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Synthesis of 3-Amino-1,4-dihydropyridine Derivative *via* an Intramolecular Rearrangement of 1,4-Dihydropyridine-3-hydroxamate

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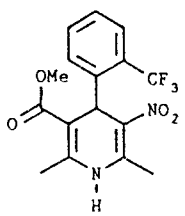
Abstract □ 2,6-Dimethyl-4-(3′-nitrophenyl)-3-methoxylaminocarbonyl-1,4-dihydropyridine-5-carboxylic acid methylester, **3b** reacted with 2-cyanoethanol or benzylalcohol to give the corresponding cyanoethylurethane compound **6c** in 40.6% yield and benzylurethane compound **6d** in 32% yield. The cyanoethylurethane **6c** was hydrolized in ethanolic NaOH to give 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-amino-5-carboxylic acid 5-methyl ester. HCl **8** in 64.8% yield. Another acid hydrolysis of benzylurethane **6d** gave 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-amino-5-carboxylic acid 5-methylester. HBr **11** in 54.7% yield.

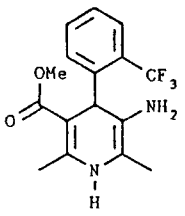
Keywords □ Rearrangement, 1,4-dihydropyridine-3-hydroxamate, 3-aminopyridine, 3-hydroxypyridine, 3-amino-1,4-dihydropyridine.

The aryldihydropyridines first prepared by Hantzsch have found to be highly effective calcium antagonists with suitable pharmacological profile. The discovery of the therapeutic activity of these substances initiated various modification of the Hantzsch condensation and the synthesis of numerous 4-aryl-dihydropyridines and related compounds[1,2]. Most extensive studies are the calcium antagonists[3,4]. Calcium agonists have been also found among 1,4-dihydropyridines. An illustrative example is 1,4-dihydro-2,6-dimethyl-5-nitro-4-[(2'-trifluoromethyl) phenyl]-3-pyridinecarboxylic acid methylester(BAY-K-8644)[5,7] The substance has positive inotropic and vasoconstrictive effects. Moreover Stoltefuss *et al.*[8,9] synthesized 3-aminodihydropyridines(BAY-138-234) from the BAY-K-8644 derivatives by catalytic hydrogenation and claimed novel cardioactivity. Hence they can be used in medicaments for influencing pathologically altered blood pressure, and the coronary therapeutics and for the treatment of cardiac insufficiency. These facts promoted us to attempt the synthesis of 3-amino-4-(3′-nitrophenyl)-1,4-dihydropyridine compound which could not be obtained from 3-nitro-4-(3′-nitrophenyl)-1,4-dihydropyridine by catalytic hydrogenation. In this paper, we report the synthesis of 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-amino-5-carboxylic acid 5-methylester *via* an intramolecular rearrangement of 4-(3′-nitrophenyl)-1,4-dihydropyridine-5-carboxylic acid methylester-3-hydroxamates followed by alkaline or acid hydrolysis[10,11]. The 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl 3-(benzotriazol-1-yl)ester **1** used as starting material can be prepared by known method[12]. The 3-(benzotriazol-1-yl)ester **1** reacted with hydroxylamine **2a** or methoxyl amine **2b** to give the corresponding 3-hydroxamate **3** in 66 and 34% yield respectively.

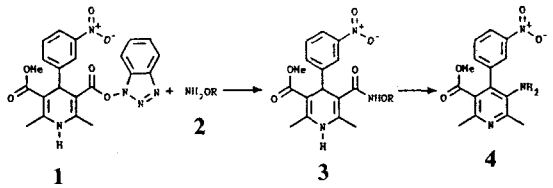
Compound **3** in DMF was heated at 80-100℃ for 2 hrs to give the undesirable compound **4** as yellow solid (Scheme 1). The reaction took place at room temperature in the presence of boron trifluoride etherate. NMR spectrum [no hydrogen signals of C_4-H and NH, 3.48(-NH_2)], IR spectrum [3433 & 3311cm^{-1}(NH_2)], elemental analysis($C_{15}H_{15}N_3O_4$) and Mass spectrum [*m/e* 301(M^+)] supported the structure for compound **4**. It is suggested that the reaction mechanism seemed to be a Lossen type rearrangement followed by oxidation. In this case, isocyanate might be produced in the course of the



