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Antivertigo Agents. III.[1] Synthesis of 5,6,7,8-Tetrahydro-1,6-naphthyridine Methyl Homologs

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5-Methyl- (**4a**), 7-methyl- (**4b**), and 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**4c**) were synthesized by chemical modification of pyridine derivatives. On the other hand, the synthesis of the compounds (**20b**, **c**) having a methyl group in the aromatic ring of 5,6,7,8-tetrahydro-1,6-naphthyridine was accomplished by the condensation of 1-benzyl-4-piperidinone with the corresponding 3-amino-enones followed by debenzylation. The pathway of the condensation is briefly discussed.

Keywords——5,6,7,8-tetrahydro-1,6-naphthyridine; lithium diisopropylamide; 1-benzyl-4-piperidinone; 3-amino-enone; methylation; pyridine cyclization; catalytic reduction; Friedländer cyclization; debenzylation; antivertigo agent

In the preceding paper of this series,[1] we reported that some 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines have marked antivertigo activity. These observations suggest that the 5,6,7,8-tetrahydro-1,6-naphthyridine moiety is important for appearance of the activity. In order to investigate the structure–activity relationships extensively, it is necessary to develop a synthetic route to C-alkyl derivatives of 5,6,7,8-tetrahydro-1,6-naphthyridine in which the 6-position is free. The present paper describes the synthesis of various C-methyl derivatives of 5,6,7,8-tetrahydro-1,6-naphthyridine as representatives of such compounds.

Firstly, 5-methyl- (**4a**), 7-methyl- (**4b**), and 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**4c**) were synthesized as illustrated in Chart 1. When 6-benzyl-1,6-naphthyridinium bromide (**1**) was treated with methylmagnesium bromide under the usual Grignard reaction conditions, 6-benzyl-5-methyl-5,6-dihydro-1,6-naphthyridine (**2**) was obtained as a light-brown liquid. Since **2** was relatively unstable during further purification, the liquid was immediately reduced with excess sodium borohydride in a methanol–phosphate buffer (pH 7.0), and 6-benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**3a**) was obtained in 91% yield from **1**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3a** clearly demonstrated the presence of a methyl group at 1.33 ppm (3H, d, $J=7.0$ Hz) and a $-CH_2-CH_2-$ moiety at 2.4—3.3 ppm (4H, m). The debenzylation of **3a** by catalytic hydrogenolysis in the presence of palladium–charcoal readily proceeded to give the desired 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**4a**).

As reported previously,[1] 6-alkyl-1,6-naphthyridinium halides were smoothly reduced to their 5,6,7,8-tetrahydro derivatives by treatment with excess sodium borohydride in aqueous methanol. In this manner, 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**5a**) was easily prepared from **1**. Deprotonation of **5a** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -70 °C and subsequent methylation of the resulting carbanion with methyl iodide afforded a monomethyl derivative of **5a**. The ^{1}H-NMR spectrum of the product (**3c**) is consistent with the 6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine structure. For

