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

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The preparation of 3,6-dinitro-2-*R*-1,8-naphthyridines (**1**, R = OH, NH_2, OC_2H_5, Cl) is described and their addition patterns with liquid ammonia are studied. Compound **1** (R = OH, NH_2) gives with liquid ammonia at −45° as well as at room temperature formation of the covalent σ-adduct 4-amino-1,4-dihydro-3,6-dinitro-2-*R*-1,8-naphthyridine (**2**, R = OH, NH_2). Compound **1** (R = OC_2H_5) yields with ammonia at −45° two σ-adducts, *i.e.* the C-4 adduct (**2**, R = OC_2H_5) and the C-5 adduct 5-amino-5,8-dihydro-3,6-dinitro-2-*R*-1,8-naphthyridine (**3**, R = OC_2H_5). The ratio is about 50:50. This ratio depends on the temperature; at room temperature the C-5 adduct is more favoured. After staying overnight the ethoxy group has been exchanged for the amino group, yielding **2** (R = NH_2). With **1** (R = Cl) both adducts **2** (R = Cl) and **3** (R = Cl) were formed, the C-4 adduct **2** (R = Cl) is more favoured at room temperature. Prolonged treatment with liquid ammonia leads to an exchange of the chloro atom by the amino group, yielding **2** (R = NH_2).

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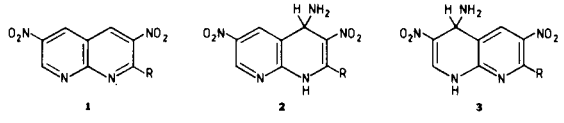
σ-Adduct formation between azines and liquid ammonia is a subject of ongoing interest in our laboratory [2]. Especially highly electron-deficient heteroazines, such as pteridines [3], triazines [4] and tetrazines [5] are good substrates for this addition reaction. With less activated azines such as quinoline [6,7], pyrimidine [8], pyrazine and pyridazine [8] the stronger nucleophilic potassium amide is required to achieve addition. In the naphthyridine field it was found that the 1,X-naphthyridines (X = 5,8) need potassium amide to convert them into their respective C-2 covalent addition products [9], but that when a nitro group is present in the naphthyridine ring liquid ammonia is able to perform addition. In 3-nitro-1,5- and 3-nitro-1,8-naphthyridine the addition takes place at C-4 [10,11]. As an extension of this work we became interested in the site(s) of addition when 3,6-dinitro-2-*R*-1,8-naphthyridines (**1**) react with liquid ammonia, especially in relation to the kinetic or thermodynamic control of the addition reaction. On dissolving 3,6-dinitro-1,8-naphthyridin-2(1*H*)-one (**1a**) and 2-amino-3,6-dinitro-1,8-naphthyridine (**1b**) in liquid ammonia at -45°, coloured solutions are obtained. The ^1H nmr spectra of both solutions feature a high field singlet at δ 5.15, together with two doublets with *meta* coupling in the range between δ 8.3 and 9.0 (see Table). These data prove that in the liquid ammonia the σ-adduct is present, formed by addition of the ammonia to C-4 in **1a,b**. The signal at δ 5.15 originates from the hydrogen at C-4 in the σ-adduct **2a,b**; the upfield shifts of this hydrogen (as calculated from the chemical shifts of H-4 in DMSO and in liquid ammonia) amounts to $\Delta\delta = 3.69$ (for **1a**) and $\Delta\delta = 4.32$ (for **1b**). These values are in agreement with those reported earlier on σ-adduct formation in related systems [10,11]. The ^1H nmr spectra did not change when the temperature increased from -45° to +20°, indicating that both adducts **2a** and **2b** are probably thermodynamically the most favoured one.



