

Department of Chemistry, Ohio University

The Skraup Syntheses and NMR Spectra of Some Methyl-naphthyridines (I)

William W. Paudler and Thomas J. Kress

Some mono- and dimethyl-naphthyridines were prepared by the application of the Skraup reaction to various 2- and 4-aminopyridines. The proton magnetic resonance spectral data assignments are reported. The chemical shifts of the methyl protons are calculated.

Some time ago, we described the syntheses and NMR spectra of some methyl-naphthyridines (2). More recently, we have reported on the application of the Skraup reaction to the syntheses of 1,8-naphthyridine (3) and of 1,6-naphthyridine (4) and we now wish to report the results of an extensive study of the applicability of the 1,8-naphthyridine synthesis to various alkyl derivatives of this ring system.

The correlation of the chemical shifts of the methyl group protons, with respect to their relative positions on the naphthyridine nucleus will also be described.

Syntheses of Various Methyl-naphthyridines.

The various naphthyridines prepared in this study are listed, along with the yields obtained, in Table I. We wish to point out, that these yields are not necessarily the maximum yields obtainable from these reactions, but are the yields obtained when identical conditions are employed for all of the condensations. The general applicability of the synthesis is obvious from an inspection of the table. It is also clearly obvious that the highest yields of naphthyridines are obtained when glycerol is used as the condensing agent. Until these reactions are studied in more detail, no mechanistic implications regarding the relative yields will be made.

The Chemical Shifts of the Methyl Protons of Some Methyl-naphthyridines.

We have previously pointed out that the chemical shift of the methyl group protons in 2-methyl-1,X-naphthyridines (X = 5, 6 or 8) can be correlated to that of the methyl group protons of 2-methylnaphthalene by including a term for the anisotropic contribution of the nitrogen atom at position one (2). The NMR data reported in Table II and Table III further confirm these conclusions by the addition of several new compounds to this correlation.

Since the NMR spectra of a rather large number of mono- and dimethyl derivatives of aza-, and of diazaphthalenes are now available, it appeared reasonable to attempt to correlate the chemical shifts of the methyl protons of the different compounds. This became especially attractive in view of the correlation of the chemical shifts of the

methyl protons in numerous mono- and dimethyl-naphthalenes which had been previously described (5). If we choose the chemical shift of the methyl group protons of 2-methylnaphthalene (6) as the reference protons, the difference between the chemical shift of the 2-methyl protons of this compound and the corresponding protons in 2-methylquinoline can be ascribed as being due to the anisotropic contribution of the heteroatom versus the effect due to an sp^2 carbon atom. This effect (ΔN_1^2) is -0.22τ .

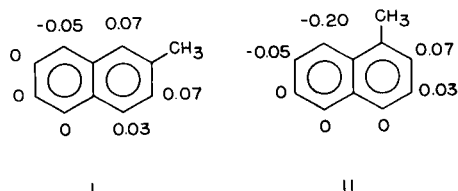
Similarly, the effect of N_1 on the methyl group protons of the 3- and of the 4-methylquinolines can be estimated by comparison of the chemical shifts of the protons of these compounds with those of 2-methyl- and of 1-methylnaphthalene, respectively. The corresponding effects, ΔN_1^3 and ΔN_1^4 , are small, as expected, and are -0.02 and 0.00τ respectively. If we further assume, that the various effects are additive, we can then estimate the contribution that the displacement of the aromatic carbon atoms, in the benzenoid ring not containing the methyl group, by a nitrogen atom, will have. We find (*cf.* Table II) that the chemical shift of the 2-methyl protons in the 2-methyl-1,5-, 2-methyl-1,6-, and 2-methyl-1,8-naphthyridines are essentially the same as those in 2-methylquinoline. The small differences are listed in Table IV. We can similarly estimate the effect that the replacement of an aromatic carbon atom by an aromatic nitrogen atom will have on the chemical shifts of the 3-methyl and of the 4-methyl group protons of 1,5- and of 1,6-naphthyridine. It is evident from the table that a significant effect is only observed in the instance of the 4-methyl-1,5-naphthyridine (7). The various δ values are listed in Table IV.

It is now possible to sum the effects due to the $=C-H \rightarrow =N-$ exchanges and those effects described in the dimethylnaphthalenes in an effort to permit one to predict the chemical shifts of various methyl groups in dimethylquinolines, dimethylnaphthyridines and other related naphthalene derivatives. Structures I and II summarize the effects (in τ) that the addition of a second methyl group will have upon the chemical shift of a 2-methyl and of a 1-methyl group in naphthalene, respectively.

