RING TRANSFORMATION OF PYRIDINES AND BENZO DERIVATIVES UNDER THE ACTION OF C-NUCLEOPHILES

Sergey P. Gromov

Center of Photochemistry, Russian Academy of Sciences, 7a ul. Novatorov, Moscow, 117421, Russia

Abstract - The data on ring transformations of heterocyclic systems containing a pyridine ring on treatment with C-nucleophiles are generalized and described systematically over the period of up to 1999.

CONTENTS

I. INTRODUCTION

Pyridine ring is relatively stable against cleavage, although it is less stable than benzene. The Zincke-König reaction,[1] i.e. cleavage of the quaternized pyridine ring on treatment with aromatic amines to give glutaconic dialdehyde dianils, was historically the first comprehensively studied example of this type of reaction. Subsequently, numerous ring transformations of the pyridine ring induced by nucleophiles have been discovered and studied.[2] They include, first of all, a number of new rearrangements some of which are general for the chemistry of heterocyclic compounds, such as the amidine rearrangement[3] and the enamine rearrangement of pyridine derivatives found in our study.[4] Nevertheless, no comprehensive and

special review on ring transformations of the pyridine ring induced by C-nucleophiles have been published so far. Since the search for new types of ring transformations of heterocycles on treatment with C-nucleophiles remains a topical problem (see, for example, a review devoted to ring transformations of pyrimidines[5]) and the interest of synthetic chemists in the development of original synthetic procedures based on these reactions persists, it appears pertinent to follow the development and the characteristic features of studies carried out along this line.

Carbanions are species presenting considerable interest, first of all, due to the fact that they have diverse structures and functional groups and thus they are potentially capable of being incorporated according to various patterns into molecules formed in the ring transformations of the pyridine ring. Carbanions are mild nucleophiles; therefore, they mainly add to a pyridine ring at position 4 rather than 2.[6-9] The resulting 1,4-dihydropyridines cannot undergo electrocyclic cleavage of the pyridine ring because it is possible only for 1,2-dihydropyridine derivatives. Apparently, this fact hampers the conduction of ring transformations of pyridine derivatives induced by C-nucleophiles. This is partly responsible for the fact that only few types of reactions involving carbanions can be found in the literature and are considered below. However, the great synthetic potential of ring transformations of the pyridine ring involving C-nucleophiles makes further efforts along this line not merely justified but even highly promising.
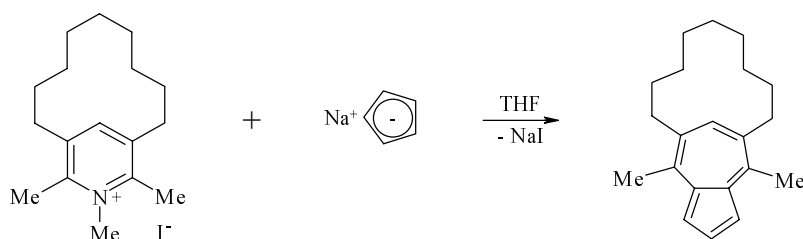
II. CYCLOPENTADIENE DERIVATIVES

The first example of ring transformation of pyridinium salts on treatment with C-nucleophiles was represented by the Ziegler-Hafner synthesis[10,11] of azulenes; one variant of this reaction makes use of pyridinium salts and appropriately substituted sodium cyclopentadienide. The reaction of 1-alkylpyridinium salts with sodium cyclopentadienide gives rise to relatively unstable 1-alkyl-2-cyclopentadienyl-1,2-dihydropyridine (**1**), which is converted into azulene on heating. The pyridine ring in the adduct (**1**) is cleaved to give fulvene (**2**), which again cyclizes with elimination of alkylamine.[12,13]

Woodward has shown that this thermal process involves electrocyclic [π10s] closure of the ring.[14,15] Certainly, it seems likely that intermediate (**3**), which has not been isolated, could result from a nucleophilic attack by atom 10 on the electron-deficient position 1 of compound (**2**). Actually, in this case, the difference between the two reaction pathways is insignificant from the mechanistic viewpoint. At the cyclization step, the σ bond is formed upon displacement of two π-electrons in the structure (**2**), which results in some loss of the resonance energy. If the cyclization is reversible, this reaction can be assumed to follow a disrotatory mechanism, which results smoothly and irreversibly in the elimination of alkylamine from the structure (**3**), which immediately affords azulene. Apparently, the cyclization step

requires a great activation energy during thermolysis and thus, it is the rate-determining step of the process.
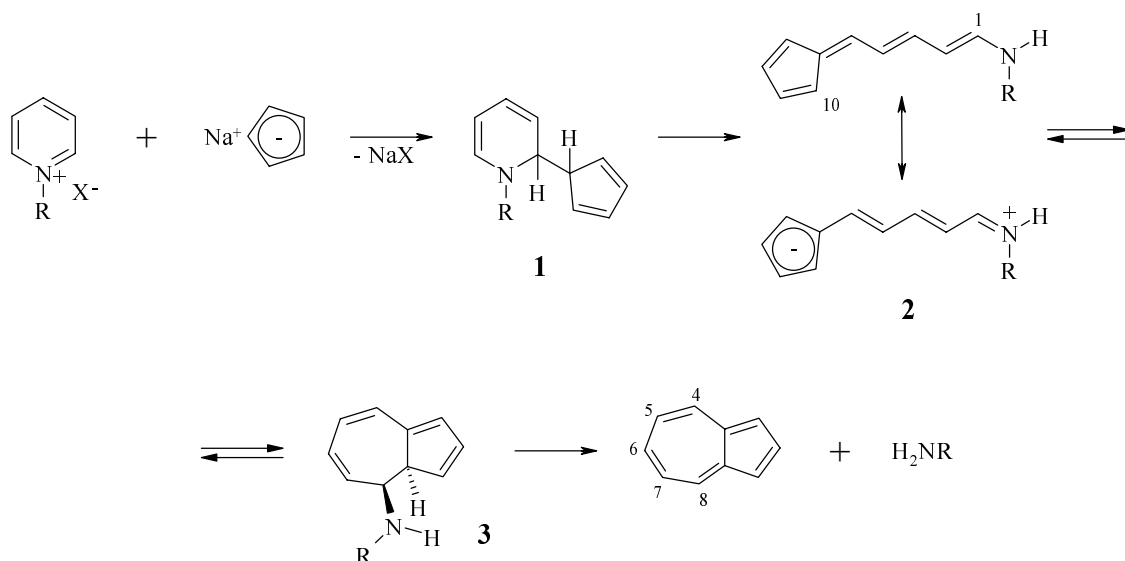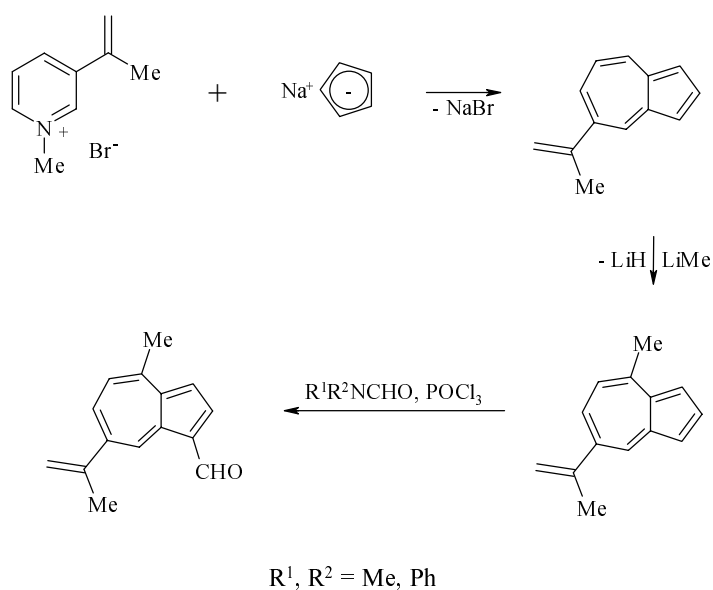

The Ziegler-Hafner synthesis of azulenes from pyridinium salts is a facile and convenient procedure; however, in the majority of cases, the yields of the target products are low.[16-17] The derivatives containing substituents in positions 5 and 7 in the seven-membered rings are formed in lower yields and are more difficult to purify than the azulene derivatives with substituents at positions 4, 6, and 8.[18] The presence of substituents at the α-position of the initial pyridinium salt is not a sufficient obstacle to the formation of the corresponding azulene; this is illustrated by the synthesis of 4,8-dimethyl-5,7-nonamethyleneazulene.[19]


The use of alkyl-substituted cyclopentadiene derivatives allows one to synthesize azulenes with substituents in the five-membered ring.[20,21] Thus the reaction of sodium 1,2,3-triphenylcyclopentadienide with 1-methylpyridinium iodide yields 1,2,3-triphenylazulene in 20% yield.[22] The Ziegler-Hafner reaction provides a pathway not only to azulenes containing substituents in either five-membered or seven-membered ring but also to those having substituents in both rings. For example, 7-ethyl-1,4-dimethylazulene (chamazulene) was prepared in this way from 5-ethyl-1,2-dimethylpyridinium bromide and sodium methylcyclopentadienide.[10]
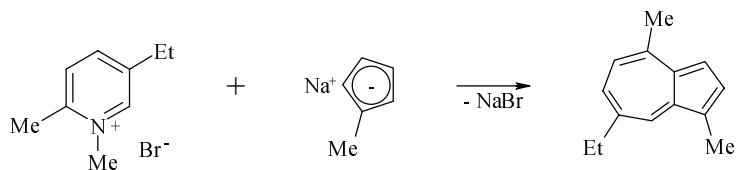
The total synthesis of 7-isopropenyl-4-methylazulene-1-carbaldehyde (lactaroviolin) has been carried out in a similar way; the first step involved treatment of 3-isopropenyl-1-methylpyridinium bromide with sodium cyclopentadienide.[23,24]


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

Benzo[f]azulene (4) has also been synthesized by the Ziegler-Hafner method in 3-4% yield.[16]
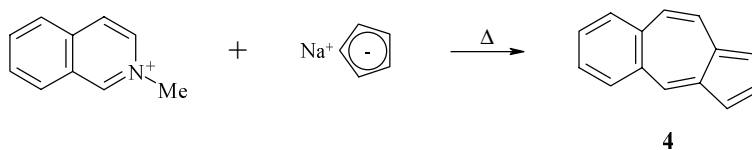
In this synthesis, the cyclopentadienyl anion enters into the reaction with 2-methylisoquinolinium iodide to give dihydroisoquinolinium, whose pyridine ring is subsequently opened. The formation of the seven-membered ring and elimination of methylamine afford benzo[f]azulene (4).

