O-Alkylations of Pyridoxine and Pyridoxamine

Taisei Ueda, Kenji Nakaya, Shin-ichi Nagai and Jinsaku Sakakibara*

Faculty of Pharmaceutical Sciences, Nagoya City University,
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

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O-Alkylations of pyridoxine **1** and pyridoxamine **5** were carried out in acetone in the presence of sodium ethoxide and potassium iodide to give 5-alkoxy-6-methyl-3,4-(bishydroxymethyl)pyridines **2a-j** and 5-alkoxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridines **6a-e**.

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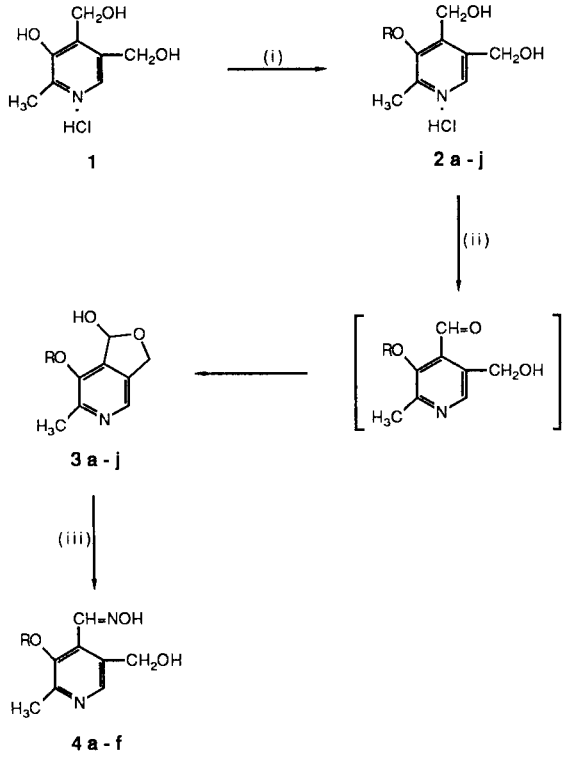
Pyridoxine, one of the B_6 group of vitamines has been the subject of numerous studies [1] because of its biological interest. Studies of chemical modification of the basic molecule have also been directed [2]. However, alkylations of the phenolic hydroxy group at the 5-position of pyridoxine have not been reported except methylation [3]. We report here *O*-alkylations of pyridoxine and pyridoxamine to synthesize 5-alkoxy-6-methyl-3,4-(bishydroxymethyl)-pyridine hydrochlorides **2a-j** and 5-alkoxy-4-aminomethyl-6-methyl-3-hydroxypyridine dihydrochlorides **6a-e**.

Scheme 1



1 2a-j 3a-j 4a-f

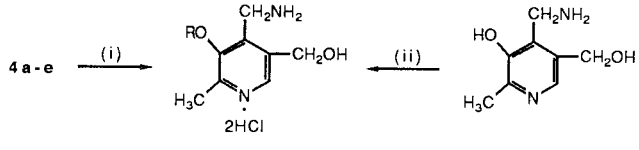
(i) RBr, NaOEt, KI/acetone, HCl/EtOH. (ii) MnO_2/acetone.
(iii) $NH_2OH \cdot HCl$, $CH_3COONa \cdot 3H_2O$/EtOH-H_2O

a, R = C_2H_5
b, R = *n*-C_3H_7
c, R = *n*-C_4H_9
d, R = *n*-C_6H_{13}
e, R = *n*-C_8H_{17}
f, R = CH_2=$CHCH_2$
g, R = CH_3-CH=$CHCH_2$
h, R = CH_2=$CHCH_2CH_2$
i, R = PhCH=$CHCH_2$
j, R = CH≡C-CH_2

The reaction of pyridoxine hydrochloride **1** with alkyl bromide such as ethyl, propyl, butyl, hexyl, octyl, allyl, crotyl, 3-butenyl, cinnamyl, and propagyl bromide was carried out in dry acetone in the presence of sodium ethoxide and potassium iodide. After ten hours reflux, treatment with hydrogen chloride in ethanol gave **2a-j** in 24-57% yields. Treatment of **2a-j** with active manganese dioxide [4] in acetone gave 3-alkoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde hemiacetals **3a-j** in quantitative yields. The ir spectra of **3a-j** did not show absorptions due to carbonyl groups. In the ^{1}H-nmr spectra the methylene protons of the 5-hydroxymethyl group were observed as double doublets. These facts indicated that **3a-j** were in the hemiacetal form. Moreover the hydroxy groups of these hemiacetals seem to chelate with the oxygen atom of the 3-alkoxy group. Successive reaction of **3a-f** with hydroxylamine hydrochloride in aqueous ethanol in the presence of sodium acetate trihydrate gave 3-alkoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde oximes **4a-f** in 52-98% yields.