TABLE I
Preparative Data of Methyl-naphthyridines

Aminopyridine	Condensing Agent	Product (yield %)	M. P.
	Crotonaldehyde	2, 4, 7-trimethyl-1, 8-naphthyridine(16)	98.5-99.5°
	Methylvinylketone Crotonaldehyde	4, 5-dimethyl-1, 8-naphthyridine(3) 2, 5-dimethyl-1, 8-naphthyridine(17)	152-153.5° 85-87°
	glycerol crotonaldehyde methylvinylketone methacrolein	3-methyl-1, 8-naphthyridine(18) 2, 6-dimethyl-1, 8-naphthyridine(1.5) 3, 5-dimethyl-1, 8-naphthyridine(3) 3, 6-dimethyl-1, 8-naphthyridine(1)	119.5-120.5° 161-163° 86-87° 192-193°
	crotonaldehyde	2, 7-dimethyl-1, 8-naphthyridine(15)	194-195°
	methacrolein	3-methyl-1, 6-naphthyridine(3)	59-61°

Thus, utilizing the data in Table II and structures I and II one can calculate the chemical shifts of the methyl protons of different dimethyl-naphthyridines and quinolines. The chemical shifts thus calculated are reported in Table V.



EXPERIMENTAL (8)

3-Methyl-1, 8-naphthyridine.

To a chilled homogeneous mixture of 117 g. of sulfo-mix (9), and

25 g. of anhydrous glycerol was added 8.6 g. (0.08 mole) of 2-amino-5-methylpyridine and 45 ml. of water. The mixture was vigorously stirred in an oil bath at 110° for 10 hours, cooled in an ice bath and made alkaline with concentrated aqueous sodium hydroxide. The solution was filtered and extracted with 4-100 ml. portions of chloroform. The combined chloroform extracts were then extracted with 4-100 ml. portions of aqueous hydrochloric acid (pH 3). The pH of the aqueous acid solution was adjusted to pH 5 and reextracted with 4-100 ml. portions of chloroform. After several of these extractions the combined chloroform solutions were dried over anhydrous magnesium sulfate, and evaporated to dryness. The solid residue was sublimed at 80°/0.1 mm. as white clusters, m.p. 119.5-120.5°, 2.0 g. (17.4%).

Anal. Calcd. for C₉H₈N₂: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.96; H, 5.56; N, 19.65.

2, 5-Dimethyl-1, 8-naphthyridine.

To a mixture of 117 g. of sulfo mix, 45 ml. of water and 8.6 g. (0.08 mole) of 2-amino-4-methylpyridine at 110° was added dropwise with vigorous stirring 19.0 g. (0.27 mole) of crotonaldehyde over 30 minutes. The remainder of procedure was the same as for the preparation of 3-methyl-1,8-naphthyridine. Sublimation at 50°/0.1 mm.

TABLE II
NMR Spectral Data of Some Methylindolethyrindines (d)

	Chemical Shift at Position (τ)								Coupling Constant (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 _{5,7}	J _{5,8}	J _{6,7}	J ₆₈	J ₇₈
	2-Me (a)	7.30	2.52	1.77	-----	1.17	2.63	1.80	---	---	8.8	0.8	---	---	4.2	1.6	8.4
	3-Me (b)	1.18	7.44	1.84	-----	1.08	2.45	1.63	---	2.0	1.0	0.8	---	---	4.2	1.8	8.2
	4-Me (a)	1.03	2.44	7.14	-----	0.88	2.28	1.47	4.4	---	0.9	---	---	---	4.1	1.8	8.7
	2-Me (a)	7.24	2.63	1.86	0.81	-----	1.26	2.17	---	---	8.2	0.9	---	0.9	---	---	6.0
	3-Me	1.07	7.46	2.01	0.80	-----	1.29	2.12	---	2.1	0.9	0.9	---	0.9	---	---	6.0
	4-Me (a)	1.03	2.68	7.24	0.47	-----	1.20	2.06	4.5	---	0.9	---	---	0.8	---	---	6.0
	2-Me (a)	7.24	2.69	1.92	1.99	2.65	0.97	-----	---	---	8.4	---	2.0	---	4.4	---	---
	3-Me	1.05	7.52	2.12	1.90	2.58	0.95	-----	---	2.2	1.0	---	2.0	---	4.1	---	---
	4-Me (c)	1.02	2.68	7.35	1.62	2.47	0.88	-----	4.2	---	0.9	---	2.0	---	4.2	---	---

(a) Taken from ref. 2. (b) Prepared by the method of H. Rapaport and A. Batcho, *J. Org. Chem.*, 28, 1753 (1963). (c) Taken from ref. 3.
(d) All spectra are in deuteriochloroform.

