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Ten π-Electron Nitrogen Heterocyclic Compounds III: The Synthesis and NMR Spectra of Some 1,6-Naphthyridines

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The synthesis of 1,6-naphthyridine and of some 4-substituted 1,6-naphthyridines are described. The analysis of the NMR spectra and a correlation between the chemical shifts of H_2, H_5, H_7, H_8, and Brown's σ_p^+ values are reported.

We have recently been studying the chemistry of some heteroaromatic systems (1,2), and now wish to report the synthesis and nmr analyses of 1,5-naphthyridine, 1,6-naphthyridine and of some 4-substituted 1,6-naphthyridines.

The 1,6-naphthyridine was prepared by modification of the procedures of Hauser (3), Albert (4), and Moeller and Suss (5).

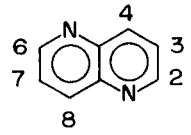
Treatment of 4-hydroxy-1,6-naphthyridine (I) with dimethyl sulfate in base yields a compound isomeric with the 4-methoxy-1,6-naphthyridine (III) obtained by treatment of the chloro compound II with sodium methoxide. Based on ample precedence in the 4-pyridone series (6), this compound is the *N*-methyl derivative VIII. The nmr spectrum (Table I) further confirms this structural assignment.

NMR Analyses

The analyses of the nmr spectra of the 1,5- and 1,6-naphthyridines are reasonably straight forward.

1,5-Naphthyridine.

As expected, the spectrum of 1,5-naphthyridine (XII) (Fig. 2) is simply that of an ABX system. The



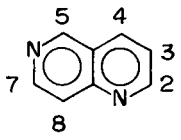
XII

most deshielded proton is H_2 (and its symmetrical counterpart H_6), since it is subject to the deshielding influence of the ring nitrogen. Analysis by first order splitting rules and consideration of the coupling constants involved, allows the assignments, reported in Table I, to be made.

1,6-Naphthyridines.

A. Chemical shifts.

Inspection of the spectrum of 1,6-naphthyridine (XIII, Fig. 1) shows the presence of the expected splitting patterns, ABX (for H_2, H_3, H_4), AX (for H_7, H_8), Y (for H_5). An expanded scale spectrum



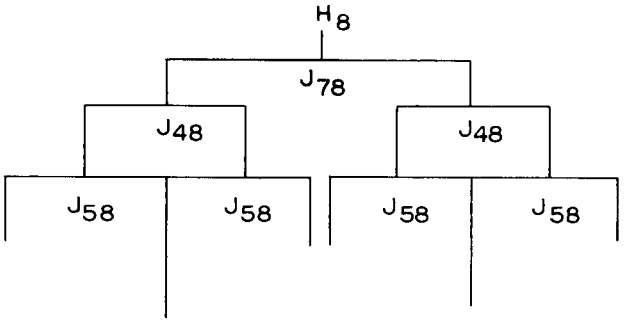
XIII

shows some additional splitting due to long-range coupling effects. The singlet at 0.72 τ is, in fact, a doublet with J = 0.45 cps. thus this proton is coupled to one of the other ring protons.

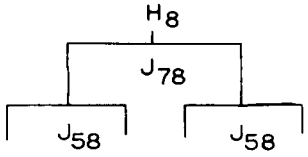
A decision as to which set of peaks is due to H_2 and H_7 (the remaining most deshielded protons) is readily possible by considering that H_2 is part of an ABX system and will contain J_{23} and J_{24}, while H_7 is part of an AX system. Thus, the peaks centered at 0.90 τ are due to H_2 and those centered at 1.24 τ are caused by H_7. The A counterpart of H_7 corresponds to the "doublet" centered at 2.07 τ and is consequently H_8. This leaves H_3 and H_4 to be identified. The nature of the splitting pattern clearly shows that the "broad doublet" centered at 1.72 τ is due to H_4, while H_3 is at 2.48 τ.

