On the Synthesis and Amination of 5-Chloro- and 5-Bromo-1,7-naphthyridine (1)

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A new synthesis of 5-chloro- and 5-bromo-1,7-naphthyridine, using 8-amino-1,7-naphthyridine as starting material is described. On amination with potassium amide in liquid ammonia, the 5-bromo compound undergoes a tele-amination into 8-amino- and 2-amino-1,7-naphthyridine and a Chichibabin reaction yielding 8-amino-5-bromo-1,7-naphthyridine. The reaction with the 5-chloro compound occurs at a much lower rate than the 5-bromo compound and only gives 8-amino-5-chloro-1,7-naphthyridine in a small yield. Convincing ^{1}H-nmr evidence is presented, showing that the 5-bromo- and 5-chloro-1,7-naphthyridine give addition of the amide ion at position 8 and that the 5-chloro compound also gives addition at position 2.

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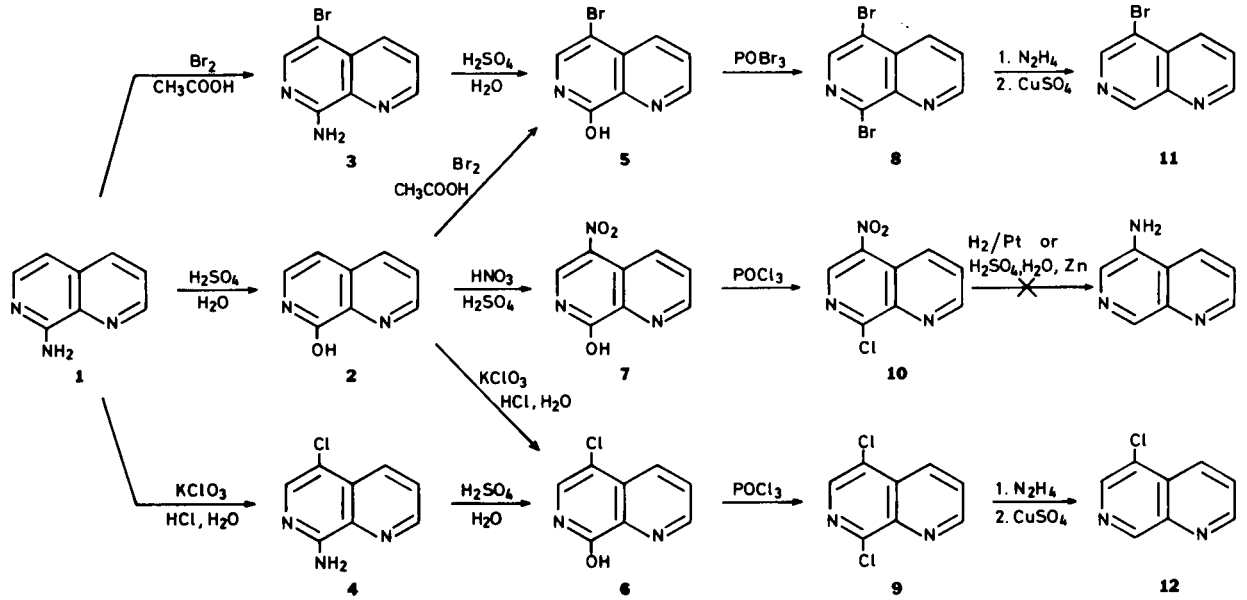
There is sound ^{1}H- and ^{13}C-nmr evidence that 1,7-naphthyridine easily gives with potassium amide in the solvent liquid ammonia three 1:1 anionic σ-adducts *i.e.*, the 2-amino-1,2-dihydro-, the 6-amino-6,7-dihydro- and the 8-amino-7,8-dihydro-1,7-naphthyridinide ions (2). With the 8-chloro(bromo) and 2-chloro(bromo)-1,7-naphthyridines a similar addition pattern has been observed (3). It has led to the discovery of the occurrence of tele-aminations in these systems (3). In order to define the scope of the tele-substitution in the 1,7-naphthyridine system we investigated the reaction of 5-chloro- (**12**) and 5-bromo-1,7-naphthyridine (**11**) in the potassium amide/ammonia system. In both compounds the halogeno atom can be expected to be unreactive in an $S_N(AE)$ process. Moreover dehydrohalogenation of **11** and **12** into 5,6-didehydro-1,7-naphthyridine seems very unlikely since the results of the amination of the 3-halogeno derivatives of pyridine (4), quinoline (5), 1,X-naphthyridines (6,7,8) and 4-halogeno-isoquinolines (9) clearly show that the formation of a didehydro bond adjacent to nitrogen never takes place. Therefore reaction of **11** and **12** can only lead to products in which the nucleophile enters into a position being different from the one vacated by the leaving group. This means that **11** and **12** are very suitable substrates to undergo tele-substitution.

