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Magnesium Ion Assisted Highly Regio- and Chemoselective Reduction of 5*H*-Pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-diones with Sodium Borohydride. A Convenient Synthesis of 6,7-Dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones

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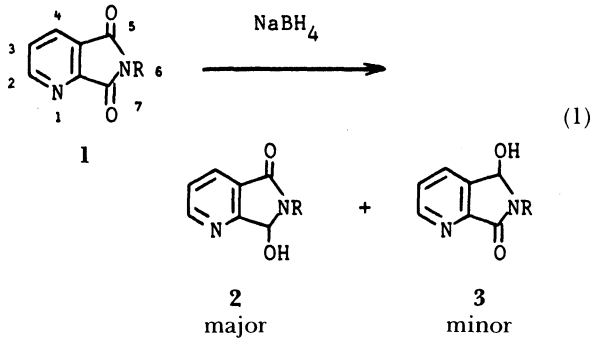
6-Substituted and unsubstituted 6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones were predominantly obtained in excellent yield by the reduction of the corresponding 5,7-diones with sodium borohydride in the presence of Mg ion at 0 °C. The highly regioselective production of the 7-hydroxy lactam in preference to the 5-hydroxy isomer was reasonably interpreted in terms of a chelate complex formation between the dione and Mg ion. The regioisomeric assignment was achieved by the transformation of the 7-hydroxy lactam to 2-(hydroxymethyl)-3-pyridinecarboxamides which could be converted to the known azaphthalide, furo[3,4-*b*]-pyridin-5(7*H*)-one. Furthermore, the high chemoselectivity was found to be retained below 0 °C to give the partial reduction product, hydroxy lactam, exclusively.

The partial reduction of 6-substituted 5*H*-pyrrolo-[3,4-*b*]pyridine-5,7(6*H*)-diones (quinolinimides **1**) with sodium borohydride ($NaBH_4$) has been known to produce 6-substituted 6,7-dihydro-7-hydroxy-5*H*-pyrrolo-[3,4-*b*]pyridin-5-ones (**2**) along with the corresponding 5-hydroxy-7-oxo isomers (**3**).[1—3] Recent attention has been directed to these hydroxy lactams as precursors to pharmacologically active compounds[1,2] or to aza analogs of fused heterocyclic systems.[3] The partial $NaBH_4$-reduction of cyclic imides, which involve alicyclics[4] and aromatics,[5] to the corresponding hydroxy lactams has been well investigated. However, in the case of the unsymmetrical imide **1**, the study on the control of the regioselectivity as well as the chemoselectivity of the reduction is scanty. We previously reported[6] that the chemoselectivity of the $NaBH_4$-reduction of *N*-unsubstituted quinolinimide (**1a**) could be thermally controlled; the partial reduction to the corresponding hydroxy lactams **2a** and **3a** was effected at −20 °C. In contrast, the regioselectivity of the reduction was unsatisfactory (**2a**:**3a**=3:1). Therefore, we turned our attention to improving the regioselectivity and expanding the scope of this method to the synthesis of *N*-substituted hydroxy lactams. Eventually, we found that the addition of Mg ion lead to the highly regioselective $NaBH_4$-reduction of *N*-substituted and *N*-unsubstituted quinolinimides (**1a—g**) to the corresponding hydroxy lactams **2a—g**. In this paper, we wish to describe the detail of this selective reduction.

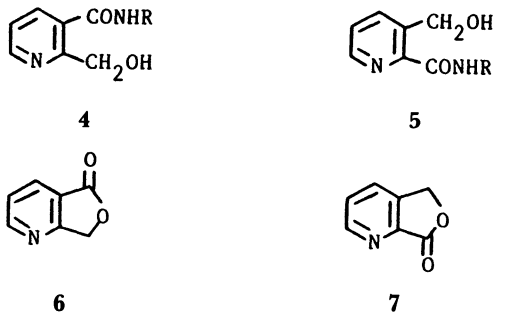


1 → **2** major + **3** minor (1)

a: R = H **e**: R = CH_2Ph
b: R = Me **f**: R = Ph
c: R = Et **g**: R = *p*-MePh
d: R = *i*-Pr

Results and Discussion

First of all, the $NaBH_4$-reduction of *N*-unsubstituted quinolinimide (**1a**) to the hydroxy lactam **2a** and **3a** was examined under the various reaction conditions as shown in Table 1. A mixed solvent (MeOH-$CHCl_3$ (1:1 (v/v)) was principally employed for the reduction because of the relatively high solubility of the substrate **1a**. Although the reduction also proceeded in MeOH uneventfully, the degree of regioselectivity was diminished (Runs 1 and 2). We could not find any merit at a lowered temperature (−40 °C, Run 3), while at an elevated temperature (0 °C), the over-reduction took place to give 3-(hydroxymethyl)-2-pyridinecarboxamide (**5a**) as a by-product (Run 4). In our further efforts to find the reaction conditions for high degree of regioselectivity, we reasoned that the formation of a chelate complex, in which the 1-nitrogen atom and the oxygen atom of 7-carbonyl group of imide **1** coordinate to



4 **5**

6 **7**

Chart 1. Over-reduction products.