B. Coupling constants.

The coupling constants for the various adjacent positions are readily obtainable from the nmr spectrum by first-order analysis. The coupling between H_7 and H_8 is shown in both "doublets" of the two hydrogens involved. J_{23}, J_{34} and J_{24} are also readily identifiable. An expanded scale spectrum of the H_4 portion of the spectrum shows secondary coupling (J = 0.45 cps) of this proton. This coupling might be due to spin-spin interaction with either H_8 or H_5. That we are dealing with a coupling between H_4 and H_8 is clearly discernable from the expanded-scale spectrum of H_8 which shows that this proton is coupled to two other protons in addition to its being coupled to H_7, as shown by the diagram below:



This now accounts for all of the observed spin-spin couplings in this molecule (see Table II). Further confirmation of the presence of J_{48} and J_{58} is found in the analysis of the 4-substituted 1, 6-naphthyridines, where H_8 has the splitting pattern:



The proton at position 5 is equally split into a doublet (see spectrum in Figure 1 and Table II). For the sake of completeness, the nmr spectrum of 2, 6-naphthyridine recently reported (7) is included in Table I.

Correlation of Proton Chemical Shifts with Substituent Constants.

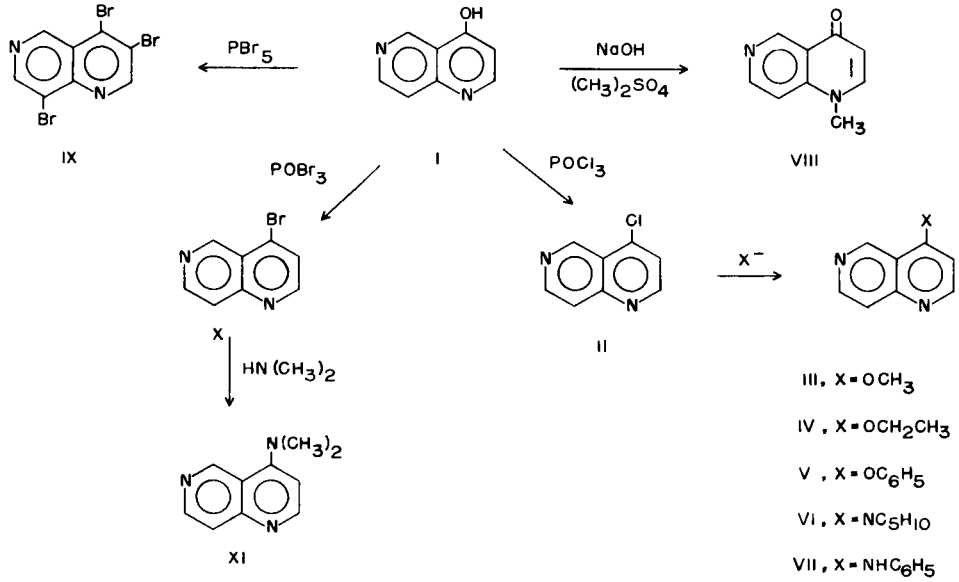
It is of interest to study the effect of various substituents in the 4-position of 1, 6-naphthyridines on the proton chemical shifts of the protons in this ring system (8). This system is unique since the substituent in the 4-position can affect the electron density of both of the nitrogen atoms by resonance, and one would anticipate that these changes would be reflected as chemical shift changes of the protons on the carbon atoms adjacent to the nitrogen atoms. Furthermore, the substituent will affect the proton on C_8 directly by resonance interaction. One consequently anticipates a linear correlation between Browns (9) σ_p^+ substituent constants and the chemical shifts of H_2, H_5, H_7 and H_8. This correlation is shown by the data presented in Fig. 3. The correlation between H_5 and σ_p^+ might well be subject to some steric interference between the substituent on C_4 and the proton C_5. We suggest that this accounts for the poor correlation between the chemical shift of H_5 and σ_p^+. Unfortunately, we have not yet been able to introduce a strongly electron-withdrawing substituent into position 4 of the 1, 6-naphthyridines.

NMR Spectra of Some Substituted-1, 6-Naphthyridines in Deuterotrifluoroacetic Acid.

Due to the poor solubility of some 3, 4-disubstituted-1, 6-naphthyridines in deuterochloroform, the spectra of the protonated compounds were obtained in deuterotrifluoroacetic acid (Table 3). In this solvent, the coupling between H_8 and H_5 is no longer observable, as evidenced by the "pure" doublet nature of H_8. The clean doublet observed for H_7 in deuteriochloroform is now further split (J = 0.7 cps.). The same coupling is observed in H_5, which now appears as a doublet (10). Thus protonation (previously shown to occur at N_6 (4)) causes coupling between H_5 and H_7.

Synthesis of 3, 4, 8-tribromo-1, 6-naphthyridine.