O-Alkylation of pyridoxamine **5** was carried out as follows. Pyridoxine hydrochloride **1** was converted to pyridoxamine **5** in 74% yield [5]. Refluxing **5** with an alkyl bromide in acetone in the presence of sodium ethoxide and potassium iodide was continued for 10 hours to give **6a-e** in 20-34% yields. Total yields from **1** were 15-25%.

Scheme 2

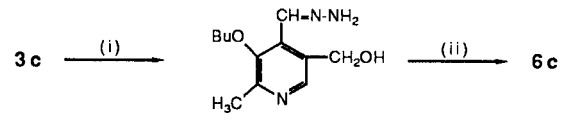


6a-e 5

(i) H_2, 5%Pd-C/EtOH-H_2O, concentrated HCl.
(ii) RBr, NaOEt, KI/acetone, HCl/EtOH.

a, R = C_2H_5
b, R = *n*-C_3H_7
c, R = *n*-C_4H_9
d, R = *n*-C_6H_{13}
e, R = *n*-C_8H_{17}

Scheme 3



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(i) $NH_2NH_2 \cdot H_2O$/EtOH-H_2O, (ii) H_2, Raney Ni/EtOH.

Compounds **6a-e** were also obtained by the reduction of **4a-e**. A solution of **4a** in aqueous ethanol in the presence of 5% Pd-C and a small amount of hydrochloric acid was stirred under hydrogen gas (2 kg/cm²) at room temperature for 6 hours to give **6a** in 57% yield. Similarly **6b-e** were obtained from **4b-e** in 38-92% yields. Total yields of **6a-e** from **1** were 11-20%. We also examined the formation of hydrazone **7** from **3c** and its catalytic reduction in the presence of Raney nickel catalyst gave **6c** in 20% yield.

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IR-810 spectro photometer. Mass spectra were measured with a JEOL JMS-DX 300 spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad; m, multiplet.

General Procedure for the Synthesis of 5-Alkoxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochlorides **2a-j**.

Pyridoxine hydrochloride **1** (2.06 g, 10 mmoles) was dissolved in 200 ml of dry acetone. To this solution 80 ml of ethanol solution of sodium ethoxide prepared from 0.15 g of sodium was added. Then alkyl bromide (11 mmoles) and potassium iodide (3.7 g) were added. The mixture was refluxed for 10 hours. After cooling insoluble substances were removed by filtration and the filtrate was evaporated to dryness. The residue was added to 50 ml of saturated bicarbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was dissolved in ethanol. Hydrogen chloride gas was passed into the solution and ether was added to obtain crystals.

5-Ethoxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2a**).

This compound was obtained as colorless needles (ethanol), mp 137-139°, yield 42%; ir (potassium bromide): ν 3380, 3330 (OH), 2680 (NH^+); ^{1}H-nmr (pyridine-d_5-deuteriochloroform): δ 1.35 (3H, t, J = 7 Hz, C5-OCH_2CH_3), 2.59 (3H, s, C6-CH_3), 3.94 (2H, q, J = 7 Hz, C5-OCH_2CH_3), 4.93 (2H, s, C3-CH_2OH), 5.01 (2H, s, C4-CH_2OH), 8.48 (1H, s, C2-H); ms: m/z 197 (M^+).

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot HCl$: C, 51.40; H, 6.90; N, 5.99. Found: C, 51.18; H, 6.84; N, 5.71.

5-Propoxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2b**).

This compound was obtained as colorless needles (ethanol), mp 153-155°, yield 47%; ir (potassium bromide): ν 3330 (OH), 2620 (NH^+), ^{1}H-nmr (pyridine-d_5): δ 0.96 (3H, t, J = 7 Hz, C5-$O(CH_2)_2CH_3$), 1.74 (2H, sextet, J = 7 Hz, C5-$OCH_2CH_2CH_3$-), 2.62 (3H, s, C6-CH_3), 3.82 (2H, t, J = 7 Hz, C5-$OCH_2CH_2CH_3$), 5.12 (2H, s, C3-CH_2OH), 5.22 (2H, s, C4-CH_2OH), 8.76 (1H, s, C2-H); ms: m/z 211 (M^+).

Anal. Calcd. for $C_{11}H_{17}NO_3 \cdot HCl$: C, 53.33; H, 7.32; N, 5.65. Found: C, 53.13; H, 7.17; N, 5.43.

5-Butoxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2c**).

