2 (X = OMe), 2826-26-8; 2 (X = $N(CH_3)_2$), 2826-28-0; 3 (X = F), 23160-10-3; 3 (X = H), 1214-54-6; 3 (X = CN), 53942-70-4; 3 (X = OMe), 15795-54-7; 3 (X = $N(CH_3)_2$), 15795-57-0; 3 (X = CH_3), 15795-51-4; 3 (X = Br), 15795-59-2; 4 (X = F), 71732-10-0; 4 (X = H), 27402-47-7; 4 (X = NO_2), 23536-26-7; 4 (X = CN), 57270-79-8; 4 (X = Cl), 27402-31-9; 4 (X = OCH_3), 49546-71-6; 4 (X = $N(CH_3)_2$), 1753-47-5; 4 (X = Me), 56504-51-9; 4 (X = Br), 49546-72-7; 5 (X = F), 16210-64-3; 5 (X = H), 5381-33-9; 5 (X = CN), 31316-87-7; 5 (X = Cl), 15875-54-4; 5 (X = OMe), 7421-76-3; 5 (X = NMe_2), 21889-13-4; 5 (X = Me), 15875-51-1; 5 (X = Br), 961-20-6.

Chichibabin Amination of 1,*X*-Naphthyridines. Nuclear Magnetic Resonance Studies on the σ Adducts of Heterocyclic Systems with Nucleophiles[1]

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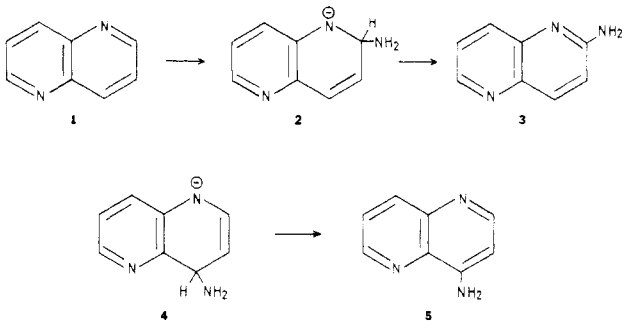
In the amination of 1,*X*-naphthyridines with potassium amide in liquid ammonia at about −35 to −40 °C the initial adduct formation is charge controlled. Thus, at these temperatures the site with the lowest electron density is most susceptible for amide attack (C-2 in 1,5-naphthyridine, C-2 in 1,6-naphthyridine, C-2 and C-8 in 1,7-naphthyridine, and C-2 in 1,8-naphthyridine), as proven by NMR spectroscopy. When the temperature was raised to about 10 °C, the site of addition has been found to change for 1,5- and 1,7-naphthyridine (NMR spectroscopy): from C-2 to C-4 in 1,5-naphthyridine and from C-2 and C-8 to C-8 only in 1,7-naphthyridine. In case of 1,6- and 1,8-naphthyridines no change was observed. Thus, the amination at about 10 °C is a process which is thermodynamically controlled. The several factors which contribute to the stability of these addition products have been discussed. It has been found that the anionic σ adducts 2(4,8)-aminodihydro-1,*X*-naphthyridinides can be easily oxidized with potassium permanganate into their corresponding 2(4,8)-amino-1,*X*-napthyridines.

The Chichibabin amination of the 1,*X*-naphthyridines has been described by several investigators.[2-4] However, contradictory results were sometimes reported, and product formation did not always follow the predictions based on calculated electron densities.[3,5,6] Moreover, 1:1 anionic σ adducts, formed on addition of the amide ion to the 1,*X*-naphthyridines,[7] were not always found to be the precursors of the products being obtained during the amination. We present here the results of detailed investigations on this subject, giving an explanation of the contradictory results which have been reported thus far.