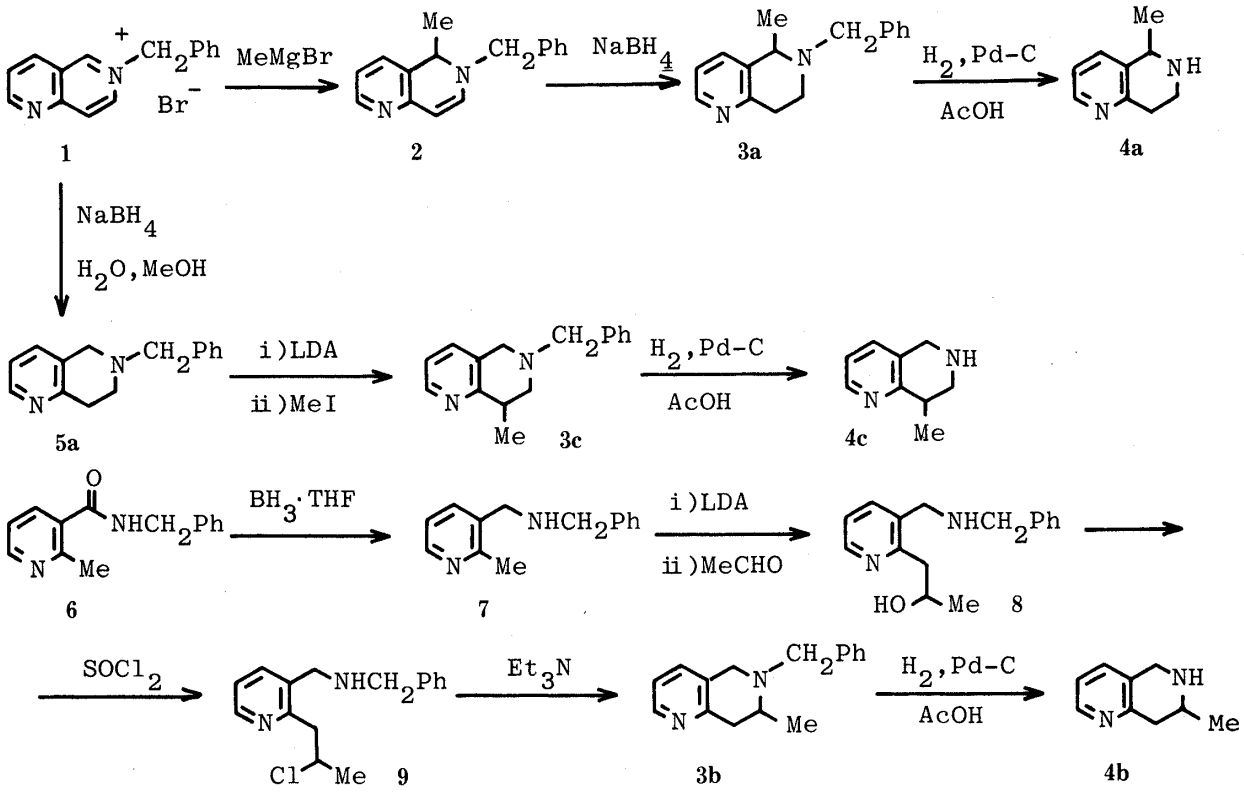


Chart 1

example, the signals due to the 5-methylene or benzyl methylene groups were observed at 3.58 (2H, s) or 3.67 ppm (2H, s).

The synthesis of 6-benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**3b**) was accomplished by the ring-closure reaction of a 2,3-disubstituted pyridine. Namely, 3-benzylaminomethyl-2-methylpyridine (**7**) prepared by the diborane reduction of 3-benzylcarbamoyl-2-methylpyridine (**6**) reacted with acetaldehyde in the presence of LDA to give 3-benzylaminomethyl-2-(2-hydroxypropyl)pyridine (**8**). The propanol (**8**) smoothly reacted with thionyl chloride to give the corresponding chloride (**9**) which cyclized to **3b** on treatment with triethylamine.

Like **3a**, the *N*-benzyl derivatives (**3b**, **c**) were debenzylated by catalytic hydrogenolysis over palladium–charcoal, and 7-methyl- (**4b**) and 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**4c**) were obtained in good yields, respectively.

Next, the synthesis of the isomers having a methyl group in the aromatic ring was investigated by pyridine cyclization. In connection with the course of the pyridine cyclization, Thummel *et al.* reported[2] that the condensation of 2-aminomethylenecyclohexanone (**10**) with cyclohexanone unexpectedly afforded 1,2,3,4,5,6,7,8-octahydroacridine (**11**) as a sole product, instead of 1,2,3,4,7,8,9,10-octahydrophenanthridine (**11′**), formation of which might be expected from the structures of the starting materials. Although no explanation was given for this abnormal cyclization in the literature,[3] the structural assignment of the product appeared to be unambiguous. Thus, in anticipation of the formation of the linear compound, **10** was reacted with 1-benzyl-4-piperidone (**12**) in the presence of ammonium acetate as a catalyst, and a single product $C_{19}H_{22}N_2$ (**13**) was obtained. The ^{1}H-NMR signals of **13** could be assigned to the linear tricyclic structure. In order to exclude the possibility of the angular structure (**13′**), the authentic 2-benzyl-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine was synthesized from *o*-aminobenzaldehyde (**15**) and **12**. Namely, the Friedländer reaction of