During an attempted synthesis of 4-bromo-1, 6-naphthyridine by displacement of the 4-hydroxyl grouping, utilizing phosphorus pentabromide, there was obtained a material which gave a correct analysis for $C_8H_3N_2Br_3$. The nmr spectrum of this compound shows three one proton singlets at 0.76 τ, 0.96 τ and 0.97 τ, respectively. The position of the three bromine atoms must consequently be such that no hydrogens are on adjacent carbon atoms of the 1, 6-napthyridine. It is certainly reasonable to expect that one of the bromine atoms is at position 4. This



requires that one of the remaining two bromine atoms is at either position 2 or 3 while the other one must be at position 7 or 8. If H_3 were still present, one would expect a singlet between 2-3 τ since H_3 in all of the 4-substituted-1,6-naphthyridines which we have studied invariably resonates in this region. The validity of this argument is strengthened since it is known that the proton chemical shifts of aromatic protons are essentially unaltered by introduction of a bromine in the *ortho* position. Consequently, the second bromine atom is at position 3. The remaining bromine atom can be placed at either position 7 or 8, with position 8 preferred, based on the same argument as applied above. This assignment is assured as being correct by the observation that the nmr spectrum of the tribromo-compound in deutero-trifluoroacetic acid again shows spin-spin coupling (J = 0.7 cps.) between H_5 and H_7. The tribromo-compound consequently is 3,4,8-tribromo-1,6-naphthyridine.

TABLE I

Proton Chemical Shifts of Various Naphthyridines (a)

Compound	Chemical Shifts (τ) at Positions:							
	1	2	3	4	5	6	7	8
1,5-Naphthyridine	--	1.03	2.42	1.60	--	1.03	2.42	1.60
2,6-Naphthyridine (b)	0.61	--	1.25	2.22	0.61	--	1.25	2.22
1,6-Naphthyridine	--	0.90	2.48	1.72	0.72	--	1.24	2.07
4-Phenoxy-1,6-Naphthyridine	--	1.18	3.35	--	0.17	--	1.18	2.08
4-Methoxy-1,6-Naphthyridine	--	1.17	3.25	--	0.45	--	1.25	2.20
4-Ethoxy-1,6-Naphthyridine	--	1.12	3.24	--	0.40	--	1.29	2.20
4-Chloro-1,6-Naphthyridine	--	1.08	2.48	--	0.38	--	1.17	2.12
4-Bromo-1,6-Naphthyridine	--	1.25	2.35	--	0.52	--	1.28	2.21
4-Dimethylamino-1,6-Naphthyridine	--	1.40	3.41	--	0.60	--	1.41	2.26
4-Anilino-1,6-Naphthyridine	--	1.26	3.05	--	0.45	--	1.26	2.26
4-Piperidyl-1,6-Naphthyridine	--	1.28	3.27	--	0.67	--	1.40	2.23
3,4,8-Tribromo-1,6-Naphthyridine	--	0.96	--	--	0.76	--	0.97	--
1-Methyl-4-oxo-1,4-dihydro-1,6-naphthyridine	--	2.38	3.86	--	0.39	--	1.21	2.73

(a) Numbering as in text, dilute solutions in $CDCl_3$. (b) Taken from ref. 7.

TABLE II

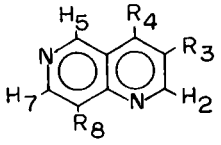
Spin-Spin Coupling Constants (cps) of Various Naphthyridines

Compound	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,8}$	$J_{7,8}$
1,5-Naphthyridine	4.1	1.8	8.0	--	--	8.0
2,6-Naphthyridine (a)	--	--	6.0	--	--	6.0
1,6-Naphthyridine	4.1	1.9	8.2	0.45	0.45	6.0
4-Phenoxy-1,6-Naphthyridine	5.0	--	--	--	0.70	6.0
4-Methoxy-1,6-Naphthyridine	5.5	--	--	--	0.45	6.0
4-Ethoxy-1,6-Naphthyridine	5.0	--	--	--	0.45	6.0
4-Chloro-1,6-Naphthyridine	5.0	--	--	--	0.45	6.0
4-Bromo-1,6-Naphthyridine	5.0	--	--	--	0.45	6.0
4-Dimethylamino-1,6-Naphthyridine	5.5	--	--	--	--	6.0
4-Anilino-1,6-Naphthyridine	5.5	--	--	--	--	6.0
4-Piperidyl-1,6-Naphthyridine	5.0	--	--	--	0.45	6.0
1-Methyl-4-oxo-1,4-dihydro-1,6-naphthyridine	8.0	--	--	--	--	6.0

(a) From ref. 7.