Compound **11** has been prepared earlier by treatment of the hydrobromide of 1,7-naphthyridine with bromine in nitrobenzene (10) and by bromination in tetrachloromethane (11). However, these methods have the disadvantage that the starting substance 1,7-naphthyridine is not easily available and that according to reference 10 besides **11** the isomeric 3-bromo-1,7-naphthyridine is formed, which mixture is difficult to separate. The synthesis of **11** outlined in Scheme I uses 8-amino-1,7-naphthyridine (**1**) as starting material, which can readily be obtained (3) by "Skrauping" of 2,3-diaminopyridine. In a similar



SCHEME I

Table I

GLC Results of Amination of 5-Bromo- (**11**) and 5-Chloro-1,7-naphthyridines (**12**)

Compound	Starting Material Recovered	Total Yield of Identified products (%)	Products: 8-Amino-1,7-naphthyridine (**1**) (%)	2-Amino-1,7-naphthyridine (**17**) (%)	5-Bromo-8-amino-1,7-naphthyridine (**3**) (%)	5-Chloro-8-amino-1,7-naphthyridine (**4**) (%)
5-bromo-1,7-naphthyridine (**11**)	19	50	42	3 (a)	5	-----
5-chloro-1,7-naphthyridine (**12**)	75	5	1	-----	-----	4

(a) The amount of this compound formed could not be determined by glc, but was determined by tlc.

Table II

^{1}H-Nmr Chemical Shifts and Coupling Constants of some 5,8- and 5-Derivatives of 1,7-Naphthyridine

Compound	Solvent	Chemical Shift (δ) H-2	H-3	H-4	H-5	H-6	H-8	Coupling Constants (Hz) $J_{2,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,8}$
5-bromo-8-amino-1,7-naphthyridine (**3**)	Deuteriochloroform-perdeuteriomethanol	8.73	7.63	8.24	-----	7.93	-----	4.3	1.8	8.6	-----
5-chloro-8-amino-1,7-naphthyridine (**4**)	Deuteriochloroform-perdeuteriomethanol	8.77	7.66	8.31	-----	7.81	-----	4.3	1.8	8.6	-----
5-bromo-8-hydroxy-1,7-naphthyridine (**5**)	DMSO (a)	8.82	7.79	8.17	-----	7.55	-----	4.4	1.7	8.2	-----
5-chloro-8-hydroxy-1,7-naphthyridine (**6**)	DMSO (a)	8.88	7.90	8.30	-----	7.65	-----	4.4	1.7	8.2	-----
5-nitro-8-hydroxy-1,7-naphthyridine (**7**)	Trifluoroacetic Acid	9.70	8.22	8.88	-----	8.71	-----	5.5	1.2	8.9	-----
5,8-dibromo-1,7-naphthyridine (**8**)	Deuteriochloroform	9.08	7.71	8.41	-----	8.47	-----	4.2	1.7	8.5	-----
5,8-dichloro-1,7-naphthyridine (**9**)	Deuteriochloroform	9.08	7.73	8.45	-----	8.33	-----	4.2	1.7	8.5	-----
5-nitro-8-chloro-1,7-naphthyridine (**10**)	Deuteriochloroform	9.19	7.88	9.10	-----	9.16	-----	4.1	1.6	8.9	-----
5-bromo-1,7-naphthyridine (**11**)	Deuteriochloroform	8.98	7.63	8.39	------	8.73	9.37	4.1	1.6	8.7	0.8
5-chloro-1,7-naphthyridine (**12**)	Deuteriochloroform	8.99	7.62	8.41	------	8.58	9.33	4.1	1.6	8.7	0.8

(a) Temperature of 140°.

manner the 5-chloro compound **12** was synthesized (see Scheme I). All the reactions were performed under standard conditions and are described in detail in the experimental part. The products have the assigned structures as proved by the microanalyses, and the ir, mass spectral, and ^{1}H-nmr data (see Table II, in Experimental Part). The following remarks about the synthesis of some of the compounds mentioned in Scheme I, can be made.