This compound was obtained as colorless needles (ethanol), mp 136-138°, yield 57%; ir (potassium bromide): ν 3340 (OH), 2650 (NH^+); ^{1}H-nmr (pyridine-d_5): δ 0.98 (3H, t, J = 7 Hz, C5-$O(CH_2)_3CH_3$), 1.55 (4H, m, C5-$OCH_2(CH_2)_2CH_3$), 2.62 (3H, s, C6-CH_3), 3.88 (2H, t, J = 7 Hz, C5-$OCH_2(CH_2)_2CH_3$), 5.14 (2H, s, C3-CH_2OH), 5.24 (2H, s, C4-CH_2OH), 8.76 (1H, s, C2-H); ms: m/z 225 (M^+).

Anal. Calcd. for $C_{12}H_{19}NO_3 \cdot HCl$: C, 55.07; H, 7.70; N, 5.35. Found: C, 55.23; H, 7.85; N, 5.35.

5-Hexyloxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2d**).

This compound was obtained as colorless needles (ethanol), mp 128-130°, yield 41%; ir (potassium bromide): ν 3360 (OH), 2650 (NH^+); ^{1}H-nmr (pyridine-d_5): δ 0.94 (3H, t, J = 7 Hz, C5-$O(CH_2)_5CH_3$), 1.28 (6H, m, C5-$O(CH_2CH_2-(CH_2)_3-CH_3$), 1.74 (2H, m, C5-$OCH_2CH_2(CH_2)_3CH_3$), 2.68 (3H, s, C6-CH_3), 3.92 (2H, t, J = 7 Hz, C5-$OCH_2(CH_2)_4CH_3$), 5.16 (2H, s, C3-CH_2OH), 5.26 (2H, s, C4-CH_2OH), 8.78 (1H, s, C2-H); ms: m/z 253 (M^+).

Anal. Calcd. for $C_{14}H_{23}NO_3 \cdot HCl$: C, 58.02; H, 8.35; N, 4.83. Found: C, 57.91; H, 8.27; N, 4.89.

5-Octyloxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2e**).

This compound was obtained as colorless needles (ethanol), mp 110-112°, yield 32%; ir (potassium bromide): ν 3350 (OH), 2650 (NH^+); ^{1}H-nmr (pyridine-d_5): δ 0.94 (3H, t, J = 7 Hz, C5-$O(CH_2)_7CH_3$), 1.20 (10H, m, C5-$OCH_2CH_2(CH_2)_5CH_3$), 1.74 (2H, m, C5-$OCH_2CH_2(CH_2)_5CH_3$), 2.68 (3H, s, C6-CH_3), 3.92 (2H, t, J = 7 Hz, C5-$OCH_2(CH_2)_6CH_3$), 5.16 (2H, s, C3-CH_2OH), 5.26 (2H, s, C4-CH_2OH), 8.78 (1H, s, C2-H); ms: m/z 281 (M^+).

Anal. Calcd. for $C_{16}H_{27}NO_3 \cdot HCl$: C, 60.46; H, 8.88; N, 4.41. Found: C, 60.33; H, 8.62; N, 4.29.

5-Allyloxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2f**).

This compound was obtained as colorless needles (ethanol), mp 127-129°, yield 53%; ir (potassium bromide): ν 3350 (OH), 2650 (NH^+); ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 2.76 (3H, s, C6-CH_3), 4.54 (2H, dd, J = 5.5, 1 Hz, C5-$OCH_2CH=CH_2$), 4.74 (2H, s, C3-CH_2OH), 4.90 (2H, s, C4-CH_2OH), 5.30 (1H, d, J = 10 Hz, *trans* H-CH=CH-CH_2-), 5.43 (1H, dt, J = 17, 1 Hz, *cis* H-CH=CH-CH_2-), 6.09 (1H, ddt, J = 17, 10, 5.5 Hz, CH_2=CH-CH_2-), 8.48 (1H, s, C2-H); ms: m/z 209 (M^+).

Anal. Calcd. for $C_{11}H_{15}NO_3 \cdot HCl$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.74; H, 6.26; N, 5.54.

5-Crotonoyloxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2g**).

This compound was obtained as colorless needles (ethanol), mp 151-152°, yield 54%; ir (potassium bromide): ν 3330 (OH), 2650 (NH^+); ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 1.78 (3H, d, J = 5 Hz, H_3C-C=C-), 2.77 (3H, s, C6-CH_3), 4.51 (2H, d, J = 5 Hz, C5-OCH_2-), 4.76 (2H, s, C3-CH_2OH), 4.94 (2H, s, C4-CH_2OH), 5.80 (2H, m, CH_3-CH=CH-CH_2-), 8.48 (1H, s, C2-H); ms: m/z 223 (M^+).

Anal. Calcd. for $C_{12}H_{17}NO_3 \cdot HCl$: C, 55.49; H, 6.99; N, 5.39. Found: C, 55.20; H, 6.85; N, 5.29.

5-Butenyloxy-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2h**).