TABLE III

Proton Chemical Shifts and Coupling Constants of
Various Naphthyridines in Deuterotrifluoroacetic Acid



Compound	H_2	R_3	H_5	H_7	H_8	$J_{2,3}$	$J_{7,8}$	$J_{5,7}$
$R_3 = CO_2Et$ $R_4 = OH$ $R_8 = H$	-0.60	5.05q. (a) 8.48t. (b)	0.87	1.09	1.67	--	8.0	0.7
$R_3 = CO_2H$ $R_4 = OH$ $R_8 = H$	0.16	--	0.78	1.09	1.63	--	8.0	0.7
$R_3 = H$ $R_4 = OH$ $R_8 = H$	1.88	3.13	0.35	1.36	1.75	8.0	8.0	0.7
$R_3 = H$ $R_4 = Cl$ $R_8 = H$	1.65	3.18	0.48	1.18	1.73	8.0	7.0	0.7
$R_3 = H$ $R_4 = NHNH_2$ $R_8 = H$	1.51	2.53	-0.25	1.00	1.60	8.0	7.0	0.7
$R_3 = H$ $R_4 = OC_6H_5$ $R_8 = H$	1.84	3.30	0.50	1.36	1.95	7.0	7.0	0.7
$R_3 = Br$ $R_4 = Br$ $R_8 = Br$	0.47	--	0.00	0.77	--	--	--	0.7

(a) q = quartet. (b) t = triplet.

