SYNTHESES OF A NATURALLY OCCURRING HYDROXAMIC ACID AND ITS ANALOGUES

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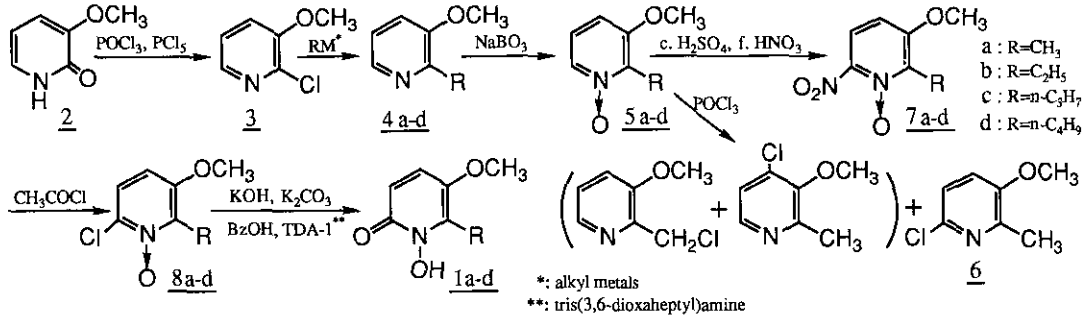
Abstract — A naturally occurring cyclic hydroxamic acid, isolated from *Pseudomonas species*, and its analogues were synthesized via six steps starting from 2-hydroxy-3-methoxypyridine. The antimicrobial activity of the synthesized compounds is described.

Hydroxamic acids in nature have detectable biological activity.[1] A cyclic hydroxamic acid (1a), isolated by Itoh et al.[2] and Barker et al.[3] from *Pseudomonas* species, has a pyridine skeleton and moderate antibiotic activity toward Gram positive and negative bacteria. While examining the palladium catalyzed cross-coupling reactions of N-heteroaromatic rings,[4] the synthesis of this compound attracted much attention of the authors. The present paper describes the successful synthesis of 1a and its analogues 1b-d and their antimicrobial activity.



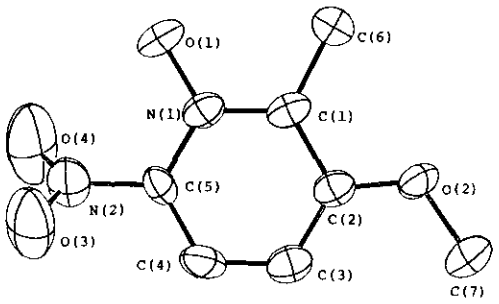
Scheme 1. Synthetic Route of 2-Alkyl-6-hydroxy-3-methoxypyridine 1-Oxides.

Commercially available 2-hydroxy-3-methoxypyridine (2) was used as the starting material for the present synthesis of compounds 1a-d according to Scheme 1. Compound 2 was heated with a mixture of phosphoryl chloride and a small amount of phosphorus pentachloride in a sealed tube to give 2-chloro-3-methoxypyridine (3)[5] in high yields. Alkyl groups, such as methyl, ethyl, propyl and butyl groups, were introduced into the pyridine ring by the cross-coupling reactions of 3 with the appropriate alkyl metals, such as trimethylaluminium, triethylborane, tetrapropyltin and tetrabutyltin, according to previously reported methods.[4,6] Although methylation product (4a) was obtained in high yields, the corresponding ethyl (4b), propyl (4c) and butyl derivatives (4d) were formed in rather unsatisfactory yields of 51, 38, and 68%, respectively. To increase the yields of alkylated products 4b-d, the method of Kumada et al.[7] using Grignard reagents and the nickel catalyst was applied, and the desired products were successfully obtained in good yields. Thus, cross-coupling reactions using Grignard reagents and the nickel catalysts may reasonably be considered superior to those using other alkyl metals and palladium catalysts for alkylation of the pyridines. The alkyl pyridines (4a-d) were oxidized with sodium perborate[8] to afford the corresponding pyridine 1-oxides (5a-d) in good yields.