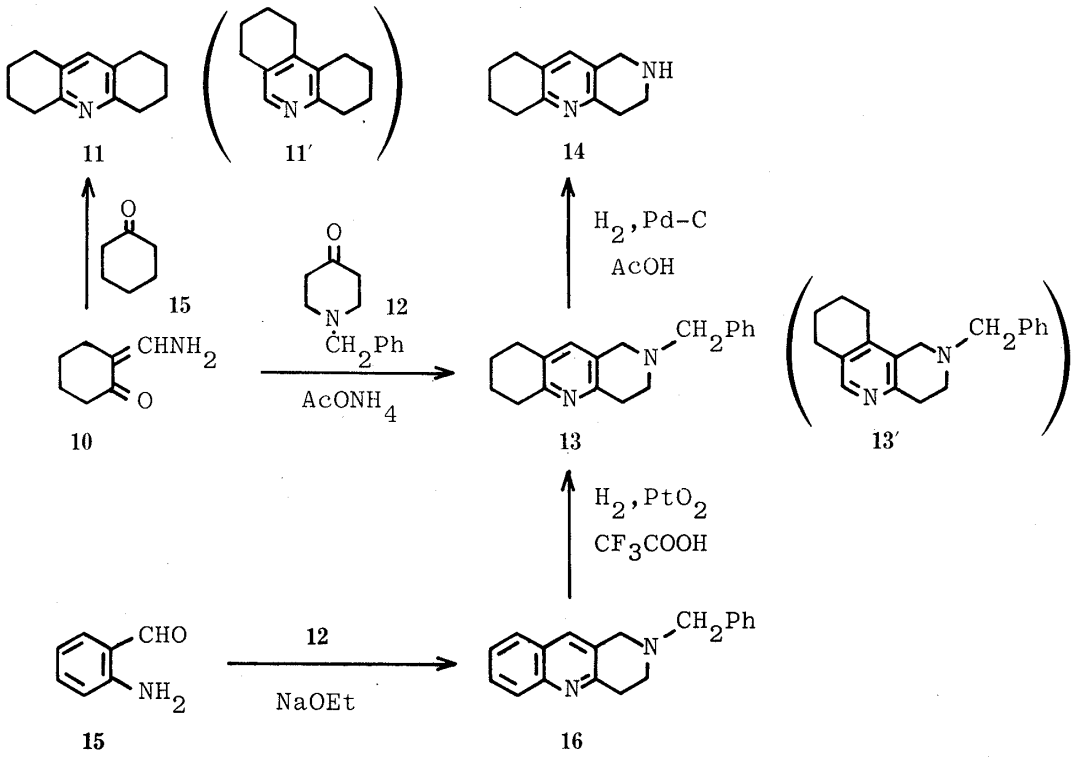


Chart 2

15 with **12** under basic conditions gave 2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (**16**). According to Vierhapper *et al.*,[4] the catalytic hydrogenation of **16** over platinum dioxide in trifluoroacetic acid provided the octahydrobenzo[*b*][1,6]naphthyridine, which was identical with **13**.

As mentioned above, no explanation has been given for the abnormal cyclization, but it is possible that the enamine (**17**) primary formed from **10** and **12** underwent a self-condensation to give the dihydropyridine (**18**) which aromatized to give the final product (**13**). The pathway is tentatively illustrated in Chart 3.

On the basis of the above experiments, 4-amino-3-buten-2-one (**19b**) and 3-aminomethacrylaldehyde (**19c**) were reacted with **12** under similar conditions to give 6-benzyl-2-methyl- (**5b**) and 6-benzyl-3-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**5c**) in 15 and 31% yields, respectively. Though the condensation of 3-aminocrotonaldehyde with **12** has not yet been tried, the reaction of 3-aminoacrylaldehyde (**19a**) with **12** gave **5a** in 40% yield. Accordingly, this type of reaction seems to have synthetic utility for the preparation of 1,6-naphthyridine derivatives.

The hydrogenolysis of **5a**—**c** and **13** under the same conditions as described for **3a**—**c** gave the corresponding debenzylated amines (**20a**—**c** and **14**) in good yields.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IR-G spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m—multiplet. Mass spectra (MS) were measured with a Shimadzu GCMS-7000 spectrometer.

6-Benzyl-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (3a)——6-Benzyl-1,6-naphthyridinium bromide (5.1 g, 50 mmol) was added portionwise to a 1 M THF solution (150 ml) of MeMgBr (150 mmol) under ice-cooling in an N_2

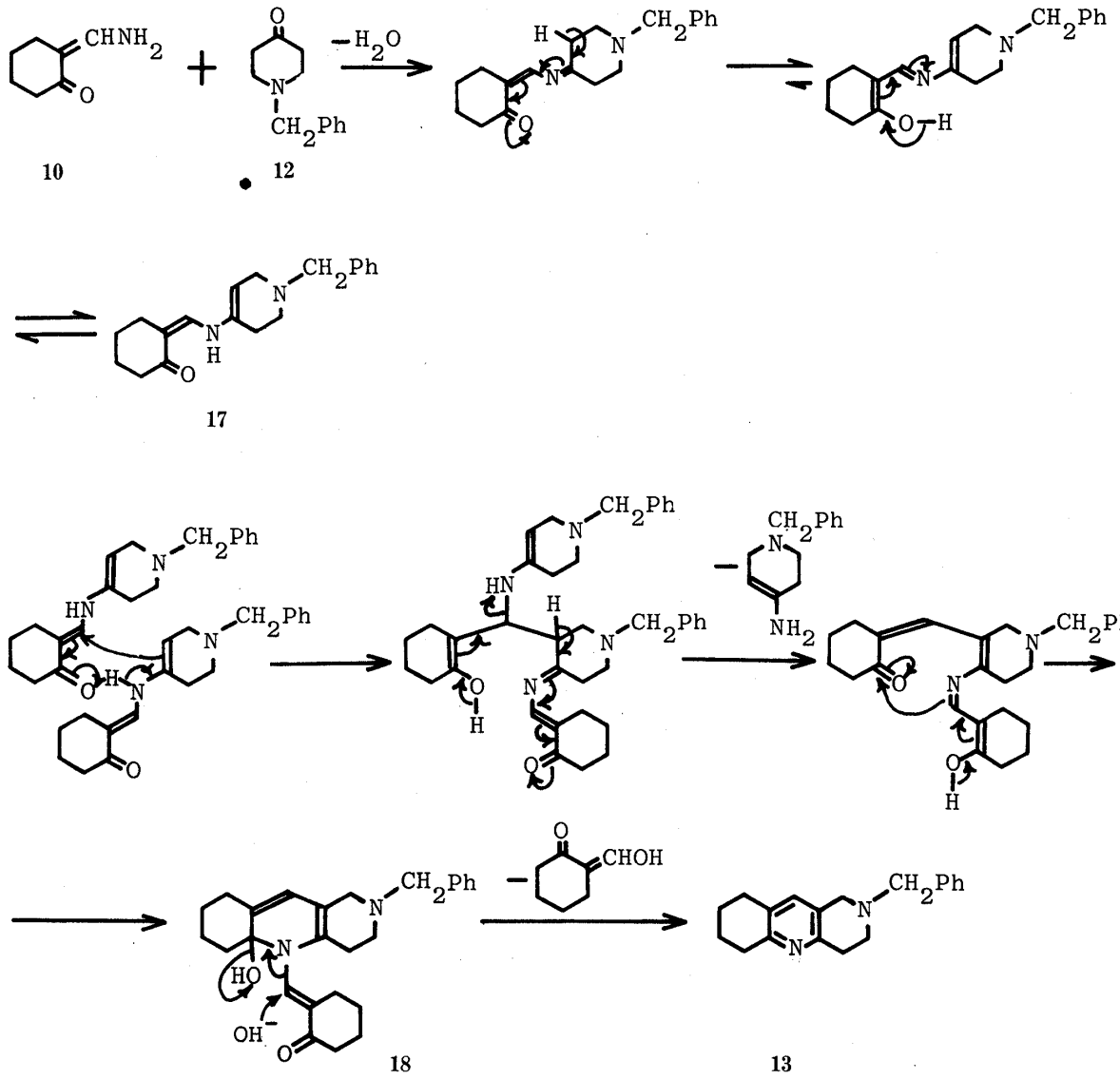
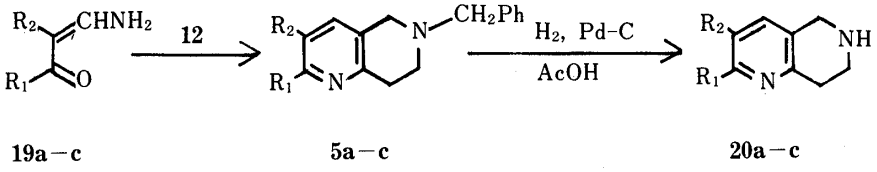


