PYRIDO[2,3-c]FUROXAN AS A PROBABLE INTERMEDIATE IN THE REACTION OF 2-NITRO-3-AZIDOPYRIDINE WITH AMINES

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Two parallel reactions, viz., cyclization of 2-nitro-3-azidopyridine to pyrido[2,3-c]furoxan, which is aminated in the 6 position of the pyridine ring with opening of the furoxan ring, and reduction of the azido group to form 2-nitro-3-aminopyridine, occur in the reaction of 2-nitro-3-azidopyridine with amines. It was established that pyrido[2,3-c]furoxan reacts with amines in aqueous media in the 1-oxide form.

In a previous communication we demonstrated that amination in the 6 position to give 2-nitro-3,6-diaminopyridine occurs in the reaction of 2-nitro-3-azidopyridine (I) with ammonium hydroxide [1]. In addition to this, 2-nitro-3-aminopyridine (II) is detected in the reaction mixture by thin-layer chromatography (TLC). We expressed the assumption that the reduction reaction that accompanies amination is due to release of hydrogen atoms by the intermediate. However, we were unable to exclude the possibility of nucleophilic substitution by ammonia of the azido group by an amino group. In addition, considering the known conversion of o-nitroazidobenzene to benzofuroxan, one might assume that pyrido[2,3-c]furoxan (III) is formed as an intermediate in the amination in our case.

To clear up the first problem in the present research we carried out the reaction of azide I with various amines, viz., methylamine, dimethylamine, ethylamine, diethylamine, n-butylamine, piperidine, and morpholine. In all cases, in addition to 2-nitro-3-aminopyridine, we obtained 2-nitro-3-amino-6-R-pyridines (V) (see the scheme below). Thus we established that nucleophilic substitution of the azido group by an amino group does not occur in the reaction of 2-nitro-3-azidopyridine with amines. We were able to isolate V in 40-45% yields in the reaction with ammonia and morpholine. In the reactions with the other amines the amination products were isolated by preparative thin-layer chromatography (TLC). Only reduction of the azido group to give 2,3-diaminopyridine occurered in the reaction of nitro azide I with hydrazine hydrate both in aqueous and alcohol solutions.

The ratio of the products of amination of V and 2-nitro-3-aminopyridine (II) under equal experimental conditions in the reaction mass was determined by quantitative comparison of the chromatograms of the reaction solutions with a Khromaskan apparatus and was found to differ as a function of the nature of the amine. Thus, whereas only very small amounts of nitroamine II were obtained in the reaction with ammonia, in the reaction with piperidine the ratio of the products of amination of V and nitro amine II was 2:1, as compared with 1:1 with methylamine and 1:1.5 with dimethylamine.

To confirm our assumption regarding the participation of pyrido[2,3-c]furoxan in the amination of 2-nitro-3-azidopyridine it was necessary to first work out a convenient method for its preparation. Pyrido[2,3-c]furoxan was previously described in [2] and was obtained by oxidation of 2-nitro-3-aminopyridine with phenyl iodosoacetate in the form of an oily substance, which was then subjected to chromatographic purification. Eatough and co-workers [2] were unable to realize the synthesis of pyridofuroxan from the corresponding o-nitro azide by heating in solvents. We have found that pyridofuroxan is obtained in 78-80% yield when nitro azide I is refluxed for 4-5 h in ethanol or in water. Furoxan III was obtained in crystalline form by this method and was used for the subsequent syntheses without additional purification.