Treatment of 5a with phosphoryl chloride produced 6-chloro-3-methoxy-2-methylpyridine (6), but as an inseparable mixture with 4-chloro-3-methoxy-2-methylpyridine and 2-chloromethyl-3-methoxypyridine. The isolation of 6 could be attended with difficulty by medium-pressure column chromatography in a low yield of only 15%. To improve this, compound 5a was nitrated by a method reported in the literature.[9] Although the structure of the product obtained had been determined spectroscopically and chemically,[9] X-ray analysis was carried out on the product 7a to confirm the position of the nitro group newly introduced and nitration was confirmed to occur, as shown in Figure 1, at C-6 of the pyridine ring of 5a. The nitration of other alkylpyridines (5b-d) also gave 6-nitro derivatives whose structures were determined by comparing their ^{1}H-nmr spectra with that of 7a. Attempted hydrolysis of 7a under alkaline conditions[10] to 1a was unsuccessful. Hence, the different approach via 6-chloro derivatives 8a-d was examined. Compounds 7a-d were converted to compounds 8a-d by treatment with acetyl chloride[11] and the products were submitted to alkaline hydrolysis according to the literature [12] to give 1a-d. The mp and ir spectrum of product 1a agreed with that reported in the literature.[2,3] Elemental analyses, ir and ^{1}H-nmr spectra of 1b-d were fully

consistent with the proposed structures.

The antimicrobial activity of 1b-d was subsequently examined and results are shown along with reported data[2] for 1a in Table 1. Although the results differed from what we expected and the antimicrobial activity was less than that of 1a, the compounds 1b-d were found moderately active toward certain bacteria.



Monoclinic, space group $P2_1/a$
a=16.744 (4) Å, b=12.797 (2) Å
c=3.9141 (8) Å, β=105.03 (2)°
V=810.2 (3) Å^3, R=0.115

Fig. 1. X-Ray Diffraction of 3-Methoxy-2-methyl-6-nitropyridine 1-Oxide (7a).

Test organisms	MIC (mcg/ml)			
	1a[2]	1b	1c	1d
Staphylococcus aureus Smith S-424	50	>100	>100	50
S. aureus No.26	50	>100	>100	50
S. epidermidis ATCC 14990	25	>100	>100	100
Bacillus anthracis No.119	12.5	100	50	25
Escherichia coli No.29	25	100	50	25
Salmonella typhi 0-901-W	12.5	12.5	12.5	12.5
S. typhimurium LT-2	50	100	50	>100
Klebsiella pneumoniae PCI 602	50	100	50	100
Proteus vulgaris OX19	25	100	50	25

Medium : Sensitivitiy disc agar-N (Nissui)

Inoculum size : 10^6 CFU/ml

Table 1. Antibacterial Activity of Synthesized Substances.

EXPERIMENTAL

No correction was made for any melting or boiling points. ^{1}H-Nmr spectral data were obtained in $CDCl_3$ by a Varian EM-390 using TMS as the internal standard. For silica gel column chromatography, Wakogel C-200 (WAKO Pure Chemical Ind. Ltd., Tokyo) was used as the packing material. Medium-pressure column chromatography was carried out using a UVILOG ALPC-100 as the pump, a UVILOG 5IIIa as the UV detector (Oyo-Bunko Kiki Co., Ltd., Tokyo) and Kieselgel 60 (Merck AG, Darmstadt) as the packing material. The following instruments were used to obtain other spectral data. Ir spectra (KBr): Japan Spectroscopic Co. A-100; Ms: Hitachi M-80B spectrometer. X-Ray diffraction data were obtained with Rigaku AFC-5 X-Ray autodiffractomer, using Mo K_α radiation.

2-Chloro-3-methoxypyridine (3)

A mixture of 2 (25 g, 200 mmol), $POCl_3$ (62.5 ml) and a small amount of PCl_5 was heated in a sealed tube at 140°C for 1 h and poured into ice-water, made alkaline with powdered K_2CO_3 and extracted with Et_2O to give a crystalline mass, which was recrystallized from hexane to give colorless prisms (25.8 g, 90%), mp 47-48°C (lit.,[5] mp 48-49°C).