1 2 3

Scheme 1

When 2-ethoxy- (**1c**) and 2-chloro-3,6-dinitro-1,8-naphthyridine (**1d**) are dissolved in liquid ammonia, more complicated ^1H nmr spectra are obtained. The ^1H nmr spectrum of a solution of **1c** in liquid ammonia exhibits *two* high field singlets, one at δ 5.29 and one at δ 5.13, strongly indicating the presence of *two* σ-adducts. In addition two doublets (δ 8.53 and 9.10) with *meta* coupling (J = 3.0 Hz) are observed, proving that one of the σ-adducts is the C-4 adduct **2c**. Furthermore in the aromatic region a signal at δ 8.49 was found representing two hydrogens. These data can only be explained if either a C-5 adduct (in which H-4 and H-7 should have the same chemical shift) or a C-7 adduct (in which H-4 and H-5 would have the same chemical shift) is formed. In order to differentiate between both possibilities, we prepared the 7-deuterio derivative of **1c** and found that this compound when dissolved in liquid ammonia still showed both high field singlets (δ 5.29 and 5.13), evidencing that the C-5 adduct **3c** is the other σ-adduct, being present in the solution. The ratio **2c/3c** as established in liquid ammonia at -45° was 60:40. Increase of the temperature from -45° to room temperature shows a slow conversion of the C-4 adduct **2c** into the thermodynamically more stable C-5 adduct **3c**. After one hour at room temperature the ratio **2c/3c** is changed to 40:60. When the liquid ammonia solution is allowed to stand overnight, a new σ-adduct is formed *i.e.* σ-adduct **2b**; apparently in the adducts **2c** and **3c** amino-deethoxylation at position 2 has occurred. No indication for the presence of σ-adduct **3b** was obtained, probably due to the fact that **3b**, if formed, quickly converts into the more stable adduct **2b**.

Table

^{1}H NMR Data of the Ring Protons of some 3,6-Dinitro-1,8-naphthyridines and their σ-Adducts in Liquid Ammonia

Compound	Solvent	Chemical shift δ of ring hydrogens H-4	H-5 [a]	H-7 [a]
3,6-Dinitro-1,8-naphthyridin-2(1*H*)-one (**1a**)	DMSO	8.84	9.11	9.38
4-Amino-1,4-dihydro-3,6-dinitro-1,8-naphthyridin-2(1*H*)-one (**2a**)	NH_3	5.15	8.36	8.81
	Δδ	3.69	0.75	0.57
2-Amino-3,6-dinitro-1,8-naphthyridine (**1b**)	DMSO	9.47	9.37	9.58
2,4-Diamino-1,4-dihydro-3,6-dinitro-1,8-naphthyridine (**2b**)	NH_3	5.15	8.29	8.99
	Δδ	4.32	1.08	0.59
3,6-Dinitro-2-ethoxy-1,8-naphthyridine (**1c**)	$CDCl_3$	8.80	9.10	9.85
4-Amino-1,4-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**2c**)	NH_3	5.29	8.53	9.10
	Δδ	3.51	0.57	0.75
5-Amino-5,8-dihydro-3,6-dinitro-2-ethoxy-1,8-naphthyridine (**3c**)	NH_3	8.49	5.13	8.49
	Δδ	0.31	3.97	1.36
2-Chloro-3,6-dinitro-1,8-naphthyridine (**1d**)	$CDCl_3$	8.92	9.22	10.00
4-Amino-1,4-dihydro-2-chloro-3,6-dinitro-1,8-naphthyridine (**2d**)	NH_3	5.30	8.55	9.11
	Δδ	3.62	0.67	0.89
5-Amino-5,8-dihydro-2-chloro-3,6-dinitro-1,8-naphthyridine (**3d**)	NH_3	8.48 [b]	5.19	8.53 [b]
	Δδ	0.44	4.03	1.47

[a] $J_{5,7}$ = 2.8-3.0 Hz. [b] These signals may be interchanged.

Similarly, the ^{1}H nmr spectrum of a solution of **1d** in liquid ammonia also showed the presence of *two* σ-adducts, *i.e.* the C-4 adduct **2d** and the C-5 adduct **3d** (as proved by comparison of the spectrum with that of the 7-deuterio derivative). The ratio **2d/3d** = 50:50 (at -45°) but changes to about 85:15, when the solution is kept for 30 minutes at room temperature. Apparently the C-4 adduct **2d** is more stable than the C-5 adduct **3d**. On prolonged keeping of the solution at room temperature the solution contains only the C-4 adduct **2b**, showing that in the σ-adduct **2d** an amino-dechlorination at C-2 has easily taken place. It is interesting to note that for R = NH_2, or Cl the C-4 adduct is the more stable one but that for R = OC_2H_5 the C-5 adduct is somewhat more stable. It is too speculative to give an explanation for this difference in thermodynamic stability.

