Tetrahedron Vol 49, No 22, pp 4945-4954, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Scheme of Transformation of 3-Nitropyridinium Salts into Indoles

Marina A. Yurovskaya*, Andrey Z. Afanasyev, Florensa V. Maximova,
Yuriy G. Bundel
Department of Chemistry, Moscow State University,
119899 Moscow, Russia

(*Received in UK* 12 *January* 1993)

Abstract: A mechanistic scheme for the transformation of 3-nitropyridinium salt into indoles by action of N-alkylketimines (or mixture of the corresponding ketones and amines) is discussed.

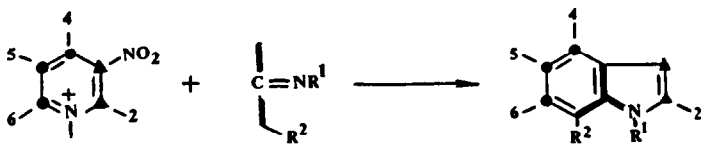
Introduction

Recently, a new synthesis of polyalkylindoles based on the treatment of N-alkyl polyalkyl-3-nitropyridinium salts with N-alkylketimines or with mixture of the corresponding ketones and amines has been developed.[1-7]

An advantage of the method is the possibility that it provides for the preparation of unknown or difficulty available polyalkylindoles containing any number and disposition of both linear and branched alkyl substituents (see Table).

The experimental simplicity of the reaction, the mild conditions and easy product isolation lead to preparatively high yields which, in general, increase with the number of alkyl substituents, and can reach 70-80%.

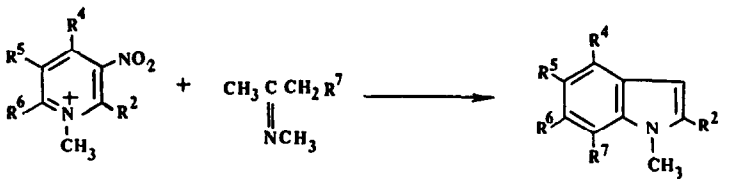
Initially, a "molecular design" of the process was described, i.e. some formal rules were laid down for the formation of the indole skeleton from the structural fragments of the starting molecules.[2] These are the following:



(i) The scission of the pyridinium cations occur at the $C_{(3)}$-$C_{(4)}$ bond

(ii) the $C_{(2)}$-$C_{(3)}$ moiety of the cation takes part in the construction of the pyrrole ring, and the $C_{(4)}$-$C_{(5)}$-$C_{(6)}$ block in the formation of the benzene ring of the indole molecule;

Table. The transformation of 3-nitropyridinium salts into indoles



R^2	R^4	R^5	R^6	R^7	Yield, %[a] A	B	Ref.
H	H	H	H	H	0		7
Me	H	H	H	H	3	7	7
H	Me	H	H	H	11	5	7
H	H	H	Me	H	0		7
Me	Me	H	H	H	22		7
Me	H	H	Me	H	4	6	7
H	Me	H	Me	H	13	10	7
Me	Me	H	Me	H	62		5
Me	H	Me	Me	H	87		5
Me	Me	Me	Me	H	55	11	5,3
Me	Et	H	Me	H	64	43	2,5
Me	n-Pr	H	Me	H		48	2
Me	t-Bu	H	Me	H	36		6
Me	CH_2-t-Bu	H	Me	H	64		6
Et	Me	H	Et	H	70		6
i-Pr	Me	H	i-Pr	H	9		6
i-Pr	i-Pr	H	i-Pr	H	37		6
Me	Me	i-Pr	Me	H	62		6
Me	Ph	H	Me	H	82		
Me	Et	H	Me	Me		67	2
Me	n-Pr	H	Me	Me		76	2
Me	Me	Me	Me	Me	57	52	3

[a] Methods A, B: see Experimental Section

(iii) the three-carbon moiety $CH_3C(=NR^1)CH_2R^2$ of the imine molecule is inserted between the above mentioned fragments of the pyridinium ring, taking part in formation of both rings of indole molecule, with R^2 occupying position 7 of the indole molecule.