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TABLE 1. Characteristics of the 2-Nitro-3-amino-6-R-pyridines (Va-g)

Compound	R	mp,* °C	λ_{max}, nm (log ε) in water	R_f†	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, %
a	NH_2	208—210	234 (4,00), 461 (3,56)	0,35	39,1	4,0	36,1	$C_5H_6N_4O_2$	39,0	3,9	36,4	70
b	$NHCH_3$	193—195	233 (4,29), 480 (3,84)	0,45	43,1	4,8	33,0	$C_6H_8N_4O_2$	42,9	4,8	33,3	70
c	$N(CH_3)_2$	130—133	244 (4,15), 506 (3,62)	0,53	45,9	5,5	30,3	$C_7H_{10}N_4O_2$	46,1	5,5	30,7	75
d	NHC_2H_5	103—105	242 (4,15), 489 (3,40)	0,31	46,3	5,8	30,7	$C_7H_{10}N_4O_2$	46,1	5,5	30,7	80
e	$N(C_2H_5)_2$	93—95	250 (4,14), 527 (3,29)	0,73	51,2	6,7	27,1	$C_9H_{14}N_4O_2$	51,5	6,7	26,7	74
f	Piperidino	110—111	245 (4,22), 480 (3,61)	0,78	54,1	6,5	25,1	$C_{10}H_{14}N_4O_2$	54,0	6,4	25,2	80
g	Morpholino	202—203	236 (3,99), 470 (3,41)	0,51	47,7	5,3	25,3	$C_9H_{12}N_4O_3$	48,2	5,4	25,0	72

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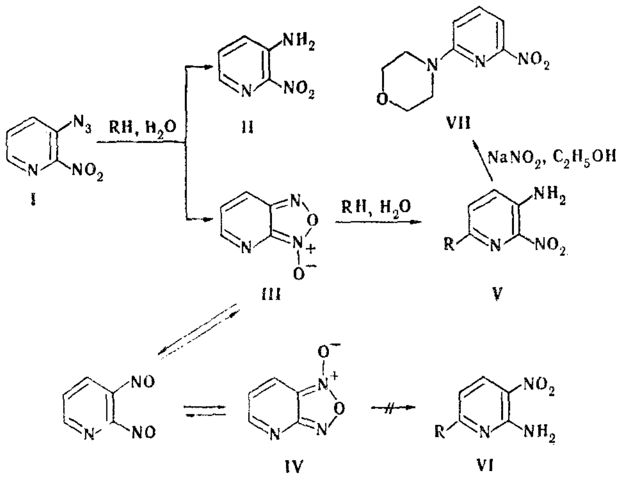
*Compound Ve was recrystallized from 30% aqueous ethanol, while the remaining compounds were recrystallized from water.
†In the case of Va, b, c, f, g the R_f values were determined in an ethanol—chloroform system (1:10), whereas in the case of Vd, e they were determined in chloroform—ethyl acetate (10:3).

Pyrido[2,3-c]furoxan reacts with amines even when warm aqueous solutions are mixed, and the corresponding 2-nitro-3-amino-6-R-pyridines are formed in 70-80% yields; 2-nitro-3-aminopyridine was not detected in the reaction medium in a single case. Thus it may be concluded that two parallel reactions, viz., cyclization to give pyrido[2,3-c]furoxan, which is aminated in the 6 position with opening of the furoxan ring, and reduction of the azido group to give 2-nitro-3-aminopyridine, occur in the reaction of 2-nitro-3-azidopyridine with amines.

Scheme 1



a $R=NH_2$, b $R=NHCH_3$, c $R=N(CH_3)_2$, d $R=NHC_2H_5$, e $R=N(C_2H_5)_2$, f R= piperidino
g R= morpholino

Having established that pyrido[2,3-c]furoxan is the intermediate in the reaction described here, it was still necessary to take into account the fact that furoxan may have the 1- or 3-oxide (III or IV) structure [2]. Thus one could have obtained 2-nitro-3-amino-6-R-pyridines (V) and 2-amino-3-nitro-6-R-pyridines (VI) in the case of amination. To pin down the structure of these compounds we carried out the deamination of one of the compounds obtained, viz., 2-nitro-3-amino-6-morpholinopyridine; we obtained 2-nitro-6-morpholinopyridine (VII), the structure of which was confirmed unambiguously by data from the PMR spectrum (signals of three pyridine protons at 7.8, 7.6, and 6.9 ppm, the spin—spin coupling constants of the corresponding 5-H, 4-H, and 3-H protons J_{45} = 8.8, J_{43} = 8.8, and

J_{35} = 0.8 Hz, and two multiplets of OCH_2 and NCH_2 groups of morpholine at 3.8 and 3.6 ppm). Structure VI was thereby excluded.

