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KOST–SAGITULLIN REARRANGEMENT AND OTHER ISOMERIZATION RECYCLIZATIONS OF PYRIMIDINES. (REVIEW)*

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Data on the isomerization recyclizations of pyrimidines, particularly the Kost–Sagitullin and other transformations accompanied by substitution of an endocyclic atom in pyrimidine by an extracyclic nitrogen or carbon atom (N–N, N–C, or C–C recyclizations), are summarized and analyzed. Data from research on the Kost–Sagitullin and certain other isomerization transformations of pyrimidines at the Institute of Organic Chemistry, National Academy of Sciences of the Republic of Armenia, in recent years are presented.

Keywords: 1,2-dialkylpyrimidinium iodides, pyrazolo[1,5-*a*]pyrimidine, pyrimidine, isomerization, nucleophilic rearrangements, recyclization.

The *meta* arrangement of the two sp^2-hybridized "pyridine" type nitrogen atoms in the pyrimidine ring make this system π-deficient. Its most characteristic reactions are therefore reactions with nucleophilic reagents, including nucleophilic recyclizations. Such transformations can take place both with and without inclusion of a fragment of the nucleophilic reagent in the new ring. Rearrangements that take place with inclusion of the reagent or its fragment in the reaction product form an extensive series of transformations differing in mechanism, i.e., transformations involving the participation of C-nucleophilics [1-9], amidines [10-14], enamines [15-16], olefins and acetylenes [17-20], amines [21, 22], hydrazines [23-29], and other types of compounds [30, 31]. These transformations were discussed in a fair amount of detail in a series of reviews [32-41]. In the present review an attempt is made to analyze and classify experimental data relating to nucleophilic transformations of pyrimidine derivatives that take through a stage involving ring opening and repeated cyclization (i.e., recyclization) but without inclusion of the reagent or its fragment in the molecule of the reaction product. In these reactions the role of the nucleophilic reagent is restricted to promotion of the transformation. In fact the rearrangement leads to the production of a compound essentially isomeric (but not necessarily in composition). The list of such recyclizations in pyrimidines is short. They include primarily Dimroth rearrangements, taking place with cleavage of the C–N bond of the pyrimidine ring and the subsequent formation of a new C–N bond. Here cyclization occurs with inclusion of the exocyclic nitrogen atom in the newly formed ring, while the nitrogen atom of the heterocycle of the initial substance is outside the ring. In so far as the rearrangement formally takes place with substitution of one nitrogen atom by another such reactions can be called N–N recyclizations.

* In memory of Aleksei Nikolaevich Kost – a distinguished scientist, a warmhearted person, and a teacher.

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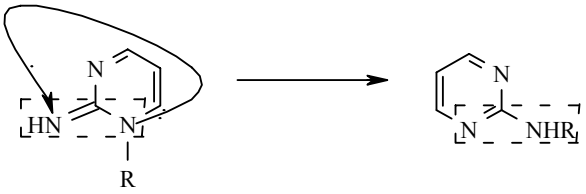
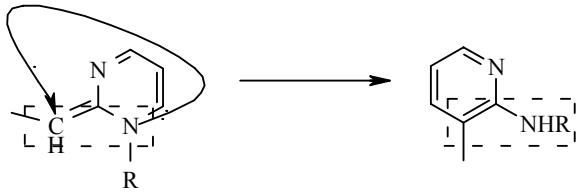
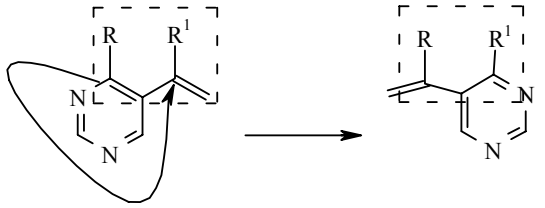


A series of reviews [42-44] and, in some cases, separate sections [45-48] have been devoted to Dimroth rearrangements, and we will not therefore dwell on them in detail in this article. We mention only that since the time of their investigation these reactions have changed from the unexpected and unusual transformation that they seemed initially into a tool of organic synthesis making it possible to produce new substances often difficult to obtain in other ways. Publications of recent years have shown that in the pyrimidine series the Dimroth rearrangement has become an important method of fine organic synthesis used for the transformation of biologically active and medicinal substances such as nucleosides [49-57] and drugs [58-63].

Another somewhat less studied type of isomerization recyclization in the pyrimidine ring is the Kost–Sagitullin rearrangement, discovered in the seventies of the last century at M. V. Lomonosov Moscow State University [5, 64-67]. This reaction, its modifications, and the concurrent transformations that accompany the process have been studied in detail in recent years. Here, unlike the Dimroth rearrangement, the exocyclic carbon atom and not the nitrogen take part in the recyclization, and as a result the transformation leads to the production of a pyridine ring and not a pyrimidine ring. Formally, the recyclization takes place with substitution of the endocyclic nitrogen atom by a carbon atom, and the term N–C recyclization is therefore used to describe such rearrangements.



In this review we also examine a series of other N–C recyclizations that can be regarded as isomerizations similar to Kost–Sagitullin rearrangements and also a type of C–C recyclization involving intramolecular substitution of an endocyclic carbon atom of pyrimidine by an exocyclic carbon atom.



During presentation of the data we used the following scheme:

Enamine (N–C) isomerization recyclizations of pyrimidines (the Kost–Sagitullin rearrangement).

Kost–Sagitullin rearrangements with inclusion of a fragment of an amine reagent in the reaction product.

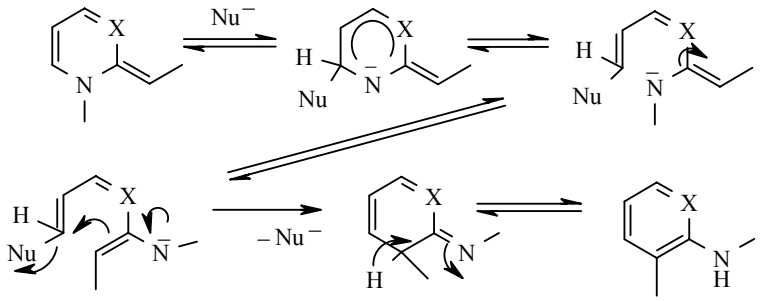
Other N–C recyclizations of pyrimidines.

Isomerization recyclization with substitution of the pyrimidine fragment.

C–C Recyclizations and anomalous Dimroth rearrangements in the pyrimidine series.

1. ISOMERIZATION N–C RECYCLIZATION (THE KOST–SAGITULLIN REARRANGEMENT)

The Kost–Sagitullin rearrangement was first discovered and studied under the leadership of Prof. A. N. Kost in derivatives of pyridine and pyrimidine [5, 64-77]. Such recyclizations were realized both in N-alkylazinium salts and in annelated azine systems containing a bridging nitrogen atom (common to the two heterocycles). As a result of these rearrangements a carbon atom of the side chain enters the (hetero)aromatic ring, while the N-alkylated nitrogen atom of the ring (in the case of the salts) or the bridging nitrogen atom of condensed systems lies outside the ring. In the course of the reaction the azine C–N bond is broken, a new C–C bond is formed as a result of the rearrangement, and the new ring contains one less nitrogen atom than the initial azine molecule.

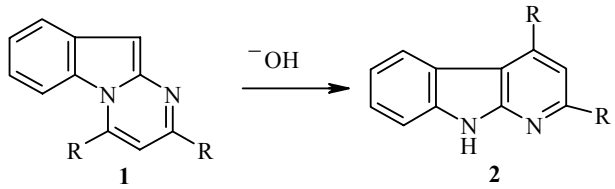


Unlike Dimroth rearrangements, in these transformations the key fragment taking part in the recyclization process is the enamine and not the amidine group of the molecule, and this rearrangement has therefore also been called the "enamine rearrangement."

Within the scope of the present review this type of rearrangement will only be discussed for the case of the transformations of pyrimidine systems.

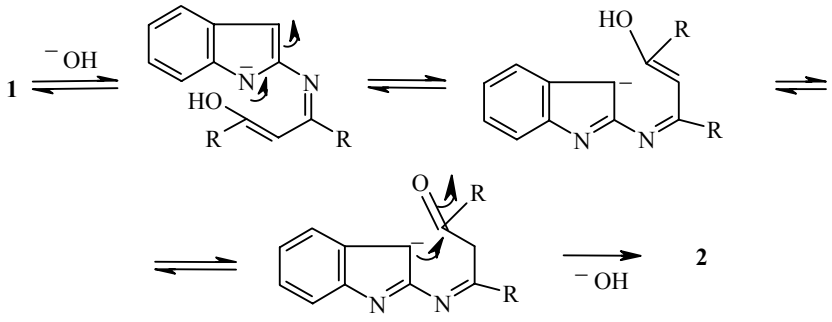
1.1. Kost–Sagitullin Rearrangement in Condensed Pyrimidines

The first example of the isomerization rearrangement of pyrimidines was discovered in the pyrimido[1,2-*a*]indole series [64]. It was shown that substituted pyrimido[1,2-*a*]indoles **1** isomerize under the influence of alkali to α-carbolins **2**.



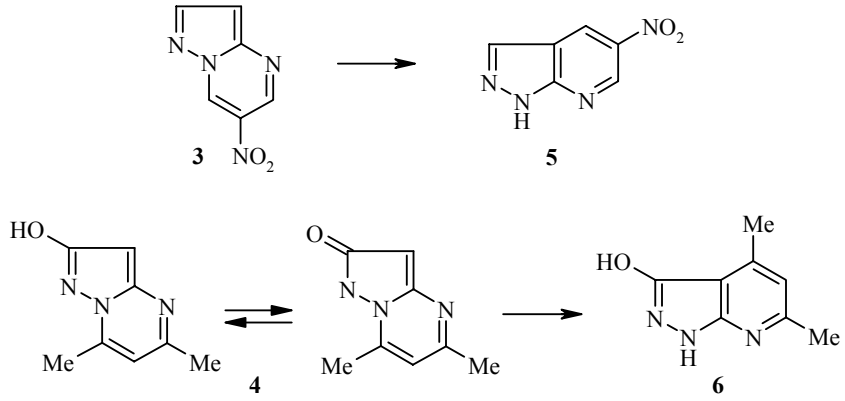
1 **2**

By analogy with the scheme of the Dimroth rearrangement the proposed scheme for this transformation included initial attack by the hydroxide ion on the pyrimidine ring, cleavage of the N–C bond of the pyrimidine fragment, rotation about the C–C single bond, and cyclization with inclusion of a carbon atom from the pyrrole ring in the newly formed pyridine ring.

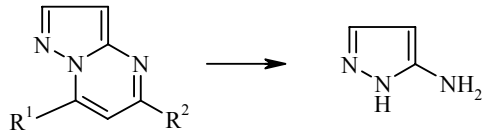


After opening of the pyrimidine ring the motivating force of the rearrangement then becomes the enamine fragment of the molecule formed in the intermediate. As a result of electron transfer from the nitrogen atom to the β-carbon atom of the enamine and final attack at the carbonyl group a new pyridine ring is formed. All stages of the recyclization except the final stage (the formation of the C–C bond) in this transformation are probably reversible.

Similar isomerization recyclization was also realized in the pyrazolo[1,5-*a*]pyrimidine series [65]. It was found that in contrast to pyrimidoindoles the rearrangement of pyrazolopyrimidine requires additional activation, i.e., by the introduction of either an electron-accepting group (nitro) into the pyrimidine ring or a hydroxyl group into the pyrazole fragment of the molecule. When boiled in a 20% solution of alkali 6-nitropyrazolo[1,5-*a*]pyrimidine (**3**) and 2-hydroxy-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**4**) rearranged to the isomeric 5-nitro- and 3-hydroxy-4,6-dimethylpyrazolo[3,4-*a*]pyridines (**5**) and (**6**).

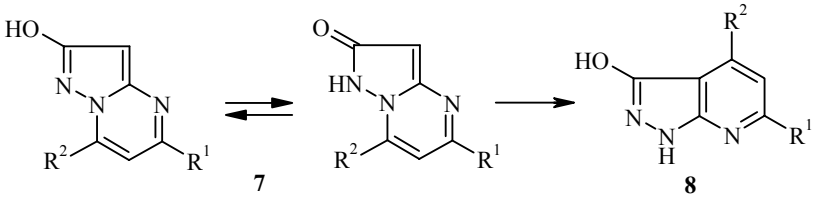


In the same paper [65] it was shown that the rearrangement cannot be detected without activation of the pyrazolopyrimidine molecule. Thus, 5,7-dimethyl- and 7-methyl-5-phenyl-substituted and unsubstituted pyrazolo[1,5-*a*]pyrimidines were only cleaved and transformed into 3-aminopyrazole when heated with alkali. That is, the first stage of the reaction (ring opening) took place readily, but the concluding stage (cyclization) did not occur, leading to hydrolysis and the production of a degradation product.