This compound was obtained as colorless needles (ethanol), mp 107-108°, yield 24%; ir (potassium bromide): ν 3340 (OH), 2650 (NH^+); ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 2.59 (2H, q, J = 7 Hz, -C=C-CH_2), 2.76 (3H, s, C6-CH_3), 4.07 (2H, t, J = 7 Hz, C5-OCH_2-$CH_2CH=CH_2$), 4.76 (2H, s, C3-CH_2OH), 4.91 (2H, s, C4-CH_2OH), 5.16 (1H, d, J = 10 Hz, *trans* H-C=C-CH_2-CH_2-O-), 5.21 (1H, d, J = 18 Hz,

cis H-C=CH$_2$-CH$_2$-O-), 5.96 (1H, ddt, J = 18, 10, 7 Hz, CH$_2$=C*H*CH$_2$-CH$_2$-O-), 8.48 (1H, s, C2-H); ms: m/z 223 (M$^+$).

Anal. Calcd. for $C_{12}H_{17}NO_3$·HCl: C, 55.49; H, 6.99; N, 5.39. Found: C, 55.19; H, 6.92; N, 5.29.

5-(3-Phenyl-2-propenyloxy)-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2i**).

This compound was obtained as colorless needles (ethanol), mp 193-194°, yield 53%; ir (potassium bromide): ν 3320 (OH), 2670 (NH$^+$); ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 2.76 (3H, s, C6-CH$_3$), 4.77 (2H, d, J = 6 Hz, C5-OC*H*$_2$CH=CHPh), 5.08 (2H, s, C3-C*H*$_2$OH), 5.21 (2H, s, C4-C*H*$_2$OH), 6.63 (1H, dt, J = 16, 6 Hz, -OCH$_2$-C*H*=CH-Ph), 6.91 (1H, d, J = 16 Hz, -OCH$_2$-CH=C*H*-Ph), 7.41 (5H, m, Ph), 8.80 (1H, s, C2-H); ms: m/z 285 (M$^+$).

Anal. Calcd. for $C_{17}H_{19}NO_3$·HCl: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.16; H, 6.17; N, 4.29.

5-(2-Propynyloxy)-6-methyl-3,4-(bishydroxymethyl)pyridine Hydrochloride (**2j**).

This compound was obtained as colorless needles (ethanol), mp 166-167°, yield 26%; ir (potassium bromide): ν 3360, 3270 (OH), 2830 (NH$^+$), 2130 (-C≡C-); ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 2.76 (3H, s, C6-CH$_3$), 3.38 (1H, t, J = 2.5 Hz, HC≡C-), 4.74 (2H, s, C3-C*H*$_2$OH), 4.84 (2H, d, J = 2.5 Hz, C5-OC*H*$_2$-C≡CH), 4.88 (2H, s, C4-C*H*$_2$OH), 8.44 (1H, s, C2-H); ms: m/z 207 (M$^+$).

Anal. Calcd. for $C_{11}H_{13}NO_3$·HCl: C, 54.22; H, 5.75; N, 54.18. Found: C, 54.18; H, 5.97; N, 5.49.

General Procedure for the Synthesis of 3-Alkoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetals **3a-j**.

A mixture of **2a-j** (5 mmoles) and active manganese dioxide (6 g) in 300 ml of acetone was stirred at 40° for 1 hour. Manganese dioxide was filtered off. The filtrate was condensed to obtain crystals.

3-Ethoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3a**).

This compound was obtained as colorless needles (ethanol-water), mp 202-205°, yield 94%; ^{1}H-nmr (pyridine-d$_5$-deuteriochloroform): δ 1.36 (3H, t, J = 7 Hz, C3-O-CH$_2$C*H*$_3$), 2.61 (3H, s, C2-CH$_3$), 4.24 and 4.59 (each 1H, dq, J = 10, 7 Hz, C3-O-C*H*$_2$-CH$_3$), 4.98 and 5.24 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 6.99 (1H, d, J = 6 Hz, C4-CH), 8.13 (1H, s, C6-H), 8.93 (1H, d, J = 6 Hz, -OH); ms: m/z 195 (M$^+$).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.23; H, 6.53; N, 7.13.

3-Propoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3b**).

This compound was obtained as colorless needles (ethanol-water), mp 175-178°, yield 100%; ^{1}H-nmr (pyridine-d$_5$): δ 0.98 (3H, t, J = 7 Hz, C3-O(CH$_2$)$_2$C*H*$_3$), 1.74 (2H, sextet, J = 7 Hz, C3-OCH$_2$C*H*$_2$CH$_3$), 2.64 (3H, s, C2-CH$_3$), 4.18 and 4.57 (each 1H, dt, J = 10, 7 Hz, C3-OC*H*$_2$-CH$_2$CH$_3$), 5.06 and 5.28 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 7.08 (1H, s, C4-CH), 8.20 (1H, s, C6-H); ms: m/z 209 (M$^+$).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.07; H, 7.10; N, 6.83.