Results and Discussion

(A) Amination of 1,5-Naphthyridine (1). The Chichibabin amination of 1 with sodamide at −33 °C was described first by Hart.[2] He claimed to have obtained 2-amino-1,5-naphthyridine (3). His results could not, however, be reproduced.[3,4] Paudler and Kress[3] reported that amination of 1 with potassium amide has to be carried out at *room temperature* in order to obtain the same compound (33%). It was shown later[4] that the amination product was not 3 but its isomer 4-amino-1,5-naphthyridine (5). When the reaction was carried out at 50 °C, the yield of 5 was considerably improved, but no further experimental details are available.[8] A few years ago it was shown by NMR spectroscopy that dissolving 1 at −40 °C in liquid ammonia containing a fourfold excess of potassium amide gives very rapid[7] formation of the 2-aminodihydro-1,5-naphthyridinide (2, Scheme I); no traces of 1 could be found, even if only a slight excess of potassium amide is used. On the basis of the Hammond postulate,[9,10] one has to conclude that, for reactions of this type, the transition state has a structure close to that of the starting material and thus that the attack of the amide ion is controlled by electron densities. This conclusion is in agreement with recent HMO calculations on nucleophilic substitution reactions in 1,*X*-naphthyridines; in these calculations the nature of the nucleophilic reagent[6] has also been taken into consideration.

Scheme I



Calculations[3,5,6] showed that position 2 in 1 has the lowest electron density and thus is most susceptible to a

(1) See for Part 24: Rykowski, A.; van der Plas, H. C. *J. Org. Chem.* **1980**, *45*, 881.
(2) Hart, E. P. *J. Chem. Soc.* **1954**, 1879.
(3) Paudler, W. W.; Kress, T. J. *J. Org. Chem.* **1968**, *33*, 1384.
(4) Brown, E. V.; Plasz, A. C. *J. Heterocycl. Chem.* **1970**, *7*, 593.
(5) Wait, S. C., Jr.; Wesley, J. W. *J. Mol. Spectrosc.* **1966**, *19*, 25.
(6) (a) Hirota, M.; Masuda, H.; Hamada, Y.; Takeuchi, I., *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1498. (b) Hirota, M.; Abe, K.; Endo, H.; Masuda, H. *Rep. Asahi Glass Found. Ind. Technol.* **1979**, *35*, 109.
(7) van der Plas, H. C.; van Veldhuizen, A.; Wozniak, M.; Smit, P. *J. Org. Chem.* **1978**, *43*, 1673.
(8) Hamada, Y.; Takeuchi, I. *Yuki Gorei Kagaku Kyokai Shi* **1974**, *32*, 602.
(9) Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzki, P. E. *J. Org. Chem.* **1973**, *38*, 1947.
(10) Hammond, S. G. *J. Am. Chem. Soc.* **1955**, *77*, 334.

0022-3263/81/1946-2134$01.25/0

Table I. ^{1}H NMR Data of 1,5- and 1,7-Naphthyridine and Their 1:1 σ Adducts with Amide Ions

compd	solvent	chemical shift,[c] δ H-2	H-3	H-4	H-5	H-6	H-7	H-8
1	$CDCl_3$	8.96	7.55	8.37		8.96	7.55	8.37
2	NH_2^-/NH_3	4.97 (3.99)	5.38 (2.17)	*a*		6.80 (2.16)	*a*	*a*
4	NH_2^-/NH_3	*a*	4.18 (3.37)	4.59 (3.78)		7.31 (1.65)	*a*	*a*
11	$CDCl_3$	9.01	7.48	8.14	7.64	8.60		9.50
12	NH_2^-/NH_3	5.02 (3.99)	5.31 (2.17)	6.28 (1.86)	6.35 (1.29)	6.76 (1.84)		7.52 (1.98)
15	NH_2^-/NH_3	7.65[b] (1.46)	6.77[b] (0.71)	6.77[b] (1.37)	4.52 (3.12)	7.01 (1.59)		5.13 (4.37)

[a] Coincidence of these signals made assignment impossible. [b] These signals show deceptive simplicity. [c] The values in parentheses are the Δδ values, i.e., the difference between the shift for a hydrogen of 1 or 11 in $CDCl_3$ and that for the corresponding hydrogen in the compounds below each.

