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NUCLEOPHILIC SUBSTITUTION IN o-NITRO AZIDES OF THE PYRIDINE SERIES

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The reactions of 2-nitro-3-azidopyridine and 3-nitro-4-azidopyridine with amines and anionic nucleophiles, viz., sodium hydroxide, sodium alkoxides, the sodium salt of p-thiocresol, and potassium cyanide, were investigated. A possible reaction mechanism is proposed.

We have previously shown that nucleophilic substitution of the hydrogen atom in the α position of the pyridine ring to give the previously inaccessible 2-nitro-3,6-diaminopyridines occurs in the reaction of 2-nitro-3-azidopyridine with amines in aqueous solution. Pyrido-[2,3-c]furoxane is an intermediate in this reaction [1].

In a continuation of our research on nucleophilic substitution in pyridine we studied the reaction of 2-nitro-3-azidopyridine with anionic nucleophiles, viz., sodium hydroxide, sodium alkoxides, the sodium salt of p-thiocresol, and potassium cyanide, and the reaction of the isomeric 3-nitro-4-azidopyridine with amines and charged nucleophiles.

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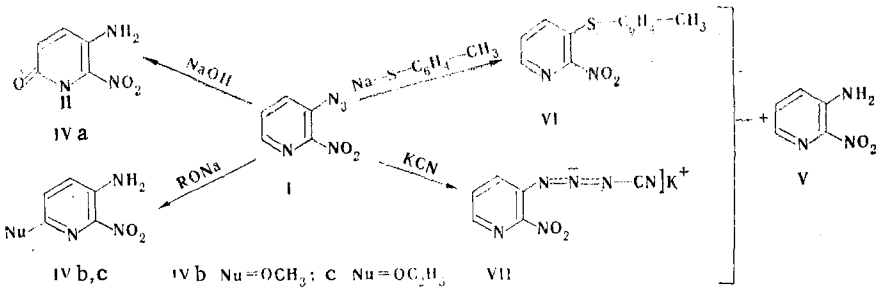
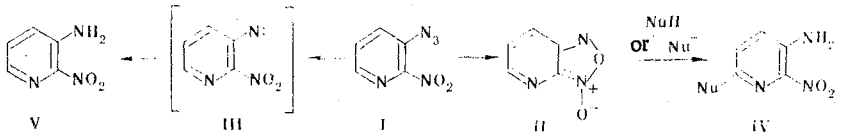


As in the reaction with amines, nucleophilic substitution of the hydrogen atom in the 6 position with the simultaneous conversion of the azide to an amine to give 2-nitro-3-amino-6-pyridone (IVa) and 2-nitro-3-amino-6-alkoxypyridines (IVb,c) in 20-30% yields occurs in the reaction of 2-nitro-3-azidopyridine (I) with sodium hydroxide and sodium alkoxides. Characteristic νNH_2 absorption bands at 3415 and 3450 cm^{-1} and intense absorption at 1683-1700 cm^{-1} (C=O) are observed in the IR spectrum of IVa. The multiplicity and position of the signals in the PMR spectra of IVa. The multiplicity and position of the signals in the PMR spectra of IVa-c correspond to the assigned structure.

2-Nitro-3-aminopyridine (V) was obtained in 25% yield in the reaction of 2-nitro-3-azidopyridine with both amines [1] and with charged nucleophiles in proton-donor solvents. 2-Nitro-3-aminopyridine is not formed when the reaction is carried out in aprotic solvents (carbon tetrachloride and dioxane).

The reactions were carried out at room temperature and were accompanied by an exothermic effect and the formation of, in addition to the chief reaction products, a black high-melting substance, which we were unable to identify.

It might be assumed that two parallel reactions occur in the reaction of 2-nitro-3-azidopyridine with nucleophiles in proton-donor solvents. An oxygen atom of the o-nitro group attacks the nitrogen atom of the azido group, and pyrido[2,3-c]furoxane (II) is formed as a result of synchronous splitting out of a molecule of nitrogen from the azido group and intramolecular cyclization. The furoxane ring is opened by the action of the nucleophile on the pyridofuroxane with simultaneous substitution of the hydrogen atom in the α' position of the pyridine ring and the formation of 2-nitro-3-amino-6-Nu-pyridines (IVa-c). The formation of aminopyridine V can be explained by the fact that nitrene III, which reacts with hydrogen-containing solvents to give 2-nitro-3-aminopyridine (V), develops as a result of nonsynchronous splitting out of a molecule of nitrogen from the azido group. Such concepts regarding the mechanism of the reaction of 2-nitro-3-azidopyridine with nucleophiles are in agreement with the literature data on the thermolysis of o-nitroaryl azides [2-4]. The following is an experimental confirmation of the proposed reaction mechanism. Pyrido[2,3-c]furoxane is formed in 78-80% yield when 2-nitro-3-azidopyridine is heated in water in the absence of a nucleophilic reagent [1]. 2-Nitro-3-aminopyridine was also identified in the reaction solution by thin-layer chromatography (TLC). Compounds IVa-c were also obtained in 80-85% yields by the action of amines [1], sodium hydroxide, and sodium alkoxides on pyrido[2,3-c]furoxane isolated in the free form; the formation of 2-nitro-3-aminopyridine is not observed in this case.

