Amination of 2,6- and 2,7-Naphthyridine (1). An NMR Study on σ-Adducts of Heterocyclic Systems with Amide Ions (2)

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A facile synthesis of 2,6-naphthyridine is described. Both 2,6- and 2,7-naphthyridine undergo with potassium amide under kinetically and thermodynamically controlled conditions σ-adduct formation at position 1. Chichibabin amination of 2,6-naphthyridine yields 1-amino-2,6-naphthyridine in 54% yield.

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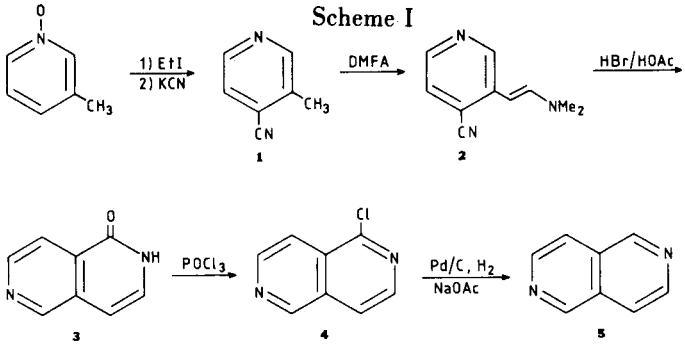
Introduction.

In a recent publication (3) we reported on the occurrence of σ-adduct formation between potassium amide and the four parent 1,X-naphthyridines under kinetically and thermodynamically controlled conditions. The relative stabilities of these σ-adducts proved to be a valuable tool for predicting the site of amination of the 1,X-naphthyridines. We now wish to report on adduct formation between potassium amide and 2,6- and 2,7-naphthyridine. Thus far, the chemistry of 2,6- and 2,7-naphthyridine is rather unexplored (4), partly due to the inaccessibility of these compounds. Paudler and Cornrich (5) published a convenient synthesis of 2,7-naphthyridine, but a facile method to synthesize the 2,6-isomer was not developed. We found however, that the procedure of Baldwin and others (6) for the synthesis of 2,7-naphthyridin-1-(2*H*)one from 3-cyano-4-pi coline could easily be adapted to synthesize 2,6-naphthyridine-1-(2*H*)one from 4-cyanopicoline (**1**). The latter compound was reported to be obtained in a 15% yield as a by-product in the reaction of 3-picoline *N*-oxide with methyl iodide and potassium cyanide at room temperature (7). However we observed that when the reaction was carried out at 55° and ethyl iodide was used instead of methyl iodide, compound **1** was obtained in a 60% yield. Reaction of **1** with dimethylformamide acetal (DMFA) into 1-*N*,*N*-dimethylamino-2-(4-cyano-3-pyridyl)ethene (**2**) and treatment of this product with hydrogen bromide in acetic acid gave 2,6-naphthyridine-1-(2*H*)one (**3**). This compound was converted with phosphorus oxychloride into 1-chloro-2,6-naphthyridine (**4**). Reduction with hydrogen and palladium-on-carbon yielded the parent 2,6-naphthyridine (**5**) (scheme 1). Since all these steps took place in reasonable yields (50-70%) 2,6-naphthyridine is now readily available.

Scheme I

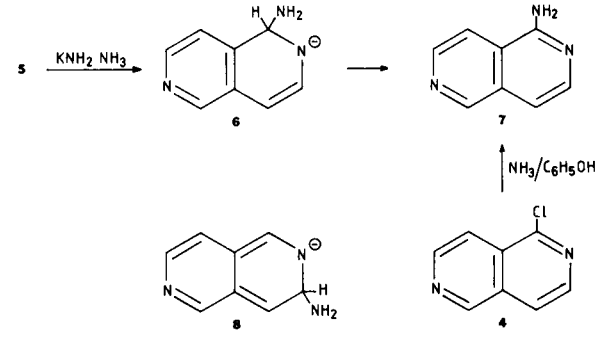


Chichibabin Amination of 2,6- and 2,7-Naphthyridine.

a) 2,6-Naphthyridine.