Table II. ^{13}C NMR Data of 1,5- and 1,7-Naphthyridine and Their 1:1 σ Adducts with Amide Ions

compd	solvent	chemical shift,[b] δ C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	$CDCl_3$	151.0	124.1	137.2		151.0	124.1	137.2	144.0	144.0
2	NH_2^-/NH_3	65.8 (85.2)	121.3 (2.8)	127.4[a] (9.8)		125.1 (25.9)	122.7 (1.4)	121.6[a] (15.6)	151.2 (−7.2)	137.3 (6.7)
4	NH_2^-/NH_3	141.8 (9.2)	92.2 (31.9)	50.9 (86.3)		134.6 (16.4)	121.2 (2.9)	125.1 (12.1)	145.8[a] (−1.8)	145.3[a] (−1.3)
11	$CDCl_3$	152.1	125.2	134.7	119.9	144.0		154.5	143.7	131.3
12	NH_2^-/NH_3	65.9 (86.2)	120.2 (5.0)	124.3 (10.4)	120.2 (−0.3)	123.8 (20.2)		142.6 (11.9)		
15	NH_2^-/NH_3	138.2 (13.9)	121.9[a] (3.3)	122.5[a] (12.2)	80.2 (39.7)	151.8 (−7.8)		71.0 (83.5)		

[a] The signals may be interchanged. [b] See footnote *c* of Table I.

charge-controlled attack of the amide ion. Therefore, the formation of **5**, which has as precursor the 4-aminodihydro-1,5-naphthyridinide (**4**), can be considered as a surprising result.

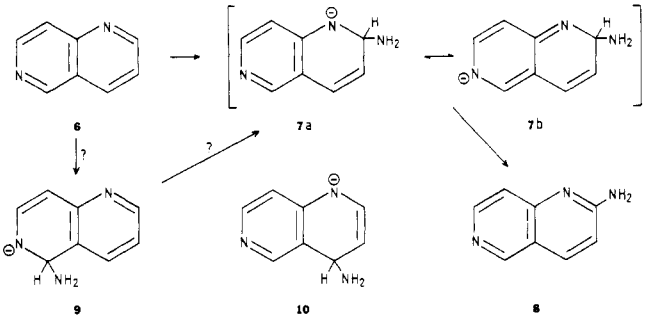
By studying the influence of the temperature on the NMR spectrum of a solution of the σ adduct **2**, we found that when a solution of **2** in liquid ammonia containing potassium amide was heated from −40 to +10 °C, the NMR spectrum of the solution drastically changed. The doublet at 4.97 ppm (H-2 of **2**) and the quartet at 5.38 ppm (H-3 of **2**) disappeared, and the spectrum featured a new doublet at 4.59 ppm and a new quartet at 4.18 ppm (see Table I). We ascribed these peaks to H-4 and H-3, respectively, in adduct **4**. The magnitude of the upfield shift of H-4 in **4** (Δδ = 3.78 ppm) is in agreement with values reported[7] and is due to a change of the hybridization of the carbon atom ($sp^2 \rightarrow sp^3$). Our observations were fully supported by ^{13}C NMR spectroscopy of both σ adducts **2** and **4** (Table II). The dependency of the position of addition of the amide ion on the temperature has already been observed in quinoline.[9]

That σ adduct **2** is less stable than σ adduct **4** can be explained by a major contribution of the allylic resonance stabilization in **4** being absent in **2**. That this stabilization is indeed important is clearly shown by the high ^{13}C Δδ value (=31.9 ppm) of C-3 in **4**, indicating that C-3 carries a considerable amount of negative charge.

Weak intramolecular hydrogen bonding between the amino protons and the lone pair of the nitrogen at position 5 may also contribute to the higher stability of **4**. This contribution will probably be weak as indicated by the fact that the C-4 adduct of quinoline in which intramolecular hydrogen bonding cannot operate is more stable than its C-2 isomer.[9]

The above-mentioned results and also those which will be discussed in the next sections strongly stress the point that in the Chichibabin amination of aza aromatics the temperature of the reaction plays a decisive role in the course of the reaction. Our results also provide us with a better understanding of the problem of why in the amination of **1** divergent results were obtained[2-4,8] and why at temperatures above 10 °C **5** instead of **3** is formed.

