Intramolecular Nucleophilic Cyclization of 3-Substituted Pyridylalkylamines onto the 2-Position of the Pyridine Ring

Edward M. Hawes and Hubert Lorne Davis

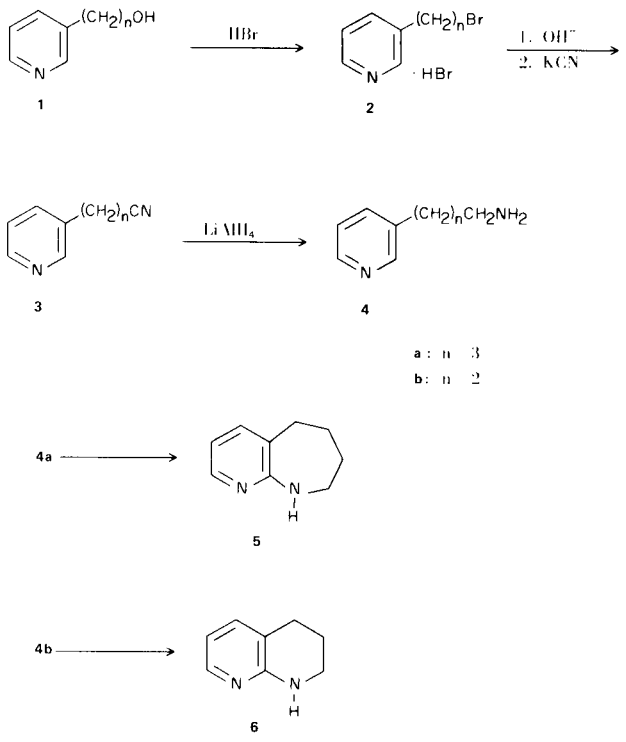
College of Pharmacy, University of Saskatchewan, Saskatoon, Canada

Received October 23, 1972

The intramolecular nucleophilic cyclization of 4-(3-pyridyl)butylamine (**4a**) to yield 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepine (**5**) was investigated. Of eleven different alkali metal reagents sodium, sodium hydride, sodium amide, and potassium hydride gave good yields of **5**. The sodium conditions when applied to 3-(3-pyridyl)propylamine (**4b**) afforded 1,2,3,4-tetrahydro-1,8-naphthyridine (**6**) in good yield.

There are few literature references to the synthesis of bicyclic systems by the intramolecular nucleophilic cyclization of substituted pyridines onto the pyridine ring. All refer to 3-pyridyl compounds, which cyclize either by addition-elimination onto the 2-position or by elimination-addition onto the 4-position of the pyridine ring. The first report in 1966 involved the cyclization of 2-phenyl-3-(3-pyridyl)propylamine to give 1,2,3,4-tetrahydro-3-phenyl-1,8-naphthyridine in good yield using sodium in toluene (1). Treatment of 2-(3-pyridyl)ethylamine with *n*-butyllithium in dioxane (2) or sodium hydride in toluene (3) afforded only trace amounts of 1*H*-pyrrolo[2,3-*b*]pyridine. Two cyclizations involving elimination-addition have been recently reported (4). It appeared to be essential to first examine the conditions necessary for achieving the addition-elimination cyclization before the versatility of this reaction could be investigated. Thus in the present work, two 3-pyridylalkylamines with saturated side chains free of substituents were synthesized, and a wide range of cyclization conditions were applied to one.

SCHEME I



The route for preparing the desired intermediates, 4-(3-pyridyl)butylamine (**4a**) and 3-(3-pyridyl)propylamine (**4b**), is summarized in Scheme I and the detailed procedures and properties of the intermediates are given in the experimental section.

The cyclization of **4a** to 6,7,8,9-tetrahydro-5*H*-pyrido-[2,3-*b*]azepine (**5**) was investigated using a wide variety of experimental conditions. The alkali metal reagents, ratios of reagent to starting material, solvents and reflux times used are summarized in Table I. Initially attempts were made to monitor the course of the reaction using pmr by following the disappearance of the pyridine α-proton. The two-phase nature of the reaction mixture and the complexity of the spectra before work-up made this impossible. Instead a glc analysis of each reaction after work-up for **4a** and **5** was undertaken. No other major products were detected by the glc conditions used. The results of these analyses were also recorded in Table I.

