Tetrahedron Letters No.31, pp. 2737-2744, 1965. Pergamon Press Ltd.
Printed in Great Britain.

SYNTHESIS OF 2,6-NAPHTHYRIDINE AND SOME OF ITS DERIVATIVES[1]

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(Received 18 June 1965)

A paper by G. Giacomello et al (1) prompts us to report on a recent work carried out in this laboratory dealing with a synthesis of 2,6-naphthyridine by the following routes.

Ethyl 3-pyridylacetate (I) was treated with 30% H_2O_2 in glacial acetic acid for 24 hours at 65-70° to obtain ethyl 3-pyridylacetate N-oxide (II), white crystals, m.p. 97-98°. Found: C, 59.72; N, 4.96; H, 606. Calcd. for $C_9H_{11}O_3N$: C, 59.67; N, 7.74; H, 6.08.

The N-oxide (II) was transformed with dimethyl sulphate into a quaternary salt, which, on treatment with

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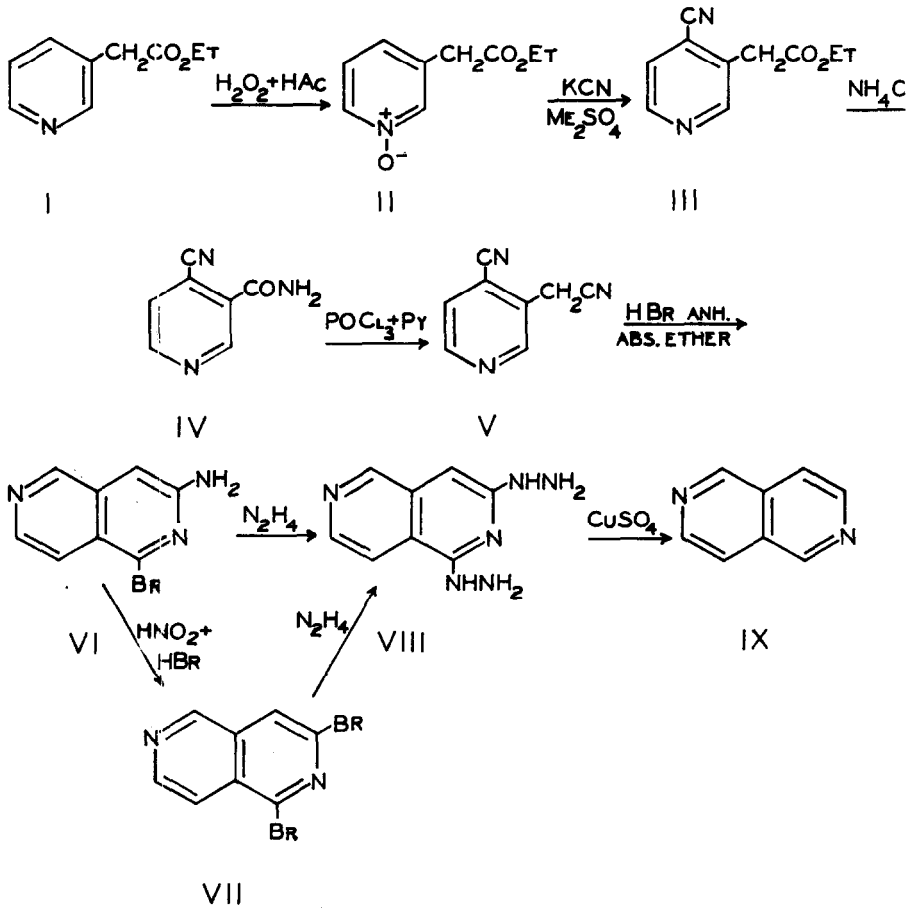
[1] This work received financial assistance from the National Research Council of Canada, Ottawa.


CH2CO2ET
H2O2+HAc
CH2CO2ET
KCN
Me2SO4
CN
CH2CO2ET
NH4C
I
II
III
CN
CONH2
POCl3+Py
CN
CH2CN
HBr ANH.
ABS. ETHER
IV
V
NH2
Br
N2H4
NHNH2
NHNH2
CuSO4
VI
HNO2+
HBr
N2H4
VIII
IX
Br
Br
VII

KCN in an ethanol-water solution at 23-25° in N_2 atmosphere, gave ethyl 4-cyano-3-pyridylacetate (III). This product was extracted from the reaction mixture with $CHCl_3$ and after removal of the solvent was distilled under vacuum at 138% 3mm. Hg (36% yield). An analytical sample was purified by chromatography yielding a colorless liquid, b.p. 130°/1.7 mm. Hg. Found: C, 63.08; H, 5.30; N, 14.66. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74.