Scheme II

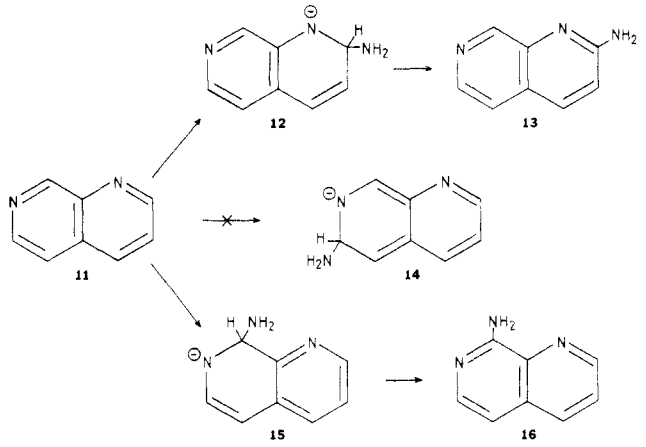


Recently the use of potassium permanganate in liquid ammonia as a useful reagent for the oxidation of 3-aminodihydro-1,2,4,5-tetrazinides, the 1:1 σ adducts of ammonia to 1,2,4,5-tetrazines, into the corresponding 3-amino-1,2,4,5-tetrazines has been reported.[11] When applying this reagent for the preparation of **3** or **5**, we found that addition of potassium permanganate to a solution of **2** in potassium amide–liquid ammonia gave **3** in 36% yield. However, if **2** was allowed to isomerize into **4** and then potassium permanganate was added, only minor traces of both **3** and **5** were obtained.

(B) Amination of 1,6-Naphthyridine (6). Amination of **6** with potassium amide in liquid ammonia has been reported to give 2-amino-1,6-naphthyridine (**8**, Scheme II) in a 33% yield at room temperature[3] and in a 83% yield when the amination was carried out at 50 °C.[8] On the basis of HMO calculations of the electron densities,[3,5,6a] it can be predicted that positions 2 and 5 of **6** have about the same susceptibility for a charge-controlled attack by the

(11) Counotte-Potman, A. D.; van der Plas, H. C. *J. Heterocycl. Chem.*, in press.

Scheme III



amide ion. However, recent PPP MO calculations on naphthyridines show that C-2 of **6** has a lower electron density than C-5, indicating that kinetic σ-adduct formation should preferably take place at C-2.[6b] By NMR spectroscopy it was shown[7] that when **6** was dissolved in liquid ammonia, containing potassium amide at −40 °C, the solution contains only one σ adduct, i.e., 2-aminodihydro-1,6-naphthyridinide (**7**); no trace of the 5-aminodihydro-1,6-naphthyridinide (**9**) could be detected.

We observed that when the temperature of the solution containing **7** was allowed to rise from −40 °C to at least +10 °C no change in the NMR spectrum was observed, indicating that σ adduct **7** was stable. That C-2 adduct **7** is thermodynamically the most stable one and not C-5 adduct **9** or 4-aminodihydro-1,6-naphthyridinide (**10**) can be explained by the fact that **7** can delocalize its negative charge over both nitrogen atoms by the para–para quinoid mesomeric contribution of **7b**, while a similar delocalization for **9** or **10** would require the contribution of ortho–para or ortho–ortho quinoid resonance structures which are reported to be of less significance.[12]

That the contribution of a para–para quinoid resonance structure is important is clearly demonstrated by the high $\Delta\delta$ values of C-6 for **2** and **12** (Table II), indicating that a considerable charge must be localized on position 6. From the results obtained with **6** we reach the conclusion that if nitrogen is present at position 6, the stabilization arising from the para–para quinoid structure **7b** even exceeds the allylic stabilization in **9** or **10**. Oxidation of a solution of **7** in liquid ammonia containing potassium amide with potassium permanganate gave the 2-amino product **8** in a 40% yield; this method forms a useful extension of the methods described for the preparation of **8**.