Chart 3



19a : R_1=H; R_2=H
19b : R_1=Me; R_2=H
19c : R_1=H; R_2=Me

Chart 4

atmosphere. The mixture was vigorously stirred for 10 min, then quenched with 20% NH_4Cl aq. solution. The THF was removed *in vacuo*, and the residue was extracted with ether. The ether was removed *in vacuo* to give 6-benzyl-5-methyl-5,6-dihydro-1,6-naphthyridine (**2**) as an oil (13.3 g). This crude oil was dissolved in MeOH (250 ml), and 0.5 M phosphate buffer solution (pH 7.0) (250 ml) was added to the solution. Then $NaBH_4$ (1.9 g, 50 mmol) was added portionwise to the mixture under ice-cooling with stirring, and the mixture was further stirred for about 10 min. After removal of the MeOH *in vacuo*, the resulting oil was extracted with ether. The ethereal layer was evaporated *in vacuo*

to give a residue, which was distilled to afford a colorless oil, bp 141—143 °C (0.3 mmHg). Yield 10.8 g (91%). MS *m/z* (relative intensity): 238 (M^+, 3.7), 224 (19.5), 223 (100.0), 91 (14.6).

6-Benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (3c)——A dry THF (50 ml) solution of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**5a**) (5.6 g, 25 mmol) was added dropwise at −68 °C with stirring to a dry THF (100 ml) solution of LDA [prepared from diisopropylamine (3.8 g, 37.5 mmol) and 1.5 M *n*-BuLi in hexane (20 ml, 30 mmol)]. The mixture was further stirred for 1 h at −68 °C. Methyl iodide (1.6 ml, 26 mmol) was added dropwise to the mixture below −55 °C and the whole was stirred for 15 min, then quenched by adding a small amount of MeOH, and permitted to warm to room temperature. After removal of the solvent, H_2O was added to the residue, and the mixture was extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was distilled to afford a colorless oil, bp 136—140 °C (0.5 mmHg). Yield 5.2 g (87%). MS *m/z* (relative intensity): 238 (M^+, 64.8), 237 (60.3), 161 (151.1), 147 (100.0), 118 (54.2).

3-Benzylaminomethyl-2-methylpyridine (7)——A dry THF (250 ml) solution of 3-benzylcarbamoyl-2-methylpyridine[5] (**6**) (22.6 g, 0.10 mol) was gradually added to a 2 M THF solution (250 ml) of borane (0.5 mol) under ice-cooling in an N_2 atmosphere. The mixture was gradually warmed, and refluxed for 2 h. It was then permitted to cool to room temperature, 6 N HCl (100 ml) was added, and the THF was removed by distillation at atmospheric pressure as H_2 was evolved owing to hydrolysis of excess reagent. The resulting solution was made alkaline with 40% NaOH and extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was distilled to give a colorless oil, bp 139—142 °C (0.6 mmHg). Yield 18.5 g (87%). IR ν_{max}^{neat} cm^{-1}: 3270, 1570, 1440. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (1H, br s, NH, exchangeable with D_2O), 2.53 (3H, s, CH_3), 3.73 (2H, s, 3-pyridyl-CH_2 or $C\underline{H}_2C_6H_5$), 3.81 (2H, s, $C\underline{H}_2C_6H_5$ or 3-pyridyl-CH_2), 7.02 (1H, dd, $J_{56}=4.5$ Hz, $J_{54}=7.5$ Hz, C_5–H), 7.32 (5H, s, C_6H_5), 7.54 (1H, dd, $J_{45}=7.5$ Hz, $J_{46}=2.0$ Hz, C_4–H), 8.35 (1H, dd, $J_{65}=4.5$ Hz, $J_{64}=2.0$ Hz, C_6–H). MS *m/z* (relative intensity): 212 (M^+, 100.0), 211 (25.8), 121 (87.8), 106 (49.8), 107 (40.2), 94 (20.6), 91 (15.8). *Anal.* Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.84; H, 7.83; N, 13.56.