The fraction distilling at 134°/1.4 mm. Hg was ethyl 2-cyano-3-pyridylacetate, an isomer of III (yield 7.4%). Found: C, 63.37; H, 5.42; N, 14.89. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74.

The cyanoderivative (III) and 28% ammonium hydroxide solution were cooled separately to -10° and then mixed together. The mixture was kept in a refrigerator for 4 days. 4-Cyano-3-pyridyl acetamide (IV), colorless prisms, m.p. 166-167°, was obtained in a 72% yield. Found: C, 59.44; H, 4.45; N, 26.23. Calcd. for $C_8H_7N_3O$: C, 59.63; H, 4.35; N, 26.09.

The amide (IV) was treated with phosphorus oxychloride in pyridine at -10° to -5°. The temperature was raised to 50° to 60° and kept there for 2.5 hours. The mixture was then poured on ice and extracted with $CHCl_3$.

Table I

N.M.R. Spectra of 3-Pyridylacetic Acid Derivatives

Name of compound	Coupling constants J (c.p.s.)					Chemical shifts (p.p.m.)								Solvent
	$J_{2,4}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{H,H}$ (CH_2–CH_3)	H_2	H_4	H_5	H_6	CH_2	$-OCH_2$	CH_3	NH_2	
Ethyl 3-pyridylacetate	2.0	8.0	2.0	5.0	7.0	8.37	7.51	7.19	8.37	3.43	4.01	1.12		CCl_4
Ethyl 3-pyridylacetate N-oxide				4.0	7.0	8.27	7.31	7.31	8.27	3.62	4.20	1.25		$CDCl_3$
Ethyl 4-cyano-3-pyridylacetate				5.0	7.0	8.60		7.46	8.60	3.77	4.14	1.21		CCl_4
4-Cyano-3-pyridylacetamide				5.0		8.60		7.65	8.55	3.50			7.57 7.02	CD_3SOCD_3
4-Cyano-3-pyridylacetonitrile				4.6		8.98		7.62	8.82	4.02				$CDCl_3$
Ethyl 2-cyano-3-pyridylacetate		8.0	1.5	4.5	7.3		7.95	7.43	8.55	3.79	4.13	1.23		CCl_4

Table II

N.M.R. Spectra of 2,6-Naphthyridines

Name of compound	Coupling constants J(c.p.s.) $J_{3,4}$	$J_{7,8}$	Chemical shifts (p.p.m.) H_1	H_3	H_4	H_5	H_7	H_8	NH_2 (NH)	CH_3	CH_2	Solvent
3-Amino-1-bromo-2,6-naphthyridine		6.0			6.65	8.89	8.09	7.41	6.38			CD_3SOCD_3
3-Acetamido-1-bromo-2,6-naphthyridine		6.0			8.28	9.07	8.34	7.57	10.38	1.88		CD_3SOCD_3
3-Amino-2,6-naphthyridine		5.5	8.78		6.63	8.88	8.03	7.47	6.13			CD_3SOCD_3
3-Acetamido-2,6-naphthyridine		6.0	9.10		8.45	9.22	8.33	7.80	10.63	2.0		CD_3SOCD_3
3-Amino-1-ethoxy-2,6-naphthyridine		5.2	7.0		6.30	8.92	8.32	7.81	4.43	1.47	4.53	$CDCl_3$
1,3-Dibromo-2,6-naphthyridine		6.0			8.05	9.21	8.86	8.01				$CDCl_3$
1,3,4-Tribromo-2,6-naphthyridine		5.6				9.70	8.99	8.04				$CDCl_3$
2,6-Naphthyridine	6.0	6.0	9.39	8.77	7.80	9.39	8.77	7.80				$CDCl_3$

After the evaporation of the solvent the residue was distilled at 118°/0.7 mm. Hg to yield 87% of a pale yellow oil which solidified. The product, 4-cyano-3-pyridylacetonitrile (V) was crystallized from a $CHCl_3$-ether mixture. Colorless prismatic plates, m.p. 78.5-79.5°. Found: C, 67.14; H, 3.58; N, 29.24. Calcd. for $C_8H_5N_3$: C, 67.13; H, 3.50; N, 29.27.

