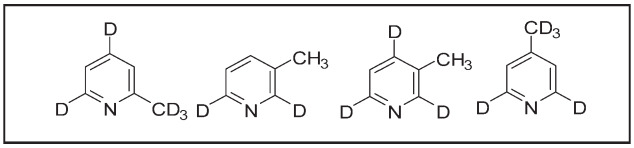
Synthesis and Spectroscopic Properties of Some Di- and Trideuterated Methylpyridines

James W. Pavlik,[a]* Tharinee Vongnakorn,[a] and Supawan Tantayanon[b]

[a]Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, Worcester, Massachusetts 01609
[b]Department of Chemistry, Chulalongkorn University, Bangkok 10330, Thailand
*E-mail: jwpavlik@wpi.edu

Received September 3, 2008
DOI 10.1002/jhet.55
Published online 13 April 2009 in Wiley InterScience (www.interscience.wiley.com).



2-Trideuteriopyridine-4,6-d_2 (**1-4,6-d_2**), 3-methylpyridine-2,6-d_2 (**2-2,6-d_2**), 3-methylpyridine-2,4,6-d_3 (**2-2,4,6-d_3**), and 4-trideuteriopyridine-2,6-d_2 (**3-2,6-d_2**) were synthesized from the appropriate 2-, 3-, or 4-methylpyridine N-oxides. These deuterated products were characterized by their ^{1}H NMR and ^{13}C NMR spectra.

J. Heterocyclic Chem., **46**, 213 (2009).

INTRODUCTION

Work in our laboratory has shown that irradiation of pyridine [1,2], cyanopyridines [3], and methylpyridines [3] in the vapor phase results in deep-seated rearrangements in which the ring atoms, along with the attached substituents, change their relative positions. To map the transpositions of these atoms within the heteroaromatic ring, the photo-rearrangements of a variety of deuterated pyridine derivatives were studied. The deuterium atoms served as positional labels and allowed determination of where a particular ring atom in the photoproduct originated in the reactant.

The synthesis and characterization of the six isomeric dideuteriopyridines and the three isomeric trideuteriopyridines [4] and three isomeric dideuteriocyanopyridines [5] have already been reported. To complete our work in this area, we now report the synthesis and characterization of the three dideuterio and one trideuteriomethylpyridines shown in Scheme 1.

RESULTS AND DISCUSSION

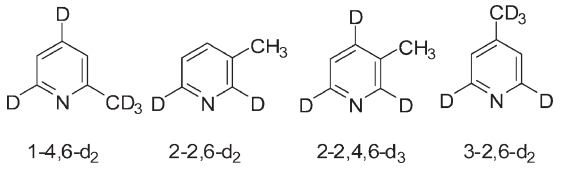
In the case of 3- and 4-methylpyridines, both open positions α to the ring nitrogen were deuterated by two successive base catalyzed H/D exchanges [6] in the commercially available 3- and 4-methylpyridine N-oxides, **4-a,b**, followed by reduction using phosphorous trichloride in dichloromethane [7] as shown in Scheme 2.

The structures of **2-2,6-d_2** and **3-2,6-d_2** were confirmed by the spectroscopic data shown in Tables 1 and 2. Deuteration at ring positions 2 and 6 of each compound was confirmed by ^{1}H NMR and ^{13}C NMR spectra. In particular, in the case of **2-2,6-d_2**, the ^{1}H NMR spectrum exhibited a pair of doublets (J = 7.6 Hz) at δ 7.18 and 7.40 where H4 and H5 are known to absorb, but only very low intensity signals at δ 8.37 and 8.38 due to residual protons at ring positions 2 and 6. Similarly, the complete proton decoupled ^{13}C NMR spectrum exhibited singlets at δ 123.4, 133.3, and 136.8 due to C5, C3, and C4 respectively and triplets at δ 146.9 (J = 28.3 Hz) and 150.2 (J = 28.4 Hz) due to C6 and C2 confirming that these ring carbon atoms are bonded to deuterium.