1. The preparation of 7,8-dihydro-8-oxo-1,7-naphthyridine (**2**) by acid treatment of **1** is a more preferred pathway than the one being performed (3,12) by a Skraup reaction of 3-amino-2-hydroxypyridine. In the last mentioned reaction the reaction product is found to be difficult to isolate and to purify.

2. 5,8-Dibromo-1,7-naphthyridine (**8**) was obtained earlier as a by-product in the reaction of **2** with phos-

phoryl bromide (3). However **8** was then always contaminated with a second by-product, which by ^{1}H-nmr spectroscopy could be identified as 3,8-dibromo-1,7-naphthyridine (3). The independent preparation of **8** as given in Scheme I has proven that our previous structure assignment based on the ^{1}H-nmr data (3) was correct.

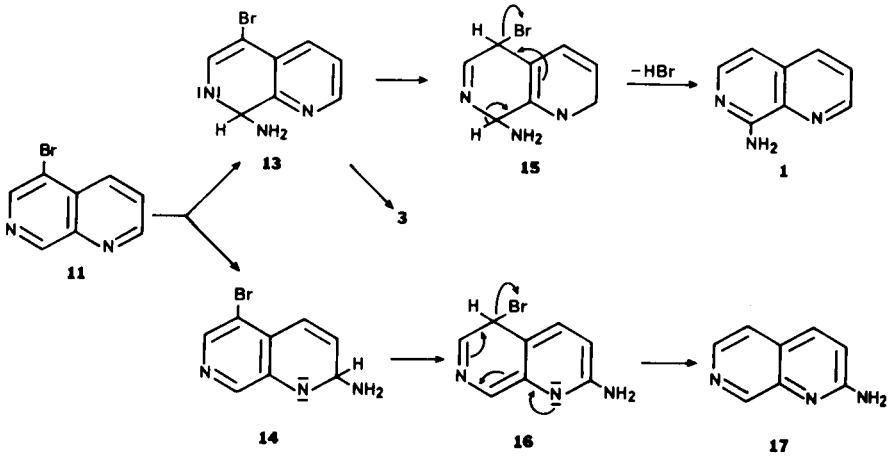
3. Treatment of **7** with phosphoryl chloride gave **10** and did not lead to the formation of product in which both oxo group and nitro broup were replaced *i.e.*, **9**. This is very different from the behaviour of 1,4-dihydro-4-oxo-3-nitro-1,7-naphthyridine which is reported to give on treatment with phosphoryl chloride exclusively 3,4-dichloro-1,7-naphthyridine (8).

4. Attempts to synthesize 5-amino-1,7-naphthyridine by treatment of **10** with hydrogen over palladium-on-charcoal or by zinc in dilute sulphuric acid failed. The last method was successfully applied to the preparation of 8-amino- (or 5-amino-) 2-methylpyridine from 6-chloro-3-nitro- (or 5-nitro-) 2-methylpyridine (13). Only black material containing many different compounds was obtained.

The amination of both compounds **11** and **12** was carried out by adding ethereal solutions of them to solutions of the five-fold molar amounts of potassium amide in liquid ammonia and allowing the reaction to proceed for 4 hours at -33°. After terminating the reaction by adding an excess of ammonium chloride, the compounds present in the reaction mixture were isolated by preparative TLC, and identified by ^{1}H-nmr and ir data, and comparison with reference samples. The quantitative composition of the reaction mixture was established by glc (see Table I).