These rules were established by the introduction of alkyl sustituents into different positions of 3-nitropyridinium ring (substituent label), and by using a mixture of deuterioacetone and methylamine (isotop label).[2]

More recently, some additional experimental data have been obtained that elucidate some mechanistical features of the reaction. The most important facts are as follows:

(i) The nitro group is eliminated in the form of nitrite ion NO_2^-, see Experimental Section).

(ii) When mixtures of secondary amines with appropriate ketones are employed, the formation of o-N,N-dialkylaminobenzylketones was observed, amongst other products, which may be regarded as stable, noncyclizable analogues of indole precursors.[8] The formation of such compounds also provides evidence that the elimination of the nitro group takes place prior to the pyrroline ring aromatization, in contrast to previous erroneous consideration.[9]

(iii) The results obtained with N-cyclohexyl acetone imine as chemical label in the reaction with sym-3-nitrocollidine methiodide showed that the nitrogen atom in the resulting indole originates from the imine moiety and not from the pyridinium salt.

Thus, there are now enough experimental data to allow the proposal of a mechanistic scheme of the indole formation. The aim of this paper is to clarify the mechanism of the transformation of 3-nitropyridinium salts into indoles.

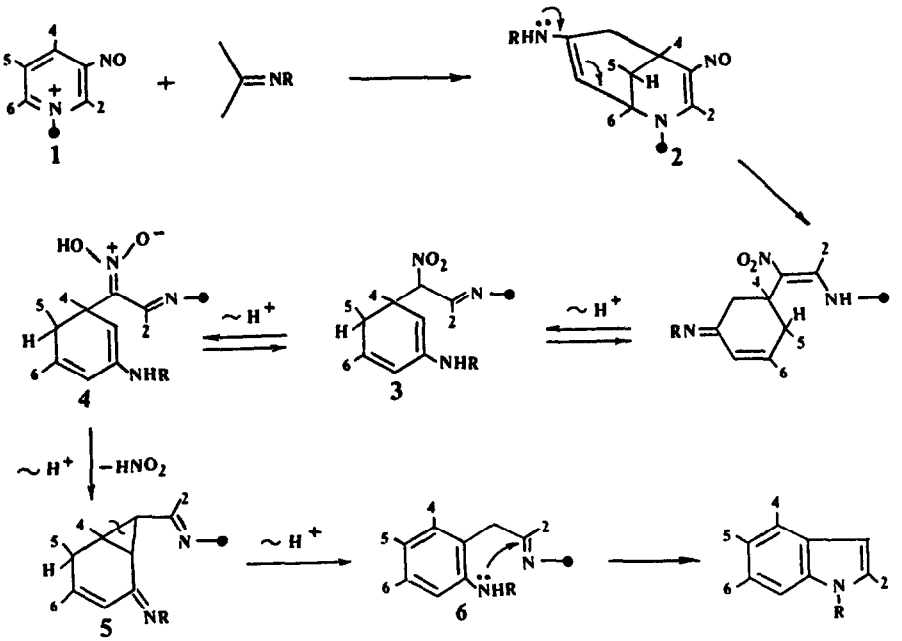
Results and Discussion

The first stage of this complex process probably a stepwise 4,6-metha-bridging of the enamine form of the ketimine to the 3-nitropyridinium cation **1** to give a bicyclic compound **2**.(Scheme 1) Examples of such meta-bridging have been found by Strauss and coworkers (see, e.g. ref.10) and by us in the case of 3-nitroquinolinium salts where the products of meta-bridging are stabilized by the annelated benzene ring and thus cannot undergo further transformation.[11]

The opening of such bicyclic system **2** ("retro-Michael" type reaction) gives rise to an intermediate **3** with a non aromatic six-membered ring. A literature analogy for these two steps of the process may be found in the

