RECYCLIZATION OF THE PYRIDINE RING UNDER THE INFLUENCE OF NUCLEOPHILES

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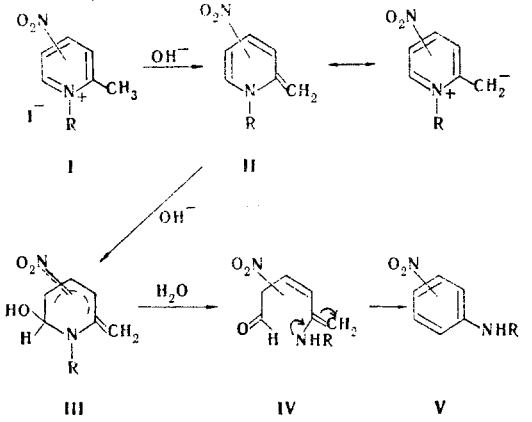
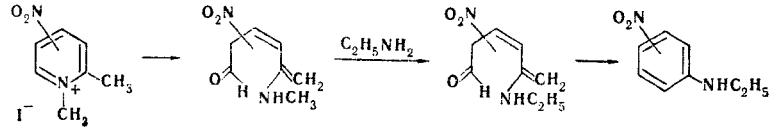
Alkyl- and dialkylanilines are formed by the action of primary and secondary amines on nitropyridinium salts. An alkylamino or dialkylamino group is included in the final product in the step involving the open form. Aqueous methylamine may lead to opening of the ring of nonquaternized nitropyridines with subsequent formation of the benzene ring of alkylanilines.

The electrophilic properties of the pyridine ring can be intensified considerably by quaternization of the nitrogen atom; this makes ring opening under the influence of alkali or amines to give glutaconic aldehyde derivatives possible [1, 2]. In contrast to primary amines, secondary amines react somewhat more slowly [3]; in this case the process terminates with the formation of a polyene dye (the Zincke–König reactions [4-6]), whereas the noncyclic enamine formed in the reaction with a primary amine can undergo recyclization to a pyridine ring, which actually leads to transamination. It has been reported that dealkylation products are formed under the influence of liquid ammonia [7] or ammonium sulfite [8]. Amide rearrangement (the Dimroth rearrangement [9]) in which exchange of the amine functions proceeds intramolecularly is a special case of transamination (e.g., see [10]).

We have established [11] that 2-methyl-3(or 5)-nitropyridine alkylhalides (I) lose a side-chain proton under the influence of aqueous alcoholic alkali (to give anhydro base II), after which they undergo recyclization to the corresponding o- or p-nitroanilines V, evidently through a step involving σ complex III.



The yields of nitroanilines are low, since the above reaction competes with hydrolytic cleavage of an amino group in the step involving open form IV. We were able to suppress the latter process by using an aqueous solution of the amine as the recyclizing agent. Transamination occurred when an amine with a different alkyl group than that in the starting



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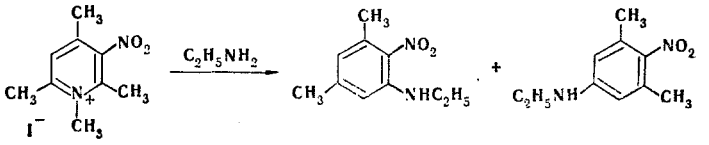
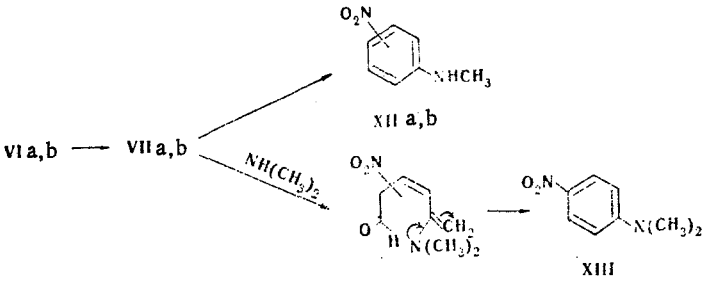
pyridinium salt was used. Thus the corresponding ortho or para isomers of N-ethylnitroaniline (VIIIa,b) are formed in the reaction of aqueous ethylamine with 1,2-dimethyl-3(or 5)-nitropyridinium iodides (VIa,b).

