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ALKYLAMINO GROUP EXCHANGE UPON RECYCLIZATION OF PYRIDINIUM SALTS INTO ANILINES

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Abstract—Nitropyridiniium salts react with primary or secondary amines to form alkyl or dialkylanilines as result of recyclization of pyridine nuclei. The alkylamine or dialkylamine group is included in the reaction final product at the open form stage. Aqueous methylamine may open even non-quaternized nitropyridines with the following ring closure to alkylanilines.

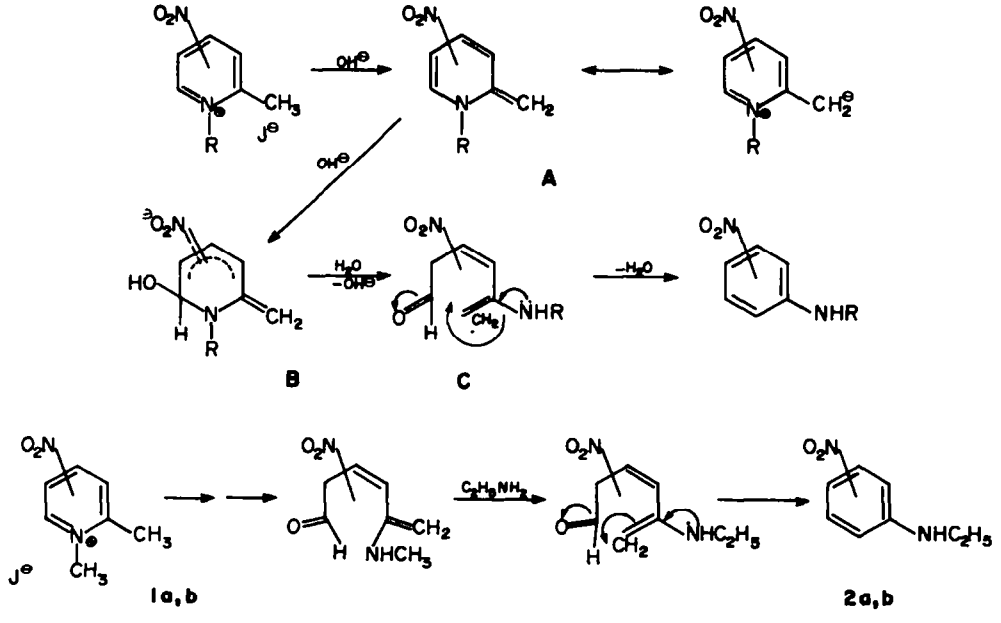
The electrophilic properties of the pyridine ring, which are still more pronounced in 1-alkyl- or 1-acylpyridinium salts (see, e.g. Ref. 1), permit the addition of nucleophiles and formation of a corresponding σ-complex for pyridines themselves,[2] or substituted 1,2- or 1,4-dihydropyridine in the case of pyridinium salts.[3] A strong nucleophile such as the hydroxyl ion opens the ring of newly emerged dihydropyridines with formation of glutaconic aldehyde, and its substituents or derivatives.[4] The intermediates of the process are capable of condensation with nucleophilic compounds.[5] We may thus suggest that the recyclization process might involve the corresponding nucleophilic fragment of the very recyclizing molecule rather than an external reagent. In other words, it appears quite reasonable to consider a model ring opening of the pyridinium salts and the subsequent formation of a new cycle with a C atom of the side chain. This transformation appears quite credible. We have found[6] that indolizines may be transformed into indoles with pyridine ring opening and subsequent ring closure. For 2-alkylpyridines the above reaction is also possible if the pyridine ring contains an electron-withdrawing group. Hence alkyl halides of 2-methyl-3(or 5)-nitropyridines when treated with aqueous alcoholic alkales loose a proton of the side chain (formation of anhydrobase A) and then, apparently through the σ-complex B and the open form C, recyclize into the corresponding *o*- or *p*-nitroanilines.[7] Anhydrobases of pyridinium salts will be known.[8]

