Selective Reductions of 1-Methyl-4-phenyl-2-pyridone

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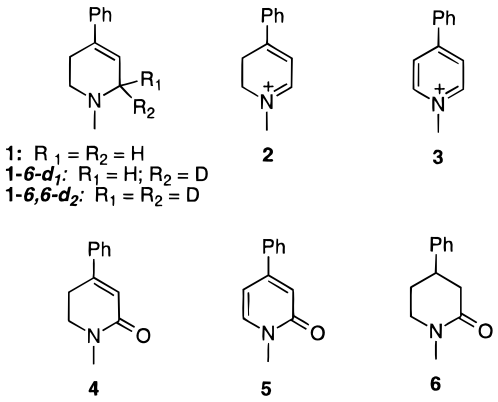
Received August 18, 1995[⊗]

We have explored the reactions of 1-methyl-4-phenyl-2-pyridone (**5**) with various reducing agents in an effort to develop synthetic approaches to specifically deuterium-labeled 1,4-disubstituted 1,2,3,6-tetrahydropyridine analogs needed for metabolic and enzyme mechanistic studies. Reactions with $NaBH_4$ in CH_3OH or THF, $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF, and $Al(i\text{-}Bu)_2H$ (DIBALH) in THF resulted in quantitative recovery of starting material. On the other hand, treatment with BH_3 in THF unexpectedly led to the formation of 4-phenylpyridine (**7**) in 98% yield. $LiAlH_4$ in THF or Et_2O and Red-Al in THF gave varying amounts of the 3,6-dihydro-2-pyridone **8** and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**). In the presence of $TiCl_3$, $LiAlH_4$ in THF at 0 °C converted **5** to **1** in 97% yield. $LiB(s\text{-}Bu)_3H$ (L-Selectride) in THF gave exclusively the 1,4-reduction product **8**. Base catalyzed isomerization of **8** provided the conjugated 5,6-dihydro-2-pyridone **4**. The applications of these reactions with deuterated reagents provide insights into the reaction pathways and several avenues for the regioselective synthesis of the required deuterium-labeled compounds.

Introduction

As part of our mechanistic and metabolic studies on the monoamine oxidase-catalyzed oxidation of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **1**) leading to the corresponding dihydropyridinium **2** and pyridinium **3** products,[1−3] we required synthetic routes to regiospecifically deuterium- and tritium-labeled 1,4-disubstituted tetrahydropyridine derivatives. The synthesis of the *6,6-d*$_2$ analog **1-*6,6-d*$_2$** has been achieved by reduction of 1-methyl-4-phenyl-5,6-dihydro-2-pyridone (**4**) with $LiAlD_4$.[4] This approach, however, appeared to be limited in terms of the regiochemistry (only the *6,6-d*$_2$ analog could be prepared) and suffered from the poor overall yield of the starting dihydropyridone.[5,6] The only other relevant literature report describes the preparation of racemic **1-*6-d*$_1$** via reduction of the corresponding dihydropyridinium species **2**.[7,8]

We recently developed a high yield synthesis of 1-methyl-4-phenyl-2-pyridone (**5**)[9] and therefore elected to focus our attention on reductions of this intermediate that could provide approaches to selectively deuterated products. Previous attempts to control the catalytic hydrogenation of **5** to generate a dihydro-2-pyridone product that might be useful for subsequent conversion to the corresponding deuterated amine gave only the corresponding 2-piperidone **6**.[4] Consequently, we turned our attention to metal hydrides that might provide the required selectivity. In this paper, we report the results of our studies on the reduction of **5** with diverse boron- and aluminum-containing hydride reagents.



Results

Tables 1, 2 and 3 and Schemes 1 and 2 summarize the salient results of these studies. Only starting material was recovered after prolonged treatment of **5** with $NaBH_4$ in either THF or CH_3OH (Table 1). On the other hand, reaction with BH_3 in THF, a well-known reagent for the reduction of amides to amines,[10] led to the consumption of all of the starting lactam. The product isolated from this reaction in high yield proved to be 4-phenylpyridine (**7**), which was readily identified by comparison of its ^{1}H NMR and GC−EI mass spectra with those of an authentic sample. Treatment of **5** with $LiB(s\text{-}Bu)_3H$ (L-Selectride, Aldrich) in THF at −35 °C also resulted in complete reaction but in this case led to the selective formation in high yield of a product which displayed GC−EI mass spectral characteristics consistent with a dihydropyridone structure. The ^{1}H NMR spectrum clearly identified this product as 1-methyl-4-phenyl-3,6-dihydro-2-pyridone (**8**). Base- or acid-catalyzed isomerization of **8** to **4** confirmed this assignment.