3-Benzylaminomethyl-2-(2-hydroxypropyl)pyridine (8)——Diisopropylamine (7.6 g, 75 mmol) was added to dry THF (200 ml) at −70 °C under an N_2 atmosphere, then 1.5 M *n*-BuLi hexane solution (40 ml, 60 mmol) was gradually added, and the mixture was stirred at −70 °C for 10 min. A dry THF (50 ml) solution of **7** (5.3 g, 25 mmol) was dropped into the above solution below −60 °C. The mixture was further stirred at −70 °C for 1 h, then freshly distilled acetaldehyde (7.0 ml, 125 mmol) was gradually added to the mixture below −50 °C. After being stirred at −70 °C for 30 min, the mixture was quenched with MeOH (20 ml), and the solvent was removed *in vacuo* to give a residue, which was acidified with 6 N HCl and washed with toluene. The aqueous solution was made alkaline with 40% NaOH and extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was distilled to afford a light yellow oil, bp 165—169 °C (0.3 mmHg). Yield 5.1 g (80%). IR ν_{max}^{neat} cm^{-1}: 3270, 1572, 1445. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, $J=6.5$ Hz, CH_3), 2.9—3.1 (2H, m, 2-pyridyl-CH_2), 3.1—4.0 (2H, br s, OH and NH, exchangeable with D_2O), 3.73 (2H, s, 3-pyridyl-CH_2 or $C\underline{H}_2C_6H_5$), 3.82 (2H, s, $C\underline{H}_2C_6H_5$ or 3-pyridyl-CH_2), 4.0—4.5 (1H, m, $CH_2C\underline{H}(OH)CH_3$), 7.05 (1H, dd, $J_{54}=7.5$ Hz, $J_{56}=5.0$ Hz, C_5–H), 7.33 (5H, s, C_6H_5), 7.52 (1H, dd, $J_{46}=2.0$ Hz, $J_{45}=7.5$ Hz, C_4–H), 8.39 (1H, dd, $J_{65}=5.0$ Hz, $J_{64}=2.0$ Hz, C_6–H). MS *m/z* (relative intensity): 256 (M^+, 5.7), 165 (28.5), 149 (100.0), 147 (36.4), 134 (35.0), 107 (58.5), 106 (42.7). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.73; H, 7.88; N, 10.69.

3-Benzylaminomethyl-2-(2-chloropropyl)pyridine Dihydrochloride (9)——Thionyl chloride (4.2 ml, 58 mmol) was gradually added to a $CHCl_3$ (20 ml) solution of **8** (5.0 g, 19.5 mmol) under ice-cooling with stirring below 20 °C. The mixture was further stirred at room temperature for 2 h and quenched with MeOH under ice-cooling. The mixture was evaporated *in vacuo* to give a residue, which was decolorized with a small amount of activated charcoal in MeOH–EtOH, to afford colorless prisms, mp 199—201 °C. Yield 5.3 g (79%). IR ν_{max}^{KBr} cm^{-1}: 2900, 2550, 1435. ^{1}H-NMR (D_2O; sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard) δ: 1.65 (3H, d, $J=6.5$ Hz, CH_3), 3.2—3.8 (2H, m, 2-pyridyl-CH_2), 4.1—4.5 (1H, m, $CH_2C\underline{H}(Cl)CH_3$), 4.53 (2H, s, 3-pyridyl-CH_2 or $C\underline{H}_2C_6H_5$), 4.66 (2H, s, $C\underline{H}_2C_6H_5$ or 3-pyridyl-CH_2), 7.66 (5H, s, C_6H_5), 8.10 (1H, dd, $J_{56}=5.5$ Hz, $J_{54}=8.5$ Hz, C_5–H), 8.7—9.0 (2H, m, C_4–H and C_6–H). *Anal.* Calcd for $C_{16}H_{19}N_2\cdot 2HCl$: C, 55.27; H, 6.09; N, 8.06. Found: C, 54.98; H, 6.01; N, 7.99.

6-Benzyl-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (3b)——Triethylamine (22.3 ml, 160 mmol) was added to a suspension of **9** (13.9 g, 40 mmol) in EtOH (120 ml), and the mixture was refluxed for 1 h. After removal of the solvent *in vacuo*, the residue was made alkaline with 20% NaOH and extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was distilled to afford a light yellow viscous oil, bp 150—153 °C (0.9 mmHg). Yield 8.7 g (91%). MS *m/z* (relative intensity): 238 (M^+, 7.7), 223 (100.0), 147 (14.0), 91 (54.2).