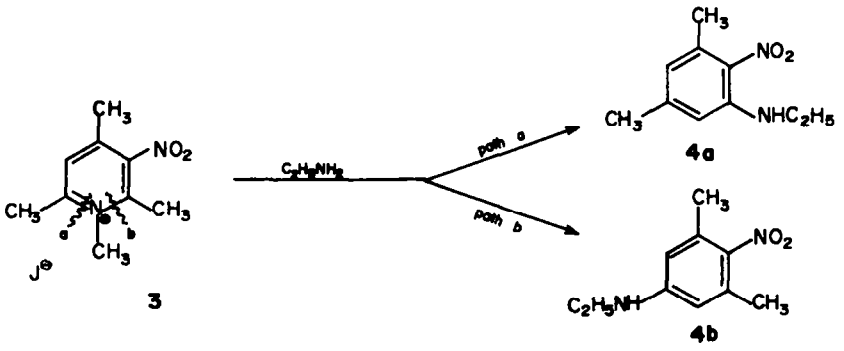
This reaction produces low yields because of the competition with hydrolytic desamination of the open form C. The latter process, however, might be suppressed by use of an aqueous solution of the corresponding amine RNH_2 as a recyclizing agent. But use of an amine with a radical R which differs from that of the initial pyridinium salt leads to transamination.

Thus, the interaction of aqueous ethylamine with 1,2 - dimethyl - 3 - nitropyridinium iodide (**1a**) or 1,2 - dimethyl - 5 - nitropyridinium iodide (**1b**) gives corresponding *o*- or *p*-isomers of N-ethylnitroaniline (**2a,b**).

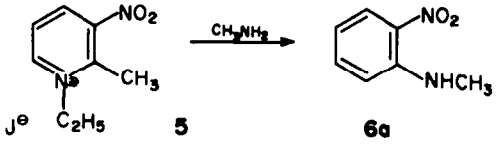
Recyclization of 1,2,4,6 - tetramethyl - 3 - nitropyridinium iodide (**3**) with excess of aqueous ethylamine yields a mixture of isomers **4a** and **4b**, since both α-Me groups of compound **3** can take part in the benzene ring formation.

When N-ethyl derivative **5** is used as a starting





material aqueous methylamine leads to exchange of the ethylamine with methylamine group and N - methyl - 2 - nitroaniline (**6a**) is obtained.



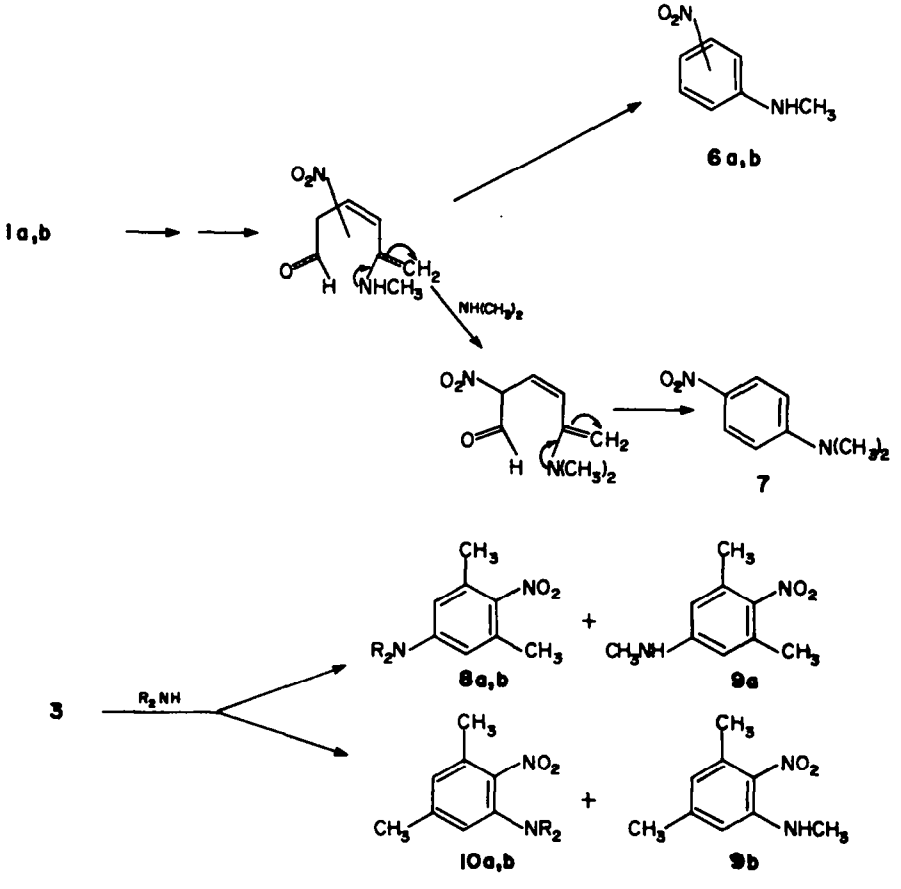
Secondary amines, which are far less capable of transamination, act mainly as bases only. For instance, 1,2 - dimethyl - 3 - nitropyridinium iodide (**1a**) with dimethylamine forms N - methyl - 2 - nitroaniline (**6a**). The isomer **1b** gives a mixture of nitroanilines **6b** and **7** (predominantly the first one).

