Synthesis of 2- and 4-Amino-1,5-naphthyridines

Ellis V. Brown and Andrew C. Plasz

Department of Chemistry
University of Kentucky

The structure of the product obtained from the reaction of potassium amide in liquid ammonia on 1,5-naphthyridine has been identified as 4-amino-1,5-naphthyridine by comparison with a known sample. The 2-amino isomer was not detected in the mixture. The NMR spectra for 2- and 4-amino-1,5-naphthyridine along with the corresponding chloroisomers are described.

Upon preparation of 2-amino-1,5-naphthyridine by Czuba's method (1) (Skraup reaction) from 2,5-diaminopyridine, it was noted that the resulting solid did not give the NMR spectrum that has been reported by Paudler and Kress (2) for 2-amino-1,5-naphthyridine prepared *via* the Chichibabin reaction on 1,5-naphthyridine. We then repeated the Chichibabin reaction of Paudler and Kress (2) and obtained a product which gave an NMR spectrum very similar to that which Paudler and Kress reported but different from the NMR spectrum of Czuba's product. The infrared spectra of the two compounds were also different. A mixed melting point of the two compounds was depressed indicating along with their NMR and infrared spectra that the two compounds were not the same.

It was now of interest to prepare 2-amino-1,5-naphthridine by a third unambiguous method in order to determine which if either of the two previously made products were correct. 2-Chloro-1,5-naphthyridine prepared by the method of Brown and Plasz (3) was mixed with phenol and acetamide and heated to 190° for 3 hours while bubbling gaseous ammonia through the mixture. The product from this reaction gave the exact NMR and infrared spectrum of Czuba's compound. A mixture melting point with a sample of the product from Czuba's Skraup reaction showed no depression. When a sample of of the Chichibabin product was mixed with the ammonolysis product, the melting point was depressed. The ammonolysis product and Czuba's product both gave the same unique mass spectrum. Their spectra were characterized in that both lost 26 mass units as C_2H_2 from the molecular ion instead of the 27 mass units as HCN which is the primary fragmentation normally found in nitrogen heterocycles. This phenomena is discussed more fully in the following paper (4). The product from the Chichibabin reaction expels HCN from the parent peak to give its largest fragment.

It has been shown that the product isolated from the Chichibabin reaction of pyridine is 2-aminopyridine (5). The 4-amino isomer may be formed but this depends upon the quantity and quality of the sodium amide used in the reaction (6). Bergstrom (7) has shown that potassium amide in liquid ammonia reacts with quinoline in a sealed tube after 8 days to give 53 percent 2-aminoquinoline and 10 percent of 4-aminoquinoline. If positions *alpha* to the nitrogen are blocked and the 4-position is free, the amino group will be introduced at the four position. This phenomenon has been shown by 2,6-dimethylpyridine (8) and quinoline-2-carboxylic acid (9). An increase in the amide used or raising the reaction temperature can also give rise to formation of the 4-isomer (6).

