The Thermally-Controlled Chemoselective Reduction of 5*H*-Pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione with Sodium Borohydride

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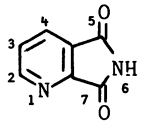
Synopsis. The title reaction produced either 2-(hydroxymethyl)nicotinamide or 6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-one as the major product at room temperature or −20 °C, respectively, along with the corresponding regioisomers as minor products. These novel compounds were converted to known compounds in order to establish their isomeric structures.

Although the reduction of phthalimide with metal borohydride to 2-(hydroxymethyl)benzamide or 2,3-dihydro-3-hydroxy-1*H*-isoindol-1-one has been well-known,[1] there has been few studies on the application of this reduction to the aza-analogs, for instance 5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione(quinolinimide **1**). Recently, Cotrel et al.[2] have reported in a patent the reduction of 6-substituted quinolinimides with potassium borohydride to 6-substituted 6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-one and the corresponding 5-hydroxy-7-oxo isomer in low yields, which were transformed to pharmacologically active compounds. The isomeric structures and the spectroscopic characterizations of these isomers, however, have not been established. In conjunction with our ongoing studies on the synthesis of 2,3-dihydro-3-(substituted amino)-1*H*-isoindol-1-ones[3a] and their 2-alkyl derivatives[3b] of which the anti-inflammatory activity has been observed,[4] our attention has been focused on the synthesis of their aza-analogs. First, we envisioned the synthesis of 6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**2**) by the reduction of quinolinimide (**1**) with sodium borohydride ($NaBH_4$) because of the easy availability of both the substrate and the reducing agent, and the feasibility of converting the hydroxyl group to various functional groups. Surprisingly, there has been no report on **2** and the corresponding regioisomer **3** in the literature to our knowledges. We wish to report in this paper the temperature-controlled chemoselective reduction of quinolinimide (**1**) with $NaBH_4$ to give the mixture either of **2** and **3** at −20 °C, or of 2-(hydroxymethyl)nicotinamide (**4**) and 3-hydroxymethyl-2-pyridinecarboxamide (**5**) at ambient temperature. The present reaction provides a convenient method for the synthesis of the novel heterocycle **2** or **4**, both of which can be easily separated from the corresponding minor regioisomer **3** or **5**.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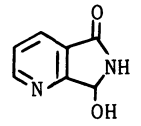
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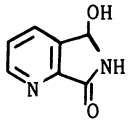
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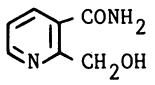
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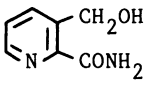
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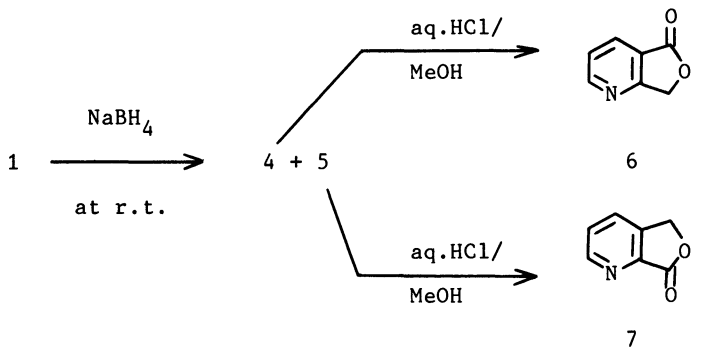
Results and Discussion

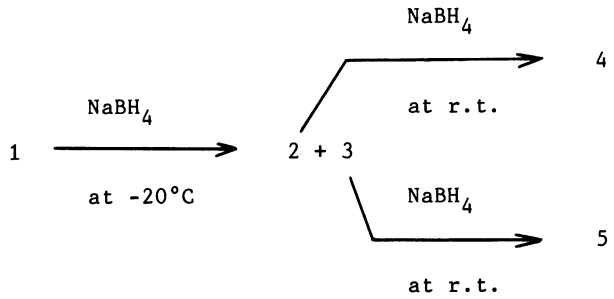
Reduction at Room Temperature. Quinolinimide (**1**) was smoothly reduced with an excess amount of $NaBH_4$ in methanol–chloroform (1 : 1 v/v) to yield two products which exhibited much different chromatographic behaviors on TLC. After the usual work-up, these components were easily separated on a silica-gel column. The analytical data of these materials indicated either chemical structure **4** or **5**; however, we could not assign the isomeric structure of each hydroxymethylcarbamoylpyridine because of their very similar spectral character. Although a description of **5** could not be found in the literature, there was only one report as to the formation of **4** from furo[3,4-