It appears from the formation of **1** and **17** that **11** mainly undergoes tele-substitution. From the fact that no trace of a 5-amino- or 6-amino-1,7-naphthyridine was found, the occurrence of an $S_N(AE)$ or $S_N(EA)$ process can be excluded, as expected. The introductory step in this tele-amination reaction is the formation of the 1:1 σ-complexes **13** and **14**. Whereas in the parent compound 1,7-napnthyridine the addition at C(2) is favoured over C(8), the addition ratio is reversed with the 5-bromo compound; addition at C(8) is preferred to addition at C(2). This is undoubtedly caused by the presence of the bromo atom in that particular ring. Experimental support for the formation of a 1:1 σ-adduct at C(8) was obtained when a solution of **11** in potassium amide/liquid ammonia was measured by ^{1}H-nmr spectroscopy. The resonance signals of H(8) being present as a singlet at δ 9.37 in a solution of deuteriochloroform (see Table II) was now found at δ 5.15, indicating an upfield shift of $\Delta\delta$ = 4.22 ppm, being in good agreement with adduct formation at C(8) (14). Similarly, the 5-chloro compound **12** also undergoes adduct formation at C(8) as observed by the upfield shift ($\Delta\delta$) of 4.21 when changing the solvent from deuteriochloroform (δ H(8) 9.33) to the potassium amide/liquid ammonia system (δ H(8) 5.12). Moreover, the solution of **12** in potassium amide/liquid ammonia showed a double doublet at δ 5.45, being ascribed to H(3) in the 1:1 σ-adduct at C(2). The signal of H(2) in the σ-adduct at C(2) coincides with that of the singlet of H(8) in the adduct at C(8). The ratio in which the adducts at C(2) and C(8) are formed could be calculated from the ^{1}H-nmr spectrum and was found to be 1:3. The addition at C(8) was further proved by measuring the adduct spectrum of 5-chloro-8-deutero-1,7-naphthyridine (55% D) (see for its preparation the experimental part) in potassium amide/liquid ammonia. It shows that the peak at δ 5.12 is considerable decreased.

The formation of **1** is explained *via* the dehydro compound **15** which undergoes a base-catalysed 1,4-dehydrohalogenation. A possible alternative pathway for the formation of **1** which is of special interest in case of the bromo compound **11**, is a base-catalysed debromination of **11** to give the parent 1,7-naphthyridine which then may undergo a Chichibabin type amination at position 8 (16). This pathway, however, can be rejected as a major route. Amination of 1,7-naphthyridine, carried out under the



SCHEME II

same conditions as used for 5-bromo-1,7-naphthyridine, gave in low yields **1** and **17** (~7%). The relative high yield in which **1** is formed from **11** indicates that the greater part of compound **1** must be formed *via* **13** → **15** → **1**. The formation of **17** can be described to occur *via* the σ-adduct **14**, which undergoes a 1,5-hydrogen shift into the anionic adduct **16**, which easily aromatized by loss of the bromide ion.

Summarizing the results of several studies on the amination of halogeno-1,7-naphthyridines with potassium amide in liquid ammonia we come to the conclusion that the 2-, 5- and 8-halogeno-1,7-naphthyridines are very suitable substrates for tele-amination. This not only occurs when both the carbon atom which is attacked by the amide ion, and the carbon atom which is attached to the leaving group, are present in the same heterocyclic ring, but also when those two carbon positions are located in different rings.

EXPERIMENTAL

Melting points (uncorrected) were measured on a Kofler plate. The ^{1}H-nmr spectra were obtained on a Tesla BS-478 (80 MHz) apparatus, using HMDSO (δ = 0.05) or DDS (δ = 0.00) as an internal standard. The ir spectra were taken on UR-20 or an Hitachi EPI-G3 apparatus in potassium bromide pellets. The mass spectra (a LKB 9000 S GC-MS mass spectrometer) and the microanalyses were carried out in the Regional Laboratory for Physicochemical Analysis and Structural Research. Mass spectra of deuterated compounds were recorded on an AE(MS-902) instrument. The ^{1}H-nmr spectra in liquid ammonia were carried out with a Jeol JNM C-60 H apparatus equipped with a JES-VT-3 variable temperature controller, using trimethylamine as an internal standard (δ 2.13).

The mass spectra of all the compounds prepared are in good agreement with the proposed structure. The ratio of the different isotope peaks for the bromo and chloro compounds are found as expected.

8-Amino-1,7-naphthyridine (**1**).

The compound was obtained by the method described previously (3); yield 20.5%, m.p. 168-169°.

7,8-Dihydro-8-oxo-1,7-naphthyridine (**2**).

