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Regioselective Heteroannelation in 4-Cyanomethyl-3,5-pyridinedicarbonitriles. Synthesis of 6-Alkoxy-3-dialkylamino-1,8-diamino-2,7-naphthyridine-4-carbonitriles

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Summary. The title naphthyridines were found to be the sole products obtained after treatment of 2-amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles with alkoxides. The starting pyridine derivatives were prepared by amination of the readily available 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile in quantitative yields.

Keywords. Alkoxides; Heterocycles; 2,7-Naphthyridines; Nucleophilic substitutions; Pyridinedicarbonitriles.

Introduction

An increasing interest in 2,7-naphthyridine derivatives in recent years has been caused by isolations of several alkaloids of this structure from the *Strychnos* plant family [1, 2]. There are jasmidine [3], jasminine [4], acanthicifoline [5], scaevodimerines [6], and neozeylanicine [2, 7] among them. In spite of the fact, that the structures of these natural compounds are not very complex, the total synthesis has been reported only for the last one [8]. Hence, synthetic approaches to 2,7-naphthyridines are not yet developed enough. The known methods of their preparation can be divided into two subgroups. The first one utilizes various derivatives of 4-piperidinone as starting materials and, therefore, results in tetrahydro-2,7-naphthyridines [9–12]. In the second one the key compounds are derivatives of nicotinic acid suitably substituted at position 4 [13–17]. In addition, a few original and highly specific approaches to 2,7-naphthyridines have been also reported [18, 19].

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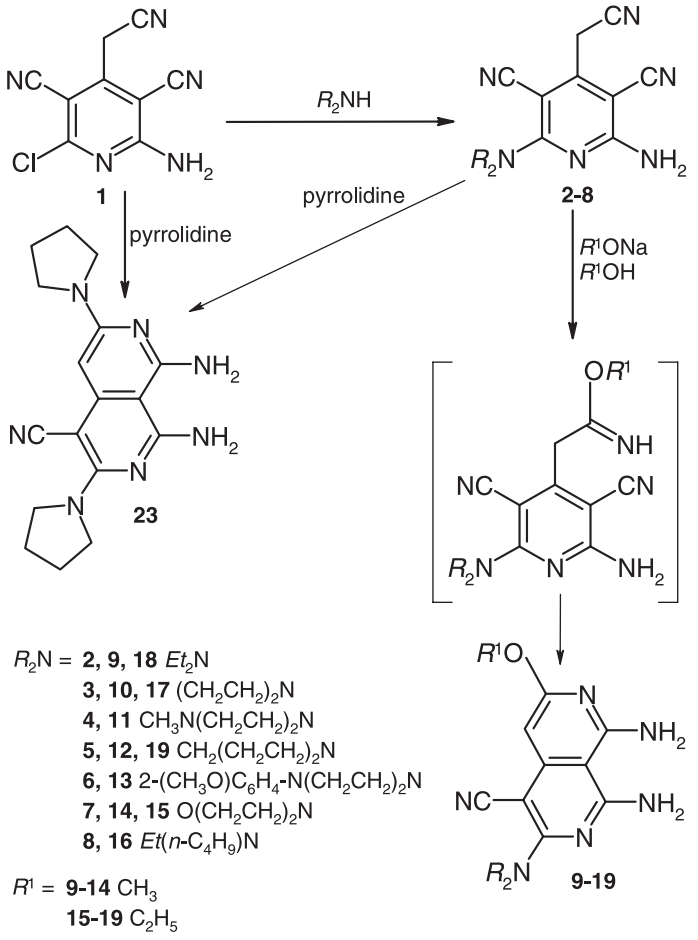
Biological investigations of 2,7-naphthyridines revealed a number of antiarrhytmic, analgesic, antiinflammatory, antimicrobial, and anxiolytic synthetic drugs [10, 11, 20–23]. Most of them possess an ester, carboxamide, or carbonitrile group at position 4 of the naphthyridine moiety. This is not surprising because the alkaloids mentioned above are derivatives of 2,7-naphthyridine-4-carboxylic acid. Nevertheless, there is a set of biologically active 2,7-naphthyridines with structures unlike those of the natural products. Mostly, they bear a substituted amino group, such as dimethylamino or piperazino, at position 1(8) of the naphthyridine nucleus [10, 20, 22]. Thus, the presence of the carboxyl derived substituent at position 4 as well as the amino group can be formulated as an attribute of sufficient activity. However, only a single synthesis of a partially hydrogenated 2,7-naphthyridine possessing both of these groups at the appropriate positions has been described [10]. Moreover, 2,7-naphthyridines substituted with two amino groups are very rare [16, 23] while derivatives of triamino-2,7-naphthyridine are hitherto unknown to our knowledge. Noteworthy, to date the 2,7-naphthyridine system remained the less investigated one among all naphthyridines (for reviews see [24–26]).

