ENAMINE REARRANGEMENT

Sergei P. Gromov* and Aleksei N. Kost ✠

Institute of Chemical Physics, Russian Academy of Sciences, Kosygin Street 4, Moscow, 117334, Russia, ✠ Deceased

Abstract - The data on enamine rearrangement of heterocyclic systems containing a pyridine ring are generalized and systematized over the period of up to 1992.

CONTENTS

I. INTRODUCTION

The pyridine ring as an aromatic system is relatively stable against cleavage, though to a lesser extent than benzene. The best studied version of pyridine ring nucleophilic opening has until recently been considered to be Zincke-König reaction,[1] that is, the quaternized pyridine ring opening by aromatic amines with formation of glutaconic dialdehyde dianils.

In recent years, however, much data have been accumulated related to the transformations of the pyridine ring under the action of nucleophiles, including a number of new rearrangements, those in particular, which are of general importance for the chemistry of heterocyclic compounds.

In our opinion, of general interest to organic chemists engaged in the chemistry of heterocycles may be the enamine rearrangement of heterocyclic compounds, discovered by us and hitherto unknown. A complete and special review on enamine rearrangement is lacking. In our review[2] the initial results were summarized on the enamine rearrangement of pyridine derivatives over the

period of up to the end of 1979. Here, the recent literature data (up to 1992) are systematized and an attempt is made to develop a general point of view on the regularities of the course of this reaction.

In a series of related reactions discussed below, the exocyclic atom which becomes incorporated into the ring, is the β-carbon atom of the enamine fragment either present in the starting molecule or appearing during the reaction. In other words, pyridine C-N bond fission occurs initially, followed by recyclization of an acyclic intermediate with the formation of a C-C bond. These reactions together may therefore be defined as an enamine rearrangement, which formally proceeds (except for the cases with the amino-group exchange) without incorporation of the reagent in the molecule formed and is isomerization in its character.[3]

The family of rearrangements revealed is similar to the amidine rearrangement (Dimroth rearrangement),[4] but differs in that a carbon-carbon rather than a carbon-nitrogen bond is formed upon ring-closure. Whereas the amidine rearrangement is, as a rule, reversible, it is only the initial stages that are reversible in the enamine rearrangement and the formation of a new carbon-carbon bond under ordinary conditions is irreversible.

On the basis of these concepts, we could predict and then realize a number of new transformations.

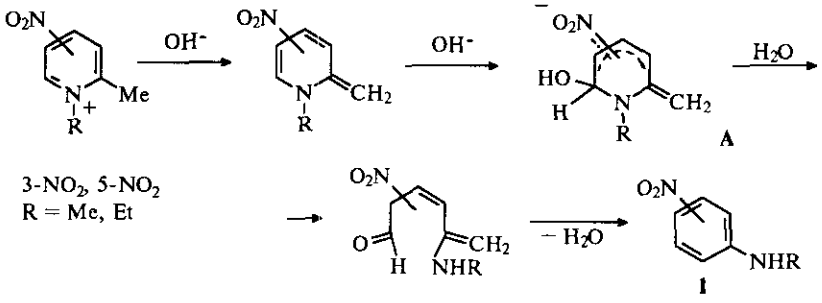
II. ENAMINE REARRANGEMENT OF PYRIDINE DERIVATIVES

The rearrangement of pyridinium salts into anilines discovered by us is a fundamental type of pyridine-into-benzene ring recyclizations.

Apparently, the simplest model of this type could be obtained from α-picoline, which following quaternization and deprotonation of the methyl group would give rise to an anhydro base where the methylene group formed functions as an electron-excessive fragment.

It was shown, however, that 1,2-dimethylpyridinium iodide, even on prolonged heating with aqueous alcoholic potassium hydroxide, was not converted into *N*-methylaniline. Introduction of a strong electron-acceptor group enhanced electrophilicity of the pyridine ring, which provided conditions for recyclization.

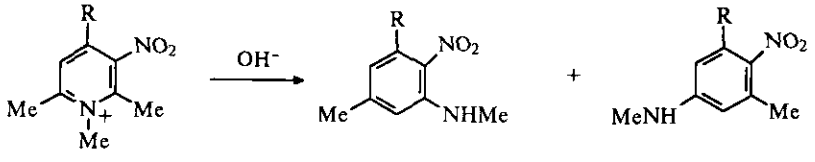
Thus, treatment of 1,2-dimethyl-3-nitropyridinium iodide with an aqueous alcoholic alkali gave *N*-methyl-2-nitroaniline, albeit in a low yield. If the reaction was carried out in aqueous methylamine, the yield of the corresponding *ortho*- and *para*-*N*-methylnitroanilines (**1**) increases to 30-50%.[5,6]



Apparently, the initially formed anhydro base adds an OH^- ion in the α-position with respect to the nitrogen atom to give an anionic σ-complex A. This is followed by ring opening and subsequent recyclization into a benzene ring.

It is of interest that 1,2-dimethyl-3-nitropyridinium iodide is converted into *N*-methyl-2-nitroaniline in higher yield (50%) than the isomeric 1,2-dimethyl-5-nitropyridinium iodide (25%), *i.e.* deprotonation involves preferential attack of the hydroxide in the *para*- rather than *ortho*-position with respect to the nitro group.

This ratio holds true with nitropyridinium iodides (**2a,b**), where compounds with an *ortho*-nitro group with respect to the methylamino group are also formed in much higher yield than the *para*-isomers. The methyl group in position 4 does not affect essentially this ratio.[5,7]



2 a, b

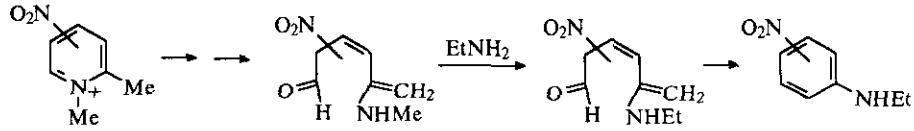
a R = H, **b** R = Me

X-Ray structural analysis allowed directly to estimate the electrophilicity of the α-positions in 1-ethyl-2-methyl-3-nitropyridinium iodide and 1,2,4,6-tetramethyl-3-nitropyridinium iodide (**2b**) with respect to nucleophiles.[8] The iodide anion proved to have closer contacts with the C(2) atoms of the pyridine ring. Apparently, the positive charge in these compounds is higher on the C(2) than on the C(6) atoms due to the inductive effect of the nitro group. This must facilitate

the base-induced deprotonation of the C(2)-methyl group. This accounts for predominant formation of *ortho*-nitroanilines in recyclization.

Recyclization of pyridinium salts into anilines proceeds through an open-chain form, which may undergo competing hydrolysis or, if amines are used as bases, form a ring with a complete or partial amine exchange.

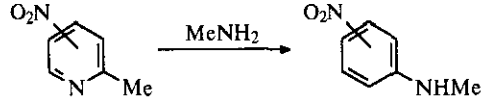
Thus the action of aqueous ethylamine on 1,2-dimethyl-3-nitropyridinium iodide or 1,2-dimethyl-5-nitropyridinium iodide results in formation of the corresponding *ortho*- or *para*-isomers of *N*-ethylnitroaniline.[9,10]



Since the reamination of enamines could be reversible, the formation of *N*-methylnitroanilines could also be expected, but due to the great excess of ethylamine this was not almost observed. Accordingly, with 1-ethyl-2-methyl-3-nitropyridinium iodide as the starting substance, the reaction with aqueous methylamine leads to recyclization with expulsion of the ethylamine residue and formation of *N*-methyl-2-nitroaniline.

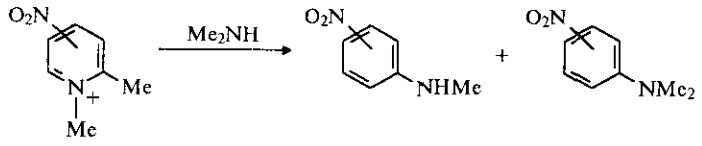
The action of aqueous methylamine on non-quaternized pyridine bases (**3a**, **b**) also results in ring opening with the substitution of methylamino group for the amine fragment and formation of recyclization products, *N*-methylnitroanilines, although in low yields.

