SYNTHESIS OF 6- and 8-NITROINDOLIZINES

A. N. Kost, R. S. Sagitullin, and S. P. Gromov

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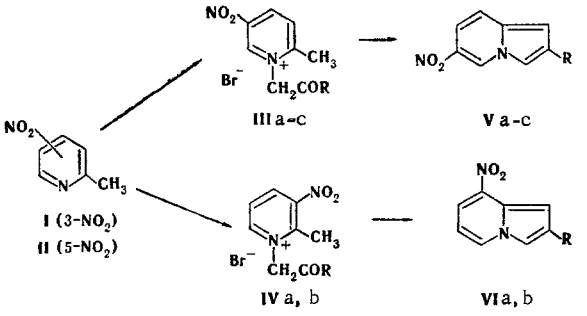
A number of 6- and 8-nitroindolizines were synthesized by quaternization of isomeric 2-methylnitropyridines by α-halo ketones and subsequent cyclization.

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 carbethoxy 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.



III-VI a R=CH_3; b R=C_6H_5; III, V c R=$C(CH_3)_3$

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-methylpyridium 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°. 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

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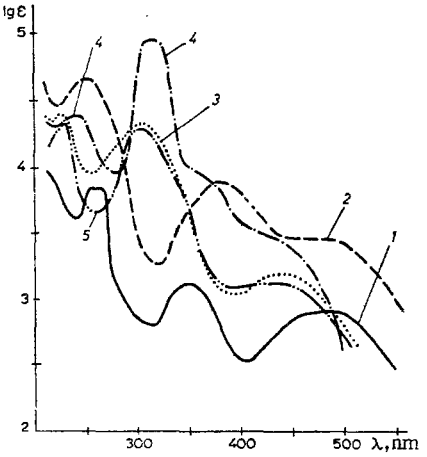
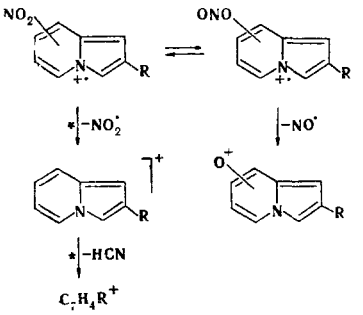


Fig. 1. UV spectra of nitroindolizines (in ethanol): 1) 2-methyl-8-nitroindolizine; 2) 2-phenyl-8-nitroindolizine; 3) 2-methyl-6-nitroindolizine; 4) 2-phenyl-6-nitroindolizine; 5) 2-tert-butyl-6-nitroindolizine.

for Va. A low yield in connection with restricted steric accesibility 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 (VIa-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, VIb 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 (VIb)] 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.

EXPERIMENTAL

The PMR spectra of acetonitrile or dimethyl sulfoxide (DMSO) solutions of the compounds were recorded with a 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 mass spectra were recorded with an MKh-1303 spectrometer at an ionizing-electron energy of 50 eV and an emission current of 1.5 mA with introduction of the substances into the ionization region at 50-150°.

3-Nitro-2-methylpyridine (I). This compound was obtained from 2,6-lutidine [3].

5-Nitro-2-methylpyridine (II). Sodiomalonic ester [obtained by dissolving 3.9 g (0.17 mole) of sodium in 27 g (0.17 mole) of malonic ester and 340 ml of absolute ether with subsequent evaporation of the mixture to dryness] was mixed with 27 g (0.17 mole) of 2-chloro-5-nitropyridine, and the mixture was heated at 120° for 1 h. The red melt was poured into 500 ml of water, and the mixture was treated with excess 2 N NaOH. The resulting dark-red solution was filtered to remove the unchanged 2-chloro-5-nitropyridine, and the filtrate was neutralized to pH 7 with HCl. The resulting yellow-red precipitate of nitropyridylmalonic ester was removed by filtration, washed with water, and dried to give 19 g (39%) of 2-(5-nitropyridyl)malonic ester with mp 97-99° (from alcohol) (mp 97-99° [4]).