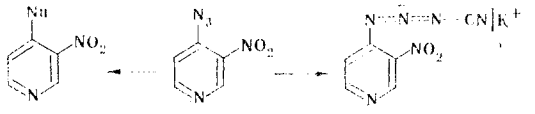


Replacement of the azido group was not observed in the reaction of 2-nitro-3-azidopyridine with amines [1], sodium hydroxide, and sodium alkoxides. Substitution occurs only by the action of a stronger nucleophile, viz., the sodium salt of p-thiocresol. 2-Nitro-3-(p-tolythio)pyridine (VI) was isolated in 25-30% yield. Three groups of signals, viz., a 6-H signal at 8.4 ppm, a group of signals at 7.3-7.8 ppm corresponding to the 4-H and 5-H protons and the protons of the phenyl ring, and a singlet of a methyl group at 2.4 ppm, are observed in the PMR spectrum of this compound. The spin–spin coupling constants (SSCC) are in agreement with the assigned structure (J_{65} = 3.7, J_{64} = 1.7, and J_{54} = 8.2 Hz).

A product of addition of potassium cyanide to the azido group, viz., 2-nitro-3-cyanotriazenopyridine potassium salt (VII), was isolated in the reaction of 2-nitro-3-azidopyri-

dine with potassium cyanide. Products of replacement of the hydrogen atom or the azido group were not detected. Signals of three pyridine protons at 8.2, 8.1, and 7.7 ppm, which, for the SSCC, correspond to the 6-H, 4-H, and 5-H protons (J_{64} = 1.5, J_{65} = 4.2, and J_{45} = 8.0 Hz), are observed in the PMR spectrum of VII. The frequency of the absorption in the IR spectrum due to the C≡N vibrations is 2170 cm^{-1}.

In contrast to the 2-nitro isomer, replacement of the azido group to give the corresponding 3-nitro-4-Nu-pyridines (IXa, ,c) occurs in the reaction of 3-nitro-4-azidopyridine (VIII) [5] with amines and sodium hydroxide.



IXa-c VIII X

IX a Nu = morpholino, b Nu = piperidino, c Nu = OH

As in the case of 2-nitro-3-azidopyridine, nucleophilic substitution does not occur in the reaction of azide VIII with potassium cyanide, but 3-nitro-4-cyanotriazenopyridine potassium salt (X) is formed.

EXPERIMENTAL

The electronic spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Perkin-Elmer R-12B spectrometer (60 MHz) with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The course of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates. Column chromatography was carried out on LSL 40/100 μ silica gel.

Reaction of 2-Nitro-3-azidopyridine with Sodium Hydroxide Solution. A solution of 0.7 g (18 mmole) of sodium hydroxide in 5 ml of water was added slowly dropwise to a solution of 2 g (12 mmole) of I in 60 ml of water (or ethanol). At the end of the exothermic reaction (15-20 min), the solution was cooled, and a black high-melting substance, the structure of which was not established, was removed by filtration. The filtrate was concentrated *in vacuo* to the minimum volume and passed through a chromatographic column by elution with chloroform–ethyl acetate (10:3). The first fraction contained 0.6 g (30%) of 2-nitro-3-aminopyridine [yellow plates with mp 194-196°C (from propanol) [6]] and 0.4 g (20%) of 2-nitro-3-amino-6-pyridone with mp 156-158°C (from ethanol). Found: C 38.9; H 3.9; N 27.1%. $C_6H_7N_3O_2$. Calculated: C 38.7; H 3.5; N 27.1%. The product had R_f 0.50 [chloroform–ethanol (5:1)]. UV spectrum (in ethanol), λ_{max} (log ε): 227 (4.30) and 4.38 (3.96). PMR spectrum (in d_6-DMSO): 7.44 (1H, d, 4-H) and 6.95 ppm (1H, d, 5-H, J_{54} = 8.6 Hz).

Reactions of 2-Nitro-3-azidopyridine with Sodium Alkoxides. The reactions were carried out in absolute ethanol in the same way as the reaction with sodium hydroxide. 2-Nitro-3-aminopyridine was obtained in 25-30% yield. 2-Nitro-3-amino-6-methoxypyridine (IVb), with mp 200-201°C (from absolute methanol), was obtained in 25-30% yield. Found: C 42.9; H 4.2; N 24.2%. $C_6H_7N_3O_3$. Calculated: C 42.6; H 4.2; N 24.5%. The product had R_f 0.70 [chloroform–ethanol (5:1)]. UV spectrum (in methanol), λ_{max} (log ε): 229 (4.30) and 431 nm (3.89). PMR spectrum (in d_6-DMSO): 8.15 (1H, d, 4-H), 6.85 (1H, d, 5-H, J_{54} = 9.1 Hz), and 3.90 ppm (3H, s, OCH_3). 2-Nitro-3-amino-6-ethoxypyridine (IVc), with mp 113-115°C (from water), was obtained in 20-25% yield. Found: C 46.2; H 4.8; N 22.8%. $C_7H_9N_3O_3$. Calculated: C 45.9; H 4.9; N 22.9%. The product had R_f 0.63 (chloroform). UV spectrum (in water), λ_{max} (log ε): 225 (4.16) and 425 nm (3.71). PMR spectrum (in d_6-acetone): 7.70 (1H, d, 4-H), 7.1 (1H, d, 5-H, J_{54} = 8.7 Hz), 4.38 (2H, q, OCH_2CH_3), and 1.35 ppm (3H, t, OCH_2CH_3).