Secondary amines are much less capable of reamination, the recyclization products are also formed that do not contain the dialkylamine fragment. For example, 1,2-dimethyl-3-nitropyridinium iodide with dimethylamine yields *N*-methyl-2-nitroaniline, although in the case of 1,2-dimethyl-5-nitropyridinium iodide a mixture of *N*-methyl-4-nitroaniline and *N*,*N*-dimethyl-4-nitroaniline was obtained with the former predominant.



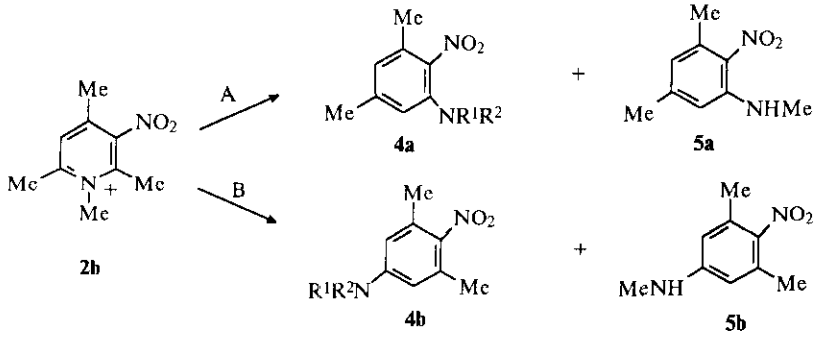
3 a, b **a** 3-NO_2, **b** 5-NO_2

That is, secondary amines, like aqueous alkali, may result in recyclization with retention of the alkylamine fragment present in the initial quaternary salt.[5,10]



When two methyl groups are present in the α-positions of the pyridine ring, and reamination is taken into account, one may expect the formation of two pairs of isomeric nitroanilines (**4a**, **b**) and (**5a**, **b**) upon recyclization. 1,2,4,6-Tetramethyl-3-nitropyridinium iodide (**2b**) proved to be a convenient model for studying steric effects in reamination. With aqueous methylamine the maximum yield of nitroanilines was observed (90%), while the *ortho*:*para*-ratio (2:1) seems to be independent of steric hindrance produced by the methylamino group during cyclization and is determined by the predominance of the attack of the hydroxide ion on the *para*-position with respect to the nitro group.

Under the action of aqueous ethyl-, *n*-propyl- and *n*-butylamines the *ortho*- and *para*-isomers (**4a**, **b**) are formed in equal amounts, which points to an increasing predominance of the reaction pathway **B**, less sensitive to the influence of the steric effects.



This ratio is practically independent of the nature of the solvent either. However, under the action of an aqueous-alcoholic solution of pentadecylamine the yield of the *ortho*-isomer suddenly increases (63%), which, apparently, may be attributed to the surfactant properties of the reagent[7]. If the reaction was carried out in aqueous isobutylamine (branching at the β-carbon atom), equal yields of the corresponding *ortho*- and *para*-nitroanilines were obtained. With isopropylamine and *sec*-butylamine the overall yield of the reamination products decreases substantially, though *para*-nitroanilines are still formed in a yield of about 40%, that is, the course of the reaction in the direction of formation of *ortho*-isomers is suppressed. Finally, with *tert*-butylamine reamination does not occur at all. Thus, this amine, like aqueous alkali, brings about recyclization with

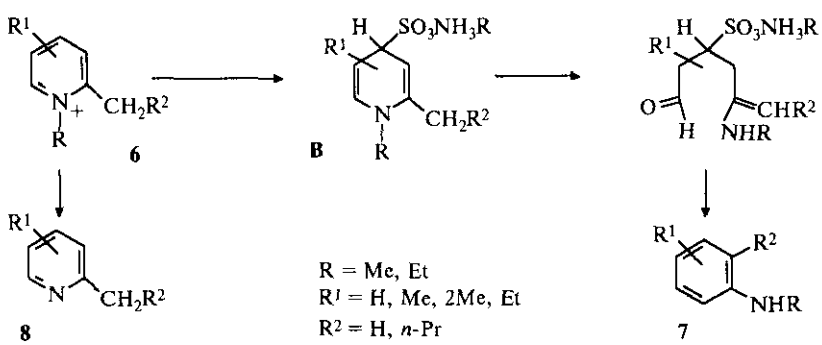
retention of the alkylamine fragment of the initial quaternary salt.

1,2,4,6-Tetramethyl-3-nitropyridinium iodide (**2b**) with primary amines (except for *tert*-butylamine) affords, in addition to two reamination products (**4a**, **b**), minor amount of *N*-methyl-3,5-dimethyl-4-nitroaniline (**5b**) and *N*-methyl-3,5-dimethyl-2-nitroaniline (**5a**). Aqueous dimethylamine and piperidine cause a similar rearrangement. In this case the direction of reamination is also largely dependent on the steric effects of the dialkylamino group.[7]

Thus, the course of the reamination during recyclization depends on the number of alkyl radicals at the amine nitrogen and their branching, especially at the α- and, to a lesser extent, at the β-carbon atoms. Steric factors decrease the content of the *ortho*-nitroanilines in the reamination products and increase that of the *para*-isomers. These data are an additional argument in favour of the above scheme of recyclization of nitropyridinium salts.

The electron-deficient pyridine ring particularly the 1-alkylpyridinium ring adds readily nucleophiles, which is known to afford not only 1,2-, but also 1,4-dihydropyridines capable of solvolytic ring opening to give glutaconic dialdehyde derivatives.[11] If a methyl group is adjacent to the carbonyl group of such an acyclic dicarbonyl compound, recyclization may occur with the formation of a carbocycle. If the nucleophile, in addition, can be eliminated from the intermediate during carbocyclization, the benzene ring may be formed. Thus, 1-alkyl-2-methylpyridinium salts on treatment, successively, with sodium bisulfite, alkali, and acid afford phenols.[12]

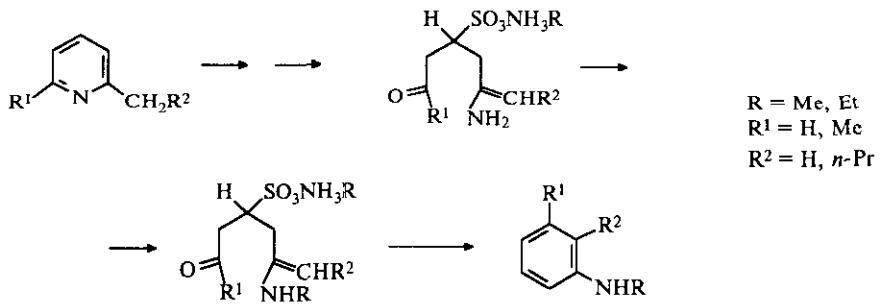
We supposed that the sulfite ion would add to 1,2-dialkylpyridinium salts to cause their recyclization into anilines even for the compounds containing no electron-acceptor group. Indeed, the heating of 1,2-dialkylpyridinium iodides (**6**) with methylammonium sulfite resulted in *N*-alkylanilines (**7**) in a yield of 40-80%.[13]



Introduction of one or several alkyl groups (R^1) reduces the electron deficiency of the ring and gives rise to steric hindrance for the sulfite ion addition. This, correspondingly, reduces the yield of the recyclization products. This effect is particularly pronounced in the case of γ-substituted 2-methylpyridines, to a lesser extent for β-substituted ones, and to a still lesser extent when the methyl group is introduced into the second α-position of the pyridine ring. This suggests that the sulfite ion adds predominantly to the C(4) atom, *i.e.* the primary reaction products are 1,4-dihydropyridines of the type **B**, which recyclize with the elimination of the reagent and formation of an aromatic ring.

A parallel process was *N*-dealkylation with formation of pyridine bases (**8**). The loss of the *N*-substituent seems to be caused by direct attack of a nucleophile on the R-N bond.