1-Methylquinolinium iodide is known to react according to a similar pattern with sodium cyclopentadienide in benzidine to give benzo[e]azulene (5); the yield of the product has not been reported.[20]
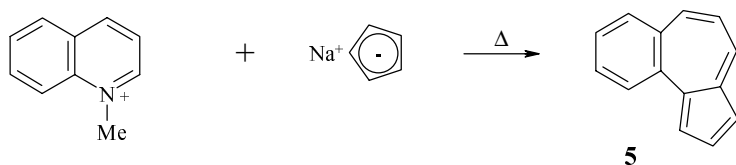
III. KETONES AND ENAMINES

Ring transformation reactions of ketones and enamines present substantial interest, on the one hand, due to the high nucleophilicity of the β-carbon atom in enamines and in the enolate ions, which are formed upon deprotonation of ketones, and on the other hand, due to the possibility that both α-carbon atoms would participate in nucleophilic reactions.

In this connection, the previously unknown dual reactivity of enaminones with *sym*-triazine with incorporation of N-C-C and C-C-C triads of enaminone atoms giving pyrimidine and pyridine derivatives, respectively, reported in our previous studies, is of interest.[25-28] Therefore, it appeared likely that the heterocyclic ring in pyridinium salts would either be directly cleaved on treatment with enamines or with substituted carbonyl compounds in the presence of bases or would act as the electron-deficient component in cycloaddition reactions. These transformation pathways of pyridinium salts could be expected to result finally in ring transformation of the heterocyclic ring.
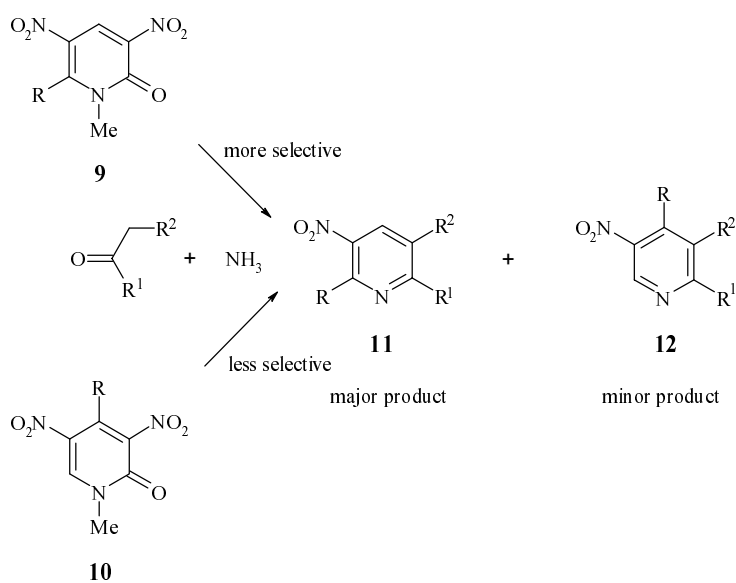
1. Ring transformations of dinitropyridones.

Indeed, the reaction of 1-methyl-3,5-dinitro-2-pyridone (**6**) with acetone and diethylamine gives rise to a bicyclic adduct, which was isolated and the structure of which was unambiguously confirmed.[29]
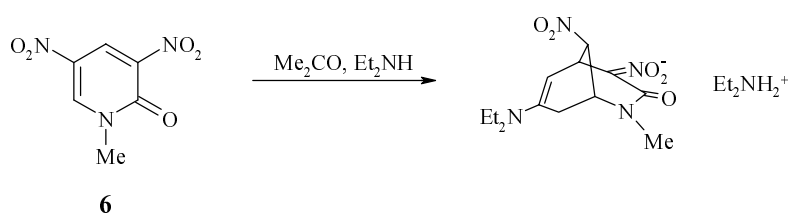
Other examples where pyridine derivatives form bicyclic adducts with bidentate nucleophiles are also known.[30] In addition, intermediate compounds of this type are presumably involved in the ring transformation of 1-methyl-3,5-dinitro-2-pyridone (**6**) into *para*-nitroanilines (**7**) and *para*-nitrophenols (**8**) on treatment with ketones and amines in pyridine.[29,31] Nitroanilines and nitrophenols are formed in high yields (up to 98%). It is noteworthy that the anionic σ-complexes with C-nucleophiles[32] and the corresponding cyclohexadiene derivatives, shown in the scheme, were isolated and characterized in this case.[29]

R = Me, 2-Py; R^1, R^2 = H, Me, Et; R^3, R^4 = H, Et, Bu, C_6H_{11}, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_4O$
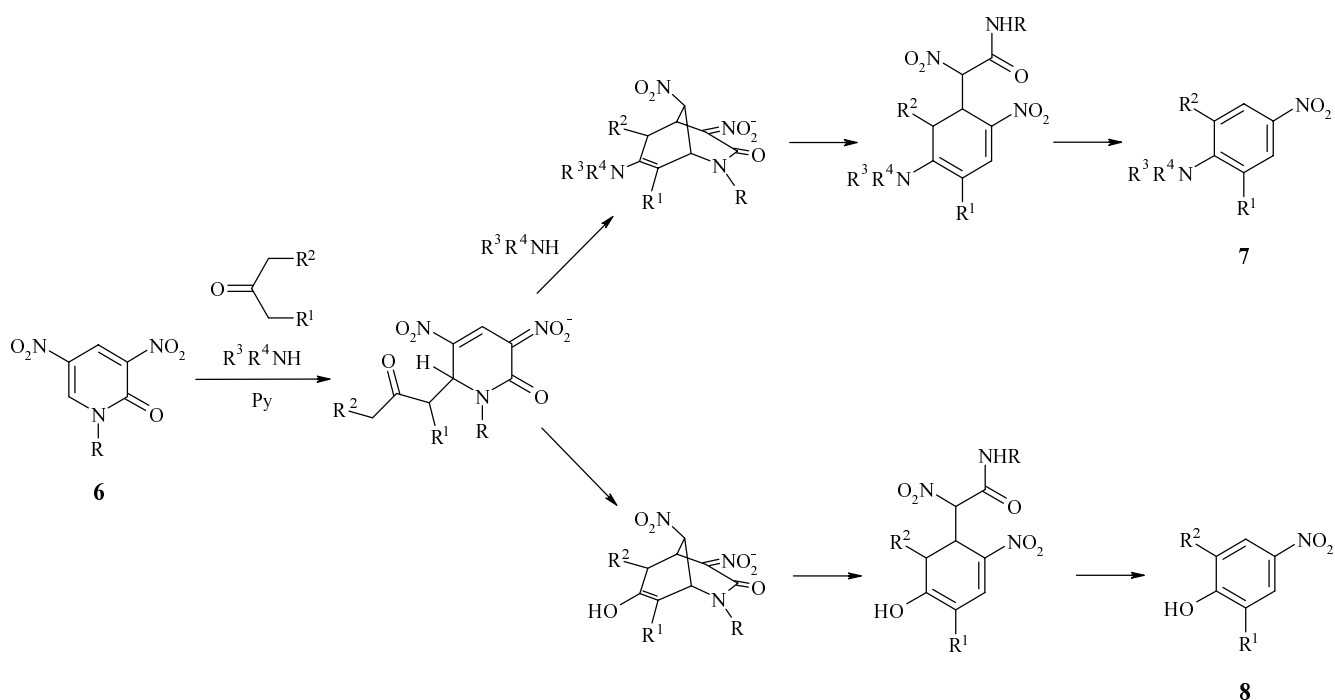
The ring transformations of 6- and 4-substituted derivatives (**9, 10**) of 1-methyl-3,5-dinitro-2-pyridone induced by ammonia and ketones or their enamines permit 2-substituted 3-nitropyridines (**11, 12**) to be synthesized in one step.[33-35] The 6-substituted derivatives (**9**) were the most selective in this case.

R^1, R^2 = H, Me, Et, *t*-Bu, $(CH_2)_3$, $(CH_2)_4$, *o*-$(CH_2)_2C_6H_4$, Ph, 2-Py;
R = D, Me, COOMe, *p*-$O_2NC_6H_4$, 4-Py, OMe

The mechanism of ring transformation has been studied comprehensively in relation to 1-methyl-3,5-dinitro-2-pyridone derivatives deuterated at positions 4 and 6.[35] Some of the intermediates formed in

these reactions were isolated and studied; they were found to have the structure of 2,6-diazabicyclo[3.3.1]nonane (**13**).

13
the most stable intermediate

11

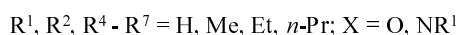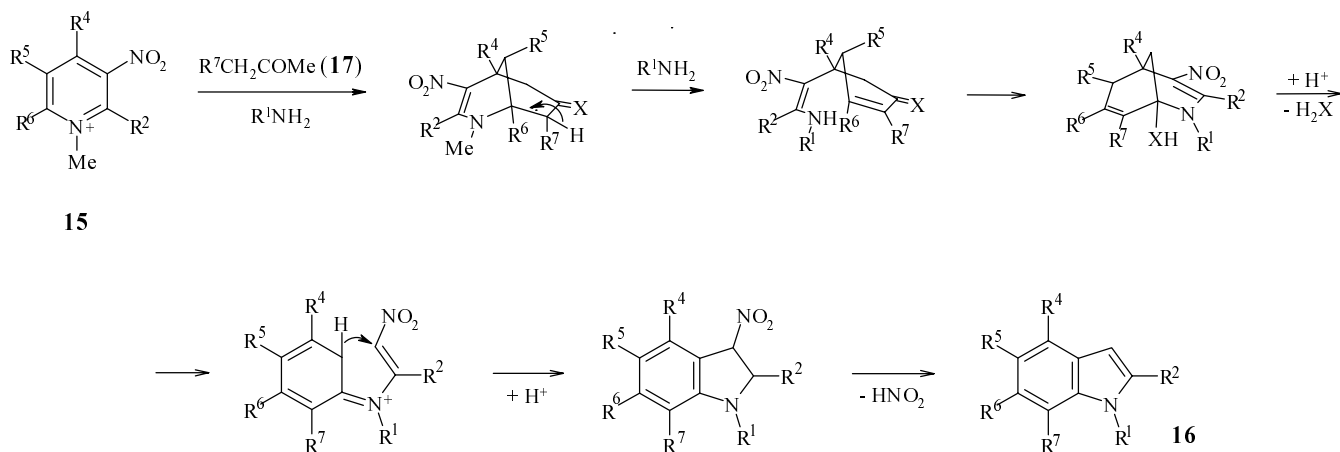a less stable intermediate