A solution of 6 g. (41 mmoles) of **1** in 45 ml. of sulphuric acid (d_{20} = 1.83) and 20 ml. of water was heated to boiling and then refluxed for 100 hours. The solution was poured onto *ca.* 100 g. of ice and basified cautiously with aqueous ammonia. The mixture was extracted continuously with chloroform for 25 hours. After evaporation of the chloroform the residue was crystallized from water yielding 4.9 g. (81%) of **2**, light yellow needles, m.p. 237-239° (lit. (3) 241-242°). The ir spectrum of **2** was fully identical with an authentic specimen (3).

5-Bromo-8-amino-1,7-naphthyridine (**3**).

To a solution of 0.5 g. (3.4 mmoles) of 8-amino-1,7-naphthyridine in 3.5 ml. of warm (~ 50°) of glacial acetic acid, 0.18 ml. of bromine was added with stirring and the mixture was heated under reflux on a water bath for 2.5 hours. Upon cooling a yellow compound crystallized out, which was collected and added to 50 ml. of aqueous ammonia (d_{20} = 1.18). This mixture was heated on a water bath for 15 minutes and cooled. The precipitate was filtered off, washed with water and recrystallized from ethanol, yielding 0.55 g. (72%) of **3**, light yellow needles, m.p. 220-221° subl.; ir: (cm^{-1}) 3380, 3310 and 3175 (NH stretching), 1670 (NH bending).

Anal. Calcd. for $C_8H_6BrN_3$: C, 42.87; H, 2.70; N, 18.75. Found: C, 42.80; H, 2.68; N, 18.49.

5-Chloro-8-amino-1,7-naphthyridine (**4**).

To a solution of 0.5 g. (3.4 mmoles) of **1** in 3.25 ml. of concentrated hydrochloric acid, a solution of 0.15 g. of potassium chlorate in 2 ml. of water was added dropwise at a temperature of 40°. After 30 minutes the reaction mixture was heated on a water bath for 2 hours. The solution was diluted with 10 ml. of water and made alkaline with aqueous ammonia. A precipitate was obtained, which was collected and recrystallized from ethanol (charcoal), yielding 0.40 g. (65.5%) of **4**, light yellow needles, m.p. 216-217° subl.; ir: (cm^{-1}) 3380, 3310 and 3175 (NH stretching), 1670 (NH bending).

Anal. Calcd. for $C_8H_6ClN_3$: C, 53.49; H, 3.36; N, 23.39. Found: C, 53.49; H, 3.39; N, 23.40.

5-Bromo-8-hydroxy-1,7-naphthyridine (**5**).

Method A.

To a solution of 1 g. (6.8 mmoles) of **2** in 6 ml. of warm (~ 50°) glacial acetic acid, 0.36 ml. of bromine was added. The mixture was heated under reflux on a water bath for 2 hours, and then cooled. The hydrobromide (m.p. 332-336° subl.) was filtered off, added to 50 ml. of aqueous ammonia and stirred for 10 minutes. The precipitate was filtered, washed with water and recrystallized from a mixture of acetic acid and water (1:1) (charcoal), yielding 0.84 g. (55%) of **5**, white needles, m.p. 333-335°; ir: (cm^{-1}) 3430 and 3150 (OH and NH stretching), 1725 (CO), 1660 (NH bending).

Anal. Calcd. for $C_8H_4BrN_2O$: C, 42.70; H, 2.56; N, 12.45. Found: C, 42.51; H, 2.23; N, 12.51.

Method B.

A solution of 0.1 g. (0.44 mmole) of **3** in 4.5 ml. of sulphuric acid (d_{20} = 1.83) and 2 ml. of water was boiled under reflux for 80 hours. The solution was poured into *ca.* 30 g. of ice and made alkaline cautiously with aqueous ammonia. The precipitate was filtered off and recrystallized from a mixture of acetic acid and water (1:1) (charcoal), yielding 0.06 g. (60%) of **5**. The compound was fully identical with the compound obtained according to method A described above.

5-Chloro-8-hydroxy-1,7-naphthyridine (**6**).

Method A.