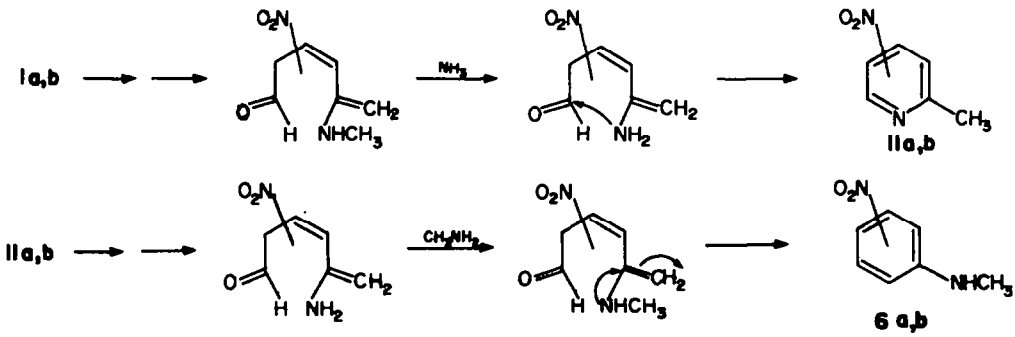
Interaction of 1,2,4,6 - tetramethyl - 3 - nitropyridinium iodide (**3**) with aqueous dimethylamine or piperidine follows the same scheme. Beside of amines **8** this reaction gives N,3,5 - trimethyl - 4 - nitroaniline (**9a**) and N,3,5 - trimethyl - 2 - nitroaniline (**9b**).

In addition, there is NMR evidence that the mixture contains sterically hindered ortho-isomers **10a,b** in a yield of 2–6%.

Of special interest are the experiments on transamination by such a weak nucleophile as ammonia. Like the above, this reaction involves methyl amine substitution by ammonia, but the final product is pyridine **11**. This means that compound **1** had lost an N-methylaminogroup. No trace of the corresponding nitroanilines was found in reaction mixtures. Probably the intermediate enamine fragment β-carbon atom is less nucleophilic than those of its N-alkylated analogues.

The σ-complexes resulting from nucleophilic attack on the N-methylpyridinium ring and the following elimination of the methylamine fragment were reported for the reactions in liquid ammonia.[9] In this case the methyl-





amine radical substitution by ammonia is reversible. Indeed, we have found that when treated with aqueous methylamine the non-quaternized pyridine bases (11a,b) open their pyridine ring, rather than eliminating ammonia and recyclising to the corresponding N-methylnitroanilines (6a,b).

Table 1. Nucleophilic recyclization of pyridinium salts into anilines

Starting material	nucleophile	product	Yield (%)	m.p.(°C) (solvent)	Ref.
1a	$EtNH_2$	2a	30	oil	15
1b	$EtNH_2$	2b	19	94–96 (benzene)	15
3	$EtNH_2$	4a	40	63–64 (hexane)	—
		4b	36	64–65 (heptane)	—
5	$MeNH_2$	6a	13	34–35 (hexane)	16
1a	Me_2NH	6a	37	34–35 (hexane)	16
1b	Me_2NH	6b	3	148–149 (benzene)	17
		7	1	159–160 (benzene)	18
1b	NH_3	11b	64	107–108 (heptane)	19
1a	NH_3	11a	65	$\frac{80–81}{5}$ (b.p.)	20
3*	Me_2NH	9b	—	81–83 (heptane)	7
		8a	63	107–109 (heptane)	—
		9a	7	88–89 (heptane)	7
3*	$(CH_2)_5NH$	9b	—	81–83 (heptane)	7
		8b	33	78–79 (heptane)	—
		9a	13	87–89 (heptane)	7
11a**	$MeNH_2$	6a	8	34–35 (hexane)	16
11b**	$MeNH_2$	6b	7	148–149 (benzene)	17

*The reaction mixture was separated in a silica gel column in benzene.
**11a,b were heated in aqueous methylamine in a sealed tube at 100° for 72 hr.