BAY-K-8644

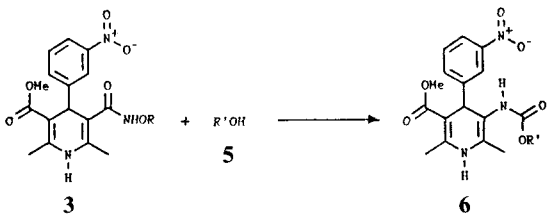


BAY-138-234



Scheme 1

reaction. Actually, the hydroxamate **3** reacted with alcohols **5** to give four urethane compounds **6** in 32-50% yield (Scheme 2). Neither methanol nor ethanol gave the corresponding urethane due to low reaction temperature. The cyanoethyl urethane compound **6c** was selectively hydrorlyzed in ethanolic sodium hydroxide solution at room temperature for 30 min[13,14]. The reaction mixture was acidified with HCl solution to give 3-hydroxyridine compound **10** as white solid. NMR spectrum [no hydrogen signals of C_4-H and NH, 5.1 (OH)] suggested the structure for compound **10**. During the reaction, HCl solution accelerated the hydrolysis of 3-amino-1,4-dihydropyridine **8** to give compound **10** *via* intermediate **9**. Compound **8** could be seperated when methanolic HCl was used instead of aqueous HCl (Scheme 3). Neither **6a** nor **6b** gave satisfactory results. 3-amino-1,4-dihydropyridine was assigned by NMR spectrum [4.8 (C_4-H), 8.75 (NH), 9.4 ($NH_2 \cdot HCl$)] and IR spectrum [3320cm^{-1} (NH)]. Another selective hydrolysis of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-[(N-benzyloxycarbonyl)amino]-5-carboxylic acid 5-methylester **6d** with glacial acetic acid saturated with hydrogen bromide gave 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-amino-5-carboxylic acid methylester hydrobromide **11** in 54.7% yield. The compound **11** was liable to hydrolysis when treated with only water to give mainly compound **10** and small amount of compound **4**[15,16](Scheme 4).



Scheme 2

EXPERIMENTAL

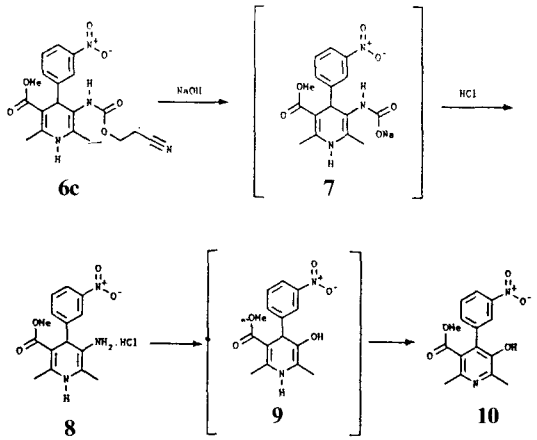
Melting points were determined on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian VXR-5200 (200 MHz). Chemical shifts are recorded in ppm with tetramethylsilane as the internal standard. The IR spectra were recorded with a Shimazu IR-435 spectrometer. Mass spectra were measured on a HP 5987X GC/MS instrument. The elemental analysis as(C, H, N) were carried out with a Carlo Erba model 1106 Elemental Analyzer.