We next examined the reaction of **5** with a variety of aluminum hydride reagents. $LiAl(O\text{-}t\text{-}Bu)_3H$ in THF and $Al(i\text{-}Bu)_2H$ (DIBALH) in THF were without effect on the lactam. $Al(i\text{-}Bu)_2H$ in Et_2O was more reactive. All of the

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

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Table 1. Reductions of 1-Methyl-4-phenyl-3,5-dihydro-2-pyridone (5) with Various Metal Hydrides[a]

			% yield			
reagent	time (h)	temp (°C)	pyridone **5**	dihydropyridone **8**	tetrahydropyridine **1**	phenylpyridine (**7**)
$NaBH_4$/MeOH	6	25	99			
$NaBH_4$/THF	15	reflux	99			
BH_3·THF/THF[b]	11	reflux				99
L-Selectride/THF[b,c]	0.75	−35		99		
LiAl(O-*t*-Bu)$_3$H/THF	16	reflux	96			4
DIBALH/THF	15	reflux	95			5
DIBALH/Et_2O	4	25		61	39	
Red-Al/THF[d]	3	15	32	32	30	6
$LiAlH_4$/Et_2O	7	25	27	37	34	3
$LiAlH_4$/THF[b]	2	0		75	25	

[a] Yields estimated by GC−MS unless otherwise noted. [b] Yields after purification. [c] L-Selectride = Li(*s*-butyl)$_3$BH. [d] Red-Al = $[NaAl(CH_3OCH_2CH_2O)_2H_2]$.

Table 2. Reduction of 1-Methyl-4-phenyl-2-pyridone (5) with $LiAlH_4$ in the Presence of Transition Metals

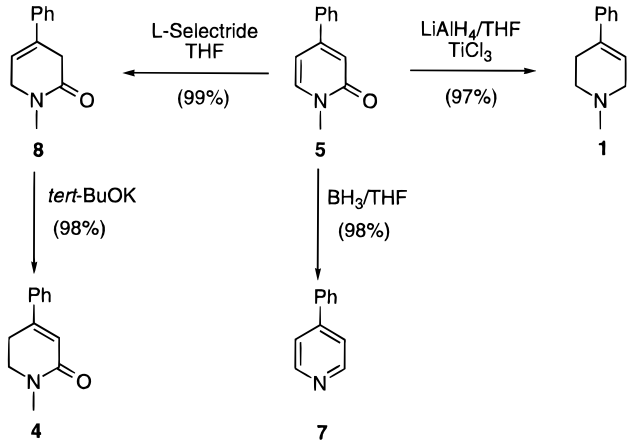
		temp	% yield		
reagent	time	(°C)	**5**	**8**	**1**
$NaBH_4$/$CoCl_2$·$6H_2O$/EtOH	15 h	reflux	99		
$LiAlH_4$/$TiCl_3$/THF	45 min	−20	5	38	57
$LiAlH_4$/$TiCl_3$/THF	25 min	0	1	2	97
$LiAlH_4$/$TiCl_4$/THF	40 min	−10	7	35	58
$LiAlH_4$/$CoCl_2$·$6H_2O$/THF	5 h	25	99		

starting material was consumed after 4 h at room temperature, and two products were produced. One of the products formed in this reaction (39% yield) was readily identified as the tetrahydropyridine **1** by comparison with the synthetic standard. The second major product (61% yield) was characterized as the same 3,6-dihydro-2-pyridone (**8**) that was obtained with L-Selectride.