As expected, the ^{1}H NMR spectrum of the more symmetrical **3-2,6-d_2** exhibited an intense singlet at δ 7.06, where H3 and H5 are known to absorb, but only a very small signal at δ 8.40, where H2 and H6 are known to absorb. In addition, the ^{13}C NMR spectrum exhibited singlets at 124.9 and 147.3 due to C3,5 and C4 respectively, and a triplet (J = 28.4 Hz) confirming that the equivalent C2,6 carbon atoms are both bonded to deuterium. These results confirm that in both compounds, deuteration has taken place exclusively at ring positions 2 and 6.

As shown in Scheme 3, **4a-2,6-d_2** is also a suitable precursor for the trideuterated methylpyridine **2-2,4,6-d_3**. As shown, the conversion involved electrophilic nitration at C4 [7], replacement of the nitro group with chloro [7], reduction of the N-oxide [6], and finally, replacement of the C4 chloro with deuterium using palladium on charcoal in a deuterium atmosphere [8]. The spectral data in Tables 1 and 2 confirm that the three-deuterium atoms are exclusively at ring positions 2, 4, and 6. In particular, the ^{1}H NMR spectrum exhibits an

Scheme 1



intense singlet at δ 7.10 indicating that the ring contains a single proton at the C5 position. Furthermore, the ^{13}C NMR spectrum shows triplets at δ 136.7 (J = 24.3 Hz), 146.9 (J = 27.3 Hz), and 150.3 Hz (J = 26.7 Hz) for C4, C6, and C2, respectively, whereas the signals at δ 123.5 and 136.7 due to C5 and C3 appeared as sharp singlets.

In the case of the 2-methylpyridine isomer, which has only one open position α to the ring nitrogen, the synthetic approach outlined in Scheme 4 was followed. Thus, commercially available 2-methylpyridine N-oxide (**8**) was first monodeuterated at ring position 6, α to the ring nitrogen, using two successive base catalyzed H/D exchanges [6]. Introduction of deuterium into ring position 4 was then accomplished by nitration [7], replacement of nitro with chloro [7], reduction of the N-oxide [6], and finally replacement of chlorine for deuterium using D_2 and Pd/C [8].

The spectral data in Tables 1 and 2 confirm that the two deuterium atoms are exclusively at ring positions 4 and 6. Accordingly, the ^1H NMR spectrum exhibited singlets at δ 7.06 and 7.13 where protons at ring positions 5 and 3 are known to absorb but signals of very low intensity at δ 7.55 and 8.40 indicating only residual protons at ring positions 4 and 6. In addition, the ^{13}C NMR spectrum exhibited a singlet for a quaternary carbon at δ 159.4 due to the C2 ring carbon and sharp singlets at δ 124.0 and 121.6 where the C3 and C5 ring carbons are known to absorb. In contrast, the signals due to the C6 and C4 carbon atoms appeared as triplets at δ 149.9 (J = 27.6 Hz) and 136.9 (J = 28.3 Hz) due to coupling of these carbon atoms with deuterium.

CONCLUSION

The synthetic procedures described allow the synthesis of the four deuterated-methylpyridines shown in Scheme 1. The positions of the deuterium atoms in the pyridine ring were unambiguously confirmed by the ^1H NMR and ^{13}C NMR data shown in Tables 1 and 2.

EXPERIMENTAL

Melting points were determined using a MEL-TEMP apparatus and are uncorrected. ^1H NMR and ^{13}C spectra were recorded at 400.1 and 100.6 MHz in acetone-d_6 on a Brucker FT-NMR system. ^1H NMR and ^{13}C chemical shifts were measured relative to internal tetramethylsilane and chloroform, respectively. All ^{13}C NMR spectra are proton-decoupled. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP 588 capillary gas chromatograph.

