to either compounds 43–53 or 38 (Scheme).

The Scheme of rearrangement includes opening of the pyrimidine ring followed by cyclization with involvement of the hydrazine nitrogen atom into the forming pyrimidine ring and cyclization of one more pyrazole ring annealed with a pyrimidine one.



The reaction of salt 1a with isoniazid – isonicotinic acid hydrazide, affords pyrazolopyrimidine derivative 42. However, when into the reaction with isonicotinic acid hydrazide was incorporated not the salt itself, but anhydrobase 3a, obtained from the pyrimidinium salt 1a, the reaction proceeded in a different direction. This led to formation of the nicotinic acid derivative containing a nucleophilic agent fragment – isonicotinic acid hydrazide [75]. That is, in this case recyclization proceeded affording the product of "rearrangement with exchange amination" .

In a paper devoted to study of the reaction of 2-(ethoxycarbonylmethyl)-1,4,6-trimethyl-pyrimidinium iodide (1a) with carboxylic acid hydrazides, we reported on the synthesis of derivatives of 1,2,4-triazolo[4,3-a]pyridine [75]. In particular, in that paper we discussed the hypothesis that when salt 1 was treated with isonicotinic acid hydrazide (56) (isoniazide), cyclization to form triazolopyridine 58 occurred through a step involving formation of the intermediate 2-hydrazidopyridine 57 (the product of a Kost–Sagitullin rearrangement). However, as shown by later X-ray diffraction studies, during the reaction we did not obtain triazolo[4,3-a]pyridines 58 but rather their isomers: derivatives of pyrazolo[1,5-a]pyrimidine 42 [48].

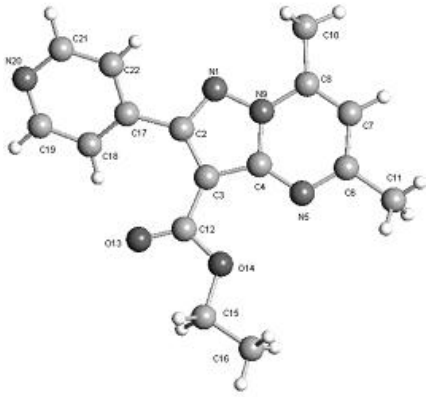
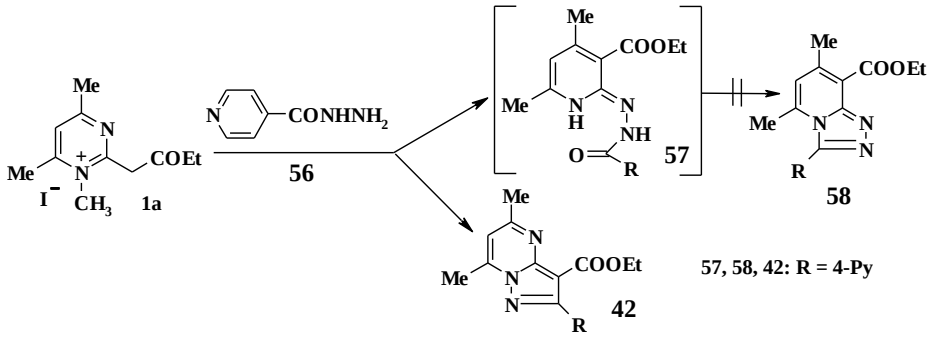


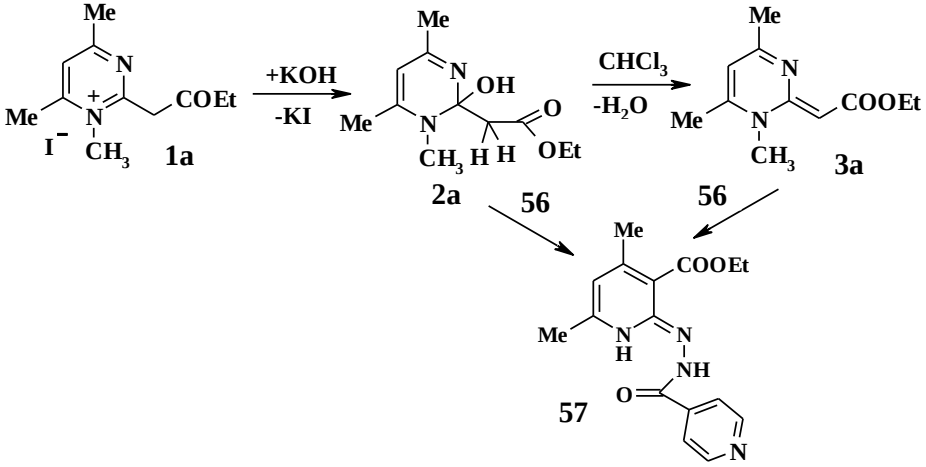
Fig. 3. Molecular structure of compound 42 according to X-ray structural analysis.



