Furopyridines. XXXI [1]. Birch Reduction of Furopyridines

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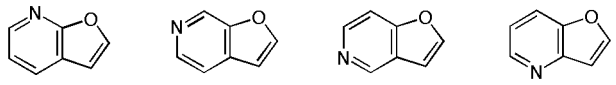
Received May 14, 2001

Birch reduction of four furopyridines **1a-d** effected the characteristic cleavage of the furan ring, giving ethnylpyridinols **2a-d**, vinylpyridinols **3b**,**d**, and ethylpyridinols **4a-d**, and the reduction of the furan ring, giving dihydrofuropyridine **5c,d**.

J. Heterocyclic Chem., **39**, 335 (2002).

Furopyridines have a fused structure containing both a π-excess furan ring and a π-poor pyridine ring, and so, being interested in their chemical properties, we have studied the synthesis and reactions of furopyridine derivatives [1-5]. In this paper we report the Birch reduction of four furopyridines **1a-d**.

Chart 1



1a **1b** **1c** **1d**

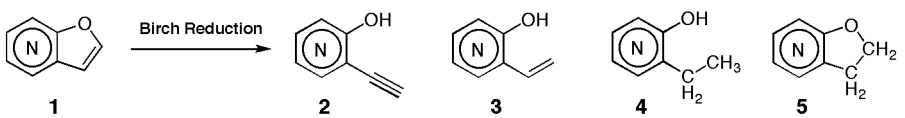
Birch reduction has been adopted for the reduction of aromatic systems, including some hetero-aromatic systems [6]. The reduction of some π-excess furans undergo a 1,4-reduction giving the corresponding 2,5-dihydrofurans. The reduction of π-poor pyridines undergo a 1,4-reduction, giving 1,4-dihydropyridines, or a cleavage of the pyridine ring, causing re-cyclization to give cyclohexenones.

Four furopyridines **1a-d** were subjected to Birch reduction using 3.3 equivalents of sodium metal in liquid ammonia [6], and the results are summarized in Table. As shown in Scheme 1, in the Birch reduction of furopyridines **1a-d**, very interestingly, all resulted in the specific cleavage of the furan ring giving a mixture of ethynylpyridinol **2**, vinylpyridinol **3**, and ethylpyridinol **4**. In the case of **1c** and **1d**, the reduction, giving dihydrofuropyridine **5c,d** was also observed.

Birch reduction of furo[2,3-*b*]pyridine (**1a**)[2] using 3.3 equivalents of sodium metal quantitatively gave two products, 3-ethynyl-2-pyridinol (**2a**) and 3-ethyl-2-pyridinol (**4a**) in the ratio of 1:2. Birch reduction of furo[3,2-*b*]pyridine (**1d**)[5] using 3.3 equivalents of sodium metal gave three products (in 88% total yield), 2-ethynyl-3-pyridinol (**2d**), 2-vinyl-3-pyridinol (**3d**), and 2-ethyl-3-pyridinol (**4d**) in the ratio of 1:2:3. Use of 1.8 equivalents of sodium metal gave four products (in 67% total yield), **2d**, **3d**, **4d**, and 2,3-dihydro[3,2-*b*]pyridine (**5d**) in the ratio of 3:4:4:1. These results suggested that the vinyl and the dihydro derivatives are the intermediates for further reduction. Birch reduction of furo[2,3-*c*]pyridine (**1b**)[3] using 3.3 equivalents of sodium metal gave three products (in 63% total yield), 4-ethynyl-3-pyridinol (**2b**), 4-vinyl-3-pyridinol (**3b**), and 4-ethyl-3-pyridinol (**4b**) in the ratio of 1:2:5. Birch reduction of furo[3,2-*c*]pyridine (**1c**)[4] using 3.3 equivalents of sodium metal also gave three products (in 50% total yield), 3-ethynyl-4-pyridinol (**2c**), 3-ethyl-4-pyridinol (**4c**), and 2,3-dihydrofuro[3,2-*c*]pyridine (**5c**) in the ratio of 1:6:2.

