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A number of 3-nitro-2-X-1,8-naphthyridines (X = H, Cl, NH₂, OEt) were successfully aminated into the corresponding 4-amino-3-nitro-2-X-naphthyridines, using liquid ammonia and potassium permanganate as reagents. 4-Amino-1,4-dihydro-3-nitro-2-X-1,8-naphthyridines are the actual species being oxidized by the potassium permanganate; their existence has been proved by ¹H nmr spectroscopy.

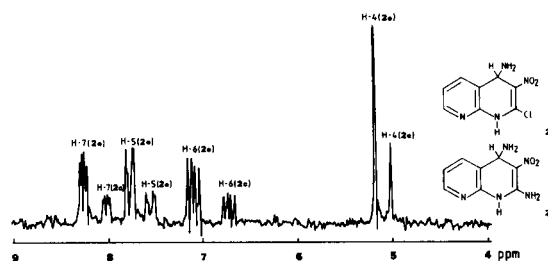
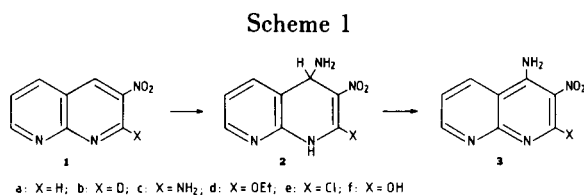
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It has been reported that the highly electron-deficient 1,2,4,5-tetrazines (3) and pteridines (4,5) undergo a Chichibabin amination, if these compounds are dissolved in liquid ammonia, containing potassium permanganate. It has been proved that the covalent σ -adducts formed by addition of ammonia across the C=N bond in the heterocycle, are the actual species involved in the oxidation. The parent naphthyridines do not form adducts with liquid ammonia. Apparently these systems are not sufficiently electron-deficient to allow addition with this neutral nucleophile. In order to study whether addition will take place, when the electron-deficiency is increased, we synthesized some nitro-1,X-naphthyridines and investigated their behavior towards addition with liquid ammonia. In this paper we report on the covalent addition of ammonia to 3-nitro-1,8-naphthyridine and some of its derivatives and the reactivity of the adducts to potassium permanganate. When 3-nitro-1,8-naphthyridine (**1a**) is dissolved in liquid ammonia the ¹H-nmr spectrum of the solution clearly shows the presence of the 1:1 σ -adduct 4-amino-3-nitro-1,4-dihydro-1,8-naphthyridine (**2a**). Compared with the spectrum of a solution of **1a** in dimethylsulfoxide, all the protons are shifted upfield (see Table). Especially the upfield shift of H-4 (4.38 ppm) is considerable and has to be ascribed to the formation of **2a**, leading for C-4 to a change of hybridisation from sp² (in **1a**) to sp³ (in **2a**) (6). That this upfield shift can indeed be ascribed to rehybridisation of C-4 and not of C-2 has been proved by measurement of the ¹H-nmr spectrum of 2-deutero-3-nitro-1,8-naphthyridine (**1b**) in dimethylsulfoxide and in liquid ammonia.

the more conventional way of amino-dehalogenation (7) requires 4-chloro-3-nitro-1,8-naphthyridine, which is less easily accessible than **1a**.

