Naphthyridine Chemistry XI. The Synthesis and Reactivity of 2,7-Naphthridine

William W. Paudler and Sandra J. Cornrich

Department of Chemistry, Clippinger Laboratories, Ohio University

While much of the basic chemistry of the 1,X-naphthyridines has recently been elucidated, the reports of the syntheses and reactions of the 2,6- and the 2,7-naphthyridines are outstanding in their great paucity (1,2). This lack of knowledge of the chemistry of these latter two naphthyridines is readily traced to the difficulties encountered in attempts at their syntheses. Even though both of these parent naphthyridines have been prepared (3,4,5), none of their chemistry is known.

We wish to report a facile synthesis of 2,7-naphthyridine and the results of studies involving some typical electrophilic and nucleophilic substitution reactions.

Some time ago, it was shown that the condensation of malononitrile with acetone dicarboxylic acid diethyl ester affords the tetraketo-compound **1** (see Scheme I) (6). This substance could readily be converted to the 1,3,6,8-tetrachloronaphthyridine **2**. However, an attempt at selectively reducing this material to the 2,7-naphthyridine (**3**) is reported to have failed. The only material that could be isolated from a reduction of the tetrachloro compound with palladium were the 1,8-dimethoxy- (**4**) and the 1,2,3,4-tetrahydro-2,7-naphthyridine (**5**) (6).

It appeared to us that further studies of selective reductions of the tetrachloro compound would be warranted. To this extent we found that treatment of this compound with hydrogen in the presence of palladium-on-carbon, in a potassium acetate buffered solution affords the parent 2,7-naphthyridine in seventy percent yield. This synthesis now makes all of the naphthyridines, but the 2,6-isomer, readily available.

The NMR spectral parameters of the 2,7-naphthyridine are listed in Table I. The melting point of the material obtained by this procedure (m.p. 96-97°) is somewhat higher than that reported in the only other synthesis of this compound (m.p. 92-94°) (3).

These data, along with the elemental analyses and the mass spectral results (see Scheme II) clearly establish the correctness of the structural assignment. The mass spectral cleavage pattern is that to be expected, namely the loss of two consecutive HCN fragments, followed by the loss of a C_2H_2 moiety. Scheme II delineates this path, with possible structures as shown.

SCHEME I

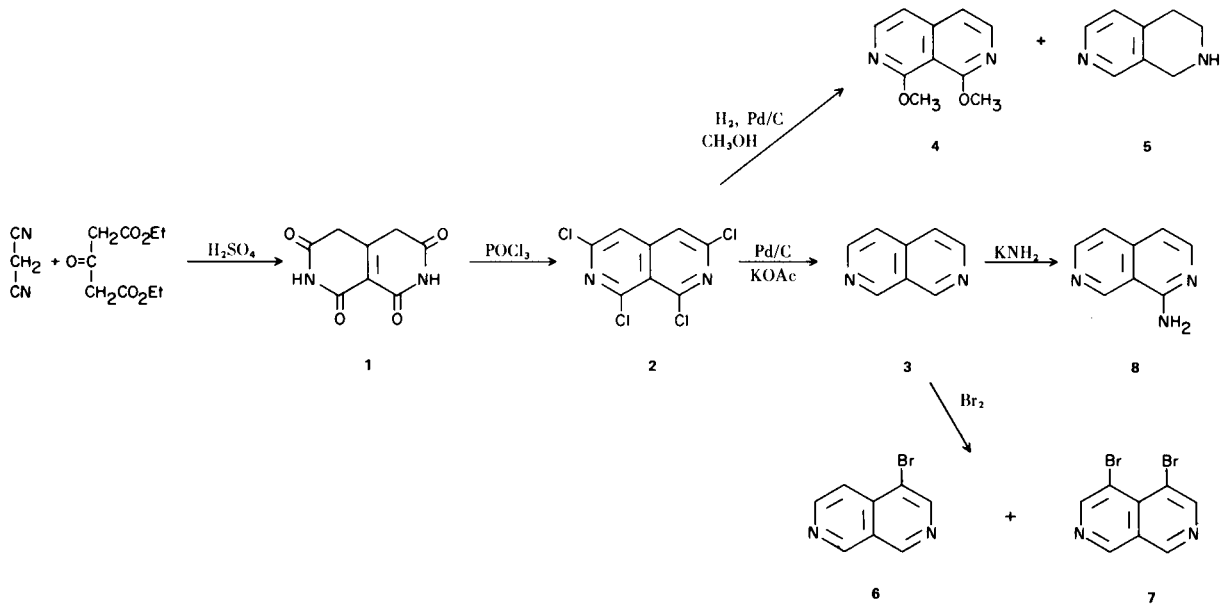
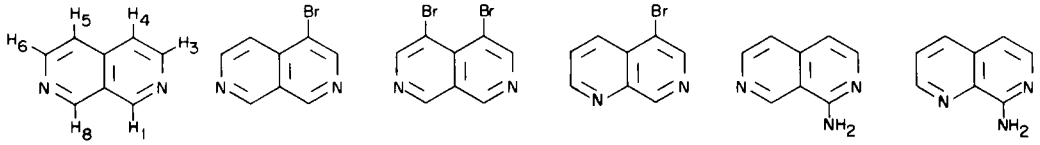


