The Preparation of Some 2- and 3-Derivatives of 1,8-Naphthyridine from 2-Amino-6-hydroxypyridine

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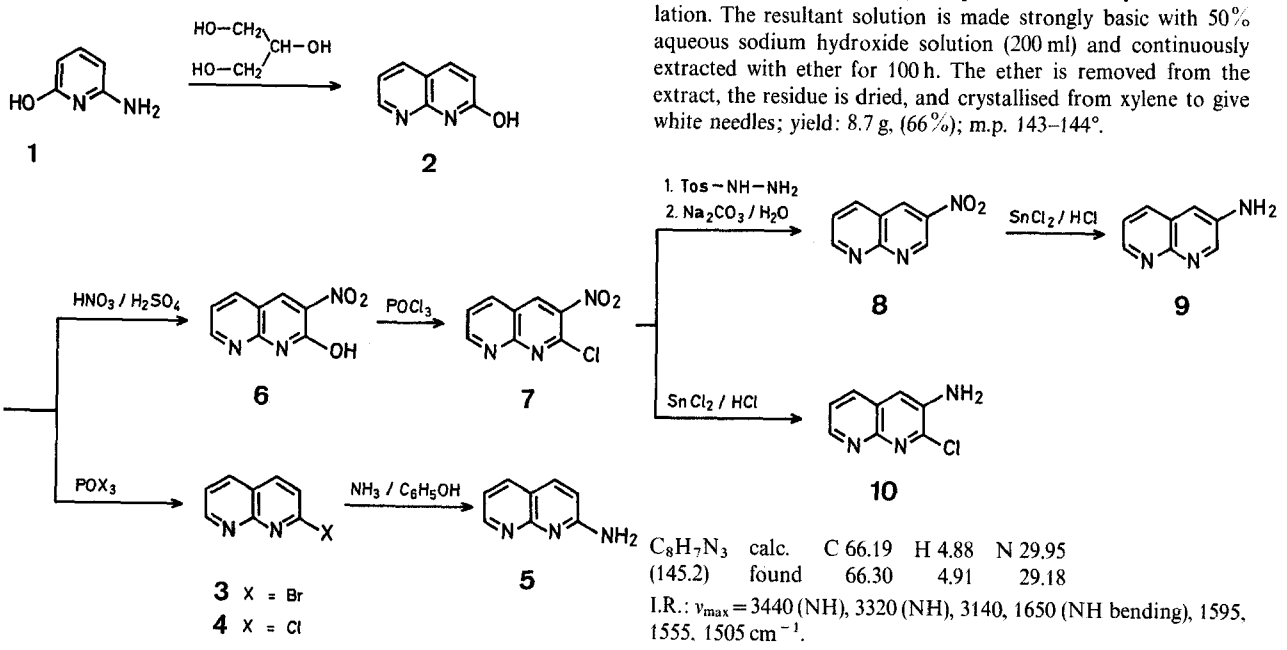
The 2- and 3-substituted derivatives of 1,8-naphthyridine are difficult to prepare. Attempts involving nitration of naphthyridines[1] or naphthyridine *N*-oxides[2] and the Skraup reaction with 2-amino-5-nitropyridine[3] were unsuccessful. 3-Nitro-1,8-naphthyridine (**8**) was previously unknown; 2-amino-1,8-naphthyridine (**5**) had been previously prepared from 1,8-naphthyridine and potassium amide[4] or from 2-aminonicotinic aldehyde and cyanoacetamide[5] but the reactions were complicated and the products difficult to purify. The Skraup reaction of 2,6-diaminopyridine gave a mixture of 2-amino-1,8-naphthyridine (**5**) and 2-hydroxy-1,8-naphthyridine (**2**) in low yields[6]. Other known methods for the preparation of **2** are complicated and involve many stages[5,7,8].