12

a less stable intermediate

14
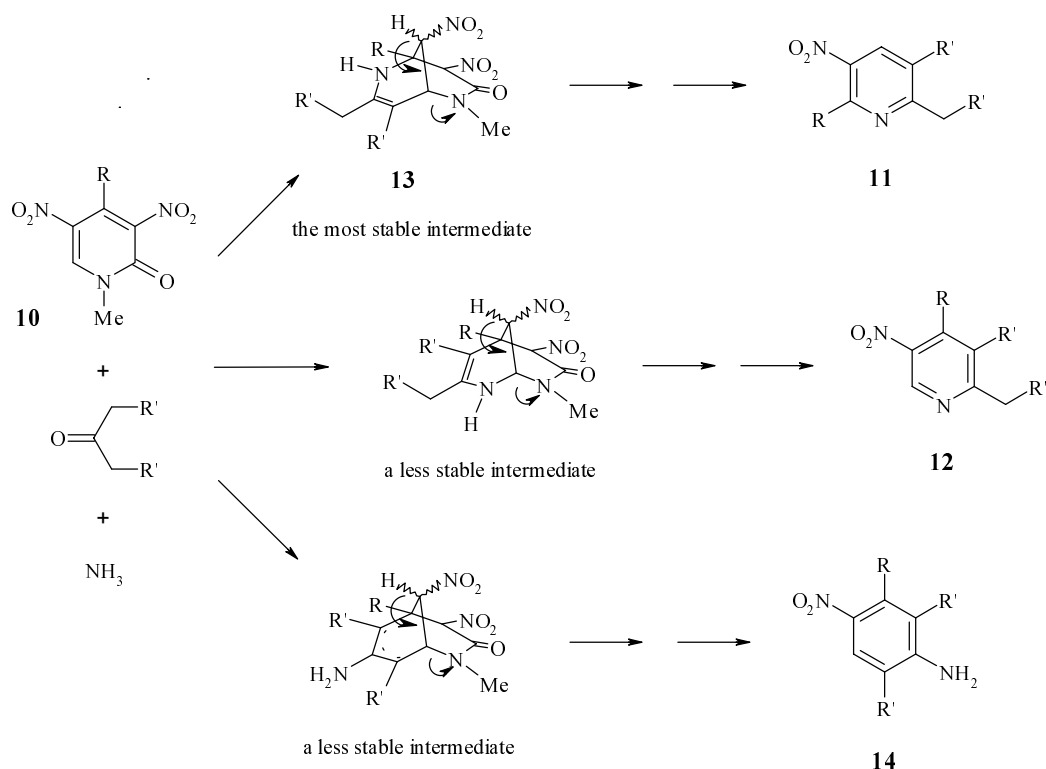
p-Nitroanilines (**14**) were produced as by-products in these transformations.

2. Ring transformations of nitropyridinium salts into indoles

We have shown that 1-alkylpyridinium salts, including those containing an electron-withdrawing substituent (nitro group) in the nucleus, do not undergo ring transformations on treatment with enamines such as 1-*N*-piperidinocyclohex-1-ene or enaminones. Nevertheless, the use of acyclic ketones containing two α-methylene groups and an increase in the electrophilicity of the pyridine ring by the introduction of a nitro group do provide conditions for ring transformation.

As a result of these studies, we proposed a new, in principle, approach to the synthesis of the indole bicyclic system based on an unusual and previously unknown transformation of the pyridine ring.[36-38]

We found that treatment of nitropyridinium salts (**15**) with substituted ketones and alkylamines afforded indole derivatives (**16**) whose yields reach 72%.[38,39]

R^{7}CH$_2$COMe (**17**)

R^{1}NH$_2$

15

R^{1}NH$_2$

+ H$^+$
− H$_2$X

+ H$^+$

− HNO$_2$

16

R^1, R^2, R^4 - R^7 = H, Me, Et, n-Pr; X = O, NR^1

Apparently, the first step is condensation of ketone (**17**) or its enamine with the pyridine nucleus; this is followed by ring cleavage with simultaneous exchange of the *N*-alkyl group, and subsequent cyclization to give indole derivatives (**16**) *via* the closure of a dihydropyrrole ring.
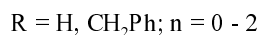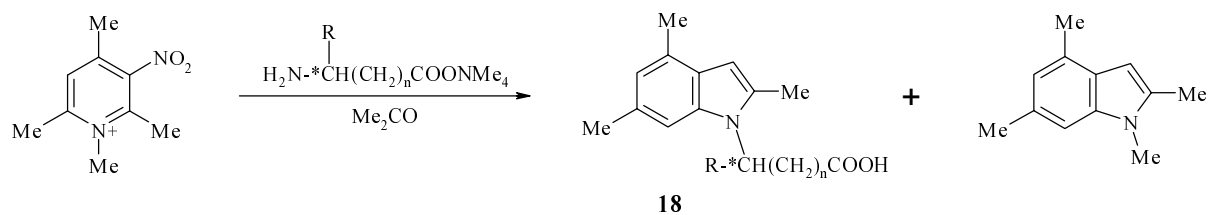
The optimum conditions for this reaction include a temperature of 40 $^{\circ}$C and long reaction times (5 to 7 days); a solution of an alkylamine in a ketone was used as the reagent.[38,39] If the reaction between, for example, 1,2,4,6-tetramethyl-3-nitropyridinium iodide and acetone is carried out in an excess of an aqueous solution of methylamine, the yield of 1,2,4,6-tetramethylindole decreases to 3% because competing hydrolytic elimination of the amino group occurs in parallel, apparently, at the step where the open form exists.

The degree of transamination in the synthesis of indoles from pyridinium salts depends on the alkyl group at the amine nitrogen atom and on the amine nucleophilicity.[40] As steric hindrance caused by the alkylamino group increases, the yields of indoles decrease, although the decrease is less pronounced than it might be expected.

The catalytic properties of surfactants are well known; in particular, they have been noted in the study of the enamine rearrangement of nitropyridinium salts.[4] In fact, we found[41] that the yield of *N*-octadecylindole substantially increases (from 5% to 18%) when an admixture of 1-cetylpyridinium bromide is used. This outcome can apparently be explained by the effect of reactant accumulation under conditions of micellar catalysis.

This method prompts a new strategy for the introduction of a chiral substituent to the indole nitrogen atom. Thus the use of amino acids including optically active ones results in previously unaccessible indole derivatives (**18**) with an asymmetrical carbon atom attached directly to the nitrogen atom of the indole nucleus, their yields being up to 25%.[42]

Me NO_2 ... Me Me Me Me

H_2N-*$CH(CH_2)_nCOONMe_4$

Me_2CO

Me Me-Me Me Me-Me

N N

R-*$CH(CH_2)_nCOOH$ Me

18

+

R = H, CH_2Ph; n = 0 - 2

Similarly, the use of racemic and, later, optically active α-phenylethylamine as the amine in this reaction made it possible subsequently to prepare the corresponding chiral indole.[40,43]

The introduction of methyl groups into positions 2 and 6 of the pyridine ring decreases the electron deficiency of the ring and hampers the competing cleavage of the pyridine ring by nucleophiles; correspondingly, the yield of indoles increases.[38] Thus treatment of 1,2,4,6-tetramethyl-3-nitropyridinium iodide with acetone and methylamine affords 1,2,4,6-tetramethylindole in 72% yield, which is the maximum yield for the series of compounds in question.[38,39] 1,2,4-Trimethyl-3-nitropyridinium iodide is converted into 1,2,4-trimethylindole in a higher yield (34%) than the isomeric 1,2,4-trimethyl-5-nitropyridinium iodide (6%), *i.e.* the addition of acetone to the pyridine nucleus during ring transformation involves preferentially the carbon atom in the *para*-position to the nitro group, which is not shielded by the methyl group. The presence of the methyl group in position 4 is the most significant for the occurrence of this reaction. Indeed, treatment of 1,2,6-trimethyl-3-nitropyridinium iodide with acetone and methylamine affords 1,2,6-trimethylindole, although in a low yield (3%). Meanwhile, it was found that the reaction of 1,4-dimethyl-3-nitropyridinium iodide (**19**) with methylamine in acetone gives 1,4-dimethylindole in 8% yield. In general, it can be stated that successive decrease in the number of methyl groups in the pyridine ring of the nitropyridinium salt diminishes the yields of methylindoles.[44]

Me NO_2

Me_2CO

$MeNH_2$

Me Me

N N

Me Me

19
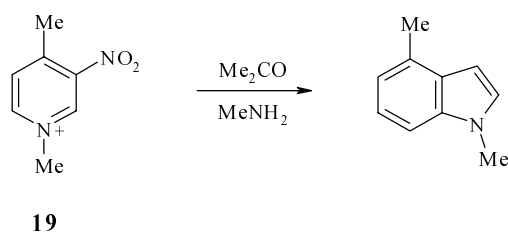
It can be expected that the complex sequence of transformations leading to indoles should be accompanied by the formation of by-products; detection of these by-products would enable one to draw certain conclusions concerning the course of the reaction as a whole. Indeed, full analysis of the products resulting from the reaction of 1,2,4,6-tetramethyl-3-nitropyridinium iodide (**20**) with methylamine in

methyl propyl ketone makes it possible to isolate 1,2,4,6-tetramethylindole (**21b**) (yield 3%) and compound (**24**) (R = *n*-Pr) (yield 22%) in addition to 7-ethyl-1,2,4,6-tetramethylindole (**21a**) (yield 8%).[44]