2-Trideuteriomethylpyridine N-oxide-6-d, (8-6-d_1), 3-methylpyridine N-oxide-2,6-d_2 (4a-2,6-d_2), and 4-trideuteromethylpyridine-2,6-d_2 (4b-2,6-d_2). The open positions α to nitrogen were deuterated by dissolving 3-methylpyridine N-oxide (4a) (1.0g, 9.0 mmol), 4-methylpyridine N-oxide (4b) (1.0g, 9.0 mmol), or 2-methylpyridine N-oxide (8) (3.4g, 36.5 mmol) in a solution of sodium carbonate (2.0 g) in deuterium oxide (20 mL). The mixture was heated in an oil bath at 110°C for 12 h. The resulting solution was allowed to cool and extracted with dichloromethane (5 × 30 mL). The combined dichloromethane extracts were dried (sodium sulfate) and concentrated to give partially deuterated product which was subjected to a second hydrogen-deuterium exchange as mentioned earlier to provide the final products, which were purified by Kugelrohr distillation (water aspirator).

Compound **4a-2,6-d_2** was obtained as a colorless liquid in a yield of 0.8 g (7.2 mmol, 80%); ^1H NMR (deuterium oxide) δ 2.3 (s, 3H), 7.26 (d, 1H, J = 8.1 Hz) 7.42 (d, 1H, J = 8.1 Hz); ^{13}C NMR (deuterium oxide) δ 18.4, 125.4, 127.8, 136.3 (t, J = 27.6 Hz), 136.6, 139.3 (t, J = 26.8 Hz).

Compound **4b-2,6-d_2** was obtained as a colorless liquid in a yield of 0.7 g (6.0 mmol, 79%); ^1H NMR (deuterium oxide) δ 2.1 (residual methyl protons), 7.28 (s, 2H); ^{13}C NMR (deuterium oxide) δ 19.8 (m), 128.4, 138.5 (t, J = 29.1 Hz), 146.2.

Compound **8-6-d_1**, was obtained as a colorless liquid in a yield of 3.0 g (27.3 mmol, 84.5%); ^1H NMR (deuterium oxide) δ 2.6 (residual methyl protons), 7.06–7.22 (m, 3H); ^{13}C NMR (deuterium oxide) δ 17.5 (m), 123.9, 126.3, 139.2 (t, J = 28.4 Hz), 149.4.

3-Methylpyridine-2,6-d_2 (2-2,6-d_2) and 4-trideuteriomethylpyridine-2,6-d_2 (3-2,6-d_2). 3-Methylpyridine N-oxide-2-6-d_2 (4a-2,6-d_2) (0.80 g, 7.2 mmol) or 4-trideuteriomethylpyridine N-oxide-2,6-d_2 (4b-2,6-d_2) (0.70 g, 6.0 mmol) dissolved in dichloromethane (40 mL) was added dropwise to phosphorous trichloride (2.4 mL) at 0°. The resulting mixture was heated at reflux for 1 h, cooled to room temperature and poured onto ice (15 g). The resulting mixture was made basic with aqueous sodium hydroxide (10%) and extracted with

Scheme 2

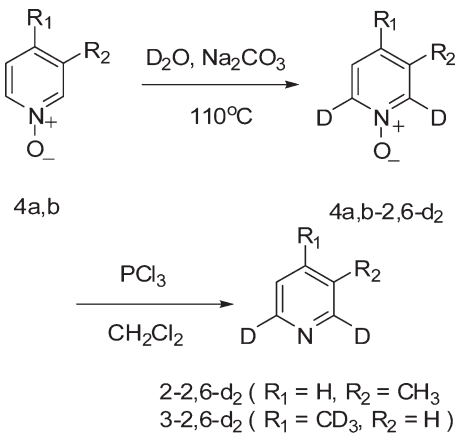


Table 1

^{1}H NMR chemical shifts (δ ppm) of deuterated methylpyridines.

	Ring position				
Compound	2	3	4	5	6
1-4,6-d_2	7.13	–	7.06, s	2.5[a]	–
2-2,6-d_2	2.20 (CH_3)	7.40,d	7.18,d J = 7.6 Hz, J = 7.6 Hz	–	–
2-2,4,6-d_3	2.40 (CH_3)	–	7.10	–	–
3-2,6-d_2	–	7.06	2.20[a]	7.06	–

[a] These signals are due to residual protons in the methyl group.

dichloromethane (5 × 5 mL). The combined extract was dried (sodium sulfate) and concentrated.