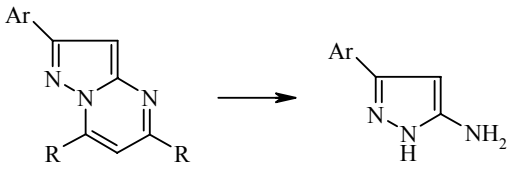
$R^1 = R^2 = H$; $R^1 = R^2 = Me$; $R^1 = Me$, $R^2 = Ph$

In number of cases (R^1 = H, R^2 = Me; R^1 = Me, R^2 = Ph; R^1 = CF_3, R^2 = Me, Ph) the base-initiated rearrangement of pyrazolo[1,5-*a*]pyrimidines **7** to pyrazolo[3,4-*b*]pyridines **8** was realized [78]. The isomerization includes addition of the base, cleavage of the bond between the carbon atoms and the nitrogen bridge of the pyrimidine ring, and recyclization with elimination of the base.



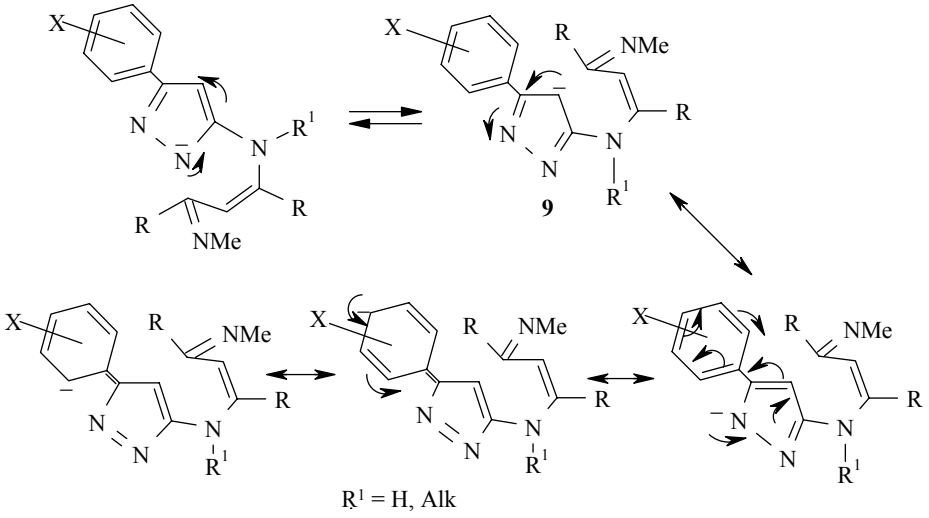
7 **8**

Attempts at recyclization of 2-aryl-5,7-dimethyl(diphenyl)pyrazolo[1,5-*a*]pyrimidines proved unsuccessful; only degradation products (5-amino-3-arylpyrazoles) or adducts from cleavage of the pyrimidine ring were isolated [79].



R = Me, Ph; Ar = Ph, 2-ClC_6H_4

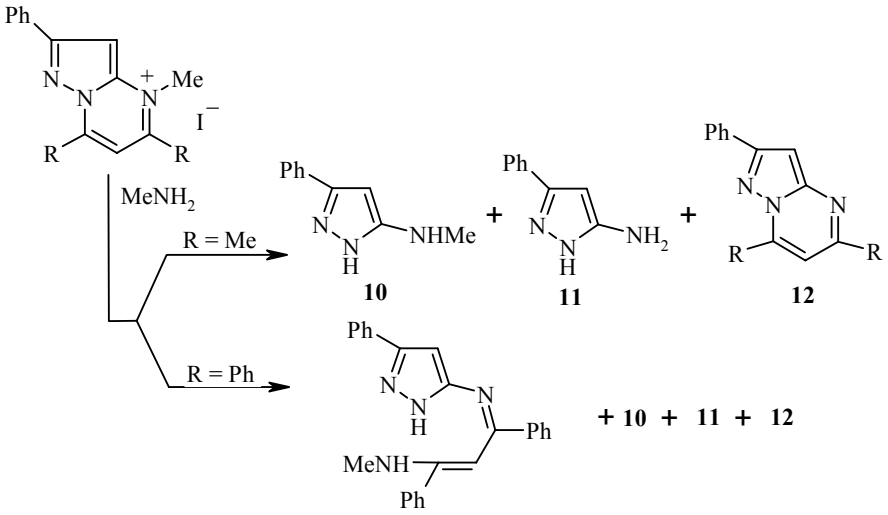
The presence of the aryl group in the five-membered ring probably leads to greater delocalization of the negative charge in the pyrazole part of the molecule of the intermediate adduct. This leads to a decrease in the electron density at the β-enamine atom $C_{(4)}$ of the intermediate **9**, which hinders the concluding stage of the rearrangement, leading to degradation and to the formation of aminopyrazoles.



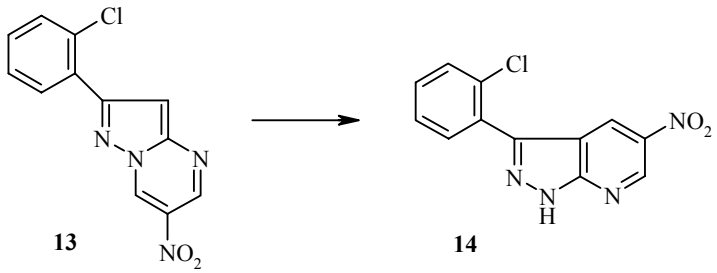
9

R^1 = H, Alk

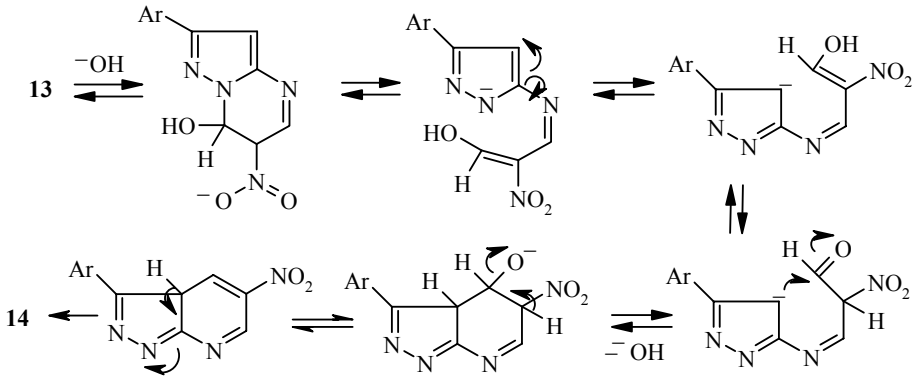
Even quaternization of the pyrimidine nitrogen atom in 2-arylpyrazolo[1,5-*a*]pyrimidines does not lead to recyclization, and only degradation products are formed [79, 80].



Recyclization of the pyrazolopyrimidine containing an aryl substituent in the pyrazole ring was promoted by the introduction of a nitro group into the pyrimidine ring; in a water–alcohol solution of alkali 2-(2-chlorophenyl)-6-nitropyrazolo[1,5-*a*]pyrimidine (**13**) rearranged to 3-(2-chlorophenyl)-5-nitropyrazolo-[3,4-*b*]pyridine (**14**) [81].

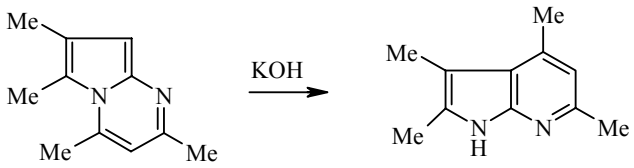


In this case the electron-withdrawing nitro group increases the electrophilicity of the carbonyl group formed in the intermediate, and this is sufficient for the cyclization and the formation of pyrazolo[3,4-*b*]pyridine **14**.



The rearrangement of pyrrolo[1,2-*a*]pyrimidine to pyrrolo[2,3-*b*]pyridine did not require the introduction of the nitro group into the pyrimidine ring. In a water–alcohol solution of potassium hydroxide 2,4,6,7-tetramethylpyrrolo[1,2-*a*]pyrimidine (**15**) isomerized to 2,3,4,6-tetramethylpyrrolo[2,3-*b*]pyridine (**16**)

with a yield of 56% [82]. Thus, increase in the nucleophilicity of the five-membered ring by substitution of the pyridine-type nitrogen atom by a methine group led to increase in the electron density at the carbon atom at the β-position of the enamine fragment, which facilitated the final stage of the isomerization.

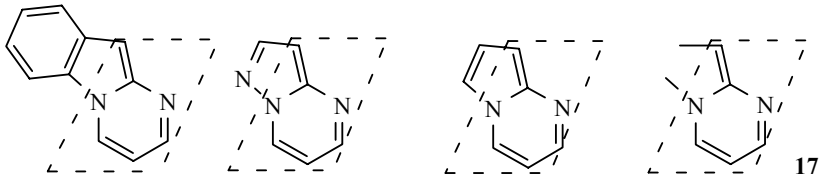


15 **16**

It is important to note that the rearrangements of all the condensed pyrimidine systems required the presence of water in the reaction mixture and were not observed in an alcohol solution of sodium ethoxide.

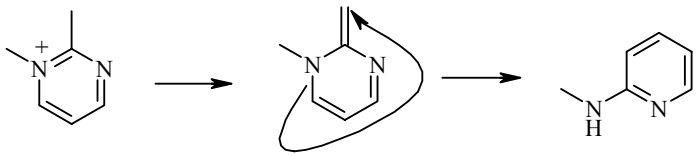
1.2. Rearrangements of 2-Alkylpyrimidinium Salts

In the examples of isomerization examined in the previous section condensed pyrimidine systems were submitted to isomerization. However, in pyrimido[1,2-*a*]indoles, in pyrazolo[1,2-*a*]pyrimidines, and in pyrazolo[1,2-*a*]pyrimidine one and the same fragment, i.e., the pyrimidine ring and the carbon atom occupying the α position exocyclic in relation to the pyrimidine, is responsible for the rearrangement.



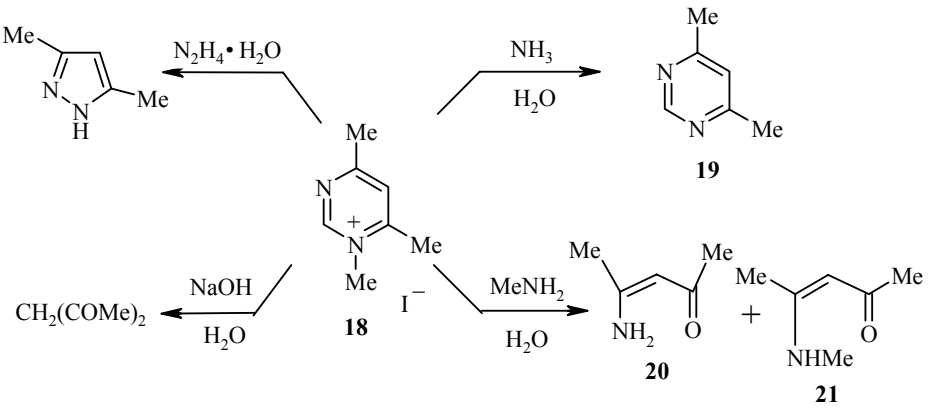
17

Logically, the next stage of the investigation of this rearrangement was to use the simplest models, i.e., 1,2-dialkylpyrimidinium salts or their anhydro bases **17**, containing all (and only!) the fragments structurally essential for the rearrangement. It was found that after cleavage of the N–C bond and subsequent formation of the C–C bond (on account of cyclization at the exocyclic carbon atom) these models can and must be transformed into 2-alkylaminopyridines.

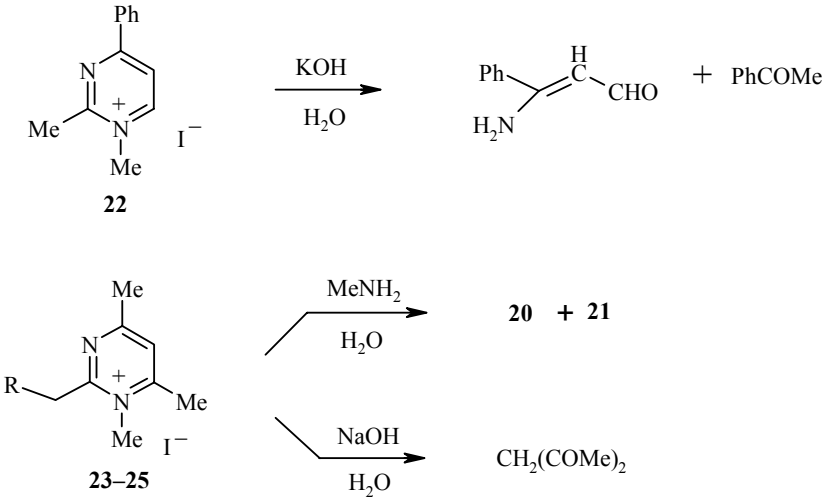


However, it was found that such recyclization of the pyrimidines **17** to derivatives of 2-alkylaminopyridines is difficult to realize if the necessary structural and electronic requirements are not met.