Continuing our research on the utility of hetarylacetonitriles in heterocyclic synthesis [27–34] we have turned our attention to the readily available 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile **1** [35]. Herein a regioselective heteroannelation observed for its derivatives is reported.

Results and Discussion

A two-step preparation of the pyridine **1** (Scheme 1) from malonodinitrile has been reported in the sixties [35]. However, since that time nothing has been published on its chemistry. Compound **1** consists of two unsymmetrical 1,5-dinitrile moieties. Thus, it would be interesting to investigate their transformation into a pyridine ring *via* the well known reaction with alkoxide, which should result in the formation of a naphthyridine. But first of all, to remove base sensitive chlorine and to introduce the desirable pharmacophore, the dialkylamino group, compound **1** was converted into the 2-amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles **2**–**8**. The substitution reaction proceeded smoothly in dry dioxane with two equivalents of amine and gave compounds **2**–**8** in approximately quantitative yields. Only in the case of the pyrrolidine derivative **3** some difficulties arose, but they were solved using one equivalent of pyrrolidine in the presence of triethylamine.

Prolonged refluxing of the pyridinedicarbonitriles **2**–**8** with an excess of sodium methoxide or ethoxide in the corresponding alcohol resulted in formation of 2,7-naphthyridine derivatives to which the structures **9**–**19** (Scheme 1) or the isomeric ones like **20**–**22** (Fig. 1) could be assigned. It should be emphasized that the reaction gave exclusively one product without detectable amounts of isomers. Conversion of the pyridines **2**–**8** into naphthyridines was confirmed by the ^{1}H NMR data. Thus, the characteristic two-proton singlet of the methylene group of **2**–**8** at 3.9–4.0 ppm disappeared from the spectra of the naphthyridines, whereas a one-proton singlet of 5-H at 5.9–6.0 ppm together with the signals from methoxy or ethoxy residues for derivatives **9**–**14** and **15**–**19** were present therein. Two broadened singlets at 6.2–6.5 and 6.6–7.0 ppm both integrating for two protons were assigned to the amino groups. Final assignment of the structures **9**–**19** for the prepared naphthyridines was made on the basis of a N*O*ESY experiment carried out for **13**. First, it revealed a correlation between the methoxy group signal at 3.81 ppm and the singlet of 5-H of the naphthyridine ring at 5.97 ppm, thus



Scheme 1

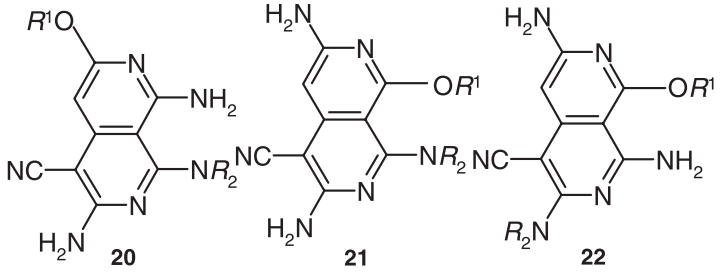


Fig. 1. Structures of compounds **20**–**22**, isomers to **9**–**19**

excluding structures of type **21** and **22**. Second, the correlation between amino groups signals at 7.00 and 6.44 ppm was observed confirming the structure **13**, while the protons of the piperazine moiety did not give a correlation with the amino group required for the structure of type **20**. Moreover, the ^{13}C NMR spectrum of compound **13** was in good agreement with the assigned structure.

It should be noted, that a similar approach has been applied for the synthesis of 1,7- and 2,6-naphthyridines *via* alkoxide induced cyclization of 2- and 4-cyano-3-pyridineacetonitriles [36]. In that case alkoxide also attacked aliphatic, but not aromatic, nitrile. However, there was no alternative direction for further heterocyclization of the intermediate imidate. Noteworthy, the corresponding benzene analogue 2-cyano-benzeneacetonitrile has yielded dimeric products under same conditions [37].