3-Methoxy-2-methylpyridine (4a)

A mixture of 3 (4.305 g, 30 mmol), Me_3Al (30 ml of a 10% hexane solution, 30 mmol) and $Pd(PPh_3)_4$ (580 mg, 0.5 mmol) in dry dioxane (150 ml) was refluxed for 5.5 h under an argon atmosphere, acidified with 2N-HCl and concentrated under reduced pressure. The residue was made alkaline with 20% NaOH and extracted with Et_2O. The Et_2O layer was dried over Na_2SO_4 and the solvent was removed by distillation to give an oil, which was purified by distillation to provide a colorless oil (3.38 g, 90%), bp 92-95°C/30 torr (lit.,[13] bp 84-86°C/15 torr). Ms: m/z 123 (M^+), 108 (M^+-CH_3); ^{1}H-nmr: δ 2.45 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.09 (d, J = 3 Hz, 2H, pyridine H), 8.05 (t, J = 3 Hz, 1H, pyridine H) ppm.

2-Ethyl-3-methoxypyridine (4b)

A mixture of 3 (5.74 g, 40 mmol), Et_3B (42 ml of 15% hexane solution, 42 mmol), K_2CO_3 (8.3 g, 60 mmol) and $Pd(PPh_3)_4$ (1.16 g, 1 mmol) in dry DMF (100 ml) was refluxed for 1 h under an argon atmosphere. After being filtered by suction, the filtrate was acidified with 2N-HCl and concentrated in vacuo. The residue was made alkaline with 20% KOH and extracted with Et_2O. The Et_2O extract was worked up as usual to give an oil which was purified by column chromatography using CH_2Cl_2-Et_2O (4:1 and 1:1) as the solvent to yield a colorless oil (2.82 g, 51%),

bp 85-90°C/20 torr. Ms: m/z 137 (M^+), 122 (M^+-CH_3); ^{1}H-nmr: δ 1.25 (t, J = 7 Hz, 3H, $CH_2\underline{CH}_3$), 2.82 (q, J = 7 Hz, 2H, $\underline{CH}_2CH_3$), 3.81 (s, 3H, OCH_3), 7.06 (d, J = 3 Hz, 2H, pyridine H), 8.08 (t, J = 3 Hz, 1H, pyridine H) ppm.

2-Ethyl-3-methoxypyridine Picrate: yellow prisms (EtOH); mp 126-127.5°C; Anal. Calcd for $C_{14}H_{14}N_4O_8$; C, 45.90; H, 3.85; N, 15.30. Found: C, 45.97; H, 3.80; N, 15.26.

2-Propyl-3-methoxypyridine (4c)

To a THF (10 ml) solution of a Grignard reagent, prepared from Mg (146 mg, 6 mg atoms) and PrBr (811 mg, 6.6 mmol), $SnCl_4$ (260 mg, 1 mmol) was added under cooling in an ice bath and the mixture was refluxed for 1 h. The solvent was removed by distillation in vacuo. Compound 3 (1 mmol, 143.5 mg), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), K_2CO_3 (207 mg, 1.5 mmol) and dry DMF (5 ml) were added to the residue. The reaction mixture was then refluxed for 5 h under an argon atmosphere, acidified with 2N-HCl and the solvent removed in vacuo. The residue was made alkaline with 20% KOH and extracted with Et_2O. The crude product was purified by column chromatography using CH_2Cl_2 as the solvent to give 4c (57.5 mg, 38%) as a colorless oil, bp 95-97°C/10 torr (lit.,[14] bp 88°C/1.1 torr). Ms: m/z 151 (M^+), 136 (M^+-CH_3); ^{1}H-nmr: δ 0.96 (t, J = 7 Hz, 3H, $CH_2CH_2\underline{CH}_3$), 1.68 (m, 2H, $CH_2\underline{CH}_2CH_3$), 2.78 (dd, J = 6 and 9 Hz, 2H, $\underline{CH}_2CH_2CH_3$), 3.80 (s, 3H, OCH_3), 7.07 (d, J = 3 Hz, 2H, pyridine H), 8.10 (t, J = 3 Hz, 1H, pyridine H) ppm.