Thus, 1,4,6-trimethylpyrimidinium iodide (**18**) is readily hydrolyzed when heated with an aqueous solution of alkali, forming acetylacetone. The action of an aqueous solution of ammonia led to N-demethylation with the formation of 4,6-dimethylpyrimidine (**19**), while an aqueous solution of methylamine gave a mixture of amines **20** and **21**. Reaction with hydrazine also did not lead to the expected Kost–Sagitullin rearrangement, and 3,5-dimethylpyrazole was isolated [5, 66].

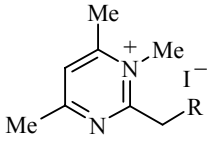


The reactions with 2-methylpyrimidinium salts **22-25** took place similarly with degradation or demethylation.

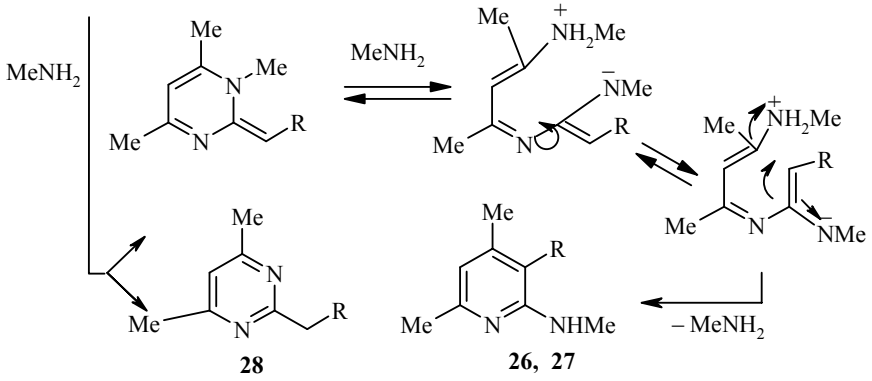


23 R = H; **24** R = Ph; **25** R = COOEt

According to the presented examples, the first stage in the recyclization of the pyrimidines takes place normally; ring opening occurs, but degradation is then usually observed. The reason for this may be either insufficient electron density at the carbon atom (the atom at which attack by the terminal carbonyl group of the intermediate should occur) or the presence of water in the solution, which promotes hydrolysis. In fact it was found that the introduction of electron-accepting groups (phenyl and ester groups) into the side chain (compounds **24** and **25**) and the exclusion of water (realization of the reaction in an alcohol solution of methylamine) led to isomerization to the 2-methylaminopyridine derivatives **26** and **27** with partial demethylation (the formation of compound **28**) [5, 66].



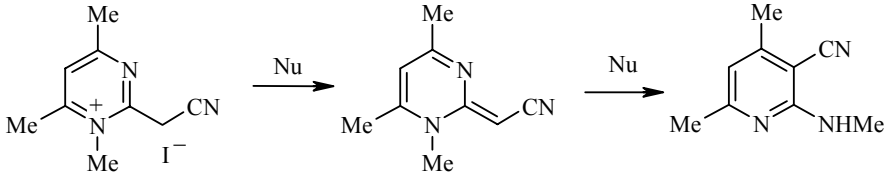
24, **25**



28 **26, 27**

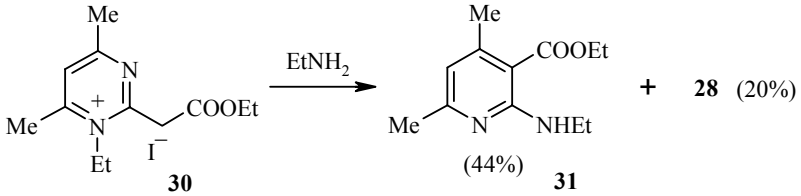
26 R = Ph (34%); **27** R = COOEt (69%)

The introduction of a nitrile group into the side chain had a more significant effect. In an alcohol solution of methylamine recyclization of the iodide **29** took place with a yield of 72%, and with sodium ethoxide the reaction was quantitative even at room temperature [83]. The ease with which the rearrangement of the iodide **29** occurred in an alcohol solution of sodium ethoxide made it possible to study the process in a CD_3OD solution containing CD_3ONa from the change in the NMR spectra. The experiments indicated the formation of the anhydro form at the first stage of the reaction as a result of the removal of a proton from the methylene group [83].



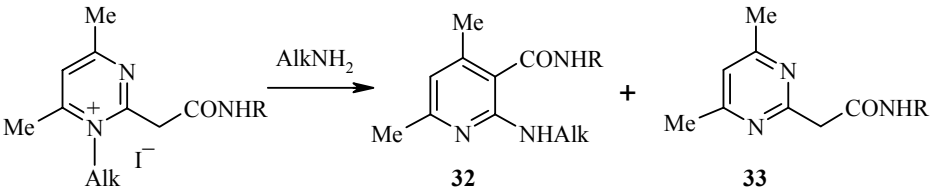
29

The ethiodides reacted similarly. In reaction with diethylamine 2-ethoxycarbonylmethyl-1-ethyl-4,6-dimethylpyrimidinium iodide **30** was converted both into the rearrangement product (the 2-ethylamino derivative of nicotinic acid **31**) and the deethylation product **28** [84].



30 (44%) **31**

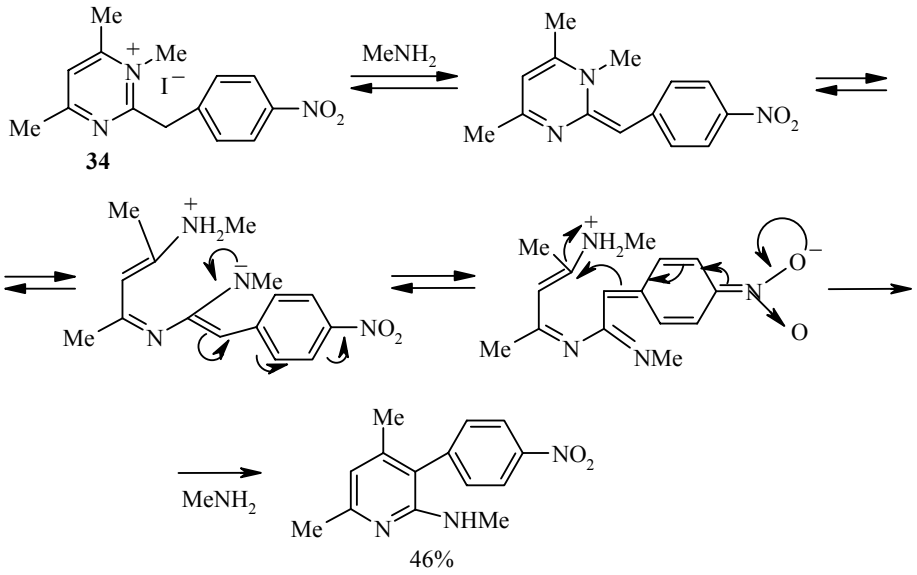
As a rule the rearrangement is promoted by the introduction of an amide group into the side chain of the salt; the yields of the nicotinamide derivatives **32** are significantly higher than the yields of the products **33** from concurrent dealkylation [85-87].



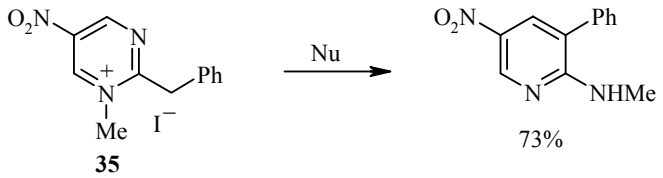
32 **33**

R	Alk	Yield, %	
		32	**33**
H	Me	50	37
H	Et	58	19
Me	Me	51	25
Et	Me	35	10
Me	Et	45	10

Similarly to the Kost–Sagitullin rearrangement it was shown that the yield of the rearrangement product increased significantly in the series of pyrazolo[1,5-*a*]pyrimidines with a nitro group in the pyrimidine ring of the pyrimidinium salts (for the case of derivatives of 2-benzyl-1-methylpyrimidinium iodide **24**) (for comparison, without the NO_2 group the rearrangement of compound **24** gave a yield of 34%) [81, 84]. The introduction of a nitro group into the benzene ring (compound **34**) helps to transfer electron density in the acyclic intermediate from the amino group toward the β-carbon atom of the enamine, thereby facilitating the cyclization stage.

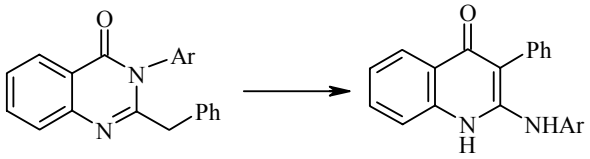


The introduction of the nitro group into the pyrimidine ring (salt **35**) facilitates ring cleavage and subsequent cyclization at the electron-deficient (on account of its proximity to the NO_2 group) terminal carbon atom.



35

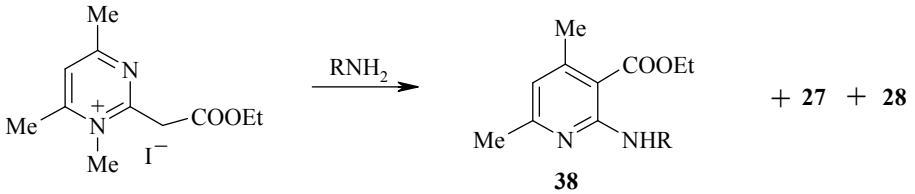
Another pyrimidine system in which the Kost–Sagitullin rearrangement occurs is quinazoline; 2-alkylquinazolones **36** isomerized to the 2-aminoquinolines **37** [67].



36 **37**

1.3. Rearrangements of 2-Alkylpyrimidinium Salts with Inclusion of the Reagent in the Recyclization Product

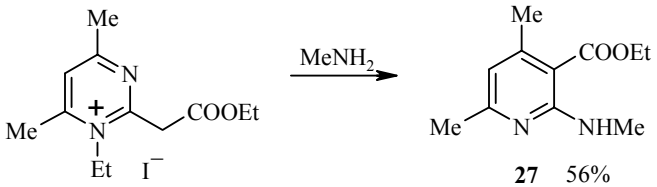
In all the rearrangements of pyrimidinium salts to derivatives of 2-alkylaminopyridine described above the reactions were carried out in alcohol solutions of alkylamines. The absence of water and the presence of a sufficiently strong nucleophilic reagent led to the production, as a rule, of two substances, i.e., the products of the Kost–Sagitullin rearrangement and dealkylation. In the last case the reaction probably took place with direct attack by the amine reagent at the quaternized nitrogen atom of the heterocycle [5, 66, 87, 89]. In all the examples given above the alkyl group of the alkylamine was the same as that at the quaternized nitrogen atom of the pyrimidinium salt. However, if an alkylamine containing a different alkyl substituent was brought into reaction with 2-ethoxycarbonylmethyl-1,4,6-trimethylpyrimidinium iodide (**25**), another product 2-alkylaminonicotinic ester **38** was isolated in addition to the expected demethylation product **28** and recyclization product 3-ethoxycarbonyl-4,6-dimethyl-2-methylaminopyridine (**27**). In this case the Kost–Sagitullin rearrangement took place in two directions: 1) with production of the usual isomerization recyclization product **27**; 2) with inclusion of the amine fragment at position 2 of the obtained pyridine and the formation of the "product from rearrangement with transamination" **38** [82, 87-95].



38

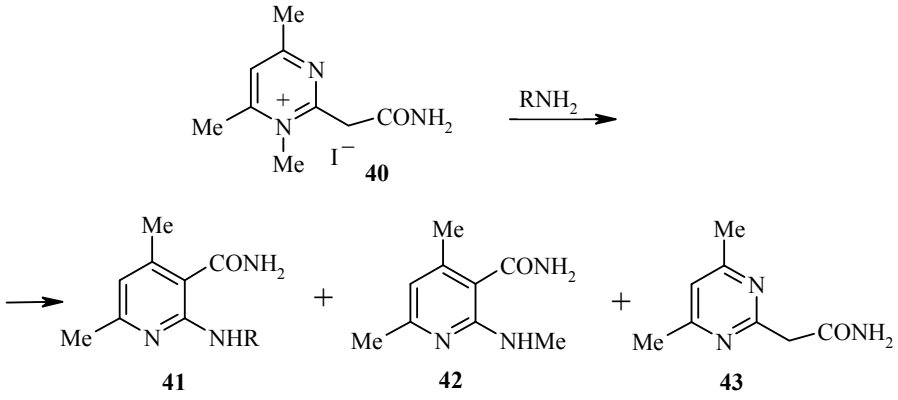
R = Et, Bn, $(CH_2)_2OH$, $(CH_2)_2CO_2Et$, $CH_2CH(OH)Ph$, $CH_2CH(OH)C_6H_4$–*p*-OH

In the reaction of the substituted ethylpyrimidinium iodide **39** with methylamine only the "product from rearrangement with transamination" 3-ethoxycarbonyl-4,6-dimethyl-2-methylaminopyridine (**27**) was isolated with a yield of 56% [84].