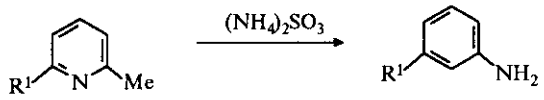
The method found permits recyclization of not only 1,2-dialkylpyridinium salts but of non-quaternized compounds as well. Namely, prolonged heating of 2-methyl-, 2,6-dimethyl-, and 2-butylpyridine with aqueous methylammonium sulfite resulted in satisfactory yields of *N*-methyl-, *N*,3-dimethyl-, and *N*-methyl-2-propylaniline, respectively. Under the action of ethylammonium sulfite on 2-methylpyridine in the presence of zinc chloride *N*-ethylaniline was also obtained.[13]



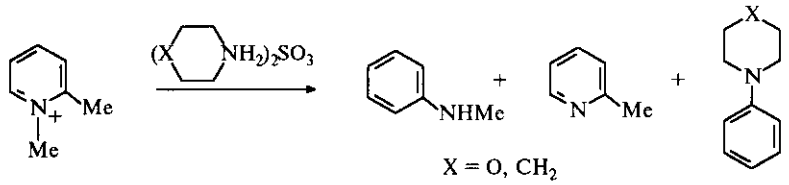
Addition of zinc chloride considerably increases the yield of *N*-methylaniline from 2-methylpyridine. The mechanism of the effect of zinc salts requires a special study, however, it may be assumed that the activation depends on the equilibrium involving the pyridinium base complex, which undergoes further transformations. This is supported by the fact that addition of Zn^{2+} ions is of little effect on the reaction with 2,6-lutidine, where the electron pair at the nitrogen atom of the pyridine ring is sterically hindered.

Dialkylamines unlike alkylamines cause no recyclization of 2-methylpyridines, but this can be performed on treatment with a mixture of aqueous ammonia, ammonium sulfite, and zinc

chloride. Aniline and 3-methylaniline were obtained in this manner in about 10% yield. This demonstrates that in principle the formation of primary arylamines is possible.[13]



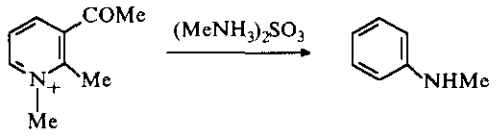
Recyclizations of the pyridinium salts under the action of alkylammonium or dialkylammonium sulfites, which involve an *N*-substituent exchange, were studied in more detail. Sulfites of heterocyclic amines (morpholine, piperidine, and piperazine) may also bring about the recyclization of the pyridinium salts into anilines, provided the amine is sufficiently basic and the *p*-pair of the electrons of the nitrogen atom is sterically accessible. In all the cases the main reaction products are *N*-methylaniline and α-picoline, the overall yield of which may be as high as 80%. The contribution of the recyclization with the amine fragment exchange (*i.e.* the yield of *N*-phenylmorpholine and *N*-phenylpiperidine) is very small (of about 6-15%), while *N*-phenylpiperazine is not formed at all.[14]



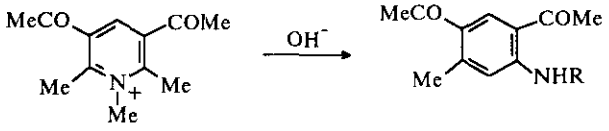
If the pyridine nitrogen atom bears a bulky substituent, *e.g.*, an isopropyl radical, reamination becomes the main process and may be used for the synthesis of both *N*-alkyl- and *N,N*-dialkylanilines.[14] Recyclization of *N*-lauryl- and *N*-cetyl-2-methylpyridinium iodides into *N*-lauryl- and *N*-cetylaniline, respectively, proceeds unexpectedly in a very high yield (up to 98%) under the action of aqueous methylammonium sulfite. Here, apparently, the increase in the yields of *N*-alkylanilines may be attributed to the surfactant properties of the starting substances, as for the interaction of pentadecylamine with nitropyridinium salts.[7]

It is important to note that 1,2-dialkylpyridinium salts containing activating electron-acceptor groups in the ring other than the nitro group do not recyclize under these conditions. 1,2-Dialkyl-3-cyanopyridinium salts undergo a rather complicated transformations to give, as a result of double rearrangement, 2-aminopyridine derivatives containing no cyano group.[15] Replacement of the nitro group in the nitropyridinium salts by the acetyl group makes the recyclization possible,

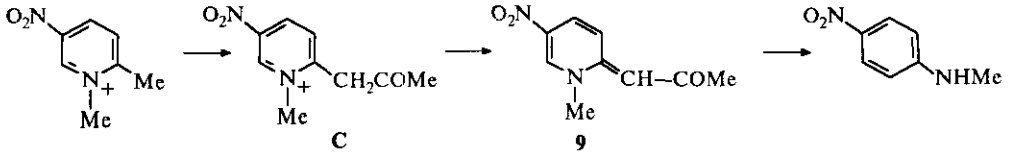
but only under the action of methylammonium sulfite and with elimination of the acetyl group.[16]



Nevertheless, it was demonstrated recently[17] that aqueous alcoholic alkali reacts with 1,2,6-trimethyl-3,5-diacetylpyridinium iodide to open the pyridine ring. The subsequent intramolecular cyclization results in high yield of the substituted aniline.



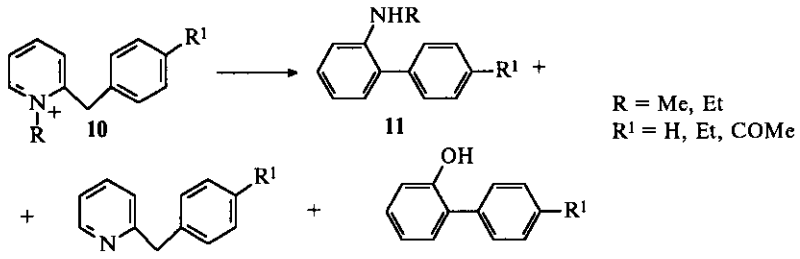
It was expected that the activation of the α-methyl group by an acceptor substituent would increase its CH-acidity thus promoting the benzene cycle formation at the stage of the open-chain intermediate. To check this assumption we have treated 1,2-dimethyl-5-nitropyridinium iodide with acetic anhydride in pyridine and obtained the anhydro base (**9**), apparently, *via* 2-acetonyl-5-nitropyridinium salt **C**. Under the action of aqueous methylamine the base is recyclized, but the acyl fragment is eliminated and this leads to *N*-methyl-4-nitroaniline.[16]



C **9**

In view of the fact that the CH-acidity of the methylene group in the benzyl radical is also considerably higher than that of the methyl group, it was expected the substitution of the benzyl group for the 2-CH_3 group in the pyridine ring to favour the rearrangement with the formation of 2-aminobiphenyls. In fact, 1-methyl-2-benzylpyridinium iodide upon prolonged heating with aqueous alkali was converted into 2-methylaminobiphenyl although in a low yield due to competitive hydrolysis of the open-chain intermediate. In aqueous methylamine, however, the yield of 2-methylaminobiphenyl is somewhat higher. In addition, 2-hydroxybiphenyl and an *N*-dealkylation product, 2-benzylpyridine are formed.[18] Comparing the results obtained with the known data on the recyclization of α-picoline,[13] we supposed that the addition of the sulfite ion to 2-benzylpyridinium salts will permit recyclization into 2-aminobiphenyls in higher yield.

Indeed, heating of 2-benzylpyridinium iodides (**10**) with alkylammonium sulfite resulted in 2-alkylaminobiphenyls (**11**) in 50-80% yield.[18,19]

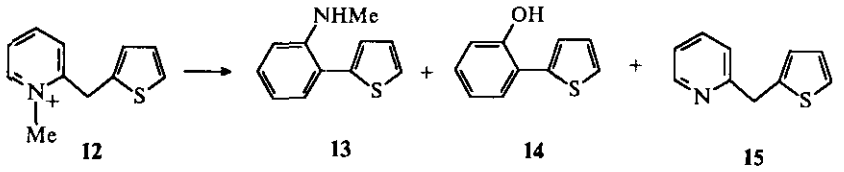


N-Dealkylation with the formation of 2-benzylpyridines proceeds in parallel.

