Amination of 3,6-Dinitro-1,8-naphthyridines [1]

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Treatment of 2-amino-3,6-dinitro-1,8-naphthyridines with liquid ammonia/potassium permanganate gives 2,4-diamino-3,6-dinitro-1,8-naphthyridine. From 2-ethoxy-3,6-dinitro-1,8-naphthyridine a mixture of 4-amino- and 5-amino-3,6-dinitro-1,8-naphthyridine was obtained. 2-Chloro-3,6-dinitro-1,8-naphthyridine afforded a mixture of four compounds *i. e.* 2,4- and 2,5-diamino-3,6-dinitro-1,8-naphthyridine and 2-chloro-5-amino-3,6-dinitro-1,8-naphthyridine and 2-amino-3,6-dinitro-1,8-naphthyridine. A study on covalent amination has shown that 4-amino-2-ethoxy-3,6-dinitro-1,8-naphthyridine undergoes covalent amination at C-5, whereupon in this adduct amino-deethoxylation takes place. In a similar way, 2-chloro- and 2-ethoxy-5-amino-3,6-dinitro-1,8-naphthyridine give covalent amination at C-4.

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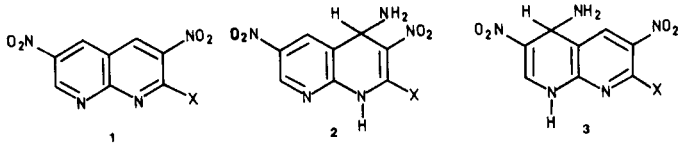
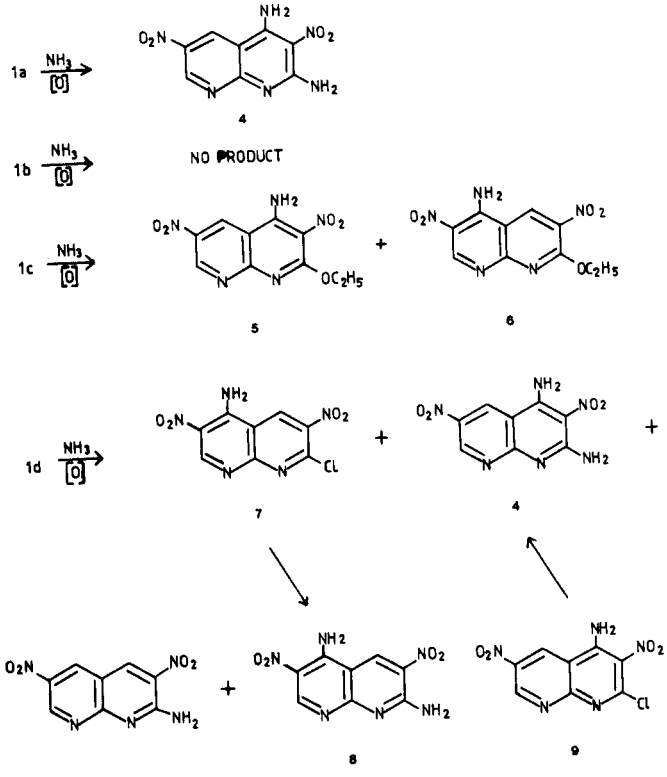
Recently we have shown [1] that the 2-X-3,6-dinitro-1,8-naphthyridines **1** easily undergo covalent amination, when dissolved in liquid ammonia. The site of addition is strongly determined by the character of the substituent at position 2. 2-Amino (**1a**)- and 2-hydroxy-3,6-dinitro-1,8-naphthyridine (**1b**) undergo addition at C-4 to yield 2,4-diamino-1,4-dihydro-3,6-dinitro-1,8-naphthyridine (**2a**) and 4-amino-1,4-dihydro-2-hydroxy-3,6-dinitro-1,8-naphthyridine (**2b**, or its anion) respectively. However, 2-ethoxy-3,6-dinitronaphthyridine (**1c**) gives with liquid ammonia a mixture of two σ-adducts *i. e.* the C-4 adduct **2c** and the C-5 adduct 5-amino-2-ethoxy-1,4-dihydro-3,6-dinitro-1,8-naphthyridine (**3c**). The same behavior is observed with 2-chloro-3,6-dinitronaphthyridine (**1d**), yielding **2d** and **3d**.