In this work we have used 2-amino-6-hydroxypyridine[9] (**1**) as starting material. The Skraup reaction of **1** and glycerol affords 2-hydroxy-1,8-naphthyridine (**2**) by a simple procedure[10]. The hydroxy group in **2** can be exchanged with chlorine or bromine to give 2-chloro- or 2-bromo-1,8-naphthyridine (**4** or **3**, respectively). Reaction of **4** on warming with ammonia in phenol gave 2-amino-1,8-naphthyridine (**5**) in good yield. Nitration of **2** using a mixture of nitric and sulphuric acids affords 2-hydroxy-3-nitro-1,8-naphthyridine (**6**) which, on treatment with phosphoryl chloride, is converted to 2-chloro-3-nitro-1,8 naphthyridine (**7**). Treatment of **7** on warming with tosylhydrazine and hydrolysis of the resultant product with aqueous sodium carbonate solution gives 3-nitro-1,8-naphthyridine (**8**). Reduction of **8** with tin(II) chloride in hydrochloric acid produces 3-amino-1,8-naphthyridine (**9**); similar reduction of **7** gives rise to 3-amino-2-chloro-1,8-naphthyridine (**10**). The compounds **3**, **6**, **7**, **8**, **9**, and **10** thus obtained were previously unknown. The reactions described here are simple to perform and open an easy access to 1,8-naphthyridine derivatives substituted on positions 2 and 3.



Melting points were measured on a Kofler plate and are uncorrected. I.R. spectra were taken on UR-20 apparatus in a suspension of paraffin oil. ^{1}H-N.M.R. spectra were obtained on a Tesla apparatus BS-478 (80 MHz) using tetramethylsilane ($\delta = 0.00$) as internal standard. The mass spectra were determined in the Regional Laboratory for Physicochemical Analysis and Structural Research on a LKB 9000 S GCMS mass spectrometer at an ionisation voltage of 70 eV.

Preparation of 2-Hydroxy-1,8-naphthyridine (2):

A mixture of sulphuric acid ($d_{20} = 1.83$; 932 g), sodium 3-nitrobenzenesulphonate (400 g), boric acid (54 g), and iron(II) sulphate hexahydrate (31 g) is cooled to 0–5°. Anhydrous glycerol (284 ml) is added with stirring followed by 2-amino-6-hydroxypyridine (**1**; 100 g) and warm (50°) water (510 ml). The mixture is heated under reflux at 135° with stirring for 4.5 h. The mixture is then cooled to room temperature, basified by addition of aqueous ammonia solution ($d_{20} = 1.19$; ~2000 ml), and cooled. The precipitate is filtered off, dried, and pulverised. The solid is placed in a Soxhlet apparatus and extracted continuously with chloroform (~2000 ml) for 15 h. The filtrate solution is also extracted with chloroform. The extracts are then combined, the solvent evaporated, and the residue crystallised twice from water and active charcoal to give white needles; yield 33 g (25%); m.p. 198–199°.

$C_8H_6N_2O$	calc.	C 65.75	H 4.10	N 19.10
(146.1)	found	65.92	4.19	19.20

Mass spectrum: $m/e = 146$ ($M^{\oplus}$, 100%) 118 ($M^{\oplus} - CO$, 47%).

I.R.: $\nu_{max} = 3385$ (NH), 3015, 1670 (CO), 1615, 1570, 1610 cm^{-1}.

Preparation of 2-Bromo-1,8-naphthyridine (3):

A mixture of 2-hydroxy-1,8-naphthyridine (**2**; 8 g) and phosphoryl bromide (40 g) is heated in a sealed tube at 125–130° for 3 h. The content is then poured on to crushed ice (300 g) and basified with aqueous ammonia solution ($d_{20} = 1.19$, ~400 ml). The precipitate is filtered off and recrystallised from water and active charcoal to give white needles; yield: 9.5 g (82%) m.p. 152–153°.

$C_8H_5BrN_2$	calc.	C 45.96	H 2.41	N 13.40
(209.0)	found	46.20	2.34	13.19

I.R.: $\nu_{max} = 1600$, 1585, 1375, 1290, 1140, 1095, 940, 800 cm^{-1}.