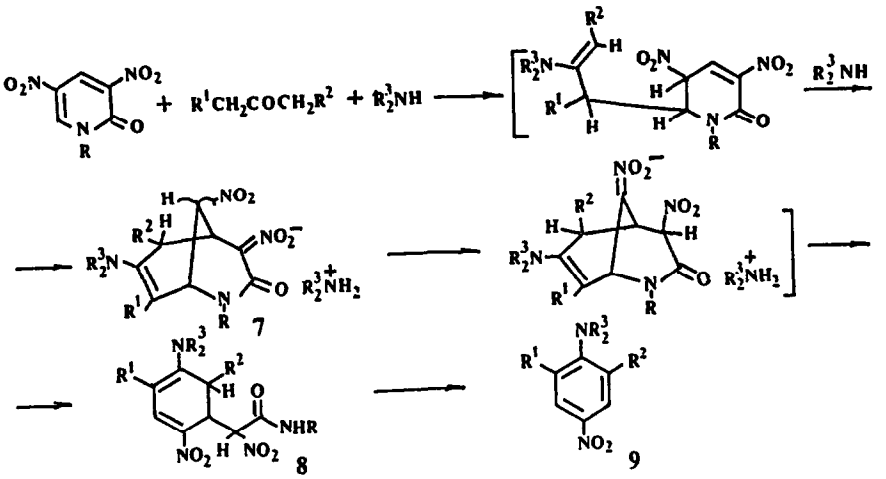
transformation of 3,5-dinitro-2-pyridones (Scheme 2) by the action of ketones and amines (in this case the enamine acts as a 1,3-binucleophile), leading to p-nitroanilines.[12]

The authors succeeded not only in isolation of the intermediate substance **7** and its ring opening product **8**, but they also showed that both compounds **7** and **8** are true intermediates in the reaction. Compound **8** aromatizes to p-nitroanilines, eliminating nitroacetamide.



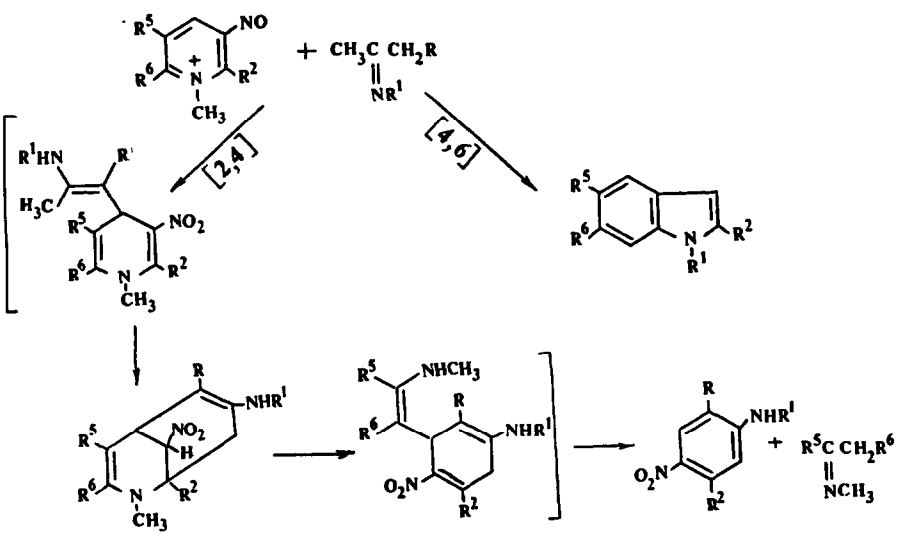
Scheme 1

Such ease of aromatization can be accounted for by the stability of leaving nitroacetamide anion and the formation of the thermodynamically favoured aromatic p-nitroaniline system, the latter factor probably prevailing. We have demonstrated that p-nitroanilines are formed only from 4-unsubstituted 3-nitropyridinium salts.[8] In this case, together with 4,6-meta-bridging, which is necessary for indole formation, 2,4-meta-bridging also takes place(Scheme 3).