22a   **23a**   **21a**

20

n-PrCOMe

MeNH₂

22b   **23b**   **21b**
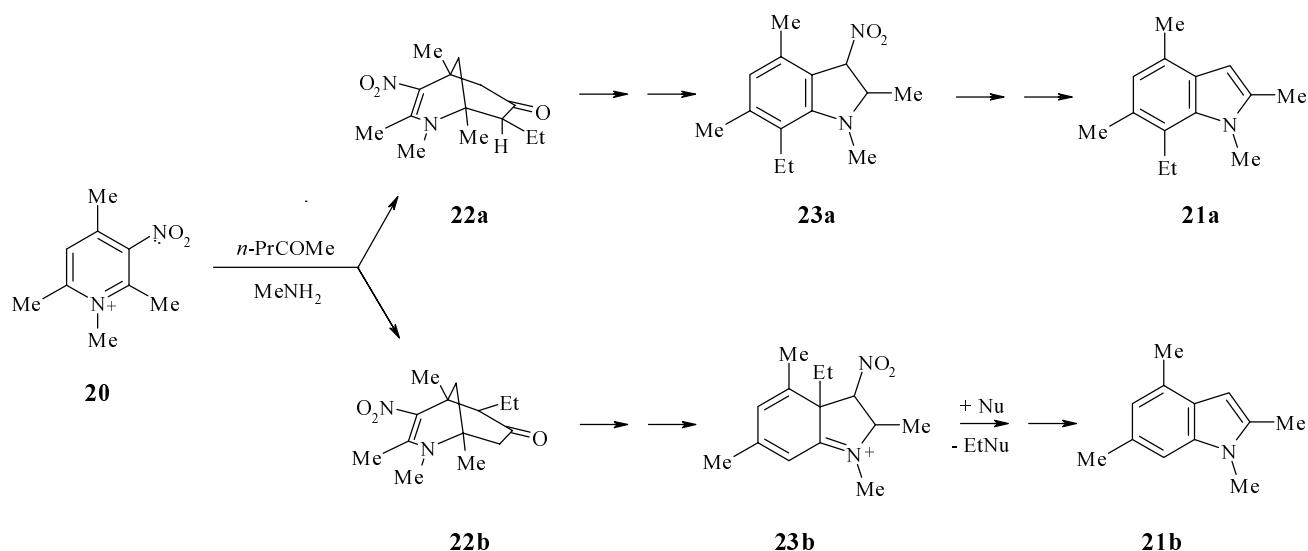
Apparently, methyl propyl ketone (or its enamine) undergoes initially stepwise condensation with the pyridine nucleus according to either of two pathways [see structures (**22a,b**) and the intermediates (**23a,b**) resulting from the subsequent sequence of transformations]. Closure of the dihydropyrrole ring induces elimination of an ethyl group from the bridgehead position of compound (**23b**), which gives rise to indole (**21b**). This process is facilitated by the aromatization of the cyclohexadiene ring in compound (**23b**). A process similar to the dealkylation involving the bridgehead position of the dihydroindole bicyclic structure, assumed by this scheme, occurs in some cases in the synthesis of indole according to Fischer.[45]

It is significant that treatment of 1,2,4,6-tetramethyl-3-nitropyridinium iodide (**20**) with ethyl methyl ketone and methylamine affords 1,2,4,6,7-pentamethylindole and compound (**24**) (R = Et) as the major reaction products, whereas 1,2,4,6-tetramethylindole (**21b**) is formed in small amounts and can be detected only by MS spectroscopy.

Thus, the new reaction pathway leading to indoles involves elimination of alkyl groups, apparently, at intermediate reaction steps. The extent to which this process occurs increases with lengthening of the alkyl radical in alkyl methyl ketone.

In addition to the indole derivatives, analysis of the products formed in the reaction of compound (**20**) with methylamine in methyl propyl ketone or ethyl methyl ketone results in the isolation of deeply colored compounds (**24**) in 22% and 14% yields, respectively.[44]
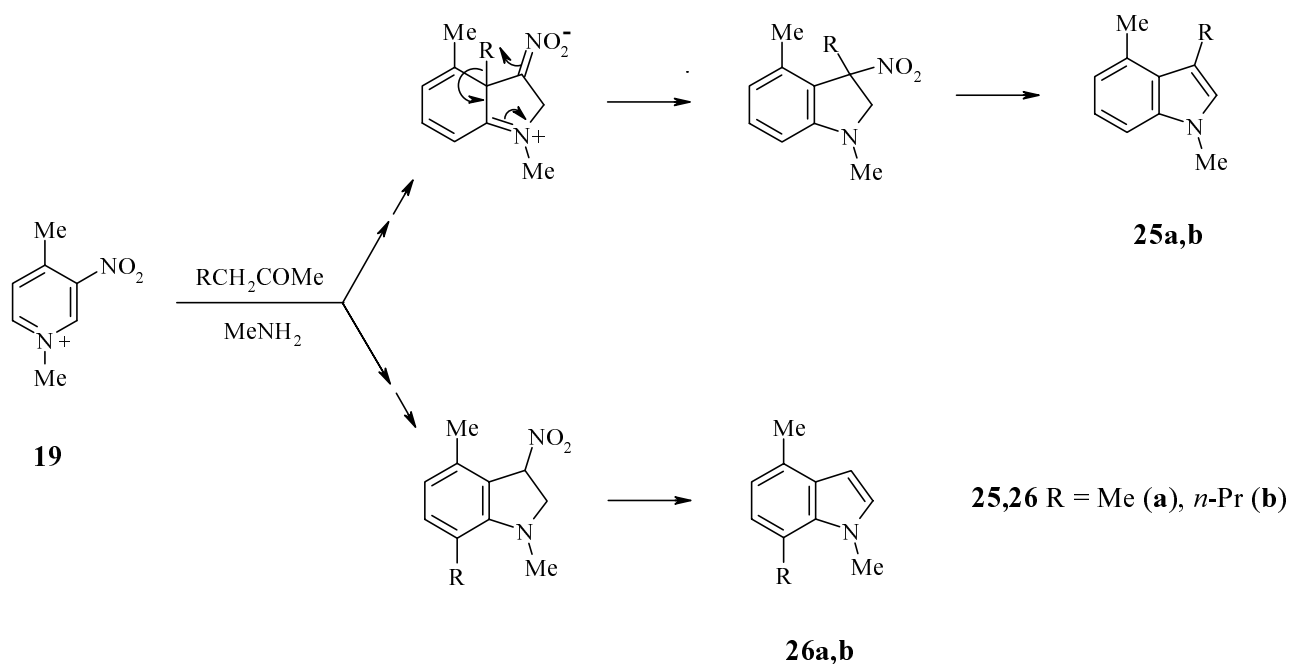
R = *n*-Pr, Et
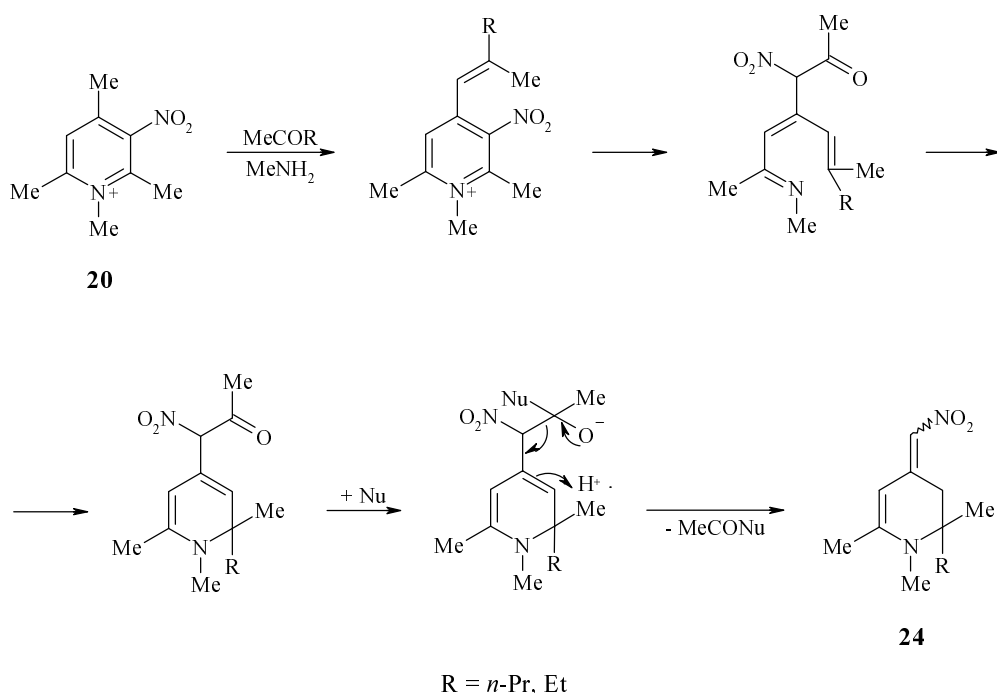
In this case, the reaction pathway includes apparently condensation of ketone at the 4-methyl group of the pyridine ring, ring opening, and the subsequent orbital symmetry-allowed cyclization giving rise to a dihydropyridine ring. The process ends with the abstraction of an acetyl group according to a mechanism reverse to *C*-acylation of nitro compounds. Interpretation of the spectra of compounds (**24**) showed that each is a pair of *Z* and *E* stereoisomers in 6 : 1 ratio.[44]

Apart from elimination, migration to an electron-rich positions of the intermediate can be conceived for an alkyl group located in the bridgehead position of a dihydroindole bicyclic system. In fact, this route has been realized by using nitropyridinium salts with one methyl group in the pyridine nucleus.[44]

Thus the reaction of 1,4-dimethyl-3-nitropyridinium iodide (**19**) with ethyl methyl ketone and methylamine affords a mixture of 1,3,4-trimethylindole (**25a**) and 1,4,7-trimethylindole (**26a**) in an overall yield of 22% and in a ratio of 3 : 2. Similarly, treatment of 1,4-dimethyl-3-nitropyridinium iodide (**19**) with butyl methyl ketone and methylamine resulted in a mixture of 1,4-dimethyl-3-propylindole (**25b**) and 1,4-dimethyl-7-propylindole (**26b**) in 2% total yield and in 11 : 9 ratio (NMR spectrum).

In the dihydroindole bicyclic system formed, an alkyl group migrates apparently from the bridgehead position to position 3 activated by the negative charge. This migration is facilitated by the accompanying aromatization of the cyclohexadiene ring in these structures. The absence of indole derivatives with a different type of substitution among the reaction products points to an intramolecular mechanism of the shift of the alkyl groups. More evidence is provided by the fact that no isomerization of the propyl group into an isopropyl group is observed in both indoles (**25b**) and (**26b**).

19

RCH_2COMe

$MeNH_2$

25a,b

25,26 R = Me (**a**), *n*-Pr (**b**)

26a,b

The synthesis of indoles by the above-described procedure is also possible with the use of pyridine bases. Thus prolonged contact of a solution of methylamine in ethyl methyl ketone with 2,4,6-trimethyl-3-nitropyridine affords 1,2,4,6,7-pentamethylindole, although its yield is low (2%).[38]

Among other reasons, the decrease in the yield of indoles[39,41] is due to the competing isomerization of nitropyridinium salts and condensation of these salts with acetone present in an excess, which usually proceed with low yields. For example, chromatographic analysis showed the presence of substituted *o*-nitroanilines (**27**) and *p*-nitroanilines (**28**), which may have resulted from the enamine rearrangement[2,4] of nitropyridinium salt (**20**).