a) X = NH_2 b) X = OH c) X = OC_2H_5 d) X = Cl

In a series of recent papers we have reported that σ-adducts formed from highly-electron deficient systems, such as nitroquinolines [2], nitro-1-X-naphthyridines (X = 5, 6, 8) [3,4,5] and pteridines [6,7], and liquid ammonia easily undergo oxidation with potassium permanganate at low temperature, affording in reasonable-to-high yields the corresponding amino compounds [8]. Based on that experience we tried to convert the σ-adducts **2** and **3** into their corresponding 4-amino- and 5-amino compounds. Two procedures are practised: addition of a substrate to a solution of potassium permanganate in liquid ammonia (method A) or addition of the potassium permanganate to the solution of the substrate for liquid ammonia (method B). We found that method A is the most appropriate procedure to convert the amino adducts **2** and **3** into the corresponding 4- and 5-amino compounds respectively, although in general the yields in these reactions are not high. From **1a** we could prepare, using method A, the unknown 2,4-diamino-3,6-dinitro-1,8-naphthyridine (**4**, yield 11%). Attempts to aminate **1b** by potassium permanganate/liquid ammonia failed; nearly exclusively the starting material was isolated. This result is possibly due to the fact that **2b** is probably present in the liquid ammonia in its anionic form, deactivating the pyridine ring. Treatment of **1c** according to method A gave *two* amino products, *i. e.* 4-amino-(**5**) (<20%) and 5-amino-2-ethoxy-3,6-dinitro-1,8-naphthyridine (**6**) (15%). The formation of both products are in agreement with the previously found σ-adduct formation at C-4 and C-5.



Addition of the 2-chloro compound **1d** to a solution of potassium permanganate in liquid ammonia and working up of the reaction mixture gave a complex mixture of products. By tlc we could isolate 5-amino-3,6-dinitro-2-chloro-1,8-naphthyridine (**7**, 16%), 2-amino-3,6-dinitro-1,8-naphthyridine (**1a**, 5%), a non-separable mixture of 2,4-diamino-(**4**) and 2,5-diamino-3,6-dinitro-1,8-naphthyridine (**8**) (combined yield **4** + **8** is 30%). Both **4** and **8** have very similar R_f values in various eluent systems. They were identified by mass spectrometry and ^1H nmr spectroscopy. Based on the peak area of the resonance signals for H-7 in **4** and in **8** the ratio **4:8** could be established at 2:1. No trace of 4-amino-2-chloro-3,6-dinitro-1,8-naphthyridine (**9**) was detected in the reaction mixture. Probably the chloro atom in **9**, being formed from **2d** by oxidation, undergoes a fast replacement with the ammonia, as also accurs in the 2-chloro compound **7**, yielding **8**. That **7** and not **9** could be detected in the reaction mixture shows that the chloro atom in **7** is less reactive than in **9**; the electron-attracting character of the 6-nitro group in **7** is diminished, due to the presence of the adjacent electron donating amino group. This effect disfavours the stabilisation of the Meisenheimer adduct in the amino-dehalogenation at C-2.

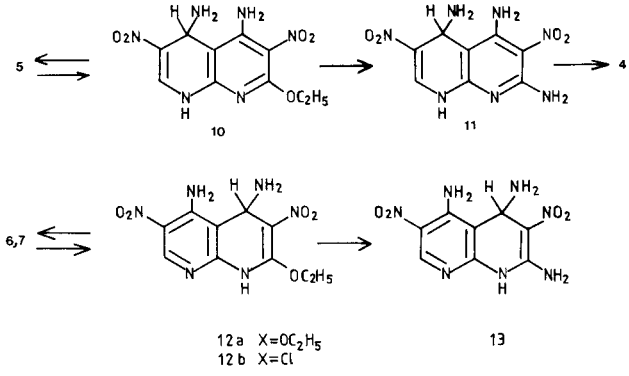
The structure of the amino compounds **4, 5, 6, 7** and **8** was established by spectroscopic data, in particular ^1H nmr spectra. Both 4-amino compounds **4** and **5** show the characteristic feature of two doublets with a *meta* coupling, assigned to H-5 and H-7. The 5-amino compounds **6, 7** and **8** exhibit two singlets, attributed to H-4 and H-7.

Formation of Covalent σ-Adducts from the 4-Amino (**5**) and 5-Amino Compounds **6, 7** and Liquid Ammonia.

When the 2,4-diamino compound **4** was added to liquid ammonia at −45° no σ-adduct was found to be formed. Also at room temperature no adduct formation was observed. However, when the 4-amino-2-ethoxy compound **5** was dissolved in liquid ammonia at −45° it was partly converted into its C-5 σ-adduct 4,5-diamino-5,8-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**10**); ratio **5:10** is about 1:1. The structure of **10** was assigned by the occurrence of a great upfield shift of H-5 ($\Delta\delta$ = 4.42 ppm), due to the change of hybridisation of the C-5 atom ($sp^2 \rightarrow sp^3$) accompanied by the change of the doublet structure of the H-5 signal (in DMSO) into a singlet (in ammonia). On standing at room temperature adduct **10** undergoes an amino-deethoxylation at C-2 leading to **11**. A subsequent release of ammonia from **11** yields the 2,4-diamino compound **4**, being the isolated product.