To a solution of 0.5 g. (3.4 mmoles) of **2** in 3.25 ml. of concentrated hydrochloric acid a solution of 0.15 g. of potassium chlorate in 3 ml. of water was added dropwise with stirring at a temperature of 40°. After 30 minutes the reaction mixture was heated on a water bath for 2 hours. The solution was diluted with 10 ml. of water and made alkaline with aqueous ammonia. The precipitate was filtered off, washed with water and recrystallized from the mixture of acetic acid and water (1:1) (charcoal), yielding 0.35 g. (57%) of **6**, white needles, m.p. 345-347° subl.; ir: (cm^{-1}) 3440, 3150 and 3090 (OH and NH stretching), 1730 (CO), 1655 (NH bending).

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.77; N, 15.51. Found: C, 53.13; H, 2.78; N, 15.59.

Method B.

This reaction was carried out by the same procedure as described in section 5 (Method B). From 0.1 g. (0.56 mmole) of **4** 0.065 g. (65%) of **6** was obtained. The compound was identical

with the one obtained according to method A described above.

5-Nitro-8-hydroxy-1,7-naphthyridine (**7**).

A mixture of 1.0 g. (6.8 mmoles) of **2**, 7 ml. of sulphuric acid (d_{20} = 1.83) and 1 ml. of nitric acid (d_{20} = 1.40) was heated on a water bath for 1 hour. The mixture was allowed to cool and then poured into ice-water (~ 200 g.). The precipitate was filtered off, washed with water and recrystallized from dimethylformamide, yielding 0.55 g. (42%) of **7**, cream plates, m.p. > 350° subl.; ir: (cm^{-1}) 3400-3470, 3150 and 3115 (OH and NH stretching) 1720 (CO), 1655 (NH bending), 1510 (-NO_2).

Anal. Calcd. for $C_8H_5N_3O_3$: C, 50.23; H, 2.61; N, 21.98. Found: C, 50.28; H, 2.62; N, 21.97.

5,8-Dibromo-1,7-naphthyridine (**8**).

A mixture of 1 g. (4.4 moles) of **5** and 10 g. of phosphoryl bromide was heated in a sealed tube at 100-110° for 2 hours. Then the contents of the tube were poured out onto about 100 g. of ice and the mixture was made alkaline with aqueous ammonia. A precipitate was obtained which was collected, washed with water and recrystallized two times from a mixture of ethanol and water (1:1) (charcoal), yielding 0.8 g. (62%) of **8**, white fluffy needles, m.p. 132-133°.

Anal. Calcd. for $C_8H_4Br_2N_2$: C, 33.33; H, 1.49; N, 9.40. Found: C, 33.46; H, 1.41; N, 9.86.

5,8-Dichloro-1,7-naphthyridine (**9**).

A mixture of 0.75 g. (4.1 mmoles) of **6** and 50 ml. of phosphoryl chloride was refluxed for 3 hours after which the excess reagent was distilled off. The residue was poured onto *ca.* 50 g. of ice and made alkaline with aqueous ammonia. The precipitate was collected, washed with water and recrystallized from a mixture of ethanol and water (1:1) (charcoal), yielding 0.55 g. (67%) of **9**, white fluffy needles, m.p. 136-137°.

Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 48.25; H, 2.01; N, 14.06. Found: C, 48.19; H, 2.02; N, 14.18.

5-Nitro-8-chloro-1,7-naphthyridine (**10**).

A mixture of 0.5 g. (2.6 mmoles) of **7** and 50 ml. of phosphoryl chloride was refluxed for fifteen hours, and the excess reagent was distilled off. The residue was poured onto *ca.* 50 g. of ice and made alkaline with aqueous ammonia. The precipitate was filtered off, washed with water and recrystallized from ethanol-water (1:1) (charcoal), yielding 0.28 g. (51%) of **10**, white needles, m.p. 139-140°.

Anal. Calcd. for $C_8H_4ClN_3O_2$: C, 45.84; H, 1.92; N, 20.04. Found: C, 46.10; H, 1.89; N, 20.03

5-Chloro-1,7-naphthyridine (**12**).