When two methyl groups are present in the α positions relative to the pyridine nitrogen atom, each of them may participate in the formation of a benzene ring, but primarily the ortho isomer is obtained.



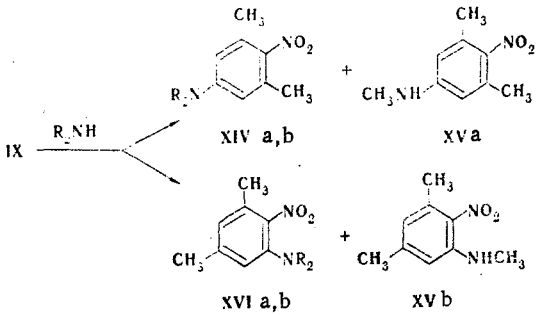
IX xa xb

1-Ethyl-2-methyl-3-nitropyridinium iodide (XI) reacts with aqueous dimethylamine with displacement of the ethylamino residue to give N-methyl-2-nitroaniline (XIIa). Iodide VIa reacts with dimethylamine to give nitroaniline XIIa, although a mixture of N-methyl-4-nitroaniline (XIIb) and N,N-dimethyl-4-nitroaniline (XIII) with predominance of the former is obtained in the case of 5-nitro isomer VIb. Thus secondary amines, like aqueous alkali, lead to recyclization with retention of the alkylamino residue, which is incorporated in the starting molecule of the quaternary salt.



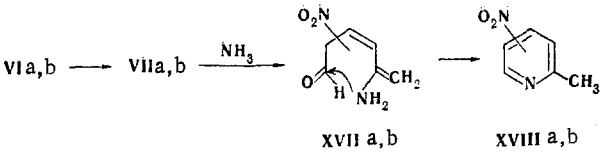
XII a,b XIII

In addition to the two transamination products XIV and XVI (the latter is obtained in very small amounts), N-methyl-3,5-dimethyl-4-nitroaniline (XVa) and N-methyl-3,5-dimethyl-2-nitroaniline (XVb) are formed from 1,2,4,6-tetramethyl-3-nitropyridinium iodide (IX) under the influence of aqueous dimethylamine (or piperidine).



XIV a,b XVa XVI a,b XVb

As in the preceding cases, we observed exchange of a methylamino group under the influence of such a weak nucleophile as ammonia, but cyclization proceeds with the formation of a pyridine ring rather than a benzene ring, i.e., only N-dealkylation actually occurs.



XVII a,b XVIII a,b

σ-complexes that are formed in the case of attack on the pyridine ring by a nucleophile and the subsequent loss of a methylamino fragment to give the corresponding pyridine deriva-

TABLE 1. Nucleophilic Recyclization of Pyridinium Salts to Anilines

Starting compound	Nucelophile	Final product	mp, °C (solvent)[a]	Yield, %
VIa	$C_2H_5NH_2$	VIIIa[b]	Oil [22]	30
VIb	$C_2H_5NH_2$	VIIIb	94—96 (A)[22]	19
IX	$C_2H_5NH_2$	Xa[c]	63—64 (B)	40
		Xb[d]	64—65 (C)	36
XI	CH_3NH_2	XIIa	34—35 (B)[23]	13
VIa	$(CH_3)_2NH$	XIIa	34—35 (B)[23]	37
VIb	$(CH_3)_2NH$	XIIb	148—149 (A)[24]	3
		XIII	159—160 (A)[25]	1
VIa	NH_3	XVIIIa	e	65
VIb	NH_3	XVIIIb	107—108 (C)[26]	64
IXf	$(CH_3)_2NH$	XVb	81—83 (C)[11]	—
		XIVag	107—109 (C)	63
		XVa	88—89 (C)[11]	7
XVIIIh	CH_3NH_2	XIIa	34—35 (B)[23]	8
XVIIIh	CH_3NH_2	XIIb	148—149 (A)[24]	7
IXf	$(CH_2)_5NH$	XVb	81—83 (C)[11]	—
		XIVbi	78—79 (C)	33
		XVa	87—89 (C)[11]	13