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl 3-(benzotriazol-1-yl)ester, 1

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-monomethyl ester[17,18] (6.65 g, 0.02 mole) was suspended in THF (50 m*l*). To the suspension were added Et_3N (3.1 m*l*, 0.022 mole) and benzotriazole-1-mesylate(4.7 g, 0.022 mole). After 24 hrs the solvent of the reaction mixture was evaporated under reduced pressure to give yellow residue, which was applied to silica gel column [EtOAc : *n*-Hex (1 : 1, v/v)]. The elute was concentrated to give yellow oil. The oil was treated with Et_2O to give light yellow solid (5.5 g, 61%). ^{1}H-NMR (DMSO-d_6): δ 2.38 (s, 3H,-CH_3), 2.24 (s, 3H, -CH_3), 3.61 (s, 3H, -OCH_3), 5.29 (s, 1H, C_4-H), 7.72-8.15 (m, 8H, Ar-H), 9.85 (s, 1H, -NH-).

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-hydroxylaminocarbonyl-5-carboxylic acid methyl ester, 3a

$NH_2OH \cdot HCl$ (**2a**, 0.19 g, 1.2eq.) was dissolved in DMF (10 m*l*). To the solution was added $KHCO_3$ (0.27 g, 1.2eq.) and the mixture was stirred at room



Scheme 3

temperature for 30 min. To the suspension was added 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl 3-(benzotriazol-1-yl) ester (1.1 g, 2.23 mmole). The reaction mixture was stirred for 24 h at room temperature and then partitioned between EtOAc and water. The organic layer was separated and washed with water and brine sufficiently and then treated with $MgSO_4$ and active carbon. The solvent was evaporated *in vacuo* and the residue was treated with Et_2O. The solid was recrystallized from acetone to afford yellow solid (0.51 g, 66.2%).

mp. 165-167℃; Anal. calcd. for $C_{16}H_{17}N_3O_6$: C 55.33, H 4.9, N 12.09, Found: C 55.77, H 5.08, N 12.05: ^{1}H-NMR(DMSO-d_6): δ 2.01 (s, 3H, -CH_3), 2.26 (s, 3H, -CH_3), 2.51 (s, 3H, -OCH_3), 4.88 (s, 1H, C_4-H), 7.57-7.96 (m, 4H, Ar-H), 8.58 (s, 1H, -NH-), 8.72 (s, 1H, -NH-), 10.32 (s, 1H, -OH): IR (KBr) cm^{-1}: 3366 (NH), 1666 (C=O).

2,6-dimethyl-4-(3'-nitrophenyl)-3-methoxylaminocarbonyl-1, 4-dihydropyridine-5-carboxylic acid methyl ester, 3b

NH_2OMe·HCl (**2b**, 25-30% in water, 3.4 m*l*) was dissolved in DMF (25 m*l*). To the solution were added $KHCO_3$ (1.0 g, 2.4eq.) and 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl 3-benzotriazol-1-yl ester (1.2 g, 4.45 mmole). The reaction suspension was stirred at room temperature for 4 days and partitioned between water and EtOAc. The organic layer was separated and washed with water and brine. The organic layer was treated with $MgSO_4$ and active carbon and filtered. The filtrate was evaporated *in vacuo* to give yellow solid, which was purified with preparative TLC to afford yellow solid (0.54 g, 33.8%).

mp. 174-176℃; Anal. calcd. for $C_{17}H_{19}N_3O_6$: C 56.50, H 5.30, N 11.63 Found: C 56.57, H 5.32, N 11.38. ^{1}H-NMR(DMSO-d_6): δ 1.98 (s, 3H, -CH_3), 2.26 (s, 3H, -CH_3), 3.45 (s, 3H, -OCH_3), 3.48 (s, 3H, -OCH_3), 4.84 (s, 1H, C_4-H), 7.52-7.52 (m, 4H, Ar-H), 8.62 (s, 1H, -NH-), 10.83 (s, 1H, -NH-): IR(KBr) cm^{-1}: 3317.5 (NH), 1700 and 1667 (C=O).

2,6-dimethyl-4-(3'-nitrophenyl)-3-aminopyridine-5-carboxylic acid 5-methyl ester, 4

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-(N-methoxylaminocarbonyl)-5-carboxylic acid methyl ester (**3b**, 360 mg, 1 mmole) was dissolved in DMF (10 m*l*), and the reaction solution was heated to 80-100℃ for 2 hrs. After cooling to room temperature, the reaction mixture was partitioned between EtOAc and water.