The difficulties in preparing **3** should be detailed here. When the reaction was carried out with two equivalents of pyrrolidine impure **3** was isolated. The impurities obviously were derived from a partial heterocyclization of **3** induced by the highly nucleophilic pyrrolidine. Indeed, treatment of **3**, obtained using stochiometric amounts of chloropyridine **1**, pyrrolidine, and triethylamine, with pyrrolidine yielded **23** (Scheme 1). The same product was also prepared directly from the pyridine **1** using a three-fold excess of pyrrolidine and prolonged reaction time. The structure of **23** was confirmed by the similarity of its spectral data with those of compounds **9**–**19**. Attempts to transform derivatives **2**–**8** or **1** into naphthyridines like **23** with other amines failed.

To resume, pyridines **2**–**8** were found to undergo a regioselective heteroannelation under treatment with alkoxide leading to the naphthyridines **9**–**19**. Therefore, the initial attack of the alkoxide occurs at the aliphatic nitrile, probably because it is not hindered sterically unlike other ones. Further ring closure involving the nitrile group at position 3 without participation of 5-CN is less understandable. It can be explained by either repulsive interaction of dialkylamino and amino groups in a structure like **20** making its formation unfavorable, or by facilitation of cyclization with 3-CN due to its activation by an intramolecular hydrogen bond with the neighboring amino group. Of course, the influence of both factors can take place.

Experimental

2-Amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (**1**) was prepared as reported [35]. Amines were commercially available and were used without additional purification. Dioxane was dried with sodium. Methanol and ethanol were dried with Mg and Ca, respectively. All mps were determined in open capillary tubes in *Thiele*'s apparatus and are uncorrected. IR spectra were obtained on a Pye Unicam SP 3-300 spectrometer for KBr tablets. ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) and Mercury 400 (400 MHz) spectrometers in *DMSO-d_6* solutions with Me_4Si as internal standard. ^{13}C and 2D NMR experiments (HSQC, HMBC) were performed on a Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer to assign signals. The purity of all compounds was checked by ^{1}H NMR and for all compounds satisfactory elemental analyses were obtained.

2-Amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles (**2**, **4**–**8**)

General Procedure

The corresponding amine (10 mmol) was added to 1.1 g of the pyridine **1** (5 mmol) in 10 cm^3 dioxane. The mixture was boiled to dissolve starting materials and then heated on a water-bath for 1 h. After cooling the precipitate formed was filtered, thoroughly washed with water to remove amine hydrochloride, and dried to give **2** and **4**–**8**. In most cases obtained materials were analytically pure. If necessary, additional purification could be achieved by recrystallization from dioxane.

2-Amino-4-(cyanomethyl)-6-(diethylamino)-3,5-pyridinedicarbonitrile (**2**, $C_{13}H_{14}N_6$)

Yield 97% (1.23 g), mp 167°C; ^{1}H NMR: $\delta = 1.19$ (t, $2CH_3$), 3.64 (q, $2NCH_2$), 4.00 (s, CH_2CN), 7.49 (s, NH_2) ppm; ^{13}C NMR: $\delta = 12.38$ (CH_3), 19.50 ($\underline{C}H_2CN$), 45.67 (NCH_2), 83.16 (3-C), 84.99

(5-C), 105.35 (3 or 5-CN), 105.46 (3 or 5-CN), 119.54 ($CH_2\underline{C}N$), 158.67 (4-C), 160.61 (6-C), 168.42 (2-C) ppm.

2-Amino-4-(cyanomethyl)-6-(4-methyl-1-piperazinyl)-3,5-pyridinedicarbonitrile (**4**, $C_{14}H_{15}N_7$)

Yield 94% (1.32 g), mp 134°C; ^{1}H NMR: $\delta = 2.24$ (s, CH_3), 2.44 (t, $2NCH_2$), 3.74 (t, $2NCH_2$), 3.97 (s, CH_2CN), 7.51 (s, NH_2) ppm; ^{13}C NMR: $\delta = 19.10$ ($\underline{C}H_2CN$), 46.85 (NCH_3), 47.82 (NCH_2), 54.82 (NCH_2), 83.84 (5-C), 84.46 (3-C), 105.67 (3 or 5-CN), 105.87 (3 or 5-CN), 119.39 ($CH_2\underline{C}N$), 156.27 (4-C), 160.23 (6-C), 168.67 (2-C) ppm.