(C) Amination of 1,7-Naphthyridine (11). Amination of **11** by potassium amide in liquid ammonia at −33 °C gave a mixture of 2-amino- (**13**) and 8-amino-1,7-naphthyridines (**16**,[13] Scheme III). The NMR spectrum of **11** in liquid ammonia containing potassium amide at −40 °C has been explained by suggesting the presence of three 1:1 σ adducts, i.e., 2-, 6-, and 8-aminodihydro-1,7-naphthyridinides (**12**, **14**, and **15**), although not all the peaks in the NMR spectrum could be assigned.[7]

More recent spectroscopic investigations on σ-adduct formation between 2,6- and 2,7-naphthyridines and amide ions[14] induced us to reconsider whether some of the peaks

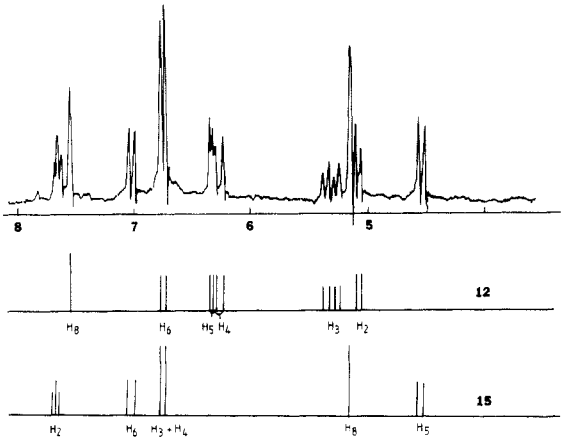
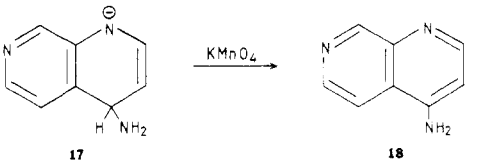


Figure 1. ^{1}H NMR spectrum of 1,7-naphthyridine (**11**) in liquid ammonia showing the assignment of the signals due to **12** and **15**.

Scheme IV



of the spectrum of **11** in the potassium amide–liquid ammonia system were correctly assigned. This reinvestigation led us to the conclusion that the peaks originally ascribed to H-6 in **14** in fact originated from H-5 in **15**. That this assignment was correct was proved by the fact that in the NMR spectrum of a solution of 6,8-dideuterio-1,7-naphthyridine in potassium amide–liquid ammonia, the H-8 singlet, being observed in **15** at 5.13 ppm (Figure 1), disappeared and that the doublet of H-5 at 4.52 ppm changed into a singlet (Table I). This considerable upfield shift for hydrogen originally attached to an aromatic carbon atom and now present in an azaallylic position ($\Delta\delta$ = 3.12 ppm) is remarkably high but not unusual. Similar upfield shifts are found for the corresponding hydrogen atoms in 1-aminodihydroisoquinolinide,[9] 1-aminodihydro-2,6-naphthyridinide,[14] and 1-aminodihydro-2,7-naphthyridinide.[14] By this reassignment the NMR spectrum of **11** in liquid ammonia–potassium amide could now be completely resolved and led to the conclusion that on dissolving **11** in liquid ammonia–potassium amide, only **12** and **15** are formed and not **14**, as originally suggested.[7] This fact is in good agreement with calculations showing that position 2 in **11** has the lowest electron density, closely followed by that on position 8.[3,5,6]

It was found that when the temperature of the solution containing this mixture of **12** and **15** was allowed to rise from −40 to +10 °C, the mixture irreversibly converts into **15**. From this observation it is clear why **16** is the only product formed when the amination takes place at room temperature,[3] whereas a mixture of **13** and **16** is formed at −33 °C.[13] The allylic resonance stabilizations, being possible in **15** but not in **12**, account for the higher thermodynamic stability of **15**. The high values for the ^{13}C and ^{1}H upfield shifts found for position 5 in **16** point in this direction (Tables I and II).

