Synthesis and Structural Study of 2,5-Dihydropyridines. Competitive Metalation of 2-Fluoropyridine

F. Marsais, P. Granger, and G. Quéguiner*

Laboratoire de Chimie Organique Hétérocyclique, Institut National Supérieur de Chimie Industrielle de Rouen et Faculté des Sciences et des Techniques de l'Université de Rouen, 76130 Mont Saint Aignan, France

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Butyllithium addition to 2-fluoropyridine occurs at low temperature. Hydrolysis of the resulting reaction mixture leads to an adduct, the structure of which is shown to be 2-butyl-6-fluoro-2,5-dihydropyridine. This result was chemically proved and conformed by ^1H and ^{13}C NMR spectroscopy (we establish, moreover, some physicochemical properties of this structure, IR, UV, etc.). The 2-fluoropyridine–butyllithium adduct reacts with various alkyl iodides, leading to the corresponding 2,5-dialkyl-6-fluoro-2,5-dihydropyridines. At lower temperatures, 2-fluoropyridine undergoes a competitive ortho lithiation. We also report the addition of butyllithium to 2-chloropyridine, which gives a 2,5-adduct which is less stable than its fluorinated homologue.

Little work has been done on 2,5-dihydropyridines, mainly because of their poor stability.[1] The reaction between electrophiles and the 2-butyl-1-lithio-1,2-dihydropyridine is assumed to involve 2,5-dihydropyridines[2] (Scheme I).

Recently Francis and co-workers[3] identified 2,5-dihydropyridines in reactions of this kind. Their assignments are based on the NMR spectra of these intermediates in the reaction mixtures. We observed such additions in studying the metalation conditions of monosubstituted pyridines[4] using butyllithium at low temperature. We report here a simple synthesis of these derivatives and a study of their structure.

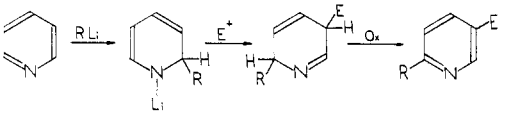
Results and Discussion

(1) Addition of *n*-Butyllithium to 2-Fluoropyridine. The butyllithium–*N,N,N',N'*-tetramethyl-1,2-diaminoethane (TMEDA) complex reacts at −40 °C in tetrahydrofuran (THF) solution with 2-fluoropyridine (1), and hydrolysis of the resulting reaction mixture leads to a dihydro compound which is slightly unstable when impure and must be purified in dry conditions under nitrogen. After distillation, 2-butyl-6-fluoro-2,5-dihydropyridine (2) is obtained in good yield and stored at 0 °C. Oxidation of 2 (by potassium permanganate in acetone) provides 3, the ^1H NMR spectrum of which, compared with that of 2-fluoro-6-methylpyridine,[5] shows that the butyl substituent is attached at position 2 on the 6-fluoro compound 3 (Scheme II).

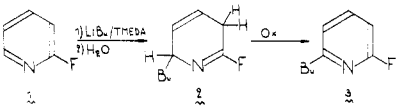
The structure of this addition compound 2 could be either that of a 2,3-dihydro or a 2,5-dihydro derivative (a 1,2-dihydro structure would have IR absorption for N–H at 3300 cm^{-1}). Structure 2 is confirmed by the fact that the reaction of butyllithium with 2-fluoropyridine (1), followed by deuterolysis, leads to the same derivative, 4, as that obtained from butyllithium addition to 3-deuterio-2-fluoropyridine (5) and protolysis (Scheme III).