In all cases, the Birch reduction of furopyridine yielded ethynylpyridiols **2** and ethylpyridinols **4**. The former ethynylpyridinols **2** were not reduction products (valence-isomerized compounds), and the latter ethylpyridinols **4** might be doubly reduced compounds. As already reported, a similar cleavage giving the correspoinding ethynylpyridinols was observed in treating 3-bromofuropyridines with alkyl lithium [7]. This suggested that sodium amide, which might be generated *in situ*, may cause a similar cleavage. To clarify this, furo[2,3-*b*]pyridine **1a** was treated with sodium amide in liquid ammonia similarly, but most of the **1a** was recovered and no cleavage of the furan ring was observed. Vinylpyridinols **3** and ethylpyridinols **4** may be formed through the corresponding dihydrofuropyridine **5**. To clarify this, dihydrofuropyridines **5a,c**, prepared by a

Scheme 1



1 **2** **3** **4** **5**

catalytic hydrogenation of the corresponding furopyridines **1a,c** [8], were subjected to a similar Birch reduction. However, both showed quite different results [9].

Table

Birch Reduction of Furopyridines

Substrate	Na	Total Yield	Calculated Yield from Product Ratio [a]			
1			**2**	**3**	**4**	**5**
1a	3.3 eq	100%	**2a** (33%)	-	**4a** (66%)	-
1b	3.3 eq	63%	**2b** (8%)	**3b** (16%)	**4b** (39%)	-
1c	3.3 eq	50%	**2c** (6%)	-	**4c** (33%)	**5c** (11%)
1d	3.3 eq	88%	**2d** (15%)	**3d** (29%)	**4d** (44%)	-
1d	1.8 eq	67%	**2d** (17%)	**3d** (22%)	**4d** (32%)	**5d** (6%)

[a] Product ratios were determined by integration of the each signal in the pmr spectra of the crude mixture.

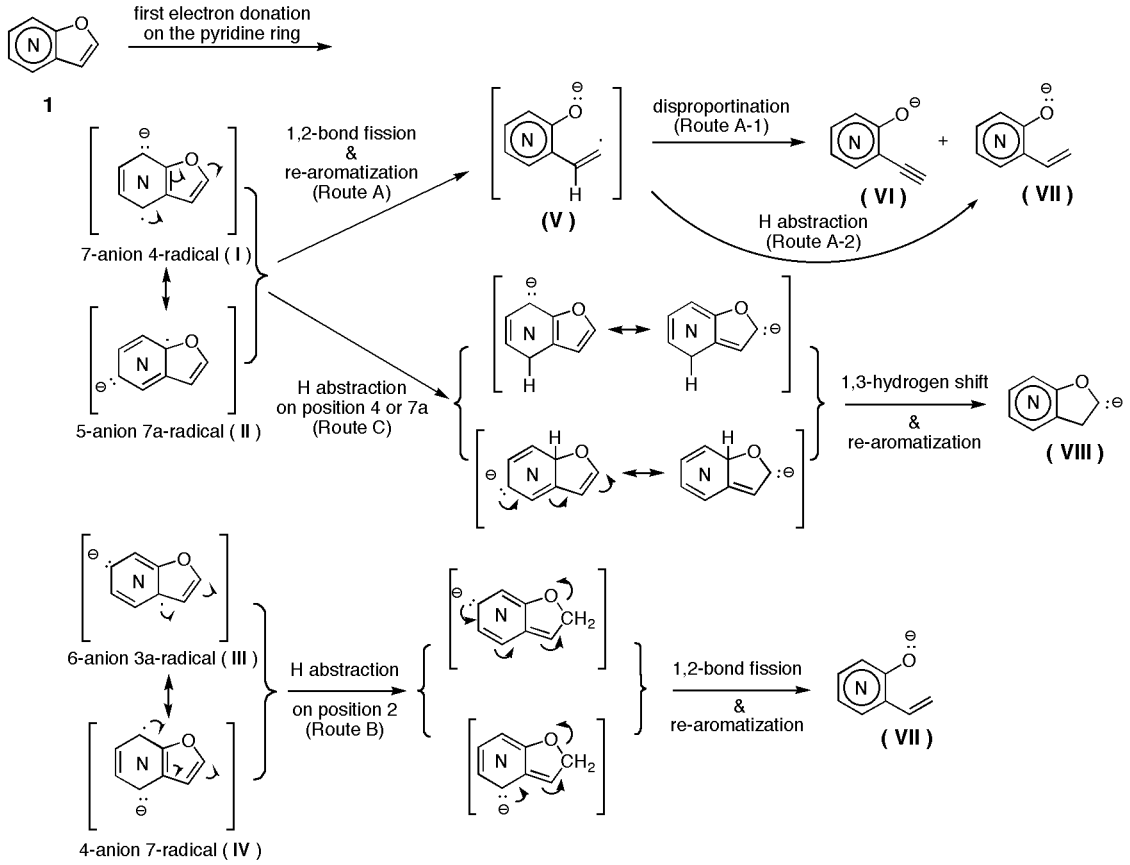
To explain these results, we propose the following mechanism shown in Scheme 2. Birch reduction of furopyridine would be caused by one-electron donation on the π-poor pyridine ring, and the formation of four 1,4-anion radicals; 7-anion 4-radical (**I**), 5-anion 7a-radical (**II**), 6-anion 3a-radical (**III**), and 4-anion 7-radical (**IV**), might be possible.