Similar results were obtained with 2-amino- (**1c**) and 2-ethoxy-3-nitro-1,8-naphthyridine (**1d**). Dissolving **1c** and **1d**, respectively, in liquid ammonia and taking the ¹H-nmr spectrum of this solution it was evident that both compounds were converted into their corresponding covalent 1:1 σ -adducts *i.e.* 2,4-diamino-3-nitro-1,4-dihydro-1,8-naphthyridine (**2c**) and 4-amino-2-ethoxy-3-nitro-1,4-dihydro-1,8-naphthyridine (**2d**), respectively (see Table). When to each of the solutions of **2c** and **2d** in liquid ammonia, potassium permanganate was added and the reaction mixture was worked up 2,4-diamino-3-nitro-1,8-naphthyridine (**3c**, 25%) and 4-amino-2-ethoxy-3-nitro-1,8-naphthyridine (**3d**, 40%), respectively, were isolated. The structure of **3c** was confirmed by an independent synthesis, involving aminolysis of 4-amino-2-chloro-3-nitro-1,8-naphthyridine (**3e**). When 2-chloro-3-nitro-1,8-naphthyridine (**1e**) was dissolved in liquid ammonia and the ¹H nmr spectrum was taken after a few minutes, the solution contained the C-4 σ -adduct **2e** (Table). However, if the solution was measured after one hour, besides **2e** a new adduct was formed. The ¹H-nmr spectrum (see Figure 1) is like that of σ -adduct **2c**, indicating that σ -adduct **2e** has undergone a slow amino-

Figure 1



On treatment of the solution of **2a** in liquid ammonia with potassium permanganate 4-amino-3-nitro-1,8-naphthyridine (**3a**) was obtained in a yield of 50%. This new method of preparation of **3a** is of synthetic interest since

Figure 1. ¹H-nmr spectrum of a solution of **2e** and **2c** in liquid ammonia, taken one hour after dissolving **1e**.

Table

¹H NMR Data of Some 3-Nitro-1,8-naphthyridines and Their σ -Complexes With Ammonia

Compound	Solvent	Chemical shift δ (ppm)						Coupling constants Hz			
		H-2	H-4	H-5	H-6	H-7	Others	J _{2,4}	J _{5,6}	J _{5,7}	J _{6,7}
3-Nitro-1,8-naphthyridine (1a)	DMSO	9.74	9.52	8.83	7.88	9.30		3.0	8.5	2.0	4.5
	Ammonia (liquid)	8.57	5.14	7.82	7.07	8.30		—	7.5	2.0	4.5
	$\Delta\delta$	1.17	4.38	1.01	0.81	1.00					
2-Amino-3-nitro-1,8-naphthyridine (1c)	DMSO	—	9.20	8.38	7.32	8.92	7.87 (NH ₂)	—	8.5	2.0	4.5
	Ammonia	—	5.06	7.59	6.75	8.07		—	8.0	2.0	5.0
	$\Delta\delta$	—	4.14	0.79	0.57	0.85					
2-Chloro-3-nitro-1,8-naphthyridine (1e)	DMSO	—	9.43	8.72	7.85	9.27		—	8.0	2.0	4.5
	Ammonia	—	5.18	7.78	7.10	8.28		—	7.5	2.0	5.0
	$\Delta\delta$	—	4.25	0.94	0.75	0.99					
2-Ethoxy-3-nitro-1,8-naphthyridine (1d)	Deuteriochloroform	—	8.63	8.22	7.45	9.08	4.77 (CH ₂), 1.52 (CH ₃)	—	8.0	2.0	4.5
	Ammonia	—	5.16	7.71	6.97	8.20	4.31 (CH ₂), (a)	—	8.0	2.0	5.0
	$\Delta\delta$	—	3.47	0.51	0.48	0.88					
3-Nitro-2-oxo-1,2-dihydro-1,8-naphthyridine (1f)	DMSO	—	8.93	8.33	7.37	8.68		—	8.0	2.0	4.5
	Ammonia	—	5.16	7.75	6.92	8.06		—	8.0	2.0	5.0
	$\Delta\delta$	—	3.77	0.58	0.45	0.62					

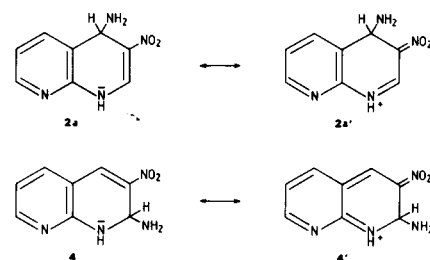
(a) The signals of methyl group are overlapped by the signal of ammonia.