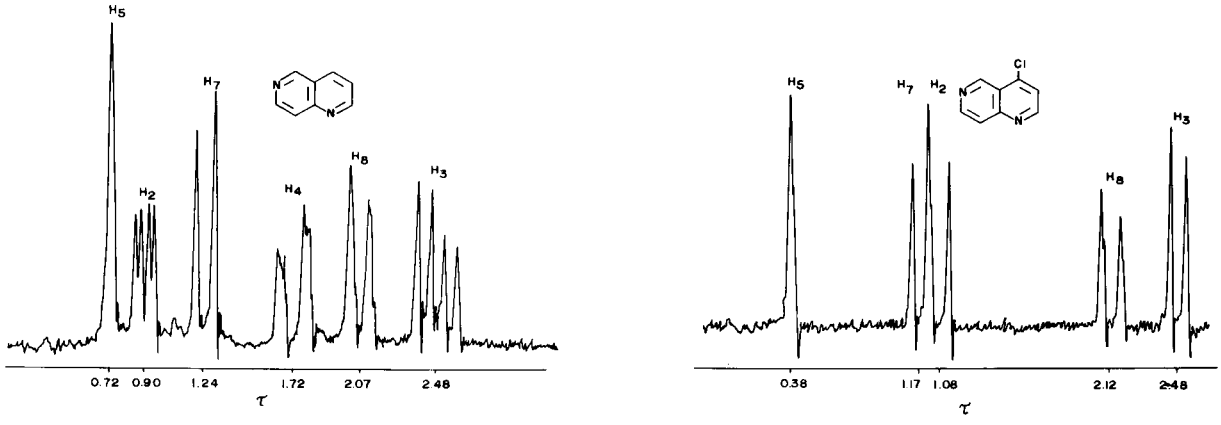


Fig. 1

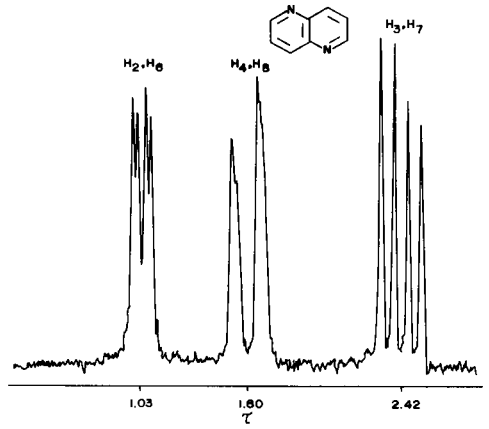


Fig. 2

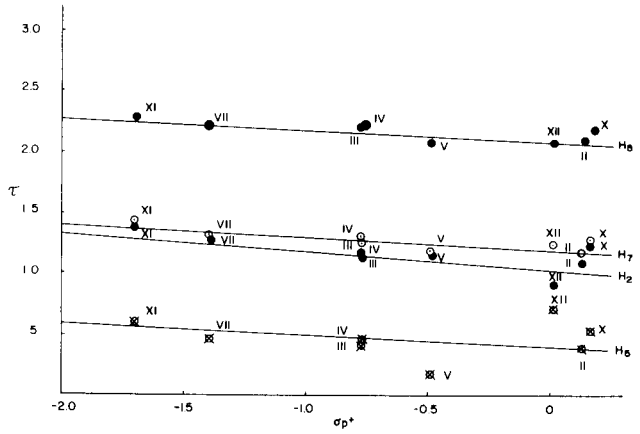


Fig. 3. τ values of 4-substituted 1,6-naphthyridines as a function of σ_p^+. Subscripted H refers to the proton in the naphthyridine ring which is correlated. To identify points see flow sheet.

EXPERIMENTAL (11)

4-Hydroxy-3-carbethoxy-1,6-naphthyridine.

This compound was prepared (3) from ethyl 1-carbethoxy-2-(4-aminopyridyl)crotonate by cyclization in Dowtherm A. It was found necessary to use a 20:1 ratio of Dowtherm A to crotonate (m.p. 74-75°) in order to obtain a satisfactory yield.

4-Hydroxy-3-carboxy-1,6-naphthyridine.

The reported procedure (5) for the preparation of this substance was modified as follows: after the saponification was completed, the reaction mixture was diluted by one third of its volume with water and neutralized with concentrated hydrochloric acid to litmus to yield 95-99% of the desired 4-hydroxy-3-carboxy-1,6-naphthyridine.

4-Hydroxy-1,6-naphthyridine (I).

The decarboxylation of 4-hydroxy-3-carboxy-1,6-naphthyridine was carried out on small amounts (5 g.) of the acid in a pyrex test tube placed in a sublimation apparatus heated to 280-285°. After the effervescence ceased the test tube was evacuated to 0.1 mm. and heated at 250-270° until sublimation was complete. This method yields I (m.p. 304-305°) as pale yellow crystals in 90-95% yield.

4-Chloro-1,6-naphthyridine.

This compound was prepared in 75% yield by the method of Goldberg, Theobald, and Williamson (12).

4-Hydrazino-1,6-naphthyridine.

This substance was obtained from the 4-chloro compound (II) and was converted to 1,6-naphthyridine (m.p. 31°) by the method described by Albert (ref. 4).

1-Methyl-4-oxo-1,4-dihydro-1,6-naphthyridine (VIII).

To a stirred solution of 310 mg. (2.12 mmole) of 4-hydroxy-1,6-naphthyridine in 15 ml. of 1% sodium hydroxide solution, cooled to 10° was added 0.3 ml. (0.4 g., 3 mmole) of dimethylsulfate, and the solution was stirred for 2 hours. The basic solution was extracted with 4 x 50 ml. portions of chloroform. Evaporation of the combined extracts gave 0.13 g. (38%) of a pale yellow solid. Sublimation at 200°/0.1 mm. gave yellow crystals, m.p. 208-209°.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.50; H, 5.03; N, 17.50. Found: C, 67.71; H, 5.35; N, 17.96.

4-Methoxy-1,6-naphthyridine (III).

A stirred solution of 165 mg. (1.00 mmole) of 4-chloro-1,6-naphthyridine, and 2.0 mmole of sodium methoxide in 3 ml. of methanol was refluxed overnight. Water was added (5 ml.) and the solution was extracted with 3 x 30 ml. portions of ethyl ether, which were dried, and evaporated. The residue was recrystallized twice from cyclohexane giving white needles m.p. 115-116°, 41 mg. (25%) of 4-methoxy-1,6-naphthyridine.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.50; H, 5.03; N, 17.50. Found: C, 67.20; H, 5.11; N, 17.40.

4-Ethoxy-1,6-naphthyridine (IV).

Absolute ethanol, 25 ml. and 300 mg. (1.80 mmole) of II was stirred and refluxed overnight, cooled to room temperature and evaporated to dryness. The residue, 0.16 g. (50%), was chromatographed on an alumina column, and eluted with ether. Three recrystallizations from cyclohexane gave 4-ethoxy-1,6-naphthyridine as white fluffy needles (m.p. 65-66°).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.83; H, 5.85; N, 16.25.