It could be expected that the introduction of an acceptor substituent into the *para*-position of the benzene ring will increase the CH-acidity of the methylene group and favour the recyclization. However, recyclization did not occur on heating 1-methyl-2-(4-nitrobenzyl)pyridinium iodide with aqueous alcoholic methylamine or methylammonium sulfite. Reduction in the nucleophilicity of the β-carbon atom of the acyclic enamine due to high acceptor power of the *p*-nitrophenyl group apparently precludes intramolecular condensation of the intermediate and, consequently, recyclization. The acetyl group in 1-methyl-2-(4-acetylbenzyl)pyridinium iodide reduces the nucleophilicity of the β-carbon atom of the enamine intermediate to a lesser extent than does the nitro group in 1-methyl-2-(4-nitrobenzyl)pyridinium iodide, though the yield of the corresponding 2-aminobiphenyl is lower than in the recyclization of 1-methyl-2-benzylpyridinium iodide.[18]

When a solution of alkylammonium sulfite with a radical other than in the original pyridinium salt is used as the recyclizing agent, reamination may occur. Thus, the interaction of methylammonium sulfite and 1-ethyl-2-benzylpyridinium iodide gives 2-methylaminobiphenyl. On the contrary, in the case of ethylammonium sulfite and 1-methyl-2-benzylpyridinium the reaction proceeds mainly with the formation of 2-methylaminobiphenyl, *i.e.* practically without reamination. Secondary amines do not undergo reamination at all. When 1-methyl-2-benzylpyridinium iodide is treated with ammonium sulfite, no formation of 2-aminobiphenyl unsubstituted at the nitrogen occurs either. To elucidate the influence of a heterocycle linked with the pyridine ring through the methylene group on the course of the reaction, the corresponding pyridinium salts containing thienyl or furyl residue in a side chain were studied. Interaction of the quaternary salt (**12**) with methylammonium sulfite resulted in rearrangement into the aniline

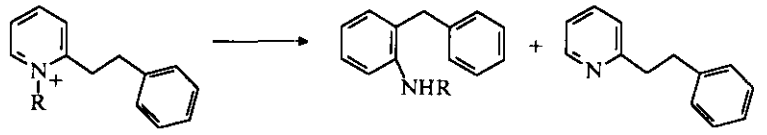
derivative (**13**). Phenol (**14**) and thienylmethylpyridine (**15**) were also identified in the reaction mixture.[20]



12 **13** **14** **15**

Interaction of 1-methyl-2-(2-furylmethyl)pyridinium iodide with methylammonium sulfite proceeds in a similar manner.

Rearrangement of 2-phenethylpyridinium salts (**16**), which contain one more methylene unit between the pyridine and phenyl rings, under the action of aqueous alkylammonium sulfites results in formation of the expected recyclization products, 2-benzyl-*N*-alkylanilines (**17**). In each case, in addition to the compounds (**17**) an *N*-dealkylation product, *viz.*, the corresponding pyridine was isolated. The yields of the recyclization products drop as the length of the alkyl radical increases.[21]



16 **17**

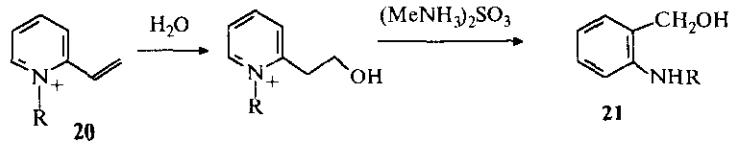
R = Me, Et, *i*-Pr, *n*-Bu

Gradual decrease in the yield of the products of the competitive reamination process is observed when recyclization of the pyridinium salt (**16**) (R=Me) is effected by ethyl-, butyl-, and isopropylammonium sulfites. Apparently, this is associated with the increase in the size of the alkyl group of the reagent. In the same series the yield of the direct recyclization product, *i.e.* of the aniline (**17**) (R=Me) increases concurrently.

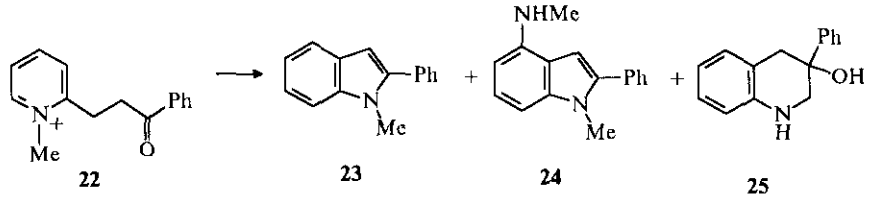
Heating of **18** (X=S) in a sealed tube with an aqueous solution of methylammonium sulfite gives thienylmethylaniline (**19**). Recyclization of the salt (**18**) (X=O) into the aniline (**19**) (X=O) occured in lesser yield, apparently, because of greater instability of the furan cycle under the reaction conditions.[20]

18 X = S, O **19**

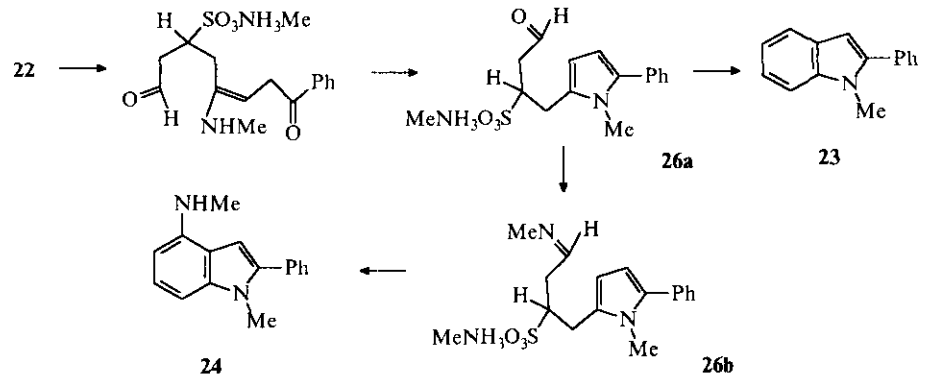
If a hydroxyl group is present in the β-position of the side chain instead of the aryl substituent, the enamine rearrangement is expected to occur under the action of nucleophilic agents on the corresponding quaternary salt. It is this process that seems to occur under the action of aqueous methylammonium sulfite on 2-vinylpyridinium iodides (**20**), which undergo recyclization with the formation of alcohols (**21**) isolated as dibenzoyl derivatives.[22] The formation of the compounds (**21**) can only be rationalized by initial hydration of the vinyl substituent with formation of an intermediate β-hydroxyethylpyridine derivative, which undergoes subsequent recyclization into the alcohol (**21**) according to a conventional scheme.



The action of bases on 1-methyl-2-(2-benzoylethyl)pyridinium iodide (**22**) gives a mixture of recyclization products with indole derivatives predominating.[23,24] Thus, recyclization of the salt (**22**) under the action of an aqueous solution of methylammonium sulfite results in 1-methyl-2-phenylindole (**23**), 1-methyl-4-methylamino-2-phenylindole (**24**), and 3-hydroxy-3-phenyl-1,2,3,4-tetrahydroquinoline (**25**).

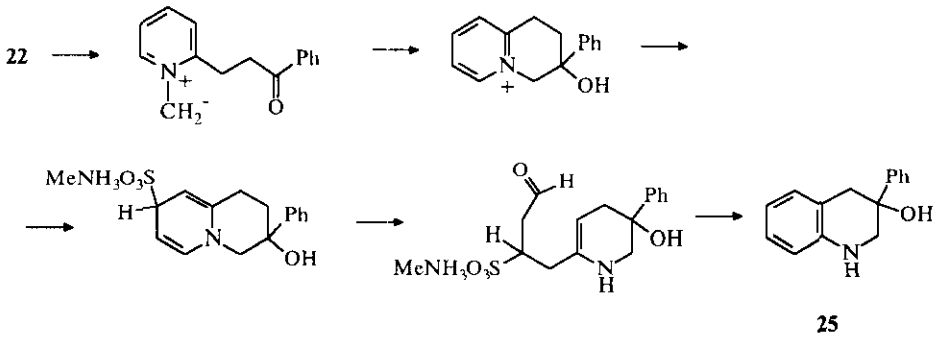


Indoles (**23**) and (**24**) are formed as a result of recyclization, which begins with the pyridine ring opening. Then the formation of the pyrrole cycle is likely to take place, which is then followed by subsequent transformations. One of the alternative pathways leads directly to 1-methyl-2-phenylindole; the other, after intermediate oxidation of an open-chain or cyclic intermediate, to the aminoindole (**24**). That the intermediates of the type (**26a**, **b**) or their cyclic derivatives were sensitive to oxidation by air oxygen was pointed out in earlier studies on isomerization and amination of indolizines.[25] Low reactivity of intermediates of the type (**26a**, **b**) can *a priori* be postulated, which is associated with insufficient nucleophilicity of the pyrrole ring with respect to the attack by the carbonyl group and proved to be the case.