The reaction of **5** with other aluminum hydride reducing agents also produced mixtures of products. NaAl-$[(CH_3OCH_2CH_2O)_2H_2]$ (Red-Al) in THF under relatively mild conditions gave a mixture of **1**, **7**, **8**, and starting material. An extended reaction time or higher reaction temperature with Red-Al led to the formation of additional side products that were detected by GC−EIMS which were not further characterized. Reductions of 2-pyridone derivatives with $LiAlH_4$ have been reported by Holik and Ferles to be a good route to the corresponding 1,2,3,6-tetrahydropyridines.[11−13] These workers also noted the formation of a dihydro-2-pyridone intermediate during the course of the reaction. In our hands, reduction of **5** with $LiAlH_4$ in Et_2O gave mixtures of products. The tetrahydropyridine **1** was detected early in the reaction, and variations in temperature and stoichiometry of the reagents did not prevent its formation. $LiAlH_4$ in THF gave the dihydro-2-pyridone **8** in 75% yield but even with these optimized conditions compound **1** was a major byproduct.

In an attempt to enhance reactivity, the reactions with $NaBH_4$ and $LiAlH_4$ were conducted in the presence of $CoCl_2$·$6H_2O$,[14] $TiCl_3$,[15] and $TiCl_4$[16] (Table 2), transition metals that are known to increase the reducing potency of metal hydrides. The titanium chlorides enhanced greatly the reactivity, but not the selectivity of the $LiAlH_4$ reductions. These reactions were complete within 45 min at −20 to −10 °C (compared to the 6 h at 25 °C with $LiAlH_4$ alone) and gave a 6:4 ratio of **1** to **8**. With $TiCl_3$ at 0 °C, the tetrahydropyridine **1** was obtained in 97% yield within 30 min, a result comparable to that reported by Ferles who used lithium aluminum hydride in the presence of $AlCl_3$ (1 h reaction in boiling THF).[13] A summary of the reaction pathways observed with these reductions of **5** is presented in Scheme 1.

Scheme 1



With the dual purpose of examining deuteration patterns and gaining insight into the pathways associated with these reactions, the incorporation of deuterium into the products generated in the $LiAlH_4$ reaction was investigated with the use of deuterated reagents. The 2-pyridone **5** was allowed to react at ambient temperature for 20 min with $LiAlH_4$ or $LiAlD_4$ in THF following which the reaction mixtures were quenched either with CH_3OH or CD_3OD (Table 3 and Scheme 2). The reaction mixtures were analyzed by GC−EIMS, and the reduction products (the 3,6-dihydro-2-pyridone **8** and the tetrahydropyridine **1**) were separated by column chromatography and analyzed by ^1H NMR spectroscopy. Treatment with $LiAlD_4$ in THF followed by a CH_3OH workup (path a) gave a monodeuterated dihydro-2-pyridone that was characterized as **8-*6-d*$_1$** and a tetradeuterated tetrahydropyridine that was characterized as **1-*2,2,3,6-d*$_4$**. The corresponding reaction employing $LiAlH_4$ followed by a CD_3OD workup (path b) yielded the dideuterodihydropyridone **8-*3,3-d*$_2$** and the tetrahydropyridine **1** containing no deuterium. Finally, $LiAlD_4$ and a CD_3OD workup (path c) gave **8-*3,3,6-d*$_3$** and **1-*2,2,3,6-d*$_4$**. Thus, in the case of the dihydropyridone reduction products, the hydride (deuteride) reagent introduced the protons (or deuterons) at the C-6 position, while the solvent provided the protons (or deuterons) at C-3. In the case of the

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(12) Ferles, M.; Attia, A.; Silhankova, A. *Collect. Czech. Chem. Commun.* **1973**, *38*, 615−619.
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(15) Ashby, E.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 2567−2572.
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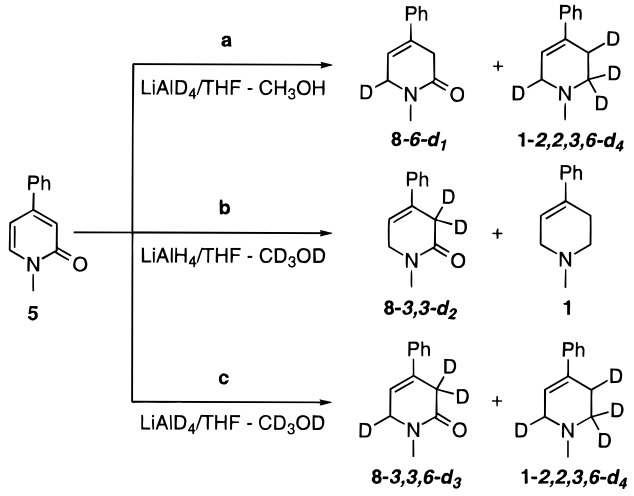
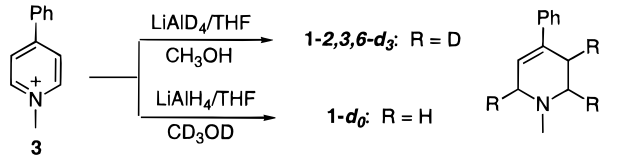
Table 3. Deuterium Incorporation Accompanying the Reduction of 1-Methyl-4-phenyl-2-pyridone (5) in THF