A number of observations are worthy of note from the quantitative study. Firstly, regarding reagents, the highest yields of **5** were obtained with sodium suspension, sodium hydride, potassium hydride, and sodium amide in boiling toluene. Also in this solvent fair yields were obtained with potassium suspension and *n*-butyllithium. Despite the

TABLE I

Cyclization of 4-(3-Pyridyl)butylamine (**4a**) to 6,7,8,9-Tetrahydro-5*H*-pyrido[2,3-*b*]azepine (**5**)

No.	Reagent	Molar Ratio	Solvent	Reflux Time (hr.)	Crude (a) (%)	**5** (b) (%)	**4a** (b) (%)	Unidentified products (a) (%)
1	Na	2:1	Toluene	6	98.3	0	38.8	59.5
2	Na	2:1	Toluene	24	98.3	12.7	14.2	71.5
3	Na	2:1	Toluene	48	76.7	57.4	0	20.1
4	Na	2:1	Toluene	72	88.3	86.5	0	3.0
5	Na	1:1	Toluene	72	91.7	16.6	12.7	52.6
6	Na	4:1	Toluene	24	93.3	19.3	7.4	67.0
7	Li	2:1	Dioxane	24	91.7	0	19.2	72.5
8	Li	2:1	Dioxane	72	95.0	0	5.9	89.1
9	Li	2:1	Toluene	72	86.7	0.9	40.4	45.4
10	Li	2:1	Xylene	72	98.3	0.7	0	97.6
11	K	2:1	Toluene	72	96.7	7.7	2.3	86.7
12 (c)	Na salt	1:1	Toluene	72	94.2	21.6	10.6	62.6
13 (c)	Li salt	1:1	Toluene	72	70.9	0	57.6	13.3
14	*n*-BuLi	2:1	Dioxane	24	65.0	0.1	14.5	50.4
15	*n*-BuLi	2:1	Toluene	72	98.3	10.3	0	88.2
16	*n*-BuLi	2:1	Xylene	72	99.2	4.1	0	95.1
17	NaH	2:1	Dioxane	72	98.3	0	23.4	74.9
18	NaH	2:1	Toluene	54	93.3	65.6	0	28.7
19	LiH	2:1	Toluene	72	71.7	0	51.3	20.4
20	LiH	2:1	Xylene	72	94.7	0.9	1.6	92.2
21	KH	2:1	Toluene	72	99.2	54.1	0	45.8
22	$NaNH_2$	2:1	Toluene	72	95.8	45.0	4.9	46.0
23	$LiNH_2$	2:1	Toluene	72	96.7	0	19.5	77.2
24	$LiNH_2$	2:1	Xylene	72	96.7	0	1.6	95.1

(a) Calculation based on starting material. (b) Determined by glc. (c) Salts prepared in ether before reaction undertaken.

exothermic nature of the reactions at room temperature when lithium reagents were added to the reaction mixtures, generally only trace amounts of **5** and large amounts of unidentified products were obtained.

Secondly, the slow nature of the cyclization was indicated by the reactions carried out with a slight excess of sodium in toluene for different times. The decrease in **4a** and other products as **5** increased suggested that these unidentified products were generally intermediates in the cyclization rather than decomposition products.

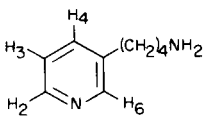
Thirdly, the importance of temperature was illustrated by the fact that toluene generally gave the highest yields. Dioxane often gave high recoveries of **4a**, while decomposition was suspected in some cases in xylene.

Lastly, the necessity for excess reagent was indicated by the comparatively low yields obtained in the reaction involving an equimolar ratio of **4a** and reagent, and the reactions where only salts were used.

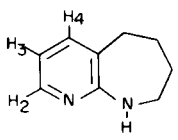
The analogy of this cyclization with the Tschitschibabin reaction of alkali metal amides is obvious (2). The experimental evidence indicates a similar S_N2 type addition-elimination mechanism to the Tschitschibabin reaction (5) and the related synthesis of 2-pyridylalkylamines (6). An alkali metal-pyridine complex is rapidly formed with **4a** at room temperature with lithium reagents and on warming with potassium and sodium reagents. Next by analogy to the literature mechanisms (5,6) rate-determining will be the addition of the side chain to the 2-position, which will be followed by rapid hydride elimination. These latter steps proceed well with sodium and potassium, but not with lithium, which is not surprising as lithium amides give poor yields of aminopyridines in the Tschitschi-

TABLE II

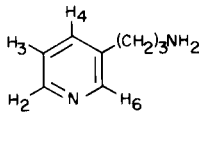
Pmr Spectra of 3-Pyridylalkylamines and their Cyclization Products (a)