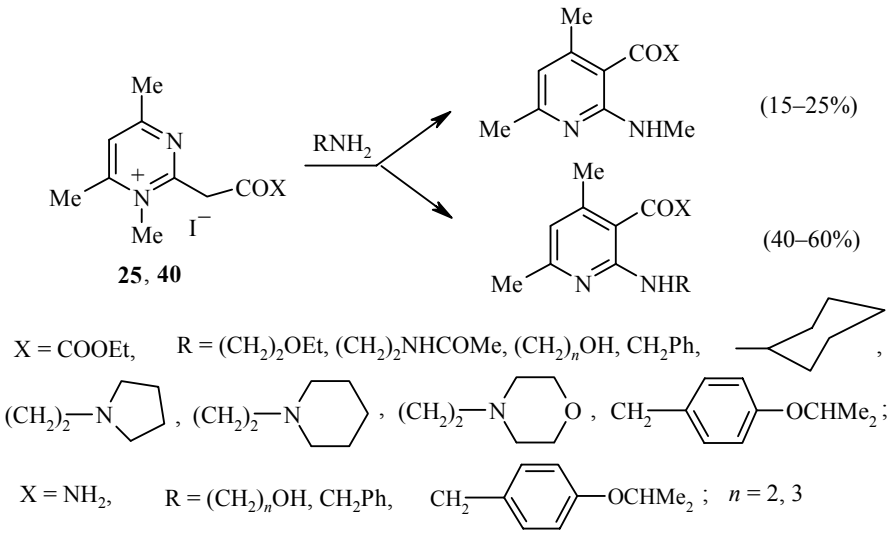


39 **27** 56%

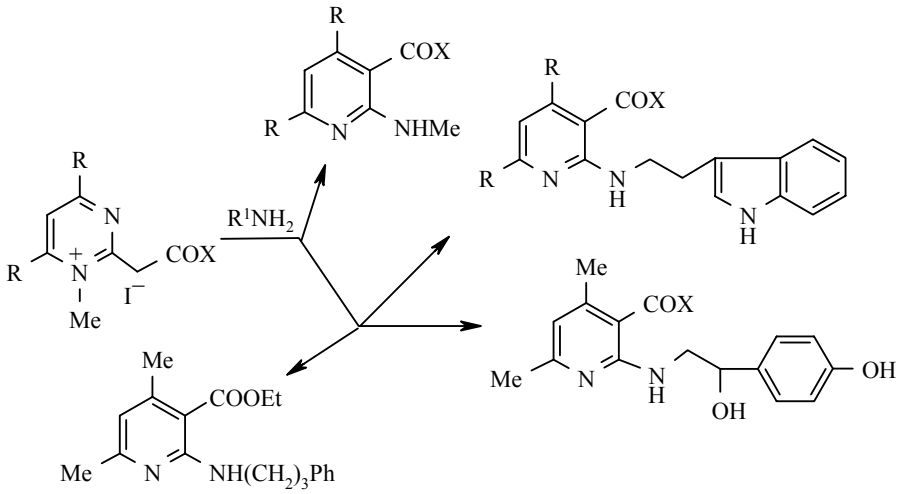
The rearrangement with transamination was also realized in the reactions of the methiodides of substituted pyrimidinylacetamides with alkylamines. In this case the product from rearrangement with transamination was usually the main product [86, 87]. Thus, with ethylamine the methiodide of pyminidinylacetamide **40** mainly forms the 2-ethylamino derivative **41** (55%), and the products of normal rearrangement (without transamination) **42** and demethylation **43** are formed with yields of only 7%.



These data indicate that the Kost–Sagitullin rearrangement with inclusion of the amine fragment in the recyclization product is general in nature in the series of pyrimidinium salts. It is important that this transformation can be used for the introduction of various amine groups at position 2 of the pyridine ring. Replacement of the amine fragments makes the reaction suitable for the synthesis of new pyridines, and by selecting a suitable amine it is possible to introduce various groups, including pharmacophoric groups, into the pyridine ring. In fact, pyrimidinium salts can react with amines containing pharmacophoric groups and rearrange with the formation of two different derivatives of 2-alkylaminonicotinic acid, i.e., without amine exchange (the 2-methylamino derivative) and with a fragment of the amine reagent [96-98]. The rearrangements of the model pyrimidinium salts **25** and **40** under the action of amino alcohols, amino esters, and diamines were studied. It was found that reaction in a fourfold excess of the amine (e.g., in the case of pyrrolidine, piperidine, and morpholine) and without a solvent increases the yield of the product from rearrangement with transamination.

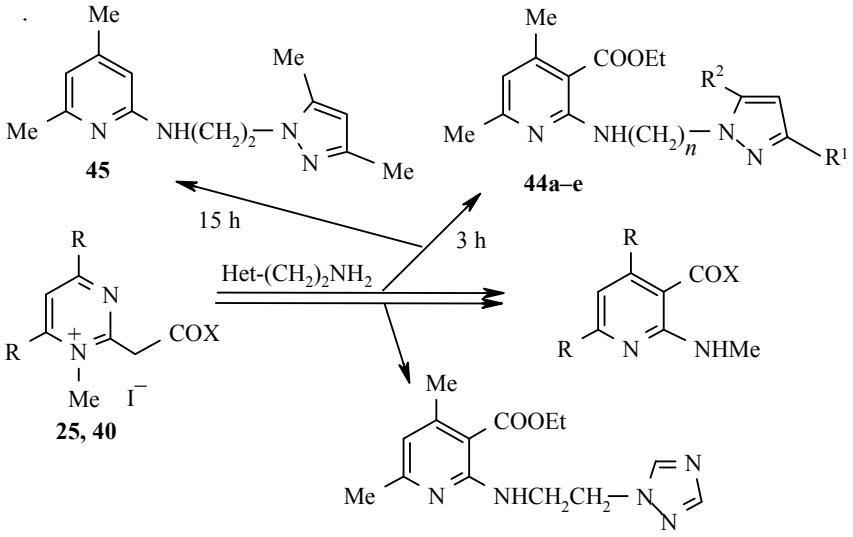


Rearrangement with transamination has also been realized by the action of such biogenic amines as tryptamine, octopamine, and 3-phenylpropylamine [96, 97]. Compounds containing fragments of two biogenic molecules (nicotinic acid and the natural amine) were obtained.



R = H, Me; X = OEt, NH_2

The iodides **25** and **40** also rearranged under the influence of amines containing the biologically active pyrazole and triazole rings [96]. It was noticed that the direction of the reaction depends on its duration. Thus, in the reaction with 3,5-dimethylpyrazolylethylamine (R = R^1 = R^2 = Me; *n* = 2) the derivative of 2-alkylaminonicotinic acid **44d** was obtained after heating for 3 h, and after 15 h the derivative of 2-alkylaminopyridine **45** was obtained (with elimination of the ester group).

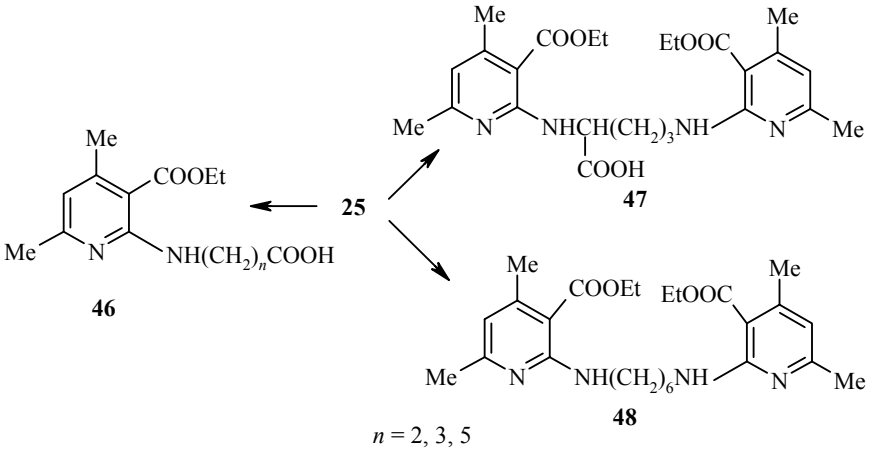


R = H, Me; X = OEt, NH_2, Het = 3-R^1, 5-R^2-pyrazol-1-yl, 1,2,4-triazol-1-yl;

44 **a** R^1 = R^2 = H; **b** R^1 = H, R^2 = Me; **c** R^1 = Me, R^2 = H;
d, e R^1 = R^2 = Me; **a–d** *n* = 2, **e** *n* = 3

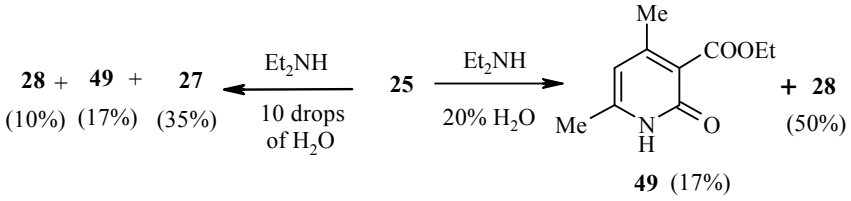
Rearrangement with exchange of the amine fragment can also take place under the action of amino acids and their esters. Derivatives of nicotinic acid **46** containing fragments of β-alanine and its ester, γ-aminobutyric acid, and aminocaproic acid were synthesized. With ornithine, which contains two amino groups, the bisadduct

47 was obtained in addition to the normal rearrangement product, and this was first observed during Kost–Sagitullin rearrangements in [97]. Similarly, reaction with the participation of both amino groups can also take place with hexamethylenediamine, where the bispyridyl derivative of hexamethylenediamine (compound **48**) was isolated with a low yield (~18%) in addition to the product of the normal rearrangement (without amine exchange) [98].

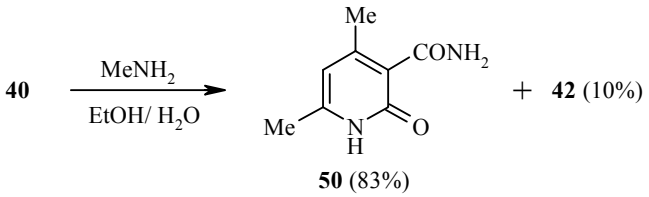


1.4. Rearrangements of the Alkiodides of 2-Pyrimidineacetic acid Derivatives in the Presence of Water

The direction of the Kost–Sagitullin rearrangement depends not only on the amine reagent used in the reaction but also on the solvent and particularly on the presence of water in the reaction medium. It has already been mentioned above that hydrolysis and degradation of the molecule compete with the rearrangement in aqueous solutions. It was found, however, that a limited amount of water does not prevent the recyclization to pyridine derivatives; in this case, it is true, the rearrangement takes place in a different way with the formation of a pyridone derivative. The amount of water in the reaction mixture can have a substantial effect on the course of the reaction. Thus, in a water–alcohol solution (~20% water) of diethylamine the iodide **25** mainly forms the demethylation product **28** (50%) and only a small amount of the pyridone **49** (17%). A smaller amount of water leads to the formation of the recyclization product **27** (35%) and the pyridone (17%) and reduces the amount of the demethylation product **28** to 10% [99].



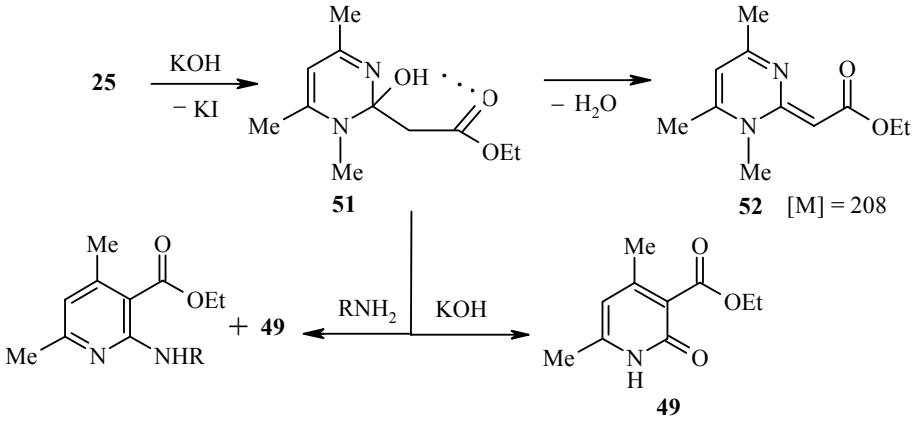
Formation of the pyridone often becomes the main direction in the Kost–Sagitullin rearrangement. Thus, when heated in a water–alcohol solution of methylamine 2-(carbamoyl)methyl-1,4,6-trimethylpyrimidinium iodide forms 3-carbamoyl-4,6-dimethyl-1,2-dihydro-2-pyridone (**50**) with a yield of 83% and also the corresponding 2-methylamino derivative, i.e., the normal rearrangement product **42** [87].