slow amino-dehalogenation at C-2. This result is not surprising as the halogen atom is in a reactive position towards the activating influence of the nitro group for nucleophilic substitution. After adding potassium permanganate to a solution of **2e** in liquid ammonia, we were able to isolate 4-amino-2-chloro-3-nitro-1,8-naphthyridine (**3e**) in 22% yield. Also 2-oxo-3-nitro-1,2-dihydro-1,8-naphthyridine (**1f**) was found to give an adduct with liquid ammonia, *i.e.*, **2f** (see Table). However, the adduct formation is not complete since unreacted starting material **1f** was still present. When the solution was kept for 5 minutes at room temperature the ratio **1f**:**2f** was about 1:2. Treatment of a solution **1f**/**2f** in liquid ammonia with potassium permanganate gave nearly exclusively **1f**. Only a trace of a byproduct was formed, of which the structure is still unknown.

From the results obtained so far it is evident that the 3-nitro-1,8-naphthyridines (**1**) easily undergo exclusive addition at C-4. Since the addition pattern of covalent amination of pteridines (5), 1,5- and 1,7-naphthyridines has been found to be temperature-dependent, we also measured ¹H-nmr spectra of a solution of **1a** in liquid ammonia from -40°C to +20°C. No change of the addition pattern in this temperature range was found, indicating that we deal in this study with a σ -adduct, which was formed under reaction conditions in which the kinetically controlled and the thermodynamically most favored adduct are the same. The probable reason why from **1a** the C-4

adduct **2a** and not the C-2 adduct **4** is formed, can be explained by the fact that resonance structure **2a'** forms a more important contribution to stabilization of **2a** = **2a'** than resonance structure **4'** to stabilization of **4** = **4'**, due to loss of aromaticity in **4'**.

Scheme 2



It is of interest to mention that a ¹H-nmr spectrum of a solution of 4-amino-3-nitro-1,8-naphthyridine when dissolved in liquid ammonia does not show any evidence for the formation of an adduct. The result seems to indicate that if position 4 is blocked, a σ -adduct at C-2 was still not formed.

EXPERIMENTAL

Melting points are uncorrected. The ¹H-nmr spectra were obtained with a Varian XL-100-15 or a Varian EM 390 spectrometer. Spectra in liquid ammonia were recorded with sealed thick-wall nmr tubes and ammonia ($\delta = 0.95$ ppm) was used as internal standard. Mass spectra were

carried out with a VG Micromass 7070 F spectrometer. The ir spectra (in potassium bromide) were measured with a Hitachi EPI-G3 apparatus. The ^1H nmr data are collected in the Table.

1. Preparation of Starting Material and Reference Compounds.

The following starting and reference compounds were prepared according to known precedures: 3-nitro-1,8-naphthyridine (**1a**) (8), 2-chloro-3-nitro-1,8-naphthyridine (**1e**) (8), 3-nitro-2-oxo-1,2-dihydro-1,8-naphthyridine (**1f**) (7) and 4-chloro-3-nitro-1,8-naphthyridine (7).

2-Deutero-3-nitro-1,8-naphthyridine (**1b**).

A mixture of 3-nitro-1,8-naphthyridine (**1a**) (100 mg, 0.57 mmoles) and 3 ml of deuterated water was reacted in a sealed tube at 200° for 8 hours. After cooling of the solution, the solid was filtered and dried (95 mg, mp $247\text{--}248^\circ$ dec). The ^1H nmr spectroscopy showed that position 2 in **1b** was fully deuterated, position 4 for ca 35% and position 7 for ca 20%.

2-Amino-3-nitro-1,8-naphthyridine (**1c**).

The compound was obtained (9) from 2-chloro-3-nitro-1,8-naphthyridine (**1e**) and ethanolic ammonia solution by heating at 110° for 4 hours, yield 70% orange needles, mp $276\text{--}277^\circ$ (from DMF).