In each case 2-butyl-5-deuterio-6-fluoro-2,5-dihydropyridine (4) is obtained, whereas a 2,3-addition would give

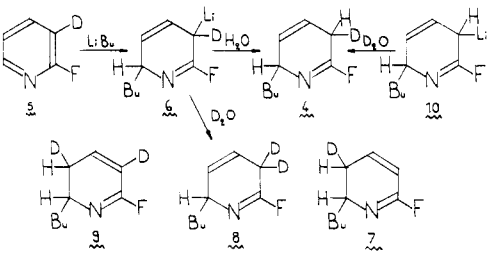
Scheme I



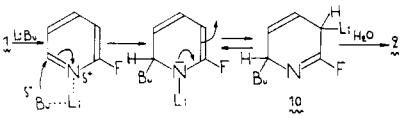
Scheme II



Scheme III



Scheme IV



2-butyl-3-deuterio-6-fluoro-2,3-dihydropyridine (7). The same reaction between butyllithium and 3-deuterio-2-fluoropyridine (5), followed by a heavy-water hydrolysis, produces the 2-butyl-5,5-dideuterio-6-fluoro-2,5-dihydropyridine (8) and not the 2,3-dihydro isomer 9. This comparative study was made by using the ^1H NMR spectra of derivatives 2, 4, and 8. Moreover, all attempts to obtain an isotopic exchange on 2 proved to be unsuccessful, thus excluding tautomery between compounds 4, 7 and 8, 9.

It may be assumed that, according to Levine and coworkers,[6] butyllithium first forms the 1,2-adduct 10′, which after isomerization reacts with water at position 5 (Scheme IV).

After a primary coordination of butyllithium by the pyridine nitrogen,[7] the nucleophilic attack of the butylcarbanion does not occur at the fluorinated carbon but at the other nitrogen-adjacent position. As in the benzenic

(1) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.
(2) Giam, C. S.; Stout, J. L. *Chem. Commun.* **1970**, 478. Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1974**, *39*, 59. Finch, N.; Gemenden, C. W. *Ibid* **1975**, *40*, 569. Knaus, E. E.; Ondrus, T. A.; Giam, C. S. *J. Heterocycl. Chem.* **1976**, *13*, 789.
(3) Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1978**, *43*, 3227.
(4) Marsais, F.; Mallet, M.; Quéguiner, G.; Pastour, P. *C. R. Hebd. Seances Acad. Sci., Ser. C*, **1972**, *275*, 1535.
(5) Roe, A.; Cheek, P. H.; Hawkins, G. F.; *J. Am. Chem. Soc.* **1949**, *71*, 4152.
(6) Levine, R.; Kadunce, W. M. *Chem. Commun.* **1970**, 921.
(7) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, 285.

0022-3263/81/1946-4494$01.25/0

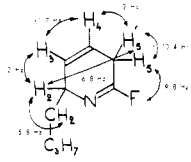
Table I. ^{13}C NMR Spectral Data of 2-Butyl-6-fluoro-2,5-dihydropyridine 2

	C_2	C_3	C_4	C_5	C_6	α-CH_2	β-CH_2	γ-CH_2	CH_3
shift (Me_4Si), δ	57.9	129.2	119.6	23.9	158.8	35.9	26.8	22.2	13.3
$^1J_{C-H}$	135	160	165	127		128	127	129	126
J_{C-F}	14.7 (^3J)		7.3 (^3J)	40 (^2J)	260 (^1J)				

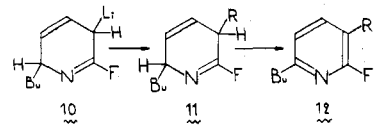
Table II. ^1H NMR Chemical Shifts and C=N Stretching Frequencies of 2,5-Dihydropyridines 2 and 11

	chemical shift, δ						$\nu_{C=N}$, cm^{-1}
R (product)	H_3 and H_4	H_2	H_5	CH_2	CH_3	R	
H (2)	5.90, 5.60	4.25	2.90, 2.80	1.80-1.10	0.90		1745
CH_3 (11a)	5.80, 5.50	4.20	2.90		0.90	1.25	1740
C_2H_5 (11b)	5.95-5.35	4.15	2.95		0.90	1.55 (CH_2), 0.90 (CH)	1730
$CH(Me)_2$ (11c)	6.00-5.40	4.15	2.90	1.70-1.20	0.90	2.20 (CH), 0.95 (CH_3)	1730

Chart I. H-H and H-F Coupling Constants of 2-Butyl-6-fluoro-2,5-dihydropyridine (2).