2-Benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (16)——A solution of *o*-aminobenzaldehyde (**15**) (16 g, 132 mmol), **12** (27.5 g, 145 mmol), and NaOMe (7.8 g, 145 mmol) in dry EtOH (300 ml) was refluxed for 3 h. The reaction mixture was evaporated *in vacuo* to give a residue, which was taken up with H_2O and toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was recrystallized from iso-Pr_2O–CH_2Cl_2 to afford colorless prisms, mp 125—126 °C (lit.[6] mp 125.5—126.5 °C). Yield 32.4 g (90%).

2-Benzyl-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (13)——i) A mixture of **16** (2.74 g, 10 mmol) and PtO_2 (274 mg) in CF_3COOH (50 ml) was hydrogenated until the theoretical amount of H_2 had been absorbed. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to give a residue. The residue was made alkaline with

40% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was evaporated *in vacuo* to give a residue, which was recrystallized from iso-Pr_2O to afford colorless prisms, mp 115—116 °C. Yield 2.4 g (87%). MS *m/z* (relative intensity): 278 (M^+, 70.8), 277 (100.0), 187 (66.7), 158 (27.9), 101 (41.7).

ii) A mixture of 2-aminomethylenecyclohexanone (**10**) (6.0 g, 48.0 mmol), **12** (10.9 g, 57.6 mmol), and $AcONH_4$ (60 mg) was heated at 120 °C for 24 h. The mixture was acidified to pH 1.0 with 6 N HCl and washed with $CHCl_3$, then it was adjusted to pH 2.0 with 40% NaOH and washed with toluene. Next, the pH value was adjusted to 6.0—7.0 with 40% NaOH, and the mixture was extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue. The residue was distilled to afford a light yellow oil, bp 150—157 °C (0.4 mmHg), which was solidified. The solid was

TABLE I. 6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridines (**3a—c**, **5a—c**, and **13**)

Compd. No.	IR ν_{max}^{KBr} (cm^{-1})	^{1}H-NMR δ ($CDCl_3$)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3a	1573 1450	1.33 (3H, d, J=7.0 Hz, CH_3), 2.4—3.3 (4H, m, C_7 and C_8–H), 3.4—4.1 (3H, m, C_5–H and $CH_2C_6H_5$), 6.90 (1H, dd, J_{32}=4.5 Hz, J_{34}=8.0 Hz, C_3–H), 7.0—7.5 (6H, m, C_4–H and C_6H_5), 8.30 (1H, dd, J_{23}=4.5 Hz, J_{24}=2.0 Hz, C_2–H)	$C_{16}H_{18}N_2$	80.63 (80.97	7.61 7.85	11.76 11.38)
3b	1578 1440	1.20 (3H, d, J=6.5 Hz, CH_3), 2.4—3.5 (3H, m, C_7 and C_8–H), 3.38 (1H, d, J=13.0 Hz, C_5–H), 3.67 (2H, s, $CH_2C_6H_5$), 3.88 (1H, d, J=13 Hz, C_5–H), 6.97 (1H, dd, J_{32}=4.5 Hz, J_{34}=7.5 Hz, C_3–H), 7.1—7.5 (6H, m, C_4–H and C_6H_5) 8.37 (1H, dd, J_{23}=4.5 Hz, J_{24}=2.0 Hz, C_2–H)	$C_{16}H_{18}N_2$	80.63 (80.96	7.61 7.84	11.76 11.52)
3c	1565 1440	1.36 (3H, d, J=7.0 Hz, CH_3), 2.3—3.3 (3H, m, C_7 and C_8–H), 3.58 (2H, s, C_5–H or $CH_2C_6H_5$), 3.67 (2H, s, $CH_2C_6H_5$ or C_5–H), 7.02 (1H, dd, J_{32}=5.0 Hz, J_{34}=7.5 Hz, C_3–H), 7.2—7.6 (6H, m, C_6H_5 and C_4–H), 8.40 (1H, dd, J_{23}=5.0 Hz, J_{24}=2.0 Hz, C_2–H)	$C_{16}H_{18}N_2$	80.63 (80.88	7.61 7.57	11.76 11.73)
5a	1595 1450	2.7—3.3 (4H, m, C_7 and C_8–H), 3.60 (2H, s, $CH_2C_6H_5$ or C_5–H), 3.68 (2H, s, C_5–H or $CH_2C_6H_5$), 7.00 (1H, dd, J_{32}=5.0 Hz, J_{34}=8.0 Hz, C_3–H), 7.2—7.5 (6H, m, C_4–H and C_6H_5), 8.35 (1H, dd, J_{23}=5.0 Hz, J_{24}=2.0 Hz, C_2–H)	$C_{15}H_{16}N_2$	80.32 (80.05	7.19 7.23	12.49 12.15)
5b	1570 1410	2.50 (3H, s, CH_3), 2.6—3.2 (4H, m, C_7 and C_8–H), 3.55 (2H, s, C_5–H or $CH_2C_6H_5$), 3.69 (2H, s, $CH_2C_6H_5$ or C_5–H), 6.85 (1H, d, J=8.0 Hz, C_3–H), 7.11 (1H, d, J=8.0 Hz, C_4–H), 7.35 (5H, s, C_6H_5)	$C_{16}H_{18}N_2$	80.63 (80.99	7.61 7.48	11.76 11.37)
5c	1565 1450	2.23 (3H, s, CH_3), 2.6—3.2 (4H, m, C_7 and C_8–H), 3.55 (2H, s, C_5–H or $CH_2C_6H_5$), 3.68 (2H, s, $CH_2C_6H_5$ or C_5–H), 7.02 (1H, s, C_4–H), 7.33 (5H, s, C_6H_5), 8.18 (1H, s, C_2–H)	$C_{16}H_{18}N_2$	80.63 (80.81	7.61 7.73	11.76 11.96)
13	1570 1450	1.5—2.1 (4H, m, C_7 and C_8–H), 2.5—3.1 (8H, m, C_3, C_4, C_6, and C_9–H), 3.53 (2H, s, C_1–H or $CH_2C_6H_5$), 3.69 (2H, s, $CH_2C_6H_5$ or C_1–H), 6.92 (2H, s, C_{10}–H), 7.1—7.5 (5H, m, C_6H_5)	$C_{19}H_{22}N_2$	81.97 (82.30	7.97 8.13	10.06 9.82)