TABLE I

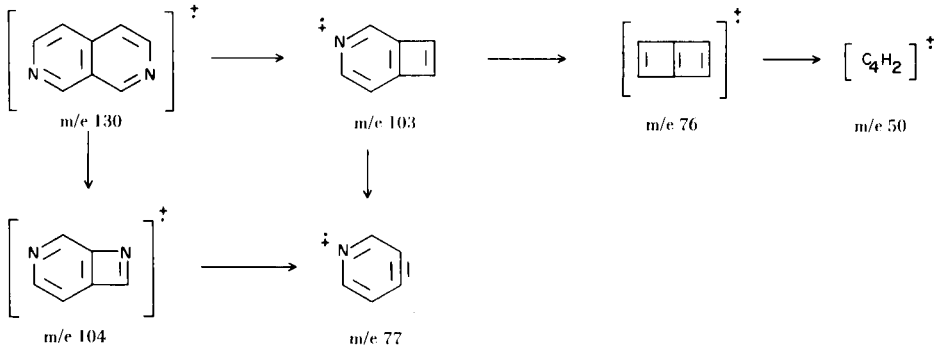
NMR Spectral Data of Some Naphthyridines



		Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	DTFAA (b)	DTFAA
	H_1		0.57	0.7	0.70	----	----	----
	H_2		----	----	----	0.95	----	1.02
	H_3		1.25	1.12	0.99	2.39	1.88	2.10
Chemical	H_4		2.36	----	----	1.57	2.60	1.75
shift (τ)	H_5		2.36	2.10	----	----	1.66	2.82
	H_6		1.25	1.16	0.99	1.20	1.08	2.30
	H_7		----	----	----	----	----	----
	H_8		0.57 (a)	0.62	0.70	0.57	-0.22	----
	J_{14}		0.8	----	----	----	----	----
	J_{15}		0.8	.8	----	----	----	----
Coupling	J_{48}		0.8	----	----	1.0	----	----
constants	J_{34}		6.0	----	----	8.5	6.0	8.2
(cps.)	J_{56}		6.0	6.0	----	----	6.5	7.0
	J_{58}		0.8	0.8	----	----	----	----
	J_{23}		----	----	----	4.0	----	4.0
	J_{24}		----	----	----	1.5	----	1.9

(a) H_8 in 1,7-naphthyridine is τ 0.34. (b) Deuteriotrifluoroacetic acid.

SCHEME II



Electrophilic Substitution.

We have recently applied the Eisch bromination procedure (7) to the bromination of the various 1,X-naphthyridines and now find that 2,7-naphthyridine can also be successfully brominated by this method. The isolated bromine-containing compounds were separated by column chromatography on neutral alumina and afforded a monobromo and a dibromo derivative. The location of the bromine atoms was established by a comparison of the NMR spectra of the compounds with those of the parent

2,7- and of 5-bromo-1,7-naphthyridine. These data, which are included in Table I, clearly establish that the monobromo compound is the 4-bromo-2,7-naphthyridine (**6**) and the dibromo compound is the 4,5-dibromo-2,7-naphthyridine (**7**). The observed substitution patterns are those expected from resonance theory considerations as well as from MO-LCAO calculations (1).

Nucleophilic Substitution.

The amination of isoquinoline is known to afford the 1-amino derivative, while the 1,6-naphthyridine yields the 2-amino- and the 1,7-naphthyridine affords the 7-amino compounds (1,2).