3-Methylpyridine-2,6-d_2 (**2-2,6-d_2**) was obtained as a colorless oil (0.50 g, 5.3 mmol, 73%); MS *m/z* (%) 95 (100), 68 (36), 67 (39). The NMR data are given in Tables 1 and 2.

4-Trideuteriomethylpyridine-2,6-d_2 (**3-2,6-d_2**) was obtained as a colorless oil (0.45 g, 4.5 mmol, 75%); MS *m/z* (%) 98 (100), 80 (5), 70 (43). The NMR data are given in Tables 1 and 2.

2-Trideuteriomethylpyridine-4,6-d_2(1-4,6-d_2)

4-Nitro-2-trideuteriomethylpyridine N-oxide-6d (9-6-d_1). 2-Trideuteriomethylpyridine N-oxide-6d_1(**8-6-d_1**) (2.5 g, 22.1 mmol) was added dropwise to a cold mixture of concentrated sulfuric acid (5.0 mL) and concentrated nitric acid (5.0 mL) while keeping the temperature below 50°C. The resulting clear solution was allowed to stir at room temperature for 10 min and then heated at 110°C for 5 h. The resulting solution was allowed to cool to room temperature and neutralized with saturated aqueous sodium bicarbonate. The neutralized solution was extracted with dichloromethane (3 × 50 mL). The extract was dried (sodium sulfate) and concentrated to give crude 4-nitro-2-trideuteriomethylpyridine N-oxide-6d_1 (**9-6-d_1**) as a yellow solid (1.7 g). Recrystallization from acetone gave **9-6-d_1** as yellow crystals; mp 153–155°C; ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 7.90 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 1.71 (m), 117.5, 120.2, 139.3 (t, J = 28.4 Hz), 141.2, 150.1.

4-Chloro-2-trideuteriomethylpyridine N-oxide-6d_1 (10-6-d_1). 4-Nitro-2-trideuterio-methylpyridine N-oxide-6d_1 (**9-6-d_1**) (1.5 g, 9.5 mmol) was dissolved in concentrated hydrochloric acid (20 mL) and heated in an oil bath at 135°C for 18 h. The reaction mixture was allowed to cool to room temperature and extracted with chloroform (5 × 20 mL). The combined chloroform extracts were dried (sodium sulfate) and concentrated to give a yellow solid (1.0g) which was subjected to column chromatography (silica gel). Elution with ethyl acetate provided unreacted starting material. Elution with methanol provided 4-chloro-2-trideuteriopyridine N-oxide-6d_1 (**10-6-d_1**) as a yellow viscous liquid (0.60 g, 4.1 mmol, 43%); ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 7.0 (s, 1H) 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 17.7 (m), 124.2, 126.8, 131.7, 140.1 (t, J = 29.1 Hz), 150.5; MS *m/z* (%), 149 (22), 147 (70), 146 (45), 129 (100), 128 (45), 92 (40).

4-Chloro-2-trideuteriomethylpyridine-6d_1 (11-6-d_1). 4-Chloro-2-trideuteriomethyl-pyridine N-oxide-6d_1 (**10-6-d_1**) (0.80 g, 5.4 mmol) dissolved in dichloromethane (40 mL) was added to phosphorous trichloride (3.0 mL) at 0°C. The resulting mixture was heated at reflux for 1 h, cooled to room temperature, and poured onto ice (20 g). The resulting mixture was made basic with aqueous sodium hydroxide (10%) and extracted with dichloromethane (5 × 30 mL). The combined extract was dried (sodium sulfate) and concentrated to give **11-6-d_1** as a brown viscous liquid (0.50 g, 3.7 mmol, 69%); ^{1}H NMR (deuteriochloroform) δ 2.3 (residual methyl protons), 6.9 (s, 1H), 7.0 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 23.9 (m), 121.1, 123.5, 144.1, 149.7 (t, J = 27.6 Hz), 159.9; MS *m/z* (%) 133 (30), 131 (100), 130 (62), 95 (33), 94 (13).