3-Butoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3c**).

This compound was obtained as colorless needles (ethanol-water), mp 156-158°, yield 93%; ^{1}H-nmr (pyridine-d$_5$): δ 0.91 (3H, t, J = 7 Hz, C3-O-(CH$_2$)$_3$C*H*$_3$), 1.60 (4H, m, C3-OCH$_2$(C*H*$_2$)$_2$CH$_3$), 2.66 (3H, s, C2-CH$_3$), 4.25 and 4.61 (each 1H, dt, J = 10, 7 Hz, C3-OCH$_2$-), 5.04 and 5.30 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 7.10 (1H, J = 6 Hz, C4-CH), 8.21 (1H, s, C6-H), 8.92 (1H, d, J = 6 Hz, -OH); ms: m/z 223 (M$^+$).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.55; H, 7.78; N, 6.12.

3-Hexyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3d**).

This compound was obtained as colorless needles (ethanol-water), mp 126-129°, yield 100%; ^{1}H-nmr (pyridine-d$_5$): δ 0.88 (3H, t, J = 7 Hz, C3-O(CH$_2$)$_5$C*H*$_3$), 1.34 (6H, m, C3-OCH$_2$CH$_2$(C*H*$_2$)$_3$), 1.82 (2H, m, C3-OCH$_2$C*H*$_2$(CH$_2$)$_3$), 2.72 (3H, s, C2-CH$_3$), 4.26 and 4.63 (each 1H, dt, J = 10, 7 Hz, C3-OC*H*$_2$-(CH$_2$)$_4$CH$_3$), 5.03 and 5.29 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 7.12 (1H, s, C4-CH), 8.19 (1H, s, C6-H); ms: m/z 251 (M$^+$).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.71; H, 8.23; N, 5.45.

3-Octyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3e**).

This compound was obtained as colorless needles (ethanol-water), mp 119-123°, yield 96%; ^{1}H-nmr (pyridine-d$_5$): δ 0.85 (3H, t, J = 7 Hz, C3-O(CH$_2$)$_7$C*H*$_3$), 1.24 (10H, m, C3-OCH$_2$CH$_2$(C*H*$_2$)$_5$CH$_3$), 1.80 (2H, m, C3-OCH$_2$C*H*$_2$-(CH$_2$)$_5$CH$_3$), 2.68 (3H, s, C2-CH$_3$), 4.27 and 4.66 (each 1H, dt, J = 10, 7 Hz, C$_3$-OCH$_2$-), 5.05 and 5.29 (each 1H, d, J = 12 Hz, C5-CH$_2$O-), 7.12 (1H, s, C4-CH), 8.19 (1H, s, C6-H); ms: m/z 279 (M$^+$).

Anal. Calcd. for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.67; H, 8.74; N, 4.91.

3-Allyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3f**).

This compound was obtained as colorless needles (ethanol-water), mp 188-189°, yield 98%; ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 2.43 (3H, s, C2-CH$_3$), 4.67 and 4.85 (each 1H, ddd, J = 13.5, 1 Hz, C3-OCH$_2$-), 4.76 and 5.01 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 5.25 (1H, d, J = 10 Hz, *trans H*-C=C-CH$_2$-), 5.41 (1H, dt, J = 17, 1 Hz, *cis H*-C=C-CH$_2$-), 6.08 (1H, ddt, J = 17, 10, 5 Hz, -C=C*H*(CH$_2$)$_2$-, 6.55 (1H, d, J = 7 Hz, C4-CH), 6.99 (1H, d, J = 7 Hz, CH-OH), 8.04 (1H, s, C6-H); ms: m/z 207 (M$^+$).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.50; H, 6.08; N, 6.62.

3-Crotonoyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3g**).

This compound was obtained as colorless needles (ethanol-water), mp 180-181°, yield 91%; ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 1.77 (3H, d, J = 5 Hz, H$_3$-C=C-), 2.48 (3H, s, C2-CH$_3$), 4.56 and 4.75 (each 1H, ddd, J = 11, 5, 0.5 Hz, C3-O-CH$_2$-), 4.90 and 5.17 (each 1H, each d, J = 13 Hz, C5-CH$_2$-O-), 5.75 (2H, m, -CH=CH-), 6.57 (1H, d, J = 7 Hz, C4-CH), 6.97 (1H, d, 7 Hz, -CHOH), 8.08 (1H, s, C6-H); ms: m/z 221 (M$^+$).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.97; H, 6.65; N, 6.07.

3-(3-Butenyloxy)-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3h**).