Scheme V



Scheme VI

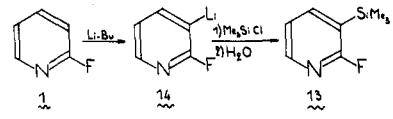


Table III. Temperature Effect upon the Competition between Addition and Metalation during Reaction of Butyllithium with 2-Fluoropyridine

	% reaction			
	1 h at −75 °C	1 h at −60 °C	0.5 h at −60 °C, 0.5 h at −40 °C	1 h at −40 °C
metalation of 13	11	20	17	0
addition of 2	15	28	60	65

series, when Meisenheimer salts are formed,[8] the nucleophilic attack is faster at position 6 of 2-fluoropyridine (1), despite activation of position 2 by the electroattractive effects of fluorine.

The unexpected stability of compound 2 is explained by the conjugation of the mesomeric effects of the fluorine and the imine bond. Analysis confirms the 2,5-dihydro structure of 2 and gives some interesting features in a series for which little information is known at this time. The ultraviolet spectrum of 2 in ethanolic solution shows maximum absorption at 204 nm with a molecular extinction coefficient of 1180. A conjugated structure would absorb light above 240 nm, and its molecular extinction coefficient would range from 3000 to 5000.[9]

With infrared spectroscopy the imine bond of 2 presents an intense absorption at 1745 cm^{-1}. This large hypsochromic effect of approximately 75 cm^{-1} arises from the presence of the fluorine atom. Similarly, Thompson and Torkington[10] have drawn attention to the remarkable increase of the C=C stretching frequency when the double bond is substituted by fluorine atoms.

^{13}C NMR spectroscopy (Table I) shows the presence within the molecule of three sp^2 carbons and six sp^3 carbons, four of which are easily attributed to the butyl substituent, by analogy with *n*-pentylamine.[11]

By use of the undecoupled ^{13}C NMR spectrum, the two remaining sp^3 carbons are found to correspond to a CH_2 and a CH. At 23.9 ppm the CH_2 presents a long-range C–F coupling of 40 hZ, characteristic of a $^2J_{C-F}$ coupling constant,[12] which leads to the assignment of this resonance to C-5. The signal at 57.9 ppm corresponds to a sp^3 CH bound to a nitrogen.[11] Its long-range C–F coupling of 15 Hz is characteristic of a carbon at three bonds from fluorine;[13] thus this signal is assigned to C-2. Moreover, apart from the fluorinated C-6 carbon at 158.8 ppm, there is no nitrogen-adjacent sp^2 carbon (its chemical shift would be greater than 140 ppm[14]). The study of the long-range C–F coupling constants shows that the two remaining carbons, C-3 and C-4, resonate respectively at 129.2 and 119.6 ppm.

The ^1H NMR spectrum of 2 (Chart I) confirms the 2,5-dihydro structure, and the H–H couplings have been measured. We show in particular the existence of a homoallylic coupling between the hydrogens H_2 and H_5, J = 6.8 Hz. Both the equivalence and value of the cis and trans H_2–H_5 coupling constants enable us to estimate that the molecule 2 is in a quasi-planar conformation or in a rapid exchange.

^{19}F resonance is found at 31.2 ppm (using $CFCl_3$ as a reference), and we find, by ^1H and ^{14}N double irradiation, an H_5–F coupling constant of 9.8 Hz.

(2) Synthesis of 5-Alkyl-2-butyl-6-fluoro-2,5-dihydropyridines. The lithiated adduct 10 reacts with alkyl iodides (Scheme V) and leads to the corresponding alkylated derivatives 11.

The principal physicochemical properties of compounds 11 are compared with those of 2 in Table II. Compounds 11 contain two asymetrical carbons, but the complexity of their ^1H NMR spectra does not enable us, at this time, to distinguish between the two diastereoisomers.