The electronic spectra of 2-nitro-3-amino-6-morpholinopyridine and the remaining products of amination of V are extremely close, and this confirms the 2-nitro-3-amino-6-R-pyridine structure. Thus on the basis of data on the structures of the amination products it may be concluded that pyrido[2,3-c]furoxan reacts with amines in aqueous solutions in the 1-oxide form.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in water were recorded with a Specord UV-vis spectrometer. The PMR spectra of solutions of the compounds in deuterochloroform were recorded with a Perkin—Elmer R-12B spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates, chromatography was performed with columns, and preparative TLC was carried out on LSL 40/100 μ silica gel.

Reaction of 2-Nitro-3-azidopyridine (I) with Amines. A 2-g (12 mmole) sample of 2-nitro-3-azidopyridine was refluxed with a 1.5-2.0-fold molar excess of the corresponding amine in 50 ml of water for 30 min. The mixture was then cooled, and the red crystalline precipitated Va, g were removed by filtration and crystallized from water; the products were obtained in 40-45% yields. In the case of the reaction with methylamine a yellow crystalline precipitate of 2-nitro-3-aminopyridine was removed by filtration after cooling. In the reactions with methylamine, dimethylamine, and piperidine, the reaction solution was concentrated *in vacuo*, the residue was extracted with acetone, and the 2-nitro-3-amino-6-R-pyridines were isolated by preparative TLC.

Pyrido[2,3-c]furoxan (III). A 1-g (6 mmole) of 2-nitro-3-azidopyridine was refluxed in 30 ml of ethanol for 4-5 h, after which the reaction solution was purified with activated charcoal and concentrated *in vacuo* to a volume of 15 ml. When the concentrate was cooled, pale yellow crystals of furoxan III (78-80%), with mp 52°C (from water), precipitated. UV spectrum, λ_{max} (log ε): 213 (4.31) and 364 nm (3.90). PMR spectrum: 9.0 (1H, q, 6-H, J_{65} = 35, J_{64} = 1.5 Hz), 8.1 (1H, q, 4-H, J_{45} = 8.9, J_{46} = 1.5 Hz), and 7.5 ppm (1H, q, 5-H, J_{54} = 8.9, J_{56} = 3.5 Hz).

Reaction of 2-Nitro-3-azidopyridine (I) with Hydrazine Hydrate. A 10-ml sample of a 50% alcohol solution of hydrazine hydrate was added to 0.5 g (3 mmole) of 2-nitro-3-azidopyridine. At the end of the exothermic reaction, the reaction solution was heated for another 30 min, after which it was purified by the addition of activated charcoal and concentrated *in vacuo* to a minimal volume, as a result of which we obtained a dark-brown resinous product, which began to crystallize on standing. It was crystallized from benzene to give 2,3-diaminopyridine (45-50%), which was identical to the product obtained in [3] with respect to its melting point and UV spectrum.

Reaction of Pyrido[2,3-c]furoxan (III) with Amines. A 1.0-1.5-fold molar excess of the amine was added at 18-25°C to a solution of 1 g (7 mmole) of pyrido[2,3-c]furoxan in 20 ml of water. The reaction solution darkened, and red crystals of V gradually precipitated. The characteristics of the 2-nitro-3-amino-6-R-pyridines are presented in Table 1.