Scheme 2

It is evident that the formation of p-nitroanilines is completely analogous to that in the reaction of 3,5-dinitro-2-pyridone (see Scheme 2).[12]

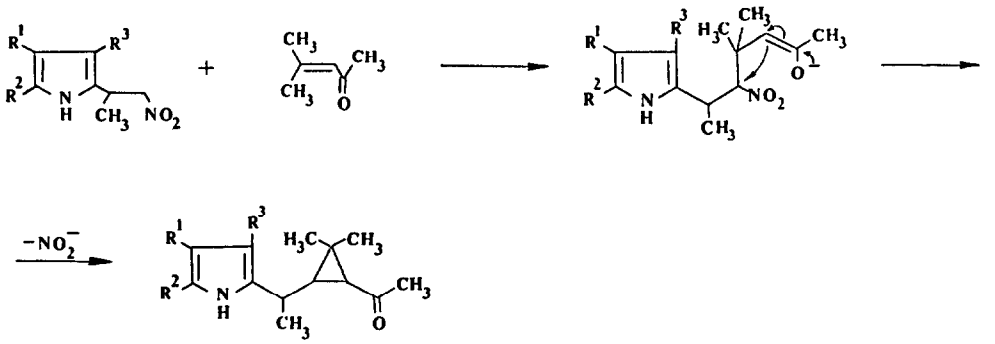


Scheme 3

The high nucleophilicity of the dienamine system in the intermediate **3**, non-conjugated with a nitro group, formed as a result of the 4,6-meta-bridging, prevents its aromatization by elimination of the nitroacetone imine moiety. Therefore the aromatization proceeds by another pathway: the attack of the β-carbon atom of the cyclic enamine system at the most electrophilic carbon atom adjacent to nitro group in its aci-form and elimination of the latter as nitrite ion, which results in formation of the cyclopropane intermediate **5**, which subsequently aromatizes (Scheme 1).

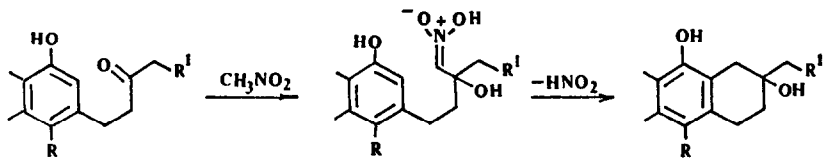
As follows from the "molecular design", such a transformation proceeds by rupture of the $C_{(3)}$-$C_{(4)}$ of the starting 3-nitropyridinium cation and formation of a new C-C bond with adjacent carbon atom (from the ketonic moiety). This particular stage is the key step in the mechanism being suggested for the formation of the indoles.

In two recent publications, it was also supposed that nucleophilic substitution of a nitro group can take place through attack by the β-position of the double bond of an enolate anion [13] or by the ortho position of a phenolic system.[14] In the study of Battersby and coworkers [13] the cyclopropane derivative **10** formed as the result of such an attack was successfully isolated.

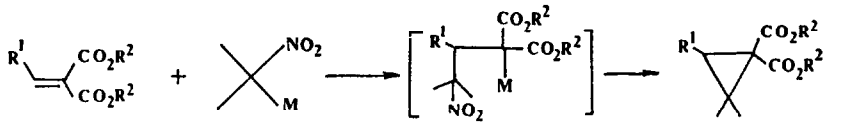


$R^1=(CH_2)_2CO_2CH_3$ $R^2=CO_2C_4H_9$-t $R^3=CH_2CO_2CH_3$

The authors of ref.[14] postulated a similar transformation as proceeding through attack at the carbon atom adjacent to the nitro group in aci-form, formation of a new C-C bond, elimination of the nitro group, and proton migration.



Formation of the cyclopropane system has also been found on interaction of 2-nitropropane anions with electrophilic alkenes.[15] This transformation represents a quite rare example of the direct nucleophilic substitution of the nitro group in the aliphatic series by a stabilized carbanion.



M = K, Na

These literature data provide good analogies to the presented scheme; the only difference is that in our case the nitro group is displaced by the very nucleophilic enamine.

The opening of the three-membered ring in intermediate **5**, initiated by aromatization of the six-membered ring, results in the migration of the $-CH_2C_{(2)}NHMe$ moiety to the adjacent ring position. It is at this stage that the earlier discussed fission of the $C_{(3)}-C_{(4)}$ bond of the starting 3-nitropyridinium cation takes place.