Since **4** as we have seen above does not give a σ-adduct it is evident that **11**, when formed, easily undergoes elimination of ammonia.

A solution of the 5-amino-2-ethoxy compound **6** in liquid ammonia clearly shows the presence of the C-4 σ-adduct 4,5-diamino-1,4-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**12a**), being in equilibrium with **6**. The upfield shift of H-4 in **12a** amounts to $\Delta\delta$ = 4.09 ppm. On standing at room temperature the C-4 adduct **12** slowly undergoes an amino-deethoxylation at C-2, yielding 2,4,5-triamino-1,4-dihydro-3,6-dinitro-1,8-naphthyridine (**13**); this adduct is stable in liquid ammonia. Adduct **13** is also formed when the 4-amino-2-chloro compound **7** is dissolved in liquid ammonia. Initially the C-4 adduct **12b** is formed, which on standing at room temperature converts into **13**.



Table

The ^1H NMR Data of the Ring Hydrogens of some Amino-3,6-dinitro-1,8-naphthyridines and their σ-Adducts with Ammonia

Compound	Solvent	H-4	H-5	H-7
4-Amino-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**5**)	DMSO	–	9.57	9.69
4,5-Diamino-5,8-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**10**)	NH_3	–	5.15	8.48
	$\Delta\delta$		4.42	1.21
5-Amino-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**6**)	DMSO	9.42	–	9.52
4,5-Diamino-1,4-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**12a**)	NH_3	5.33		8.93
	$\Delta\delta$	4.09		0.59
5-Amino-2-chloro-3,6-dinitro-1,8-naphthyridine (**7**)	DMSO	9.41	–	10.09
2-Chloro-4,5-diamino-1,4-dihydro-3,6-dinitro-1,8-naphthyridine (**12b**)	NH_3	5.43	–	8.95
	$\Delta\delta$	3.98	–	1.14

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler plate. The ^1H nmr spectra were recorded on a Varian EM-390 spectrometer equiped with a Varian EM-3940 variable temperature controller. Tetramethylsilane was used as internal standard, in liquid ammonia the solvent peak was used as the standard. The spectra were converted to the TMS scale by addition of 0.95 ppm. Mass spectra were carried out with an AEI MS 902 mass spectrometer. The ir spectra (in potassium bromide) were measured with a Jasco A-100 apparatus.

Amination of the 3,6-Dinitro-1,8-naphthyridine (**1a-1d**).

1. General Procedure.

To a solution of 0.6-0.8 g of potassium permanganate in 30-40 ml of liquid ammonia 0.2-0.5 g of the appropriate 3,6-dinitro-1,8-naphthyridine **1** was added. After the mixture was stirred for 20-25 minutes, ammonia

was evaporated off (*ca.* 1 hour) and to the residue obtained 40-50 ml of water was added. The mixture was then continuously extracted with chloroform for 40 hours. The crude residue remaining after evaporation of the chloroform was worked up in the manner given below.

2. Amination of 2-Amino-3,6-dinitro-1,8-naphthyridine (**1a**).

For the amination 0.2 g (0.85 mmole) of **1** was used. The residue obtained after evaporation of chloroform was dissolved in 1 ℓ of boiling methanol, filtered, concentrated to *ca.* 50 ml and cooled. A yellow precipitate was obtained, which was filtered off and again dissolved in boiling methanol. The solution was concentrated to *ca.* 30 ml and cooled. The precipitate was filtered off, washed with methanol and dried to give 22 mg (11%) of 2,4-diamino-3,6-dinitro-1,8-naphthyridine (**4**) as yellow plates, mp > 350°; ^{1}H nmr (dimethylsulphoxide): δ 9.63 (H-7, d), 9.43 (NH_2, broad s), 9.37 (H-5, d), 8.21 (NH_2, broad s), $J_{5,7}$ = 2.0 Hz; ir (cm^{-1}): 3490, 3370, 3340, 3250 (NH stretching), 1630 (NH bending).

Anal. Calcd. for $C_8H_6N_6O_4$: C, 38.40; H, 2.42; Found: C, 37.93; H, 2.83.