The maximum yield (35%) of 1-methyl-2-phenylindole was achieved with a mixture of alcoholic methylamine and sodium sulfite used as the base. If a mixture of alcoholic methylamine and methylammonium sulfite was used instead, the main product was 1-methyl-4-methylamino-2-phenylindole.[24]

Compound (**25**) is formed, apparently, as a result of deprotonation of the *N*-methyl group followed by quinolizine ring closure and its recyclization.[24]



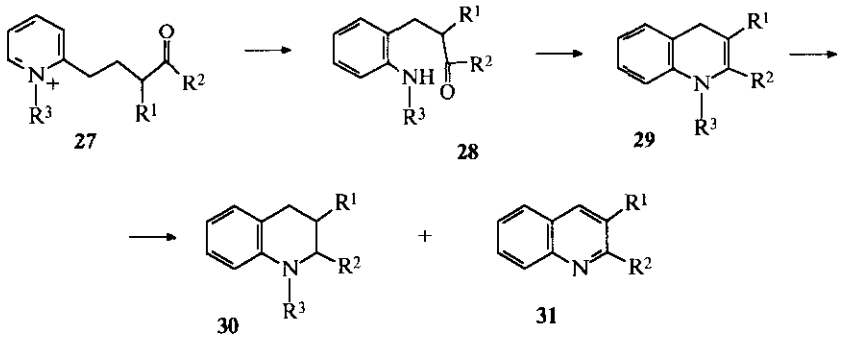
25

The use of a mixture of alcoholic methylamine and sodium sulfite as the reagent led to an increase in the yield of indoles and the tetrahydroquinoline (**25**).

The latter reaction was studied by us[24] with a view to broaden the scope of applicability of the enamine rearrangement to such models which would permit the synthesis of compounds of a more complicated structure than the *N*-alkylaniline derivatives. The key step in this reaction is still the enamine rearrangement, which is characterized first of all by the pyridine ring carbon-nitrogen bond cleavage and by carbon-carbon bond formation under the action of nucleophilic agents. This allows us to discuss the reaction under study and similar ones in this section of the review. Rearrangement of pyridinium salts with a 2-(δ-oxoalkyl) side chain under the action of

nucleophiles was studied to reveal the influence of structural factors on the process of recyclization of such structurally complex pyridinium salts.

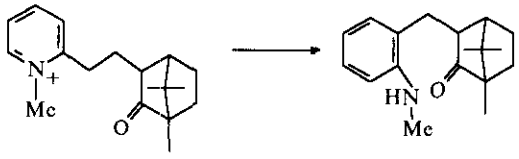
The rearrangement was carried out by heating the quarternary salts of the ketones (**27**) with an aqueous solution of alkylammonium sulfite. Tetrahydroquinolines (**30**) were the main products isolated from the reaction mixture in all cases (yields up to 48%). In some cases, the quinolines (**31**) were additionally isolated. The primary recyclization products (**28**) could not be detected, and the 1,4-dihydroquinoline derivatives (**29**) in certain cases were only identified by mass spectrometry.[26]



The preferential formation of the tetrahydroquinolines (**30**) over the dihydroquinolines (**29**) may apparently be accounted for by reduction of the latter by the excess of alkylammonium sulfite and also by their disproportionation, which leads to the simultaneous formation of the quinolines (**31**) as well.

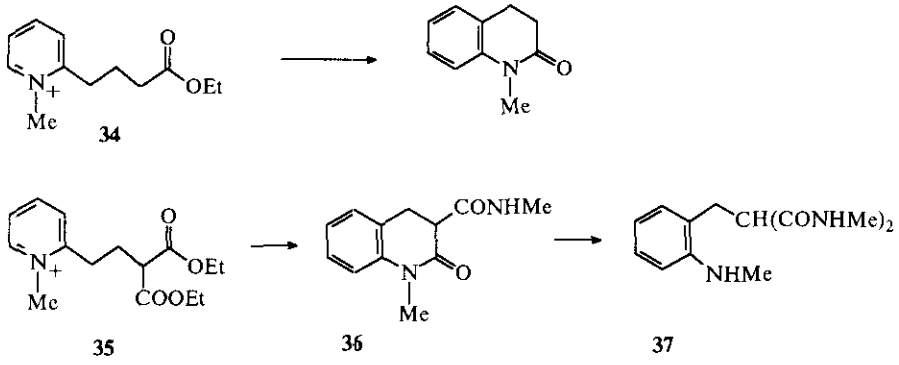
The method found was extended to carbocyclic carbonyl compounds and this allowed to obtain a series of polyhydroacridine derivatives and their analogs.

Recyclization of the salts of the majority of pyridylethylated cyclanones, like that of the open-chain compounds, does not stop at the stage of aminophenylketone formation (**28**). However, considerable steric hindrances in certain cases may prevent from subsequent cyclization into quinoline derivatives and thus stabilize the intermediate product (**28**). Thus, recyclization of the quaternary salt (**32**) containing a camphor residue resulted in a sufficiently stable aminophenylketone (**33**).[27]



32 33

The enamine rearrangement of pyridylethylated acids results in 2-quinolone and its derivatives. Thus, prolonged heating of the salt (**34**) with aqueous methylamine led to 1-methyl-2-quinolone as the main reaction product.



34 35 36 37

Recyclization of the quaternary salt (**35**) with a 3,3-di(ethoxycarbonyl)propyl side chain resulted in two products, of which one proved to be the tetrahydro-2-quinolone (**36**) and the other, the primary rearrangement product, the aniline (**37**). Heating of the latter to 130°C gave the substituted tetrahydroquinolone (**36**).[28]

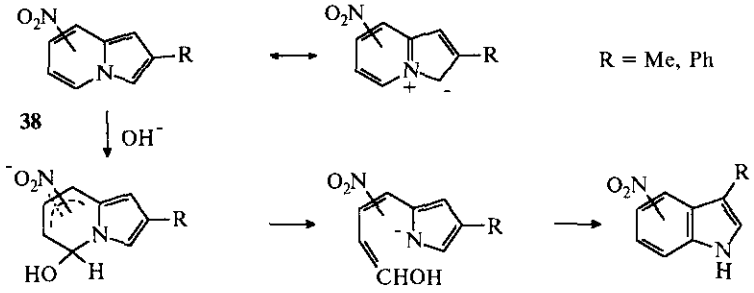
III. ENAMINE REARRANGEMENT OF CONDENSED SYSTEMS CONTAINING A PYRIDINE RING

If we consider the structural aspect of the recyclization of pyridinium salts into anilines, the pyridine ring is evidently the simplest heteroaromatic system capable of enamine rearrangement. In other words, it could be expected that the rearrangement studied by us is of general significance in the chemistry of heteroaromatic compounds. This reaction may be predicted, for example, to occur for condensed systems containing a pyridine ring. Thus, the simplest condensed heteroaromatic system potentially capable of rearrangement of this type is indolizine, which eventually became the first system tested for the ability to isomerization.

The nitrogen atom of the indolizine pyridine ring possesses definite positive charge due to considerable contribution of an ylide structure and indolizine was expected to undergo pyridine-ring opening under the action of a strong nucleophile with subsequent recyclization due to the intramolecular attack of the intermediate on the electron-excessive fragment of the molecule.

