SYNTHESIS OF 6- AND 8-NITROINDOLIZINES

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A number of 6- and 8-nitroindolizines were synthesized by quaternization of isomeric 2-methylnitropyridines by α-halo ketones and subsequent cyclization.

The known methods for the synthesis of indolizines in most cases lead to pyrrole-ring-substituted derivatives. Synthetic methods have been proposed [1] only for certain structures that have, for example, a carboxethoxy group in the 7 position, but there are no available data on the possibility of the preparation of indolizines with a nitro group in the pyridine ring. We have used the Chichibabin condensation [2] of the corresponding 2-methylpyridines with α-halo ketones for the synthesis of 6- and 8-nitroindolizines.

\[ \text{Br CH}_{2}COR \rightarrow \text{NO}_{2} /\]  

\[ \text{NO}_{2} /\]  

\[ \text{Br-CH}_{2}COR \]

The 3-nitro-2-methylpyridine (I) necessary for this synthesis was obtained from 2,6-lutidine by nitration and subsequent oxidation of one of the methyl groups and decarboxylation [3]. The described synthesis of 5-nitro-2-methylpyridine (II) [4] starts from 2-chloro-5-nitropyridine, in which a malonic ester residue is introduced in place of the chlorine atom with subsequent hydrolysis and decarboxylation. We modified the method: II was purified by chromatography with a column filled with aluminum oxide rather than by vacuum distillation. The synthesis of 4-nitro-2-methylpyridine from the difficult-to-obtain 4-amino-2-methylpyridine has been described [5]. We therefore chose a method consisting in nitration of 2-methylpyridine N-oxide [6] and subsequent deoxidation with phosphorus trichloride, in analogy with the method described for 4-nitropyridine N-oxide [7].

No difficulties were encountered in the preparation of quaternary salts III–IV from nitropyridines with a 1.5-2-fold excess of bromo ketone, and their purity was sufficient to allow their use in the subsequent reaction without additional purification. However, we were able to synthesize 1-pinacolonyl-5-nitro-2-methylpyridinium bromide (IIIc) only under severe conditions. We were unable to isolate pure 1-acetonyl-3-nitro-2-methylpyridinium bromide (IVA) in the reaction of bromoacetone with 3-nitro-2-methylpyridine, but the crude substance was, nevertheless, converted to the corresponding indolizine (VIA). We were unable to bring about quaternization of 4-nitro-2-methylpyridine under the influence of bromoacetone or bromoacetophenone in various solvents at 50 to 120 °C. The low nucleophilicity of the pyridine nitrogen atom in this case is explained by efficient transmission of the effect of the nitro group from the γ position.

Bromides IIIa,c were cyclized by heating in absolute alcohol with the addition of solid sodium bicarbonate. The yield of 2-tert-butyl-6-nitroindolizine (Vc) was considerably lower for sterically hindered model IIIc than...
Fig. 1. UV spectra of nitroindolizines (in ethanol): 1) 2-methyl-8-nitroindolizine; 2) 2-phenyl-8-nitroindolizine; 3) 2-methyl-6-nitroindolizine; 4) 2-phenyl-6-nitroindolizine; 5) 2-tert-butyl-6-nitroindolizine.

for Va. A low yield in connection with restricted steric accessibility was noted in the synthesis of 2-tert-butylindolizine, which does not have a nitro group [8]. The cyclization of salts IIIb and IVb, which have a phenyl group adjacent to the reacting carbonyl group, proceeds better when they are heated in aqueous solution even at pH 2-3, where the certain excess acidity of the medium resulted in protonation of the carbonyl group; however, it was necessary to neutralize the mixture in order to complete the reaction. It is interesting that 2-phenyl-6-nitro (Vb) and 2-phenyl-8-nitroindolizine (VIb) were obtained in almost identical yields (93 and 86%, respectively). Consequently, the nitro in the ortho position group in structure IVb does not hinder cyclization, although the methyl group that participates in this reaction has substituents on both sides.

The UV spectra of the nitroindolizines contain three absorption bands; this is also characteristic for indolizine itself [8]. The first long-wave band in the spectra of our models is observed at from 480 to 430 nm, the second higher-intensity band is observed from 380 to 300 nm, and the third intense band is observed from 270 to 220 nm. The long-wave absorption band in the spectra of 2-phenylnitroindolizines appears as an inflection. Thus all of the absorption bands in the spectra of the nitroindolizines undergo a bathochromic shift as compared with unsubstituted indolizines (absorption bands at 330-360, 270-300, and 220-240 nm [8]), and in the case of the 8-nitro compounds (Vla-b) all of the bands are shifted to the long-wavelength region as compared with the 6 isomers (Va-c) (Fig. 1).

As one should have expected, the introduction of a nitro group in the pyridine ring of the indolizine increases the number of pathways of fragmentation of the molecular ion in the mass spectra, and this leads to a decrease in the stability (thus, for example, Vb has $W_M$ 16.2 and 2-phenylindolizine has $W_M$ 33.6 [9]). As in the case of many aromatic nitro compounds, nitrite-nitrate rearrangement of the molecular ion is recorded in the spectra of these substances.

Depending on the electronic configuration and steric effects, ($M - NO$)$^+$ and ($M - NO_2$)$^+$ ions are formed with differing probabilities for the isomers: The relative intensity of the ($M - NO$)$^+$ ions changes in the case of nitroindolizines from zero [for 2-methyl-6-nitroindolizine (Va)] to 9.6% [for 2-phenyl-8-nitroindolizine (Vb)] from the intensity of the ($M - NO_2$)$^+$ ions. The primary pathway of fragmentation of the molecular ion consists in the successive loss of a nitro group and HCN molecules; this is confirmed by the corresponding metastable transitions.