4-Phenoxy-1,6-naphthyridine (V).

A solution of 695 mg. (1.22 mmole) of potassium hydroxide, 5 g. of phenol and 200 mg. (1.22 mmole) of II was heated at 150° for 3 hours, cooled and poured into an excess of 2 *N* sodium hydroxide, and extracted with 4 fifty ml. portions of ether. The extracts were combined, washed with water, dried and evaporated to dryness. The residue was chromatographed on Grade 3 neutral alumina. Elution with ether yielded 0.15 g. of V as white needles (m.p. 86-87°), from ether; (55% of theory).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.40; H, 4.73; N, 12.30.

4-(1-Piperidyl)-1,6-naphthyridine (VI).

A mixture of 0.670 g. (4.0 mmole) of II and 0.79 ml. (0.68 g., 8.2 mmole) of piperidine was warmed on a steam bath for 5 minutes, cooled and 10 ml. of 10% aqueous sodium hydroxide solution was added. The resulting solution was then extracted with 4 fifty ml. portions of chloroform and the combined chloroform extracts were dried over anhydrous sodium carbonate. Removal of the chloroform under reduced pressure left an oil which was chromatographed on neutral, grade 3 (Brockman) alumina. Elution with ether yielded a low melting solid which was pure by TLC. For analysis this material was converted to the picrate (m.p. 216-218°).

Anal. Calcd. for $C_{19}H_{18}N_6O_7$: C, 51.58; H, 4.10; N, 19.00. Found: C, 51.36; H, 4.00; N, 19.09.

3,4,8-Tribromo-1,6-naphthyridine (IX).

A mixture of 400 mg. (2.74 mmole) of I and 11.8 g. (27 mmole) of phosphorus pentabromide was heated on a steam bath for one hour, cooled in an ice bath and diluted with 25 ml. of water. The mixture was filtered and the filtrate was extracted with hot chloroform, which was dried (anhydrous sodium carbonate) and evaporated giving tan needles (m.p. 171-173°). Three recrystallizations from cyclohexane yielded pale yellow needles (0.2 g., 21% of theory, m.p. 177-179°).

Anal. Calcd. for $C_8H_3Br_3N_2$: C, 26.18; H, 0.82; N, 7.63. Found: C, 25.84; H, 0.80; N, 7.37.

4-Bromo-1,6-Naphthyridine (X).

Molten phosphorus oxybromide (10.0 g.) was added to 1.00 g. (6.8 mmole) of I and the resulting slurry was heated on a steam bath for one hour, cooled and slowly poured into ice-water (100 ml.). The clear solution was neutralized with sodium acetate (to Congo red paper) and extracted with three 75 ml. portions of chloroform. The extracts were washed with three 100 ml. portions of aqueous sodium bicarbonate followed by two portions of 100 ml. of water. The dried chloroform solution was then evaporated to dryness to yield 0.813 g. (57% of theory) of X (m.p. 92-93°). Recrystallization from ether did not alter the melting point.

Anal. Calcd. for $C_8H_5BrN_2$: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.66; H, 2.37; N, 13.28.

4-Dimethylamino-1,6-Naphthyridine (XI).

4-Bromo-1,6-naphthyridine (300 mg., 1.43 mmole) and 2.0 ml. (1.36 g., 30 mmole) of dimethyl amine were heated in a sealed tube at 135° for 16 hours. The cold reaction mixture was dissolved in dilute hydrochloric acid and made alkaline with 10 *N* aqueous sodium hydroxide. The oily layer was separated and the excess dimethyl amine was removed by warming the solution under reduced pressure. The oil was converted to the picrate for analysis (m.p. 207-209°).

Anal. Calcd. for $C_{16}H_{14}N_6O_7$: C, 47.77; H, 3.51; N, 20.89. Found: C, 47.92; H, 3.46; N, 20.70.

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(10) A similar observation has recently been made for purine (*cf.* ref. 8).

(11) NMR spectra were obtained with a Varian A-60 spectrometer. The spectra are in $CDCl_3$ at approximately 1 *M* concentration. The microanalyses were performed by Mrs. C. Warner of this department. Melting points are corrected. 1,5-Naphthyridine was purchased from Aldrich Chemical Company, Inc.

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