The 2,5-dihydropyridines 11, when oxidized by potassium permanganate in acetone, give the corresponding

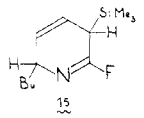
(8) Crampton, M. R.; El Ghariani, M. A.; Khan, H. A. *Tetrahedron* **1972**, *28*, 3299.
(9) Fry, E. *J. Org. Chem.* **1963**, *28*, 1869. Meyers, A. I.; Schneller, J.; Ralhan, N. K. *J. Org. Chem.* **1963**, *28*, 2944.
(10) Torkington, P.; Thompson, H. W. *Trans. Faraday Soc.* **1945**, *41*, 236.
(11) Eggert, H.; Djerassi, C. D. *J. Am. Chem. Soc.* **1973**, *95*, 3710.
(12) Vanderkelen, G. P.; Eeckhaut, Z. *J. Mol. Spectrosc.* **1963**, *10*, 141.
(13) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.
(14) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972.
(15) Paschal, J. W.; Rabideau, P. W. *J. Am. Chem. Soc.* **1974**, *96*, 272. Grossel, M. C.; Perkins, M. J. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1544.

2,5-dialkyl-6-fluoropyridines (12) with good yields (Scheme V).

(3) Effect of Temperature on the Addition Reaction. On lowering the temperature of the butyllithium reaction with 2-fluoropyridine (1), we observe a simultaneous metalation of 1. This is experimentally proved by reaction of chlorotrimethylsilane on the mixture. 2-Fluoro-3-(trimethylsilyl)pyridine (13) comes from 2-fluoro-3-lithiopyridine (14), which is the metalation intermediary of 2-fluoropyridine (1; Scheme VI). 2-Fluoro-3-(trimethylsilyl)pyridine (13) and 2-butyl-6-fluoro-2,5-dihydropyridine (2) are obtained in varying proportions, depending on the reaction temperature (Table III).

The position of metalation is confirmed by preparing 14 by halogen–metal exchange starting from 3-bromo-2-fluoropyridine[16] (^{1}H NMR spectra of the resulting trimethylsilyl derivatives are identical).

It must be noted that the expected product 15, resulting



15

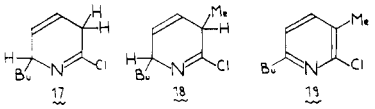
from the reaction of the lithiated adduct 10 with chlorotrimethylsilane, was not isolated. It is likely that compound 15 is formed in situ and then decomposed, due to its instability in the presence of nucleophilic reagents; structures like $\equiv SiCH_2Z$ are easily cleaved at the Si—CH_2 bond. This reaction is favored when the anion Z—CH_2^- is stabilized by resonance,[17] as it is the case here.

Recently we reported the considerable utility of direct metalation of monofluoro- and monochloropyridines[18] and quinolines[19] by using lithium diisopropylamide. Metalation of 3-chloropyridine in the same conditions has been studied by Gribble[20] and by us.[21] We have also achieved ortho lithiation of 2-fluoropyridine (1)[22] with lithium diisopropylamide with excellent regioselectivity and good yield (82% of silylated derivative 13).

(4) Addition of Butyllithium onto 2-Chloropyridine. The butyllithium–TMEDA complex adds to 2-chloropyridine (16) in THF solution at −40 °C. As in the case of 2-fluoropyridine (1), hydrolysis of the resulting reaction mixture leads to the 2-butyl-6-chloro-2,5-dihydropyridine (17). This derivative is, however, less stable than its fluorinated analogue and has been characterized by its ^{1}H NMR spectrum. The presence of traces of the rearomatized compound has sometimes been observed.

Reaction of methyl iodide with the adduct of butyllithium and 2-chloropyridine (16) allows us to isolate in good yield 2-butyl-6-chloro-5-methyl-2,5-dihydropyridine (18).

