NUCLEOPHILIC AMINATION AND RECYCLIZATION OF THE INDOLIZINE NUCLEUS

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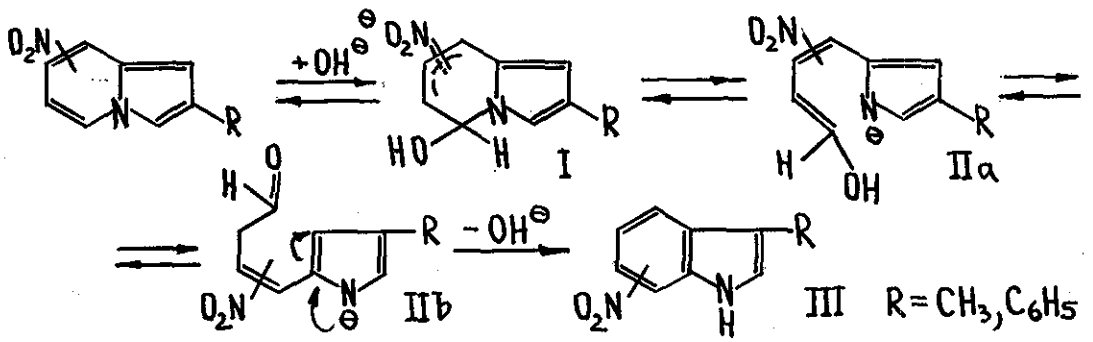
Treatment of 6- or 8-nitroindolizines with aqueous alcoholic alkaline solution forms 5- or 7-nitroindoles (III) by ring transformation. Primary or secondary amines reacted with 8-nitroindolizines (IV) to form δ-complexes which transformed into 5-amino-8-nitroindolizines (V) by air oxidation.

Because of an excess of total electron on the indolizine nucleus, no example of its reactions with nucleophiles has yet been known (see reviews[1,2]). The fact that pyrimido[1,2-a]indoles, structure analogues of indolizines, may rearrange to α-carbolines under the action of bases[3], however, allows us to expect that indolizines may undergo nucleophilic recyclization as well. We have found that 2-methylindolizine does not react with aqueous and alcoholic alkaline solutions. The introduction of nitro function into the pyridine ring, facilitates recyclization process. The nitro derivatives readily react with aqueous alcoholic alkaline solution under heating to yield the corresponding nitroindoles. The reaction

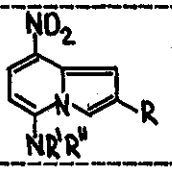
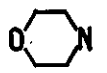
begins with the attack by the hydroxyl anion on the N(4)-C(5) bond to give anionic δ-complex I identified by its UV and NMR spectra showing a 2.4-2.6 ppm upfield shift of C(5) proton in a comparison with that of the starting material. After cleavage of the C-N bond, complex I gives acyclic anion II which recyclizes to nitroindole III. These transformations represent the first example of a nucleophilic reaction of the indolizine nucleus, the new type of rearrangement, and the novel and original route to indoles.[4]



It is likely that prior to cyclization the anion IIa undergoes conversion to the oxo form IIb, since the action of alkoxide anions does not lead to isomerization, though it generates the corresponding δ-complexes. Thus, the H(5) signal of 2-methyl-8-nitroindolizine observed in DMSO-d_6 at 8.5 ppm in NMR spectrum irreversibly shifts to 6.1 ppm under the action of sodium methoxide: NMR spectrum (DMSO-d_6) 2.20(s, CH_3), 2.98(s, CH_3O), 5.29(m, J = 4.0, J = 10 Hz, 6H), 6.11 (d, J = 4.0 Hz, 5H),

6.68-6.74(s, 1H, s, 3H), 7.43(d, J = 10 Hz, 7H). Similar assignments have been suggested for the δ-complexes of 6- and 8-nitroimidazo[1,2-a]pyridines that occur in the Dimroth

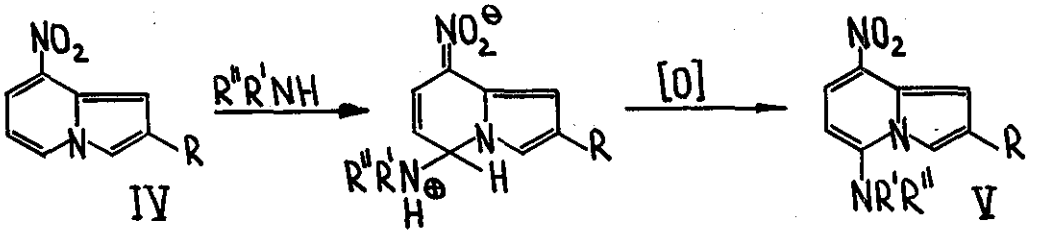
5-Amino-8-nitroindolizines

V 		Reaction time, days	Yield, %	M.p., °C (from CH_3NO_2)	$\lambda_{max}^{C_2H_5OH}$ nm (log ε)
R	NR'R"				
C_6H_5		90	50	216-218	250,368,483 (4.52,3.84,3.84)
C_6H_5		30*	62	141-142	252,283,368,510 (4.42,4.20,3.81,3.91)
C_6H_5		10	68	212-213	249,297,515 (4.43,4.27,4.13)
C_6H_5	$(CH_3)_3CNH$	30	72	226-227	252,293,363,518 (4.37,4.33,3.69,4.13)
C_6H_5	$C_2H_5(CH_3)CHNH$	210	55	209-210	249,292,353,498 (4.40,4.38,3.69,4.13)
C_6H_5	$CH_3CH_2CH_2CH_2NH$	270	53	222-224	250,292,355,500 (4.49,4.48,3.78,4.27)
CH_3		20	46	92-94	271,346,492 (4.30,3.75,3.86)
CH_3		5	77	200-201	283,521 (4.21,4.22)

*After 6 hours at 110°, the yield is 40%.

rearrangement.[5] Like with alkoxide anions, the attack by primary and secondary amines on the N(4)-C(5) bond does not cause isomerization, but gives the corresponding δ-complexes, e.g. the pyrrolidine complex of 2-methyl-8-nitroindolizine forms: NMR spectrum (pyrrolidine) 5.46(m, J = 4.0, J = 10 Hz, 6H), 5.69(d, J = 4.0, 5H), 6.67-6.83 (s, 1H, s, 3H), 7.30(d, J = 10 Hz, 7H). Under the action of air oxygen in the absence of moisture, the complex is slowly oxidized at room temperature to the corresponding 5-amino-8-nitroindolizine (0.1 g of IV in 6 ml of thoroughly dried amine gives 50 to 70 % yields of the oxidation product).

Branching at the α-carbon atom in primary amines has no significant effect on the yields. Secondary amines are somewhat more reactive than primary ones; pyrrolidine is the most efficient reagent. Bubbling air through the heated reaction mixture considerably accelerates the process, however the yields decrease because of resinification.



The structure depicted are based on the combined evidence of the UV, NMR, and mass spectra, and the elemental analysis, and on the results of an X-ray investigation of 5-piperidyl- and 5-tert-butylamino-8-nitro-2-phenylindolizines.

To sum up, the action of primary and secondary amines on the indolizine nucleus results in the replacement of hydrogen rather than recyclization. The fact that the position 5 of the nucleus is attacked by the amino group has been supported by the CNDO-2 calculations[6] which indicated this position to be the lowest electron density site.

The amination reaction which goes under mild conditions is the first example of a nucleophilic substitution in the indolizine nucleus.

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