3-Amino-1-bromo-2,6-naphthyridine (VI) was obtained by cyclization of (V) with anhydrous hydrogen bromide (2) in dry ethyl ether at -5°. A hydrogen bromide salt of VI precipitated. The reaction mixture was poured slowly into a sodium bicarbonate solution. The free compound VI was crystallized from dioxane, yield 80.3%. It formed yellow needles, m.p. 199.5° (dec.). Found: C, 42.82; H, 2.32; N, 18.66; Br, 35.59. Calcd. for $C_8H_6N_3Br$: C, 42.88; H, 2.68; N, 18.76; Br, 35.67.

N-Acetyl derivative of VI, yellow prisms (from dioxane), m.p. 243° (decomp.). Found: C, 45.25; H, 3.14; N, 15.56; Br, 29.96. Calcd. for $C_{10}H_8N_3O$: C, 45.13; H, 3.01; N, 15.79; Br, 30.04.

3-Amino-2,6-naphthyridine was obtained by hydrogenation of VI in absolute ethanol in the presence of KOH and Pd/C, (30 min., pressure 25 lbs/sq.in.). The product

was crystallized from a CH_2Cl_2-C_6H_6 mixture and was obtained in the form of yellow prismatic plates, m.p. 153.5-154.5°. Found: C, 66.20; H, 5.03; N, 28.91. Calcd. for $C_8H_7N_3$: C, 66.21; H, 4.83; N, 28.96.

3-Acetamido-2,6-naphthyridine, pale yellow needles (from ethanol), m.p. 245-246°. Found: C, 64.14; H, 4.74; N, 22.48. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.84; N, 22.44.

3-Amino-1-ethoxy-2,6-naphthyridine was obtained as a by-product in the hydrogenation reaction of VI and was purified on an Al_2O_3 column with a C_6H_6-C_6H_{12} mixture as eluent. Yellow crystals, m.p. 159-160°. Found: C, 63.39; N, 22.38; H, 5.98. Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; N, 22.21; H, 5.85.

3-Amino-1-bromo-2,6-naphthyridine (VI) gave a yellow substance (66% yield) on diazotation in 48% hydrobromic acid at temperatures from -4° to -2°, which on purification by thin layer chromatography gave 1,3-dibromo-2,6-naphthyridine (VII) in 22% yield. Recrystallization of VII from hexane gave colorless needles, m.p. 132-133°. Found: C, 33.50; H, 1.51; N, 9.66; Br, 55.41. Calcd. for $C_8H_4N_2Br_2$: C, 33.36; H, 1.39; N, 9.73; Br, 55.56.

1,3,4-Tribromo-2,6-naphthyridine was isolated from TCL as a by-product of VII (yield 22%). It formed color-

less needles, m.p. 160.5-161°. Found: C, 26.35; H, 0.82; N, 7.53; Br, 65.19. Calcd. for $C_8H_3N_2Br_3$: C, 26.18; H, 0.82; N, 7.63; Br, 65.37.

1,3-Dibromo-2,6-naphthyridine and hydrazine hydrate produced 1,3-dihydrazino-2,6-naphthyridine (VIII) in quantitative yield at room temperature in 2 days.

3-Amino-1-bromo-2,6-naphthyridine (VI) and hydrazine hydrate were refluxed in dioxane solution for one hour at 125°. The yellow precipitate formed was 1,3-dihydrazino-2,6-naphthyridine (86% yield).

1,3-Dihydrazino-2,6-naphthyridine was dissolved in dilute acetic acid and poured into a hot copper sulphate solution. The mixture was boiled for 15 min. and was then made alkaline with a 20% sodium hydroxide solution. 2,6-Naphthyridine (IX) was extracted with ether and the solution was dried over Na_2SO_4. The solvent was evaporated leaving a pale yellow solid in 52% yield. Analytical sample of IX was obtained by chromatography and recrystallized twice from hexane. White crystals, m.p. 118-119°.

Acknowledgements

Microanalyses were performed by A. Bernhardt, Muhlheim/Ruhr, W. Germany. The N.M.R. spectra were recorded by Dr. C. Stammer and Mr. K. Valentin.

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