The radicals **I** and **II**, keeping the radical at position 4 or 7a, may cause a 1,2-bond fission following re-aromatization to give the corresponding *O*-anion vinyl radicals **V** (Route A) or a hydrogen abstraction following rearomatization (*via* 1,3-hydrogen shift) to give anion **VIII** (for giving the corresponding dihydrofuropyridines **5**). The vinyl radical **V** on Route A would cause two types of hydrogen abstraction; one is the abstraction from the homologous *O*-anion vinyl radical (**V**) (disproportionation), giving a couple of ethynylpyridinolate (**VI**) and vinylpyridinolate **VII** (Route A-1), and another is the abstraction from ammonia, giving vinylpyridinolate **VII** (Route A-2).

The radicals **III** and **IV**, keeping the radical at position 3a or 7, respectively, would cause the hydrogen abstraction at position 2 following the re-aromatization (*via* a 1,2-bond fission) to give the corresponding vinylpyridinolate **VII** (Route B).

Ethylpyridinols **4** might be derived by further electron-donating reduction of the corresponding vinylpyridinolate **V**, as shown in Scheme 3. In the reduction of **1a** and **1c**, the absence of vinylpyridinols **3a,c** might be due to the possible 2-pyridone **VIa'** or 4-pyridone structure **VIIc'**, shown in Chart 2, where the pyridine ring is activated by the pyridinone structure to accelerate the further reduction.