3. Amination of 2-Ethoxy-3,6-dinitro-1,8-naphthyridine (**1c**).

Compound **1c** (0.3 g, 1.14 mmoles) was aminated according to general procedure, given above. A yellow residue, remaining after extraction, was dissolved in a small amount of a mixture of chloroform and methanol (1:1) and applied on two plates (20 x 40 cm) covered with 2 mm layer of silicagel PF_{254}. The chromatograms were developed 3 times with a mixture of petroleum ether (40-60°)/ethyl acetate/methanol (5:1:0.5). Three main bands were obtained. They all were extracted with a mixture of methanol/chloroform (1:1). From the extract of the first band (the highest R_f), after crystallization from petroleum ether (100-140°), 28 mg (10%) of **1c** was recovered.

The residue remaining after evaporating of the solvent from the extract of the second band, was crystallized from benzene to give 62 mg (20%) of 4-amino-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**5**), light-yellow needles, mp 239-240°; ms: 279 (M^+); 251 (M^+ -C_2H_4); ^{1}H nmr (deuteriomethanol/deuteriochloroform): δ 9.69 (H-7, d); 9.57 (H-5, d); 4.72 (CH_2, q), 1.48 (CH_3, tr), $J_{5,7}$ = 2.72 Hz, J_{CH_2,CH_3} = 7.5 Hz; ir (cm^{-1}): 3450, 3330, 3210 (NH stretching); 1640 (NH bending).

Anal. Calcd. for $C_{10}H_9N_5O_5$: C, 43.01; H, 3.23; Found: C, 43.12; H, 3.22.

Material obtained during extraction of the third band was also crystallized from benzene to afford 45 mg (14%) of 5-amino-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**6**), light-yellow needles, mp 243-244°; ms: 279 (M^+), 251 (M^+ -C_2H_4); ^{1}H nmr (deuteriomethanol/deuteriochloroform): δ 9.52 (H-7, s), 9.42 (H-4, s), 4.75 (CH_2, q), 1.50 (CH_3, tr), J_{CH_2,CH_3} = 7.5 Hz; ir (cm^{-1}): 3410, 3290, 3150 (NH stretching), 1635 (NH bending).

Anal. Calcd. for $C_{10}H_9N_5O_5$: C, 43.01; H, 3.23. Found: C, 43.01; H, 3.07.

4. Amination of 2-Chloro-3,6-dinitro-1,8-naphthyridine (**1d**).

The reaction was carried out with 0.5 g (1.95 mmoles) of **1d**. After reacting and extraction, a yellow solid was obtained. The solid was dissolved in a mixture of methanol and acetone (1:1) and applied on three plates (20 x 40 cm) covered with 2 mm layer of silicagel PF_{254}. The chromatograms were developed three times with a mixture of chloroform/ethyl acetate/methanol (8:2:1). Four main bands were obtained showing uv absorbance. They all were extracted with a mixture methanol/chloroform (2:1). From the first band 5 mg of the starting material was isolated. Extraction of the second band gave a solid, which was extracted twice with 80 ml of boiling toluene. After concentrating to 10 ml and cooling 82 mg (16%) of 5-amino-2-chloro-3,6-dinitro-1,8-naphthyridine (**7**) was obtained, yellow plates, mp >330°; ms: 271, 269 (M^+, ratio 1:3); ^{1}H nmr (dimethylsulphoxide): δ 10.09 (H-7, s), 9.41 (H-4, s), 9.8-8.9 (NH_2, broad absorption); ir (cm^{-1}): 3425, 3330, 3200 (NH stretching), 1630 (NH bending).

Anal. Calcd. for $C_8H_4ClN_5O_4$: C, 35.64; H, 1.50; Found: C, 36.04; H, 1.86.

After extraction of the third band and evaporation of the solvent 25 mg (5%) of 2-amino-3,6-dinitro-1,8-naphthyridine (**1a**) was obtained. The compound was identified by comparing the physical properties (R_f, mp, ir and ^{1}H nmr) with a reference sample.

Extraction of the fourth band (the lowest R_f) gave a yellow solid; it was identified as a mixture of 2,4-diamino-3,6-dinitro-1,8-naphthyridine (**4**) and 2,5-diamino-3,6-dinitro-1,8-naphthyridine (**8**), yield 145 mg (30%). The mass spectrum of the solid showed a parent peak only at m/e = 250 (100%); ^{1}H nmr (dimethylsulphoxide): δ 9.79 (H-7 of **8**, s); 9.63 (H-7 of **4**, d), 9.37 (H-5 of **4**, d), 8.40 (H-4 of **8**, s), 9.6-9.0 and 8.5-8.0 (NH_2 groups, broad absorption). Doublets at δ 9.63 and 9.37 were identical with those of reference sample **4** (prepared from **1**, see section 2). From the area of the doublet at δ 9.63 and that of singlet at δ 9.79 the ratio of **4**:**8** was calculated about 2:3.

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