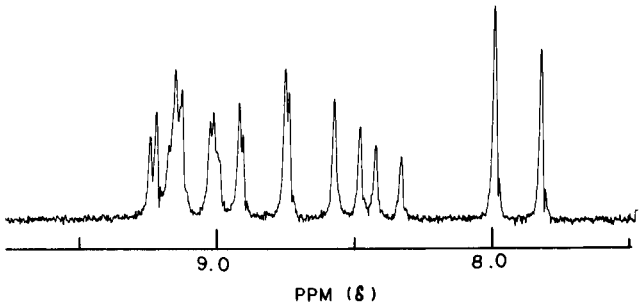

FIGURE 1

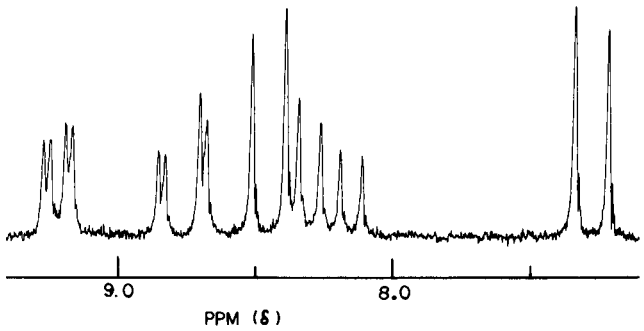

FIGURE 2

Hart (12) has prepared 2-amino-1,5-naphthyridine from the Chichibabin reaction. The conditions Hart used were relatively mild. He dissolved sodium in liquid ammonia, added the 1,5-naphthyridine and let the ammonia evaporate. After addition of 20% sodium hydroxide solution, the product was filtered and characterized by the picrate it formed and conversion to 2-hydroxy-1,5-naphthyridine by diazotization. We have repeated Hart's Chichibabin procedure on 1,5-naphthyridine without success. Neither 2-amino nor 4-amino-1,5-naphthyridine was detected in the reaction products. The only organic material isolated was unreacted 1,5-naphthyridine. It might be noted that Paudler and Kress (2) also could not duplicate Hart's Chichibabin reaction.

It has been shown fairly conclusively above that 1,5-naphthyridine does not yield the expected 2-amino isomer under the conditions of the Chichibabin reaction using potassium amide in liquid ammonia in a sealed tube. Since it has also been shown above that the 4-isomer is possible, 4-amino-1,5-naphthyridine was synthesized according to Case and Brennan (10). The NMR, infrared, and mass spectra of 4-amino-1,5-naphthyridine were identical to the corresponding spectra of the product isolated from the Chichibabin reaction. A mixture melting point of 4-amino-1,5-naphthyridine with the Chichibabin product was not depressed. Thus, it is clearly established that the structure of the Chichibabin product depends on the conditions employed. The expected 2-amino derivative being obtained under "mild" conditions and the unexpected 4-amino derivative being formed under "severe" conditions.

The NMR spectrum of the crude material obtained after removal of the organic solvents gave no indication that any 2-amino-1,5-naphthyridine was present in the sealed tube Chichibabin reaction. The NMR spectrum of the solids remaining after evaporation of the aqueous solution gave the same result. Unreacted 1,5-naphthyridine was detected in the spectra however.

The NMR spectrum of 1,5-naphthyridine in deuterated trifluoroacetic acid shows a downfield shift from TMS when compared to its spectrum in deuteriochloroform. Similar results have been noted in 1,6- and 1,7-naphthyridine (11). The data for both spectra appear in Table I. The NMR spectra of 2-chloro- and 4-chloro-1,5-naphthyridine are also described in Table I. Both spectra have the expected AB system for the substituted ring and AMX system for the unsubstituted ring, along with typical chemical shifts and coupling constants. The spectral data for 2-amino-1,5-naphthyridine (Fig. 1) and 4-amino-1,5-naphthyridine (Fig. 2) are in Table I. Both spectra show the expected AB and AMX systems with typical chemical shifts and coupling constants. In the spectra of the Chichibabin ammination product (4-amino), the chemical shifts are slightly different from the published values (11); however, on saturation of the solution a closer approximation to the published values was obtained.

TABLE I

NMR Spectra of Some 1,5-Naphthyridines
Chemical Shifts (a)