A 12-g (0.04 mole) sample of 2-(5-nitropyridyl)malonic ester was refluxed with 100 ml of 30% H_2SO_4 for 2 h, after which the solution was cooled, made alkaline with sodium carbonate, and extracted with ether. The ether was removed by distillation, and the residue was dissolved in benzene and chromatographed with a column filled with aluminum oxide with elution by benzene. Recrystallization of the product from heptane gave 3.5 g (62%) of nitropyridine II with mp 110-112° (mp 110-112° [4]).

4-Nitro-2-methylpyridine. A 10-g (0.06 mole) sample of 4-nitro-2-methylpyridine N-oxide [6] was suspended in 150 ml of chloroform, and the suspension was cooled to 0°, after which 18 ml of phosphorus trichloride was added dropwise with stirring. The mixture was then heated at 70-80° for 1 h, after which it was cooled and poured into water. The aqueous mixture was neutralized with sodium carbonate and extracted with chloroform. The chloroform extract was dried with $MgSO_4$ and evaporated, and the dry residue was dissolved in chloroform and chromatographed with a column filled with aluminum oxide by elution with chloroform. Recrystallization of the product from heptane gave 5 g (54%) of 4-nitropicoline with mp 32-34° (mp 32-34° [5]).

1-Acetonyl-2-methyl-5-nitropyridinium Bromide (IIIa). A solution of 1 g (7.2 mmole) of 5-nitro-2-methylpyridine and 1.5 g (10.8 mmole) of freshly distilled (bp 40-43° at 13 mm) bromoacetone in 3 ml of acetone was refluxed for 14 h, and the resulting precipitate was removed by filtration and washed with acetone to give 1.1 g (55%) of bromide IIIa. Another 0.68 g (4.9 mmole) of bromoacetone was added to the filtrate, and the mixture was heated again for 18 h to give an additional 0.45 g of salt IIIa. The overall yield of product with mp 168-170° (dec., from alcohol) was 1.55 g (78%). Found: C 39.3; H 4.1; Br 29.1%. $C_9H_{11}BrN_2O_3$. Calculated: C 39.1; H 4.0; Br 29.3%.

1-Phenacyl-2-methyl-5-nitropyridinium Bromide (IIIb). This compound, with mp 190-192° [dec., from ethanol–methanol (1 : 1)], was obtained in 72% yield by the method used to prepare IIIa. Found: C 49.8; H 3.9%. $C_{14}H_{13}BrN_2O_3$. Calculated: C 49.7; H 3.9%.

1-Pinacolonyl-2-methyl-5-nitropyridinium Bromide (IIIc). A solution of 0.2 g (1.44 mmole) of 5-nitro-2-methylpyridine and 0.4 g (2.16 mmole) of 4-bromo-2,2-dimethyl-3-butanone in 1 ml of acetophenone was heated at 110° for 18 h, and the resulting acicular crystals of IIIc were removed by filtration and washed with acetone to give 0.13 g (28%) of a product with mp 241-244°. Found: C 45.3; H 5.5%. $C_{12}H_{17}BrN_2O_3$. Calculated: C 45.3; H 5.4%.

1-Phenacyl-2-methyl-8-nitropyridinium Bromide (IVb). This compound, with mp 163-165° (dec., from propanol) was obtained in 80% yield by heating the starting materials in ethyl methyl ketone at 80°. The procedure was similar to that used for the preparation of IIIa. Found: C 49.7; H 4.0; Br 23.8%. $C_{14}H_{13}BrN_2O_3$. Calculated: C 49.7; H 3.9; Br 24.0%.

2-Phenyl-6-nitroindolizines(Va). A mixture of 1.4 g (5.1 mmole) of bromide IIIa and 1 g (11.9 mmole) of $NaHCO_3$ was refluxed with vigorous stirring in 20 ml of absolute alcohol in a stream of argon for 1 h 45 min, after which the sodium bromide was removed by filtration, and the filtrate was vacuum evaporated. The dry residue was treated with hot heptane, and the heptane extract was cooled to precipitate 0.69 g of red crystals of Va.