	MPTP **1**					dihydropyridone **8**				
system	d_0	d_1	d_2	d_3	d_4	d_0	d_1	d_2	d_3	d_4
$LiAlH_4/CH_3OH$	1.00	0	0	0	0	1.00	0	0	0	0
$LiAlD_4/CH_3OH$	0	0	0.04	0.10	0.86	0	0.96	0.04	0	0
$LiAlH_4/CD_3OD$	1.00	0	0	0	0	0	0.03	0.97	0	0
$LiAlD_4/CD_3OD$	0	0	0	0.08	0.92	0	0	0.15	0.78	0.07

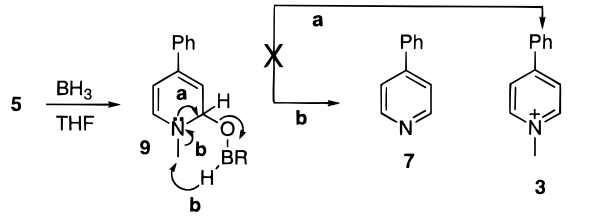
Scheme 2



Scheme 3



Scheme 4



tetrahydropyridine reduction products the hydride (deuteride) reagent was the source of all newly introduced protons (or deuterons). In order to provide additional evidence for the pathways leading to the incorporation patterns observed in these experiments, we also examined reduction of the pyridinium compound **3** (Scheme 3). As predicted from the above results, $LiAlD_4$ followed by CH_3OH or CD_3OD workup gave **1-*2,3,6-d*$_3$** whereas $LiAlH_4$ followed by CH_3OH or CD_3OD work-up gave **1-*d*$_0$**, that is, all newly introduced protons (deuterons) in the tetrahydropyridine product were derived from the hydride (deuteride) reagent.

Discussion

The conversion of the pyridone **5** to 4-phenylpyridine (**7**) by BH_3 was unexpected since BH_3 in THF is a well-known reagent for the reduction of amides to amines.[10] The pathway for this reaction is likely to proceed via the 1,2-reduction product **9** (Scheme 4). Intermediates such as **9** normally undergo elimination to form the corresponding iminium species (pathway a); in this case, the pyridinium compound **3**. Since compound **3** is stable when treated with BH_3/THF, it may be reasonable to propose that in this case the 1,2-reduction product **9** undergoes an alternative, intramolecular hydride transfer reaction (pathway b) that is accompanied by C−N bond scission to yield the observed 4-phenylpyridine (**7**) as shown in Scheme 4. The stability of **7** may account for the unexpected behavior of **9**.

Although spectroscopic evidence[17] argues that the lactam is the energetically preferred form of the starting material **5**, the general behavior of this molecule toward hydride reagents may be better described in terms of the corresponding oxypyridine form. This form in general will be favored in the presence of metallic cations because of the increased stabilization gained through resonance of the resulting pyridinium species **10** (Scheme 5).[18−21] In this case, 1,4 attack by the various hydride reagents examined will afford intermediate **11**. The presence of weak ions (1−5%) with *m*/*z* values corresponding to the pyridone +30 amu (AlH_3) or 33 amu (AlD_3) in hydride/deuteride reaction mixtures indicates that metal complexes (such as **10**) could be involved and supports the hypothesis of a chelation of the metal to the pyridone.

The results obtained with $LiAlD_4$ (Table 3, Scheme 2) provide some support for this pathway. Thus, the deuterium found at C-6 of **8** is derived exclusively from the $LiAlD_4$ while the protons or deuterons at C-3 are derived from solvent. Since workup with CD_3OD introduces two deuterium atoms at C-3 (**8-*3,3,6-d*$_3$** and **8-*3,3-d*$_2$**), we postulate the further conversion of **11** to the *bismetallic* species **12** which, upon treatment with CD_3OD, would lead to the *3,3-d*$_2$ products. The possibility that the protons at C-3 may undergo exchange could be ruled out since **8-*3,3-d*$_2$** was stable in the presence of NaOH and H_2O during the workup.