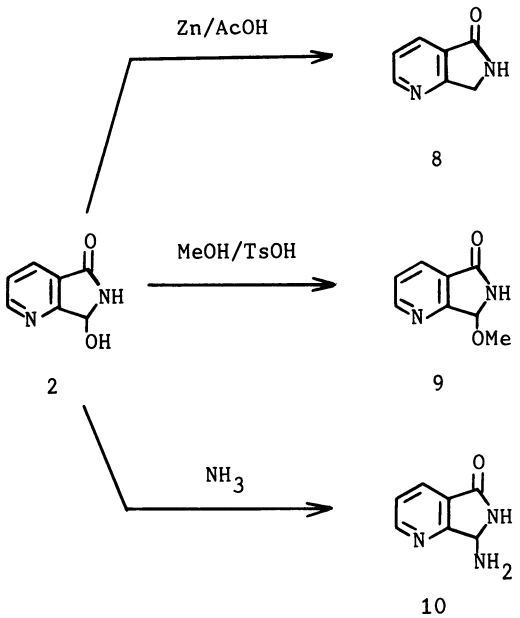
Scheme 1.

b]pyridin-5(7*H*)-one (**6**) with ammonia by Sato et al.[5] The melting point and IR spectra reported by them were identical with those of our sample of **4**. In order to obtain a further confirmation of the assignment, we achieved the transformations of **4** and **5** to the known azaphthalide **6** and **7**,[6] respectively (Scheme 1). Thus, **4** and **5** were smoothly hydrolyzed and cyclized in hot acidic methanol to produce **6** and **7** in 74 and 78% yield, respectively. Consequently, it was revealed that the yields of **4** and **5** were 50 and 23%, respectively, from quinolinimide (**1**). The moderate yield of **4** might be synthetically acceptable in view of the availability of the substrate **1** and reducing agent, and the simple, one-step procedure starting from **1**.

Reduction at −20 °C. The reduction of **1** with $NaBH_4$ also proceeded smoothly at −20 °C to lead a mixture involving two components, **2** and **3**, quantitatively. The ^1H NMR of the mixture showed that the ratio of **2** and **3** was 3:1; the cleanly chemoselective formation of **2** and **3** without the contamination of **4** and **5** was achieved. Fortunately, isomerically pure **2** was obtained by recrystallization of the mixture two times in a moderate yield (53%), in spite of the very similar chromatographic property of **2** and **3**. Isomerically pure **3** was obtained from the mother liquor after recrystallization only in very low yield. Since **2** and **3** were novel compounds, as far as we know, their chemical structures were determined by elemental analysis and spectral data. Isomeric assignments were easily achieved by the transformation of **2** and **3** to **4** and **5**, respectively, with $NaBH_4$ at room temperature in good yields (Scheme 2).



Scheme 2.



Scheme 3.

Since the hydroxy lactam **2** has been available in multigram scale through the procedure described above, we preliminarily tried to convert the hydroxyl group to other functional groups, as shown in Scheme 3. Thus, the reduction of **2** with zinc powder in acetic acid gave 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**8**)[7] in good yield (71%). The treatment of **2** with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid[8] afforded **9** in excellent yield (94%). Finally, the desired 7-amino derivative **10** was obtained by the amination of **2** with liquid ammonia in high yield (83%). The chemical structures of these novel compounds, **9** and **10**, were confirmed by elemental analysis and spectral data.

In summary, we achieved the chemoselective synthesis of either **2** or **4**, along with **3** or **5**, which are interesting intermediates for the synthesis of some biologically active compounds, and some of their fundamental derivations. Further applications of these compounds will soon be reported elsewhere.

Experimental

Melting points were uncorrected. NMR, IR, and mass spectra were recorded with HITACH R-22, HITACH 295, and HITACH RUM-6M, respectively. Elemental analyses were determined with YANAGIMOTO MT-3.