2,6-Naphthyridine (**5**) is reported (8) to have the lowest electron density on position 1. Based on earlier conclusions we may expect the kinetic attack of the amide anion to occur on this site, giving the 1-amino-1,2-dihydro-2,6-naphthyridimide (**6**) (scheme 2).

Scheme 2



When the nmr spectrum of a solution of **5** in liquid ammonia containing potassium amide was measured, it showed a singlet at 5.03 ppm (H-1) and an AB quartet at 4.70 and 7.09 ppm (H-4 and H-3 respectively). The upfield shifts of H-1 (4.24 ppm) and H-4 (2.99 ppm) are characteristic for σ-adduct formation at position 1 in isoquinoline-like systems (3,9) (Table I).

^{13}C-nmr spectroscopy confirms this observation (Table II).

The spectrum of **6** remains essentially unchanged when

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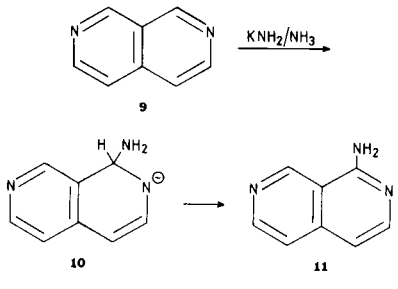
the temperature was raised to +20° so **6** is also the thermodynamically most stable σ-adduct. The great stability of **6** is due to the azaallylic stabilization, and in agreement with conclusions previously drawn with 1,X-naphthyridines (3). The great upfield shift of C-4 ($\Delta\delta$ = 40.0 ppm), indicating the presence of considerable negative charge on C-4, supports this. Adduct formation on position 3 yielding 3-amino-2,3-dihydro-2,6-naphthyridimide (**8**) is less likely, since it disturbs the aromaticity of the other ring; thus **8** is thermodynamically less stable then **6**. Amination of **5** with potassium amide at room temperature (a procedure previously employed for 1,X-naphthyridines (8)) yielded 54% of 1-amino-2,6-naphthyridine (**7**). It was identical to the product obtained when treating **4** with phenol and ammonia. Oxidation of anionic σ-adducts with potassium permanganate is a very useful method for the preparation of amino compounds (3,10). When this method was applied for the oxidation of **6** only 18% of **7** was yielded.

b) 2,7-Naphthyridine.

Paudler and Cornrich (5) reported the formation of 1-amino-2,7-naphthyridine (11) on aminatin of 2,7-naphthyridine (**9**) with potassium amide at room temperature. The low electron density of position 1 predicts the formation of the 1-amino-1,2-dihydro-2,7-naphthyridinide (**10**) on dissolving **9** in liquid ammonia containing potassium amide (scheme 3).

Scheme 3



Indeed, nmr spectroscopy of such a solution shows the formation of anion **10**, as indicated by the upfield shift of 4.24 ppm for H-1 and of 3.10 ppm for H-4 (table I). The large upfield shifts of H-4 and C-4 (table II) show that a considerable amount of negative charge must be present on position 4 of **10**. Due to this azaallylic stabilization, anion **10** is expected to be also the thermodynamically most favourable σ-adduct from **9** with potassium amide. This was substantiated by the observation that on raising the temperature of the solution containing **10** from −40° to +20° the nmr spectrum did not alter.

Oxidation of **10** with potassium permanganate at −40° gave **11** in a low yield (8%).

EXPERIMENTAL

All 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. For ^{1}H-nmr spectra in liquid ammonia, ammonia (δ = 0.95 ppm) was used as internal standard. ^{13}C spectra were recorded with a Varian Fourier transform unit. The pulse separation was chosen as 0-1.25 seconds, the spectral width was 5000 Hz (1.25 Hz/point); trimethylamine was used as internal standard (δ = 47.5 ppm).

Synthesis.

2,7-Naphthyridine.

This compound was prepared as described in the literature (5).

4-Cyano-3-picoline.