This compound was obtained as colorless needles (ethanol-water), mp 150-151°, yield 98%; ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 2.41 (3H, s, C2-CH$_3$), 2.49 (2H, q, J = 7 Hz, -C=C-CH$_2$), 4.12 and 4.37 (each 1H, dt, J = 10, 7 Hz, C3-OCH$_2$-), 4.86 and 5.08 (each 1H, each d, J = 12 Hz, C5-CH$_2$-O-), 5.13 (1H, d, J = 18 Hz, *cis H*-C=C-CH$_2$-), 5.18 (1H, d, J = 10 Hz, *trans H*-C=C-CH$_2$-), 5.91 (1H, ddt, J = 18, 10, 7 Hz, -C=C*H*(CH$_2$-)), 6.54 (1H, d, J = 7 Hz, C4-CH-), 6.99 (1H, d, J = 7 Hz, -CH-O*H*), 8.04 (1H, s, C6-H); ms: m/z 221 (M$^+$).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.93; H, 6.69; N, 6.13.

3-(3-Phenyl-2-propenyloxy)-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3i**).

This compound was obtained as colorless needles (ethanol-water), mp 148-150°, yield 92%; ^{1}H-nmr (dimethylsulfoxide-d$_6$-deuteriochloroform): δ 2.45 (3H, s, C2-CH$_3$), 4.58 and 4.79 (each 1H, each d, J = 12.5 Hz, C3-O-CH$_2$), 4.86 and 5.10 (each 1H, each d, J = 12 Hz, C5-CH$_2$-), 6.45 (1H, dt, J = 16, 5 Hz, -C=C*H*(CH$_2$-), 6.57 (1H, d, J = 7 Hz, C4-CH-), 6.74 (1H, d, J = 16 Hz, Ph-C*H*=C), 7.02 (1H, d, J = 7 Hz, -C*H*OH), 7.83 (5H, m, Ph), 8.09 (1H, s, C6-H); ms: m/z 283 (M$^+$).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.96; H, 5.84; N, 4.69.

3-(2-Propynyloxy)-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hemiacetal (**3j**).

This compound was obtained as colorless needles (ethanol-water), mp 214-216°, yield 85%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 2.47 (3H, s, C2-CH_3), 3.38 (1H, t, J = 2.5 Hz, HC≡C-), 4.87 and 5.09 (each 1H, d, J = 12 Hz, C5-CH_2-O-), 4.91 (2H, d, J = 2.5 Hz, C3-O-CH_2-CH_2-), 6.57 (1H, d, J = 7 Hz, C4-C*H*OH), 7.08 (1H, d, J = 7 Hz, CHO*H*), 8.10 (1H, s, C6-H); ms: m/z 205 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.63; H, 5.66; N, 6.83.

General Procedure for the Synthesis of 3-Alkoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oximes **4a-f**.

A solution of sodium acetate trihydrate (0.82 g, 6 mmoles) and hydroxylamine hydrochloride (0.22 g, 3.2 mmoles) dissolved in 25 ml of water was added to a solution of **3a-f** (2 mmoles) in 100 ml of ethanol. The mixture was refluxed for 40 minutes. The reaction mixture was condensed to 20 ml. The resulting crystals were collected by filtration.

3-Ethoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4a**).

This compound was obtained as colorless needles (ethanol-water), mp 189-190°, yield 52%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 1.44 (3H, t, J = 7 Hz, C3-OCH_2CH_3), 3.08 (3H, s, C2-CH_3), 3.90 (2H, q, J = 7 Hz, C3-OCH_2CH_3), 4.64 (2H, s, C5-CH_2O-), 8.30 (1H, s, C4-CH=N-), 8.42 (1H, s, C6-H), 11.80 (1H, s, =NOH); ms: m/z 210 (M^+), 193 (M^+-17).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.22; H, 6.73; N, 13.32.

3-Propoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4b**).

This compound was obtained as colorless needles, mp 167-168°, yield 62%; ^{1}H-nmr (pyridine-d_5): δ 0.98 (3H, t, J = 7 Hz, C3-$O(CH_2)_2CH_3$), 1.72 (2H, sextet, J = 7 Hz, C3-$OCH_2CH_2CH_3$), 2.60 (3H, s, C2-CH_3), 3.72 (2H, t, J = 7 Hz, C3-$OCH_2CH_2CH_3$), 5.18 (2H, s, C5-CH_2-O-), 6.28 (1H, br, C5-CH_2OH), 8.90 (1H, s, C4-CH=N-), 8.94 (1H, s, C6-H); ms: m/z 207 (M^+-17).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.13; H, 7.04; N, 12.40.

3-Butoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4c**).