Table 1. Partial $NaBH_4$-Reduction of *N*-Unsubstituted Quinolinimide (**1a**)[a]

Run	Solvent	React. temp/°C	$Mg(ClO_4)_2$ /mmol	Yield of **2a**+**3a**/%	Regioisomer ratio (**2a** : **3a**)[b]
1	MeOH-$CHCl_3$[c]	−20	None	93[d]	76 : 24
2	MeOH	−20	None	89[d]	66 : 34
3	MeOH-$CHCl_3$[c]	−40	None	77[d]	75 : 25
4	MeOH-$CHCl_3$[c]	0	None	69[d,f]	72 : 28
5	MeOH-$CHCl_3$[c]	−20	2	97[e]	>99 : 1
6	MeOH-$CHCl_3$[c]	0	2	95[e]	>99 : 1
7	MeOH-$CHCl_3$[c]	r.t.	2	70[e,g]	>99 : 1

a) **1a**, 1 mmol; $NaBH_4$, 1.5 mmol; solvent, 10 ml; reaction time, 30 min. b) Determined by ^1H NMR integration. c) MeOH : $CHCl_3$=1 : 1(v/v). d) Isolated by column chromatography. e) Isolated by continuous extraction with $CHCl_3$ for 4 d. f) **5a** was obtained as a by-product in 17% yield. g) **6** was obtained as a by-product in 21% yield.

Table 2. Partial $NaBH_4$-Reduction of *N*-Methylquinolinimide (**1b**)

Run[a]	Solvent	React. temp/°C	Metal salt (mmol)	Yield of **2b**+**3b**/%[e]	Regioisomer ratio (**2b** : **3b**)[b]
1[f]	MeOH-$CHCl_3$[c]	0	None	99	67 : 33
2	MeOH-$CHCl_3$[c]	0	$Mg(ClO_4)_2$(0.5)	93	87 : 13
3	MeOH-$CHCl_3$[c]	0	$Mg(ClO_4)_2$(1)	95	90 : 10
4	MeOH-$CHCl_3$[c]	0	$Mg(ClO_4)_2$(2)	99	94 : 6
5	MeOH-$CHCl_3$[c]	0	$Mg(ClO_4)_2$(3)	93	95 : 5
6	MeOH-$CHCl_3$[c]	−20	$Mg(ClO_4)_2$(2)	99	94 : 6
7	MeOH-$CHCl_3$[c]	−40	$Mg(ClO_4)_2$(2)	96	94 : 6
8[g]	MeOH-$CHCl_3$[c]	0	$Mg(ClO_4)_2$(20)	99	96 : 4
9	EtOH	0	$Mg(ClO_4)_2$(2)	96	90 : 10
10	MeCN	0	$Mg(ClO_4)_2$(2)	93	90 : 10
11[f]	MeOH-$CHCl_3$[c]	0	$LiClO_4$(2)	88	74 : 26
12	MeOH-$CHCl_3$[c]	0	$AgClO_4$(2)	34	74 : 26
13	MeOH-$CHCl_3$[c]	0	$Zn(ClO_4)_2$(2)	4	—[d]
14	EtOH	0	$Zn(ClO_4)_2$(2)	4	—[d]
15	MeCN	0	$Zn(ClO_4)_2$(2)	13	—[d]

a) **1b**, 1 mmol; $NaBH_4$, 2 mmol; solvent, 10 ml; reaction time, 15 min. b) Determined by ^1H NMR integration. c) MeOH : $CHCl_3$=1 : 1 (v/v). d) Not observed. e) Isolated by continuous extraction with $CHCl_3$ for 1 d. f) Reaction time, 30 min. g) 10-fold scale.