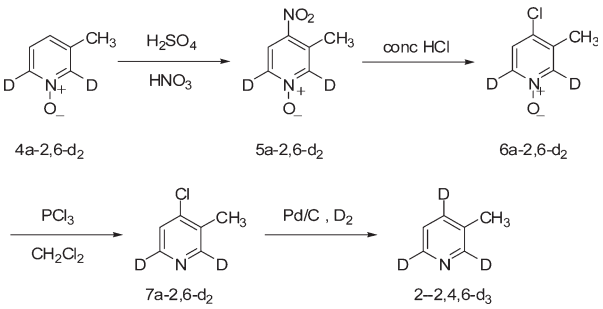
2-Trideuteriomethylpyridine-4,6-d_2 (1-4,6-d_2). 4-Chloro-2-trideuteriomethylpyridine-6-d_1) (**11-6-d_1**) (0.50 g, 3.8 mmol) dissolved in diethyl ether (20 mL) was placed in a Büchner

Table 2

Decoupled ^{13}C NMR chemical shifts (δ ppm) of deuterated methylpyridines.

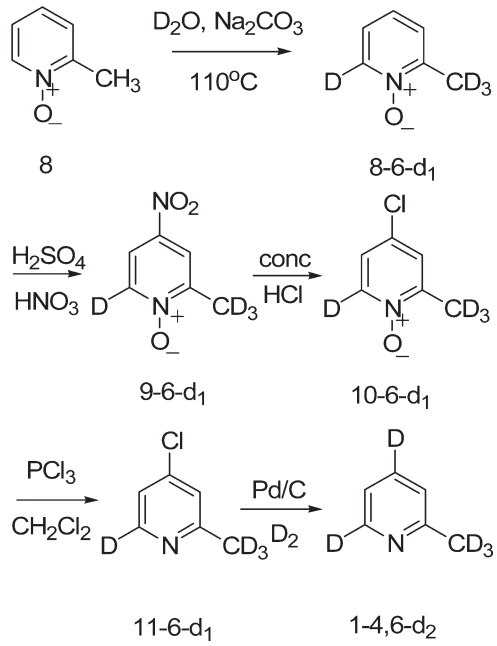
	Ring position					
Compound	2	3	4	5	6	$CH_3(CD_3)$
1-4,6-d_2	159.4,s	124.0,s	136.9,t J = 28.3 Hz	121.6,s	149.4,t J = 27.6 Hz	(24.1)
2-2,6-d_2	150.2,t J = 28.4 Hz	133.3,s	136.8,s	123.4,s	146.9,t J = 28.3 Hz	17.5
2-2,4,6-d_3	150.3,t J = 26.7 Hz	136.7,s	136.7,t J = 24.3 Hz)	123.5,s	146.9,t J = 27.3 Hz	18.7
3-2,6-d_2	149.5,t (J = 28.4 Hz)	124.9,s	149.5,s	124.9s	149.5,t	(20.5,m) (J = 28.4 Hz)

Scheme 3



flask containing potassium carbonate (1.5 g), Pd-C (10%, 0.030g), and a magnetic stirring bar. The flask was sealed with a septum and equipped with a balloon at the side arm. A side-arm test tube containing sodium metal (1.2 g) was sealed with a septum and the side-arm was connected to the Büchner flask. The entire system was purged with nitrogen for 10 min. Deuterium oxide (3.0 mL) was then added through the septum to the sodium in the side-arm test tube. The deuterium gas generated filled the system and caused the balloon to expand. The reaction mixture in the Büchner flask was stirred in the deuterium atmosphere for 4 h. The Pd-C was removed by filtration and washed with dichloromethane. The combined ether and dichloromethane was concentrated by distillation through a Vigreux column to give a brown liquid residue (0.30 g) which was purified by Kugelrohr distillation (atm. pressure, oven temperature 130°C). **1-4,6-d$_2$** was collected as a clear liquid

Scheme 4



(0.13 g, 1.3 mmol, 34%); MS *m/z* (%), 98 (100), 70 (42), 69 (12). See Tables 1 and 2 for NMR data.