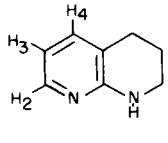
4a



5



4b



6

Compound	Chemical Shifts δ (ppm) H_2	H_3	H_4	H_6	Alkyl	N-H	J (cps) $J_{2,3}$	$J_{3,4}$	$J_{2,4}$
4a	8.43	7.20	7.50	8.43	2.67 and 1.57	1.20	4.9	8.0	2.4
5	7.97	6.66	7.30	---	3.17, 2.70, and 1.77	5.0	4.8	8.0	1.9
4b	8.48	7.17	7.53	8.48	2.70 and 1.88	1.48	4.5	8.0	2.5
6(b)	7.97	6.67	7.27	---	3.53, 2.77, and 2.00	5.70	4.5	7.8	1.8

(a) For ease of comparisons **4a**, **4b**, and **6** are numbered non-systematically as shown. Measurements were taken in deuteriochloroform using tetramethylsilane as internal reference. (b) These assignments are in agreement with those of Armarego (8).

babin reaction (7).

The preparative capability of the synthesis was investigated by applying the optimum conditions found from the quantitative analyses to **4a** and **4b**. Thus treatment of these 3-pyridylalkylamines with a slight excess of sodium in boiling toluene for three days gave good yields of **5** and 1,2,3,4-tetrahydro-1,8-naphthyridine (**6**) respectively. Both products were stable and were purified by vacuum distillation. Compound **5** is a new ring system, apparently unreported hitherto. Compound **6** has been previously reported in the literature, and was found to be identical in physical and spectral characteristics to an authentic sample (8).

Initial evidence that cyclization had indeed occurred came from the mass spectra where the parent ions of **5** and **6** were two mass units lighter than the corresponding starting material ions. That the cyclization had actually occurred in the 2-position is best proven by comparison of the pmr spectra recorded in Table II. On cyclization of **4a** and **4b** the α-proton disappeared and the aromatic region of the spectra of **5** and **6** simplified to an ABX proton system.

EXPERIMENTAL

Infrared spectra were recorded on a Unicam SP200G spectrometer. Pmr spectra were obtained with a Varian T-60 spectrometer in deuteriochloroform using tetramethylsilane as internal reference. The mass spectral measurements were taken on an AEI-MS12 single focussing mass spectrometer. Melting points were determined on a Gallenkamp block and are uncorrected. Elemental analyses were determined by Dr. Strauss, Oxford, England. Gas-chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph equipped with a flame-ionization detector.

All of the starting materials used in this work were obtained from commercial sources. Sodium hydride (57% in oil), potassium hydride (50% in oil) and *n*-butyllithium (22% in *n*-hexane) were purchased as dispersions or solutions.

3-(3-Bromopropyl)pyridine Hydrobromide (**2a**).

A mixture of 58.5 g. (0.4 mole) of 3-(3-pyridyl)-1-propanol (**1a**) and 548 ml. of 48.3% hydrobromic acid was heated under reflux for 9 hours. The reaction mixture was evaporated *in vacuo*, cooled, and 120 ml. of acetone added. The precipitate was collected and crystallized from acetone to yield 69.5 g. (62%) of **2a**, as tan crystals, m.p. 107-109°; ir (potassium bromide) $\overset{+}{\text{N}}$H 2800-2500 cm^{-1} (=NH); pmr δ 12.78 (s, 1, *H*-Br), 9.08 (m, 2, $J_{6,4}$ = 2.0 Hz and $J_{6,5}$ = 5.5 Hz, C_6-*H* and C_2-*H*), 8.68 (d of d, 1, $J_{4,6}$ = 2.0 Hz and $J_{4,5}$ = 8.5 Hz, C_4-*H*), 8.29 (d of d, 1, $J_{5,6}$ = 5.5 Hz and $J_{5,4}$ = 8.5 Hz, C_5-*H*), 3.67 (t, 2, -CH_2-Br), 3.34 (d of d, 2, -CH_2-$(CH_2)_2$Br) and 2.50 ppm (m, 2, -CH_2-CH_2Br).

Anal. Calcd. for $C_8H_{11}Br_2N$: C, 34.19; H, 3.95; Br, 56.88; N, 4.99. Found: C, 34.36; H, 3.90; Br, 57.04; N, 5.14.

3-(2-Bromoethyl)pyridine Hydrobromide (**2b**).