RNH_2

20   **27**   +   **28**

R = Me, $C_{18}H_{37}$
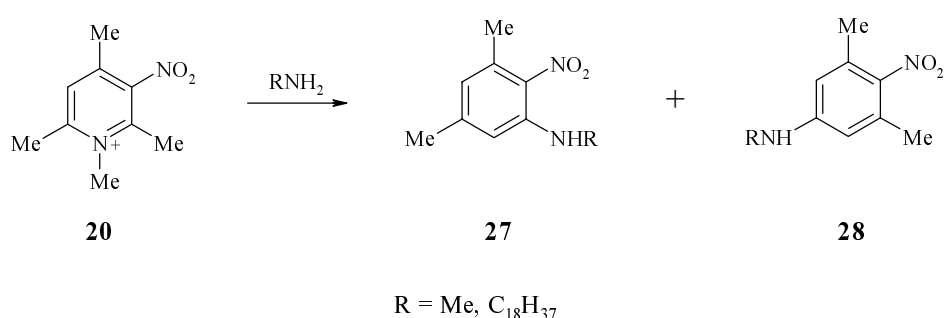
The well-known Fischer synthesis of indoles[46,47] belongs to the most important methods for the preparation of alkylindoles substituted at the pyrrole ring. The reaction mechanism is complex and includes the formation of a pyrrole ring during the process. The Bischler synthesis of indoles,[46,47] based on the reaction of arylamines with α-halo-, α-hydroxy-, or α-arylamino ketones in an acid medium, leads to the indole bicyclic system also *via* the formation of a pyrrole ring.

Thus, the previously unknown transformation of pyridinium salts into indoles is also a new, in principle, approach to the synthesis of the indole system based on the formation of both pyrrole and benzene rings during the reaction. This method is also distinguished by simplicity of the experimental procedure.

It is of interest to determine the structures of the resulting indole derivatives. The indole nature of these products, the number of alkyl substituents, and the pattern of distribution of the substituents in the pyrrole moiety of the molecule were established back in the first publication dealing with this subject.[36] However, the positions of substituents in the benzene moiety of the synthesized indoles had to be determined more exactly. This was done using the ^{13}C NMR spectra in relation to 4-ethyl- and 4-propyl-1,2,6,7-tetramethylindoles and to 1,4-dimethylindole, which was prepared from the compounds and by the procedure proposed by the author of this review.[44,49] Simultaneously, similar results have been obtained from ^{1}H NMR spectroscopy taken 1,4,5-trimethylindole as an example.[38] The results of this comprehensive analysis of the structures of the compounds synthesized have been reported at conferences.[49,50] At present, this structure of indoles is regarded as indubitable, after X-Ray diffraction analysis of one indole derivative synthesized *via* the reaction in question.[51]

The pathway from nitropyridinium salts to indoles discussed here seems to be a complex and unusual process. Therefore, it would be fairly interesting to study the mechanism of formation of the indole bicyclic system. These studies were undertaken and gave the following main results.

Thus the earlier assumption[38] that ketone enamine can enter into condensation with a nitropyridinium salt was confirmed. More precisely, ketimines can be introduced in the indole synthesis in a pure state, instead of a mixture of ketone and amine, which contains only equilibrium amounts of the ketimine and the enamine forms.[52,53] For instance, the reaction of 1,2,4,6-tetramethyl-3-nitropyridinium iodide (**20**) directly with acetone methylimine provides 1,2,4,6-tetramethylindole in the same yield as the reaction using an acetone solution of methylamine.[38] Evidently, these data do not rule out the possibility of direct reaction of nitropyridinium salts with ketones in water-containing media, as has been done previously.[44] Moreover, we found that a small amount of water is necessary for the reaction and increases the yields of indoles.[39] When investigating the reaction of nitropyridinium salts with ketimines in various solvents, authors[53] arrived at the conclusion that polar aprotic solvents such as DMF or pyridine substantially accelerate the indole formation, although the yield of indoles either does not change significantly in the presence of these solvents or even decreases.[39] However, the use of ketimines is relatively unpromising from the practical viewpoint because they are difficult to obtain;[54] and, in addition, the number of steps in the process increases.

Numerous examples of the formation of adducts, bicyclo[3.3.1]nonane derivatives, from nitro compounds of the pyridine and benzene series and bidentate nucleophiles including ketones can be found in the

literature (see, for example, several studies[55,29,30]). Adducts of this type have also been proposed in our study[38] in order to interpret the possible mechanism of the formation of indoles. Later, these intermediates have been detected for 3-nitroquinoline derivatives;[56] by analogy with the study by Matsumura *et al.*,[29] these compounds have also been proposed as intermediates *en route* to nitroanilines, which are formed as by-products in the reaction of nitropyridinium salts with ketones and amines.[41,57]

In addition to indole-type compounds, authors[57] isolated derivatives of alkyl *o*-aminobenzyl ketones, which were proposed as intermediate compounds directly preceding the formation of indoles at the final steps of ring transformation of the pyridine ring.[58] Indeed, substituted aniline (**30**) was detected in the multicomponent mixture of products formed in the reaction of salt (**29**) with acetone and piperidine and isolated in 16% yield.
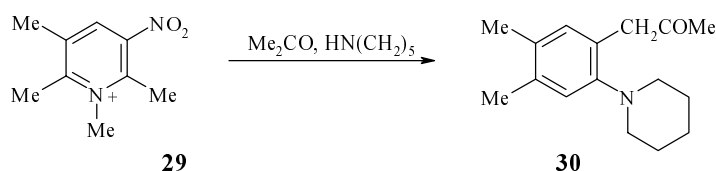

In accordance with these views, the nitrate ion is detached from the intermediate compound at an even earlier step than we have suggested in a previous study.[38] If this assumption is true, the shift of the bridgehead alkyl fragments into the β-position of indole can be interpreted in terms of the following scheme:[59]
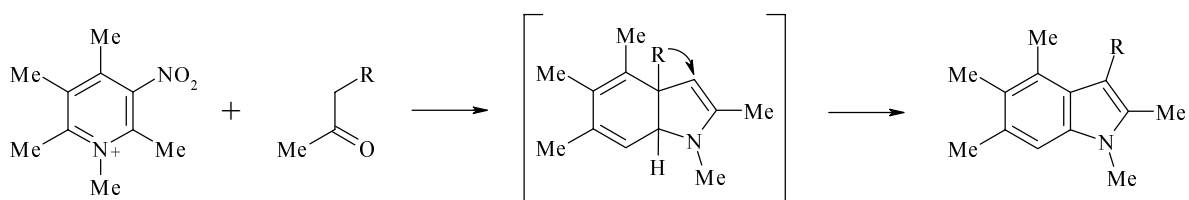
Comparison of these chart with the alternative scheme of the formation of **25a,b** points that the latter should be preferred; in our opinion, this scheme explains fairly reasonably both the shift and elimination of the substituent R from the intermediate. According to the scheme proposed by authors,[59] elimination of the radical R can be represented as either a free radical process or a synchronous process coupled with elimination of RH, which is unlikely. Therefore, alkyl *o*-aminobenzyl ketones are not intermediates in the ring transformation of the pyridine ring into the indole ring on treatment with ketones and amines; instead, they rather represent one more reaction pathway leading to by-products. This is all the more true because ring transformation of nitropyridinium salts into indoles yields lots of unusual by-products. For example, dihydroquinoline (**31**) and tetrahydroquinoline (**32**)[60,39] derivatives formed in 4-18% and 2-6%

yields, respectively, were detected, apart from indoles, in a study of the reaction of 4-alkyl-2,6-dimethyl-3-nitropyridinium iodides with *N*-methylacetoneimines in DMF.
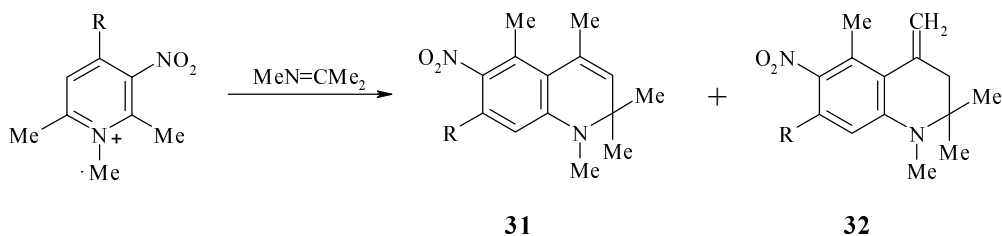
It has been noted[60] that the basic difference between this reaction route and the previous ones is participation of two ketone fragments in the construction of the quinoline skeleton with cleavage of the C(4)-C(5) bond in the initial salt.

Previously, we have shown that the degrees of transamination in the synthesis of indoles from pyridinium salts are relatively high, even in the case of *sec*-butylamine and *tert*-butylamine (the yields of indoles are 35% and 3%, respectively). This indicates that the sensitivity of ring transformation to the steric hindrance induced by substituents is lower than one could have expected.[40] Similar observations have been done in a study of ring transformation into indoles of nitropyridinium salts containing *tert*-butyl and *iso*-propyl substituents in positions 2, 4, and 6 of the pyridine nucleus.[61]

Thus, the whole set of currently available data concerning the mechanism of ring transformation of pyridinium salts into indoles does not contradict the scheme of these transformations that we proposed previously.[38] Moreover, the initial and final steps of this process have been confirmed experimentally in subsequent studies.

The new method for the synthesis of indoles from nitropyridinium salts, acetone, and alkylamine served as the basis for a method for the synthesis of quaternary polyalkylindoleninium salts, which are widely employed in the construction of dyes of various classes.[39,62-69] Practically, the introduction of additional alkyl groups into an indoleninium residue provides the possibility of controlling the hydrophilic—lipophilic balance of the synthesized dyes and of increasing their stability to photodegradation.

IV. β-DICARBONYL COMPOUNDS AND CARBOXYLIC ACIDS

Examples of participation of β-dicarbonyl compounds in ring transformations of pyridine ring are less numerous than those for ketones. Like ketones, β-dicarbonyl compounds act in these reactions as bidentate nucleophiles, which are incorporated in the newly formed rings as C_3 fragments.