2-Butyl-3-methoxypyridine (4d)

A solution of 3 (4.305 g, 30 mmol), $Pd(PPh_3)_4$ (1.74 g, 1.5 mmol), K_2CO_3 (6.225 g, 45 mmol) and Bu_4Sn (12 ml, 30 mmol) in dry DMF (75 ml) was refluxed for 3 h under an argon atmosphere, acidified with 2N-HCl and then concentrated in vacuo. The residue was made alkaline with 20% KOH and extracted with Et_2O. The Et_2O extract was worked up as usual, the product was purified by column chromatography using Et_2O as the solvent and distilled to give 4d (3.391 g, 68%) as a colorless oil (bp 91-92°C/6 torr). Ms: m/z 166 (M^++1), 150 (M^+-CH_3); ^{1}H-nmr: δ 0.92 (t, J = 7 Hz, 3H, $CH_2(CH_2)_2\underline{CH}_3$), 1.51 (m, 4H, $CH_2(\underline{CH}_2)_2CH_3$), 2.80 (t, J = 7 Hz, 2H, $\underline{CH}_2(CH_2)_2CH_3$), 3.80 (s, 3H, OCH_3), 7.05 (d, J = 3 Hz, 2H, pyridine H), 8.06 (t, J = 3 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.43; H, 9.19; N, 8.39.

General Procedure for the Preparation of 2-Alkyl-3-methoxypyridines (4b-d) Using Grignard Reagents and a Nickel Catalyst

An Et_2O solution of a Grignard reagent, prepared from Mg (2.43 g, 100 mg atoms),

an alkyl bromide (120 mmol) in Et_2O (30 ml), was added dropwise to a solution of 3 (40 mmol) and Ni(dppp)Cl_2 (21.7 mg, 0.04 mmol) in Et_2O (70 ml) over a period of 1 h under ice-cooling. The reaction mixture was allowed to stand for 2 h at room temperature and refluxed for 1 h. After being treated with H_2O and acidified with 2N-HCl, the H_2O layer was separated. This layer was made alkaline with powdered K_2CO_3 and extracted with Et_2O. The Et_2O layer was worked up as usual to give a pale yellow oil, which was purified by column chromatography using Et_2O as the solvent, followed by distillation to provide a colorless oil. Yields; 4b: 80%; 4c: 93%; 4d: 94%.

Preparation of 2-Alkyl-3-methoxypyridine 1-Oxides (5a-d)

A mixture of a 2-alkyl-3-methoxypyridine (33 mmol) and $NaBO_3$ (6.13 g, 40 mmol) in AcOH (150 ml) was heated at 80°C for 5.5 h. After removing the solvent by distillation in vacuo, the viscous oily residue was triturated with H_2O, made alkaline with powdered K_2CO_3 and extracted with $CHCl_3$. The crude product was purified by column chromatography using $CHCl_3$-AcOEt as the solvent to give the desired product.

3-Methoxy-2-methylpyridine 1-Oxide (5a): colorless prisms (Me_2CO-Et_2O); yield: 90%; mp 65-66°C (lit.,[15] mp 65°C); ms: m/z 139 (M^+), 122 (M^+-OH); ^{1}H-nmr: δ 2.45 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.89 (d, J = 9 Hz, 1H, pyridine H), 7.03 (dd, J = 6 and 9 Hz, 1H, pyridine H), 7.95 (d, J = 6 Hz, 1H, pyridine H) ppm.