This sequence of transformations gives rise to o-aminobenzyl-ketoneimines **6**, stable analogues of which can be isolated when the reaction is carried out with a mixture of ketones and secondary amines [8], which undergo spontaneous cyclization to polyalkylindoles.

An alternative aromatization of the six-membered ring in the intermediate 3 - direct migration of the $-CH(NO_2)CHNMe$ moiety to the adjacent carbon atom - can by ruled out for the following reasons:

(i) The absence of substituents at the 4-position of the 3-nitropyridinium cation does not prevent indole formation, although in this case the migration of the a fore mentioned fragment is not necessary for aromatization.

(ii) Indolization of the 2,6-dimethyl-3-nitro-4-phenylpyridinium salt takes place in rather high yield (see Table). If aromatization of the intermediate 3 had been determined by direct migration of one of the geminal 4-substituents the phenyl group would have migrated in preference, and the indole yield would not have been so high.

Experimental Section

Polyalkylindoles (general procedures). A. 3 Mmol of N-methylketimine was added to a DMF (5 mL) solution of the salt 1 (1 mmol) at 0-5°C and left at RT for 1-7 days. The reaction mixture was treated as follows:

(i) poured into 10 mL of mixture benzene/water (1/1 v/v), extracted 3x10 mL benzene, the combined organic layers washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by silica gel (40-100 mkm) column chromatography (benzene/hexane, 1/3).

(ii) To the reaction mixture an equal volume of water was added with cooling and stirring. After 10-20 min the precipitated indole was filtered, washed with small amount of water and dried. The filtrate was processed by the method (i).

B. 3-Nitropyridinium salt 1 (1 mmol) was added to a solution of methylamine (3 mmol) in the appropriate ketone (acetone or methyl ethylketone, 15 mmol) at 5-10°C with stirring. The mixture was kept at RT for 2-7 days and evaporated. The residue was purified by silica gel (40-100 mkm) column chromatography (benzene/hexane, 1/3).

The yields of the indoles are presented in the Table.

2,6-Dimethyl-3-nitro-4-phenylpyridine: Ethyl malonate (68 mL, 0.45 mol) was added to a solution of 10.9 g (0.47 mol) Na in methanol (200 mL). Methanol was evaporated under reduced pressure. The residue was dissolved in 240 mL of absolute DMF, and solution of 23.8 g (0.095 mol) of 2-chloro-6-methyl-3-nitro-4-phenylpyridine[16] in 320 mL DMF was added dropwise with

stirring. DMF was evaporated to dryness in vacuo. The residue was dissolved in 600 mL of 18% HCl an dissolved in 600 mL of 18% HCl an filtered. The filtrate was slightly alkalized with solution of NaOH (pH 8) and extracted with benzene. The organic layer was dried over Na_2SO_4 and evaporated to dryness in vacuo. Recrystallization of residue from light petroleum yielded pure 2,6-dimethyl-3-nitro-4-phenilpyridine (9 g, 40%); mp 68-70°C; H^1-NMR (CCl_4, δ ppm): 2.46 (s, 6H, 2-, 6-CH_3),6.85 (s, 1H, 5-H), 7.26 (s, 5H, Ph).

1,2,6-Trimethyl-3-nitro-4-phenylpyridinium methosulphate: A solution of 2,6-dimethyl-3-nitro-4-phenilpyridine (9 g, 0.04 mol) in 8 mL of dimethylsulphate was heated at 120-125°C for 1 h. After cooling to a RT the crystals were filtered, washed with absolute ether and dried: 13.3 g (95%); mp 162-164°C; 1H-NMR (DMSO-D_6,δ ppm): 2.81 (s, 3H, 6-CH_3), 2.88 (s, 3H, 2-CH_3), 3.35 (s, 3H, CH_3SO_4-), 4.26 (s, 3H, N-CH_3), 7.60 (s, 5H,Ph), 8.31 (s, 1H, 5-H). (Found: C 50.3, H 5.3, N 7.8%. $C_{15}H_{18}N_2O_6S$ requires: C 50.8, H 5.1, N 7.9%).