Scheme 2



Scheme 3

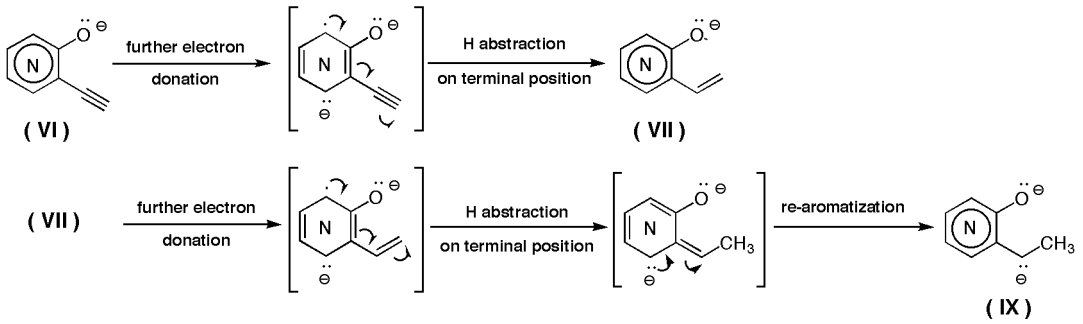
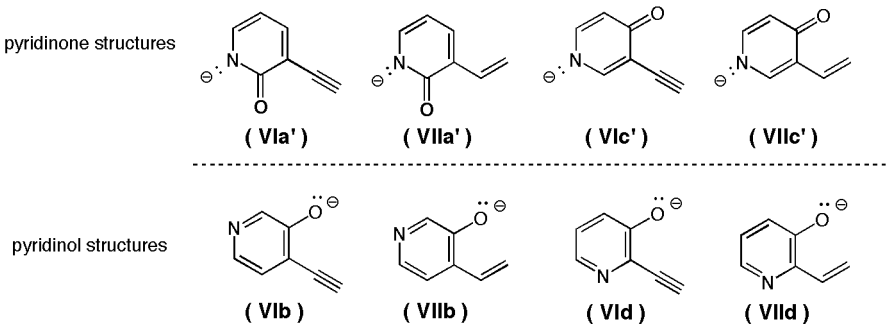


Chart 2

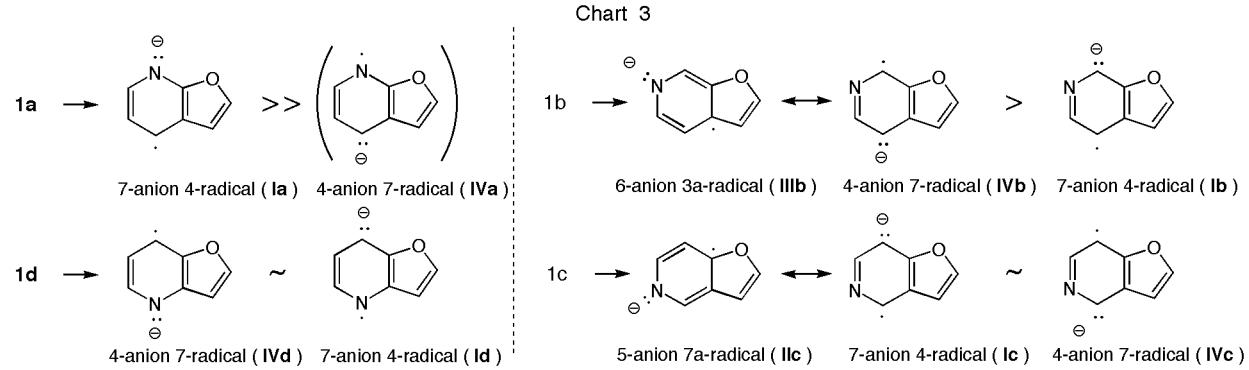


In the reduction of **1a**, one-electron donation may form only the stable 7-anion 4-radical **Ia**, keeping the aromaticity of the furan ring and the anion on the nitrogen. The 7-anion 4-radical **Ia** would follow the route A-1 and A-2 to form 3-ethynyl-2-pyridinolate **VIa** and 3-vinyl-2-pyridinolate **VIIa**, and all of **VIIa**, having the 2-pyridinone structure **VIIa'**, cause a further reduction to give 3-ethyl-2-pyridinol (**4a**).

In the reduction of **1d** using 3.3 equivalents of a sodium metal, one-electron donation to furo[3,2-*c*]pyridine **1d** would form two stable anion radicals, the 7-anion 4-radical **Id** and the 4-anion 7-radical **IVd**, keeping the aromaticity of the furan ring. The anion radicals **Id** would follow the routes A-1 and A-2 to form 2-ethynyl-3-pyridinolate **VId** and 2-vinyl-3-pyridinolate **VIId**. The anion radical **IVd** would follow the route B to give **VIId**. A part of the 2-vinyl-3-pyridinolate **VIId**, thus formed, causes a further reduction to give di-anion **IX** for 3-ethyl-2-pyridinol (**4d**). Birch reduction of **1d** using 1.8 equivalent of sodium indicated a lower yield in ethynylpyridinol **2d**. This indicated that the formation of the 4-anion 7-radical **IVd** (for the route B), with the anion on the nitrogen, is more favorable than the formation of the 7-anion 4-radical **Id** (for the route A).