In studying the reaction of recyclization intermediates 2a and 3a with isoniazide 56, we obtained a compound with a structure matching that of the initially proposed structure for the intermediate product of "rearrangement with transamination" (compound 57) [76].

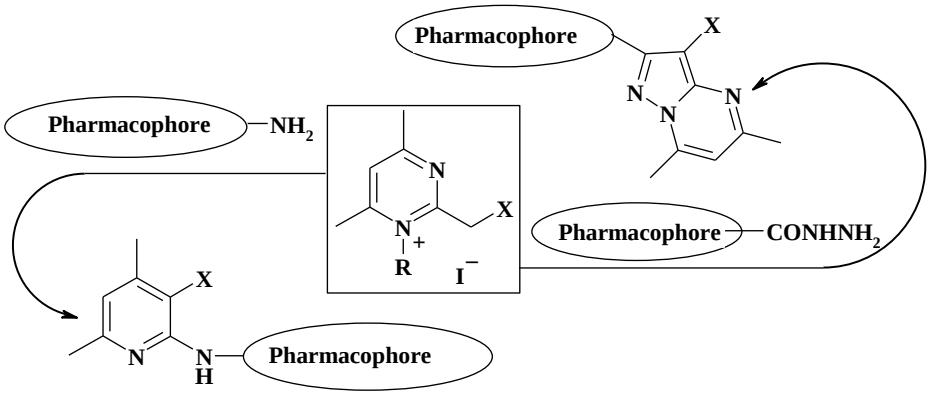
Probably during the reaction, the pseudobase 2a, by eliminating a water molecule, was converted to the anhydro base 3a, which also underwent the indicated transformation.

For compound 57 the presence of NH-group signals in the area of 9.27 and 10.64 ppm in the ^{1}H-NMR spectrum is characteristic and together with other spectra data of ^{1}H- and ^{13}C-NMR and mass-spectroscopy confirm our proposed structure.



Thus for the first time we have observed a Kost–Sagitullin rearrangement with insertion of a carboxylic acid hydrazide moiety into the molecule of the reaction product.

Thus, we succeeded in elaboration of two novel original routes for the synthesis of biologically active compounds based on pyrimidinium salts. Schematically it may be presented in the following way:



The study was performed in the Russian-Armenian University out of the funds allocated under the RF Ministry of Education grants to finance research activities of RAU, as well as within the "Program for the Russian-Armenian University development 2014-2016".

ԿԵՆՍԱԾԻՆ ԵՎ ԴԵՂԱԿԻՐ ՀԱՏՎԱԾՆԵՐ ՊԱՐՈՒՆԱԿՈՂ ՆՈՐ ՊԻՐԻԴԻՆՆԵՐԻ ԵՎ ՊԻՐԱԶՈԼՈ[1,5-a]ՊԻՐԻՄԻԴԻՆՆԵՐԻ ՍԻՆԹԵԶՆԵՐ՝ՊԻՐԻՄԻԴԻՆԱՅԻՆ ՕՂԱԿԻ ՌԵՑԻԿԼԱՑՄԱՄԲ

Գ. Ն. ԴԱՆԱԳՈՒԼՅԱՆ

Ակնարկը նվիրված է պիրիմիդինիլքացախաթթվի ածանցիալների յոդ ալկիլատների երկու տարբեր ռեցիկլացման կենսածին և դեղակիր խմբեր պարունակող առաջնային ամինների և կարբոնաթթուների հիդրազիդների ազդեցությամբ: Ռեակցիաները հանգեցնում են այլ ճանապարհներով դժվարնականորեն անհասանելի նիկոտինաթթվի և պիրազոլո[1,5-a]պիրիմիդինի ածանցիալների ստացման:

Պիրիմիդինիլքացախաթթվի ածանցիալների ազդեցությամբ տարբեր առաջնային ամինների հետ հաջողվում է ստանալ պիրիդինի ածանցիալներ, որոնք 2-րդ դիրքում պարունակում են ամինային ազդակի հատված: Ցույց է տրվել, որ ելնելով պիրիմիդինի մեկ կամ մի քանի ածանցիալներից, ամինների զանազանման ճանապարհով (նաև բառյալ նաև կենսածին և կենսակտիվ), հաջողվում է ստանալ նիկոտինաթթվի նոր ածանցիալների շարքեր: Ռեակցիայի միջանկյալ արգասիքների անջատմամբ և վերջիններիս հաջորդող ներդրավմամբ ռեակցիայի մեջ՝ ամինային ռեագենտների հետ, հնարավորություն է ընձեռվել որոշելու վերախմբավորման ուրվագիծը և ազդակի առաջնային հարձակման ուղղությունը:

Ակնարկի երկրորդ մասը նվիրված է լաբորատորիայում հայտնաբերված պիրիմիդինոմային աղերի նոր վերախմբավորմանը՝ կարբոնաթթուների հիդրազիդների ազդեցությամբ ընթացող փոխազդեցության սահմանների ուսումնասիրմանը: Այս ռեակցիան բերում է պիրազոլո[1,5-a]պիրիմիդինի բազմատեղակալված ածանցիալների ստացման՝ մոլեկուլի պիրազոլային հատվածում հիդրազիդային ռադիկալի մնացորդով:

Այս՝ նախկինում չնկարագրված փոխարկումը իրականցվում է մեկ փուլով՝ չնորհիվ ելային աղի $N(1)-CH_3$ հատվածի տեղակալմամբ՝ հիդրազիդային խմբի ծայրային ազոտի ատոմով և հաջորդող ներմոլեկուլյար ցիկլացմամբ, որը բերում է պիրիմիդինի հետ համակցված պիրազոլային օղակի առաջացման:

Ակնարկը ընդհանրացնում է հեղինակի և իր աշխատակիցների կողմից ստացված հետազոտության արդյունքները, նվիրված պիրիմիդինիումային աղերի նուկլեոֆիլ վերախմբավորումների ուսումնասիրությանը:

СИНТЕЗЫ НОВЫХ ПИРИДИНОВ И ПИРАЗОЛО[1,5-a]ПИРИМИДИНОВ, СОДЕРЖАЩИХ БИОГЕННЫЕ И ФАРМАКОФОРНЫЕ ФРАГМЕНТЫ, РЕЦИКЛИЗАЦИЕЙ ПИРИМИДИНОВОГО КОЛЬЦА

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Обзор посвящен двум рециклизациям йодалкилатов производных пиримидинилуксусных кислот под действием биогенных и фармакофорсодержащих первичных аминов и гидразидов карбоновых кислот. Реакции приводят к практически недоступным другими путями производным никотиновой кислоты и пиразоло[1,5-a]пиримидина.

Реакцией солей производных пиримидинилуксусной кислоты с различными первичными аминами удается получать производные пиридина, содержащие в положении 2 фрагмент аминного реагента. Показано, что благодаря этому можно, исходя из одного или нескольких производных пиримидина, варьированием аминов (включая также биогенные и биоактивные) получать серии новых производных никотиновой кислоты. Путем выделения интермедиатов реакций и последующего их введения в реакции с аминными реагентами определены схемы перегруппировок и направление первичной атаки реагента.

Вторая часть обзора посвящена изучению границ открытой в лаборатории новой перегруппировки солей пиримидиния под действием гидразидов карбоновых кислот. Эта реакция приводит к получению полизамещенных производных пиразоло[1,5-a]пиримидина, содержащих в пиразольной части молекулы остаток радикала гидразида.

Эта не описанная ранее трансформация осуществляется одностадийно за счет замещения фрагмента N(1)–CH_3 исходной соли концевым атомом азота гидразидной группы, с последующей внутримолекулярной циклизацией, приводящей к образованию конденсированного с пиримидиновым пиразольного цикла.

Обзор обобщает результаты исследований, полученных автором и его сотрудниками по изучению нуклеофильных перегруппировок пиримидиниевых солей.

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