The second product formed in this reaction is the tetrahydropyridine **1**. This product may be formed via the pathway **13** → **14** → **15** → **1** as shown in Scheme 5. The results with the deuterated reagents provide some support for this sequence. Workup of intermediate **15** (R = D) derived from the $LiAlD_4$ reaction with CH_3OH gave **1-*2,2,3,6-d*$_4$** rather than the tetrahydropyridine bearing only three deuterium atoms (i.e., **1-*2,6,6-d*$_3$**) that would result from replacement of the carbon−metal bond with H from the CH_3OH. Similarly, workup of the $LiAlH_4$ reaction product **15** (R = H) with CD_3OD gave the d_0 product (**1-*d*$_0$**) rather than the monodeuterated product (**1-*1-d*$_1$**). To account for these results, we propose that the metal bonded at C-3 in intermediate **15** is displaced by H^- or D^- to yield the final products observed in the reactions. Analogous incorporation results were observed with the $LiAlH_4$ and $LiAlD_4$ reductions of the 1-methyl-4-phenylpyridinium species **3** (Scheme 3). For

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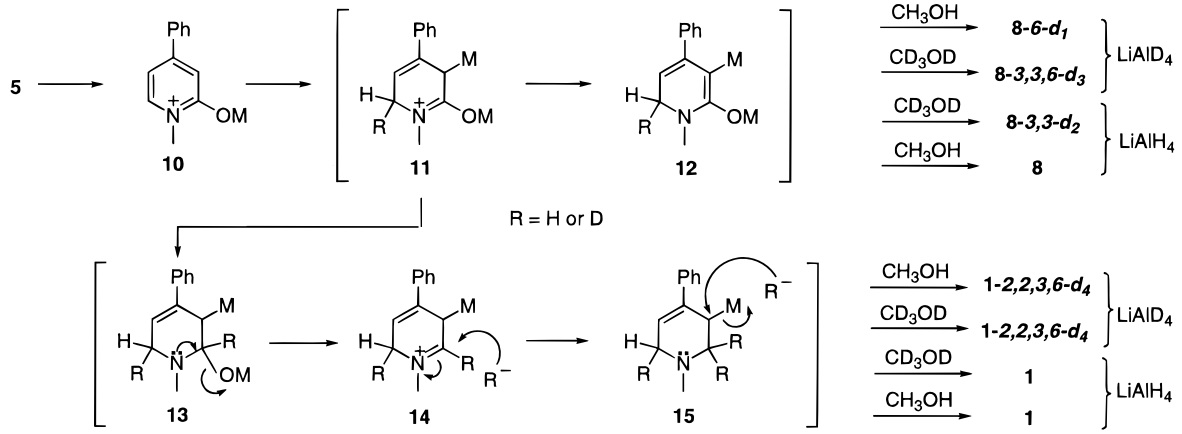
(19) Handel, H.; Pierre, J. L. *Tetrahedron* **1975**, *31*, 2799−2802.
(20) Handel, H.; Pierre, J. L. *Tetrahedron* **1975**, *31*, 997−1000.
(21) Pierre, J. L.; Handel, H.; Perraud, R. *Tetrahedron* **1975**, *31*, 2795−2798.

Scheme 5



example, the observed formation of **1-*2,3,6-d*$_3$** from the reaction with $LiAlD_4$ followed by workup with CH_3OH requires that all three newly introduced atoms be derived from the hydride reducing reagent. This incorporation pattern was achieved only following prolonged reaction times, suggesting that the C_3−M bond, if present, is cleaved slowly.

Conclusion

In conclusion, we have exploited the selective reactivity of various hydride reagents to achieve reductions of 1-methyl-4-phenyl-2-pyridone that can be applied to the regioselective synthesis of deuterium-labeled 1,4-disubstituted 1,2,3,6-tetrahydropyridines of biological interest. L-Selectride gives the 3,6-dihydro-2-pyridone **8** that can be isomerized to the conjugated 5,6-dihydro-2-pyridone **4**, whereas borane leads to 4-phenylpyridine **7**. In addition to dihydropyridones and phenylpyridine, the 1,2,3,6-tetrahydropyridine **1** was readily obtained by reduction of the 2-pyridone with $LiAlH_4$ in the presence of $TiCl_3$. The starting 2-pyridone, therefore, can lead to four compounds in excellent yields depending on the reduction system used.