Preparation of 2-Chloro-1,8-naphthyridine (4):

The product was obtained from 2-hydroxy-1,8-naphthyridine and phosphoryl chloride according to Ref.[5]; yield: 70%; m.p. 138–139°.

Preparation of 2-Amino-1,8-naphthyridine (5):

Dry ammonia is passed through a solution of 2-chloro-1,8-naphthyridine (**4**; 15 g) in phenol (60 g) at 170–175° for 5 h. The mixture is then cooled, diluted with water (100 ml), acidified with hydrochloric acid ($d_{20} = 1.19$, 5 ml), and phenol removed by steam distillation. The resultant solution is made strongly basic with 50% aqueous sodium hydroxide solution (200 ml) and continuously extracted with ether for 100 h. The ether is removed from the extract, the residue is dried, and crystallised from xylene to give white needles; yield: 8.7 g, (66%); m.p. 143–144°.

$C_8H_7N_3$	calc.	C 66.19	H 4.88	N 29.95
(145.2)	found	66.30	4.91	29.18

I.R.: $\nu_{max} = 3440$ (NH), 3320 (NH), 3140, 1650 (NH bending), 1595, 1555, 1505 cm^{-1}.

Table. ^{1}H-N.M.R. Data for Some Substituted 1,8-Naphthyridines

Product	Solvent	Chemical Shifts δ (ppm)						Coupling Constants (Hz)				
		H-2	H-3	H-4	H-5	H-6	H-7	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
2	$CDCl_3/CD_3OD$	–	6.65	7.80	7.96	7.21	8.57	–	9.5	8.0	2.0	4.5
3	$CDCl_3$	–	7.52	8.00	8.16	7.48	9.00	–	8.5	8.0	2.0	4.0
5	CD_3OD	–	6.79	7.78	7.93	7.09	8.57	–	8.5	7.5	2.0	4.5
6	DMSO-d_6	–	–	8.98	8.39	7.42	8.74	–	–	8.0	2.0	5.0
7	DMSO-d_6	–	–	9.46	8.77	7.89	9.31	–	–	8.0	2.0	4.0
8	DMSO-d_6	9.75	–	9.53	8.83	7.87	9.32	3.0	–	8.0	2.0	4.0
9	CD_3OD	8.57	–	7.22	8.00	7.34	8.59	3.0	–	8.0	2.0	4.0
10	DMSO-d_6	–	–	6.13	8.24	7.49	8.75	–	–	8.0	2.0	4.0

Preparation of 2-Hydroxy-3-nitro-1,8-naphthyridine (6):
A mixture of 2-hydroxy-1,8-naphthyridine (**2**; 0.5 g), sulphuric acid (d_{20} = 1.83, 3.5 ml), and nitric acid (d_{20} = 1.40, 0.3 ml) is heated on a water bath for 1 h. The mixture is then allowed to cool and is poured into ice/water (~100 g). The precipitate is filtered off, washed with water, and recrystallised twice from water and active charcoal to give yellow needles; yield: 0.2 g (40%); melting range (with sublimation): 265–320°.

$C_8H_5N_3O_2$	calc.	N 21.98	
(191.1)	found	21.68	

I.R.: ν_{max} = 3180 (NH), 1695 (CO), 1640, 1540 (≥C—NO_2), 1375, 1230, 785 cm^{-1}.

Preparation of 2-Chloro-3-nitro-1,8-naphythyridine (7):
A mixture of 2-hydroxy-3-nitro-1,8-naphthyridine (**6**; 1,2) and phosphoryl chloride (15 ml) is heated to boiling for 0.5 h. Excess phosphoryl chloride is then removed under reduced pressure, the residue is poured on to ice (~10 g), basified with potassium carbonate, and extracted continuously with chloroform for 10 h. The chloroform extract is dried ($MgSO_4$), filtered, the solvent removed, and the residue is crystallised from isopropyl alcohol with active charcoal to give light yellow needles; yield: 0.75 g (57%); m.p. 267–268° (decomp).