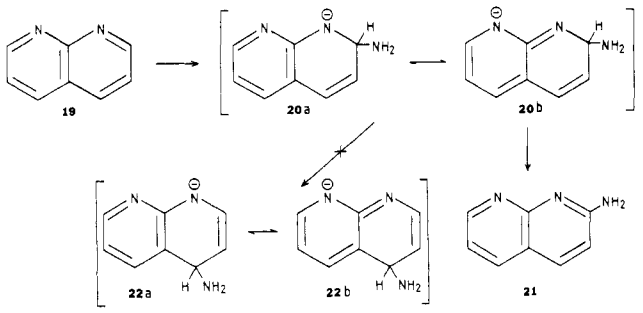
When the solution of **12** and **15** in liquid ammonia–potassium amide at −40 °C was treated with potassium permanganate, a mixture of 2-amino- (**13**, 26%) and 8-amino-1,7-naphthyridine (**16**, 19%) was obtained, together

(12) Shepherd, R. G.; Fredrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.

(13) Wozniak, M.; van der Plas, H. C. *J. Heterocycl. Chem.* **1978**, *15*, 731.

(14) The authors have a publication on this subject in preparation.

Scheme V



with, unexpectedly, some 4-amino-1,7-naphthyridine (18, 10%; see Scheme IV). The formation of 18 suggests the intermediacy of the σ adduct 4-aminodihydro-1,7-naphthyridinide (17). Its formation is kinetically less favorable than that of 12 and 15, as indicated by the higher electron density at C-4 in 11, but it is possible than on addition of the permanganate, 17 is formed as a short-lived intermediate which is immediately oxidized to 18.

(D) Amination of 1,8-Naphthyridine (19). Amination of 19 with potassium amide in liquid ammonia has been reported to give at room temperature as well as at 50 °C the 2-amino-1,8-naphthyridine (21, Scheme V) in yields of 29% at room temperature[3] and 78% at 50 °C.[8] It was already previously observed[7] that when 19 was dissolved in liquid ammonia–potassium amide at −40 °C, only the σ adduct 2-aminodihydro-1,8-naphthyridinide (20) is formed. These results are in good accordance with calculations, predicting position 2 has the lowest electron density. We found, however, that when the temperature of the liquid ammonia solutions containing 20 was raised to 10 °C, no change was observed, and 20 was still the only adduct present. Apparently, adduct 20 is kinetically favored as well as being thermodynamically the most stable one. This seems surprising since the C-4 adduct of quinoline with amide, i.e., 4-amino-1,4-dihydroquinolinide,[9] and the C-4 adduct of 1,5-naphthyridine with amide, i.e., 4 (see section A), are more stable than their isomeric C-2 adducts. The reason why the C-2 adduct 20 is more stable than 4-aminodihydro-1,8-naphthyridinide (22) can be explained by a contribution of the ortho–para quinoid resonance structure **20b**, which is of more importance than the ortho–ortho resonance contribution of **22b**. Treatment of the solution of 20 in liquid ammonia with potassium permanganate gave 21 in only a low yield (10%).

Experimental Section

All NMR spectra were obtained with a Varian XL-100-15 spectrometer. Spectra in liquid ammonia were recorded with sealed, thick-walled NMR tubes. The procedure for measurement in liquid ammonia containing potassium amide has been described earlier.[15] For ^1H spectra in liquid ammonia, ammonia (δ 0.95) was used as an internal standard.

^{13}C spectra were recorded with a Varian Fourier transform unit. The pulse separation was chosen as 0–1.25 s, the spectral width was 5000 Hz (1.25 Hz/point), and $(CH_3)_3N$ (δ 4.75) was used as an internal standard.

