

Naphthyridine Chemistry X. Protonation and Methylation of the 1,X-Naphthyridines (I)

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The site of protonation in the 1,X-naphthyridines which, of course, is only questionable in the 1,6- and the 1,7-isomers, has never been proven.

Albert (2) has suggested that, since isoquinoline is a stronger base than quinoline, protonation should occur at the N₆ and at the N₇ position in the 1,6- and in the 1,7-naphthyridine, respectively. The pK_a values of the various naphthyridines, quinoline, and of isoquinoline are listed in Table I. The base-lowering effect of the second nitrogen atom in the naphthyridines, as compared to the quinolines, is clearly evident from these data.

TABLE I

Ionization Constants (a)

Compound	pK _a (in water, 20°)
1,5-Naphthyridine	2.91
1,6-Naphthyridine (V)	3.78
1,7-Naphthyridine (IX)	3.63
1,8-Naphthyridine (I)	3.39
Quinoline	4.94
Isoquinoline	5.40

(a) Values taken from reference 2.

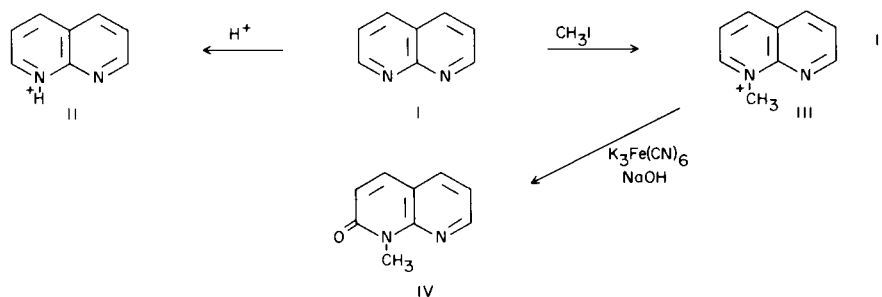
One method with which to establish the site of protonation in the unsymmetrical 1,X-naphthyridines appeared to us to lie in a comparison of the nmr spectra of the mono-N-methylmethiodides of the naphthyridines, with those of the monoprotonated species. If the spectra of the two classes of compounds are similar, we can reasonably conclude that the sites of protonation and N-methylation are the same. This is not necessarily to be expected since protonation is a kinetically controlled process, while alkylation is a thermodynamically controlled one.

The data presented in Table II do, however, clearly show that both of these processes involve the same nitrogen atom. This is especially borne out by the fact that the methylated and the protonated 1,6- and 1,7-naphthyridines show the across-nitrogen coupling only observed in those naphthyridines (3) where the nitrogen lone-pair has been removed by alkylation or by protonation (J_{5,7} and J_{6,8} in the 1,6- and the 1,7-isomers, respectively).

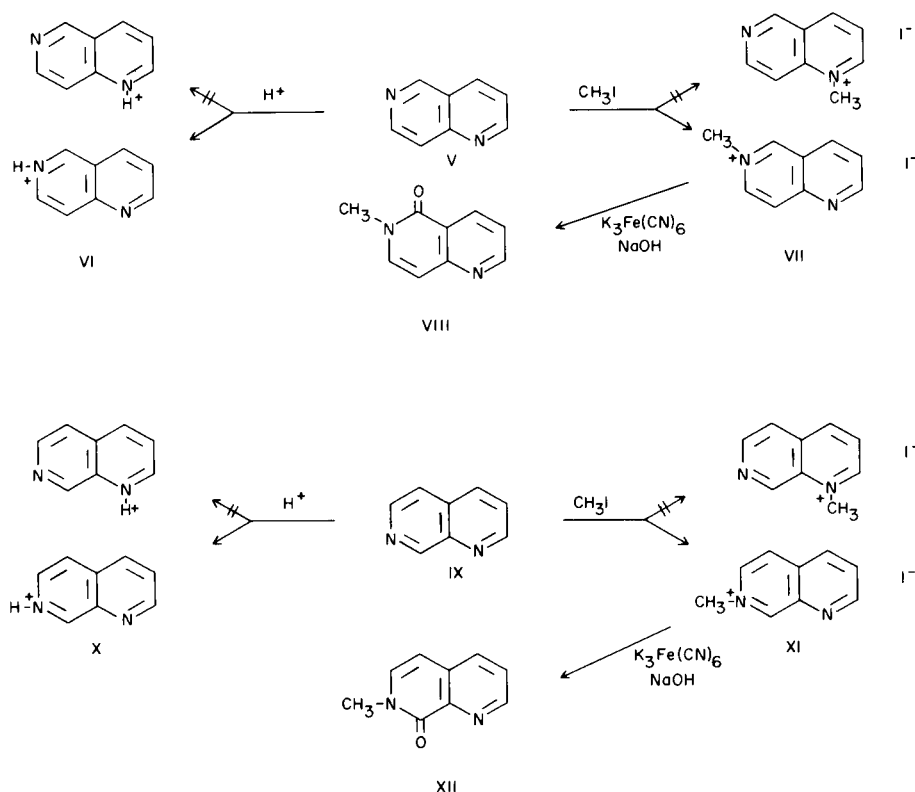
The elucidation of the site of N-methylation in the 1,6- and in 1,7-naphthyridine is based upon the identification of the oxidation products resulting from potassium ferricyanide oxidation of the respective methiodides. These considerations are outlined in the equations in Scheme I.