1,2,6-Trimethyl-4-phenylindole was prepared from 1,2,6-trimethyl-3-nitro-4-phenylpyridinium methosulphate by the method A. Mp 62°C. 1H-NMR (aceton-D_6,δ ppm): 2.288 (s, 3H, 2-CH_3), 2.452 (s, 3H, 6-CH_3), 3.513 (s, 3H, N-CH_3), 6.298 (s, 1H, 3-H), 6.342 (s, 1H, 5-H), 7.037 (s, 1H,7-H), 7.285 (1H, p-H), 7.412 (2H, m-H), 7.650 (2H, o-H). (Found: C 86.5,H 7.6, N 5.6%. $C_{17}H_{17}N$ requires: C 86.8, H 7.2, N 5.9%).

Determination of nitrite-ion in reaction mixture. Reaction mixture obtained by methods A or B was treated by water. Nonpolar substances were deleted by extraction with benzene. The aqueous layer was acidified. In the case of secondary amines the evolution of nitrogen oxides was observed, while the presence of primary amines (or ketimines) in reaction mixture caused N_2 evolution due to intermediate alkyldiazonium salts decomposition.

References

1. Gromov, S.P.; Bundel, Yu.G. *Dokl. Akad. Nauk SSSR.* **1985**, 281, 558-588.

2. Yurovskaya, M.A.; Chertkov, V.A.; Afanasyev, A.Z.; Ienkina, F.V.; Bundel, Yu.G. *Khim. Geterotsikl. Soedin.* **1985**, 509-518.

3. Yurovskaya, M.A.; Bchaumik, M.; Bundel, Yu.G. *Vest. Mosk. Gos. Univer., Ser.Khim.* **1985**, 26, 490-494.

4. Afanasyev, A.Z.; Yurovskaya, M.A.; Bundel, Yu.G. *Khim. Geterotsikl. Soedin.* **1987**, 134.
5. Yurovskaya, M.A.; Afanasyev, A.Z.; Chertkov, V.A.; Gizatullina, E. M.; Bundel, Yu.G. *Khim. Geterotsikl. Soedin.* **1987**, 1625-1628.
6. Yurovskaya, M.A.; Afanasyev, A.Z.; Druzina, S.L.; Bundel, Yu.G. *Khim.Geterotsikl.Soedin.* **1989**, 805-810.
7. Afanasyev, A.Z. "The reaction of 3-nitropyridinium salts with ketones and amines" Diss.Moscow State University, **1988**.
8. Yurovskaya, M.A.; Afanasyev, A.Z.; Chertkov, V.A.; Bundel, Yu. G. *Khim. Geterotsikl.Soedin.* **1988**, 1212-1221.
9. Gromov, S.P.; Bchaumik, M.; Bundel, Yu.G. *Khim. Geterotsikl. Soedin.* **1987**, 488-469.
10. Bord,R.; Strauss, M.J.; Topolosky, S.A. *J. Org. Chem.* **1977**, 42, 2589-2593.
11. Yurovskaya, M.A.; Afanasyev, A.Z.; Chertkov, V.A.; Smirnova, N.M.; Zacharov, P.I.; Bundel Yu.G. *Khim. Geterotsikl. Soedin.* **1988**, 1385-1393.
12. Matsumara, E.; Tohda, Y.; Ariga, M. *Bull Chem. Soc. Japan.* **1982**, 55, 2174-2180.
13. Arnott, D.; Harrison, P.J.; Henderson, G.B.; Sheng Zhi-Chu; Leeper, F.J.; Battersby, A.R. *J. Chem. Soc., Perkin Trans. I.* **1989**, 265-279.
14. Krohn, K.; Priiyono, W. *Angew. Chem.* **1986**, 98, 338-339.
15. Krief, A.; Hevesi, L.; Chaboteaux, G.; Mathy, P.; Severin, M.; Devos, M.J. *J. Chem. Soc., Chem. Comm.* **1985**, 1693-1695.
16. Kametani, T.; Ogasawara, K.; Yamanaka, T. *J. Chem. Soc. (C)*, **1968**, 1006-1007.