A mixture of 2.25 g. (11.3 mmoles) of **9** and 7 ml. of 80% hydrazine hydrate in 400 ml. of ethanol were stirred at room temperature for 18 hours, then cooled to *ca.* -10°. The precipitate was collected and washed with ethanol; yield 1.5 g., white needles, m.p. 180-182° dec. The filtrate was quickly concentrated *in vacuo* to *ca.* 50 ml., cooled to -10° and an additional amount of precipitate, 0.5 g. light yellow needles, m.p. 175-181° dec., was filtered off and washed with ethanol. The combined dry precipitate (2.0 g.) was dissolved in 200 ml. of water containing 24 ml. of acetic acid. After heating to boiling, portions of a hot solution of 3 g. of cupric sulphate in 40 ml. of water were added. The resulting mixture was heated to boiling for an additional 15 minutes, then cooled and made alkaline with 50% aqueous sodium hydroxide. The mixture was continously extracted with chloroform for 10 hours. The chloroform extract (120 ml.) was dried over magnesium sulfate and passed through a column filled with alumina (2 x 5 mm) using 100 ml. of chloroform as eluent. The eluent was evaporated and the residue (A) was boiled for 5 minutes with 150 ml. of ether. The ether solution was passed through a column (filled with alumina, 15 x 1 cm), using 30 ml. of ether as eluent. Then the chloroform solution (100 ml.) of the residue (A) was passed through the same column, using 100 ml. of chloroform as eluent. After evaporation of the chloroform, the residue was sublimed twice at 90°/0.2 mm, yielding 0.55 g. (29%) of **12**, m.p. 75-76° (after crystallization from petroleum ether (40-60°)).

Anal. Calcd. for $C_8H_5ClN_2$: C, 58.37; H, 3.06; N, 17.03. Found: C, 58.47; H, 3.05; N, 17.04.

5-Bromo-1,7-naphthyridine (**11**).

This compound was prepared similarly to the preparation of **12** described in previous section, using 1.50 g. (5.2 mmoles) of **8** as starting material and 2.3 ml. of 80% hydrazine hydrate in 180 ml. of ethanol. After extraction with chloroform and concentration to a small volume, the solution was applied to two plates (20 x 40 cm) covered by a 2 mm layer of silica gel PF_{254}; The chromatograms were developed with a mixture of ethyl ether/petroleum ether (40-60°) (ratio 1:1). Two bands were obtained, showing uv absorbance; they were all extracted with chloroform in a Soxhlett apparatus for 8 hours.

After evaporation of the solvent from the extract of the first band (the lowest R_f) and sublimation of the residue at 90°/0.2 mm, 0.12 g. (18%) of 1,7-naphthyridine was obtained. The residue obtained from the extract of the second band was sublimed twice at 90° (0.2 mm), yielding 0.25 g. (23%) of **11**, white needles, m.p. 72-74° (lit. (10) 75-76°). The ir spectrum of this compound is fully identical with that of the product obtained by bromination of 1,7-naphthyridine (10).

Anal. Calcd. for $C_8H_5BrN_2$: C, 45.96; H, 2.41; N, 13.40. Found: C, 46.32; H, 2.42; N, 13.35.

5-Chloro-8-deutero-1,7-naphthyridine.

A mixture of 100 mg. of 5-chloro-1,7-naphthyridine and 3 ml. of deuterium oxide was heated in a sealed tube for 12 hours. The mixture was cooled and then extracted continuously with chloroform for 2 hours. The solvent was evaporated off and the residue was sublimed at 90°/0.2 mm Hg, yielding 85 mg. of 5-chloro-8-deutero-1,7-naphthyridine. No depression of the melting point was observed on mixing of this compound with **12**. ^{1}H-nmr data showed that deuteration had taken place 55% at position 8, 22% at position 6 and 9% at position 2. Mass spectral data oD 44.7%, 1D 45.8%, 2D 9.5%.

Amination of 5-bromo-1,7-naphthyridine (**11**).

A solution of 0.16 g. (0.75 mmole) of **11** in 4 ml. of absolute ether was added with stirring to a solution of potassium amide in liquid ammonia (prepared from 0.16 g. (4 mgat) of potassium and 6 ml. of liquid ammonia) at -33°. After reaction at -33° for 4 hours the reaction was stopped by adding 0.25 g. of ammonium chloride. The ammonia and ether were evaporated, 25 ml. of water were added and the solution was made alkaline with an aqueous solution of potassium hydroxide. Then the mixture was extracted continuously with chloroform for 25 hours. After distilling off the chloroform, 0.11 g. of dark yellow solid remained as residue. This residue was dissolved in a mixture of chloroform/methanol (ratio 1:1) and brought by an autoliner on plate (20 x 40 cm) covered with a 2 mm layer of silica gel PF_{254}. The chromatograms were developed two times with a mixture of benzene/ethyl acetate/methanol (10:2:1). Three main bands were obtained showing uv absorbance. They were all extracted in a Soxhlett apparatus with a mixture of chloroform/methanol (ratio

