Tetrahedron Letters No.12, pp. 1233-1237, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A NEW SYNTHESIS OF 1,7-NAPHTHYRIDINE[1]

Rosita Tan[2] and Alfred Taurins

Department of Chemistry, McGill University,

Montreal, Quebec, Canada

(Received 4 December 1965; in revised form 25 January 1966)

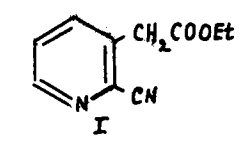
J.G. Murray and C.R. Hauser (1) synthesized 3-carbethoxy-4-hydroxy-1,7-naphthyridine 7-oxide, and N. Ikekawa (2) transformed it via 4-chloro-1,7-naphthyridine into 1,7-naphthyridine. We wish to report on a synthesis of 1,7-naphyridine by a different method using ethyl 2-cyano-3-pyridylacetate (3), as a starting material.

Ethyl 2-cyano-3-pyridylacetate (I) (22.4 g) and 28% NH_4OH (60 ml) were mixed, stirred at 10° for 5 hrs. and kept at 0° for 2 days. The white crystals of 2-cyano-3-pyridylacetamide (II) obtained were purified by chromatography and crystal-

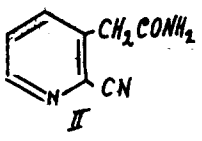
---

1 This work received financial support from the National Research Council of Canada, Ottawa.

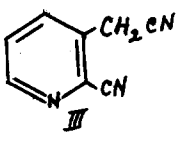
2 Holder of the National Research Council Studentship 1964-65 and 1965-66.



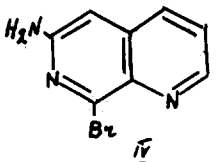
I



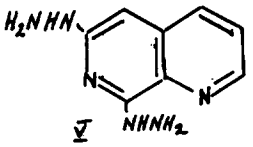
II



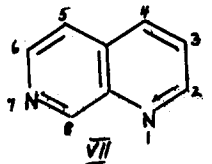
III



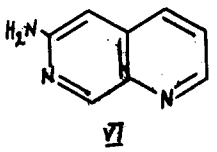
IV



V



VII



VI

lization from tetrahydrofuran, m.p. 145.5-146° (corr.) Found: C, 59.86; H, 4.50; N, 25.92. Calc. for $C_8H_7N_3O$: C, 59.63; H, 4.35; N, 26.09.

2-Cyano-3-pyridylacetamide (II) (4.4 g; 0.0273 mole) was treated with phosphorus oxychloride in pyridine at -10° to 5° and the mixture was kept at 65° for $2\frac{1}{2}$ hours. It was extracted with dichloromethane. The 2-cyano-3-pyridylacetonitrile (III) formed white prisms, m.p. 64-65.5° (corr.), (from hexane-benzene mixture). Found: C, 67.11; H, 3.62; N, 29.24. Calcd. for $C_8H_5N_2$: C, 67.13; H, 3.50; N, 29.37.

2-Cyano-3-pyridylacetonitrile (III) was cyclized into a derivative of 1,7-naphthyridine by treatment with

anhydrous hydrogen bromide (4) in ether mixture was poured into a sodium bicarbonate solution, and 6-amino-8-bromo-1, 7-naphthyridine (IV) was obtained (yield 72%). Yellow prisms, m.p. 181° (decomp.) (from benzene-chloroform mixture). Found: C, 42.80; H, 2.71; N, 18.64; Br, 35.85. Calcd. for $C_8H_6N_2Br$: C, 42.88; H, 2.68; N, 18.76; Br, 35.67.

Hydrogenation of IV in alcoholic KOH solution (10% Pd-C) produced 6-amino-1,7-naphthyridine VI (81% yield). Yellow crystals, m.p. 174-174.5° (corr.), from CH_2Cl_2-C_6H_6 mixture. Found: C, 66.12; H, 4.94; N, 28.90. Calcd. for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.96.

A mixture of 6-amino-1,7-naphthyridine (IV) (1.5 g) in dioxane (20 ml) and hydrazine hydrate (10 ml) was refluxed at 110° for an hour. The yellow needles of 6,8-dihydrazino-1,7-naphthyridine (V) were obtained in a 64.5% yield. M.p. 147.5 - 149.5° (Corr.). Found: C, 50.75; H, 5.50; n' 44.19. Calcd. for $C_8H_{10}N_6$; C, 50.51; H, 5.30; N, 44.19.

6,8 -Dihydrazino-1,7-naphthyridine (V) was dissolved in 30% acetic acid and the solution was poured slowly into a hot copper sulfate solution. The mixture was boiled for 15 minutes, made alkaline with 20% NaOH, and extracted continuously with ether. The residue obtained was purified by chromatography and crystallization from petroleum either to obtain pure 1.7-naphthyridine (VII) (18% yield), white needles, m.p. 61.62° (corr.). 1,7-Naphthyridine monopicrate, m.p. 196.5 - 197.5° (corr.)

Found: C, 46.97; H, 2.72; N, 19.25. Calcd. for $C_{14}H_9N_5O_7$: C, 46.80; H, 2.52; N, 19.49.

The UV spectrum of 1,7-naphthyridine (VII) was identical with that recorded in the literature (2). The NMR spectrum of VII in $CDCl_3$ (TMS = 0) consisted of 3 quartets centered at 9.14, 8.26 and 7.67 p.p.m. which were assigned to protons 2,4 and 3 respectively. The 2 doublets at 8.73 and 7.22 p.p.m. were exhibited by protons 6 and 5 resp., and the singlet at 9.66 p.p.m. to proton 8.

The NMR spectra of 1,7-naphthyridines (Table I) were recorded on a Varian A60 spectrometer.

REFERENCES

1. J.G. Murray and C.R. Hauser, J. Org. Chem. 19, 2004 (1954)
2. N. Ikekawa, Chem. Pharm. Bull (Tokyo), 6, 401 (1958); C.A. 53, 3226e (1959)
3. R. Tan and A. Taurins, Tetrahedron Letters No. 31, 2737 (1965)
4. F. Johnson and W.A. Nasutavicus, J. Org. Chem. 27, 3953 (1962)

Table I

N.M.R. Spectra of 1,7-Naphthyridines

Name of compound	Coupling constants (c.p.s.)				Chemical shifts (p.p.m.)							Solvent
	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	H_2	H_3	H_4	H_5	H_6	H_8	NH_2	
6-Amino-8-bromo-1,7-naphthyridine	4.0	1.6	8.6		8.47	7.33	7.98	6.50			6.25	$(CD_3)_2SO$
6-Amino-1,7-naphthyridine	4.0	1.5	8.4		8.39	7.22	7.80	6.49		8.77	5.98	$(CD_3)_2SO$
1,7-Naphthyridine	4.2	1.6	8.4	5.6	9.14	7.67	8.26	7.72	8.73	9.66		$CDCl_3$