It was shown, however, that 2-methylindolizine even upon prolonged boiling with an aqueous alcoholic solution of alkali recovers unchanged. This is consistent with the known data that indolizine is an electron-excessive compound, susceptible first of all to the electrophilic attack directed at the pyrrole part of the molecule. Thus, data on hydrogen nucleophilic substitution in the indolizine nucleus are lacking. An attempt of indolizine amination according to Chichibabin also failed.[29]

Consequently, to create the necessary electrophilicity, which would ensure the nucleophilic attack on the pyridine ring, it was necessary to introduce an electron-acceptor group into indolizine molecule. To this end we have synthesized 6- and 8-nitroindolizines.[30] We have demonstrated that introduction of a nitro group into pyridine moiety of the indolizine molecule in fact appreciably increased the sensitivity of the compound to nucleophiles. Heating of the nitroindolizines (**38**) in aqueous alcoholic alkali led to their isomerization into the corresponding nitroindoles (**41**) in 20-90% yields.[31]



This is the first example of nucleophilic reaction with the participation of the indolizine ring, a new isomerization version of the enamine rearrangement, and at the same time a practically valuable, original way of indole synthesis.[25,32]

Apparently, the nucleophilic attack by the hydroxide ion leads initially to the formation of an anionic σ-complex (**39**) followed by ring opening to produce an anion (**40**) and aromatization due to benzene ring closure.

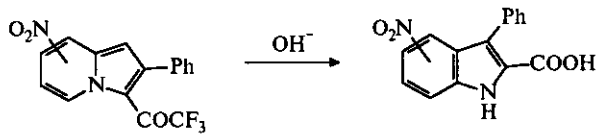
The reaction is much faster and with better yields with 6-nitroindolizines than with the corresponding 8-isomers; apparently, this is associated with a greater stability of the anionic σ-complex in the *ortho*-position with respect to the nitro group. The formation of this kind of σ-complexes with the hydroxide ion is confirmed by uv and nmr spectral studies. An intriguing fact is that solely the hydroxide ion causes the isomerization into indoles. In anhydrous medium with alkoxide ions or amines as nucleophiles, the pyridine ring does not open, though the formation of stable σ-complexes with nucleophiles was observed by nmr. In the presence of atmospheric oxygen the σ-complexes with aliphatic amines were readily oxidized with the formation of 5-amino-8-nitroindolizines.[25]

The last stage, transformation of the anion (**40**) into indole (**41**), depends strongly on steric factors, first of all on the bulk of the radical R. Thus, 2-*tert*-butyl-6-nitroindolizine does not undergo the reaction under the conditions described.

With the aid of X-ray analysis we have investigated the structural parameters of the initial molecules responsible for the potential ability to isomerization recyclization. It turned out that the introduction of the nitro group leads to alternation of the bond lengths in the molecule, such an alternation being especially pronounced in 2-phenyl-6-nitroindolizine. The polyene character of the pyridine fragment of the indolizine molecule is an indication of the decrease in its aromaticity, which favors the formation of stable σ-complexes upon the nucleophilic attack and, correspondingly, isomerization into indoles.[8]

Isomerization of indolizines into indoles was shown to be very sensitive to the decrease in acceptor ability of the pyridine ring substituent. Thus, the enamine rearrangement could not be performed with 7-hydroxy-8-nitroindolizines[33] and indolizines containing cyano or acetyl group in position 6 or 8.[34] Attempts to activate the indolizine nucleus with respect to the nucleophilic recyclization by complexation with transition metals also failed, as was exemplified by $(CO)_3Cr$-(2-phenylindolizine) π-complex.[35]

At the same time, it was established that introduction of an acceptor substituent into the pyrrole part of indolizine does not prevent recyclization. Thus, under the action of aqueous alcoholic alkali 3-trifluoroacetyl-6(8)-nitro-2-phenylindolizines (**42**) are transformed into 5(7)-nitro-3-phenylindole-2-carboxylic acids (**43**).[36]



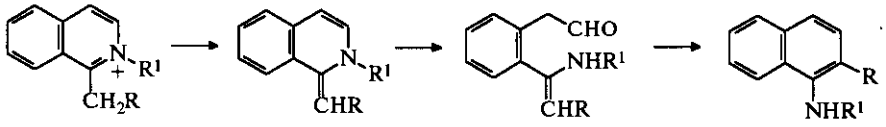
42 43

In this case the transformation of the heterocycle is accompanied by haloform reaction.

By analogy with the isomerization of indolizines into indoles and of pyridinium salts into anilines, one could suppose that the rearrangement of isoquinolinium salts into naphthylamines is also possible, assuming that under the action of bases the pyridine cycle will open with subsequent ring closure with involvement of a side-chain methylene group possessing sufficient CH-acidity.

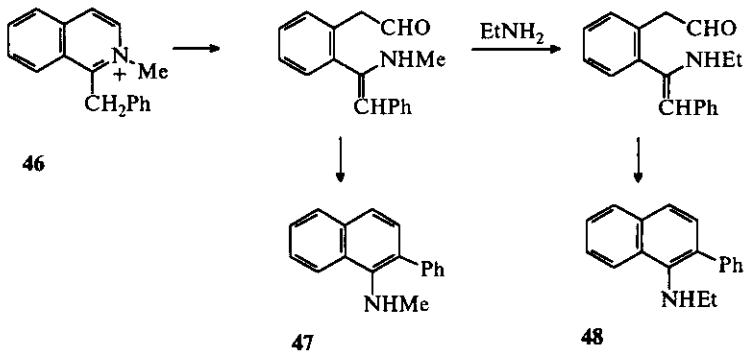
Indeed, treatment of 1-benzyl-2-methylisoquinolinium iodide with alcoholic methylamine resulted in high yield of 1-methylamino-2-phenylnaphthalene.[37] With aqueous methylamine a complex mixture was obtained wherein, in addition to the corresponding naphthylamine, 1-benzylisoquinoline and 2-phenyl-1-naphthol were identified. The yield of 1-methylamino-2-phenylnaphthalene was lower in this case.

Thus, the optimum conditions for recyclization of the isoquinolinium salts (**44**) into *N*-alkylnaphthylamines (**45**) is the use of alcoholic alkylamine, however, minor amounts of water are needed for promoting the reaction.



44 R = H, Ph R^1 = Me, Et 45

With the quaternary salt (**46**) and aqueous ethylamine two processes are observed, rearrangement with the formation of the amine (**47**) and rearrangement with the amino group exchange leading to the amine (**48**).



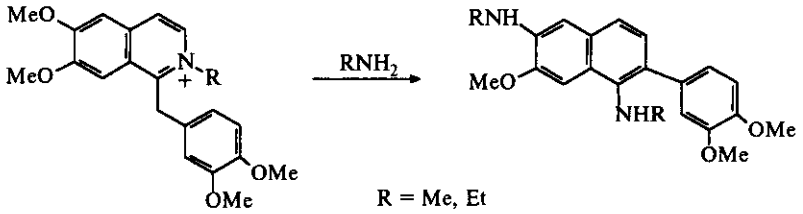
46 47 48

The formation of the amine (**47**) testifies the rearrangement to proceed with C(3)-N rather than C(1)-N bond cleavage.

Interaction of 1-benzyl-2-ethylisoquinolinium iodide with methylamine, the steric requirements of which are substantially lower than of ethylamine, results in complete alkylamino group exchange and formation of only the amine (**47**).

1,2-Dimethylisoquinolinium iodide (where the CH-acidity of the 1-methyl group is lower than that of 1-benzyl) requires longer heating that naturally leads to the appearance of side products. Thus, prolonged heating of 1,2-dimethylisoquinolinium iodide with alcoholic methylamine gave 1-methylaminonaphthalene and 1-naphthol. The reaction of this salt with ethylamine proceeds cleaner than of the benzyl analog, but a mixture of amines is again formed, in which 1-ethylaminonaphthalene prevails, i.e. the process with exchange of the amine fragment occurs predominantly. Interaction of 1-methyl-2-ethylisoquinolinium iodide with methylamine gave only 1-methylaminonaphthalene, which is formed with the alkylamino group exchange.[37]

Quaternary salts of the alkaloid papaverine also undergo similar recyclization. Prolonged heating of papaverine methiodide with excess of alcoholic methylamine results in rearrangement of the isoquinoline moiety into the naphthalene one with simultaneous substitution of one of the methoxy groups by the methylamino group.