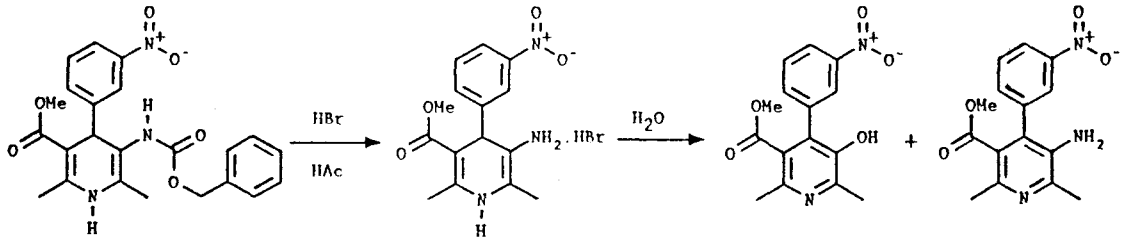
The organic layer was separated and washed with water and brine sufficiently. The organic layer was treated with $MgSO_4$ and active carbon and filtered. The filtrate was evaporated and the residue was triturated with Et_2O to give yellow solid (37 mg. 12.2%).

mp. 177-179℃; Anal. calcd. for $C_{15}H_{15}N_3O_4$: C 56.79, H 5.02, N 13.95 Found: C 56.57, H 5.16, N 13.77. MS: *m/e* 301 (M^+): ^{1}H-NMR ($CDCl_3$): δ 2.48 (s, 6H, -CH_3x2), 3.48 (s, 2H, -NH_2), 3.54 (s, 3H, -OCH_3), 7.65-8.22 (m, 4H, Ar-H): IR (KBr) cm^{-1}: 3433 & 3311 (NH_2), 1726 (C=O).

2,6-dimethyl-4-(3'-nitrophenyl)-3-(1'-butoxycarbonylamino)-1,4-dihydropyridine-5-carboxylic acid methylester, 6a

A mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-hydroxylaminocarbonyl-5-carboxylic acid methyl ester (**3a**, 700 mg, 2 mmole) and 1-butanol (10 m*l*) was heated to reflux overnight under nitrogen atmosphere. After cooling to room temperature, 1-butanol was distilled off under reduced pressure and then the oily residue was applied to silicagel column chromatography [EtOAc : *n*-Hex (1:1, v/v)]. The elute was concentrated *in vacuo* to give yellow oil, which was cystallized in Et_2O (400 mg, 50%).

mp. 173-176℃; Anal. calcd. for $C_{20}H_{25}N_3O_6$: C 59.54, H 6.25, N 10.42 Found: C 59.21, H 6.18, N 10.55: ^{1}H-NMR ($CDCl_3$): δ 0.83 (t, 3H, -CH_3), 1.09-1.67 (m, 4H, -CH_2-X2), 1.67 (s, 3H, -CH_3), 2.24 (s, 3H, -CH_3), 3.41 (s, 3H, -OCH_3), 3.86 (t, 2H,



6d 11 10 4

Scheme 4

-OCH_2-), 4.76 (s, 1H, C_4-H), 7.49-8.04 (m, 4H, Ar-H), 7.92 (s, 1H, -NHO-), 8.23 (s, 1H, NH): IR (KBr) cm^{-1}: 3256 (NH), 1699 & 1676 (C=0).