2-Ethoxy-3-nitro-1,8-naphthyridine (**1d**).

A solution of 2-chloro-3-nitro-1,8-naphthyridine (**1e**, 450 mg, 2.15 mmoles) in 100 ml of ethanol containing 0.7 g of potassium hydroxide was kept, with stirring, at room temperature overnight. Then the solution was acidified with aqueous solution of hydrochloric acid (10%) to pH 3-4 and ethanol was evaporated off. To the residue obtained 60 ml of water was added and the solution was made alkaline with potassium carbonate. The mixture was extracted with chloroform and the chloroform extracts were dried with anhydrous magnesium sulphate. Chloroform was evaporated off and the residue was crystallized from petroleum ether (br $80\text{--}100^\circ$) (charcoal), yielding 0.22 g (47%) of white needles, mp $130\text{--}131^\circ$; ms: m/e (relative intensity, %) 219 (M^+ , 10), 181 ($\text{M}^+\text{-C}_2\text{H}_4$, 100); ir: (cm^{-1}) 1540 (ν as NO_2), 1320 (ν s NO_2). For ^1H -nmr data see Table.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}_3$: C, 54.80; H, 4.24. Found: C, 55.36; H, 4.24.

2. Aminations. General Procedure.

To a solution of the 3-nitro-1,8-naphthyridines **1a**, **1c**, **1d** or **1e** (0.15-0.2 g) in 20-25 ml of liquid ammonia 0.18 g of potassium permanganate (1.14 mmoles) was added and the mixture was stirred for 15 minutes. Liquid ammonia was evaporated and to the residue obtained 30 ml of warm ($\sim 50^\circ$) water and 1 ml of methanol were added. The mixture was continuously extracted with chloroform for 25 hours. The residue obtained after evaporation of chloroform was crystallized from the appropriate solvent (see below).

4-Amino-3-nitro-1,8-naphthyridine (**3a**).

3-Nitro-1,8-naphthyridine (**1a**) (0.2 g, 1.14 mmoles) was aminated according to the general procedure. Crystallization from water gave 95 mg (45%) of bright-yellow needles, mp $> 350^\circ$. The ir spectrum of this product was fully identical with that of 4-amino-3-nitro-1,8-naphthyridine obtained from 4-chloro-3-nitro-1,8-naphthyridine (7).

4-Amino-2-chloro-3-nitro-1,8-naphthyridine (**3e**).

2-Chloro-3-nitro-1,8-naphthyridine (**1e**) (0.2 g, 0.95 mmoles) was aminated according to the procedure described above. The crude reaction product was crystallized twice from a mixture of DMF and water (1:1), yielding 45 mg (22%) of light-yellow needles. The compound does not melt below 350° . Above 280° the color changes to black; ms: m/e (relative intensity, %) 226, 224 (M^+ ; 100,33) 196, 194 ($\text{M}^+\text{-NO}$; 12,4); ir (cm^{-1}): 3390, 3300, 3130 (NH stretching); 1655 (NH bending), 1535 (ν as NO_2), 1330 (ν s NO_2) ^1H -nmr (DMSO): δ 8.88 (H-5, dd), 7.61 (H-6, dd), 9.00

(H-7, dd), 8.36 (NH_2 , broad), $J_{5,6} = 8.0$, $J_{5,7} = 2.0$, $J_{6,7} = 4.5$ Hz.

Anal. Calcd. for $\text{C}_8\text{H}_5\text{ClN}_4\text{O}_2$: C, 42.78; H, 2.24. Found: C, 43.00; H, 2.52.

2,4-Diamino-3-nitro-1,8-naphthyridine (**3c**).

Method A.