recrystallized from iso-Pr_2O to give colorless prisms, mp 114—115 °C. Yield 5.5 g (41%).

6-Benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine (5a)——A mixture of 3-aminoacrylaldehyde (**19a**) (2.1 g, 30 mmol), **12** (3.8 g, 20 mmol), Et_3N (1.5 ml), and piperidinium acetate (30 mg) was heated at 120 °C for 24 h. The reaction mixture was dissolved in 3 N HCl and washed with $CHCl_3$. The aqueous layer was made alkaline with saturated Na_2CO_3 aq. solution and extracted with $CHCl_3$. The $CHCl_3$ was evaporated off *in vacuo* to give a residue, which was distilled under reduced pressure to give a light yellow oil, bp 108—112 °C (0.5 mmHg). Trituration of the oil with Et_2O–petr. ether gave a solid which was recrystallized from Et_2O–petr. ether to afford colorless prisms, mp 80—81 °C. Yield 1.7 g (37%). MS *m/z* (relative intensity): 224 (M^+, 23.8), 223 (22.7), 147 (15.1), 133 (46.4), 91 (100.0).

6-Benzyl-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (5b)——A mixture of 4-amino-3-buten-2-one (**19b**) (133.8 g, 1.57 mol), **12** (298 g, 1.57 mol), and $AcONH_4$ (4 g) was heated at 120 °C for 20 h. The reaction mixture was acidified to pH 1.0 with 6 N HCl and washed with $CHCl_3$. The pH value of the aqueous solution was adjusted to 4.0 with 40% NaOH, and the mixture was washed with toluene. Next, the pH was adjusted to 6.5 with 40% NaOH, and the mixture was extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue. The residue was distilled to afford a light yellow oil, which was gradually solidified. The solid was recrystallized from iso-Pr_2O to give colorless needles, mp 79—80 °C. Yield 99.9 g (27%). MS *m/z* (relative intensity): 238 (M^+, 74.4), 237 (100.0), 161

TABLE II. 5,6,7,8-Tetrahydro-1,6-naphthyridines (**4a—c**, **14**, and **20a—c**)