2,6-Dimethyl-4-(3'-nitrophenyl)-3-(1'-octoxycarbonyl-amino)-1,4-dihydropyridine-5-carboxylic acid methyl ester, 6b

A mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-hydroxylaminocarbonyl-5-carboxylic acid methyl ester (**3a**, 3 g, 8.6 mmol) and 1-octanol (30 m*l*) was heated to 150-160℃ for 5 hrs under nitrogen atmosphere. After cooling to room temperature, 1-octanol was distilled off under reduced pressure and then the oily residue was applied to silica-gel column [EtOAc : *n*-Hexane (1 : 1, v/v)]. The elute was concentrated *in vacuo* to give yellow oil, which was crystallized in ethyl ether (1.41 g, 33%).

mp. 145-148℃: ^{1}H-NMR ($CDCl_3$): δ 0.88 (t, 3H, -CH_3), 1.17-1.26 (m, 10H, -CH_2-X5), 1.52-1.58 (m, 2H, -CH_2), 1.83 (s, 3H, -CH_3), 2.33 (s, 3H, -CH_3), 3.52 (s, 3H-OCH_3), 4.02 (t, 2H, -OCH_2-), 4.71 (s, 1H, C_4-H), 5.24 (s, 1H, -NH-), 5.38 (s, 1H, NH-), 7.37-8.12 (m, 4H, Ar-H): IR (KBr) cm^{-1}: 3326 (NH), 1704 & 1674 (C=0).

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-[N-(2'-cyanoethoxycarbonyl) amino]-5-carboxylic acid 3-methyl ester, 6c

A mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-3-methoxylaminocarbonyl-1,4-dihydropyridine-5-carboxylic acid methyl ester (**3b**, 7.3 g, 0.02 mole) and 2-cyanoethanol (50 m*l*) was degassed with He gas for 30 min and then charged with N_2 gas. The reaction mixture was heated to 100-120℃ for 5 hrs. After the solvent was evaporated *in vacuo*, the residue was partitioned between ethyl acetate and water. The organic layer was washed with d-HCl, water and brine, and then dried over sodium sulfate. The solvent was evaporated and the residue was applied to silica gel column [EtOAc : *n*-Hexane (3 : 1, v/v)]. The elute was evaporated and the residue was treated with ethanol to give heavy yellow solid (3.32 g, 40.6%).

mp. 171-173℃; Anal. calcd. for $C_{19}H_{20}N_4O_6$: C 56.99, H 5.04, N 13.99. Found: C 56.89, H 5.18, N 13.88: ^{1}H-NMR ($CDCl_3$): δ 1.69 (s, 3H, -CH_3), 2.42 (s, 3H, -CH_3), 2.76 (m, 2H, -CH_2CN), 3.40 (s, 3H, -OCH_3), 4.05 (m, 2H, -OCH_2-), 4.76 (s, 1H, C_4-H), 7.52-8.02 (m, 4H, Ar-H), 8.16 (s, 1H, NH-), 8.29 (s, 1H, -NH-): IR (KBr) cm^{-1}: 3335 (NH), 1723 & 1677 (C=0).

2,6-Dimethyl-4-(3'-nitrophenyl)-3-hydroxypyridine-5-carboxylic acid 5-methyl ester, 10

NaOH (0.89 mg, 1.2eq) was dissolved in EtOH (5 m*l*). To the solution was added compound **6c** (386 mg, 1 mmol). After 30 min the solution was acidified with 4N-hydrochloric acid and then partitioned between ethyl acetate and water. The organic layer was separated and washed with water and brine, and then treated with sodium sulfate and active carbon. The filtrate was evaporated and the residue was recrystallized from ethanol (52 mg, 17.1%).

mp. 200-202℃; ^{1}H-NMR ($CDCl_3$): δ 2.56 (s, 3H, -CH_3), 2.58 (s, 3H, -CH_3), 3.58 (s, 3H, -OCH_3), 5.1 (sb, 1H, -OH), 7.62-8.38 (m, 4H, Ar-H): IR (KBr) cm^{-1}: 3400 (OH), 1726 (C=0).

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3-amino-5-carboxylic acid 5-methyl ester hydrochloride, 8

NaOH (0.25 g, 1.2eq) was dissolved in EtOH (10 m*l*). To the solution were added anhydrous sodium sulfate (1 g) and then compound **6c** (2 g, 5.18 mmole). The mixture was stirred for 2 hrs. To the reaction suspension was added methanolic hydrochloric acid to precipitate white solid. The solid was

filtered off and the filtrate was evaporated and then the residue was solidified in acetonitrile to give yellow solid (1.14 g, 64.8%).