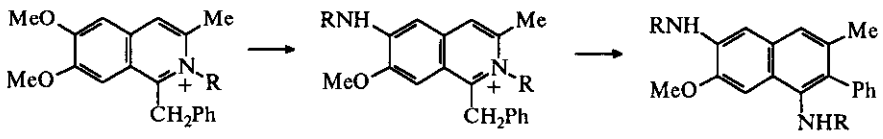


R = Me, Et

Recyclization of papaverine ethiodide under the action of alcoholic ethylamine is also accompanied by substitution of the methoxy group in the position 6 of isoquinoline by the ethylamino group with the formation of diaminonaphthalene.[38]

Recyclization of isoquinolinium salts (**49**) under similar conditions involves only the benzyl methylene group as the CH-acidity of this group is higher than that of the methyl group in the position 3 of isoquinoline. Simultaneously with the rearrangement of these salts, substitution of the methoxy group in the position 6 occurs and diaminonaphthalenes (**50**) are formed.[38] If alkylammonium acetate in alcohol is used as the reagent for recyclization, the rearrangement of papaverine salts proceeds with the retention of the methoxy group in the position 6.

Apparently, heating of the salts (**49**) with alcoholic alkylamines results in initial substitution of the methoxy group followed by rearrangement into the diaminonaphthalene (**50**).



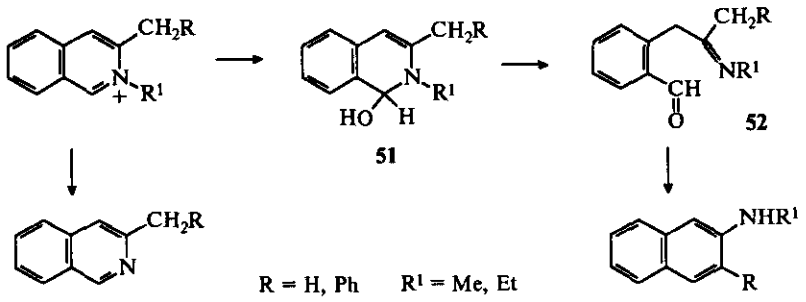
49 R = Me, Et **50**

Under the optimum conditions, the yield of the diaminonaphthalenes (**50**) is 7-24%, whereas the rearrangement of the salts (**44**) occurs in 70-90% yield. The introduction of electron-donor substituents into the benzene ring lowers the electrophilicity of the pyridine ring of the isoquinolinium salt, hampers the nucleophilic attack and the pyridine ring opening.

Comparison of reactivity of the isoquinolinium salt (**49**) with that of 1,2-dialkylpyridinium salts, which rearrange only in specific cases under the action of alcoholic and aqueous alkylamines, indicates that annelation of the pyridine ring with the benzene one, even with donor substituents, favors recyclization.

The nucleophilic attack on isoquinoline occurs predominantly at the C(1) atom, thus, in the presence of an alkyl or aralkyl substituent in the position 3, a similar rearrangement with the C(1)-N bond cleavage and formation of β-naphthylamines may be expected. Indeed, when 2,3-dimethylisoquinolinium iodide was heated with alcoholic methylamine, the expected recyclization did occur and 2-methylaminonaphthalene was formed. In addition, the isoquinolinium salt dealkylation takes place due to the nucleophilic attack on the carbon atom of the *N*-methyl group. When an aqueous solution of methylamine was used as the reagent, the role of the competitive

reactions increased and the yield of 2-methylaminonaphthalene dropped.[39]

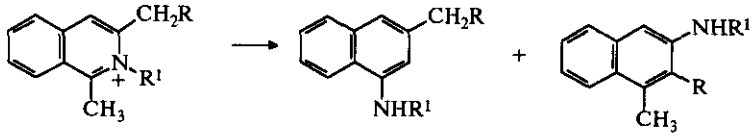


It is of note that the formation of an open-chain intermediate **(52)** *via* the pseudobase **(51)** is not the only possible pathway. It is believed that the process involves an anhydrobase which originates due to deprotonation of the methyl group of the isoquinolinium cation. Interaction of 2,3-dimethylisoquinolinium iodide with alcoholic ethylamine resulted in two rearrangement products, *viz.*, 2-methylaminonaphthalene, which is a minor product of a direct recyclization, and 2-ethylaminonaphthalene, which is the major recyclization product with an exchange of the methylamine fragment for the ethylamine one. The rearrangement of 2-ethyl-3-methylisoquinolinium iodide under the action of alcoholic methylamine also proceeds predominantly with the alkylamino group exchange.

The CH-acidity of the methylene group in the benzyl radical is known to be appreciably higher than that of the methyl group. Therefore, it could be expected that the replacement of the CH_3 group in the position 3 of isoquinoline for the benzyl one will favor the rearrangement with the formation of β-naphthylamine. Indeed, heating of 3-benzyl-2-methylisoquinolinium iodide with alcoholic methylamine gave 2-*methylamino*-3-*phenylnaphthalene* in the yield of 50%. Simultaneously, dealkylation with the formation of 3-benzylisoquinoline also took place.[39]

The reactions of 3-benzylisoquinolinium salts with alkylamines, whose alkyl groups differ from those at the quaternary nitrogen, were studied. Interactions of 3-benzyl-2-methylisoquinolinium iodide with ethylamine and of 3-benzyl-2-ethylisoquinolinium iodide with methylamine occur with almost complete alkylamino group exchange. If an isoquinoline molecule contains only one methyl group in the position 1 or 3, recyclization can only occur with the participation of this particular group. But if methyl groups are simultaneously present in positions 1 and 3, the reaction may be expected to proceed in both directions. Indeed, interaction of

1,2,3-trimethylisoquinolinium iodide with alcoholic methylamine gives a mixture of 1-methylamino-3-methylnaphthalene in 68% yield and 2-methylamino-4-methylnaphthalene in 7% yield.[39]



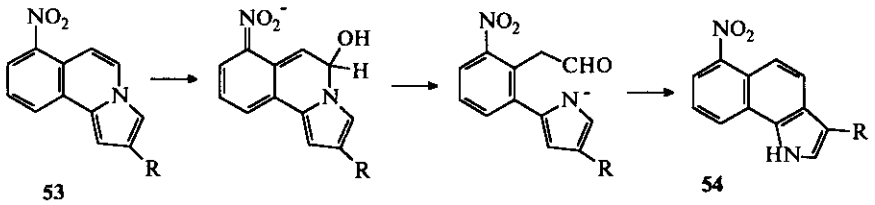
R = H, Ph R^1 = Me, Et

On the basis of data on the recyclization of 3-methylisoquinolinium and 3-benzylisoquinolinium salts , it is to be expected that the replacement of the methyl group for the benzyl one will increase the probability of the recyclization with involvement of this group. It turned out, that the interaction of 3-benzyl-1,2-dimethylisoquinolinium iodide and 3-benzyl-2-ethyl-1-methylisoquinolinium iodide with methylamine and ethylamine, respectively, gave α-naphthylamines in almost the same yield as in the case of 1,2,3-trimethylisoquinolinium iodide, whereas the yield of β-naphthylamines increased to 24%. In other words, the rearrangement of 3-benzyl-1-methylquinolinium salts also involves predominantly the methyl group in the position 1, in spite of the presence of the benzyl group in the position 3.

It could be supposed that pyrrolo[2,1-*a*]isoquinoline, containing the fragments of both the indolizine and isoquinoline systems, will also be potentially capable of recyclization under the action of bases.

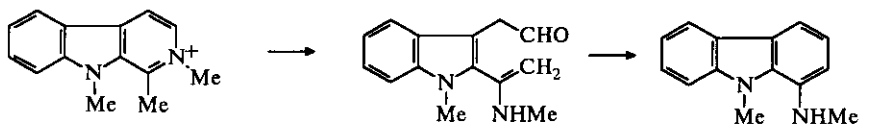
Unsubstituted pyrroloisoquinoline was shown to be highly resistant to the action of nucleophilic agents.