Reaction of 2-Nitro-3-azidopyridine with p-Thiocresol Sodium Salt. A 3.5-g (22.5 mmole) sample of p-thiocresol sodium salt was added with stirring to a solution of 2.5 g (15 mmole) of 2-nitro-3-azidopyridine (I) in 50 ml of absolute ethanol, during which the solution took on a dark-red coloration. The reaction mass was allowed to stand at room temperature for 24-26 h, after which it was concentrated *in vacuo* to the minimum volume, and the mixture was passed through a column by elution with chloroform–ethyl acetate (10:3). The first fraction contained 0.7 g (30%) of 2-nitro-3-aminopyridine (V). Workup of the second fraction gave 1.2 g (30%) of 2-nitro-3-(p-tolylthio)pyridine (VI) with mp 110°C (from ethanol). Found: C 58.8; H 4.5; N 11.7; S 12.7%. $C_{12}H_{10}N_2O_2S$. Calculated C 58.5; H 4.2; N 11.4; S 13.0%.

The product had R_f 0.44 [chloroform–ethyl acetate (10:3)]. UV spectrum (in ethanol), λ_{max} (log ε): 222 (4.40), 272 (4.02), and 360 nm (3.65).

Reaction of 2-Nitro-3-azidopyridine with Potassium Cyanide. A 1.5-g (24 mmole) sample of potassium cyanide was added to a solution of 2 g (12 mmole) of I in 60 ml of ethanol, and the mixture was refluxed for 1 h. It was then cooled, and the yellow crystals were removed by filtration to give 1.4 g (50%) of 2-nitro-3-cyanotriazenopyridine potassium salt (VII) with 250-252°C (from water). Found: C 31.4; H 1.6; N 36.5%. $C_6H_3KN_6O_2$. Calculated: C 31.3; H 1.3; N 36.5%. The product had R_f 0.30 [chloroform–ethyl acetate (10:3)]. UV spectrum (in water), λ_{max} (log ε): 200 (4.20) and 318 nm (4.18). Concentration of the reaction solution gave 0.17 g (10%) of 2-nitro-3-aminopyridine.

Reaction of 3-Nitro-4-azidopyridine with Amines. A sixfold molar excess of the amine was added to a solution of 2 g (12 mmole) of azide VIII in 30 ml of water, and the mixture was refluxed for 5-10 min. It was then cooled and extracted with chloroform, and the extract was dried with sodium sulfate and concentrated *in vacuo*. This procedure gave 3-nitro-4-morpholinopyridine (IXa), with mp 130-131°C (from water), in 45-50% yield. Found: C 51.6; H 5.3; N 20.1%. $C_9H_{11}N_3O_3$. Calculated: C 51.7; H 5.3; N 20.1%. The product had R_f 0.60 [chloroform–ethanol (10:1)]. UV spectrum (in water), λ_{max} (log ε): 225 (4.16) and 400 nm (3.38). PMR spectrum (in d_6-acetone): 8.80 (1H, s, 2-H), 8.60 (1H, d, 5-H), and 7.30 ppm (1H, d, 6-H, J_{65} = 6.0 Hz). Also obtained was 3-nitro-4-piperidinopyridine (IXb), with mp 43-44°C (from water), in 43-45% yield. Found: C 58.2; H 6.3; N 20.3%. $C_{10}H_{13}N_3O_2$. Calculated: C 58.0; H 6.3; N 20.3%. The product had R_f 0.34 [chloroform–ethyl acetate (10.3)]. UV spectrum (in water), λ_{max} (log ε): 250 (4.27) and 390 nm (3.48).

Reaction of 3-Nitro-4-azidopyridine with Sodium Hydroxide Solution. A solution of 1.6 g (40 mmole) of sodium hydroxide in 5 ml of water was added to a solution of 2 g (12 mmole) of VIII in 40 ml of water, and the mixture was refluxed for 30 min. The reaction solution was refluxed with activated charcoal and filtered, and the filtrate was cooled to give 0.7 g (41%) of 3-nitro-4-hydroxy pyridine [yellow crystals with mp 278-279°C (from water) [7]].

Reaction of 3-Nitro-4-azidopyridine with Potassium Cyanide. This reaction was carried out in the same way as the reaction of 2-nitro-3-azidopyridine with potassium cyanide. Workup gave 3-nitro-4-cyanotriazenopyridine potassium salt (X), with mp 180-182°C (from water), in 43-45% yield. Found: C 31.5; H 1.5; N 36.6%. $C_6H_3KN_6O_2$. Calculated: C 31.3; H 1.3; N 36.5%. The product had R_f 0.28 [chloroform–ethyl acetate (10:3)].

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