Our experiments on recyclization of pyridinium salts were made at room temperature by treatment of aqueous amines. No nitroanilines were formed in the absence of water, thus the OH ion plays a significant role.

This recyclization of pyridine derivatives into anilines may attract attention as a new chemical transformation in which the non-quaternized pyridine ring opens while being attacked by nucleophilic agents. Only a few examples of such ring opening have been reported (see, e.g. Refs. (10, 11)), when the reagents used were much more powerful.

This transformation may be compared with known recyclisation of pyridinium salts, containing Me groups in α-position, to phenols, as well as isoquinolinium salts to α-naphthols.[12–14] These examples in our opinion are the result of processes competing with the above-described ones. The conditions used were too harsh, so the open form was hydrolysed and lost the amino group.

EXPERIMENTAL

The NMR spectra were recorded by Varian T-60 spectrometre in CCl_4, the internal standard-GMDS. The UV spectra were recorded in EtOH by Cary-15. Processes were controlled by TLC on Silufol UV-254.

Interaction of pyridinium salts with amines (general technique). To 1 mmol of a pyridinium salts dissolved in the minimum quantity of water was added while stirring 20 ml of 25–30% aqueous amine. After standing for 24 hr the mixture was extracted with benzene. The extract was dried with $MgSO_4$ and evaporated. The product was separated on a silica gel column (L-40/100μ) in chloroform soln.

N-Ethyl-2-nitroaniline (**2a**). NMR δ: 133 (t, Me, $J_{CH_3CH_2}$ = 8 Hz), 3.30 (m, CH_2, $J_{CH_3CH_2}$ = 8 Hz, J_{CH_2NH} = 6 Hz), 6.36–8.10 (m, 4 H) ppm.

N - Ethyl - 3,5 - dimethyl - 2 - nitroaniline (**4a**). NMR δ: 1.26 (t, Me, $J_{CH_3CH_2}$ = 7 Hz), 2.18–2.33 (s, 3-Me, s, 5-Me), 3.20 (m, CH_2, J_{CH_2NH} = 5 Hz, $J_{CH_3CH_2}$ = 7 Hz), 6.30–6.43 (s, 4-H, s, 6-H), 6.76 (N–H) ppm. UV λ_{max} nm (log ϵ): 238(4.19), 292(3.56), 423(3.57). Found: C, 61.69; H, 7.35. $C_{10}H_{14}N_2O_2$ requires: C, 61.86; H, 7.22%.

N - Ethyl - 3,5 - dimethyl - 4 - nitroaniline (**4b**). NMR δ: 1.17 (t, Me, $J_{CH_3CH_2}$ = 7 Hz), 2.10 (s, 3-Me, 5-Me), 3.03 (q, CH_2, $J_{CH_3CH_2}$ = 7 Hz), 4.00 (N–H), 6.00 (s, 2-H, 6-H) ppm. UV λ_{max} nm (log ϵ): 246(3.92), 305(3.45), 392(3.79). Found: C, 61.58; H, 7.58. $C_{10}H_{14}N_2O_2$ requires: C, 61.86; H, 7.22%.

N,N,3,5 - Tetramethyl - 4 - nitroaniline (**8a**). NMR δ: 2.17 (s, 3-Me, 5-Me), 2.86 (NMe_2), 6.03 (s, 2-H, 6-H) ppm. UV λ_{max} nm (log ϵ): 249(3.98), 308(3.47), 393(3.79). Found: C, 61.43; H, 7.01. $C_{10}H_{14}N_2O_2$ requires: C, 61.86; H, 7.22%.

1 - Piperidyl - 3,5 - dimethyl - 4 - nitrobenzene (**8b**). NMR δ: 1.59 ($-CH_2CH_2CH_2-$), 2.20 (s, 3-Me, 5-Me), 3.17 ($-CH_2NCH_2-$), 6.36 (s, 2-H, 6-H) ppm. UV λ_{max} nm (log ϵ): 253 (4.00), 305 (3.51), 391 (3.76). Found: C, 66.52; H, 8.00. $C_{13}H_{18}N_2O_2$ requires: C, 66.67; H, 7.69%.

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