3-Picoline *N*-oxide (30 g, 0.28 mole) was stirred during 16 hours with 50 ml of ethyl iodide (0.62 mole). Then 300 ml of water were added, and the water layer was separated and washed with ether. The water layer was heated to 50° and a solution of 35 g of potassium cyanide in 90 ml of water was added during 1 hour. After stirring for 1 hour at 50° the mixture was allowed to cool and after that extracted with ether. The ether layer was dried over magnesium sulfate and the ether was evaporated *in vacuo*. Destillation of the residue (90-100°/14 mm) gave 19.4 g (yield 60%) of a white solid which was not further purified but found sufficiently pure for use in the next step.

1-*N*,*N*-dimethylamino-2-(4-cyano-3-pyridyl)ethene (**2**).

4-Cyano-3-picoline (19.4 g 0.16 mole) was heated under nitrogen with 200 ml of dimethylformamide and 30 ml (0.25 mole) of dimethylformamide acetal (DMFA) during 5 days. Each day an additional 5 ml of DMFA was added. The solution was then evaporated to dryness and the residue was crystallized from petroleum ether (bp 60-80°) giving 13.1 g (yield 46%) of **2**. An analytical sample was prepared by repeated crystallization from cyclohexane, mp 85-86.5°; ^{1}H-nmr (deuteriochloroform): δ 2.93 pm (6H, s), 5.24 ppm (1H, d, J = 13.5 Hz), 7.12 ppm (1H, d, J = 13.5 Hz), 7.18 ppm (1H, d, J = 5 Hz), 8.06 ppm (1H, d, J = 5 Hz), 8.63 ppm (1H, s).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40. Found: C, 69.63; H, 6.64.

2,6-Naphthyridin-1-(2*H*)one (**3**).

Compound **2** (13 g, 75 mmoles) was dissolved in 125 ml of glacial acetic acid and heated to 40°. Under mechanical stirring 250 ml of 30%

Table I

^{1}H-NMR Data of 2,6- and 2,7-Naphthyridine and Their 1:1 σ-Adducts with Amide Anions

Compound	Solvent	H-1	H-3	H-4	H-5	H-6	H-7	H-8
5	$CDCl_3$	9.27	8.65	7.69	9.27	-	8.65	7.69
6	NH_2^-/NH_3	5.03	7.09	4.70	7.78	-	7.64	6.84
	$\Delta\delta$	4.24	1.56	2.99	1.49	-	1.01	0.85
9	$CDCl_3$	9.37	8.68	7.59	7.59	8.68	-	9.37
10	NH_2^-/NH_3	5.03	7.16	4.59	6.28	7.63	-	7.67
	$\Delta\delta$	4.34	1.52	3.00	1.31	1.05	-	1.70

Table II

^{13}C-NMR Spectra of 2,6- and 2,7-Naphthyridine and Their 1:1 σ-Adducts with Amide Anions

Compound	Solvent	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
5	$CDCl_3$	152.0	144.9	119.3	152.0	-	144.9	119.3	130.3	130.3
6	NH_2^-/NH_3	68.3	152.0	79.3	140.0	-	137.5	121.3	128.3	134.3
	Δδ	83.7	−7.1	40.0	12.0	-	7.4	−2.0	2.0	−4.0
9	$CDCl_3$	152.9	147.1	119.1	119.1	147.1	-	152.9	123.9	138.5
10	NH_2^-/NH_3	66.7	153.8	82.5	111.1	145.4	-	147.0	118.1	142.3
	Δδ	86.2	−6.7	36.6	8.0	1.7	-	5.9	5.8	−3.8

hydrogen bromide in acetic acid were added dropwise in a 1½ hour period. The mixture was stirred at 55° for an additional 2 hours and then evaporated to dryness. The residue was treated with ice, neutralized with sodium carbonate and continuously extracted with chloroform (A previous extraction with ether did not yield any bromonaphthyridines). Evaporation of the chloroform and sublimation of the residue at 180°/0.1 mm gave 7.2 g (66%) of **3**, mp 248-251° (from methanol, followed by recrystallization from water). ^{1}H-nmr (DMSO): δ 6.64 ppm (1H, d, J = 7.0 Hz), 7.30 ppm (1H, d, J = 7.0 Hz), 7.95 ppm (1H, d, J = 5.3 Hz), 8.59 ppm (1H, d, J = 5.3 Hz), 9.02 ppm (1H, s).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14. Found: C, 65.91; H, 4.29.