On the other hand, in the reduction of **1b** and **1c**, one-electron donation would form three anion radicals; **1b** gives the 7-anion 4-radical **Ib**, the 6-anion 3a-radical **IIIb**, and the 4-anion 7-radical **IVb**. Whereas **1c** give the 7-anion 4-radical **Ic**, the 5-anion 7a-radical **IIc**, and the 4-anion 7-radical **IVc**. These anion radicals keep either the aromaticity of the furan ring or the anion on the nitrogen, and,

Chart 3



therefore, the anion radicals from **1b,c** might not be as stable as the anion radicals from **1a,d**. These are reflected in the total yields; the yields in **1b,c** are not so high (**1b**: 63%, **1c**: 50%) as those in **1a,d** (**1a**: 100%, **1d**: 88%). The 7-anion 4-radical **Ib,c** would follow the routes A-1 and A-2 to form ethynylpyridinolates **VIb,c** and vinylpyridinolates **VIIb,c**. The 6-anion 3a-radical **IIIb** and the 4-anion 7-radicals **IVb,c** would follow route B to form the corresponding vinylpyridinolates **VIIb,c** (for **3b,c**). And, a part of the 4-vinyl-3-pyridinolate **VIIb** causes a further reduction to give the 4-ethyl-3-pyridinol **4b**, and all of the 3-vinyl-4-pyridinolate **VIIc**, having a 4-pyridinone structure **VIIc'**, cause a further reduction to give 3-ethyl-4-pyridinol **4c**.

The 5-anion 7a-radical **IIc** and the 7-anion 4-radical **Id** would follow route C to give the corresponding dihydrofuropyridines **5c,d**.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are unccorected. The ir spectra were recorded on a JASCO FT/IR spectrometer in liquid films or potassium bromide disks, the uv spectra were recorded on a Hitachi 220A spectrophotometer, the pmr spectra were recorded on a JEOL MAC-FX (90MHz) or A440 (400MHz) spectrometer in deuteriochloroform solution, and the mass spectra were recorded on a JEOL JMS-OISG-2 spectrometer.

General Procedure for Birch Reduction of **1a-d**.

A solution of furopyridine **1a-d** [2-5] (1.0 mmol) in dry ether (*ca*. 3 ml) was added to liquid ammonia (10 ml), and sodium metal (3.0 or 1.8 mmol) was then added to the solution, and the mixture was stirred for 30 minutes. The resulting mixture was treated with ammonium chloride and the ammonia was allowed to evaporate. The residue was treated with a small amount of water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was chromatogramed on a silica-gel column to give corresponding ethynylpyridinols **2a-d**, vinylpyridinols **3b,d**, ethylpyridinols **4a-d**, and dihydrofuropyridine **5c**. Each product was isolated by silica-ge column chromatography with hexane-ethyl acetate as eluents). The product ratios were determined by the pmr spectra of the crude mixture.

Birch Reduction of **1a**.

3-Ethynyl-2(1*H*)-pyridinone **2a'** (corresponded to 3-ethynyl-2-pyridinol **2a**); mp 148-150 °C (lit. 148-151 °C). This compound was identical with the sample obtained by metalation of 3-bromofuro[2,3-*b*]pyridine [7]; ir: ν_{OH} 3444, ν_{NH} 3217, $\nu_{ethynyl}$ 2101, $\nu_{C=O}$ 1634, $\nu_{C=C}$ 1609, $\nu_{pyridine}$ 1555, 1464, 1429, 1244, 893, 772 cm^{-1}; pmr ($CDCl_3$): δ 3.40 (s, 1H, CH in ethynyl), 6.31 (t, 1H, 5-H, J = 7.0 Hz), 7.52 (dd, 1H, 6-H, J = 7.0 and 2.1 Hz), 7.74 (dd, 1H, 7.0 and 2.1 Hz), 13.0-14.0 ppm (br, 1H, NH); ms: m/z 119 (M^+).