2-Amino-3-nitro-1,8-naphthyridine (**1c**) (0.15 g, 0.59 mmoles) was aminated according to the general procedure. The product was crystallized from acetic acid and recrystallized from ethanol yielding 40 mg (25%) of yellow-orange plates mp $> 350^\circ$; ms: m/e (relative intensity, %) 205 (M^+ , 100), 188 ($\text{M}^+\text{-OH}$, 51); ir: (cm^{-1}) 3480, 3350, 3220 (NH stretching), 1630 (NH bending), 1550 (ν as NO_2), 1345 (ν s NO_2); ^1H -nmr (DMSO): δ 9.17 (NH_2 , broad), 8.66 and 8.61 (H-7, H-5, m), 7.76 (NH_2 , broad), 7.10 (H-6, dd), $J_{5,6} = 8.0$ Hz, $J_{6,7} = 4.5$ Hz.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{N}_5\text{O}_2$: C, 46.83; H, 3.44. Found: C, 46.34; H, 3.56.

Method B.

A solution of 30 mg of 4-amino-2-chloro-3-nitro-1,8-naphthyridine (**3e**) in 5 ml of ethanol, saturated at 0° with gaseous ammonia, was heated in a sealed tube at 140° for 5 hours. After cooling, a crystalline precipitate was filtered off and washed with ethanol. Yellow-orange plates 18 mg (56%) were obtained which showed to be identical (mp, ir spectrum) with the compound obtained according to method A.

4-Amino-2-ethoxy-3-nitro-1,8-naphthyridine (**3d**).

2-Ethoxy-3-nitro-1,8-naphthyridine (**1d**) (0.2 g, 0.95 mmole) was aminated according to the general procedure. The product was crystallized twice from a mixture of ethanol/water (1:1) to give 85 mg (40%) of pale-yellow needles, mp $230\text{--}231^\circ$; ms: m/e (relative intensity, %) 234 (M^+ , 7,5), 206 ($\text{M}^+\text{-C}_2\text{H}_4$, 100); ir (cm^{-1}) 3450, 3240 (NH stretching), 1615 (NH bending), 1525 (ν as NO_2), 1335 (ν s NO_2); ^1H -nmr (DMSO): δ 8.84 (H-7, multiplet), 8.78 (H-5, multiplet), 8.15 (NH_2 , broad), 7.41 (H-6, dd), 4.51 (CH_2 , q), 1.37 (CH_3 , t), $J_{5,6} = 8.0$ Hz, $J_{6,7} = 4.5$ Hz.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_3$: C, 51.28; H, 4.30; Found: C, 51.36; H, 4.42.

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REFERENCES AND NOTES

- (1) Part 17 on Naphthyridine Chemistry from this laboratory. For the previous paper in these series see M. Wozniak and H. C. van der Plas, *Heterocycles*, **19**, 363 (1982).
- (2) Part 33 on Formation of σ -adducts. For previous paper, see H. J. W. van den Haak, and H. C. van der Plas, *J. Org. Chem.*, **47**, 1673 (1982).
- (3) A. D. Counotte-Potman and H. C. van der Plas, *J. Heterocyclic Chem.*, **18**, 123 (1981).
- (4) H. Hara and H. C. van der Plas, *ibid.*, in press.
- (5) A. Nagel, H. C. van der Plas, A. van Veldhuizen, *Rec. Trav. Chim.*, **94**, 95 (1975); J. P. Geerts, A. Nagel and H. C. van der Plas, *Org. Magn. Reson.*, **8**, 607 (1976); H. C. van der Plas, *Lectures in Heterocyclic Chemistry*, Vol VI, S-1 ed., R. N. Castle and Th. Kappe, HeteroCorporation 1982.
- (6) The magnitude of this upfield shift is in accordance with values, reported for pyrimidines, triazines, etc. (see H. C. van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978).
- (7) M. Wozniak, *Pol. J. Chem.*, **53**, 1665 (1979).
- (8) W. Rosiewicz, M. Wozniak, *Synthesis*, 691 (1976).