This background suggests that the Chichibabin amination of 2,7-naphthyridine should afford the 1-amino-2,7-naphthyridine (**8**), an expectation that was experimentally verified. Again, the NMR spectrum of this compound in conjunction with that of 8-amino-1,7-naphthyridine (see Table I) testifies to the correctness of the structural assignment.

The reactivities of the nitrogen atoms of this and all of the 1,X-naphthyridines will be the subject of a forthcoming publication.

EXPERIMENTAL (9).

1,3,6,8-Tetrachloro-2,7-naphthyridine (**2**).

The tetra-keto compound **1** (6) (3.0 g., 0.015 mole) was heated with phosphoryl chloride (25 ml.) in a Carius tube (2 x 60 cm.) at 180° for 24 hours. The reaction mixture was poured on ice (500 g.) and the resulting suspension was made alkaline with potassium carbonate. The mixture was then filtered and the insoluble material was extracted in a Soxhlet extractor with ether for a period of 24 hours. The pale yellow powder obtained after removal of the ether *in vacuo* was sublimed at 130°/0.1 mm. to yield 3.3 g. (82 percent of theory) of yellow crystals (m.p. 157-160°, lit. (6) m.p. 157-161°) of compound **2**.

2,7-Naphthyridine (**3**).

To the tetrachloronaphthyridine **2** (1 g., 0.0037 mole), dissolved in 300 ml. of dry methanol, were added fused potassium acetate (6 g.), and 10 percent palladium-on-carbon (100 mg.). The mixture was then stirred with hydrogen at atmospheric pressure until the theoretical amount of hydrogen had been absorbed. After filtration, the solvent was removed *in vacuo*, and the residue was dissolved in aqueous sodium carbonate. This solution was then extracted with chloroform (3 x 50 ml.). The solvent was removed under vacuum and the residue was purified by sublimation at 70°/0.1 mm., to yield colorless crystals, m.p. 96-97° (350 mg., 71 percent of theory) (lit. (3) m.p. 92-94°) of 2,7-naphthyridine (**3**). Mass spectral data ((m/e; percent relative abundance); 130 (100), 104 (25), 103 (40), 77 (35), 76 (20), 50 (29).

Bromo-2,7-naphthyridines.

The general bromination procedure previously employed for the bromination of the 1,X-naphthyridines (8) was utilized starting with 500 mg. (0.0038 mole) of 2,7-naphthyridine. The crude mixture of bromination products was then chromatographed on neutral Brockman Grade III alumina.

4,5-Dibromo-2,7-naphthyridine (**7**).

Elution with carbon tetrachloride yielded 52 mg. (4.7 percent of theory) of a colorless powder (m.p. 187-190°). Sublimation of this material at 60°/0.1 mm. afforded a compound which analyzed correctly for 4,5-dibromo-2,7-naphthyridine (see Table I for NMR data).

Anal. Calcd. for $C_8H_4Br_2N_2$: C, 33.36; H, 1.40; N, 9.73. Found: C, 33.46; H, 1.55; N, 9.86.

4-Bromo-2,7-naphthyridine (**6**).

Further elution with a mixture of 1:1 carbon tetrachloride and benzene afforded 380 mg. (47.8 percent of theory) of a colorless powder (m.p. 123-124°). Sublimation of this product at 90°/0.1 mm. afforded a compound which analyzed correctly for 4-bromo-2,7-naphthyridine (see Table I for NMR data).

Anal. Calcd. for $C_8H_4BrN_2$: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.87; H, 2.40; N, 13.36.

1-Amino-2,7-naphthyridine (**8**).

The general amination procedure previously employed for the amination of the 1,X-naphthyridines (8) was utilized starting with 1.1 g. (0.0084 mole) of 2,7-naphthyridine. Removal of the organic solvents gave a dark brown solid which was sublimed at 180°/0.1 mm. to give 273 mg. (22.5 percent of theory) of a colorless powder, m.p. 227-228° (see Table I for NMR data).

Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 38.95. Found: C, 65.96; H, 4.86; N, 28.78.

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(9) PMR spectra were obtained as dilute solutions (5 percent w/v) with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. K. Decker of this department. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E mass spectrometer, with an ionization potential of 80 eV and an inlet system temperature of 180°. The molecular weights of all of the 2,7-naphthyridines were determined and are in agreement with the theoretical values. Melting points are corrected.

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