1-Chloro-2,6-naphthyridine (**4**).

One g (6.1 mmoles) of **3** was refluxed with 40 ml of phosphorous oxychloride during 1½ hour. The excess phosphorus oxychloride was evaporated *in vacuo*, the residue was treated with ice and the mixture was carefully neutralized with sodium bicarbonate. Extraction of the mixture with ether, drying of the ether layer with magnesium sulfate and evaporation of the solvent gave 0.97 g of 1-chloro-2,6-naphthyridine, which is sufficiently pure for use in the next step (yield 77%), mp 92-93° (from petroleum ether bp 60-80°); ^{1}H-nmr (deuteriochloroform): δ 7.68 ppm (1H, d, J = 6.0 Hz), 7.97 ppm (1H, d, J = 6.0 Hz), 8.40 ppm (1H, d, J = 6.0 Hz), 8.75 ppm (1H, d, J = 6.0 Hz), 9.28 ppm (1H, s).

Anal. Calcd. for $C_8H_5ClN_2$: C, 58.37; H, 3.06. Found: C, 58.65; H, 3.21.

2,6-Naphthyridine (**5**).

Compound **4** (1.2 g, 9.2 mmoles) was hydrogenated at 40 psi in a Parr hydrogenation apparatus with 0.8 g of 13% palladium on carbon, 6 g of anhydrous sodium acetate and 200 ml of methanol. After uptake of the theoretical amount of hydrogen (requiring about 10 minutes) the mixture was filtered, the methanol was evaporated *in vacuo* and 50 ml of water and 10 ml of concentrated ammonia solution were added to the residue. This mixture was extracted with chloroform, the chloroform was dried over magnesium sulfate and evaporated. The residue was purified by chromatography on a silicon dioxide column using chloroform as eluent; 0.67 g of **5** was obtained (yield 71%), mp 117-119° (lit (11) 118-119°).

1-Amino-2,6-naphthyridine (**7**).

A solution of 0.97 g (5.9 mmoles) of **4** in 6 g of phenol was heated at 175° and ammonia was bubbled through during 6 hours. One hundred ml of sulfuric acid (1*N*) was added to the cooled mixture, which was then steam destilled until no more phenol passed over. The residue was basified with an aqueous solution of sodium hydroxide (10%) and this solution was extracted continuously with chloroform. The solid residue which was obtained after evaporation of the chloroform *in vacuo* was sublimed at 180°/0.05 mm, giving 0.50 g of 1-amino-2,6-naphthyridine (**7**) (yield 58%), mp 243-244° (from water); ^{1}H-nmr (deuteriochloroform/deuteriomethanol): δ 7.01 ppm (1H, d, J = 5.7 Hz), 7.84 ppm (1H, d, J = 5.7 Hz), 7.88 ppm (1H, d, J = 5.7 Hz), 8.43 ppm (1H, d, J = 5.7 Hz), 8.96 ppm (1H, s).

Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86. Found: C, 66.40; H, 4.67.

Amination of **5**.

This amination was carried out at room temperature as described in the literature for the amination of **9** (6). The solid residue obtained on evaporation of the organic layer was suspended in concentrated ammonia solution. The mixture was continuously extracted with chloroform. After evaporation of the chloroform the residue was dissolved in the minimum volume of methanol. This solution was placed on four plates (20 × 20 cm) covered with 0.5 mm of silicon dioxide. The chromatograms were developed with a chloroform-ethanol mixture (10:1). No starting material was found. Extraction of the band, containing the product with methanol gave **7** (yield 54%).

Oxidation of σ-Adducts with Potassium Permanganate.

The procedure has been described previously (1). The crude product obtained on continuous extraction of the reaction mixture was purified by thick-layer chromatography as described above, yield of **7** from **6**, 18%; yield of **11** from **10**, 8%.

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