5*H*-Pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (1) was prepared from commercially available 2,3-pyridinedicarboxylic acid and acetamide according to a procedure in a literature.[7]

6,7-Dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (2) and 5,6-Dihydro-5-hydroxy-7*H*-pyrrolo[3,4-*b*]pyridin-7-one (3) by the Reduction of 1 with $NaBH_4$. Into a solution of **1** (2.96 g, 20 mmol) in 200 ml of methanol–chloroform (1:1 v/v) cooled at −20 °C under agron was added $NaBH_4$-powder (1.13 g, 30 mmol). After 30 min, the reaction mixture was acidified with aqueous HCl approximately to pH 3. The resulting mixture was stirred for 10 min and basified with aqueous NaOH approximately to pH 9. Throughout the procedure the reaction mixture was kept at about −20 °C. After being warmed up to room temperature, the mixture was concentrated in vacuo to give a solid. This material was purified over a short silica-gel column (methanol–chloroform, 1:5 v/v) to give the mixture of **2** and **3** (2.9 g, 96%). The mixture was recrystallized from ethanol two times to give isomerically pure **2** as white crystals (1.59 g, 53%): mp 201 °C (decomp); ^1H NMR (DMSO-d_6) δ=5.82 (1H, d, J=9 Hz, H-7), 6.49 (1H, d, J=9 Hz, OH), 7.50 (1H, dd, J=7 and 5 Hz, H-3), 8.03 (1H, dd, J=7 and 2 Hz, H-4), 8.75 (1H, dd, J=5 and 2 Hz, H-2), and 9.04 (1H, br s, NH); IR (KBr) 1740 (C=O), 3000 and 3270 (NH and OH) cm^{-1}; MS (70 eV) m/z 150 (M^+); Found: C, 56.39; H, 4.08; N, 18.72%. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66%.

The solid residue (1.05 g) from the mother liquor was triturated in hot methanol–chloroform (1:5 v/v, 30 ml) for 1 h. Then, the unsoluble material was filtered, washed with the same solvent, and recrystallized from methanol–ether to give isomerically pure **3** as white crystals (0.23 g). Decomp

185 °C; ^{1}H NMR (DMSO-d_6) δ=5.94 (1H, d, J=9 Hz, H-5), 6.53 (1H, d, J=9 Hz, OH), 7.57 (1H, dd, J=9 and 6 Hz, H-3), 8.01 (1H, dd, J=9 and 2 Hz, H-4), 8.74 (1H, dd, J=6 and 2 Hz, H-2), and 9.24 (1H, br s, NH); IR (KBr) 1710 (C=O), 3230 (NH and OH) cm^{-1}; MS (70 eV) m/z 150 (M^+); Found: C, 56.35; H, 4.02; N, 18.41%. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66%.

2-(Hydroxymethyl)nicotinamide (4) and 3-Hydroxymethyl-2-pyridinecarboxamide (5) by the Reduction of 1. Compound **1** (1.48 g, 10 mmol) in 100 ml of methanol–chloroform (1 : 1 v/v) was reduced with $NaBH_4$ (0.76 g, 20 mmol) at room temperature (about 20 °C) for 1 h by a procedure similar to that described above. When the crude product was chromatographed (silica gel, MeOH–$CHCl_3$ (1 : 5 v/v)), **5** was obtained from the first fraction as white crystals (0.36 g, 23%): mp 154 °C (from ethanol); ^{1}H NMR (DMSO-d_6) δ=4.89 (2H, d, J=6 Hz, CH_2), 5.31 (1H, t, J=5 Hz, OH), 7.50 (1H, br s, NH), 7.54 (1H, dd, J=9 and 5 Hz, H-5), 8.02 (1H, br s, NH), 8.10 (1H, dd, J=9 and 1 Hz, H-4), and 8.46 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1710 (C=O), 3100 and 3350 (NH and OH) cm^{-1}; MS (70 eV) m/z 152 (M^+); Found: C, 55.54; H, 5.28; N, 18.45%. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41%.

The second fraction gave **4** (0.76 g, 50%) as white crystals: mp 148 °C (from ethanol, lit,[5] 146—147 °C); ^{1}H NMR (DMSO-d_6) δ=4.68 (2H, d, J=5 Hz, CH_2), 5.22 (1H, t, J=5 Hz, OH), 7.35 (1H, dd, J=8 and 5 Hz, H-5), 7.58 (1H, br s, NH), 7.89 (1H, dd, J=8 and 2 Hz, H-4), 8.00 (1H, br s, NH), and 8.54 (1H, dd, J=5 and 2 Hz, H-6); IR (KBr) 1640, 1680 (C=O), 3150 and 3340 (NH and OH) cm^{-1}; MS (70 eV) m/z 152 (M^+); Found: C, 55.04; H, 5.26; N, 18.49%. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41%.