In the presence of water or oxygen, 18 is rapidly oxidized to 19. Nevertheless, we have purified 18 and recorded its



17 18 19

^{1}H NMR spectrum. The infrared spectrum of 18 presents an intense absorption at 1680 cm^{-1}, which is due to the chlorinated imine bond of 18. The hypsochromic effect produced by the chlorine atom is significantly lower than in the case of fluorine. We find a difference of 65 cm^{-1} between compounds 11 and 18. This is in good agreement with the difference observed between acyl chlorides and fluorides.[22]

Experimental Section

The ^{13}C and ^{1}H NMR spectra were recorded by using Brucker WH-90 and Varian A-60 instruments ($CDCl_3$ was the solvent and Me_4Si the internal standard). Infrared spectra were obtained as thin films from a Perkin-Elmer R-12 spectrophotometer. Elemental analyses were performed on a Technicon instrument. The mass spectrum of compound 2 was measured with a JEOL D-100 spectrometer (75 eV, 300 μA).

Purchased reagents were obtained from Aldrich Chemical Co. (*n*-butyllithium in hexane, 2-fluoropyridine, and 2-chloropyridine). Solvents were distilled from $LiAlH_4$ and were stored over molecular sieves (3 Å). Diisopropylamine, TMEDA, and chlorotrimethylsilane were redistilled from CaH_2 and were stored over CaH_2.

(1) General Procedure for Preparing the 2-Butyl-6-fluoro-2,5-dihydropyridines. Dry THF (250 mL), *n*-butyllithium (1.6 M in hexane, 34.5 mL, 0.055 mol), and dry TMEDA (6.4 g, 0.055 mol) were introduced into a 500-mL flask under a dry nitrogen stream. The solution was cooled to −40 °C, and 2-fluoropyridine (4.85 g, 0.050 mol) in dry THF (25 mL) was added dropwise. After the yellow mixture was stirred for 1 h at −40 °C, a THF (25 mL) solution of the suitable reagent was added, and the mixture was allowed to stand for an additional period at −40 °C. The solution was warmed to −10 °C, and water (150 mL) was slowly added. The aqueous layer was extracted twice with ethyl ether (150 mL), and the combined ether extract was dried over anhydrous sodium sulfate. Solvent removal on a rotary evaporator provided a red oil, which was distilled at 15 mm of pressure (the distillation flask was continuously swept with dry nitrogen). The purified product was stored at 0 °C under a dry nitrogen atmosphere.

2-Butyl-6-fluoro-2,5-dihydropyridine (2) was prepared according to the procedure described previously, after reaction of a mixture of C_2H_5OH (10 mL), H_2O (1 g), and THF (25 mL). Distillation yielded a colorless liquid: 5.1 g (65%); bp 85 °C (15 mm); IR (film) 3050, 2970, 2940, 2880, 2870, 1745, 1460, 1430 cm^{-1}; NMR ($CDCl_3$) δ 0.90 and 1.40 (m, 9 H, $CH_2CH_2CH_2CH_3$), 2.85 (m, 2 H, H_5 and H_5'), 4.25 (m, 1 H, H_2), 5.90 and 5.60 (m, 2 H, H_3 and H_4); UV (C_2H_5OH) λ_{max} 204 nm (ε 1180); mass spectrum, *m/e* 155, 112, 98, 78.

Anal. Calcd for $C_9H_{14}FN$: C, 69.65; H, 9.34; N, 9.02. Found: C, 69.6; H, 9.22; N, 8.86.

2-Butyl-5-deuterio-6-fluoro-2,5-dihydropyridine (4) was prepared according to the procedure described previously, after reaction of a mixture of C_2H_5OD (10 mL), D_2O (1 g), and THF (25 mL). Distillation yielded a colorless liquid: 5.1 g (65%); bp 85 °C (15 mm); NMR ($CDCl_3$) δ 2.85 (m, 1 H, H_5).

2-Butyl-5,5-dideuterio-6-fluoro-2,5-dihydropyridine (8) was prepared from 3-deuterio-2-fluoropyridine (5) by the procedure described for 2, after reaction of a mixture of C_2H_5OD (10 mL), D_2O (1 g), and THF (25 mL). Distillation yielded a colorless liquid: 5.2 g (66%); bp 85 °C (15 mm); NMR ($CDCl_3$) δ 2.85 (no signal).