2-Phenyl-6-nitroindolizines (Vb). A 1-g (2.96 mmole) sample of IIIb was heated with 100 ml of water for 1 h, after which the mixture was neutralized with a few drops of ammonium hydroxide and heated for another 30 min. The yellow precipitate of Vb was removed by filtration and dried to give 0.65 g of product.

TABLE 1. Properties of the Compounds Obtained

Compound	mp, °C (crystallization solvent)	R_f (Silufol, elution with benzene)	Color	Empirical formula	Found			Calc.			Yield, %
					C, %	H, %	N	C, %	H, %	N	
Va	87—90 (heptane)	0.64	Red	$C_9H_8N_2O_2$	61.4	4.6	176	61.4	4.6	176	77
Vb	206—208 (ethyl acetate)	0.68	Yellow	$C_{14}H_{10}N_2O_2$	70.6	4.4	238	70.7	4.2	238	93
Vc	95—97 (heptane)	0.80	Dark-red	$C_{12}H_{14}N_2O_2$	66,0	6,6	218	66,0	6,4	218	31
VIa	103—104 (heptane)	0.57	Dark-red	$C_9H_8N_2O_2$	61,5	4.8	176	61,4	4.6	176	36
VIb	172—173 (ethyl acetate)	0,57	Red	$C_{14}H_{10}N_2O_2$	70,7	4.5	238	70.7	4.2	238	86

TABLE 2. UV and PMR Spectral Data

Compound	UV spectrum (in ethanol)		Chemical shifts, δ, ppm					
	λ_{max}, nm	lg ε	1-H	6-H	5-H	3-H	7-H	8-H
Va	225, 300, 434	4.35; 4.29; 3.16	6.33*		8.93	7.13—7.26		
Vb	240, 312, sh 350—450	4.35; 4.26 3,9—3,4	—	—	—	—		
Vc	228, 303, 430	4.30; 4,23; 3.09	6.53*		9,07	7.23—7,43		
VIa	256—264, 350, 475	3,79—3.81 3.10; 2.90	6,85†	6,60	8.54	7,54	7,84	—
VIb	248, 375, sh 450—500	4.62; 3.85 ≈3,4	7,95†	7,05	8,98	8,55	8,28	—

*In acetonitrile.
†In dimethyl sulfoxide.

2-tert-Butyl-6-nitroindolizine (Vc). This compound was obtained by the method used to prepare Va.

2-Methyl-8-nitroindolizine (VIa). A mixture of 0.5 g (3.6 mmole) of 3-nitro-2-methylpyridine and 2 g (14.4 mmole) of bromoacetone was heated at 90° for 6 h, and the resulting solid resinous mass was heated with water acidified to pH 2-3 with hydrochloric acid. The insoluble residue was removed by filtration, and the filtrate was saturated with sodium bicarbonate. The mixture was then heated to the boiling point, cooled, and extracted with chloroform. The extract was dried with $MgSO_4$ and evaporated. The indolizine was purified with a column filled with silica gel (L 40/100 nm, chloroform) to give 0.23 g of VIa.

2-Phenyl-8-nitroindolizine (VIb). This compound was obtained by the method used to prepare Vb.

Data on indolizines V and VI are presented in Tables 1 and 2.

Reaction of 4-Nitro-2-methylpyridine with Bromoacetophenone. A solution of 0.12 g (0.72 mmole) of 4-nitro-2-methylpyridine and 0.2 g (1 mmole) of bromoacetophenone in 1 ml of acetophenone was heated at 110° for 10 h, during which no precipitation was observed. The mixture was then poured into 10 ml of water, and the aqueous mixture was heated with excess sodium bicarbonate for 1 h. It was then extracted with chloroform. 2-Methyl-7-nitroindolizine was not detected (Erlich's reagent) in the reaction mixture by TLC.

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