a metal ion, should activate the 7-carbonyl group in preference to the 5-carbonyl group for the reduction. Indeed, when magnesium perchlorate was added into the reduction system, ^1H NMR of the product indicated the predominant formation of 7-hydroxy lactam **2a**. Unfortunately, the hydroxy lactam **2a** could not be separated from the magnesium salt by usual methods because **2a** was less soluble in normal organic solvents such as chloroform. When a polar solvent such as methanol was employed as an eluent for column chromatography, a mixture of the hydroxy lactam and the magnesium salt was obtained. The similar problem also occurred in the case of using magnesium chloride instead of the perchlorate. This trouble could be avoided by "continuous extraction." Thus, the worked-up reaction mixture was continuously extracted with refluxing chloroform for 4 d to give the hydroxy lactam **2a** in an excellent yield (Run 5). Surprisingly, in the presence of Mg salt, the chemoselectivity was completely retained at 0 °C (Run 6). Even at r.t., the hydroxy lactam was obtained in 70% yield along with a minor over-reduction product (Run 7). It deserves emphasis that this result is a striking contrast to the reduction in the absence of Mg ion at r.t., in which the over-reduction products, 2-(hydroxymethyl)-3-pyridinecarboxamide (**4a**) and its regioisomer **5a** was produced exclusively.[6] In a word, Mg ion controlled not only the regioselectivity but also the chemoselectivity.

Encouraged by the success of this selective reduction, we turned to the synthesis of *N*-substituted hydroxy lactams. In order to obtain the best reaction conditions, *N*-methylquinolinimide (**1b**) was reduced under the various reaction conditions as shown in Table 2. The Mg ion was apparently effective for the highly regioselective reduction (Runs 1—4), and the degree of regioselectivity came to a maximum when two equivalents of Mg ion was used (Runs 4 and 5). On the other hand, lowered temperatures (−20 and −40 °C) did not influence the regioselectivity (Runs 6 and 7). This highly regioselective and chemoselective reduction could be also carried out in a synthetic scale (Run 8). The major regioisomer **2b** was readily available in the pure form by the recrystallization of the crude product obtained by the continuous extraction.

Although the minor product **3b** could not be isolated in the pure form, the formation of **3b** was confirmed by the conversion of **3b** to the over-reduction product, 3-(hydroxymethyl)-2-pyridinecarboxamide (**5b**). It should be noted that the present reduction was also successful in EtOH (Run 9) and MeCN (Run 10), since it has been reported that the partial reduction of cyclic imide required MeOH as a solvent[7] or an addition of acid in EtOH.[8] The univalent Li and Ag ions have no essential effect for the regioselectivity (Runs 11 and 12). This fact suggests the formation of a divalent metal ion chelate complex at the initial stage of the reaction (vide infra). Although an alternative divalent ion, Zn^{2+}, was expected the desirable effect as well as Mg^{2+}, the continuous extraction of the reaction mixture gave only low yield of the hydroxy lactam without any other products and recovered substrate (Run 13). Furthermore, we observed a similar unsuccessful result with $Zn(BH_4)_2$. The reasons for the unusual low yields in the presence of Zn ion as well as Ag ion (Run 12) are uncertain. It is likely that in the methanol-involved solvent, Zn or Ag ion accelerates the formation of hemiacetal or acetal of the imide, which inhibits the $NaBH_4$-reduction.[9] But, this possibility is ruled out because (i) we could not observe any products such as acetal before addition of $NaBH_4$ into the solution of the substrate and the metal salt, and (ii) similarly low yield was obtained with dry acetonitrile (Run 15). Hence, it is supposed that another pathway lead to a product which could not be obtained by the continuous extraction.