2-Amino-4-(cyanomethyl)-6-(1-piperidinyl)-3,5-pyridinedicarbonitrile (**5**, $C_{14}H_{14}N_6$)

Yield 99% (1.32 g), mp 144°C; ^{1}H NMR: $\delta = 1.62$ (m, $3CH_2$), 3.73 (t, $2NCH_2$), 4.02 (s, CH_2CN), 7.59 (s, NH_2) ppm.

2-Amino-4-(cyanomethyl)-6-[4-(2-methoxyphenyl)-1-piperazinyl]-3,5-pyridinedicarbonitrile (**6**, $C_{20}H_{19}N_7O$)

Yield 95% (1.77 g), mp 172°C; ^{1}H NMR: $\delta = 3.06$ (t, $2NCH_2$), 3.81 (s, OCH_3), 3.91 (t, $2NCH_2$), 4.02 (s, CH_2CN), 6.55–6.97 (m, C_6H_4), 7.26 (s, NH_2) ppm.

2-Amino-4-(cyanomethyl)-6-(4-morpholinyl)-3,5-pyridinedicarbonitrile (**7**, $C_{13}H_{12}N_6O$)

Yield 98% (1.31 g), mp 201°C; ^{1}H NMR: $\delta = 3.70$ (t, $2NCH_2$), 3.78 (t, $2OCH_2$), 3.94 (s, CH_2CN), 7.33 (s, NH_2) ppm.

2-Amino-6-(butylethylamino)-4-(cyanomethyl)-3,5-pyridinedicarbonitrile (**8**, $C_{15}H_{18}N_6$)

Yield 96% (1.36 g), mp 153°C; ^{1}H NMR: $\delta = 0.94$ (t, CH_3), 1.20 (t, CH_3), 1.35 (m, CH_2), 1.61 (m, CH_2), 3.57 (t, NCH_2), 3.68 (q, NCH_2), 3.94 (s, CH_2CN), 7.33 (s, NH_2) ppm.

2-Amino-4-(cyanomethyl)-6-(1-pyrrolidinyl)-3,5-pyridinedicarbonitrile (**3**, $C_{13}H_{12}N_6$)

Pyrrolidine (0.36 g, 5 mmol) and 0.7 cm^3 of triethylamine (5 mmol) were added to 1.1 g of **1** (5 mmol) in 10 cm^3 of dioxane. The mixture was boiled to dissolve starting materials, then heated on a water-bath for 40 min and elaborated as above to yield 1.1 g (87%) of **3**, mp 185°C; ^{1}H NMR: $\delta = 1.93$ (t, CH_2CH_2), 3.70 (t, $2NCH_2$), 3.94 (s, CH_2CN), 7.31 (s, NH_2) ppm.

6-Alkoxy-3-dialkylamino-1,8-diamino-2,7-naphthyridine-4-carbonitriles (**9**–**19**)

General Procedure

Na (0.23 g, 0.01 mol) was dissolved in 30 cm^3 of the corresponding alcohol and then 4 mmol of the pyridine **2**–**8** were added. The mixture was refluxed for 3 days. After cooling the precipitate formed was filtered, washed with H_2O, and recrystallized from an appropriate solvent to yield the 1st portion of the target naphthyridines **9**–**19**. The alcoholic mother liquor was evaporated to dryness *in vacuo*, the residue was treated with H_2O, filtered, and recrystallized to give the 2nd portion of **9**–**19**.

1,8-Diamino-3-(diethylamino)-6-methoxy-2,7-naphthyridine-4-carbonitrile (**9**, $C_{14}H_{18}N_6O$)

Yield 81% (0.93 g, from ethanol), mp 167°C; ^{1}H NMR: $\delta = 1.21$ (t, $2CH_3$), 3.66 (q, $2NCH_2$), 3.81 (s, OCH_3), 5.95 (s, 5-H), 6.33 (s, NH_2), 6.79 (s, NH_2) ppm.

1,8-Diamino-6-methoxy-3-(1-pyrrolidinyl)-2,7-naphthyridine-4-carbonitrile acetate (**10** · CH_3COOH, $C_{14}H_{16}N_6O \cdot C_2H_4O_2$)

Yield 78% (1.07 g, from *Ac*OH), mp 232°C; ^{1}H NMR: $\delta = 1.90$ (m, CH_2CH_2, *Ac*OH), 3.70 (t, $2NCH_2$), 3.81 (s, OCH_3), 5.93 (s, 5-H), 6.33 (s, NH_2), 6.80 (s, NH_2), 11.86 (s, AcOH) ppm.