For instance, treatment of 3,5-dinitro-2-pyridone derivatives (**33**) with the sodium salt of β-oxo ester shown below results in ring transformation giving rise to the corresponding ethyl 2-hydroxy-5-nitrobenzoates (**34**) in yields of up to 98% and nitroacetamide (**35**).[29,55,70-72]
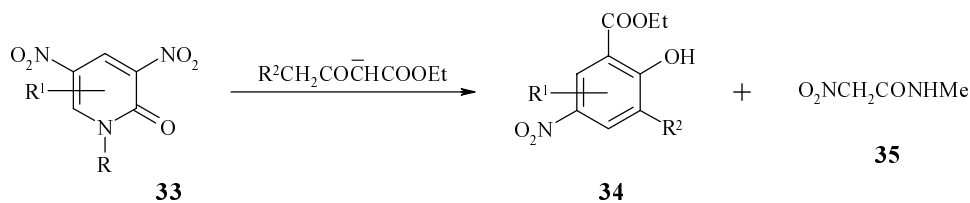
R = H, Me, *m*-$O_2NC_6H_4CH_2$, 2-PyCH$_2$, 2-Py, 2-(4-Me)C$_5$H$_3$N, 2-(5-Me)C$_5$H$_3$N,
2-(6-Me)C$_5$H$_3$N, 2,4-$(O_2N)_2C_6H_3$, HO, MeO, *p*-$O_2NC_6H_4CH_2O$;
R^1 = H, Me, 4-MeO; R^2 = H, COOEt

Apparently, the C-anion adds initially to position 6 or 4 to give the Meisenheimer complex, and subsequently the other nucleophilic center attacks the position 4 or 6, thus giving rise to a bicyclic intermediate, which is converted into benzoate (**34**) and nitroacetamide (**35**) after rupture of the N(1)-C(6) and C(3)-C(4) bonds.

The reaction of diethyl sodio-3-oxopentanedioate with *N*-substituted 3,5-dinitro-4-pyridone derivatives (**36**) occurs as ring transformation resulting in *N*-substituted 3,5-bis(ethoxycarbonyl)-4-pyridones (**37**).
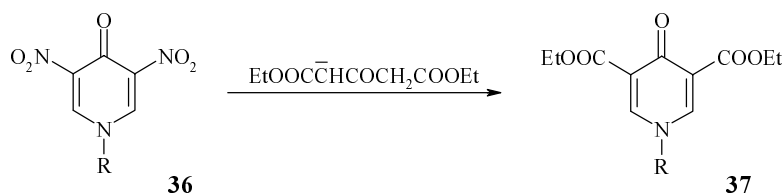
R = Me, 2-Py, 4-Py, 2-(6-Me)C$_5$H$_3$N

Unlike 2-pyridones, in this case, the bonds to be cleaved are C(2)-C(3) and C(5)-C(6); correspondingly, this gives rise to pyridone (**37**).[55,73]

On the other hand, the reactions of the 4-pyridones (**36**) with ethyl sodioacetoacetate give ethyl 4-hydroxy-3,5-dinitrobenzoate.
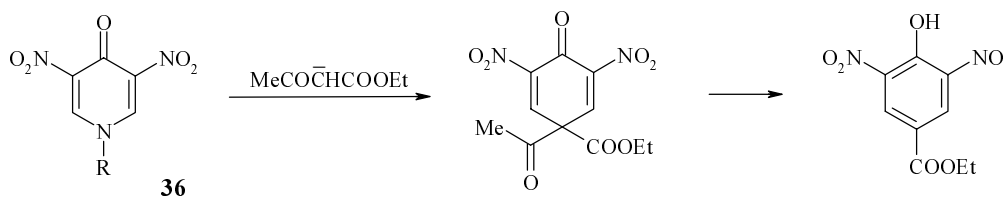

R = 2-Py, 4-Py, 2-(6-Me)C$_5$H$_3$N

On the basis of the concept of soft and hard acids and bases, a stepwise nucleophilic attack of the anion of β-keto esters at the electrophilic center of the 2 and 3-positions or 2 and 6-positions of the 4-pyridones was proposed to interpret the variations of the reaction courses.[73]

The carboxy group exhibits weaker acceptor properties than a carbonyl group and, hence, it does not stabilize sufficiently the carbanion arising upon deprotonation of the α-methylene group. Therefore, only one example of ring transformation of a pyridine ring involving a C-nucleophile of this type has been known until recently. Thus it was found that treatment of pyridine with a mixture of potassium acetate with sodium amide at 200 °C and 50 atm yields potassium benzoate. Apart from sodium amide, sodium, sodium hydride, potassium, and butyllithium react in a similar way. The yields of benzoic acid vary from 0.5 to 6%, depending on the reagent used and the reaction conditions. The greater part of pyridine does not react, being recovered unchanged.[74]
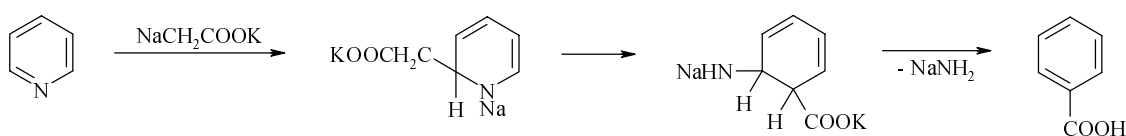
Study of the transformations under the Perkin reaction conditions, i.e. using a mixture of acetic anhydride with sodium acetate as the reagents allows the ring transformation of the pyridine ring involving a carboxylic acid residue to be performed under milder conditions. For example, treatment of 2-methylisoquinolinium iodide with sodium acetate in acetic anhydride provides β-naphthylacetate in 15% yield. A bridge mechanism has been proposed to rationalize the formation of these products.[75,76]
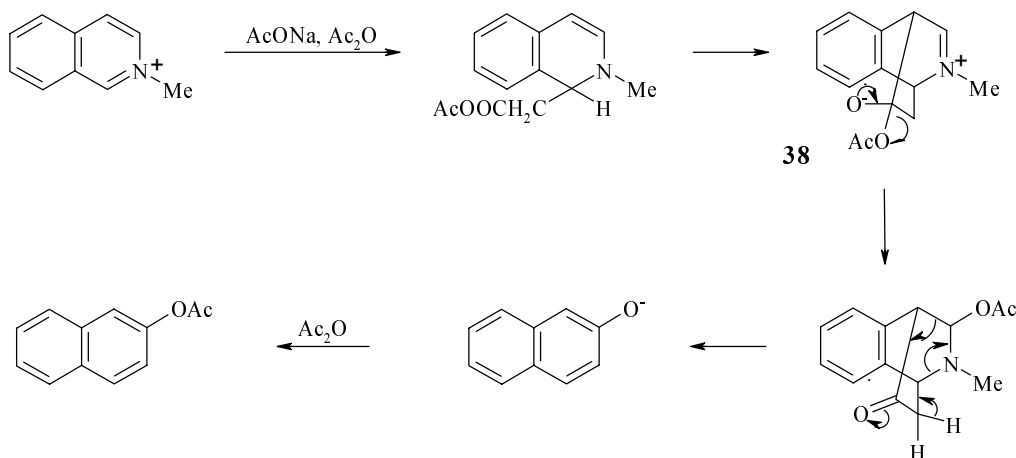
A nucleophilic attack by the acetic anhydride anion on the C-1 atom of isoquinoline followed by intramolecular acylation of enamine yields bridging intermediate (**38**). Elimination of nitrogen upon rupture of the N(2)-C(1) bond affords β-naphthol, which is converted into β-naphthyl acetate upon

acetylation with excess acetic anhydride. Thus, two carbon atoms of the acetyl residue are involved in the formation of the β-naphthyl acetate benzene ring.

The reaction of benzo[b]quinolizinium bromide with sodium acetate in acetic anhydride has also been studied. The resulting product was a tricyclic ester, namely, 1-(2'-pyridyl)-2-naphthyl acetate (40), which is formed apparently from the intermediate tetracyclic ketone (39).

39   **40**
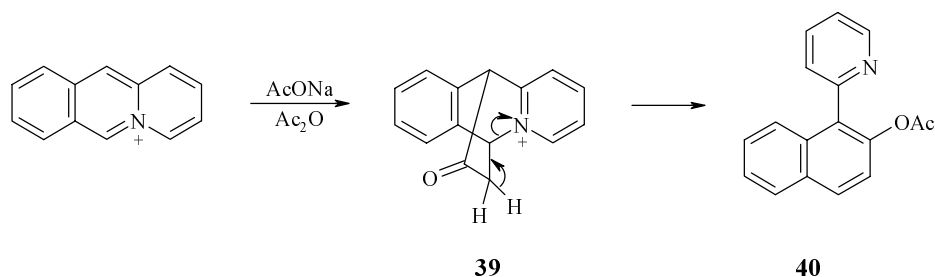
The next compound, which can be prepared from papaverine, was a protoberberinium salt, 2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride (41). On heating with sodium propionate and propionic anhydride, the protoberberinium salt (41) is converted into 1-(β-naphthyl)isoquinolinyl propoinate (42) in a good yield.[76]

41   **42**

R = H, Me
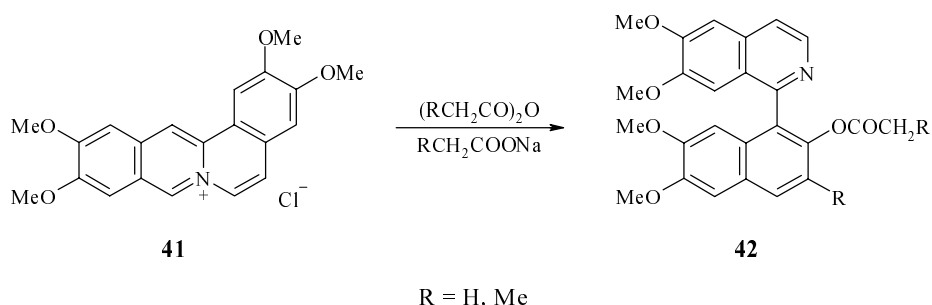
Finally, heating of berberine chloride with sodium acetate in acetic anhydride gives rise to two reaction products, (44) and (45). This reaction is also likely to proceed by a bridge mechanism, which is confirmed by the fact that berberine salt (43) does not react with sodium benzoate and benzoic anhydride or sodium trifluoroacetate and trifluoroacetic anhydride.[75,76]