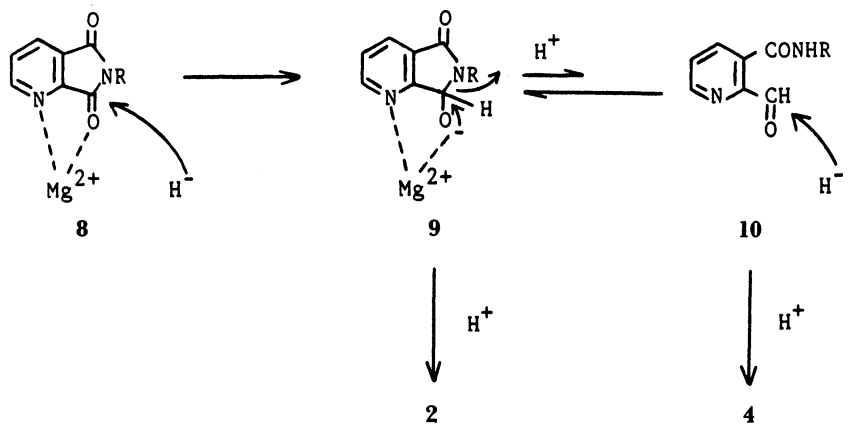
According to Speckamp and co-workers,[10] the present reduction will proceed through the pathways depicted in Scheme 1. As aforementioned, in the presence of Mg ion, a chelate complex **8** might be formed, and then 7-carbonyl group would be more strongly activated for the attack of a hydride ion in comparison with 5-carbonyl group. As the result, oxide anion **9** will be produced regioselectively. The formation of such a magnesium ion chelate on a pyrrolo[3,4-*b*]-pyridine[3] or furo[3,4-*b*]pyridine[11] ring has been suggested in the case of regioselective addition reactions of magnesium Grignard reagents. However, as far as we know, the present reaction is the first example of Mg ion assisted regioselective reduction on the pyrrolo-[3,4-*b*]pyridine ring. If the oxide anion **9** undergoes ring-cleavage to formyl amide **10**, the over-reduction will readily occur to afford the hydroxymethyl amide **4**. It is easily envisioned, however, that in the presence Mg ion, the oxide anion would be stabilized by the chelation, and the ring-cleavage might become an unfavorable pathway. Ultimately, direct protonation of **9** would afford the hydroxy lactam **2**. Thus, Mg ion precludes the over-reduction to improve the chemoselectivity as mentioned above. In the case of the reduction of *N*-methylquinolinimide (**1b**), the high chemoselectivity was retained at 0 °C even in the absence of Mg ion (Run 1, Table 2). This is not surprising when one considers that the methyl group is an electron-donating group, and the ring-cleavage of *N*-methylated **9** to **10** will be more unfavorable in comparison with *N*-unsubstituted one.

Since we have been able to optimize the reaction conditions, we applied this selective reduction to several *N*-alkylated and *N*-arylated quinolinimides (**1c—g**) in a synthetic scale to demonstrate the general synthetic utility of this method. As listed in Table 3, the

Table 3. Partial $NaBH_4$-Reduction of *N*-Substituted Quinolinimides (**1c—g**)[a]

Imide	*N*-Substituent	Yield of **2**+**3**/%	Regioisomer ratio (**2**:**3**)[b]
1c	Et	95[c]	96:4
1d	*i*-Pr	97[c]	98:2
1e	$PhCH_2$	96[d]	92:8
1f	Ph	92[d]	93:7
1g	*p*-MePh	96[d]	92:8

a) **1**, 10 mmol; $NaBH_4$ 20 mmol; $Mg(ClO_4)_2$, 20 mmol; solvent, MeOH-$CHCl_3$ (1:1 v/v 100 ml); reaction temperature, 0 °C; reaction time, 15 min. b) Determined by ^1H NMR integration. c) Isolated by continuous extraction for 1 d. d) Isolated by continuous extraction for 2 d.



Scheme 1.

reduction was smoothly effected in the presence of Mg ion to produce the corresponding hydroxy lactams **2c—g** in excellent yields with high degree of regioselectivity and chemoselectivity. Consequently, the present method is potentially fruitful for the synthesis of the 7-hydroxy lactam **2** because of excellent yield, high selectivity, simple manipulation, and easy availability of the substrate and reducing reagent.

Finally, we studied the assignment of the regioisomeric structure of **2b—g**. Although Hitchings and Vernon described the regioisomeric assignment of such a hydroxy lactam by ^{1}H NMR,[3] the directly definitive evidence has not been obtained. In our previous study,[6] the regioisomeric assignment of hydroxy lactams **2a** and **3a** has been clearly attained by transformation of **2a** and **3a** to the corresponding (hydroxymethyl)pyridinecarboxamides **4a** and **5a**, which could be converted to the known azaphthalides **6** and its regioisomer **7**, respectively. Because the (hydroxymethyl)pyridinecarboxamides **4** and **5** are key compounds to determine the regioisomeric structures, our initial attention was focused on the preparation of the over-reduction products, *N*-substituted (hydroxymethyl)pyridinecarboxamides **4b—g** and **5b—g** from the corresponding quinolinimide **1b—g** followed by the conversion to **6** and **7**, respectively. When *N*-methylquinolinimide (**1b**) was treated with $NaBH_4$ in MeOH-$CHCl_3$ at r.t. according to previous report,[6] the desired products **4b** and **5b** were produced in very low yield. After examining reaction conditions, the best result was obtained in EtOH at 50 °C for 1.5 h. These conditions could be applied with equal success to other *N*-substituted quinolinimides **1c—g** as shown in Table 4. Table 4 also exhibits that the hydrolysis and cyclization of the (hydroxymethyl)pyridinecarboxamide **4b—g** and **5b—g** smoothly proceeded in hot acidic methanol to give the known azaphthalides **6** and **7**, respectively. Consequently, we could assign the regioisomeric structures of **4** and **5**. Eventually, we carried out the reduction of aforementioned hydroxy lactams **2b—g** with $NaBH_4$ to confirm their regioisomeric structure. As listed in Table 5, the 2-(hydroxymethyl)-3-pyridinecarboxamides (**4b—g**) were obtained in moderate to good yields. From the synthetic point of view, it is noteworthy that the sequential combination of the two steps (**1**→**2**→**4**) amounts to a regioselective synthesis of *N*-substituted 2-(hydroxymethyl)-3-pyridinecarboxamides (**4**), which can be recognized as a precursor to nicotinamide derivatives bearing side chain on 2-position.