a) Solvents: A is benzene, B is hexane, and C is heptane. The literature citations pertain to the physical constants of the compounds. b) PMR spectrum, δ: 1.33 (t, CH_3, J = 8 Hz), 3.30 (m, CH_2, $J_{CH_3CH_2}$ = 8 Hz, J_{CH_2NH} = 6 Hz), and 6.36-8.10 ppm (m, 4H). c) PMR spectrum, δ: 1.26 (t, CH_3, J = 7 Hz), 2.18 and 2.33 (s, 3- and 5-CH_3), 3.20 (m, CH_2, J_{CH_2NH} = 5 Hz, $J_{CH_3CH_2}$ = 7 Hz), 6.30 and 6.43 (s, 4- and 6-H), and 6.76 ppm (N-H). UV spectrum, λ_{max} (log ε): 238 (4.19), 292 (3.56), and 423 nm (3.57). Found: C 61.7; H 7.4%. $C_{10}H_{14}N_2O_2$. Calculated: C 61.9; H 7.2%. d) PMR spectrum, δ: 1.17 (t, CH_3, J = 7 Hz), 2.10 (s, 3- and 5-CH_3), 3.03 (q, CH_2, J = 7 Hz), 4.00 (N-H), and 6.00 ppm (s, 2- and 6-H). UV spectrum, λ_{max} (log ε): 246 (3.92), 305 (3.45), and 392 nm (3.79). Found: C 61.6; H 7.6%. $C_{10}H_{14}N_2O_2$. Calculated: C 61.9; H 7.2%. e) This compound had bp 80-81°C (5 mm) [27]. f) The reaction mixture was separated with a column filled with silica gel (elution with benzene). g) PMR spectrum, δ: 2.17 (s, 3- and 5-CH_3), 2.86 s, $N(CH_3)_2$, and 6.03 ppm (s, 2- and 6-H). UV spectrum, λ_{max} (log ε): 249 (3.98), 308 (3.47), and 393 nm (3.79). Found: C 61.4; H 7.0%. $C_{10}H_{14}N_2O_2$. Calculated: C 61.9; H 7.2%. h) Compounds XVIa,b were heated with aqueous methylamine in a sealed ampule at 100°C for 72 h. i) PMR spectrum, δ: 1.59 (m, $-CH_2CH_2CH_2-$), 2.20 (s, 3- and 5-CH_3), 3.17 (m, $-CH_2NCH_2-$), and 6.36 ppm (s, 2- and 6-H). UV spectrum, λ_{max} (log ε): 263 (4.00), 305 (3.51), and 391 nm (3.76). Found: C 66.5; H 8.0%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.7; H 7.7%.

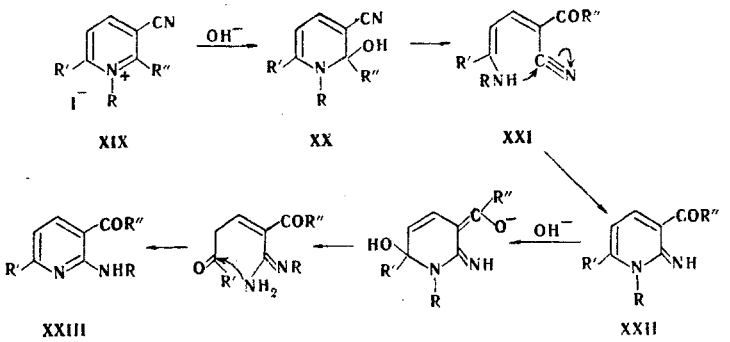
tives have been previously observed in liquid ammonia [12]. Our process took place under very mild conditions (an aqueous solution of NH_3); in this case also the exchange of a methylamino residue for ammonia is reversible. Thus the pyridine ring undergoes opening with the exchange of an amino fragment and the formation of the recyclization product, i.e., N-methylnitroanilines XIIa,b (although in low yields), in the reaction of aqueous methylamine with nonquaternized bases XVIIIa,b.