2-(3-Pyridyl)ethanol (**1b**), (39.6 g., 0.3 mole) prepared by lithium aluminum hydride reduction of ethyl 3-pyridylacetate according to the procedure described by Barnden (9) for methyl 3-pyridylacetate, was treated by the above method to yield 46.2 g. (75%) of **2b**, m.p. 124-125°; ir (potassium bromide) 2800-2400 cm^{-1} ($\overset{+}{\text{N}}$H=NH); pmr δ 11.75 (s, 1, *H*-Br), 9.05 (m, 2, $J_{6,4}$ = 1.5 Hz and $J_{6,5}$ = 5.0 Hz, C_6-*H* and C_2-*H*), 8.65 (d of d, 1, $J_{4,6}$ = 1.5 Hz and $J_{4,5}$ = 8.0 Hz, C_4-*H*), 8.18 (d of d, 1, $J_{5,6}$ = 5.0 Hz and $J_{5,4}$ = 8.0 Hz, C_5-*H*) and 3.72 ppm (m, 4, -$(CH_2)_2$-Br).

Anal. Calcd. for $C_7H_9Br_2N$: C, 31.49; H, 3.40; Br, 59.85; N, 5.25. Found: C, 31.50; H, 3.80; Br, 60.20; N, 5.37.

3-(3-Pyridyl)butyronitrile (**3a**).

A solution of 56.2 g. (0.2 mole) of **2a** in 500 ml. of water, overlayed with 200 ml. of chloroform, was treated with 40 ml. of 50% sodium hydroxide. The free base was extracted into chloroform, the extract dried over magnesium sulfate, and evaporated to dryness at low temperature and reduced pressure.

The viscous oil was immediately dissolved in 200 ml. of ethanol and a solution of 14.3 g. of potassium cyanide in 160 ml. of water was added dropwise with stirring. The solution was heated under reflux for 3 hours. 400 ml. of water was added and the solution extracted with chloroform (3 x 100 ml.). The combined extracts were dried over magnesium sulfate and evaporated to yield a black oil, which on distillation *in vacuo* yielded 21.2 g. (72.6%) of **3a** as a colorless oil, b.p. 146-148°/0.2 mm; ir (potassium bromide) 2230 cm^{-1} (C≡N), pmr δ 8.50 (m, 2, $J_{6,4}$ = 2.0 Hz and $J_{6,5}$ = 4.5 Hz, C_6-*H* and C_2-*H*), 7.53 (d of d, 1, $J_{4,6}$ = 2.0 Hz and $J_{4,5}$ = 8.0 Hz, C_4-*H*), 7.23 (d of d, 1, $J_{5,6}$ = 4.5 Hz and $J_{5,4}$ = 8.0 Hz, C_5-*H*), 2.80 (t, 2, -CH_2-CN), 2.36 (ddd, 2, -CH_2-$(CH_2)_2$CN) and 2.03 ppm (m, 2, -CH_2-CH_2CN).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.18. Found: C, 73.91; H, 7.05; N, 18.93.

2-(3-Pyridyl)propionitrile (**3b**).

This compound was prepared from 66.75 g. (0.25 mole) of **2b** by the method described for **3a**; the yield was 18.8 g. (57%), b.p. 150-152°/0.9 mm; ir (potassium bromide) 2240 cm^{-1} (C≡N); pmr δ 8.83 (m, 2, $J_{6,4}$ = 2.0 Hz and $J_{6,5}$ = 4.8 Hz, C_6-*H* and C_2-*H*), 7.63 (d of d, 1, $J_{4,6}$ = 2.0 Hz and $J_{4,5}$ = 8.0 Hz, C_4-*H*), 7.33 (d of d, 1, $J_{5,6}$ = 4.8 Hz and $J_{5,4}$ = 8.0 Hz, C_5-*H*), and 2.83 ppm (m, 4, -$(CH_2)_2$-CN).

Anal. Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.10; N, 21.2. Found: C, 72.57; H, 6.15; N, 20.99.

4-(3-Pyridyl)butylamine (**4a**).

A solution of 17.5 g. (0.12 mole) of **3a** in 240 ml. of sodium dried ether was slowly added dropwise with vigorous stirring to a cooled slurry of 7.6 g. (0.2 mole) of lithium aluminum hydride in 80 ml. of sodium dried ether. The mixture was stirred at room temperature for a further 2 hours, and then decomposed with a minimum amount of water. The suspension was filtered, and the solid washed several times with hot benzene. The combined extracts were dried over magnesium sulfate, and evaporated to yield a yellow oil, which on distillation *in vacuo* yielded 12.2 g. (66%) of **4a** as a colorless oil, b.p. 128-129°/0.3 mm; ir (liquid film) 3360 and 3290 (N-H stretching) and 1570 cm^{-1} (N-H bending); pmr data, see Table II.

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.95; H, 9.40; N, 18.65. Found: C, 71.97; H, 9.20; N, 18.32. Mol. wt. (mass spectra): Calcd.: 150. Found: 150.