3-Ethyl-2(1*H*)-pyridinone **4a'** (corresponded to 3-ethyl-2-pyridinol **4a**)[10]; mp 124-125 °C (lit. 121-121.5 °C); ir: ν_{OH} 3446, $\nu_{C=O}$ 1664, 1647, $\nu_{C=C}$ 1616, $\nu_{pyriudine}$ 1568, 1481, 1069, 776 cm^{-1}; pmr ($CDCl_3$): δ 1.22 (t, 3H, CH_3, J = 7.5 Hz), 2.58 (q, 2H, CH_2, J = 7.5 Hz), 6.24 (t, 1H, 5-H, J = 6.6 Hz), 7.29 (d, 2H, 4-H and 6-H, J = 6.6 Hz), 12.4-13.4 ppm (br, 1H, NH); ms: m/z 123 (M^+).

Birch Reduction of **1b**.

4-Ethynyl-3-pyridinol (**2b**).

This compound could not be isolated, but identified with the pmr data of the sample obtained by metalation of 3-bromofuro[2,3-*c*]pyridine [7]; pmr ($CDCl_3$): δ 3.52 ppm (s, 1H, CH in ethynyl).

4-Vinyl-3-pyridinol (**3b**).

This compound could not be isolated; pmr: δ 5.52 (d, 1H, $C=CH_{cis}$, J = 11.1 Hz), 6.04 (d, 1H, $=CH_{trans}$, J = 15.9 Hz), 7.05 (dd, 1H, $=CH_{gem}$, J = 15.9 and 11.1 Hz).

4-Ethyl-3-pyridinol (**4b**) [11].

This compound has mp 92-94 °C (lit. 93.5-95 °C); ir: ν_{OH} 3446, $\nu_{pyridine}$ 1663 and 1647 cm^{-1}; pmr ($CDCl_3$): δ 1.19 (t, 3H, CH_3 in ethyl, J = 7.4 Hz), 2.64 (q, 2H, CH_2 in ethyl, J = 7.4 Hz), 7.08 (d, 1H, 5-H, J = 4.8 Hz), 7.93 (d, 1H, 6-H, J = 4.8 Hz), 8.16 (s, 1H, 2-H), 8.0-8.6 ppm (br, 1H, OH); ms: m/z 123 (M^+).

Birch Reduction of **1c**.

3-Ethynyl-4(1*H*)-pyridinone (**2c'**) (corresponded to 3-ethynyl-4-pyridinol **2c**).

This compound could not be isolated, and was identified with the pmr data of the sample obtained by metalation of 3-bromofuro[3,2-*c*]pyridine [7].

3-Ethyl-4(1*H*)-pyridinone (**4c'**) (corresponded to 3-ethyl-4-pyridinol **4c**).

This compound has ir: ν_{OH} 3446, $\nu_{pyridine}$ 1663 and 1647 cm^{-1}; pmr ($CDCl_3$): δ 1.19 (t, 3H, CH_3, J = 7.3 Hz), 2.55 (q, 2H, CH_2, J = 7.3 Hz), 6.42 (d, 1H, 5-H, J = 7.3 Hz), 7.50-7.62 ppm (m, 2H, 2-H and 6-H); ms: m/z 123 (M^+).

Anal. *Calcd*. for $C_7H_9NO \cdot 1/2H_2O$: C, 63.61, H, 7.64, N, 10.60. Found: C, 63.83, H, 7.27, N, 10.38.