$$\text{XVIII a,b} \longrightarrow \text{XVII a,b} \xrightarrow{CH_3NH_2} \text{VIIa,b} \longrightarrow \text{XII a, b}$$

Let us note that this is a new case of opening of a nonquaternized pyridine ring under the influence of nucleophilic agents. Only a few examples of opening of a pyridine ring that is not activated by quaternization under the influence of extremely strong reagents have been described [13, 14].

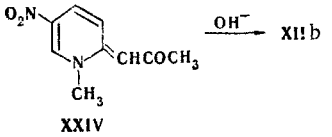
In the series of examples presented above we increased the activity of the pyridine ring by the introduction of a nitro group in the β position. In principle, the necessary result can also be achieved by using a different acceptor, but side processes sometimes occur in this case.

For example, in the reaction of an aqueous solution of an alkylamine with a 1-alkyl-2-methyl-3(or 5)-cyanopyridinium salt (XIX) the initially formed covalent adduct (XX) undergoes ring opening with cleavage of the C-N bond, but subsequent ring closing takes place at the electron-deficient carbon atom of the cyano group to give a 1,2-dihydropyridine derivative (XXII) rather than at the methyl group, as in the case of nitropyridinium salts. Under the reaction conditions structures of the XXII type undergo repeated rearrangement (of the amidine type this time) to give 2-alkylamino-3-acylpyridines (XXIII) in 50-70% yields [15]. Side transamination in the step involving open intermediate XXI may also occur in this case.



XIX XX XXI XXII XXIII

One might have expected that activation of the α-methyl group by the introduction of an acceptor substituent in the side chain would increase the CH acidity and thus promote the formation of a benzene ring in the step involving the open intermediate. However, under the influence of alkaline agents the initially formed anhydro base (XXIV) readily splits out an acyl fragment to give N-methyl-4-nitroaniline (XIIb).



XXIV

If the acyl group is located in the ring, ring opening occurs readily, but in this case solvolysis of the carbon–carbon bond (evidently in the step involving the open structure) is the preferred process, since the final product is N-methylaniline [16].

Thus under the influence of bases pyridine derivatives that contain both exocyclic and endocyclic acetyl groups undergo recyclization to anilines with acidic cleavage of an acyl fragment.

The described conversion of pyridinium salts to anilines is not only of theoretical value but also expands the synthetic methods for the construction of a benzene ring (see also [17]). This sort of recyclization is also possible for condensed structures that include a pyridine ring with a nitrogen atom in the bridge position [18]. It has been reported [19, 20] that pyridinium salts that contain methyl groups in the α position can be converted to phenols under the influence of bases, just as isoquinolinium salts form α-naphthols [21]. However, these were examples of side processes that compete with the process described above. Other researchers [19-21] have used conditions that were too severe and led to hydrolysis of the open form with the loss of an amino group. Our described conversions of pyridinium salts to anilines constitute a new type of recyclization that has not been previously observed in the chemistry of pyridine.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in carbon tetrachloride were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra of ethanol solutions of the compounds were recorded with a Cary-15 spectrophotometer. The course of the reactions was monitored by means of thin-layer chromatography (Silufol UV-254).

Reaction of Pyridinium Salts with Amines (general method). A 20-ml sample of 25-30% ammonium hydroxide was added with stirring to a solution of 1 mmole of the pyridinium salt dissolved in the minimum amount of water, and the mixture was allowed to stand for 24 h. It was then extracted with benzene, and the extract was dried with $MgSO_4$ and evaporated. The product (see Table 1) was purified with a column filled with L-40/100MK silica gel (elution with chloroform).

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