In summary, the present partial $NaBH_4$-reduction of quinolinimide **1** in the presence of Mg ion proceeded with high degree of regioselectivity and chemoselectivity. This procedure provides an attractive synthetic route to the 7-hydroxy lactam **2** as a useful synthetic precursor to biologically active compounds, whose isomeric structure can be clearly established by the conversion to the known azaphthalide **6** via (hydroxymethyl)pyridinecarboxamide **4**.

Table 4. Reduction[a] of *N*-Substituted Quinolinimides (**1b—g**) with $NaBH_4$ to **4b—g** and **5b—g**, and Transformation[b] of **4b—g** and **5b—g** to **6** and **7**

Imide	*N*-Substituent	Isolated yield/%			
		4	**5**	**6**	**7**
1b	Me	44	31	64	69
1c	Et	47	31	62	74
1d	*i*-Pr	43	31	70	72
1e	$PhCH_2$	41	31	71	67
1f	Ph	35	30	53	66
1g	*p*-MePh	32	31	64	71

a) **1**, 10 mmol; $NaBH_4$ 20 mmol; solvent, EtOH (100 ml); reaction temperature, 50 °C; reaction time, 1.5 h. b) 2 or 3, 1 mmol; reaction temperature 80 °C; reaction time, 2 d.

Table 5. Reduction of Hydroxy Lactams **2b—g** with $NaBH_4$ to **4b—g**[a]

Lactam	*N*-Substituent	Isolated yield of **4**/%
2b	Me	71
2c	Et	73
2d	*i*-Pr	67
2e	$PhCH_2$	58
2f	Ph	51
2g	*p*-MePh	48

a) **2**, 1 mol; $NaBH_4$, 2 mmol; solvent, EtOH (10 ml); reaction temperature, 50 °C; reaction time, 1 h.

Experimental

Measurements. Melting points were uncorrected. ^{1}H NMR spectra at 90 MHz were recorded with Hitachi R-22. IR spectra were recorded with Hitachi 295 and 260-50. Mass spectra were recorded with Hitachi RMU-6M and M-2000. Elemental analyses were determined with Yanagimoto MT-3.

Materials. Magnesium, zinc, and lithium perchlorate were dried over phosphorus pentachloride for 1 d under reduced pressure at 100 °C. Acetonitrile was dried over calcium hydride and distilled before use.

6-Substituted and Unsubstituted 5*H*-Pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (1a—g) were prepared according to a procedure in the literature.[12]

Partial $NaBH_4$-Reduction of 1. A representative procedure is described with **1a**: Into a solution of **1a** (0.148 g, 1 mmol) and $Mg(ClO_4)_2$ (0.446 g, 2 mmol) in MeOH-$CHCl_3$ (10 ml (1:1 v/v)) cooled at 0 °C under argon was added $NaBH_4$-powder (0.057 g, 1.5 mmol) with stirring. After 30 min, the reaction mixture was acidified with aqueous HCl approximately to pH 2. The resulting mixture was stirred for 10 min and basified with aqueous NaOH approximately to pH 11. After being warmed up to room temperature, the mixture was concentrated in vacuo until the evaporation of water began. This aqueous residue was continuously extracted with refluxing $CHCl_3$ for 4 d. The extract was concentrated in vacuo to give a colorless solid of **2a** (0.146 g, 97%).[6]

1b—g were reduced to **2b—g** with a similar procedure.