This compound was obtained as colorless needles (ethanol-water), mp 149-151°, yield 62%; ^{1}H-nmr (pyridine-d_5): δ 0.90 (3H, t, J = 7 Hz, C3-$O(CH_2)_3CH_3$), 1.52 (4H, m, C3-$OCH_2(CH_2)_2$-), 2.62 (3H, s, C2-CH_3), 3.78 (2H, t, J = 7 Hz, C3-$OCH_2(CH_2)_2CH_3$), 5.22 (2H, s, C5-CH_2OH), 8.92 (1H, s, C4-CH=N-), 8.98 (1H, s, C6-H); ms: m/z 221 (M^+-17).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.69; H, 7.50; N, 11.70.

3-Hexyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4d**).

This compound was obtained as colorless needles (ethanol-water), mp 139-140°, yield 98%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 0.88 (3H, t, J = 7 Hz, C3-$O(CH_2)_5CH_3$), 1.36 (6H, m, C3-$OCH_2CH_2(CH_2)_3$), 1.78 (2H, m, C3-$CH_2CH_2(CH_2)_3CH_3$), 2.48 (3H, s, C2-CH_3), 3.76 (2H, t, J = 7 Hz, C3-$OCH_2CH_2(CH_2)_3CH_3$), 4.60 (2H, s, C5-CH_2OH), 8.28 (1H, s, C4-CH=N-), 8.42 (1H, s, C6-H), 11.80 (1H, br, =NOH); ms: m/z 266 (M^+), 249 (M^+-17).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.31; H, 8.28; N, 10.50.

3-Octyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4e**).

This compound was obtained as colorless needles (ethanol-water), mp 123-124°, yield 91%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 0.93 (3H, t, J = 7 Hz, C3-$O(CH_2)_7CH_3$), 1.37 (10 H, m, C3-$OCH_2CH_2(CH_2)_5CH_3$), 1.84 (2H, m, C3-OCH_2CH_2-$(CH_2)_5CH_3$), 2.55 (3H, s, C2-CH_3), 3.83 (2H, t, J = 7 Hz, C3-$OCH_2CH_2(CH_2)_5CH_3$), 4.62 (2H, s, C5-CH_2OH), 8.24 (1H, s, C4-CH=N-), 8.42 (1H, s, C6-H), 11.94 (1H, s, =NOH); ms: m/z 294 (M^+), 277 (M^+-17).

Anal. Calcd. for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.17; H, 8.72; N, 9.41.

3-Allyloxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Oxime (**4f**).

This compound was obtained as colorless needles (ethanol-water), mp 186-188°, yield 76%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 2.48 (3H, s, C2-CH_3), 4.38 (2H, dd, J = 5.5, 1 Hz, C3-OCH_2=CH-CH_2), 4.70 (2H, s, C5-CH_2O-), 5.31 (1H, d, J = 10 Hz, *trans* *H*-C=C-CH_2-), 5.45 (1H, dt, J = 17, 1 Hz, *cis* *H*-C=C-CH_2), 6.11 (1H, ddt, J = 17, 10, 5.5 Hz, -C=C*H*(CH_2-), 8.35 (1H, s, C4-CH=N-), 8.37 (1H, s, C6-H), 11.82 (1H, s, =NOH); ms: m/z 222 (M^+), 205 (M^+-17).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.46; H, 6.22; N, 12.46.

General Procedure for the Synthesis of 5-Alkoxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochlorides **6a-e**.

A solution of **4a-e** (1 mmole) dissolved in 180 ml of ethanol-water (5:1) was reduced for 6 hours in the presence of 5% Pd-C (100 mg) and concentrated hydrochloric acid under hydrogen gas (2 kg/cm^2). The catalyst was removed by filtration and the filtrate was condensed to give crystals.

5-Ethoxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochloride (**6a**).

This compound was obtained as colorless needles (ethanol-ether), mp 186-188°, yield 57%; ^{1}H-nmr (trifluoroacetic acid-d_1): δ 1.72 (3H, t, J = 7 Hz, C5-OCH_2CH_3), 3.00 (3H, s, C6-CH_3), 4.42 (2H, q, J = 7 Hz, C5-OCH_2CH_3), 4.92 (2H, s, C4-CH_2N), 5.28 (2H, s, C3-CH_2O-), 8.70 (1H, s, C2-H).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$·2HCl: C, 44.62; H, 6.74; N, 10.41. Found: C, 44.44; H, 6.60; N, 10.39.

5-Propoxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochloride (**6b**).

This compound was obtained as colorless needles (ethanol-ether), mp 183-185°, yield 83%; ^{1}H-nmr (trifluoroacetic acid-d_1): δ 1.16 (3H, t, J = 7 Hz, C5-$O(CH_2)_2CH_3$), 2.02 (2H, sextet, J = 7 Hz, C5-$OCH_2CH_2CH_3$), 2.92 (3H, s, C6-CH_3), 4.20 (2H, t, J = 7 Hz, C5-$OCH_2CH_2CH_3$), 4.84 (2H, s, C4-CH_2N), 5.19 (2H, s, C3-CH_2OH), 8.72 (1H, s, C2-H).