Introduction of a nitro group into the benzene moiety of the pyrroloisoquinoline molecule had to increase the sensitivity of the system to the action of the nucleophiles and to provide more favorable conditions for the recyclization. Indeed, upon heating of the 7-nitropyrrolo[2,1-*a*]isoquinolines (**53**) with aqueous alcoholic alkali with exclusion of oxygen, they underwent high-yield isomerization into the corresponding benz[*d*]indoles (**54**).[40]



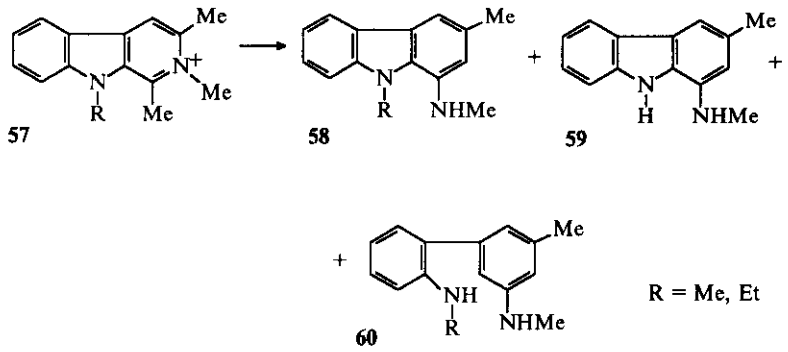
53 R = Me, Ph 54

Interaction of quaternized forms of alkaloids of the β-carboline series and their derivatives with alkali was investigated. Methylharman methiodide (**55**) on interaction with an alcoholic alkali undergoes the pyridine ring opening followed by closure of the open-chain form into the carbazole derivative (**56**). This is the main reaction product formed in the yield of 43%.[41]



55 56

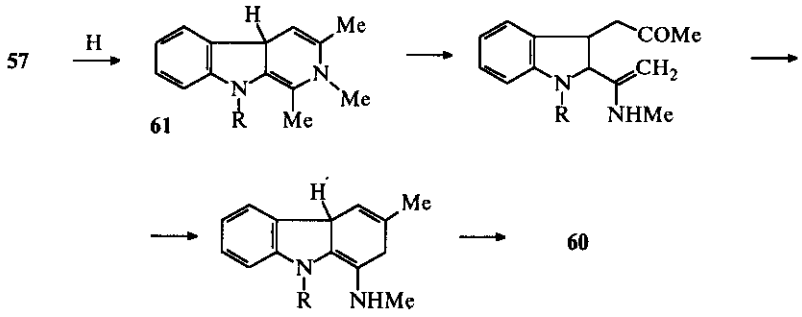
Interaction of the 1,3-dimethyl-β-carboline derivatives (**57**) with alkali resulted only in 1-methylaminocarbazoles (**58**) and (**59**). The methyl group in the position 3, in contrast to the isoquinolinium salts, proved to be completely unreactive. In addition, the recyclization was accompanied by dealkylation at the indole nitrogen atom, which led to the carbazole derivative (**59**).[41] Diaminodiphenyl derivatives (**60**) were also isolated from the reaction mixture in small yield.



57 58 59 60 R = Me, Et

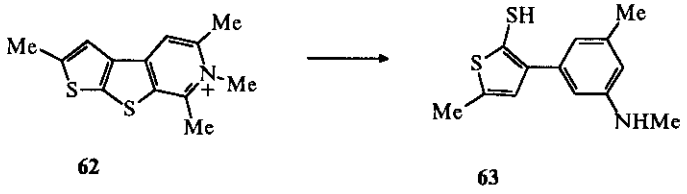
The formation of these compounds was not rationalized.[41] In our opinion, recyclization in this case seems to begin with the reduction of the pyridine ring at the γ-position with the formation of the 1,4-dihydropyridine (**61**). This is followed by dihydropyridine ring opening and closure of a new cycle with the C-C bond formation. The reductive recyclization of such a type of pyridinium

salts into cyclohexenones under the action of alkali is documented.[42]



After the cyclohexadiene ring closure its further aromatization may easily take place as a result of the arylamino group elimination under the action of base.

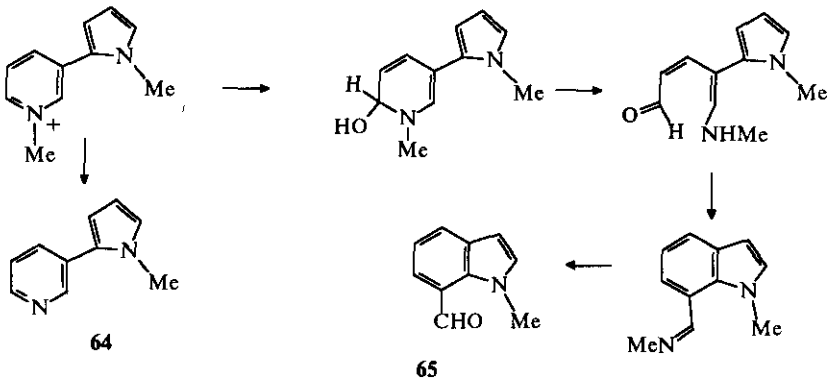
Most likely, recyclization of the thienopyridine (**62**) into the *meta*-toluidine (**63**) under the action of alkali[43] occurs in a similar manner.



The reaction scheme suggested,[43] according to which the thiophene ring opening occurs as a result of the nucleophilic attack at the sulfur atom by the hydroxide ion due to the involvement of the free *d*-orbitals of sulfur is in our opinion highly improbable. This conclusion is based on the fact that the preceding and obviously related reaction cannot be rationalized by the participation of the nitrogen atom *d*-orbitals. The above-discussed pyridine ring recyclizations include the reactions involving the α-carbon atom attached to the position 2 of the pyridine ring, that is, the enamine fragment of the corresponding anhydropyridine. A formal structural approach, however, allows to suggest that the recyclization can also involve more remote fragments of the molecule.

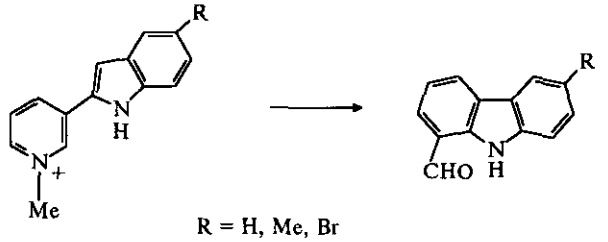
In fact, nicotyrine methiodide under the action of alkali undergoes recyclization leading to 7-formyl-1-methylindole.[44] Here the substituent subjected to the attack is attached to the position 3 of the pyridine ring, while the necessary nucleophilicity is provided by the general electron excess of the pyrrole ring. If the rearrangement is carried out under the action of methylammonium sulfite, the corresponding aldimine (**65**) can be isolated. In both cases a competitive nucleophilic attack on the Me-N bond takes place and this leads to demethylation of

the initial compound to give nicotyrine **(64)** as a side product.



64 65

Recyclization of 1-methyl-3-(2-indolyl)pyridinium iodide into 1-formylcarbazole[45] proceeds in a similar manner.



R = H, Me, Br

IV. CONCLUSION

The previously unknown recyclization reviewed here is not characteristic of only the structures that contain a pyridine ring, though in this particular case the reaction has been studied in most detail. We have also established that base-catalyzed recyclizations may occur in monocyclic and fused structures containing a pyrimidine ring. For example, 1,2-dialkylpyrimidinium salts may be converted into 2-alkylaminopyridines.[46] The transformation of the pyrimidine ring into the pyridine structure under the action of bases on pyrazolo[1,2-*a*]pyrimidines[47] or pyrimido[1,2-*a*]indoles[48] occurs in a similar manner. Recently, an enamine rearrangement with involvement of a pyrazine ring has been exemplified by recyclization of pyrrolo[1,2-*a*]pyrazinium into 8-aminoindolizines.[49]

Further investigations of the enamine rearrangement appear to be very promising, especially in view of the fact that the general concepts developed by us[3] allowed to formulate the requirements

in the initial structure and in the reagent for the reaction to occur and the undesirable processes to be suppressed, this providing a possibility for predicting and carrying out novel chemical transformations.

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Received, 24th November, 1992