2b: Mp 146—147 °C (from MeCN); ^{1}H NMR ($CDCl_3$) δ= 3.14 (3H, s, CH_3), 5.84 (1H, s, H-7), 6.87 (1H, s, OH), 7.37 (1H, dd, J=8 and 5 Hz, H-3), 8.02 (1H, dd, J=8 and 3 Hz, H-4), and 8.57 (1H, dd, J=5 and 3 Hz, H-2); IR (KBr) 1710 (C=O) and 3070 (OH) cm^{-1}; MS (70 eV) m/z 164 (M^+); Found: C, 58.64; H, 4.90; N, 16.99%. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06%.

2c: Mp 153—154 °C (from MeCN); ^{1}H NMR ($CDCl_3$) δ= 1.30 (3H, t, J=8 Hz, CH_3), 3.3—4.0 (2H, m, CH_2), 5.99 (1H, s, H-7), 6.95 (1H, s, OH), 7.41 (1H, dd, J=8 and 5 Hz, H-3), 8.06 (1H, dd, J=8 and 2 Hz, H-4), and 8.60 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1670 (C=O) and 3150 (OH) cm^{-1}; MS (70 eV) m/z 178 (M^+); Found: C, 60.67; H, 5.65; N, 15.77%. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72%.

2d: Mp 169—170 °C (from MeCN); ^{1}H NMR ($CDCl_3$) δ= 1.50 (6H, d, J=7 Hz, CH_3×2), 4.46 (1H, quint, J=7 Hz , CH), 6.10 (1H, d, J=8 Hz, H-7), 6.75 (1H, d, J=8 Hz, OH), 7.42 (1H, dd, J=8 and 5 Hz, H-3), 8.06 (1H, dd, J=8 and 2 Hz, H-4), and 8.62 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1660 (C=O) and 3150 (OH) cm^{-1}; MS (70 eV) m/z 192 (M^+); Found: C, 62.45; H, 6.31; N, 14.78%. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57%.

2e: Mp 192—193 °C (from EtOH); ^{1}H NMR (DMSO-d_6) δ=4.41 and 4.96 (2H, d+d, J_{gem}=16 Hz, $PhCH_2$), 5.65 (1H, d, J=9 Hz, H-7), 6.93 (1H, d, J=9 Hz, OH), 7.2—7.4 (5H, m, arom), 7.50 (1H, dd, J=8 and 5 Hz, H-3), 8.10 (1H, dd, J=8 and 2 Hz, H-4), and 8.77 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1650 (C=O) and 3170 (OH) cm^{-1}; MS (70 eV) m/z 240 (M^+); Found: C, 70.07; H, 4.97; N, 11.73%. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%.

2f: Mp 209—210 °C (from MeOH); ^{1}H NMR (DMSO-d_6) δ=6.44 (1H, d, J=10 Hz, H-7), 7.00 (1H, d, J=10 Hz, OH), 7.1—7.9 (6H, m, arom+H-3), 8.14 (1H, dd, J=8 and 2 Hz, H-4), and 8.83 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1700 (C=O) and 3150 (OH) cm^{-1}; MS (70 eV) m/z 226 (M^+); Found: C, 69.24; H, 4.40; N, 12.52%. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38%.

2g: Mp 216—218 °C (from MeOH); ^{1}H NMR (DMSO-d_6) δ=2.30 (3H, s, CH_3), 6.40 (1H, d, J=10 Hz, H-7), 6.99 (1H, d, J=10 Hz, OH), 7.22 (2H, d, J=9 Hz, arom), 7.58 (1H, dd, J=8 and 5 Hz, H-3), 7.66 (2H, d, J=9 Hz, arom), 8.13 (1H, dd, J=8 and 2 Hz, H-4), and 8.82 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1710 (C=O) and 3100 (OH) cm^{-1}; MS (70 eV) m/z 240 (M^+); Found: C, 70.15; H, 5.09; N, 11.55%. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%.

***N*-Substituted 2-(Hydroxymethyl)-3-pyridinecarboxamides (4b—g) and 3-(Hydroxymethyl)-2-pyridinecarboxamides (5b—g) by the Reduction of 1b—g with $NaBH_4$.** As a general procedure, into a solution of **1** (10 mmol) in EtOH (100 ml) was added $NaBH_4$-powder (20 mmol) at room temperature. After 15 min, the solution was heated at 50 °C for 1.5 h. The reaction mixture was cooled to room temperature and acidified with aqueous HCl approximately to pH 2. The resulting mixture was stirred for 5 min and basified with aqueous NaOH approximately to pH 9. The evaporation of the solvent in vacuo gave a solid which was extracted with hot ethanol (30 ml×4). The combined extracts were concentrated in vacuo to give the mixture of **4** and **5**. When the crude product was chromatographed (silica gel, MeOH-$CHCl_3$ (1 : 10 v/v)), **5** was obtained from the first fraction. The second fraction gave **4**.