3-Methylpyridine-2,4,6-d$_3$ (2-2,4,6-d$_3$)

3-Methyl-4-nitropyridine N-oxide-2,6-d$_2$ (5a-2,6-d$_2$). 3-Methylpyridine N-oxide-2,6-d$_2$ (4a-2,6-d$_2$) (1.9 g, 17.2 mol) was treated as for the nitration of 8-6-d$_1$ presented earlier to give 5a-2,6-d$_2$ as yellow crystals (1.3 g, 8.3 mmol, 48%, mp 154–157°C); ^{1}H NMR (deuteriochloroform), δ 2.60 (s, 3H), 8.00 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 18.5, 122.5, 133.2, 137.9 (t, J = 28.4 Hz); 141.8 (t, J = 26.8 Hz), 143.4; MS *m/z* (%) 156 (100), 140 (7), 139 (13), 84 (30).

4-Chloro-3-methylpyridine N-oxide-2,6-d$_2$ (6a-2,6-d$_2$). 3-Methyl-4-nitropyridine N-oxide-2,6-d$_2$ (**5a-2,6-d$_2$**) (1.3 g, 8.3 mmol) was treated as for the conversion of **9-6-d$_1$** to **10-6-d$_1$** presented earlier to give **6a-2,6-d$_2$** as a yellow viscous liquid (0.5 g, 3.5 mmol, 42%); ^{1}H NMR (deuteriochloroform) δ 2.2 (s, 3H), 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 16.8, 124.3, 132.3, 144.4, 148.2 (t, J = 28.4 Hz), 151.5 (t, J = 28.4 Hz); MS *m/z* (%) 145 (100), 129 (63), 94 (42), 54 (47).

4-Chloro-3-methylpyridine-2,6-d$_2$ (7-2,6-d$_2$). **6a-2,6-d$_2$** (0.5 g, 3.5 mmol) was treated as for the conversion of **10-6-d$_1$** to **11-6-d$_1$**, presented earlier to give **7a-2,6-d$_2$** as a brown viscous liquid (0.3 g, 2.3 mmol, 66%); ^{1}H NMR (deuteriochloroform) δ 2.3 (s, 3H), 6.9 (s, 1H), 7.2 (s, 1H); ^{13}C NMR (deuteriochloroform) δ 16.8, 124.2, 132.5, 148.2 (t, J = 28.4 Hz), 151.6 (t, J = 28.4 Hz); MS *m/z* (%) 131 (35), 129 (100), 94 (87), 66 (74).

3-Methylpyridine-2,4-6-d$_3$ (2-2,4,6-d$_3$). **7a-2,6-d$_2$** (0.25 g, 1.9 mmol) in methanol (10 mL) was treated as for the conversion of **11-6-d$_1$** to **1-4,6-d$_2$**. Kugelrohr distillation of the crude product (atmospheric pressure, oven temperature 130° C) gave **2-2,4,6-d$_3$** as a clear liquid (0.1 g, 1.0 mmol, 53%): MS *m/z* (%) 96 (100), 29 (37), 68 (46), 67 (31). See Tables 1 and 2 for NMR data.

Acknowledgments. Tharinee Vongnakorn acknowledges financial support from the Development and Promotion of Science and Technology Talent Project, Bangkok, Thailand.

REFERENCES AND NOTES

[1] Pavlik, J. W.; Laohhasurayotin, S. J Tetrahedron Lett 2003, 44, 8109.

[2] Pavlik, J. W.; Laohhasurayotin, S. J Org Chem 2008, 73, 2746.

[3] Pavlik, J. W.; Laohhasurayotin, S.; Vongnakorn, T. J Org Chem 2007, 72, 7116.

[4] Pavlik, J. W.; Laohhasurayotin, S. J Heterocyclic Chem 2007, 44, 1485.

[5] Pavlik, J. W.; Laohhasurayotin S. J Heterocyclic Chem 2005, 42, 73.

[6] Matsuki, Y.; Katakuse, Y.; Katashima, M.; Matsaura, H.; Goromaru, T. Chem Pharm Bull 1989, 37, 1637.

[7] Proffit, E.; Steinke. W. J Prakt Chem 1961, 13, 58.

[8] Azzam, R.; Borggraeve, W. D.; Compernolle, F.; Hoornaert, G. J. Tetrahedron Lett 2004, 45, 1885.