1.5. The Direction of Initial Attack of the Nucleophile in the Kost–Sagitullin Rearrangement

From the very beginning, after discovery of the Kost–Sagitullin rearrangement, the mechanism of this transformation was described by analogy with the more closely studied Dimroth rearrangement as attack at position 6. However, the results of quantum-chemical calculations showed that the preferred direction of attack may be position 2 of the pyrimidine ring, particularly for the rearrangements taking place with transamination [100].

Experimental evidence for the possibility of attack by the nucleophile at position 2 was obtained during the reaction (in the cold) of the pyrimidinium salt **25** with an alcohol solution of potassium hydroxide; the intermediate compound **51**, the structure of which was confirmed by NMR, IR, and mass spectrometry, was isolated [101].



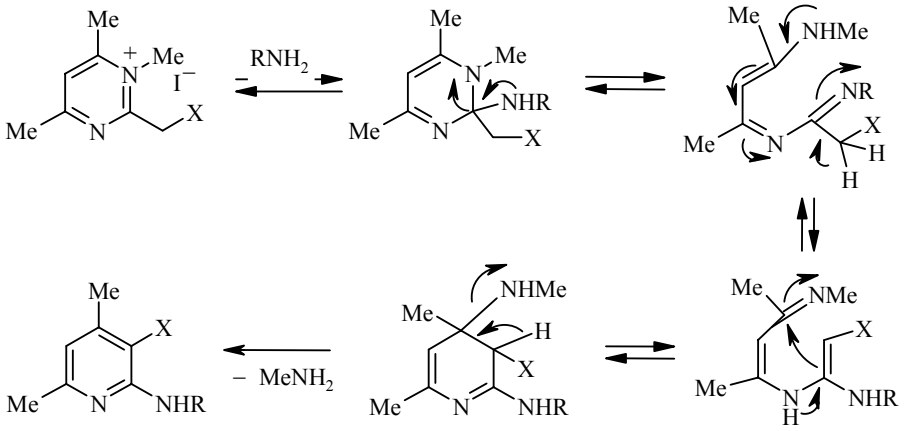
In the IR spectrum of compound **51** the frequency of the stretching vibrations of the ester carbonyl group underwent a significant shift (by 90 cm^{-1}) compared with the absorption region of this group in the initial pyrimidinium salt **25** (1640 instead of 1730 cm^{-1}). A band for the hydroxyl group in the region of 3300-3500 cm^{-1}, absent in the IR spectrum of the initial salt, was also observed in the spectrum of **51**. It is significant that dilution of a solution of **51** in carbon tetrachloride did not shift the absorption frequency of the carbonyl group, indicating unambiguously the presence of an intramolecular and not an intermolecular hydrogen bond in the investigated sample. This is only possible if the hydroxyl group adds to the $C_{(2)}$ atom of the pyrimidine.

The ^1H NMR spectrum of the base **51** contains a broad signal for the proton of the hydroxyl group and also reveals an upfield shift of the signals for the protons of all the groups attached to the pyrimidine ring.

In the mass spectrum of the adduct **51** a molecular ion $[M]^+$ 208, corresponding to its anhydro base **52** formed during the elimination of water from compound **51**, is observed.

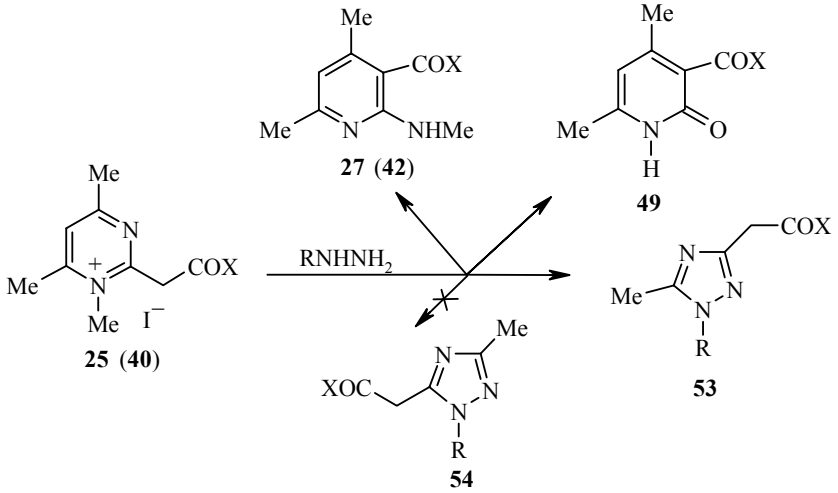
When compound **51** was heated in an alcohol solution of potassium hydroxide the pyridone **49**, also released during Kost–Sagitullin rearrangements, was obtained with a yield of 35%. In the reaction of the same substance **51** with alcohol solutions of various amines (methylamine, benzylamine, ethanolamine) it was

transformed into the corresponding aminopyridines – the products from rearrangement with transamination. The pyridone **49** was also the main product in these reactions. All this made it possible to propose a scheme for the rearrangement with transamination through initial attack by the nucleophile at position 2 of the pyrimidine ring.



1.6. Transformations of Pyrimidinium Salts under the Influence of Hydrazine Derivatives

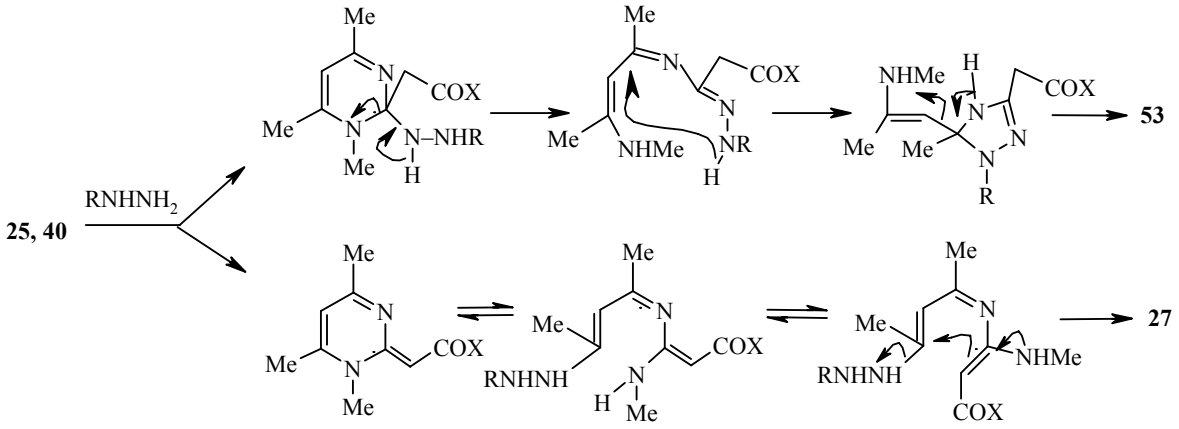
1.6.1. Reaction of Pyrimidinium Salts with Monosubstituted Hydrazines. As a rule, the reactions of hydrazine derivatives with pyrimidines and pyrimidinium salts lead to the formation of pyrazole derivatives [24-27]. More rarely, 1,2,4-triazoles are formed [102-105]. In the reaction of the pyrimidinium methiodides **25** and **40** with monosubstituted hydrazines the transformations can take place both with the production of Kost–Sagitullin rearrangement products (derivatives of 2-methylaminonicotinic acid **27**, **42**, or **49** were isolated) and with the formation of 1,2,4-triazole derivatives **53** [97, 98, 106].



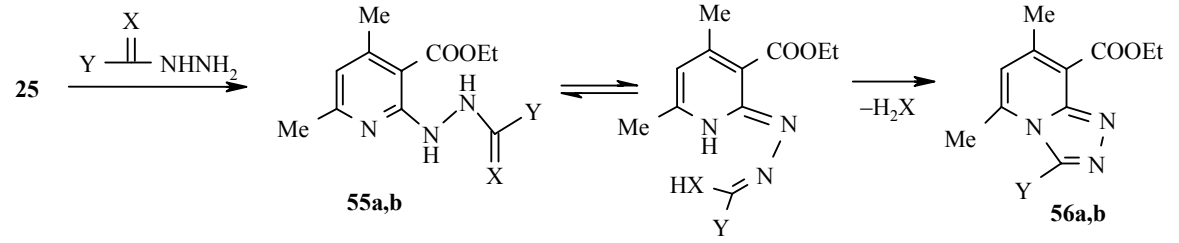
X = OEt, NH_2; R = CH_2CH_2CN, CH_2COOEt, Ph, *p*-$HO_2CC_6H_4$, 2-benzyl-6-methylpyrimid-4-yl

During the formation of the triazole derivative the first stage of recyclization (attack by the hydrazine derivative) probably takes place at position 2 of the pyrimidine, and subsequent heterocyclization involving the second nitrogen atom of the hydrazine leads to closure of the 1,2,4-triazole ring. However, the transformation also takes place through attack by the nucleophile at position 6, leading to isomerization recyclization to pyridine derivatives.

It was shown on the basis of the NOESY ^{1}H NMR spectra that in all cases only one of the possible isomers of 1,2,4-triazole is formed, i.e., the ester (or amide) of 1-substituted 5-methyl-1,2,4-triazole-3-acetic acid **53**. In the spectra of all the compounds a cross peak is observed between the protons of the substituent at the $N_{(1)}$ atom and the methyl group [106]. Thus, if the substituent at position 1 of the triazole ring is a phenyl group or its *para*-substituted analog a cross peak is observed between the signals of the methyl group and the *ortho*-protons of the benzene ring, indicating conclusively that the methyl group is at position 5 of the triazole. Similarly, the spectra of compounds **53**, which are products from reaction of the salts **25** and **40** with 2-benzyl-4-hydrazino-6-methylpyrimidine, contain a clear cross peak between the protons of the methyl group of the triazole ring and the H-5 proton of the pyrimidine fragment. The same pattern is observed in the case of aliphatic substituents at position 1. Interaction between the protons of the substituent at the $N_{(1)}$ atom and the methylene group of the acetic acid fragment was not observed in any of the spectra, and this could indicate the formation of compound **54**. The scheme of the transformations is presented below:

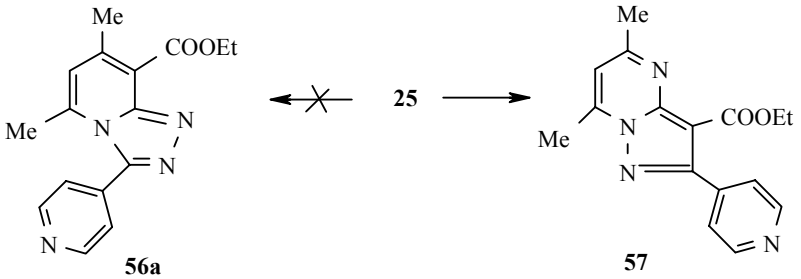


1.6.2. Reaction of Pyrimidinium Salts with the Hydrazides of Carboxylic Acids. The reaction of the iodide **25** with the hydrazides of carboxylic acids was studied in a continuation of investigations into the reactions of substituted hydrazines with 1,2-dialkylpyrimidinium salts. In this case the reactivity of one of the nitrogen atoms of the reagent, attached to the acyl group, could be insufficient for participation in the heterocyclization process. A possible Kost–Sagitullin rearrangement with inclusion of a fragment of the amine reagent (compound **55**) was not therefore ruled out. However, it was found that the transformation here takes place in a different direction. Substances assigned the structure of 1,2,4-triazolo[1,5-*a*]pyridine derivatives **56a**,**b** on the basis of NMR spectroscopy and mass spectrometry were isolated during the reaction of the salt **25** with isonicotinohydrazide and aminoguanidine together with the demethylation product, and in the case of aminoguanidine, the product from the normal Kost–Sagitullin rearrangement (compound **27**) [107]. It was assumed that after the formation of the "product from rearrangement with transamination" (compound **55**) repeated cyclization with the formation of the triazole ring occurs.