4b: Mp 88—89 °C (from MeCN); ^{1}H NMR ($CDCl_3$) δ= 2.94 (3H, d, J=5 Hz, CH_3), 4.78 (2H, d, J=5 Hz, CH_2O), 5.39 (1H, t, J=5 Hz, OH), 7.23 (1H, dd, J=9 and 5 Hz, H-5), 7.60 (1H, br s, NH), 7.89 (1H, dd, J=9 and 2 Hz, H-4), and 8.50 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1630 (C=O) and 3250 (NH and OH) cm^{-1} ; MS (70 eV) m/z 166 (M^+); Found: C, 57.96; H, 6.06; N, 16.89%. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07, N, 16.86%.

5b: Mp 58—59 °C (from Et_2O); ^{1}H NMR ($CDCl_3$) δ=3.00 (3H, d, J=5 Hz, CH_3), 4.81 (2H, d, J=8 Hz, CH_2O), 5.29 (1H, t, J=8 Hz, OH), 7.34 (1H, dd, J=9 and 5 Hz, H-5), 7.75 (1H, dd, J=9 and 2 Hz, H-4), and 8.45 (2H, dd+br s, J=5 and 2 Hz, H-6 and NH); IR (KBr) 1650 (C=O) and 3230 (NH and OH) cm^{-1}; MS (70 eV) m/z 166 (M^+); Found: C, 57.91; H, 6.07; N, 16.79%. Calcd for $C_8H_{10}H_2O_2$: C, 57.82; H, 6.07, N, 16.86%.

4c: Mp 76—77 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ= 1.23 (3H, t, J=7 Hz, CH_3), 3.3—3.6 (2H, m, CH_2), 4.81 (2H, s, CH_2O), 5.25 (1H, br s, OH), 7.24 (2H, dd+br s, J=8 and 5 Hz, H-5 and NH), 7.88 (1H, dd, 8 and 2 Hz, H-4), and 8.50 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1640 (C=O) and 3280 (NH and OH) cm^{-1}; MS (70 eV) m/z 180 (M^+); Found: C, 59.99; H, 6.73; N, 15.53%. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55%.

5c: Mp 32—34 °C (from Et_2O); ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, t, J=8 Hz, CH_3), 3.4—3.7 (2H, m, CH_2), 4.82 (2H, d, J=8 Hz, CH_2O), 5.32 (1H, t, J=8 Hz, OH), 7.36 (1H, dd, J=8 and 5 Hz, H-5), 7.73 (1H, dd, J=8 and 2 Hz, H-4), and 8.46 (2H, dd+br s, J=5 and 2 Hz, H-6 and NH); IR (KBr) 1660 (C=O) and 3340 (NH and OH) cm^{-1}; MS (70 eV) m/z 180 (M^+); Found: C, 57.90; H, 6.70; N, 15.48%. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55%.

4d: Mp 86—87 °C (from AcOEt);^{1}H NMR ($CDCl_3$) δ=1.24 (6H, d, J=7 Hz, CH_3×2), 4.0—4.4 (1H, m, CH), 4.74 (2H, d, J=6 Hz, CH_2O), 5.41 (1H, t, J=6 Hz, OH), 7.17 (1H, dd, J=9 and 5 Hz, H-5), 7.35 (1H, br s, NH), 7.83 (1H, dd, J=9 and 2 Hz, H-4), and 8.43 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1650 (C=O) and 3370 (NH and OH) cm^{-1}; MS (70 eV) m/z 194 (M^+); Found: C, 61.92; H, 7.36; N, 14.57%. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42%.

5d: Mp 40—41 °C (from Et_2O-hexane); ^{1}H NMR ($CDCl_3$) δ=1.29 (6H, d, J=7 Hz, CH_3×2), 4.1—4.4 (1H, m, CH), 4.81 (2H, d, J=8 Hz, CH_2O), 5.35 (1H, t, J=8 Hz, OH), 7.37 (1H, dd, J=9 and 5 Hz, H-5), 7.73 (1H, dd, J=9 and 2 Hz, H-4), 8.17 (1H, br s, NH), and 8.46 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1640 (C=O), 3420 and 3280 (NH and OH) cm^{-1}; MS (70 eV) m/z 194 (M^+); Found: C, 61.92; H, 7.33; N, 14.47%. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42%.