$C_8H_4ClN_3O_2$	calc.	C 45.84	H 1.92	N 20.04
(209.6)	found	46.05	1.99	19.93

I.R.: ν_{max} = 1600, 1550 (≥C—NO_2), 1240, 1020, 840, 805, 795 cm^{-1}.

Preparation of 3-Nitro-1,8-naphthyridine (8):
A solution of 2-chloro-3-nitro-1,8-naphthyridine (**7**; 1.25 g) and tosylhydrazine[11] (1.1 g) in chloroform (90 ml) is boiled for 24 h. The yellow precipitate [yield: 1.9 g; m.p. 219–222°] is filtered off, washed with chloroform, and heated with a solution of sodium carbonate (1.5 g) in water (40 ml) under reflux on a water bath for 2 h. The mixture is then extracted continuously with chloroform for 14 h. The chloroform extract is dried ($MgSO_4$) and filtered, then the solvent is removed and the residue recrystallised twice from isopropyl alcohol with charcoal to give white needles; yield: 0.25 g (24%); m.p. 247–248° (decomp.).

$C_8H_5N_3O_2$	calc.	C 54.86	H 2.87	N 23.99
(175.1)	found	54.96	2.92	23.89

Mass spectrum: m/e = 175 ($M^{\oplus}$, 91%), 145 ($M^{\oplus}$ – NO, 8%), 129 ($M^{\oplus}$ – NO_2, 33%).

I.R.: ν_{max} = 1615, 1545 (≥C—NO_2), 1355, 1230, 1190, 1105, 1020, 950, 820, 780 cm^{-1}.

Preparation of 3-Amino-1,8-naphthyridine (9):
3-Nitro-1,8-naphthyridine (**8**; 1 g) is added in portions over 5 min to a warm (80–100°) solution of tin(II) chloride (4.9 g) in hydrochloric acid (d_{20} = 1.19, 10 ml). The mixture is cooled and made strongly basic by addition of 50% aqueous sodium hydroxide (~200 ml) and extracted continuously with chloroform for 22 h. The chloroform is then removed from the extract and the residue recrystallised twice from water with active charcoal to give light yellow needles; yield: 0.3 g (36%); m.p. 141–142°.

$C_8H_7N_3 \cdot 1.5\,H_2O$	calc.	N 24.40	
(172.1)	found	24.13	

Mass spectrum: m/e = 145 ($M^{\oplus}$, 100%), 118 ($M^{\oplus}$ – HCN, 83%), 91 ($M^{\oplus}$ – 2HCN, 80%), 18 ($H_2O^{\oplus}$, 5%).

I.R.: ν_{max} = 3440 (NH), 3230 (NH), 3340 (NH), 3170, 1620 (NH-bending), 1570, 1375, 1280, 1245, 1230 cm^{-1}.

Preparation of 3-Amino-2-chloro-1,8-naphthyridine (10):
2-Chloro-3-nitro-1,8-naphthyridine (**7**; 1 g) is added in portions over 5 min to a warm (80–100°) solution of tin(II) chloride (4.1 g) in hydrochloric acid (d_{20} = 1.19, 8.2 ml) and the resultant mixture is warmed on a water bath for 30 min. The mixture is then cooled, basified with 50% aqueous sodium hydroxide (~100 ml), and extracted continuously with ether for 30 h. The ether is removed from the extract and the residue crystallised from water with active charcoal to give white needles; yield: 0.3 g (33%); m.p. 213–215°.

$C_8H_6ClN_3$	calc.	C 53.49	H 3.36	N 23.39
(179.6)	found	53.27	3.40	23.47

I.R.: ν_{max} = 3435 (NH), 3275 (NH), 1625 (NH-bending), 1595, 1560, 1330, 1245, 1130, 1050, 795 cm^{-1}.

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