1,8-Diamino-6-methoxy-3-(4-methyl-1-piperazinyl)-2,7-naphthyridine-4-carbonitrile (**11**, $C_{15}H_{19}N_7O$)

Yield 74% (0.93 g, from *i-Pr*OH), mp 143°C; ^{1}H NMR: $\delta = 2.24$ (s, NCH_3), 2.40 (t, $2NCH_2$), 3.75 (t, $2NCH_2$), 3.81 (s, OCH_3), 5.94 (s, 5-H), 6.41 (s, NH_2), 6.94 (s, NH_2) ppm; ^{13}C NMR: $\delta = 46.85$ (NCH_3), 47.82 (NCH_2), 53.85 (OCH_3), 54.43 (NCH_2), 74.15 (4-C), 85.98 (5-C), 92.51 (8a-C), 119.98 (CN), 151.71 (4a-C), 157.98 (3-C), 158.38 (8-C), 160.34 (6-C), 163.10 (1-C) ppm.

1,8-Diamino-6-methoxy-3-(1-piperidinyl)-2,7-naphthyridine-4-carbonitrile (**12**, $C_{15}H_{18}N_6O$)

Yield 85% (1 g, from *i-Pr*OH), mp 129°C; ^{1}H NMR: $\delta = 1.62$ (m, $3CH_2$), 3.73 (t, $2NCH_2$), 3.82 (s, OCH_3), 5.95 (s, 5-H), 6.34 (s, NH_2), 6.85 (s, NH_2) ppm.

1,8-Diamino-6-methoxy-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2,7-naphthyridine-4-carbonitrile (**13**, $C_{21}H_{23}N_7O_2$)

Yield 82% (1.33 g, from ethanol), mp 181°C; ^{1}H NMR: $\delta = 3.06$ (t, $2NCH_2$), 3.81 (s, OCH_3), 3.82 (s, OCH_3), 3.91 (t, $2NCH_2$), 5.97 (s, 5-H), 6.44 (s, NH_2), 6.55–6.97 (m, C_6H_4), 7.00 (s, NH_2) ppm; ^{13}C NMR: $\delta = 47.06$ (NCH_2), 50.19 (NCH_2), 53.15 (OCH_3), 55.30 (OCH_3), 69.40 (4-C), 86.22 (5-C), 92.33 (8a-C), 111.92 (3′-C_{Ph}), 118.17 (6′-C_{Ph}), 119.62 (CN), 120.79 (5′-C_{Ph}), 122.68 (4′-C_{Ph}), 140.77 (1′-C_{Ph}), 150.91 (2′-C_{Ph}), 151.99 (4a-C), 158.18 (3-C), 158.51 (8-C), 159.93 (6-C), 163.86 (1-C) ppm.

1,8-Diamino-6-methoxy-3-(4-morpholinyl)-2,7-naphthyridine-4-carbonitrile (**14**, $C_{14}H_{16}N_6O_2$)

Yield 68% (0.82 g, from toluene), mp 243°C; ^{1}H NMR: $\delta = 3.69$ (t, $2NCH_2$), 3.72 (t, $2OCH_2$), 3.82 (s, OCH_3), 5.95 (s, 5-H), 6.44 (s, NH_2), 7.00 (s, NH_2), ppm.

1,8-Diamino-6-ethoxy-3-(4-morpholinyl)-2,7-naphthyridine-4-carbonitrile (**15**, $C_{15}H_{18}N_6O_2$)

Yield 65% (0.82 g, from toluene), mp 157°C; ^{1}H NMR: $\delta = 1.33$ (t, CH_3), 3.69 (t, $2NCH_2$), 3.72 (t, $2OCH_2$), 4.26 (q, OCH_2), 5.96 (s, 5-H), 6.25 (s, NH_2), 6.87 (s, NH_2) ppm; ^{13}C NMR: $\delta = 14.73$ (CH_3), 49.20 (NCH_2), 61.56 (OCH_2), 66.45 (OCH_2), 68.70 (4-C), 85.95 (5-C), 95.51 (8a-C), 119.37 (CN), 153.50 (4a-C), 158.28 (3-C), 160.18 (8-C), 160.23 (6-C), 163.50 (1-C) ppm.