The preparation of **1a-1d** deserves the following comments. Introduction of nitro groups at both positions 3 and 6 in 1,8-naphthyridines was only achieved so far by nitration of 1,8-naphthyridines, in which an activating group is present in each of the pyridine rings. Examples are the formation of 3,6-dinitro-1,8-naphthyridine-2,7-(1*H*,8*H*)-dione [12,13] of 3,6-dinitro-1,8-naphthyridine-4,7-(1*H*,8*H*)-dione [14] and the corresponding amino compounds. We found however that nitration of 1,8-naphthyridin-2(1*H*)-one under drastic conditions (fuming nitric acid and sulphuric acid at 100° for 30 hours) lead to the introduction of two nitro groups at C-3 and C-6. 2) The conversion of the 2-chloro compound **1d** (prepared from **1a** with phosphorusoxychloride) into the 2-amino compound **1b** by heating with ethanolic ammonia at 100-120° in a sealed tube failed; use of liquid ammonia proved to be appropiate. Treatment of 2-ethoxy-3,6-dinitro-1,8-naphthyridine with methanolic ammonia at room temperature also gave **1b** in good yield. Many attempts were carried out to obtain the parent system 3,6-dinitro-1,8-naphthyridine from the 2-chloro compound **1d**: i) reaction with *p*-toluenesulphonylhydrazide and base treatment [15] gave a very complex mixture, ii) treatment with hydrazine and oxidation with cupric sulphate [16] gave black tarry material, iii) reaction with cupper in benzoic acid or butyric acid [17,18] gave hydrolysis into **1a**, iv) treatment of **1d** with sodium iodide in acetone [18,19] only yielded unreacted material.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded on a Varian EM-390 spectrometer with TMS as internal standard (δ = 0 ppm). In liquid ammonia the chemical shifts of the protons were measured against the ammonium signal (δ = 0.95 ppm) as standard. The mass spectra were determined using an AEI MS-902 mass spectrometer, equipped with a VG-ZAB console. Preparative thin layer chromatography was carried out on standard plates (20 × 40 cm) covered with a 2 mm layer of Merck Silica gel 60 PF 254. The ir spectra were measured on a Jasco A-100. The ^{1}H nmr measurements of the liquid ammonia solution were carried out as described before.

Synthesis of Starting Material.

3,6-Dinitro-1,8-naphthyridin-2(1*H*)-one (**1a**).

A solution of 8.5 g (5.8 mmoles) of 1,8-naphthyridin-2(1*H*)-one [15] in 85 ml of fuming nitric acid (d = 1.51) and 85 ml of fuming sulphuric acid containing 20% sulphur trioxide, was heated at 100° on a boiling water bath for 30 hours. The solution was cooled and poured on a 500 g of crushed ice and the mixture was neutralized to *p*H ~ 6 with ammonia. A yellow precipitate was obtained, which was filtered off, washed with water and recrystallized from *ca.* 5 ℓ of water to give 7.65 g (56%) of **1a** as

yellow needles, melting range 302-310° dec; ms: 236 (M^+, 100), 206 (M^+-NO, 3.5), 190 (M^+-NO_2, 5.1), 178 (M^+-NO-CO, 31.0); for ^1H nmr data see Table.

Anal. Calcd. for $C_8H_4N_4O_5$: C, 40.68; H. 1.71; N, 23.73. Found: C, 40.83; H, 1.63; N, 23.65.