3-(3-Pyridyl)propylamine (**4b**).

This compound was prepared from 21.75 g. (0.15 mole) of **3b** by the method described for **4a**; the yield was 11.65 g. (52%), b.p. 130-132°/0.6 mm; ir (liquid film) 3365 and 3295 (N-H stretching), and 1580 cm^{-1} (N-H bending); pmr data, see Table II.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.54; H, 8.88; N, 20.57. Found: C, 70.52; H, 8.82; N, 20.28. Mol. wt. (mass spectra): Calcd.: 136. Found: 136.

Quantitative Determination of **4a** to **5** Conversions.

A mixture of 0.600 g. (0.004 mole) of **4a**, the particular alkali metal reagent in the appropriate amount, and 5 ml. of the particular solvent were heated under reflux for the recorded time, as shown in Table I. In the case of the salts (Table I, No. 12 and 13), these were prepared quantitatively in advance and added to the reaction mixture with no additional quantities of reagent added. The sodium salt (No. 12) was prepared with sodium amide in ether under reflux while the lithium salt (No. 13) was prepared using *n*-butyllithium in ether at 0°.

In each case, the excess base reagent was decomposed in an ice bath by the cautious addition of 4 ml. of water. After adding a further 15 ml. of water, the mixture was extracted with chloroform (4 x 10 ml.), the combined extracts dried over magnesium sulfate, and evaporated to yield dark oils. The crude percentage yield recorded in Table I was calculated in terms of starting material.

The extracts were analysed by glc using analytically pure samples of **4a** and **5**, which have significantly different retention times. The analysis was performed isothermally at 107° on a 6 foot column packed with silicone gum UC W-98 (10%) on Diatoport S (80-100 mesh) using nitrogen as carrier (3.6 l/h). The actual yields of **4a** and **5** were calculated using internal standards and are recorded in Table I. The yield of unidentified products was calculated in terms of starting material by subtracting the actual recovery of **4a** and the corrected yield of **5** from the crude percentage yield.

6,7,8,9-Tetrahydro-5*H*-pyrido[2,3-*b*]azepine (**5**).

A mixture of 4.5 g. (0.03 mole) of **4a**, 1.38 g. (0.06 mole) of sodium suspension and 30 ml. of sodium dried toluene were heated under reflux for 72 hours. The excess sodium was decomposed by the cautious addition of water to the ice-cooled mixture. The mixture was extracted several times with chloroform, the extracts dried over magnesium sulfate and evaporated to yield a dark brown oil. Distillation *in vacuo* yielded 1.55 g. (35%) of **5** as a colorless oil, b.p. 125-127°/2 mm. which solidified on cooling; ir (liquid film) 3265 cm^{-1} (N-H); pmr data, see Table II.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.91. Found: C, 72.63; H, 8.26; N, 19.11. Mol. wt. (mass spectra): Calcd.: 148. Found: 148.

1,2,3,4-Tetrahydro-1,8-naphthyridine (**6**).

This compound was prepared from 1.36 g. (0.01 mole) of **4b** by the method described for **5**; the yield was 0.40 g. (30%), b.p. 115-117°/2.5 mm. The pmr is recorded in Table II. The product was identical (m.p., ir, glc) with an authentic sample of **6** (8). Mol. wt. (mass spectra): Calcd.: 134. Found: 134.

Acknowledgement.

We are indebted to the Medical Research Council of Canada for the award of a studentship to one of us (H.L.D.) and for a research grant in support of this work (Grant No. MA-3150).

REFERENCES

(1) E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. (C)*, 315 (1966).

(2) R. A. Abramovitch and J. G. Saha, *Adv. Heterocyclic Chem.*, **6**, 229 (1966).

(3) R. Herbert and D. G. Wibberley, *J. Chem. Soc. (C)*, 1505 (1969).

(4) T. Kauffmann and R. Wirthwein, *Angew. Chem., Intern. Edit. Engl.*, **10**, 20 (1971).

(5) R. A. Abramovitch, F. Helmer, and J. G. Saha, *Can. J. Chem.*, **43**, 725 (1965).

(6) T. Vajda and K. Kovács, *Rec. Trav. Chim.*, **80**, 47 (1961).

(7) C. S. Giam, First International Congress of Heterocyclic Chemistry, Albuquerque, Nex Mexico, June, 1967.

(8) W. L. F. Armarego, *J. Chem. Soc. (C)*, 377 (1967) prepared this compound by a totally different procedure. The authors are grateful to Dr. Armarego for a reference sample of his compound.

(9) R. L. Barnden, *J. Chem. Soc.*, 3734 (1953).