1,8-Diamino-3-(butylethylamino)-6-ethoxy-2,7-naphthyridine-4-carbonitrile (**16**, $C_{17}H_{24}N_6O$)

Yield 79% (1.04 g, from ethanol), mp 148°C; ^{1}H NMR: $\delta = 0.97$ (t, CH_3), 1.23 (t, CH_3), 1.35 (m, CH_3, CH_2), 1.67 (m, CH_2), 3.59 (t, NCH_2), 3.68 (q, NCH_2), 4.25 (q, $2OCH_2$), 5.99 (s, 5-H), 6.07 (s, NH_2), 6.54 (s, NH_2) ppm.

1,8-Diamino-6-ethoxy-3-(1-pyrrolidinyl)-2,7-naphthyridine-4-carbonitrile (**17**, $C_{15}H_{18}N_6O$)

Yield 86% (1 g, from ethanol), mp 178°C; ^{1}H NMR: $\delta = 1.31$ (t, CH_3), 1.92 (m, CH_2CH_2), 3.69 (m, $2NCH_2$), 4.23 (q, OCH_2), 5.91 (s, 5-H), 6.27 (s, NH_2), 6.78 (s, NH_2) ppm; ^{13}C NMR: $\delta = 14.07$ (CH_3),

25.71 (CH_2CH_2), 51.20 (NCH_2), 62.42 (OCH_2), 75.48 (4-C), 84.94 (5-C), 93.51 (8a-C), 119.99 (CN), 150.50 (4a-C), 156.94 (3-C), 159.57 (6-C), 160.18 (8-C), 164.50 (1-C) ppm.

1,8-Diamino-3-(diethylamino)-6-ethoxy-2,7-naphthyridine-4-carbonitrile (**18**, $C_{15}H_{20}N_6O$)

Yield 85% (1.02 g, from ethanol), mp 145°C; ^{1}H NMR: $\delta = 1.21$ (t, $2CH_3$), 1.31 (t, CH_3), 3.66 (q, $2NCH_2$), 4.24 (q, $2OCH_2$), 5.94 (s, 5-H), 6.23 (s, NH_2), 6.74 (s, NH_2) ppm.

1,8-Diamino-6-ethoxy-3-(1-piperidinyl)-2,7-naphthyridine-4-carbonitrile (**19**, $C_{16}H_{20}N_6O$)

Yield 77% (0.96 g, from *i-Pr*OH), mp 143°C; ^{1}H NMR: $\delta = 1.33$ (t, CH_3), 1.65 (m, $3CH_2$), 3.73 (t, $2NCH_2$), 4.24 (q, $2OCH_2$), 5.96 (s, 5-H), 6.11 (s, NH_2), 6.64 (s, NH_2) ppm.

1,8-Diamino-3,6-bis(1-pyrrolidinyl)-2,7-naphthyridine-4-carbonitrile (**23**, $C_{17}H_{21}N_7$)

Method A. Pyrrolidine (0.85 g, 12 mmol) was added to 0.87 g of **1** (4 mmol) in 20 cm^3 of dioxane and the mixture was refluxed for 3 h. The solvent was removed *in vacuo*, the residue was treated with H_2O, filtered, and recrystallized from ethanol to give 0.80 g (62%) of **23**, mp 231°C; ^{1}H NMR: $\delta = 1.93$ (m, $2CH_2CH_2$), 3.41 (t, $2NCH_2$), 3.68 (t, $2NCH_2$), 5.58 (s, 5-H), 5.87 (s, NH_2), 6.54 (s, NH_2) ppm; ^{13}C NMR: $\delta = 25.82$ ($2CH_2CH_2$), 50.71 (NCH_2), 51.21 (NCH_2), 70.33 (4-C), 86.76 (5-C), 98.53 (8a-C), 119.49 (CN), 153.66 (3-C), 153.98 (4a-C), 155.16 (6-C), 160.26 (8-C), 165.57 (1-C) ppm.

Method B. Pyrrolidine (0.31 g, 4.4 mmol) was added to 1 g of **3** (4 mmol) in 20 cm^3 of dioxane, the mixture was refluxed for 3 h, and then elaborated as in method A to give 0.98 g (76%) of **23**.

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