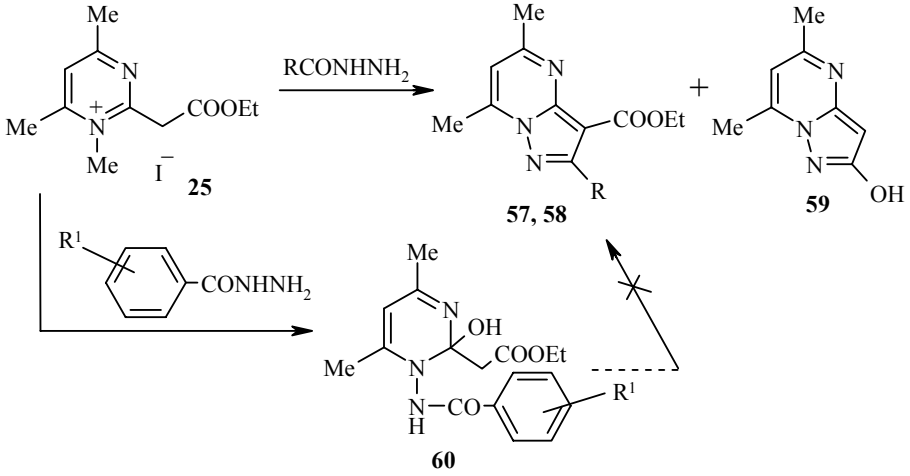


a X = O, Y = 4-Py; **b** X = NH, Y = NH_2

More recently, however, it was demonstrated on the basis of X-ray crystallographic analysis of the isolated compound **56a** (the product from reaction of the salt **25** with isonicotinohydrazide) that the assigned structure was incorrect. It was proved unambiguously that the isomeric 3-ethoxycarbonyl-5,7-dimethyl-2-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidine (**57**) and not the 1,2,4-triazolo[1,5-*a*]pyridine derivative **56a** is formed [97, 98].



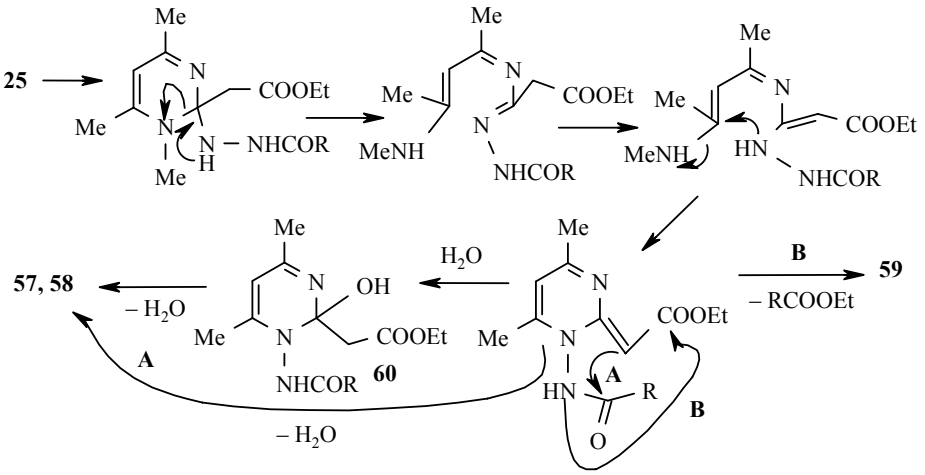
A similar result was observed during X-ray crystallographic analysis of the product from reaction of the salt **25** with cyanoacetohydrazide. It was shown that 2-cyanomethyl-3-ethoxycarbonyl-5,7-dimethyl-pyrazolo[1,5-*a*]pyrimidine (**58**) is formed together with the 2-methylaminopyridine **27**. Similar rearrangement of a pyrimidinium salt to a pyrazolo[1,5-*a*]pyrimidine derivative was also detected during the action of the hydrazides of certain other carboxylic acids, demonstrating the general nature of this previously undescribed recyclization of 1,2-dialkylpyrimidinium salts. In reactions with the hydrazides of aliphatic carboxylic acids (formic, acetic, cyanoacetic, substituted pyrimidinylacetic) recyclization leads to the formation of yet another derivative of pyrazolo[1,5-*a*]pyrimidine, i.e., 2-hydroxy-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**59**). It is interesting that the intermediate pseudo bases **60** and not the pyrazolo[1,5-*a*]pyrimidine derivatives were isolated in the reactions with the hydrazides of benzoic acids.



R = NH_2, Me, CH_2CN, 3-pyrazolyl, 4-Py, (4,6-dimethyl-2-pyrimidyl)methyl;

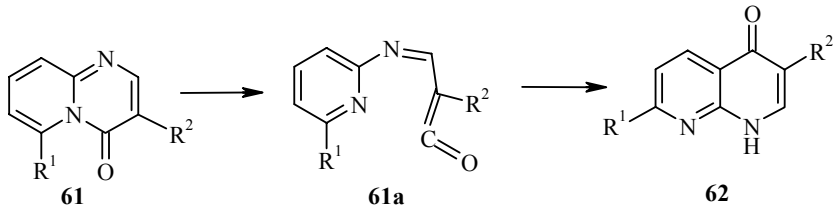
R^1 = H, *p*-NO_2, *m*-NO_2, *o*-OH

A possible scheme for the transformations is given below.



2. OTHER N–C RECYCLIZATIONS OF PYRIMIDINES

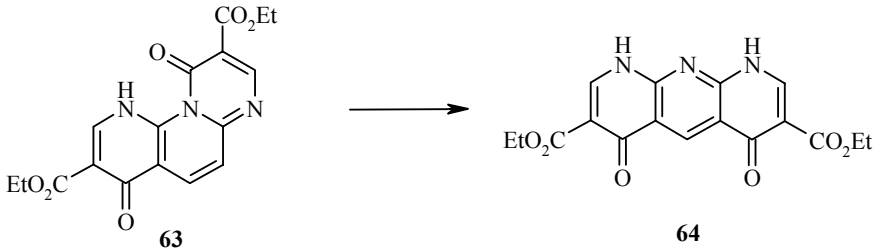
Several examples of recyclizations where a pyrimidine ring, being annelated with a six-membered ring at bond *a* or *b*, can undergo thermal or nucleophilic rearrangement to a pyridine ring condensed with the same six-membered ring have been reported. An example of such a transformation is thermally initiated acyl transfer from a nitrogen to a carbon atom with rearrangement of pyrido[1,2-*a*]pyrimidine derivatives **61** to the corresponding pyrido[2,3-*b*]pyridines ([1,8]naphthyridines) **62** [108-110].



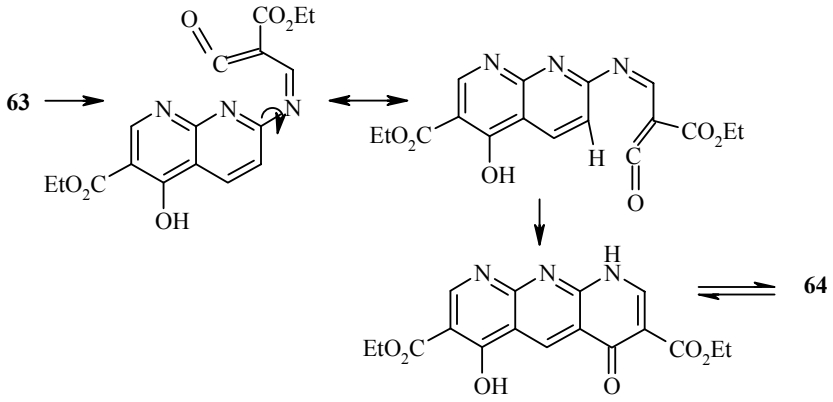
R^1 = Me, Et, OEt, OH, NHAc; R^2 = CO_2Et, COMe, CN, $COCF_3$, Me, Et, Ph

The rearrangement requires the presence of a substituent in the pyridine ring at the position adjacent to the bridging nitrogen atom. The authors consider that the presence of the oxo group and the other substituent adjacent to the nitrogen atom in one plane leads to strain in the $C_{(4)}$–$C_{(5)}$ bond, as a result of which the latter is deformed. The removal of such deformation is the motivating force of the isomerization. It was suggested that the reaction takes place through the intermediate ketene **61a**.

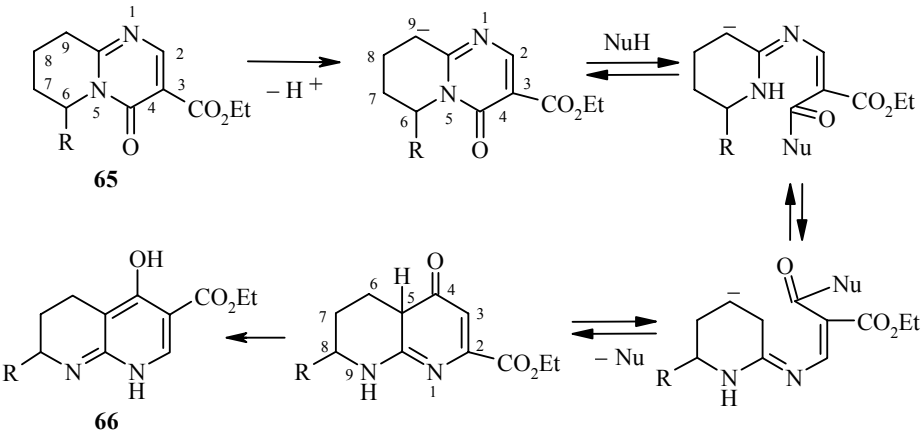
Similar acyl migration from a nitrogen atom to a carbon atom was observed during the isomerization of pyrimido[1,2-*a*][1,8]naphthyridine **63** to the naphthyridine derivative **64** [110].



The rearrangement takes place with cleavage of the N–C bond and the formation of a new C–C bond.



In water in the presence of pyrrolidine or piperidine (20°C, 2 h) 3-ethoxycarbonyl-6-methyl(ethyl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidines (**65**) were rearranged with yields of 60-90% to the 3-ethoxycarbonyl-7-methyl(ethyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-4-ones (**66**) [111, 112]. The authors mentioned that the rearrangement takes place very slowly in the absence of the base; with R = Me and at 20°C the reaction took six months, and with R = Et it took several years. It was also noted that it is not desirable to use bases with more clearly defined nucleophilic character (NH_3, NH_2OH), since they react with the ester group [112].

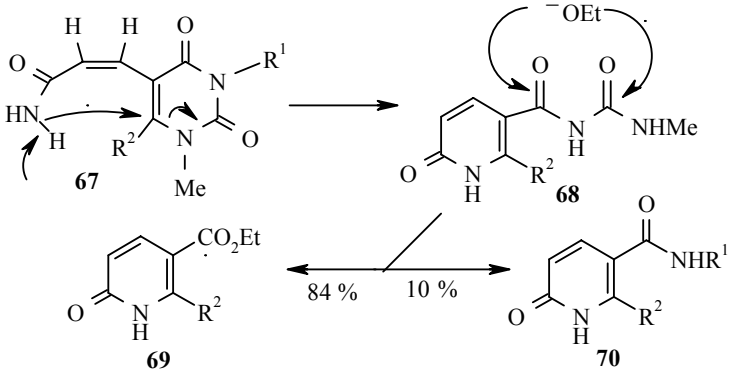


Schematically, the described rearrangements are similar to the Kost–Sagitullin rearrangement and are examples of N–C recyclization.

3. ISOMERIZATION RECYCLIZATION WITH SUBSTITUTION OF THE NCNC FRAGMENT OF PYRIMIDINE BY THE NCCC FRAGMENT OF THE SIDE CHAIN

Substitution of the four-atom fragment of the pyrimidine ring was observed in the reactions of certain derivatives of uracil containing a substituent with the CCCN fragment at position 5. Treatment of the *Z*-isomer of 1,3-dialkyl-5-(2-carbamoylvinyl)uracil **67** with an ethanol solution of sodium ethoxide leads to initial attack by the terminal amino group of the side chain at position 6 of the uracil molecule. Cleavage of the $C_{(6)}$–$N_{(1)}$ bond

and formation of the C–N bond give the pyridin-6(1H)-one **68**. Subsequent attack by the ethoxide ion at the carbonyl groups of the side chain leads to two derivatives of pyrid-6-one **69** and **70** [113]. Analogous results were obtained for the *E*-isomer.



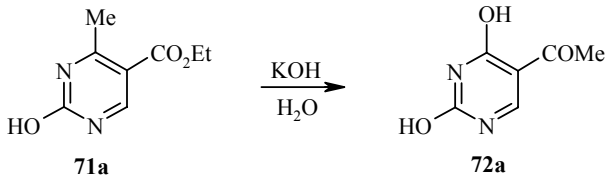
R^1 = Me, R^2 = H; R^1 = Et, R^2 = H; R^1 = R^2 = Me

At the stage of the transition from the initial pyrimidine to the intermediate adduct **68**, i.e., before its transformation into the stable pyridones, the recyclization is isomerization recyclization, since it is realized on account of the participation of only the fragments of the initial substance in the transformation. At the same time it differs from the Dimroth and Kost–Sagitullin rearrangements in that it is in fact essentially an example of intramolecular substitutive recyclization, in which the new heterocycle is formed as a result of substitution of the four-atom fragment (NCNC) of the pyrimidine by the four-atom fragment (NCCC) of the side chain.