2,3-Dihydrofuro[3,2-*c*]pyridine (**5c**).

This compound was identical with the sample obtained by hydrogenation [8]; ir: $\nu_{pyridine}$ 1605, 1587, 1493, 1277, 1237, 976, 938, 867, 824 cm^{-1}; pmr: δ 3.24 (t, 2H, 3-CH_2, J = 8.8 Hz), 4.65 (t, 2H, 2-CH_2, J = 8.8 Hz), 6.73 (d, 1H, 7-H, J = 5.3 Hz), 8.28 (d, 1H, 6-H, J = 5.3 Hz), 8.34 ppm (s, 1H, 4-H); ms: m/z 121 (M^+).

Birch Reduction of **1d**.

2-Ethynyl-3-pyridinol (**2d**) [7].

This compound has mp 148-150 °C (lit. 149.5-150.5 °C), this compound was identified by comparison of the ir and pmr spectra with those of the sample obtained by metalation of 3-bromofuro[3,2-*b*]pyridine [7]; ir: ν_{OH} 3446, $\nu_{ethynyl}$ 2100 cm^{-1}; pmr ($CDCl_3$): δ 3.58 (s, 1H, CH in ethynyl), 7.11-7.27 (m, 2H, 4-H and 5-H), 8.07 ppm (dd, 1H, 6-H, J = 4 .0 and 2.0 Hz); ms: m/z 119 (M^+).

2-Vinyl-3-pyridinol (**3d**).

This compound has mp 148-149 °C; ir: ν_{OH} 3446, $\nu_{ethynyl}$ 2100 cm^{-1}; pmr ($CDCl_3$): δ 5.49 (dd, 1H, 2'-H_{trans}, J = 11.1 and 2.1 Hz), 6.25 (dd, 1H, 2'-H_{cis}, J = 17.6 and 2.1 Hz), 7.42-6.97 (m,

3H, 4-H, 5-H, and 1'-H), 8.00 ppm (dd, 1H, 6-H, J = 4.2 and 1.9 Hz); ms: m/z 121 (M^+).

Anal. Calcd. for C_7H_7NO: C, 69.41, H, 5.82, N, 11.56. Found: C, 69.25, H, 5.97, N, 11.49.

2-Ethyl-3-pyridinol (**4d**) [12].

This compound has mp 129-133 °C (lit. 135 °C); ir: ν_{OH} 3437 cm^{-1}, $\nu_{pyridine}$ 1586, 1576, 1458, 1300, 1262, 1116, 782 cm^{-1}; pmr ($CDCl_3$): δ 7.05 (dd, 1H, 5-H, J = 7.9 and 4.4 Hz), 7.21 (dd, 1H, 4-H, J = 7.9 and 1.8 Hz), 8.00 (dd, 1H, 6-H, J = 4.4 and 1.8 Hz), 8.7-9.1 ppm (br, 1H, 3-OH); ms: m/z 123 (M^+).

2,3-Dihydrofuro[3,2-*b*]pyridine (**5d**).

This could not be isolated, but identified with the pmr data of the sample derived by hydrogenation of furo[3,2-*b*]pyridine **1d** [8].

Acknowledgements.

The authers would like to thank Juzen Chemical Corporation for financial support.

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[9] Birch reduction of **5a** resulted in recovery of the starting compound, and the Birch reduction of **1c** gave a different cleavage, giving pyridine-3-ethanol; pmr: δ 2.86 (t, 2H, 3-CH_2, J = 6.5 Hz), 3.88 (t, 2H, 2-CH_2, J = 6.5 Hz), 4.03 (br, 1H, OH), 7.23 (dd, 1H, 5-H, J = 7.6 and 5.0 Hz), 7.56 (dt, 1H, 4-H, J = 7.6 and 2.0 Hz), 8.34 (dd, 1H, 6-H, J = 5.0 and 2.0 Hz), 8.44 ppm (d, 1H, 2-H, J = 2.0 Hz).

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