2-Butyl-6-fluoro-5-methyl-2,5-dihydropyridine (11a) was prepared by the procedure described for 2, after reaction of methyl iodide in THF (25 mL). Distillation gave 11a: 5.6 g (66%); bp 96 °C (15 mm); IR (film) 3040, 2960, 2940, 2880, 1740, 1460 cm^{-1}; NMR ($CDCl_3$) δ 0.90, 1.25 and 1.40 (m, 12 H, CH_3 and $CH_2CH_2CH_2CH_3$), 2.90 (m, 1 H, H_5), 4.20 (m, 1 H, H_2), 5.50 and 5.80 (m, 2 H, H_3 and H_4).

Anal. Calcd for $C_{10}H_{16}FN$: C, 70.97; H, 9.53; N, 8.27. Found: C, 71.0; H, 9.49; N, 8.25.

(16) Mallet, M.; Quéguiner, G.; Pastour, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 719. Mallet, M.; Marsais, F.; Quéguiner, G.; Pastour, P. *Ibid.* **1972**, *275*, 1439.

(17) Hauser, C. R.; Hance, C. R. *J. Am. Chem. Soc.* **1951**, *73*, 5846. Sommer, L. H.; Tyler, L. J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 2872.

(18) Marsais, F, personnal communication at the SCF Congress, Bordeaux, September 1980.

(19) Marsais, F.; Bouley, E.; Quéguiner, G. *J. Organomet. Chem.* **1979**, *171*, 273.

(20) Gribble, G. W.; Saulnier, M. C. *Tetrahedron* **1980**, *21*, 4137.

(21) Marsais, F.; Bréant, P.; Ginguéné, A.; Quéguiner G. *J. Organomet. Chem.*, in press.

(22) Güngör, T; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.*, in press.

(23) Ramsey, J. A.; Ladd, J. A. *J. Chem. Soc. B* **1968**, *1*, 119.

2-Butyl-5-ethyl-6-fluoro-2,5-dihydropyridine (**11b**) was prepared as described in the previous section by using ethyl iodide: 5.7 g (62%); bp 107 °C (15 mm); IR (film) 3040, 2960, 2940, 2860, 1730, 1460 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 6 H, CH_3), 1.50 (m, 8 H, CH_2), 2.95 (m, 1 H, H_5), 4.15 (m, 1 H, H_2), 5.65 (m, 2 H, H_3 and H_4).

Anal. Calcd for $C_{11}H_{18}FN$: C, 72.08; H, 9.89; N, 7.64. Found: C, 72.2; H, 10.0; N, 7.32.

2-Butyl-6-fluoro-5-isopropyl-2,5-dihydropyridine (**11c**) was prepared as described in the previous section by using isopropyl iodide: 6.0 g (61%); bp 115 °C (15 mm); IR (film) 3040, 2960, 2940, 2860, 1730, 1460 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (m, 9 H, CH_3), 1.40 (m, 6 H, CH_2), 2.20 (m, 1 H, CH), 2.90 (m, 1 H, H_5), 4.15 (m, 1 H, H_2), 5.70 (m, 2 H, H_3 and H_4).

Anal. Calcd for $C_{12}H_{20}FN$: C, 73.05; H, 10.22; N, 7.10. Found: C, 73.2; H, 10.3; N, 6.98.

(2) General Procedure for Oxidizing the 2,5-Dihydropyridines. Various 2-butyl-6-fluoro-2,5-dihydropyridines (3 g) were dissolved in acetone (50 mL), and powdered potassium permanganate was added portionwise with magnetical stirring. The mixture was stirred for 2 days at room temperature, and the excess of $KMnO_4$ was destroyed with ethanol. The solution was filtered over asbestos to remove the dark precipitate, and it was dried over anhydrous sodium sulfate. Removal of the solvent afforded a colorless oil (further purification was not necessary for spectral and elemental analyses).