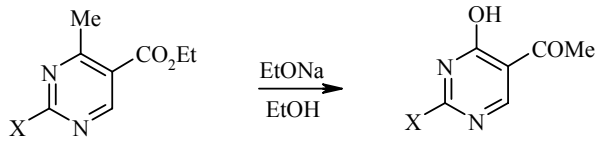
4. C–C RECYCLIZATIONS AND ANOMALOUS DIMROTH REARRANGEMENTS IN THE PYRIMIDINE SERIES

4.1. C–C Recyclizations of 5-Ethoxycarbonylpyrimidines

Until recently there had only been a few fragmentary and unsystematic references to examples of such transformations. Thus, in 1933 Bergmann and Johnson noted that 5-ethoxycarbonyl-2-hydroxy-4-methylpyrimidine **71a** is converted (with a small yield) into 5-acetyl-2,4-dihydroxypyrimidine (**72a**) when heated in aqueous potassium hydroxide solution [114].



In 1982 Vartanyan and coworkers were able to subject 2-mercapto- and 2-amino-5-ethoxycarbonyl-4-methylpyrimidines **71b**,**c** to such a transformation. Under the influence of an alcohol solution of sodium ethoxide they rearranged into the corresponding 5-acetyl-4-hydroxypyrimidines **72b**,**c** [115].

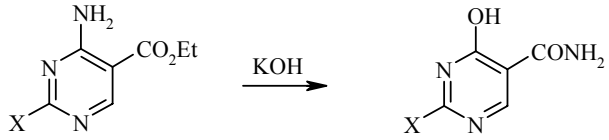


71 **72**

a X = OH; **b** X = SH; **c** X = NH_2

However, in the cited papers, both then and later, neither the above-mentioned nor other authors have made any attempts to study such transformations in greater detail.

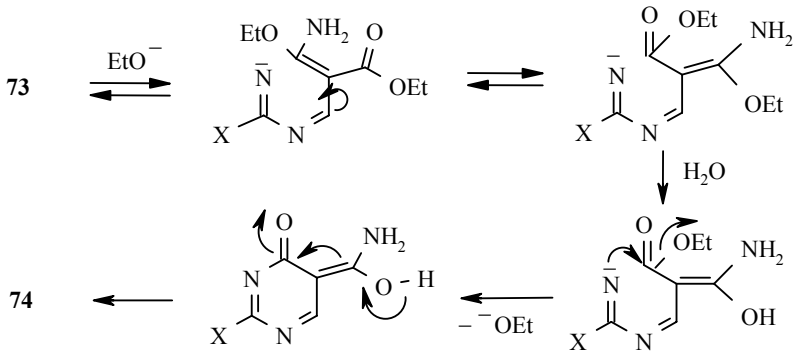
Recently it was shown that during brief boiling in an aqueous solution of alkali the substituted 4-amino-5-ethoxycarbonylpyrimidines **73a-c** rearrange with yields of 48-59% into derivatives of 5-carbamoyl-4-hydroxypyrimidine **74a-c**. Such a transformation does not take place in an alcohol solution of sodium ethoxide [116].



73a–c **74a–c**

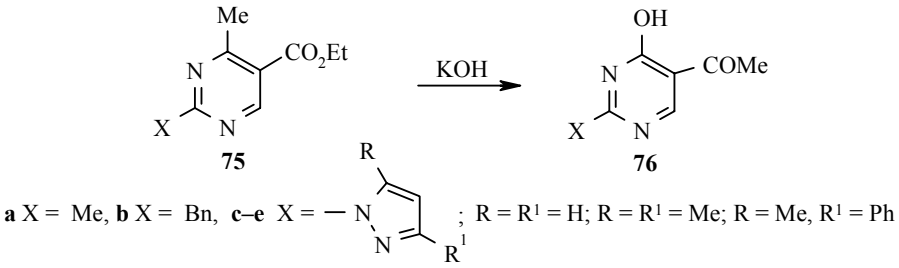
73, **74** **a** X = OH; **b** X = SH; **c** X = $PhCH_2$

The described recyclization takes place by substitution of a ring carbon atom ($C_{(4)}$) by the exocyclic carbon of the ester group. Nucleophilic attack and ring opening in this transformation can probably take place reversibly under the influence of the ethoxide ion. However, the last stage of recyclization (ring formation) can and must be realized only with the addition of water, which probably allows the acyclic intermediate to be stabilized as a result of conversion of the enolic form into the carbonyl form. The presence of alkali is an essential condition for the rearrangement.

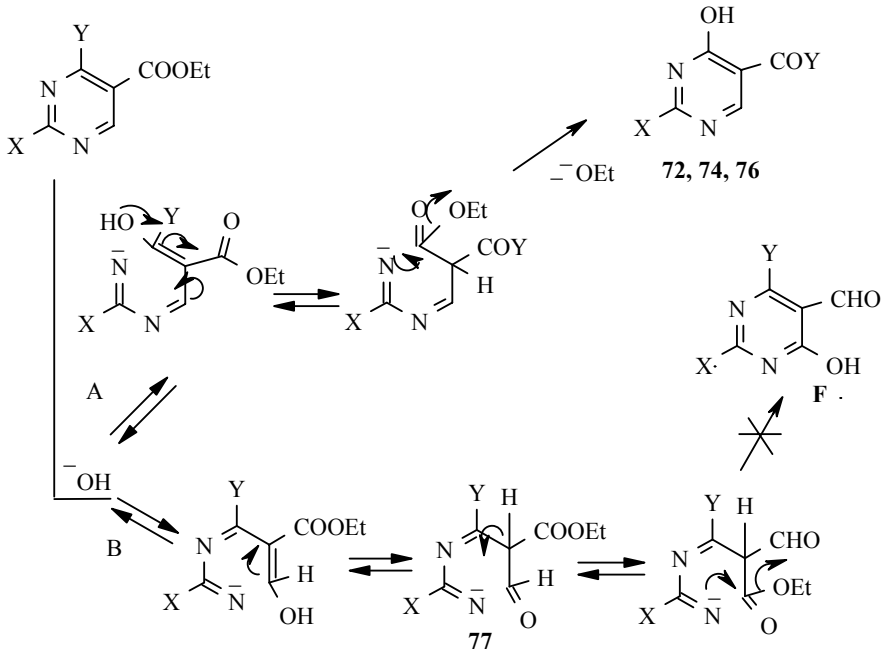


We note that this result, i.e., the need for the presence of hydroxide ion in the reaction medium, is in keeping with data recorded earlier during the Kost–Sagitullin rearrangement for condensed systems containing a bridging nitrogen atom [65, 78, 80].

A similar transformation is observed in the reaction of 5-ethoxycarbonyl-2,4-dimethylpyrimidine (**75a**), 2-benzyl-5-ethoxycarbonyl-4-methylpyrimidine (**75b**), and 5-ethoxycarbonyl-4-methyl-2-(1-pyrazolyl)-pyrimidines **75c-e** with alkali. When 5-ethoxycarbonylpyrimidines **75a**,**b** are boiled briefly with an alcohol solution of potassium hydroxide and, in the case of the pyrazolylpyrimidine derivatives **75c-e**, even at room temperature, the corresponding 5-acetyl derivatives **76** are formed with yields of 73-82% [117, 118].

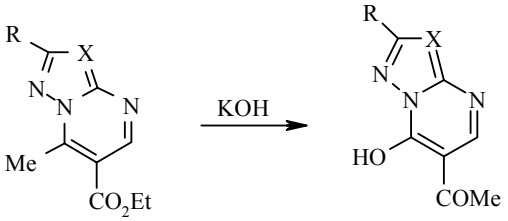


In all the described examples of the rearrangements (4-amino and 4-methyl derivatives) the reaction probably begins with attack at position 4 of the pyrimidine and goes through subsequent opening of the ring and cyclization with attack by the nitrogen atom at the carbon atom of the ester group (path A). It was expected that the preferred direction of attack by the nucleophile might be attack at the unsubstituted position 6 of the pyrimidine ring and, as a consequence of such recyclization, formation of the 5-formylpyrimidine derivative **F** (path B). However, the probable formation of the intermediate **77**, containing the more electrophilic and consequently more active formyl group, at the cyclization stage during attack and opening of the pyrimidine ring in such a direction should probably exclude the possibility of concurrent attack at the ester carbon atom and should, as a result, lead to the reversible formation of the initial molecule. Conversely, attack at position 4 will lead irreversibly to the thermodynamically more favorable configurations of the 5-acetyl- or 5-carbamoylpyrimidine derivatives **72**, **74**, and **76**.



4.2. C–C Recyclizations in the Azolo[1,5-*a*]pyrimidine Series

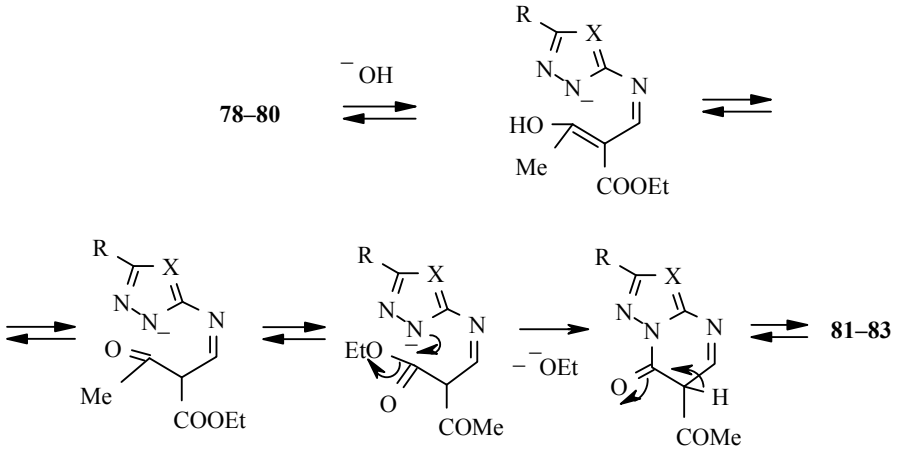
C–C Recyclization was observed in the condensed pyrimidine series; 6-ethoxycarbonyl-7-methyl-azolo[1,5-*a*]pyrimidines **78**-**80** were transformed after a few minutes into the corresponding 6-acetyl-7-hydroxy derivatives **81**-**83** (with yields of 58-67%) even at room temperature [119, 120].



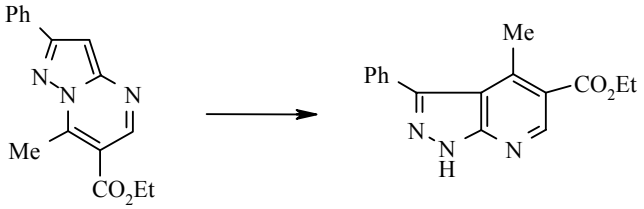
78–80 **81–83**

X = CH, N

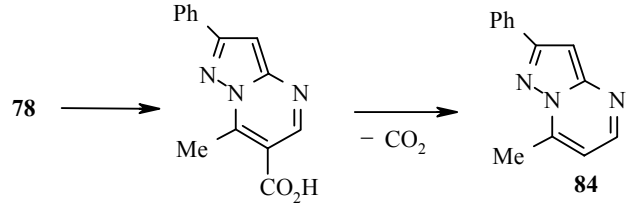
The scheme of such a transformation is presented below.



During study of the rearrangement of pyrazolo[1,5-*a*]pyrimidines the possibility of another transformation (concurrent C–C recyclization) to pyrazolo[3,4-*b*]pyridine derivatives (the Kost–Sagitullin rearrangement type) was not ruled out. Such a transformation could take place as a result of cleavage of the N–$C_{(7)}$ bond of the pyrimidine ring followed by cyclization with attack at the $C_{(4)}$ atom of the azole.

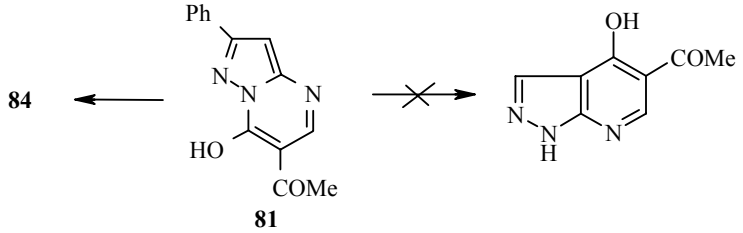


However, when 6-ethoxycarbonyl-7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**78**) was boiled for 20 h with a 15% water–alcohol solution of potassium hydroxide, 7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**84**) and not the expected Kost–Sagitullin rearrangement product was formed.