2-Ethyl-3-methoxypyridine 1-Oxide (5b): colorless prisms (cyclohexane); yield: 71%; mp 71-72°C; ms: m/z 153 (M^+), 136 (M^+-OH); ^{1}H-nmr: δ 1.20 (t, J = 7 Hz, 3H, $CH_2\underline{CH}_3$), 3.01 (q, J = 7 Hz, 2H, $\underline{CH}_2CH_3$), 3.86 (s, 3H, OCH_3), 6.76 (d, J = 9 Hz, 1H, pyridine H), 7.02 (dd, J = 6 and 9 Hz, 1H, pyridine H), 7.92 (d, J = 6 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.57; H, 7.34; N, 9.04.

3-Methoxy-2-propylpyridine 1-Oxide (5c): colorless prisms (isoPr$_2$O); yield: 92%; mp 42-44°C, bp 126°C/2 torr; ms: m/z 167 (M^+), 150 (M^+-OH); ^{1}H-nmr: δ 0.97 (t, J = 7 Hz, 3H, $CH_2CH_2\underline{CH}_3$), 1.66 (m, 2H, $CH_2\underline{CH}_2CH_3$), 2.95 (dd, J = 6 and 9 Hz, 2H, $\underline{CH}_2CH_2CH_3$), 3.85 (s, 3H, OCH_3), 6.76 (d, J = 9 Hz, 1H, pyridine H), 7.02 (dd, J = 6 and 9 Hz, 1H, pyridine H), 7.92 (d, J = 6 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.40; H, 8.00; N, 8.32.

2-Butyl-3-methoxypyridine 1-Oxide (5d): colorless prisms (isoPr$_2$O); yield: 85%; mp 56-59°C, bp 100°C/6 torr (oil bath temp.); ms: m/z 181 (M^+), 164 (M^+-OH); ^{1}H-nmr: δ 0.92 (t, J = 7 Hz, 3H, $CH_2(CH_2)_2\underline{CH}_3$), 1.50 (m, 4H, $CH_2(\underline{CH}_2)_2CH_3$), 2.98

(t, J = 7 Hz, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 3.86 (s, 3H, OCH_3), 6.78 (d, J = 9 Hz, 1H, pyridine H), 7.01 (dd, J = 6 and 9 Hz, 1H, pyridine H), 7.92 (d, J = 6 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.33; H, 8.34; N, 7.64.

Reaction of 3-Methoxy-2-methylpyridine 1-Oxide (5a) with $POCl_3$

A mixture of 5a (1.395 g, 10 mmol) and $POCl_3$ (40 ml) was heated under refluxing for 1 h and poured into ice-water. The mixture was made alkaline with powdered K_2CO_3 and extracted with Et_2O to give a yellow oil, which was purified by medium-pressure column chromatography using hexane-AcOEt as the solvent. By this procedure, only 6 was obtained in pure form. Colorless prisms (H_2O); yield: 15%; mp 43-45°C; ms: m/z 157 (M^+), 142 (M^+-CH_3); ^{1}H-nmr: δ 2.43 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.09 (s, 2H, pyridine H) ppm; Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.00; H, 5.04; N, 8.91.

Nitration of 2-Alkyl-3-methoxypyridine 1-Oxides (5a-d)

A pyridine 1-oxide (24.4 mmol) was added to a mixture of c. H_2SO_4 (80 ml) and f. HNO_3 (3.75 ml) under stirring at room temperature and the reaction mixture was heated in a boiling water bath for 2 h. After being poured into ice-water, the mixture was extracted with CH_2Cl_2 to give a yellow crystalline mass, which was subsequently purified by recrystallization to give yellow prisms.

3-Methoxy-2-methyl-6-nitropyridine 1-Oxide (7a): pale yellow prisms (benzene); yield: 40%; mp 148-150°C (lit.,[9] mp 141-143°C); ms: m/z 184 (M^+), 167 (M^+-OH); ^{1}H-nmr: δ 2.43 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.87 (d, J = 9 Hz, 1H, pyridine H), 7.60 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.75; H, 4.33; N, 15.02.