2-Nitro-6-morpholinopyridine (V). A 1-g (4.5 mmole) sample of 2-nitro-3-amino-6-morpholinopyridine was suspended in 10 ml of absolute ethanol, 1.2 ml of concentrated sulfuric acid was added dropwise at 0-5°C, and the mixture was treated with 0.45 g (6.4 mmole) of sodium nitrite in 2 ml of water. The diazo solution was transferred to a reaction flask, another 10 ml of absolute ethanol was added, and the mixture was heated on a boiling-water bath for 2 h. The reaction solution was extracted with chloroform, and the extract was dried with sodium sulfate and concentrated *in vacuo* to a minimal volume. The bright-yellow crystals of 2-nitro-6-morpholinopyridine were purified to remove the admixed red substance with a chromatographic column by elution with chloroform. The product was obtained in 55% yield and had mp 117-118°C (from water) and R_f 0.65 [chloroform—ethyl acetate (10:3)]. Found: C 51.7; H 5.3; N 20.1%. $C_9H_{11}N_3O_3$. Calculated: C 51.7; H 5.3; N 20.1%.

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CALCULATION OF THE ELECTRONIC SPECTRUM WITHIN THE CNDO/S (COMPLETE NEGLECT OF DIFFERENTIAL OVERLAP/S) APPROXIMATION AND CHARACTER OF THE LONG-WAVE ABSORPTION BAND OF 2-N-PYRIDINIA-1,3-INDANDIONE BETAINE

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The electronic spectrum of 2-N-pyridinia-1,3-indandione betaine was calculated by the MO LCAO method within the CNDO/S approximation with the Del Bene—Jaffe parametrization in order to refine the concepts regarding the character of the long-wave absorption band of this compound. It was established that the long-wave absorption band of this compound is due to an electron transition with charge transfer and has a vibrational structure.

The energy of the long-wave transition for 2-N-pyridinia-1,3-indandione betaine corresponds to the value expected on the basis of general concepts regarding intramolecular charge transfer [1]. A comparison of the dipole moments in the ground and first excited states [2] also constitutes evidence that the long-wave transition is a transition with charge transfer from the anionic to the cationic part of the betaine. The results of a calculation by the Hückel MO method [3] are in poor agreement with the experimental data as a consequence of the well-known inadequacies of this method [4].

The long-wave band in the electronic absorption spectrum of 2-N-pyridinia-1,3-indandione betaine in all solvents is clearly asymmetrical, whereas in the case of solutions in n-hexane one even observes a weakly expressed inflection (Fig. 1). The latter phenomenon may, in principle, also be due to the fact that the long-wave band arises as a consequence of the existence of two closely located electron transitions. In order to explain the experimental data, in the present research we calculated the 2-N-pyridinia-1,3-indandione betaine molecule

TABLE 1. Electron Transitions for 2-N-Pyridinia-1,3-indandione Betaine

No.	Calculated						Experimental	
	λ, nm	contribution of the orbital transitions	classification	polarization	oscillator force (f)	$\varepsilon^{a} = 5 \cdot 10^{4} f$	λ, nm	ε^{b}
1	463	96% 41—42	$\pi-\pi^*$	X	0,383	19 150	431	33 490
2	360	86% 41—43	$\pi-\pi^*$	Y	0,003	150	365 pl.	3 060
3	334	93% 41—44	$\pi-\pi^*$	Y	0,023	1 150	340	1 800
4	317	86% 38—42	$n^{-}-\pi^*$	—	0,000	0,0	310	1 600
5	314	74% 38—44	$n^{-}-\pi^*$	—	0,000	0,0		
6	254	93% 39—42	$\pi-\pi^*$	X	0,013	650		
7	249	82% 40—42	$\pi-\pi^*$	Y	0,025	1 250		
8	248	71% 36—42	$\pi-\pi^*$	Y	0,23	11 500	243	32 790
9	241	69% 41—45	$\pi-\pi^*$	X	0,198	9 900		
10	228	71% 41—46	$\pi-\pi^*$	Y	0,29	14 500		
11	218	89% 39—45	$\pi-\pi^*$	X	0,03	1 500	—[c]	
12	212	72% 41—47	$\pi-\pi^*$	Y	0,013	650		
13	206	98% 39—43	$\pi-\pi^*$	Y	0,002	100		
14	205	43% 36—43	$\pi-\pi^*$	X	0,946	47 300		

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[a] This is the extinction coefficient. [b] Solution in n-hexane.
[c] The maximum of the band was not recorded.

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