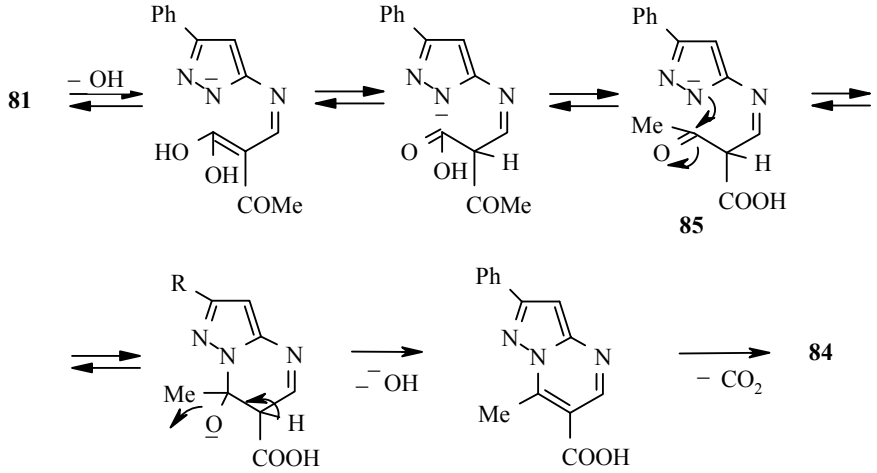


84

An attempt at rearrangement of the 6-acetyl derivative **81** under the same conditions also did not lead to the corresponding Kost–Sagitullin recyclization product; the only isolated substance was the same pyrazolo-[1,5-*a*]pyrimidine **84** [120, 121].



The formation of one and the same compound **84** in the two reactions can probably be explained by the occurrence of a series of successive recyclization transformations, including opening of the pyrimidine ring, its cyclization, and decarboxylation. Evidence for the chain of recyclizations is also provided by the chromatographic detection and disappearance of compound **81** during the transformation of compound **78** into compound **84**.

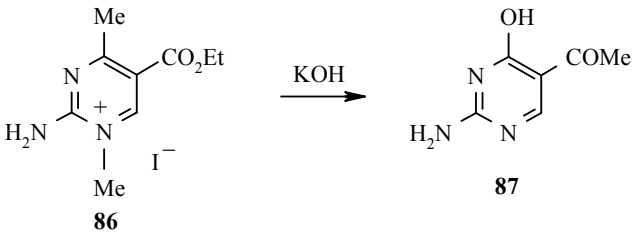


The production of compound **84** and the absence of the Kost–Sagitullin rearrangement are explained by the insufficient nucleophilicity of the $C_{(4)}$ atom of the pyrazole ring formed in the intermediate **85** compared with the $N_{(1)}$ atom.

4.3. Examples of C–C Recyclizations in the Series of Pyrimidinium Salts

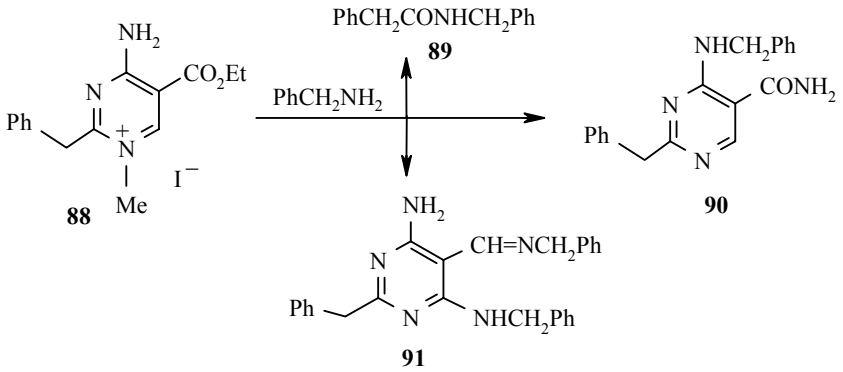
Attempts were made to study the recyclization of pyrimidines on models that are potentially capable of entering simultaneously into Dimroth and/or Kost–Sagitullin rearrangements and undergoing transformations of the C–C recyclization type.

5-Acetyl-2-amino-4-hydroxypyrimidine (**87**) was obtained with a yield of 77% by the reaction of 2-amino-5-ethoxycarbonyl-1,4-dimethylpyrimidinium iodide (**86**) with an alcohol solution of potassium hydroxide.



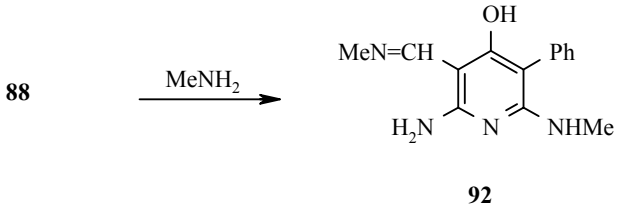
86 **87**

A mixture of three substances, i.e., the degradative aminolysis product **89** and the two products from C–C recyclization 2-benzyl-4-benzylamino-5-carbamoylpyrimidine (**90**) and 4-amino-2-benzyl-6-benzylaminopyrimidine-5-carbaldehyde benzylimine (**91**), was obtained in the reaction of 4-amino-2-benzyl-5-ethoxycarbonyl-1-methylpyrimidinium iodide (**88**) with benzylamine [119]. The formation of compounds **90** and **91** results from C–C recyclizations taking place with attack at positions 4 and 6 respectively.



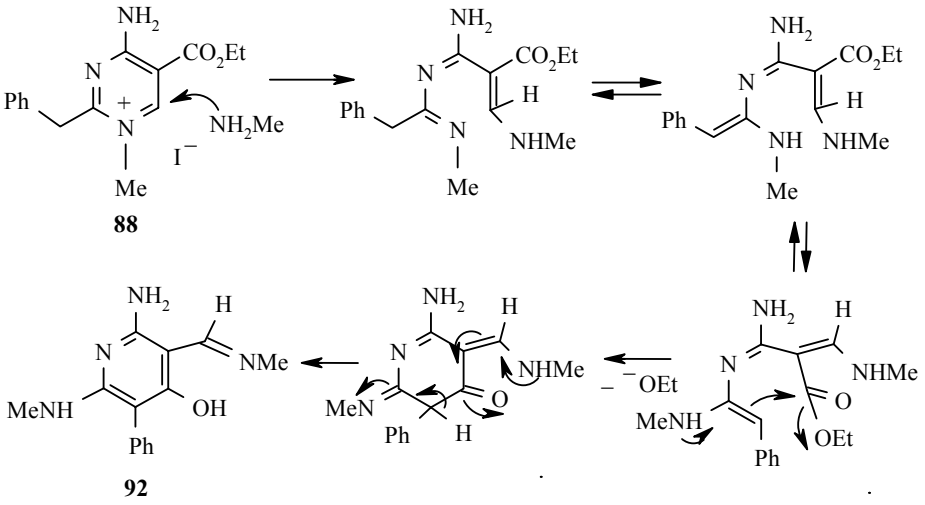
88 **90** **91**

Heating of the same salt **88** with an alcohol solution of methylamine led with a yield of 55% to 2-amino-4-hydroxy-6-methylamino-5-phenylpyridine-3-carbaldehyde methylimine (**92**).



92

The transformation scheme, presented below, includes opening of the pyrimidine ring at the $N_{(1)}$–$C_{(6)}$ bond, subsequent synchronous rotation [i.e., occurring simultaneously (in parallel) both about the $C_{(2)}$–$N_{(3)}$ bond and about the $C_{(4)}$–$C_{(5)}$ bond), and finally the cyclization that completes the rearrangement (formally two rearrangements – Kost–Sagitullin and C–C recyclization).



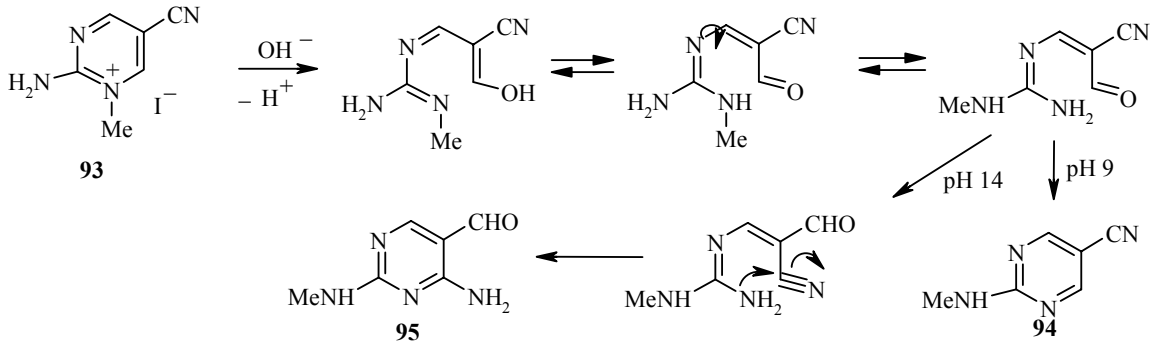
88

92

4.4. Anomalous Dimroth Rearrangements

While determining the point of C–C recyclization in a series of other isomerization recyclizations of pyrimidines, it should be noted that this transformation, while differing from the Dimroth and Kost–Sagitullin rearrangements, does have some features in common with it. All these rearrangements are recyclizations taking place by the so-called ANRORC mechanism, which includes three main stages, giving it the name: Additional Nucleophile – Ring Opening – Ring Closure [38]. The closest to the C–C recyclizations and, more importantly, to the above-mentioned rearrangement of the iodide **88** to the methylimine **92** are the anomalous Dimroth rearrangements, which also take place with ring opening (cleavage of the N–C bond) but take part in the reaction at the cyclization stage through the exocyclic carbon atom (like the C–C recyclizations).

This applies in particular to rearrangements of the 5-cyano derivatives of 2-imino-1-methyl-1,2-dihydropyrimidines **93**. After ring opening (the usual first stage of the reaction for Dimroth rearrangements) the next stage of the anomalous recyclization takes place in a different way with participation of the carbon of the nitrile group. Thus, whereas the reaction of compound **93** with alkali at pH 9 leads to the expected Dimroth rearrangement product 5-cyano-2-methylaminopyrimidine (**94**), the main product of the transformation at pH 14 is 6-amino-5-formyl-2-methylaminopyrimidine (**95**) [122].

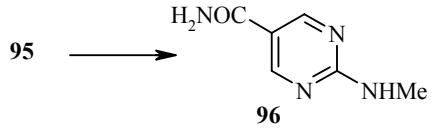


93

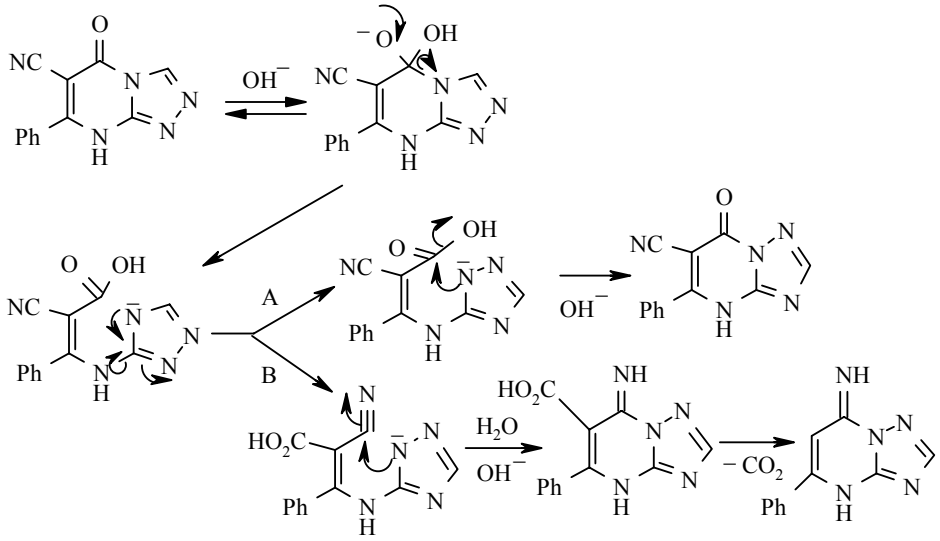
95

94

After prolonged treatment in an alkaline solution another substance is formed, i.e., the product from a repeated anomalous Dimroth recyclization [122].



This form of the Dimroth rearrangement, i.e., with inclusion of the exocyclic carbon atom in the recyclization process, has been called the "anomalous Dimroth rearrangement." A similar anomalous transformation was observed during the rearrangements of triazolopyrimidines (path B) and takes place in parallel with the classical Dimroth rearrangement (path A) [123].



Thus, as the present review has demonstrated, in spite of difficulties arising from the possibility of easy degradation of the molecule involving cleavage of the C–N bonds in the ring or the occurrence of alternative transformations, study of nucleophilic recyclizations, including Kost–Sagitullin rearrangements, in pyrimidines is extremely interesting. This region of heterocyclic chemistry is still largely uninvestigated and is full of uncertain transformations. With the appropriate choice of reaction conditions, reagents, and pyrimidine substrates it is possible to obtain unexpected results that are of interest both at the preparative level and from the standpoint of revealing the essential characteristics of this heterocyclic system. Consequently, in spite of more than 125 years of history of research into the chemistry of pyrimidine, these recyclization transformations retain their relevance and continue to be of interest to research workers.

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