TABLE III

NMR Spectral Data of Some Di- and Trimethyl-1,8-naphthyridines

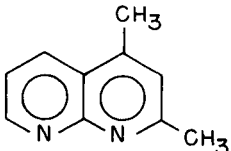
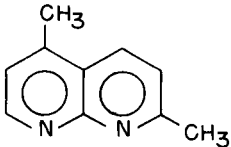
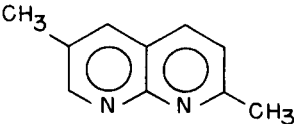
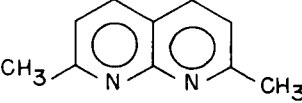
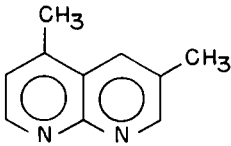
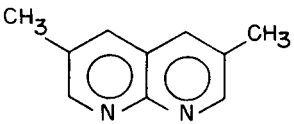
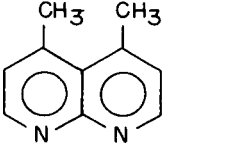
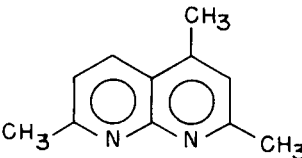
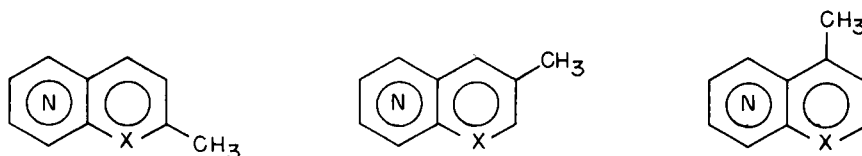
	Chemical Shift at Position (τ)						Coupling Constant (cps)					
	2	3	4	5	6	7	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
	7.28	2.85	7.40	1.74	2.60	0.84	---	---	0.90	8.2	2.0	4.2
	7.24	2.69	1.80	7.38	2.80	1.10	---	---	8.5	0.90	---	4.2
	7.25	2.72	2.05	2.18	7.52	1.12	---	---	---	0.90	2.2	---
	7.24	2.72	2.00	2.00	2.72	7.24	---	---	8.2	---	---	---
	1.07	7.47	1.92	7.34	2.75	1.12	---	2.2	1.0	0.9	---	4.3
	1.05	7.47	2.12	2.12	7.47	1.05	---	2.3	1.0	1.0	2.3	---
	1.08	2.77	7.09	7.09	2.77	1.08	4.2	---	0.9	0.9	---	4.2
	7.29	2.90	7.42	1.86	2.74	7.25	---	---	0.90	8.2	---	---

TABLE IV

Empirical Correction Values (τ) for Methyl Group Protons
of Some Methyl Monoaza- and Diazanaphthalenes



Reference methyl group X = -CH=	7.52	7.52	7.35
Methylquinolines X = -N=	7.30	7.50	7.35
ΔN_1 (y)	-0.22	-0.02	0
ΔN_8 (y)	-0.06	+0.02	0
ΔN_5 (y)	-0.00	-0.06	-0.21
ΔN_6 (y)	-0.06	-0.04	-0.11

(y) Refers to the position of the methyl group with respect to the atom X. The subscript refers to the position of the heteroatom in question.