Compound	Solvent	H_2	H_3	H_4	H_6	H_7	H_8	Coupling Constants (b)
1,5-Naphthyridine (d)	$CDCl_3$	8.97	7.52	8.40	8.97	7.52	8.40	$J_{2,3}$ 4.1, $J_{2,4}$ 1.8 $J_{3,4}$ 8.0 $J_{4,8}$ 0.6
1,5-Naphthyridine (c)	DTFAA	9.52	8.52	9.43	9.52	8.52	9.43	$J_{2,3}$ 3.3 $J_{3,4}$ 8.1
2-Amino-1,5-Naphthyridine (c)	DTFAA	---	7.90	8.78	9.13	8.42	9.02	$J_{3,4}$ 9.5 $J_{6,7}$ 5.0 $J_{6,8}$ 1.2 $J_{7,8}$ 8.0 (e)
4-Amino-1,5-Naphthyridine (c)	DTFAA	8.36	7.24	---	9.08	8.14	8.65	$J_{2,3}$ 7.0 $J_{6,7}$ 4.5 $J_{6,8}$ 1.3 $J_{7,8}$ 8.2
2,Chloro-1,5-Naphthyridine (c)	CCl_4	---	7.48	8.19	8.78	7.53	8.16	$J_{6,8}$ 1.6 $J_{7,8}$ 8.6 $J_{3,4}$ 8.0 $J_{6,7}$ 4.3
4-Chloro-1,5-Naphthyridine (c)	CCl_4	8.66	7.45	---	8.89	7.41	8.27	$J_{2,3}$ 4.5 $J_{6,7}$ 4.0 $J_{6,8}$ 1.5 $J_{7,8}$ 8.4

(a) Chemical shifts (δ) are recorded as ppm downfield from TMS. (b) Coupling constants (J) are in cps. (c) Concentration 25 mg. of compound in 0.5 ml. of solvent. (d) Reference (11) 1.0 *M* solution. (e) $J_{4,8}$ 0.7 was measured from spectra run on Varian HA-60. All other data obtained from spectra run on Varian T-60.

EXPERIMENTAL

The melting points were taken on a Fisher-Johns block and are corrected. Infrared spectra were taken with a Beckman IR-8 spectrometer using potassium bromide pellets. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer with an ionizing potential of 70 eV and inlet temperature at 200°. The nuclear magnetic resonance spectra were obtained with Varian T-60 spectrometer and also with a Varian HA-60 spectrometer for the 2- and 4-amino-1,5-naphthyridines. All NMR spectra were obtained using 25 mg. of sample and 0.5 ml. of solvent.

Preparation of 2-Amino-1,5-naphthyridine.

Method A. Skraup Reaction.

2-Amino-1,5-naphthyridine was prepared by the method of Czuba (1). The crude amine was sublimed twice under vacuum at 190-200° and then recrystallized from ethanol to give light yellow clusters melting at 207-207.5° (lit. (1) 204-205°).

Method B. Ammonolysis Reaction.

Two g. of 2-chloro-1,5-naphthyridine (3) was mixed with 6 g. of phenol and 4 g. of acetamide and heated to 190° in an oil bath. Gaseous ammonia was passed through the mixture for three hours while maintaining the temperature around 190°. The mixture was cooled and 20 ml. of 50 percent sodium hydroxide was added. The precipitated solids were filtered and gave 0.60 g. of recovered 2-chloro-1,5-naphthyridine melting at 109-112°. The mother liquor was then basified with sodium hydroxide pellets until a yellow precipitate formed. This was filtered and washed with two 5 ml. portions of ice cold water and dried at 110° overnight. The 0.70 g. (39.8%) of crude amine was sublimed under vacuum. The first fraction 100-160° yielded 0.32 g. (18.2%) melting at 203-206°. The second fraction, 160-170° gave 0.19 g. (10.8%) melting at 206-208°. The mixture melting point of fraction two with the product from the Skraup reaction melted at 206-208°. The NMR, infrared and mass spectra of both fractions were the same as Czuba's compound. The picrate was prepared and melted at 275-277° (lit. 273-274° (1), 270° (12)).

Preparation of 4-Amino-1,5-naphthyridine.

Method A. Ammonolysis Reaction.

4-Amino-1,5-naphthyridine was prepared by the method of Case and Brennan (10). The crude amine was sublimed twice under vacuum at 160-180° to give white cubes melting at 203.5-204.5° (lit. (10) 202-203°).