The nmr spectra of the various 1,8-naphthyridines (II-IV) serve as unequivocal references for the changes in chemical shifts of the various protons as these transformations take place. A similar set of transformations for

Scheme I



Scheme I (continued)



1,5-naphthyridine has been reported by Rapoport and Batcho (4). The nmr data for these transformations are recorded in Table II. Clearly, the protonation and *N*-methylation in the 1,6- and 1,7-naphthyridine occurs at N_6 and at N_7 , respectively.

EXPERIMENTAL (5)

1,X-Naphthyridines.

The 1,6-, 1,7-, and 1,8-naphthyridines were prepared by previously reported procedures (1).

Methiodide Salts.

The methiodide salts were prepared by the following procedure: A solution of the naphthyridine in acetone containing a twofold excess of methyl iodide was heated under reflux overnight. The resulting precipitate was collected and recrystallized several times from ethyl acetate-methanol, to afford the methiodides in yields of 85-95%.

Anal. Calcd. for $C_9H_9N_2I$: C, 39.72; H, 3.33; N, 10.30.
 1,6-Naphthyridine Methiodide, m.p. 153-155,
Found: C, 39.67; H, 3.17; N, 10.27.
 1,7-Naphthyridine Methiodide, m.p. 226-228,
Found: C, 39.83; H, 3.42; N, 10.53.
 1,8-naphthyridine Methiodide, m.p. 180-182,
Found: C, 39.51; H, 3.52; N, 10.31.

Oxidation of Methiodide Salts.

The procedure for the preparation of the *N*-methyl-naphthyridones by potassium ferricyanide oxidation of the corresponding methiodide salts was that of Rapoport and Batcho (4).

5-Keto-6-methyl-5,6-dihydro-1,6-naphthyridine (VIII).

The yield was 67% of the theoretical. Two sublimations at $90^\circ/1.0$ mm. gave white cottony needles, m.p. $97-98^\circ$.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49.
Found: C, 67.41; H, 5.04; N, 17.53.

7-Methyl-8-keto-7,8-dihydro-1,7-naphthyridine (XII).

A portion of the clear oil, isolated from the reaction mixture and purified (4), was converted to the monopicrate for elemental analysis.

Anal. Calcd. for $C_{15}H_{11}N_5O_8$: C, 46.28; H, 2.85; N, 17.99.
Found: C, 46.01; H, 3.01; N, 18.12.

1-Methyl-2-keto-1,2-dihydro-1,8-naphthyridine (IV).

Evaporation of the chloroform extract gave a pale yellow solid was sublimed at $60^\circ/1.0$ mm. affording white clusters (50%), m.p. $94-95^\circ$.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49.
Found: C, 67.80; H, 5.25; N, 17.71.

TABLE II

NMR Spectral Data of Some Naphthyridines

Compound (solvent)	Chemical Shift (τ)								Coupling Constants (cps)								
	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	J ₂₃	J ₂₄	J ₃₄	J ₄₈	J ₅₆	J ₅₇	J ₅₈	J ₆₇	J ₆₈	J ₇₈
1,6-Naphthyridine VI (DTFAA)	0.25	1.65	0.68	-0.15	-	0.82	1.13	4.8	1.8	8.7	0.8	-	0.8	0.8	-	-	6.7
1,6-Naphthyridine Methiodide VII (D ₂ O)	0.52	1.89	0.97	0.00	-	1.09	1.42	4.3	1.7	8.6	0.5	-	1.2	0.5	-	-	7.0
5-Keto-6-methyl-5,6-dihydro-1,6-naphthyridine VIII (CDCl ₃)	1.18	2.65	1.39	-	-	2.70	3.30	4.5	1.9	8.0	0.9	-	-	-	-	-	7.5
1,7-Naphthyridine X (DTFAA)	0.52	1.73	1.23	1.38	1.13	-	1.05	4.3	1.7	8.8	0.8	6.5	-	0.7	-	0.7	-
1,7-Naphthyridine Methiodide XI (D ₂ O)	0.49	1.69	1.09	1.07	1.24	-	0.30	4.2	1.9	9.0	0.9	7.0	-	0.8	-	0.7	-
7-Methyl-8-keto-7,8-dihydro-1,7-naphthyridine XII (CDCl ₃)	1.12	2.45	2.07	3.54	2.71	-	-	4.0	2.0	8.0	-	7.0	-	-	-	-	-
1,8-Naphthyridine II (DTFAA)	0.39	1.62	0.71	0.71	1.62	0.39	-	4.5	2.0	8.0	-	8.0	2.0	-	4.5	-	-
1,8-Naphthyridine Methiodide III (D ₂ O)	0.23	1.58	0.57	0.97	1.77	0.51	-	5.5	1.6	8.5	-	8.5	1.8	-	4.4	-	-
1-Methyl-2-keto-1,2-dihydro-1,8-naphthyridine IV (CDCl ₃)	-	3.30	4.39	2.15	2.87	1.44	-	-	-	9.0	-	8.0	2.0	-	4.5	-	-

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- (2) A. Albert, *J. Chem. Soc.*, 1790 (1960).
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(4) H. Rapoport and A. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

(5) The nmr spectra were obtained with a Varian A-60 spectrometer. The microanalyses were performed by Mrs. K. Decker of this Department. Melting points are corrected.

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