Anal. Calcd. for $C_{11}H_{18}N_2O_2$·2HCl: C, 46.65; H, 7.12; N, 9.89. Found: C, 46.50; H, 6.88; N, 9.72.

5-Butoxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochloride (**6c**).

This compound was obtained as colorless needles (ethanol-ether), mp 187-188°, yield 92%; ^{1}H-nmr (trifluoroacetic acid-d_1): δ 1.08 (3H, t, J = 7 Hz, C5-$O(CH_2)_3CH_3$), 1.60 (2H, m, C5-$OCH_2CH_2CH_2CH_3$), 2.02 (2H, m, C5-$OCH_2CH_2CH_2CH_3$), 2.94 (3H, s, C6-CH_3), 4.26 (2H, t, J = 7 Hz, C5-$OCH_2(CH_2)_2CH_3$), 4.86 (2H, s, C4-CH_2N), 5.20 (2H, s, C3-CH_2OH), 8.64 (1H, s, C2-H).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$·2HCl: C, 48.49; H, 7.46; N, 9.42. Found: C, 48.36; H, 7.50; N, 9.31.

5-Hexyloxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochloride (**6d**).

This compound was obtained as colorless needles (ethanol-ether), mp 173-174°, yield 65%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 0.91 (3H, t, J = 7 Hz, C5-$O(CH_2)_5CH_3$), 1.39 (6H, m, C5-OCH_2CH_2-$(CH_2)_3$-CH_3), 1.88 (2H, m, C5-O-CH_2CH_2-$(CH_2)_3CH_3$), 2.75 (3H, s, C6-CH_3), 4.07 (2H, t, J = 7 Hz, C5-OCH_2-$(CH_2)_5CH_3$), 4.18 (2H, s,

C4-CH_2N), 4.86 (2H, s, C3-CH_2OH), 8.52 (1H, s, C2-H).

Anal. Calcd. for $C_{14}H_{24}N_2O_2 \cdot 2HCl$: C, 51.70; H, 8.06; N, 8.61. Found: C, 51.80; H, 7.94; N, 8.48.

5-Octyloxy-4-aminomethyl-6-methyl-3-hydroxymethylpyridine Dihydrochloride (**6e**).

This compound was obtained as colorless needles (ethanol-ether), mp 180-183°, yield 38%; ^{1}H-nmr (dimethylsulfoxide-d_6-deuteriochloroform): δ 0.37 (3H, t, J = 7 Hz, C5-O(CH_2)$_7$-CH_3), 1.31 (10H, m, C5-OCH_2CH_2-(CH_2)5-CH_3), 1.86 (2H, m, C5-OCH_2CH_2-(CH_2)$_5$$CH_3$), 2.74 (3H, s, C6-$CH_3$), 4.06 (2H, t, J = 7 Hz, C5-OC$H_2$$CH_2$-($CH_2$)$_5$$CH_3$), 4.24 (2H, s, C4-$CH_2N$), 4.86 (2H, s, C3-$CH_2O$-), 8.51 (1H, s, C2-H).

Anal. Calcd. for $C_{16}H_{28}N_2O_2 \cdot 2HCl$: C, 54.39; H, 8.56; N, 7.93. Found: C, 54.65; H, 8.38; N, 7.69.

3-Butoxy-5-hydroxymethyl-2-methyl-4-pyridinecarboxaldehyde Hydrazone (**7**).

Compound **3c** (1.13 g, 5.1 mmoles) was dissolved in a mixture of ethanol-water (1:1) (100 ml). The solution was adjusted to *p*H 8 by adding potassium carbonate. Hydrazine hydrate (4 ml) was added and the mixture was stirred for 10 minutes. The reaction mixture was condensed to about 10 ml and extracted with chloroform. The extract was dried over magnesium sulfate and the solvent was distilled. The residue was washed with ether and recrystallized from ethanol-ether to give yellow needles, mp 122-125°, yield 383 mg (32%); ir (potassium bromide): ν 3380, 3310 (NH_2); ^{1}H-nmr (pyridine-d_5): δ 0.84 (3H, t, J = 7 Hz, C3-O(CH_2)$_3$CH_3), 1.46 (4H, m, C3-OCH_2(CH_2)$_2$$CH_3$), 2.60 (3H, s, C2-$CH_3$), 3.66 (2H, t, J = 7 Hz, C3-OCH_2-), 5.08 (2H, s, C5-CH_2O-), 8.44 (1H, s, C6-H), 8.76 (1H, s, C4-CH=N-).

Anal. Calcd. for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 61.02; H, 8.01; N, 17.61.

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