Compd. No.	mp (°C) or bp (mmHg)	Yield (%)	IR ν_{max}^{neat} (cm^{-1})	^{1}H-NMR δ ($CDCl_3$)	Analysis (%) Calcd	(Found)
4a	81—86 (0.5)	95	3300 1580 1450	1.45 (3H, d, J=7.0 Hz, CH_3), 1.78 (1H, s, NH, exchangeable with D_2O), 2.7—3.6 (4H, m, C_7 and C_8–H), 4.10 (1H, q, J=7.0 Hz, C_5–H), 7.07 (1H, dd, J_{32}=5.0 Hz, J_{34}=8.0 Hz, C_3–H), 7.47 (1H, dd, J_{42}=1.5 Hz, J_{43}=8.0 Hz, C_4–H), 8.37 (1H, dd, J_{23}=5.0 Hz, J_{24}=1.5 Hz, C_2–H)	$C_9H_{12}N_2$ C 72.94 H 8.16 N 18.90	(72.63) (8.28) (18.75)
4b	89—90 (0.5)	92	3250 1573 1440	1.26 (3H, d, J=6.0 Hz, CH_3), 2.88 (1H, s, NH, exchangeable with D_2O), 2.2—3.4 (3H, m, C_7 and C_8–H), 4.03 (2H, s, C_5–H), 7.00 (1H, dd, J_{32}= 4.5 Hz, J_{34}=7.5 Hz, C_3–H), 7.28 (1H, dd, J_{42}= 1.5 Hz, J_{43}=7.5 Hz, C_4–H), 8.34 (1H, dd, J_{23}= 4.5 Hz, J_{24}=1.5 Hz, C_2–H)	$C_9H_{12}N_2$ C 72.94 H 8.16 N 18.90	(72.86) (8.21) (18.76)
4c	76—80 (0.8)	92	3250 1570 1440	1.72 (3H, d, J=6.5 Hz, CH_3), 1.93 (1H, s, NH, exchangeable with D_2O), 2.6—3.6 (3H, m, C_7 and C_8–H), 4.00 (2H, s, C_5–H), 6.98 (1H, dd, J_{32}= 4.5 Hz, J_{34}=7.5 Hz, C_3–H), 7.23 (1H, dd, J_{42}= 1.5 Hz, J_{43}=7.5 Hz, C_4–H), 8.44 (1H, dd, J_{23}= 4.5 Hz, J_{24}=1.5 Hz, C_2–H)	$C_9H_{12}N_2$ C 72.94 H 8.16 N 18.90	(73.22) (8.10) (18.69)
14[a]	99—100	96	3150 1560 1410	1.5—2.3 (4H, m, C_7 and C_8–H), 2.05 (1H, s, NH, exchangeable with D_2O), 2.5—3.5 (8H, m, C_3, C_4, C_6, and C_9–H), 3.97 (2H, s, C_1–H), 7.00 (2H, s, C_{10}–H)	$C_{12}H_{16}N_2$ C 76.55 H 8.57 N 14.88	(76.27) (8.73) (14.94)
20a	103—110 (5.0)	94	3250 1572 1445	1.92 (1H, s, NH, exchangeable with D_2O), 2.8—3.4 (4H, m, C_7 and C_8–H), 4.01 (2H, s, C_5–H), 7.01 (1H, dd, J_{32}=4.5 Hz, J_{34}=7.5 Hz, C_3–H), 7.32 (1H, dd, J_{42}=1.95 Hz, J_{43}=7.5 Hz, C_4–H), 8.36 (1H, dd, J_{23}=4.5 Hz, J_{24}=1.95 Hz, C_2–H)	$C_8H_{10}N_2$ C 71.61 H 7.51 N 20.88	(71.72) (7.46) (20.92)
20b	80—84 (0.5)	87	3240 1570 1460	1.95 (1H, s, NH, exchangeable with D_2O), 2.53 (3H, s, CH_3), 2.7—3.4 (4H, m, C_7 and C_8–H), 3.98 (2H, s, C_5–H), 6.92 (1H, d, J= 8.0 Hz, C_3–H), 7.23 (1H, d, J=8.0 Hz, C_4–H)	$C_9H_{12}N_2$ C 72.94 H 8.16 N 18.90	(73.31) (7.92) (18.61)
20c[b]	48—49	71	3250 1560 1460	1.84 (1H, s, NH, exchangeable with D_2O), 2.29 (3H, s, CH_3), 2.6—3.4 (4H, m, C_7 and C_8–H), 3.96 (2H, s, C_5–H), 7.10 (1H, s, C_4–H), 8.20 (1H, s, C_2–H)	$C_9H_{12}N_2$ C 72.94 H 8.16 N 18.90	(72.58) (8.34) (19.27)

a) This compound was recrystallized from iso-Pr_2O and the IR spectrum was measured in a KBr disk.
b) This compound was recrystallized from Et_2O–petr. ether and the IR spectrum was measured in a KBr disk.

(23.2), 147 (88.0), 119 (18.0), 91 (36.0).

6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (5c)——A mixture of 3-aminomethacrylaldehyde (**19c**) (41.1 g, 480 mmol), **12** (109.9 g, 580 mol), and $AcONH_4$ (0.6 g) was heated at 120 °C for 24 h. The mixture was acidified with 6 N HCl and washed with $CHCl_3$. The aqueous layer was adjusted to pH 4.0 with 40% NaOH and extracted with toluene. The toluene layer was evaporated *in vacuo* to give a residue, which was fractionally distilled: 1st fraction, bp 109 °C (0.45 mmHg), 23.2 g; 2nd fraction, bp 125 °C (0.45 mmHg), 20.3 g; and 3rd fraction, bp 140—150 °C (0.45 mmHg), 28.9 g. A solution of the 3rd fraction (28.9 g, 120 mmol) in CH_3COCH_3 (100 ml) was gradually added to a hot solution of fumaric acid (20.9 g, 180 mmol) in CH_3COCH_3 (2 l) with stirring. The mixture was further stirred at room temperature. The resulting solid was filtered off and recrystallized from CH_3COCH_3. The fumarate was decomposed with saturated Na_2CO_3 aq. solution, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated *in vacuo* to give an oil, which gradually solidified. The solid was recrystallized from petr. ether to give colorless prisms, mp 80—81 °C. Yield 26.6 g (23%). MS *m/z* (relative intensity): 238 (M^+, 91.1), 237 (77.8), 161 (22.2), 147 (100.0).

Debenzylation of 6-Benzyl-5,6,7,8-tetrahydronaphthyridines (3a—c, 5a—c, and 13)——A mixture of a 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine (40 mmol) and 10% Pd–C (2 g) in AcOH (100 ml) was hydrogenated at 50—60 °C. After absorption of the theoretical amount of H_2, the catalyst was filtered off. The filtrate was concentrated *in vacuo* to give a residue, which was made alkaline with 40% NaOH and extracted with toluene. The toluene was removed *in vacuo* to give a residue, which was purified by distillation or recrystallization.

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References and Notes

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