2-Butyl-6-fluoropyridine (**3**): 2.7 g (91%); IR (film) 3080, 2960, 2930, 2870, 2860, 1690, 1610, 1575, 1450, 1435; NMR ($CDCl_3$) δ 0.90 and 1.60 (m, 7 H, $CH_2CH_2CH_3$), 2.80 (t, 2 H, CH_2–pyridine, J = 7, 5 Hz), 6.75 (dd, 1 H, H_3, J = 8, 2.5 Hz), 7.05 (dd, 1 H, H_5, J = 7, 2.5 Hz), 7.70 (dd, 1 H, H_4, J = 8, 7 Hz).

Anal. Calcd for $C_9H_{12}FN$: C, 70.55; H, 7.89; N, 9.14. Found: C, 70.3; H, 8.01; N, 9.42.

6-Butyl-2-fluoro-3-methylpyridine (**12a**): 1.0 g (33%); bp 94 °C (12 mm); IR (film) 3040, 2960, 2930, 2870, 1620, 1590, 1475, 1400 cm^{-1}; NMR ($CDCl_3$) δ 0.90 and 1.50 (m, 7 H, $CH_2CH_2CH_3$), 2.20 (s, 3 H, CH_3), 2.70 (t, 2 H, CH_2–pyridine, J = 7.5 Hz), 6.90 (dd, 1 H, H_5, J = 7.5, 2 Hz), 7.45 (dd, 1 H, H_4, J = 10, 7.5 Hz).

Anal. Calcd for $C_{10}H_{14}FN$: C, 71.82; H, 8.44; N, 8.32. Found: C, 71.6; H, 8.51; N, 8.20.

6-Butyl-3-ethyl-2-fluoropyridine (**12b**): 2.5 g (84%); IR (film) 3040, 2960, 2930, 2860, 1680, 1630, 1580, 1520, 1475 cm^{-1}; NMR ($CDCl_3$) δ 0.90 and 1.50 (m, $CH_2CH_2CH_3$), 1.20 (t, CH_3, J = 7.5 Hz), 2.60 (q, ethyl CH_2, J = 7.5 Hz), 2.70 (t, butyl CH_2, J = 7.5 Hz), 6.90 (dd, 1 H, H_5, J = 7.5, 2 Hz), 7.45 (dd, 1 H, H_4, J = 10, 7.5 Hz).

Anal. Calcd for $C_{11}H_{16}FN$: C, 72.89; H, 8.90; N, 7.73. Found: C, 72.8; H, 8.84; N, 7.72.

(3) Metalation of 2-Fluoropyridine with *n*-Butyllithium. Into a cold solution (−60 °C) of dry THF (250 mL) and *n*-butyllithium (1.6 M in hexane, 31.5 mL, 0.05 mol) under nitrogen contained in a 500-mL flask was added dropwise a THF (25 mL) solution of 2-fluoropyridine (4.85 g, 0.05 mol), and the mixture was allowed to stand for 1 h at −60 °C. Chlorotrimethylsilane (6.0 g, 0.055 mol) dissolved in dry THF (25 mL) was added dropwise with stirring, and the mixture was allowed to stand at −60 °C for 1 h. The reaction mixture was allowed to warm to −10 °C, and H_2O (150 mL) was added. The aqueous layer was extracted with ethyl ether (2 × 150 mL), and the combined extract was dried over anhydrous sodium sulfate. Solvent removal led to a red oil. The bulk of the oil distilled to give a mixture of 2-butyl-6-fluoro-2,5-dihydropyridine (**2**) and 2-fluoro-3-(trimethylsilyl)pyridine (**13**). Yields were calculated by using the ^1H NMR spectrum of the raw product. Compound **13** was purified by preparative GPC (SE-30): IR (film) 3080, 3050, 2960, 2900, 1590, 1585, 1555, 1415, 1395 cm^{-1}; NMR ($CDCl_3$) δ 0.35 (d, 9 H, $Si(CH_3)_3$), 7.15 (octet, 1 H, H_5, J = 7, 5, 3 Hz), 7.85 (octet, 1 H, H_4, J = 8, 7, 2), 8.20 (octet, 1 H, H_6, J = 5, 2, 0.5 Hz).