Experimental Section

Caution: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**) is a known nigrostriatal neurotoxin and should be handled using disposable gloves in a properly ventilated hood. Detailed procedures for the safe handling of MPTP have been reported.[22]

General. See ref 9.

4-Phenylpyridine (7). The pyridone **5** prepared following the reported procedure[9,23] (1 mmol, 185 mg) was dissolved in anhydrous THF (15 mL), and BH_3·THF (5 mL, 1 M, 5 mmol) was added. The reaction mixture was heated under reflux for 11 h, and after cooling, water (10 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried over $MgSO_4$ and evaporated to give 4-phenylpyridine (**7**, 152 mg, 99%) which displayed properties identical to the commercial sample.

1-Methyl-4-phenyl-3,6-dihydro-2-pyridone (8). Reduction with L-Selectride. To a stirred solution of the 2-pyridone **5** (185 mg, 1 mmol) in THF (15 mL) maintained at −35 °C was added slowly a 1 M solution of L-Selectride in THF (2 mL, 2 mmol). After 45 min, brine (2 mL) was added, and after the mixture was warmed to 0 °C an aqueous solution of 30% hydrogenperoxide (5 mL) was added slowly followed by 3 M NaOH (2 mL). This mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give pure **8** (186 mg, 99%) as a white solid: mp 88−89 °C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 7.37 (m, 5H), 6.10 (tt, J = 1.6, 3.4 Hz, 1H), 4.10 (dd, J = 4.8, 3.4 Hz, 2H), 3.35 (dd, J = 1.6, 4.8 Hz, 2H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 167.6, 138.3, 132.9, 128.59, 127.9, 124.8, 116.2, 76.0, 51.2, 33.8; GC−MS (EI) m/z (rel int) 187 (100), 158 (49), 144 (53), 129 (31), 115 (54); IR ($CHCl_3$, cm^{-1}) 1640, 1515, 1477, 1219, 1018; UV (MeOH, nm) 250, 206. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.42. Found: C, 76.77; H, 7.23; N, 7.32.

1-Methyl-4-phenyl-5,6-dihydro-2-pyridone (4). Alkaline Conditions. To a stirred solution of the 3,6-dihydro-2-pyridone **8** (50 mg, 0.27 mmol) in 2-methyl-2-propanol (8 mL) was added potassium *tert*-butoxide (105 mg, 0.94 mmol). After the mixture was stirred for 18 h at ambient temperature, HCl (200 μL, 37%) was added, and after the addition of water (12 mL), the reaction mixture was extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 49 mg (98%) of pure 1-methyl-4-phenyl-5,6-dihydro-2-pyridone (**4**) as a white solid. **Acidic Conditions.** A mixture of the 3,6-dihydro-2-pyridone **8** (50 mg, 0.27 mmol), *p*-toluenesulfonic acid (160 mg, 1 mmol), and toluene (8 mL) was heated under reflux for 16 h. After cooling, water (10 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 49 mg (98%) of the dihydropyridone **4** as a white solid: mp 94−95 °C (lit.[5] mp 94−95 °C); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 7.53 (m, 2H), 7.49 (m, 3H), 6.30 (t, J = 1.4 Hz, 1H), 3.58 (t, J = 7.1 Hz, 2H), 3.02 (s, 3H), 2.81 (td, J = 1.4, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 165.6, 148.9, 137.5, 129.4, 128.7, 125.7, 119.9, 47.5, 34.2, 26.4; GC−MS (EI) m/z (rel int) 187 (83), 158 (11), 144 (100), 129 (10), 115 (78); IR ($CHCl_3$, cm^{-1}) 1634, 1528, 1477, 1218, 1018; UV (MeOH, nm) 272, 260, 216, 210.

Reductions with Red-Al and DIBALH were performed under anhydrous conditions at the temperatures indicated in Table 1, using 2 equiv of reducing agent. The reactions were monitored by GC−EIMS. The products were not isolated.