43   **44**   **45**
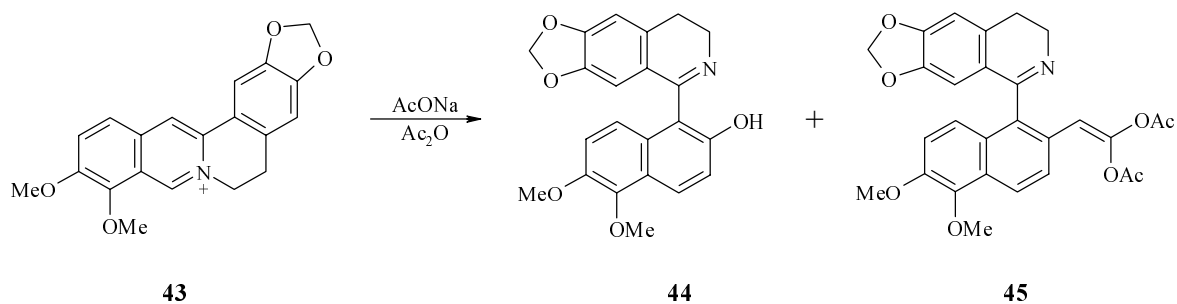
V. NITROALKANES AND SULFOXIDES

The nitro group, which is a strong electron-withdrawing substituent, can largely stabilize the carbanion formed upon deprotonation. Nevertheless, pyridine ring ring transformations involving nitroalkanes have been barely studied. The only known example is the formation of 2-nitronaphthalene (yield 9%) from 2-methylisoquinolinium iodide and nitromethane induced by alkali. The reaction starts apparently with the attack by the carbanion on position 1 of the isoquinoline bicyclic system and ends, after elimination of a methylamine molecule, with the incorporation of the methyl carbon atom of nitromethane into the benzene ring formed.[77]
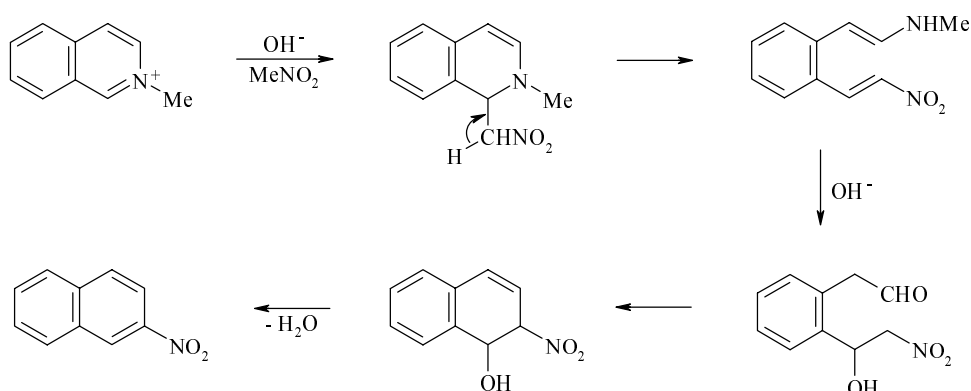
An unusual formation of phenanthrene has been observed on attempted methylation of benzo[*h*]quinoline *N*-oxide with the methylsulfinyl anion. Instead of the expected methylbenzo[*h*]quinoline, the reaction gave phenanthrene in 86% yield. Phenanthroline *N*-oxides react in a similar way, giving rise to benzo[*h*]quinoline derivatives.[78-80]

$R^1, R^2, R^3 = H, Me; \quad X = CH, N$
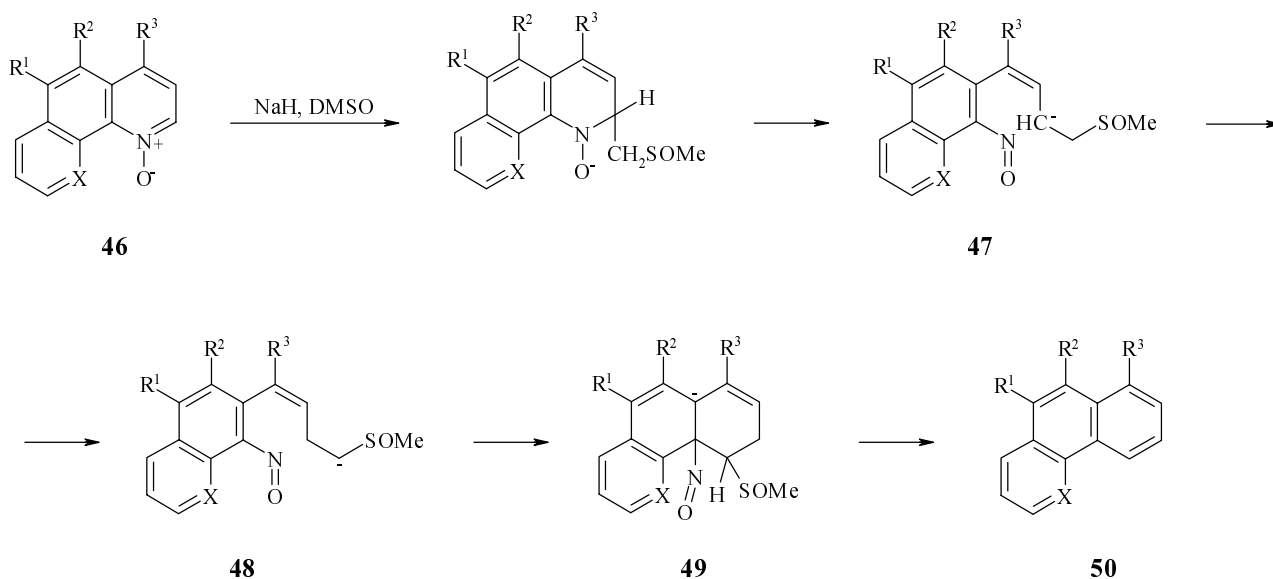
The initial nucleophilic attack of *N*-oxide (**46**) by the methylsulfinyl carbanion leads to the rupture of the C-N bond of the *N*-oxide group to give carbanion (**47**), which rapidly isomerizes to more stable carbanion (**48**). Subsequently, anion (**48**) is subjected to intramolecular nucleophilic attack yielding carbocyclic product (**49**), which undergoes elimination reactions providing compound (**50**) as the final product.

Similarly, benzo[*f*]quinoline *N*-oxide (**51**) is methylated by the methylsulfinyl anion to give phenanthrene in 88% yield.[80]

51
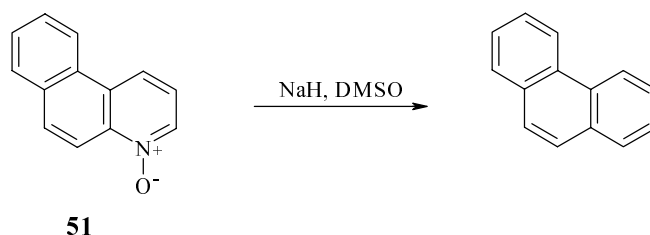
Later, it has been found that the reactions of quinoline and isoquinoline *N*-oxides with sodium hydride in dimethyl sulfoxide under the same conditions can also afford naphthalene.[79]
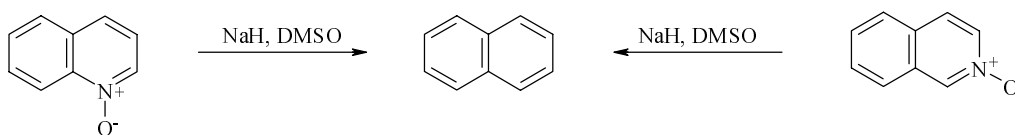
VI. CONCLUSION

Thus, the pyridine ring transformations studied most extensively by now are those induced by C-nucleophiles and giving rise to hetero- and carbocycles; they are accompanied by elimination or exchange of a quaternary nitrogen atom, which naturally reflects the enhanced susceptibility of the N=CH bond in pyridine ring to nucleophilic attack. The main structural factors and necessary conditions influencing the ring transformation pathway, identified to date, provide grounds to expect great prospects for further research along this line. A promising reaction is the unusual ring transformation of nitropyridinium salts into indoles, discovered by me, which represents a non-traditional approach to the construction of the indole bicyclic system and demonstrates latent reserves in the studies of C-nucleophile-induced ring transformations of the pyridine ring. Examples of ring transformations of pyridine derivatives not activated additionally by quaternization are few. In this case, most of C-nucleophiles are unable to add to the aromatic ring to give ring transformation products, apparently, due to the insufficient polarization of the pyridine nucleus.

REFERENCES

1. J. Becher, *Synthesis*, 1980, **8**, 589.

2. A. N. Kost, S. P. Gromov, and R. S. Sagitullin, *Tetrahedron*, 1981, **37**, 3423.

3. M. Wahren, *Z. Chem.*, 1969, **7**, 241.

4. S. P. Gromov and A. N. Kost, *Heterocycles*, 1994, **38**, 1127.

5. V. L. Rusinov, O. N. Chupakhin, and H. C. van der Plas, *Heterocycles*, 1995, **40**, 441.

6. T. Severin, H. Lerche, and O. Batz, *Chem. Ber.*, 1969, **102**, 2163.

7. A. A. Onishchenko, T. V. Ternikova, O. A. Luk'yanov, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1976, 2530 [*Russ. Chem. Bull.*, 1976, **25** (Engl. Transl.)].

8. J. Kava'lek, A. Lycka, V. Macha'cek, and V. Sterba, *Coll. Czech. Chem. Comm.*, 1976, **41**, 67.

9. J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.*, 1976, **41**, 1308.

10. K. Hafner, *Angew. Chem.*, 1958, **70**, 419.

11. K. P. Zeller, 'Methoden der organischen Chemie: Carbocyclische π-Elecktronensysteme,' Georg Thieme, Stutgart, 1985, 199.

12. W. Konig and H. Rosler, *Naturwis.*, 1955, **42**, 211.

13. K. Haffner and K. Ziegler, *Angew. Chem.*, 1955, **67**, 301.

14. R. B. Woodward and R. Hoffmann, *Angew. Chem.*, 1969, **81**, 797.

15. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 761.

16. C. W. Muth, M. L. De Matte, A. R. Urbanik, and W. G. Isner, *J. Org. Chem.*, 1966, **31**, 3013.

17. R. N. McDonald, N. L. Wolfe, and H. E. Petty, *J. Org. Chem.*, 1973, **38**, 1106.

18. R. W. Alder and G. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1975, 714.

19. S. Kurokawa and A. G. Anderson, *Bull. Chem. Soc. Japan*, 1979, **52**, 257.

20. K. Ziegler and K. Hafner, U. S. Pat. 2805266, 1957 (*Chem. Abstr.*, 1958, **52**, 6409).

21. K. Hafner, Studienges Kohle GmbH, Erf., Ger., 1.027.200 (*Chem. Abstr.*, 1960, **54**, 10901).

22. N. R. Slobodkin, *J. Org. Chem.*, 1960, **25**, 273.

23. E. Heilbronner and R. W. Schmid, *Helv. Chim. Acta*, 1954, **37**, 2018

24. F. Sorm, V. Bene'sova, J. Krupicka, V. Sheberk, L. Dolejs, V. Herout, and J. Sicher, *Chem. Ind.*, 1954, 1511.

25. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and A. N. Kost, USSR Pat. 1049484, 1983 (*Chem. Abstr.*, 1984, **100**, 120898d).

26. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and A. N. Kost, USSR Pat. 1051080, 1983 (*Chem. Abstr.*, 1984, **101**, 38467z).

27. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and Yu. G. Bundel, *Dokl. Akad. Nauk SSSR*, 1987, **292**, 364 [*Dokl. Chem.*, 1987, **292**, 12 (Engl. Transl.)].

28. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1992, 1243 [*Chem. Heterocycl. Comp.*, 1992 (Engl. Transl.)].

29. E. Matsumura, Y. Tohda, and M. Ariga, *Bull. Chem. Soc. Japan*, 1982, **55**, 2174.

30. R. R. Bard, M. J. Strauss, and S. A. Topolosky, *J. Org. Chem.*, 1977, **42**, 2589.

31. Y. Tohda, M. Ariga, T. Kawashima, and E. Matsumura, *Bull. Chem. Soc. Japan*, 1987, **60**, 201.

32. Y. Tohda, M. Ariga, T. Kawashima, and E. Matsumura, *Chem. Lett.*, 1983, 715.

33. Y. Tohda, M. Eiraku, T. Nakagawa, Y. Usami, M. Ariga, T. Kawashima, K. Tani, H. Watanabe, and Y. Mori, *Bull. Chem. Soc. Japan*, 1990, **63**, 2820.

34. Y. Tohda, T. Kawara, M. Eiraku, K. Tani, M. Ariga, and Y. Mori, *Heterocycles*, 1991, **32**, 2079.

35. Y. Tohda, T. Kawahara, M. Eiraku, K. Tani, N. Nisiwaki, and M. Ariga, *Bull. Chem. Soc. Japan*, 1994, **67**, 2176.

36. S. P. Gromov and Yu. G. Bundel, Uspekhi khimii azotistykh geterotsiklov [Advances in the Chemistry of Nitrogenous Heterocycles], Rostov-on-Don, 1983, 167.

37. S. P. Gromov and Yu. G. Bundel, USSR Pat. 1081162, 1984 (*Chem. Abstr.*, 1984, **101**, 130587m).

38. S. P. Gromov and Yu. G. Bundel, *Dokl. Akad. Nauk SSSR*, 1985, **281**, 585 [*Dokl. Chem.*, 1985, **281**, 93 (Engl. Transl.)].

39. S. P. Gromov, M. V. Fomina, and M. V. Alfimov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1625 [*Russ. Chem. Bull.*, 1993, **42**, 1561 (Engl. Transl.)].

40. S. P. Gromov, M. M. Bhaumik, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1985, 522 [*Chem. Heterocycl. Comp.*, 1985 (Engl. Transl.)].

41. S. P. Gromov, M. V. Fomina, G. K. Chudinova, V. A. Barachevsky, and M. V. Alfimov, *Dokl. Akad. Nauk*, 1991, **321**, 739 [*Dokl. Chem.*, 1991, **321**, 375 (Engl. Transl.)].

42. S. P. Gromov and M. V. Fomina, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1505 [*Russ. Chem. Bull.*, 1993, **42**, 1443 (Engl. Transl.)].

43. A. V. Karchava, M. A. Yurovskaya, T. R. Wagner, B. L. Zybailov, and Y. G. Bundel, *Tetrahedron: Asymmetry*, 1995, **6**, 2895.

44. S. P. Gromov, M. M. Bhaumik, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1987, 488 [*Chem. Heterocycl. Comp.*, 1987 (Engl. Transl.)].

45. B. Robinson, *Chem. Rev.*, 1969, **69**, 227.

46. R. J. Sundberg, 'The Chemistry of Indoles,' N. Y., Academic Press, 1970.

47. R. K. Brown, 'Indoles,' ed. by W. J. Houlihan, N. Y., Willey-Intersci., 1972.

48. M. A. Yurovskaya, V. A. Chertkov, A. Z. Afanasyev, F. V. Yenkina, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1985, 509 [*Chem. Heterocycl. Comp.*, 1985 (Engl. Transl.)].

49. Yu. G. Bundel, S. P. Gromov, and M. A. Yurovskaya, Novoe v khimii azinov [New in the Chemistry of Azines], Abstrs II All-Union.Conf. on the Chemistry of Azines, Sverdlovsk, 1985, 46.

50. Yu. G. Bundel, S. P. Gromov, M. A. Yurovskaya, and A. Z. Afanasyev, Khimiya, biokhimiya i farmakologiya proizvodnykh indola [Chemistry, Biochemistry, and Pharmacology of Indole Derivatives], Abstrs. I All-Union Conf., Tbilisi, 1986, 21.

51. S. P. Gromov, S. A. Sergeev, S. I. Druzhinin, M. V. Rusalov, B. M. Uzhinov, L. G. Kuz'mina, A. V. Churakov, J. A. K. Howard, and M. V. Alfimov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 530 [*Russ. Chem. Bull.*, 1999, **48**, 525 (Engl. Transl.)].

52. A. Z. Afanasyev, M. A. Yurovskaya, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1987, 134 [*Chem. Heterocycl. Comp.*, 1987 (Engl. Transl.)].

53. M. A. Yurovskaya, A. Z. Afanasyev, V. A. Chertkov, E. M. Gizatullina, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1987, 1625 [*Chem. Heterocycl. Comp.*, 1987 (Engl. Transl.)].

54. American Home Products corp. *U.S. Pat.* 702985 (*Chem. Abstr.*, 1955, **49**, 5515).

55. E. Matsumura, M. Ariga, and Y. Touda, *Heterocycles*, 1978, 108.

56. M. A. Yurovskaya, A. Z. Afanasyev, V. A. Chertkov, N. M. Smirnova, P. I. Zakharov, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1988, 1385 [*Chem. Heterocycl. Comp.*, 1988 (Engl. Transl.)].

57. M. A. Yurovskaya, A. Z. Afanasyev, V. A. Chertkov, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1988, 1213 [*Chem. Heterocycl. Comp.*, 1988 (Engl. Transl.)].

58. M. A. Yurovskaya, A. Z. Afanasyev, F. V. Maximova, and Yu. G. Bundel, *Tetrahedron*, 1993, **49**, 4945.

59. M. A. Yurovskaya, M. M. Bhaumik, and Yu. G. Bundel, *Vestn. Mosk. Univ., Ser. 2, Khim.*, 1985, **26**, 490 (*Chem. Abstr.*, 1986, **105**, 24145p).

60. M. A. Yurovskaya, A. Z. Afanasyev, V. A. Chertkov, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1988, 854 [*Chem. Heterocycl. Comp.*, 1988 (Engl. Transl.)].

61. M. A. Yurovskaya, A. Z. Afanasyev, S. L. Druzina, and Yu. G. Bundel, *Khim. Geterotsikl. Soedin.*, 1989, 805 [*Chem. Heterocycl. Comp.*, 1989 (Engl. Transl.)].

62. S. P. Gromov, M. V. Fomina, E. N. Ushakov, I. K. Lednev, and M. V. Alfimov, *Dokl. Akad. Nauk SSSR*, 1990, **314**, 1135 [*Dokl. Chem.*, 1990, **314**, 279 (Engl. Transl.)].

63. M. V. Alfimov, S. P. Gromov, and I. K. Lednev, *Chem. Phys. Lett.*, 1991, **185**, 455.

64. S. P. Gromov and M. A. Razinkin, *Izv. Akad. Nauk, Ser. Khim.*, 1991, 1704 [*Russ. Chem. Bull.*, 1991, **40**, 1513 (Engl. Transl.)].

65. I. K. Lednev, M. V. Fomina, S. P. Gromov, O. B. Stanislavsky, M. V. Alfimov, J. N. Moore, and R. E. Hester, *Spectrochim. Acta*, 1992, **48A**, 931.

66. M. V. Alfimov, S. P. Gromov, V. B. Nazarov, O. M. Pilyugina, and M. V. Fomina, *Dokl. Akad. Nauk SSSR*, 1993, **330**, 453 [*Dokl. Chem.*, 1993, **330** (Engl. Transl.)].

67. S. P. Gromov, O. A. Fedorova, M. V. Fomina, and M. V. Alfimov, RF Pat. 2012574, 1991 (*Chem. Abstr.*, 1995, **123**, 289605s).

68. S. P. Gromov, O. A. Fedorova, and M. V. Alfimov, *Mol. Cryst. Liq. Cryst.*, 1994, **246**, 183.

69. S. P. Gromov, O. A. Fedorova, M. V. Alfimov, S. I. Druzhinin, M. V. Rusalov, and B. M. Uzhinov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 2003 [*Russ. Chem. Bull.*, 1995, **44**, 1922 (Engl. Transl.)].

70. E. Matsumura, M. Ariga, and Y. Tohda, *Tetrahedron Lett.*, 1979, 1393.

71. E. Matsumura, M. Ariga, and Y. Tohda, *Bull. Chem. Soc. Japan*, 1979, **52**, 2413.

72. M. Ariga, Y. Tohda, and E. Matsumura, *Bull. Chem. Soc. Japan*, 1985, **58**, 393.

73. E. Matsumura, M. Ariga, and Y. Tohda, *Bull. Chem. Soc. Japan*, 1980, **53**, 2891.

74. L. Schmerling and W. G. Toekelt, *J. Am. Chem. Soc.*, 1964, **86**, 1259.

75. M. Shamma, L. A. Smeltz, J. L. Moniot, and L. Töke, *Tetrahedron Lett.*, 1975, 3803.

76. M. Shamma, J. L. Moniot, L. A. Smeltz, W. A. Shores, and L. Töke, *Tetrahedron*, 1977, **33**, 2907.

77. N. J. Leonard and G. W. Leubner, *J. Am. Chem. Soc.*, 1949, **71**, 3405.

78. Y. Hamada, I. Takeuchi, and M. Hirota, *Tetrahedron Lett.*, 1974, 495.

79. Y. Hamada, I. Takeuchi, I. Ozawa, T. Ogaki, and K. Morishita, *Hukusokan Kagaku Toronkai Koen Yoshishu*, 1975, **8**, 139 (*Chem. Abstr.*, 1976, **84**, 180002).

80. Y. Hamada and I. Takeuchi, *J. Org. Chem.*, 1977, **42**, 4209.