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

A mixture of 6 g (25.4 mmoles) of **1a** and 200 ml of phosphorus oxychloride was heated at boiling point under reflux for 8 hours. Excess of phosphorus oxychloride was distilled off and the residue was poured on *ca.* 100 g of crushed ice. After neutralization of the mixture with ammonia, a precipitate was obtained, which was filtered off, washed with water, dried and extracted four times with 100 ml portions of boiling benzene. Benzene was distilled off and the residue remaining was recrystallized from toluene (charcoal) to give 4.25 g (66%) of **1d** as light-yellow needles, mp 204-206°; ms: 256, 254 (M^+, 33.1, 100), 210, 208 (M^+-NO_2, 29.9, 88.5); ^1H nmr: see Table.

Anal. Calcd. for $C_8H_3ClN_4O_4$: C, 37.71; H, 1.18; N, 22.00. Found: C, 37.92; H. 1.15; N, 21.88.

2-Amino-3,6-dinitro-1,8-naphthyridine (**1b**). Method A.

A mixture of 1 g (3.9 mmoles) of **1d** and 50 ml of liquid ammonia was stirred at -33° for 3 hours. Ammonia was evaporated and a red solid was obtained which in a period of 5-10 minutes changed the color from red to yellow. The yellow solid was extracted two times with 25 ml of boiling benzene. From benzene solution 0.18 g of starting material was recovered. The residue, which did not dissolve in benzene was crystallized from nitromethane to give 0.55 g (60%) of **1b** as yellow needles, mp >350°; ms: 235 (M^+, 100), 189 (M^+-NO_2, 16); ^1H nmr: see Table.

Anal. Calcd. for $C_8H_5N_5O_4$: C, 40.85; H, 2.13; N, 29.79. Found: C, 40.73; H, 2.14; N, 30.27.

Method B.

One hundred mg (0.38 mmole) of 2-ethoxy-3,6-dinitro-1,8-naphthyridine (**1c**) was dissolved in 5 ml of methanol, saturated at 0° with gaseous ammonia. The red solution was kept over 15 hours at room temperature. The solution was concentrated *in vacuo* until the volume was 5 ml. Yellow crystals were obtained, which were filtered off and washed with methanol. The compound was identical (mp, ir and ^1H nmr with 2-amino-3,6-dinitro-1,8-naphthyridine obtained according to method A, yield 80 mg (90%).

3,6-Dinitro-2-ethoxy-1,8-naphthyridine (**1c**).

To a solution of 0.54 g of sodium in 200 ml of absolute ethanol 2 g of **1d** (7.8 mmoles) was added and the mixture was stirred at room temperature for 2 hours. The red solution obtained was neutralized with 10% of aqueous acetic acid and evaporated off to dryness *in vacuo*. To the residue 30 ml of water was added, the mixture was stirred and the brown solid was filtered off, washed with water and dried. The solid was boiled with 100 ml of benzene (charcoal), the solution was filtered and the solvent was stripped off. The residue obtained was recrystallized from petroleum ether (100-140°) (charcoal) to give 1.35 g (65%) of 2-ethoxy-3,6-dinitro-1,8-naphthyridine as light-yellow needles, mp 160-161°; ms: 264 (M^+, 5.0), 236 (M^+-C_2H_4, 100); ^1H nmr data: see Table.

Anal. Calcd. for $C_{10}H_8N_4O_5$: C, 45.45; H, 3.03; N, 21.20. Found: C, 45.55; H, 3.07; N, 21.17.

7-Deuterio-1,8-naphthyridin-2(1*H*)-one.

A mixture of 1.7 g of 1,8-naphthyridin-2(1*H*)-one [15] and 10 ml of deuterium oxide was heated in a sealed tube at 230° for 35 hours. After cooling a light-yellow precipitate was obtained, yield 1.5 g; ^1H nmr analysis (in perdeuteriomethanol/deuteriochloroform) showed that the contents of deuterium at position 7 was >95%.

2-Chloro- and 2-ethoxy-7-deuterio-3,6-dinitro-1,8-naphthyridines.

These compounds were obtained according to procedures given for the undeuterated compounds starting from 7-deuterio-1,8-naphthyridin-2-(1*H*)-one (see above). The ^1H nmr spectroscopy showed that the amount of deuterium at position 7 in the chloro and ethoxy compound was about 90%.

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