1:1) for 8 hours. After evaporation of the solvent from the extract of the third band (the highest R_F) a residue was obtained which was sublimed at 90°/0.2 mm, yielding 15 mg. of starting material. The residue remaining after sublimation was recrystallized from ethanol yielding 5 mg. of 8-amino-5-bromo-1,7-naphthyridine (**3**). The compound was identified by comparison of its properties (ir spectrum, m.p. and retention time) with those of a reference sample. Evaporation of the solvent from the extract of the second band afforded 37 mg. of crude 8-amino-1,7-naphthyridine (**1**) (m.p. 165-169°). Sublimation at 160°/0.2 mm gave light yellow needles, m.p. 168-169°. The compound has identical properties (ir spectrum, m.p. and retention time) as those of a reference sample. The concentrated solution containing the extract from the first band (the lowest R_F) was applied to a plate (10 x 10 cm) covered with a 2 mm layer of silica gel PF_{254}. After development of the chromatogram with a mixture of benzene/ethyl acetate/methanol (ratio 4:2:1), 3 mg. of yellow solid was separated which had identical ir spectrum and retention time as a reference sample of 2-amino-1,7-naphthyridine (**17**). In the first band there are still very small amounts of a few other compounds which could not be identified.

Amination of 5-Chloro-1,7-naphthyridine (**12**).

This reaction was carried out and products were separated in the same manner as described in previous section for the amination of **11**. From the third band (the highest R_F), starting material (by sublimation) and 5-chloro-8-amino-1,7-naphthyridine (**4**) (by crystallization from ethanol) were separated. From the second band, 8-amino-1,7-naphthyridine (**1**) was separated. All these compounds were identified by comparison of their properties (ir, m.p. and retention times) with those of reference samples. In the first band there were also very small amounts of a few compounds which could not be identified.

Amination of 1,7-naphthyridine.

A solution of 65 mg. (0.5 mmole) of 1,7-naphthyridine in 2 ml. of absolute ether was added with stirring to a solution of potassium amide (100 mg., 2.5 mg.-atoms) in 6 ml. of liquid ammonia. Further amination was carried out in the same manner as described for 5-bromo-1,7-naphthyridine (-33°, 4 hours). A yellow oil obtained after extraction was subjected to sublimation at 100°/0.2 mm yielding 45 mg. (70%) of recovered 1,7-naphthyridine. The yellow residue remaining after sublimation was dissolved in the mixture of chloroform and methanol (1:1) and applied for the plate (10 x 10 cm) covered with silica gel PF_{254}. The chromatogram was developed with a mixture of benzene/ethyl acetate/methanol (4:2:1). From the first band (the higher R_F), 5 mg. of crude 8-amino-1,7-naphthyridine (**1**) and from the second band, 5 mg. of crude 2-amino-1,7-naphthyridine (**17**) were isolated. These compounds were identified by comparison of properties with reference samples. The chromatogram showed still the presence of small amounts of two compounds which could not be identified.

GLC Analyses.

The analyses of the reaction mixture obtained by amination of **11** and **12** was carried out with Becker gas chromatograph (Delft, The Netherlands) with flame-ionisation detection and nitrogen as a carrier gas, using stainless steel column (length 200 cm, internal diameter 1/8 inch) filled with 2.1 g. of 9.2% OV-275 on Chromosorb W. HP 100-200 mesh. The column temperature was 217°, and the flow rate of the carrier gas 10 ml./23 seconds. Relative retention times were 5-chloro-1,7-naphthyridine 0.32; 5-bromo-1,7-naphthyridine 0.44; 8-amino-1,7-naphthyridine 0.83; 5-chloro-8-amino-1,7-naphthyridine 1.00 (used as reference); 5-bromo-8-amino-1,7-naphthyridine 1.46. For the analysis of the product of the amination of 5-chloro-1,7-naphthyridine, 5-bromo-8-amino-1,7-naphthyridine was used as reference.

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