Reaction of 2-Pyridone 5 with $LiAlH_4$/$LiAlD_4$. Variations in temperature, order of addition of reagents, and reaction times were examined. The following conditions are optimized for the best yield of **8** and were used in studies with deuterated reagents. $LiAlH_4$ (104 mg, 2.8 mmol) was added all at once to a stirred solution of 2-pyridone **5** (185 mg, 1 mmol) in anhydrous THF (15 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and, after being cooled to −78 °C, was treated dropwise with CH_3OH (200 μL) and subsequently at room temperature with 1 N NaOH (1 mL) and then H_2O (1 mL and then 10 mL). The resulting mixture was extracted with Et_2O (3 × 15 mL), and the combined organic phase was washed with water and brine and then dried over

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$MgSO_4$ and evaporated under reduced pressure. The crude extract was chromatographed (SiO_2, EtOH:EtOAc:Hex, 10:40:50) to give 1-methyl-4-phenyl-3,6-dihydro-2-pyridone (**8**, 134 mg, 0.75 mmol, 75%) as a white solid and the tetrahydropyridine **1** as a white, low-melting solid (36 mg, 0,21 mmol, 21%).

Deuteration Studies. The procedures followed using the deuterated reagents were the same as that summarized above. The following summarizes the ^{1}H NMR and GC−EI mass spectral characteristics of the resulting products.

1-Methyl-4-phenyl-3,6-dihydro-2-pyridone-6-*d*$_1$ (8-*6*-*d*$_1$): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 7.37 (m, 5H), 6.10 (m, 1H), 4.10 (m, 1H), 3.35 (d, J = 4.6 Hz, 2H), 3.07 (s, 3H); GC−MS (EI) *m*/*z* (rel int) 188 (100), 159 (41), 145 (30), 144 (43), 130 (30), 116 (44), 115 (38), 97 (16), 96 (16).

1-Methyl-4-phenyl-3,6-dihydro-2-pyridone-*3,3*-*d*$_2$ (8-*3,3*-*d*$_2$): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 5H), 6.11 (t, J = 3.4 Hz, 1H), 4.11 (d, J = 3.4 Hz, 2H), 3.07 (s, 3H); GC−MS (EI) *m*/*z* (rel int) 189 (100), 160 (41), 144 (25), 131 (27), 117 (23), 116 (24), 98 (25).

1-Methyl-4-phenyl-3,6-dihydro-2-pyridone-*3,3,6*-*d*$_3$ (8-*3,3,6*-*d*$_3$): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 5H), 6.10 (bs, 1H), 4.07 (bs, 1H), 3.05 (s, 3H); MS (EI) *m*/*z* (rel int) 190 (100), 161 (25), 146 (80),145 (63), 132 (20), 118 (52), 117 (82), 116 (55), 92 (14).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-*2,3,6,6*-*d*$_4$ (1-*2,2,3,6*-*d*$_4$): ^{1}H-NMR (DMSO-d_6, 270 MHz) δ 7.43 (m, 2H), 7.30 (m, 3H), 6.14 (m, 1H), 2.56 (bs, 1H), 2.47 (bs, 1H), 2.27 (s, 3H); GC−MS (EI) *m*/*z* (rel int) 177 (100), 176 (81), 155 (8), 146, (22), 145 (19), 132 (46), 117 (34), 116 (29), 100 (70), 92 (20).

Reduction with $LiAlH_4$ and $TiCl_3$. The reaction was run under the same conditions as with $LiAlH_4$, at 0 °C in anhydrous THF (1 mmol of **5**, 185 mg). $TiCl_3$ (1 mmol, 154 mg) was added prior to $LiAlH_4$. Product formation was monitored by GC−EI mass spectrometry. After 25 min of reaction, NaOH 1 N (1mL) was added followed by 5 mL of water. The reaction mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude extract was purified by silica gel chromatography (EtOH:EtOAc:Hex, 15:35:50) to give **1** (168 mg, 0.97 mmol, 97%) as a low-melting white solid.

Acknowledgment. This work was supported by a Lavoisier fellowship to S.M. (Ministère des Affaires Etrangères, France), by the National Institute of Neurological and Communicative Disorders and Stroke (NS 28792), and by the Harvey W. Peters Center for the Study of Parkinson's Disease.

JO951529V