Anal. Calcd for $C_8H_{12}FNSi$: C, 56.76; H, 7.14; N 8.27. Found: C, 57.0; H, 7.04; N, 8.22.

(4) Synthesis of 2-Fluoro-3-(trimethylsilyl)pyridine (13) from 3-Bromo-2-fluoropyridine by Metal–Halogen Exchange with *n*-Butyllithium. 3-Bromo-2-fluoropyridine[16] (17.6 g, 0.1 mol) in dry ethyl ether (25 mL) was added with stirring under dry nitrogen to a solution of *n*-butyllithium (1.6 M in hexane, 63 mL, 0.10 mol) in dry ethyl ether (250 mL) at −60 °C. After the mixture was stirred for 1 h at −60 °C, chlorotrimethylsilane (12.0 g, 0.11 mol) in dry ethyl ether (25 mL) was added dropwise, and the solution was allowed to react for 1 h at −60 °C. The reaction mixture was treated with water (200 mL) at −10 °C, and the aqueous layer was extracted twice with ethyl ether (2 × 150 mL). Drying of the etheral extract over anhydrous sodium sulfate and removal of the ether afforded a yellow oil. Distillation at 15 mm of pressure gave **13**: 11.8 g (70%); bp 83 °C (15 mm).

(5) 3-Deuterio-2-fluoropyridine (5)[16] was prepared by the procedure described in the previous section by using a mixture of C_2H_5OD (10 g), D_2O (2 g), and dry THF (25 mL) instead of chlorotrimethylsilane: 5.0 g (51%); bp 127 °C; NMR ($CDCl_3$) δ 7.15 (hextet, 1 H, H_5, J = 7.5, 5, 3 Hz), 7.80 (m, 1 H, H_4), 8.25 (octet, 1 H, H_6, J = 5, 3, 1 Hz).

(6) 2-Butyl-6-chloro-2,5-dihydropyridine (17) was prepared according to the procedure described for the fluorinated isomer **2**: NMR ($CDCl_3$) δ 0.90 and 1.40 (m, 9 H, $CH_2CH_2CH_2CH_3$), 3.10 (dd, 2 H, H_5 and H_5), 4.30 (m, 1 H, H_2), 5.70 (s, 2 H, H_3 and H_4).

(7) 2-Butyl-6-chloro-5-methyl-2,5-dihydropyridine (18) was prepared according to the procedure described for the fluorinated isomer **11a**: 6.0 g (65%); bp 118 °C (15 mm). The pale yellow product was redistilled just before the spectral and elemental analyses: IR (film) 3040, 2960, 2930, 2860, 1680, 1460 cm^{-1}; NMR ($CDCl_3$) δ 0.95 and 1.50 (m, 9 H, $CH_2CH_2CH_2CH_3$), 1.40 (d, C H_3–pyridine, J = 7 Hz), 3.05 (q, 1 H, H_5), 4.30 (m, 1 H, H_2), 5.70 (s, 2 H, H_3 and H_4).

Anal. Calcd for $C_{10}H_{16}ClN$: C, 64.68; H, 8.68; N, 7.54. Found: C, 64.9; H, 8.49; N, 7.61.

After being allowed to stand for a short time in the NMR tube, compound **18** was completely oxidized into 6-butyl-2-chloro-3-methylpyridine (**19**): NMR ($CDCl_3$) δ 0.95 and 1.50 (m, 7 H, $CH_2CH_2CH_3$), 2.50 (s, 3 H, CH_3), 3.05 (t, 2 H, CH_2–pyridine, J = 7 Hz), 7.35 (d, 1 H, H_5, J = 8 Hz), 7.90 (d, 1 H, H_4, J = 8 Hz).

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