TABLE V

Calculated and Observed Chemical Shifts (τ)
of Various Monoaza- and Diazadimethylnaphthalenes



Compound	Methyl Position	Calc.	Obs.	Compound	Methyl Position	Calc.	Obs.
2,4-dimethyl-	2-	7.27	7.28	2,4-dimethyl	2-	7.33	7.30
	4-	7.38	7.40		4-	7.38	7.34
2,5-dimethyl-	2-	7.24	7.24	2,6-dimethyl	2-	7.30	7.28
	5-	7.35	7.38		6-	7.54	7.50
2,6-dimethyl-	2-	7.24	7.25				
	6-	7.52	7.52				
2,7-dimethyl-	2-	7.24	7.24				
	7-	7.24	7.24				
3,5-dimethyl-	3-	7.47	7.47				
	5-	7.30	7.34				
3,6-dimethyl-	3-	7.52	7.47				
	6-	7.52	7.47				
4,5-dimethyl-	4-	7.15	7.09				
	5-	7.15	7.09				
2,4,7-trimethyl-	2-	7.27	7.29				
	4-	7.38	7.42				
	7-	7.24	7.25				

gave 2.1 g. (17%) of white clusters, m.p. 85-87°.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.89; H, 6.27; N 17.90.

3-Methyl-1,6-naphthyridine.

The procedure used was the same as that described for the preparation of 4-methyl-1,6-naphthyridine except for the substitution of methacrolein for methyl vinyl ketone. Chromatography on alumina (grade III) and elution with anhydrous ethyl ether gave white hygroscopic needles, m.p. 59-61°.

Anal. Calcd. for $C_9H_8N_2$: P(m/e 144), 100%; P+1(m/e 145) 10.62%; P+2(m/e 146) 0.51%. Found: P(m/e 144), 100%; P+1(m/e 145) 10.0%; P+2(m/e 146) 0.6%.

2,4,7-Trimethyl-1,8-naphthyridine.

The same procedure was used as for the preparation of 2,5-dimethyl-1,8-naphthyridine except for the changes listed in Table I. Sublimation at 90°/0.05 mm. gave white clusters m.p. 98.5-99.5°, 2.2 g. (16.5%).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.90; H, 6.80; N, 16.50.

4,5-Dimethyl-1,8-naphthyridine.

The general procedure was followed as for 3-methyl-1,8-naphthyridine and the reagents used are listed in Table I. Sublimation at 90°/0.1 mm. gave white needles, m.p. 152-153.5°.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.85; H, 6.39; N, 17.41.

2,6-Dimethyl-1,8-naphthyridine.

The reagents used are described in Table I. The product was sublimed yielding a white solid, m.p. 161-163°, 0.20 g. (1.5%).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.20; H, 6.36; N, 17.82.

2,7-Dimethyl-1,8-naphthyridine.

Sublimation at 100°/0.1 mm. of the product obtained by the general procedure gave 1.8 g. (15%) m.p. 194-195°.

Anal. Calcd. for $C_{10}H_{10}N_2$: P(m/e 158), 100%; P+1(m/e 159), 11.73%; P+2(m/e 160) 0.63%. Found: P(m/e 158), 100%; P+1(m/e 159), 12.0%; P+2(m/e 160), 0.80%.

3,5-Dimethyl-1,8-naphthyridine.

The usual procedure and sublimation of the product (at 50°/0.1 mm.) gave 300 mg. of the product (m.p. 86-87°).

Anal. Calcd. for $C_{10}H_{10}N_2$: P(m/e 158), 100%; P+1(m/e 159), 11.73%; P+2(m/e 160), 0.63%. Found: P(m/e 158), 100%; P+1(m/e 159), 11.5%; P+2(m/e 160), 0.70%.

3,6-Dimethyl-1,8-naphthyridine.

The general procedure followed by sublimation at 100°/0.05 mm. gave 150 mg. (1%), m.p. 192-193° product, (lit. value (10) 191-192°).

Anal. Calcd. for $C_{10}H_{10}N_2$: P(m/e 158), 100%; P+1(m/e 159), 11.73%; P+2(m/e 160), 0.63%. Found: P(m/e 158), 100%; P+1(m/e 159), 12.0%; P+2(m/e 160), 0.80%.

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- (5) B. Nagasampagi, R. Pandey and V. Pansare, *Tetrahedron Letters*, 411 (1964).
- (6) The chemical shift of the methyl protons of 2-methyl and of 1-methyl naphthalene used in this communication are those reported in reference 4 and are used in this paper since they are apparently more accurate than the value reported in "Nuclear Magnetic Resonance Spectral Data" (A.P.I. Research Project 44).
- (7) We have previously commented on this (*cf.* ref. 2).
- (8) NMR spectra were obtained with a Varian A-60 spectrometer. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E instrument with the liquid sample injection unit at 200° and the ionizing voltage at 80 volts. Conventional elemental analyses were done by Mrs. S. De Boer of this department.
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Athens, Ohio 45701