4e: Mp 79—80 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ= 4.52 (2H, d, J=7 Hz, CH_2Ph), 4.74 (1H, s, CH_2O), 5.15 (1H, br s, OH), 7.1—7.3 (6H, m, arom+H-5), 7.82 (2H, dd+br s, J=9 and 2 Hz, H-4 and NH), and 8.42 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1660 (C=O) and 3250 (NH and OH) cm^{-1}; MS (70 eV) m/z 242 (M^+); Found: C, 69.46; H, 5.81; N, 11.53%. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82, N, 11.56%.

5e: Mp 65—66 °C (from Et_2O); ^{1}H NMR ($CDCl_3$) δ=4.63 (2H, d, J=6 Hz, CH_2Ph), 4.83 (2H, d, J=8 Hz, CH_2O), 5.19 (1H, t, J=8 Hz, OH), 7.2—7.4 (6H, m, arom+H-5), 7.73 (1H, dd, J=8 and 3 Hz, H-4), 8.42 (1H, dd, J=5 and 3 Hz, H-6) and 8.66 (1H, br s, NH); IR (KBr) 1650 (C=O), 3340 and 3430(NH and OH) cm^{-1}; MS (70 eV) m/z 242 (M^+); Found: C, 69.38; H, 5.81; N, 11.52%. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%.

4f: Mp 118—120 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ= 4.86 (2H, s, CH_2O), 5.39 (1H, br s, OH), 7.0—7.7 (7H, m, H-5+arom+NH), 8.04 (1H, dd, J=8 and 2 Hz, H-4), and 8.48

(1H, dd, J=6 and 2 Hz, H-6); IR (KBr) 1660 (C=O) and 3280 (NH and OH) cm^{-1}; MS (70 eV) m/z 228 (M^+); Found: C, 68.40; H, 5.28; N, 12.20%. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30, N, 12.27%.

5f: Mp 108—109 °C (from AcOEt); ^1H NMR ($CDCl_3$) δ= 4.90 (3H, s, CH_2O+OH), 7.1—7.8 (7H, m, H-5,+arom+NH), 7.82 (1H, dd, J=9 and 2 Hz, H-4), and 8.53 (1H, dd, J=9 and 2 Hz, H-6); IR (KBr) 1680 (C=O), 3320 and 3500 (NH and OH) cm^{-1}; MS (70 eV) m/z 228 (M^+); Found: C, 68.30; H, 5.25; N, 12.27%. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30, N, 12.27%.

4g: Mp 155—156 °C (from AcOEt); ^1H NMR (DMSO-d_6) δ=2.27 (3H, s, CH_3), 4.75 (2H, d, J=6 Hz, CH_2O), 5.30 (1H, t, J=6 Hz, OH), 7.15 (2H, d, J=8 Hz, arom), 7.42 (1H, dd, J=8 and 5 Hz, H-5), 7.61 (3H, d, J=8 Hz, arom+NH), 7.96 (1H, dd, J=8 and 2 Hz, H-4), and 8.60 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1650 (C=O) and 3280 (NH and OH) cm^{-1}; MS (70 eV) m/z 242 (M^+); Found: C, 69.54; H, 5.78; N, 11.50%. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%.

5g: Mp 117—118 °C (from AcOEt). ^1H NMR (DMSO-d_6) δ=2.27 (3H, s, CH_3), 4.97 (2H, d, J=6 Hz, CH_2O), 5.34 (1H, t, J=6 Hz, OH), 7.12 (2H, d, J=8 Hz, arom), 7.59 (1H, dd, J=8 and 5 Hz, H-5), 7.70 (3H, d, J=8 Hz, arom+NH), 8.17 (1H, dd, J=8 and 3 Hz, H-4), and 8.53 (1H, dd, J=5 and 3 Hz, H-6); IR (KBr) 1670 (C=O) and 3320 (NH and OH) cm^{-1}; MS eV) m/z 242 (M^+); Found: C, 69.28; H, 5.78;N, 11.61%. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82, N, 11.56%.

Starting with **2b—g**, a similar procedure gave **4b—g**, respectively.

Furo[3,4-*b*]pyridin-5(7*H*)-one(6) and Furo[3,4-*b*]pyridin-7(5*H*)-one(7). As a general procedure, a solution of **4** or **5** (1 mmol) in MeOH (5 ml) added HCl (1 mol dm^{-3}, 5 ml) was heated at 80 °C for 2 d. The reaction mixture was neutralized with aqueous NaOH and concentrated in vacuo. After the residue was extracted with $CHCl_3$ (10 ml×5), the combined extracts were washed with water, dried over Na_2SO_4, and concentrated in vacuo to afford spectroscopically pure **6** or **7**.[13]

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