Starting with **2** or **3** (0.15 g, 1 mmol), a similar reduction gave the same products, **4** or **5**, in 78 or 99% yield, respectively.

Furo[3,4-*b*]pyridin-5(7*H*)-one (6). Into a solution of **4** (0.46 g, 3 mmol) in 15 ml of methanol was added 6 ml of concd HCl and the mixture was heated at 80 °C for 1.5 h. The reaction mixture was neutralized with aqueous NaOH, and concentrated in vacuo. After the residue was extracted with chloroform (10 ml×3), the combined extracts were washed with water, dried with sodium sulfate, and concentrated in vacuo to afford spectroscopically pure **6** (0.30 g, 74%) as white crystals (mp 144 °C, from chloroform–hexane, lit,[6] 142 °C; Found: C, 62.46; H, 3.71; N, 10.39%. Calcd for $C_7H_5NO_2$: C, 62.22, H, 3.73, N, 10.37%).

Furo[3,4-*b*]pyridin-7(5*H*)-one (7) was obtained from **5** with the same procedure for **6** in 72% yield as white crystals (mp 164 °C, from chloroform–ether, lit,[6b] 162 °C; Found: C, 62.40; H, 3.69; N, 10.37%. Calcd for $C_7H_5NO_2$: C, 62.22, H, 3.73, N, 10.37%).

6,7-Dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (8) was obtained from **2** with zinc powder in acetic acid according to von Dobeneck's procedure[7] in 71% yield as white crystals (mp 204 °C, from ethanol, lit,[7] 204—206 °C; ^{1}H NMR (DMSO-d_6) δ=4.44 (2H, s, H-7), 7.50 (1H, dd, J=8 and 5 Hz, H-3), 8.10 (1H, dd, J=8 and 2 Hz, H-4), and 8.75 (2H, dd+br s, J=5 and 2 Hz, H-2+NH).

6,7-Dihydro-7-methoxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (9). A solution of **2** (1.50 g, 10 mmol) and *p*-toluenesulfonic acid (0.04 g, 0.2 mmol) in 50 ml of methanol was refluxed for 24 h. After the reaction mixture was concentrated in vacuo, aqueous $NaHCO_3$ was added to the residue, and the resulting mixture was sufficiently extracted with chloroform. The combined organic layers were dried with sodium sulfate and concentrated in vacuo to give practically pure **9** (1.5 g, 94%) as white crystals: mp 150 °C (from chloroform–hexane); ^{1}H NMR (DMSO-d_6) δ=3.43 (3H, s, CH_3), 5.88 (1H, s, H-7), 7.46 (1H, dd, J=8 and 6 Hz, H-3), 8.10 (1H, br s, NH), 8.13 (1H, dd, J=8 and 2 Hz, H-4), and 8.79 (1H, dd, J=6 and 2 Hz, H-2); IR (KBr) 1720 (C=O), 3100 and 3180 (NH) cm^{-1}; MS (70 eV) m/z 164 (M^+); Found: C, 58.88; H, 4.91; N, 17.12%. Calcd for $C_8H_8N_2O_2$: C, 58.53; 4.91; N, 17.06%.

6,7-Dihydro-7-amino-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (10). A solution of **2** (0.30 g, 2 mmol) in 20 ml of liquid ammonia was heated in an autoclave at 110 °C for 48 h. After the evaporation of ammonia at room temperature, the residue was chromatographed over silica gel (methanol–chloroform, 1 : 5 v/v) to afford **10** (0.25 g, 83%) as white crystals: decomp 160 °C (from methanol); ^{1}H NMR (DMSO-d_6) δ=2.44 (2H, br s, NH_2), 5.32 (1H, s, H-7), 7.47 (1H, dd, J=8 and 5 Hz, H-3), 7.99 (1H, dd, J=8 and 2 Hz, H-4), and 8.72 (2H, dd+br s, J=5 and 2 Hz, H-2+NH); IR (KBr) 1720 (C=O) and 3160 (NH and NH_2) cm^{-1}; Found: C, 56.40; H, 4.74; N, 27.84%. Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17%.

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