Starting Materials. The following compounds were prepared according to known procedures: 1,5-naphthyridine,[16] 1,6-naphthyridine,[16] 1,7-naphthyridine,[17] 1,8-naphthyridine,[16] 2-amino-1,5-naphthyridine,[18] 4-amino-1,5-naphthyridine,[3,4] 2-amino-1,6-naphthyridine,[3] 2-amino-1,7-naphthyridine,[19] 4-amino-1,7-naphthyridine,[17] 8-amino-1,7-naphthyridine,[3] and 2-amino-1,8-naphthyridine.[3]

Formation of the Amino-1,X-naphthyridines. To 15 mL of liquid ammonia containing potassium amide, obtained by a reaction with 0.15 g of potassium, was added all 0.20 g of the required 1,X-naphthyridine. After the mixture was stirred for 10 min and 0.80 g of $KMnO_4$ added in small portions, the mixture was stirred for another 10 min. The potassium amide was then decomposed with $(NH_4)_2SO_4$ (1 g). After evaporation of the ammonia, a concentrated aqueous solution of ammonia was added, and the mixture was continuously extracted with chloroform during 48 h. The residue obtained on evaporation of the chloroform was taken up in the minimum amount of methanol and developed by use of an Autoliner Desaga Model 121000 on a plate (20 × 40 cm) covered by a 2-mm layer of silica gel DF_{254}.

The method of isolation of the amino compounds from the plates depends on the 1,X-naphthyridine used.

(i) 1,5-Naphthyridine. Elution with chloroform–ethanol (10:1) gave one band which was extracted with methanol. Evaporation of the methanol gave 80 mg (36%) of 2-amino-1,5-naphthyridine (3), mp 203.5–205 °C (lit.[18] mp 204–205 °C).

(ii) 1,6-Naphthyridine. The reaction was carried out as described above: yield 90 mg (40%) of 2-amino-1,6-naphthyridine (8); mp 238–240 °C (lit.[3] mp 238–240 °C).

(iii) 1,7-Naphthyridine. Elution with chloroform–ethanol (10:1) gave three bands. The lower band gave on extraction with methanol 22 mg (10%) of 4-amino-1,7-naphthyridine (18), mp 258–259 °C (lit.[17] mp 259–260 °C). Extraction of the middle band gave 57 mg (26%) of 2-amino-1,7-naphthyridine (13), mp 235–238 °C (lit.[18] mp 236–238 °C). The upper band was subjected to a second preparative TLC procedure with chloroform as eluent. Two elutions gave two separate bands. Extraction with methanol of the lower band gave 42 mg (19%) of 8-amino-1,7-naphthyridine (16), mp 166–167 °C (lit.[3] mp 165–166 °C). Extraction of the upper band gave 7 mg of 1,7-naphthyridine, mp 63–65 °C (lit.[17] mp 65–66 °C).

(iv) 1,8-Naphthyridine. The reaction was carried out as described for 1,5-naphthyridine: yield 22 mg (10%) of 2-amino-1,8-naphthyridine (20); mp 135–138 °C (lit.[3] mp 141–142 °C).

Registry No. 1, 254-79-5; 2, 65594-18-5; 3, 17965-80-9; 4, 76648-98-1; 5, 27392-68-3; 6, 253-72-5; 8, 17965-81-0; 11, 253-69-0; 12, 65594-20-9; 13, 54920-84-2; 15, 76648-99-2; 16, 17965-82-1; 18, 58680-41-4; 19, 254-60-4; 21, 15992-83-3.

(15) Geerts, J. P.; Rasmussen, C. A. H.; van der Plas, H. C.; van Veldhuizen, A. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 231.

(16) Hamada, Y.; Takeuchi, I. *Chem Pharm. Bull.* **1971**, *19*, 1857.

(17) Albert, A. *J. Chem. Soc.* **1960**, 1790. Armarego, W. L. F.; Batterham, T. J. *J. Chem. Soc. B* **1966**, 750.

(18) Czuba, W. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 988.

(19) Czuba, W.; Wozniak, M. *Rocz. Chem.* **1974**, *48*, 1815.

(20) Wozniak, M.; Czuba, W.; van der Plas, H. C. *Rocz. Chem.* **1976**, *50*, 451.