2-Ethyl-3-methoxy-6-nitropyridine 1-Oxide (7b): pale yellow plates ($isoPr_2O$); yield: 56%; mp 93-94°C; ms: m/z 198 (M^+), 181 (M^+-OH); ^{1}H-nmr: δ 1.20 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$), 3.03 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 3.97 (s, 3H, OCH_3), 6.84 (d, J = 9 Hz, 1H, pyridine H), 7.59 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.35; H, 5.05; N, 13.85.

3-Methoxy-6-nitro-2-propylpyridine 1-Oxide (7c): pale yellow plates ($isoPr_2O$); yield: 68%; mp 90-91°C; ms: m/z 212 (M^+), 195 (M^+-OH); ^{1}H-nmr: δ 0.98 (t, J = 7 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.66 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.97 (dd, J = 6 and 9 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.96 (s, 3H, OCH_3), 6.84 (d, J = 9 Hz, 1H, pyridine H), 7.58 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.84; H, 5.68; N, 13.17.

2-Butyl-3-methoxy-6-nitropyridine 1-Oxide (7d): pale yellow needles ($isoPr_2O$); yield: 41%; mp 84-85°C; ms: m/z 227 (M^++1), 209 (M^+-OH); ^{1}H-nmr: δ 0.90 (t, J = 7 Hz, 3H, $CH_2(CH_2)_2C\underline{H}_3$), 1.47 (m, 4H, $CH_2(C\underline{H}_2)_2CH_3$), 3.00 (t, J = 7 Hz, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 3.96 (s, 3H, OCH_3), 6.81 (d, J = 9 Hz, 1H, pyridine H), 7.58 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.12; H, 6.32; N, 12.27.

Preparation of 2-Alkyl-6-chloro-3-methoxypyridine 1-Oxides (8a-d)

A mixture of 2-alkyl-3-methoxy-6-chloropyridine 1-oxide (11.8 mmol) and AcCl (5.4 ml) was stirred for 20 min at room temperature. After being poured into ice-water, the mixture was made alkaline with powdered K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ layer was worked up as usual to give a crystalline mass, which was purified by medium-pressure column chromatography using hexane-AcOEt as the solvent and recrystallized.

6-Chloro-3-methoxy-2-methylpyridine 1-Oxide (8a): colorless needles (hexane); yield: 34%; mp 124-126°C; ms: m/z 173 (M^+), 156 (M^+-OH); ^{1}H-nmr: δ 2.50 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.82 (d, J = 9 Hz, 1H, pyridine H), 7.30 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_7H_8ClNO_2$: C, 48.43; H, 4.65; N, 8.07. Found: C, 48.69; H, 4.57; N, 8.28.

6-Chloro-2-ethyl-3-methoxypyridine 1-Oxide (8b): colorless plates (hexane); yield: 50%; mp 87-88°C; ms: m/z 187 (M^+), 170 (M^+-OH); ^{1}H-nmr: δ 1.20 (t, J = 7 Hz, 3H, $CH_2C\underline{H}_3$), 3.05 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 3.87 (s, 3H, OCH_3), 6.78 (d, J = 9 Hz, 1H, pyridine H), 7.29 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_8H_{10}ClNO_2$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.28; H, 5.33; N, 7.32.

6-Chloro-3-methoxy-2-propylpyridine 1-Oxide (8c): colorless plates (hexane); yield: 68%; mp 114-115°C; ms: m/z 201 (M^+), 184 (M^+-OH); ^{1}H-nmr: δ 0.98 (t, J = 7 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.68 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.99 (dd, J = 6 and 9 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.86 (s, 3H, OCH_3), 6.76 (d, J = 9 Hz, 1H, pyridiene H), 7.28 (d, J = 9 Hz, 1H, pyridine H); Anal. Calcd for $C_9H_{12}ClNO_2$: C, 53.60; H, 6.00; N, 6.95. Found: C, 53.77; H, 6.01; N, 6.93.