Method B. Chichibabin Reaction on 1,5-naphthyridine.

The method of Paudler and Kress (2) was followed exactly and after 8 days the tube was opened and worked up following their directions. After the organic layer was separated from the aqueous layer, the organic solvents were evaporated to give 0.32 g. of yellow solid. The NMR spectrum corresponded to 4-amino-1,5-naphthyridine with some unreacted 1,5-naphthyridine as an impurity. The aqueous layer was extracted 3 times with 25 ml. of benzene and the benzene evaporated to give 0.72 g. of yellow solid whose NMR again corresponded to 4-amino-1,5-naphthyridine with 1,5-naphthyridine as an impurity.

These two fractions were combined and sublimed under vacuum at 160° to give 0.79 g. of light yellow powder melting at 188-197°. An additional sublimation did not alter the melting point. This was then recrystallized from ethanol to give 0.44 g. yellow cubes at 200-202°. The mixed melting point with 4-amino-1,5-naphthyridine was 200-201° and the NMR, infrared and mass spectra of the two compounds were identical.

An NMR of the solids from the evaporated aqueous layers showed only a trace of the 4-amino isomer. In none of the reaction mixture was any 2-amino-1,5-naphthyridine detected. It was found when repeating the reaction that freshly sublimed 1,5-naphthyridine gave a 25 percent better yield than 1,5-naphthyridine which has been stored in a desiccator for two weeks. The picrate of 4-amino-1,5-naphthyridine was prepared and melted at 238-239.5°.

Hart's Chichibabin Reaction.

Ammonium nitrate (0.1 g.) was dissolved in 40 ml. of liquid ammonia. Sodium (0.1 g.) was added and formed a deep purple flocculent solid. After the sodium had reacted, 0.40 g. of 1,5-naphthyridine (m.p. 75°) was added. The ammonia was allowed to evaporate and 5 ml. of 20% sodium hydroxide added to the crusty residue. The white solids which did not dissolve were filtered. This material (0.14 g.) was identified as 1,5-naphthyridine by its NMR spectrum and melting point 73-75°. No 2-amino or 4-amino-1,5-naphthyridine could be detected in this fraction. The mother liquor from the reaction mixture was evaporated to dryness and an NMR spectrum on the solids dissolved in deuterated trifluoroacetic acid showed no organic material present in any significant amount. The remaining inorganic solids (1.26 g.) were sublimed under vacuum at 200° for 1 hour. A very small amount of material was obtained and identified by its NMR spectrum as 1,5-naphthyridine.

REFERENCES

(1) W. Czuba, *Rec. Trav. Chim.*, 82, 988 (1963).

(2) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, 33, 1384 (1968).

(3) E. V. Brown and A. C. Plasz, *ibid.*, 32, 241 (1967).

(4) E. V. Brown, A. C. Plasz and S. R. Mitchell, *J. Heterocyclic Chem.*, 7, (1970), submitted for publication.

(5) A. E. Chichibabin and O. A. Seide, *J. Russ. Phys. Chem. Soc.*, 46, 1216 (1914); *Chem. Abstr.*, 9, 1901 (1915).

(6) M. T. Leffler, "Org. Reactions," 1, 91 (1942) and references contained therein.

(7) F. W. Bergstrom, *J. Org. Chem.*, 2, 411 (1937).

(8) A. E. Chichibabin, *J. Russ. Chem. Phys. Soc.*, 47, 835 (1915).

(9) F. W. Bergstrom, *J. Org. Chem.*, 3, 233 (1938).

(10) F. H. Case and J. A. Brennan, *J. Am. Chem. Soc.*, 81, 6297 (1959).

(11) W. W. Paudler and T. J. Kress, "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., John Wiley and Sons, Inc., New York, N. Y., 1969, pp. 86-121.

(12) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).

Received January 26, 1970 Lexington, Kentucky 40506