^{1}H-NMR (DMSO-d_6): δ 1.95 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 3.49 (s, 3H, -OCH_3), 4.8 (s, 1H, C_4-H), 7.5-8.15 (m, 4H, Ar-H), 8.75 (s, 1H, -NH-), 9.4 (br, 3H, -NH_2 & HCl).

2,6-Dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-[N-(benzyloxy)amino]-5-carboxylic acid 3-methyl ester, 6d

A mixture of 2,6-dimethyl-4-(3′-nitrophenyl)-3-methoxylaminocarbonyl-1,4-dihydropyridine carboxylic acid methyl ester (**3b**, 5 g, 13.7 mmole) and benzyl alcohol (30 m*l*) was degassed with He gas for 30 min and then charged with N_2 gas. The reaction solution was heated to 120-130℃ for 5 hrs. After the solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic layer was separated and washed with d-HCl, water and brine, and then dried with sodium sulfate. The solvent was evaporated and the residue was applied to silica gel column [EtOAc : *n*-Hexane (1 : 1 v/v)]. The elute was evaporated *in vacuo* and the residue was recrystallized from ethanol (1.92 g, 32%).

mp. 199-201℃; Anal. calcd. for $C_{23}H_{23}N_3O_6$: C 63.15, H 5.30, N 9.61. Found: C 63.07, H 5.43, N 9.85: ^{1}H-NMR (DMSO-d_6): δ 1.68 (s, 3H, -CH_3), 2.24 (s, 3H, -CH_3), 3.40 (s, 3H, -OCH_3), 4.76 (s, 1H, C_4-H), 4.96 (s, 2H, -OCH_2-), 7.18-8.01 (m, 9H, Ar-H), 7.92 (s, 1H, -NH-), 8.22 (s, 1H, -NH): IR (KBr) cm^{-1}: 3319 (NH), 1695 (C=0).

2,6-Dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3-amino-5-caboxylic acid 5-methyl ester hydrobromide, 11

2,6-dimethyl-4-(3′-nitrophenyl)-3-[N-(benzyloxycarbonyl) amino]-1,4-dihydropyridine-5-carboxylic acid methyl ester (**6d**, 0.87 g, 2 mmol) was dissolved in 30% HBr in acetic acid solution (5 m*l*) and the mixture was stirred for 5 hrs. The reaction solution was diluted with ethyl ether (50 m*l*) to precipitate reddish yellow solid. The solid was recrystallized from acetonitrile to afford yellow solid (0.42 g, 54.7 %).

mp. 150-152℃; ^{1}H-NMR (DMSO-d_6): δ 1.92 (s, 3H, -CH_3), 2.26 (s, 3H, -CH_3), 3. 49 (s, 3H, -OCH_3), 4.76 (s, 1H, C_4-H), 7.63-8.13 (m, 4H, Ar-H), 8.73 (s, 1H, -NH-), 9.01 (br, 3H, -NH_2 & HBr): IR (KBr) cm^{-1}: 3266 (NH), 1731 & 1667 (C=0).

Hydrolysis of 3-amino-1,4-dihydropyridine compound 11 in water

2,6-dimethyl-4-(3′-nitrophenyl)-3-amino-5-carboxylic acid methyl ester hydrobromide (11, 60 mg, 1.56 mmole) was stirred in water (5 m*l*). After two hours, the reaction mixture was partitioned between EtOAc and saturated sodium bicarbonate solution. The orgainic layer was separated and washed with water and brine, and then treated with activated carbon and anhydrous sodium sulfate overnight. After filtration, the filtrate was evaporated and the residue was applied to Low pressure L. C. [silicagal column, EtOAc : *n*-Hexane : EtOH = 10 : 10 : 1 (v/v)] to give 150 mg of 3-hydroxypyridine compound **11** and 30 mg of 3-aminopyridine compound **4**.

ACKNOWLEDGEMENT

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