2-Butyl-6-chloro-3-methoxypyridine 1-Oxide (8d): colorless needles (hexane); yield: 69%; mp 66-67°C; ms: m/z 215 (M^+), 198 (M^+-OH); ^{1}H-nmr: δ 0.93 (t, J = 7 Hz, 3H, $CH_2(CH_2)_2C\underline{H}_3$), 1.44 (m, 4H, $CH_2(C\underline{H}_2)_2CH_3$), 3.01 (t, J = 7 Hz, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 3.85 (s, 3H, OCH_3), 6.75 (d, J = 9 Hz, 1H, pyridine H), 7.28 (d, J = 9 Hz, 1H, pyridine H); Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.71; H, 6.59; N, 6.46.

Preparation of 2-Alkyl-6-hydroxy-3-methoxypyridine 1-Oxides (1a-d)

A 2-alkyl-6-chloro-3-methoxypyridine 1-oxide (1 mmol) was added to a suspension of powdered KOH (224 mg, 4 mmol) and K_2CO_3 (138 mg, 1 mmol) in a mixture of dry toluene (10 ml) and $PhCH_2OH$ (0.16 ml). After adding TDA-1 (32 mg), the reaction mixture was refluxed for 2 h, treated with H_2O and then washed with Et_2O. The H_2O layer was acidified with 2N-HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was worked up as usual to give a yellowish crystalline mass, which was purified by sublimation and subsequent recrystallization.

6-Hydroxy-3-methoxy-2-methylpyridine 1-Oxide (1a): colorless plates ($isoPr_2O$); yield: 34%; mp 114-115°C (lit.,[2] mp 115°C); ms: m/z 155 (M^+), 140 (M^+-CH_3); ir: 1640 (C=O) cm^{-1}; ^{1}H-nmr: δ 2.43 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.13-5.47 (broad s, 1H, OH), 6.57 (d, J = 9 Hz, 1H, pyridine H), 7.18 (d, J = 9 Hz, 1H, pyridine H) ppm.

2-Ethyl-6-hydroxy-3-methoxypyridine 1-Oxide (1b): colorless plates (AcOEt); yield: 15%; mp 139-140°C; ms: m/z 169 (M^+), 153 (M^+-O); ir: 1655 (C=O) cm^{-1}; ^{1}H-nmr: δ 1.26 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.92 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 3.77 (s, 3H, OCH_3), 6.58 (d, J = 9 Hz, 1H, pyridine H), 6.87-7.16 (broad s, 1H, OH), 7.22 (d, J = 9 Hz, 1H, pyridine H) ppm; Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.78; H, 6.61; N, 8.23.

6-Hydroxy-3-methoxy-2-propylpyridine 1-Oxide (1c): colorless plates (Et_2O); yield: 13%; mp 104-105°C; ms: m/z 183 (M^+), 166 (M^+-OH); ir: 1650 (C=O) cm^{-1}; ^{1}H-nmr: δ 0.98 (t, J = 7 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.85 (dd, J = 6 and 9 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.75 (s, 3H, OCH_3), 6.66 (d, J = 9 Hz, 1H, pyridine H), 7.22 (d, J = 9 Hz, 1H, pyridine H), 9.85-10.05 (broad s, 1H, OH) ppm; Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.02; H, 7.23; N, 7.61.

2-Butyl-6-hydroxy-3-methoxypyridine 1-Oxide (1d): colorless plates ($isoPr_2O$); yield: 14%; mp 91-92°C; ms: m/z 197 (M^+), 181 (M^+-O); ir: 1640 (C=O) cm^{-1}; ^{1}H-nmr: δ 0.93 (t, J = 7 Hz, 3H, $CH_2(CH_2)_2\underline{CH_3}$), 1.52 (m, 4H, $CH_2(\underline{CH_2})_2CH_3$), 2.87 (t, J = 7 Hz, 2H, $\underline{CH_2}(CH_2)_2CH_3$), 3.74 (s, 3H, OCH_3), 6.56 (d, J = 9 Hz, 1H, pyridine H), 7.18 (d, J = 9 Hz, 1H, pyridine H), 8.52-8.72 (broad s, 1H, OH) ppm; Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.98; H, 7.71; N, 7.08.

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