STUDIES ON 3,5-DIOXOPIPERIDINES:[1,2] NOVEL AND FACILE SYNTHETIC ROUTES TO 3-AMINO-5-HYDROXYPYRIDINE DERIVATIVES

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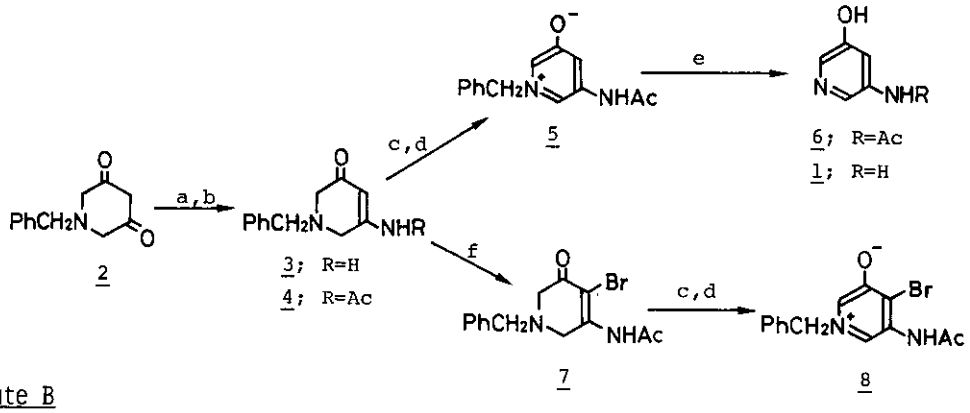
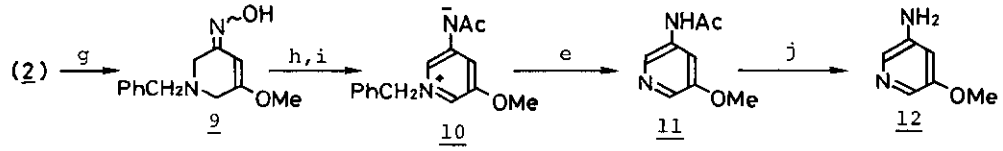
Abstract —— Three novel synthetic routes to the title compounds were described. Modified Polonovski reaction of 3-acetamido-1-benzyl-5-oxo-3,4-dehydropiperidine (4) or Semmler-Wolff aromatization of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine oxime (9) followed by reductive debenzylations gave 3-acetamido-5-hydroxypyridine (6) or 3-acetamido-5-methoxypyridine (11), respectively. Nucleophilic replacement of 3,5-dibromopyridine N-oxide (13) with methoxy and amino groups followed by deoxygenation gave 3-amino-5-methoxypyridine (12).

In the course of synthesizing new drugs in which the benzene ring of the clinically used drugs is replaced by the pyridine ring,[3] we required the derivatives of 3-amino-5-hydroxypyridine (1) as key intermediates. The synthesis of 3-amino-5-ethoxypyridine has been performed by bromination of pyridine to 3,5-dibromopyridine followed by substitution with ethoxy and amino groups.[4,5] The route, however, is not satisfactory because of the lack of a convenient brominating method of pyridine,[6] the extremely low overall yield, and the tedious reaction conditions.[7] Recently, we have reported a modified Polonovski reaction of 3-alkoxy-1-methyl-5-oxo-3,4-dehydropiperidines to 5-alkoxy-1-methyl-3-oxidopyridiniums[8] and a convenient method for the Semmler-Wolff aromatization of 3-alkoxy-2-cyclohexen-1-one oximes to m-alkoxy-acetanilides.[9] Application of these high-yield and general aromatizing methods to 1-benzyl-3,5-dioxopiperidine derivatives enabled us to establish the synthetic routes for the desired pyridines (Routes A and B). In the present communication, a useful synthesis of N-acetyl (6), O-methyl (12), and other derivatives (5, 8, 10, and 11) of 1 by three novel routes A-C is described.

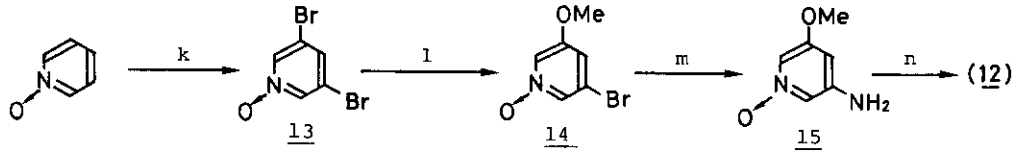
Route A



Route B



Route C



(a) NH_3-CH_3CN; (b) Ac_2O-pyridine; (c) m-CPBA; (d) IRA-410; (e) H_2/Pd-C; (f) CF_3CO_2H-NBS; (g) $NH_2OH \cdot HCl$-MeOH; (h) $ClCO_2Et$-pyridine; (i) AcCl; (j) aq·NaOH; (k) Br_2-Ac_2O-AcONa; (l) KOH-MeOH; (m) aq·NH_3-$CuSO_4$; (n) H_2/Ra-Ni.

Route A —— Heating of 2 with ammonia bubbling through a CH_3CN solution for 4h gave 3-amino-1-benzyl-5-oxo-3,4-dehydropiperidine (3) [mp. 86-87° ($CHCl_3$), ν_{max} 1505 and 1275 cm^{-1}, m/e 202 (M^+)] in 57% yield. Acetylation of 3 using Ac_2O-pyridine provided the acetate (4) [mp. 152-154° (CH_3COCH_3), ν_{max} 1720, 1620, 1540, and 1525 cm^{-1}] in 45% yield, which was aromatized by the previously reported method[8] using m-CPBA to give a 95% yield of the betaine (5) (syrup, ν_{max} 1615, 1575, and 1490 cm^{-1}). Debenzylation of 5 by the catalytic reduction on 5% Pd-C at about 70° and 4 atm hydrogen pressure gave a quantitative yield of 3-acetamido-5-hydroxypyridine (6) [mp. 275-276° (MeOH), ν_{max} 1660, 1620, 1580, and 1430 cm^{-1}]. Bromination of 4 using CF_3CO_2H-NBS gave the bromide (7) [mp. 148-149° (AcOEt),

ν_{max} 1725, 1670, and 1600 cm^{-1}, m/e 323 (M^+)] in 98% yield, which was aromatized by the treatment with m-CPBA in CH_2Cl_2 to give the betaine (8) [syrup, ν_{max} 3390, 1690, 1550, 1480, and 1390 cm^{-1}, m/e 321 (M^+)] in 87% yield.

Route B —— Oximination of the diketone (2) by the previously reported method[10] using $NH_2OH \cdot HCl$ in MeOH gave directly a 70% yield of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine oxime (9) [syrup, a mixture of (Z)- and (E)-isomers (Z:E=1:1), ν_{max} 3600, 3300, 1635, and 1235-1200 cm^{-1}, m/e 232 (M^+)]. Treatment of 9 with $ClCO_2Et$-pyridine gave the oxime O-carboxylate, which was submitted to the Semmler-Wolff aromatization using AcCl to give a 75% yield of the betaine (10) (syrup, ν_{max} 2900, 1585, and 1380 cm^{-1}). Debenzylation of 10 by the catalytic reduction on 5% Pd-C at room temperature and 4 atm hydrogen pressure gave a 73% yield of 3-acetamido-5-methoxypyridine (11) [mp. 136° (lit.[5] 133-134°)]. Deacetylation of 11 using aqueous NaOH at 65° for 1h gave a 67% yield of 3-amino-5-methoxypyridine (12) [mp. 54-55° (C_6H_6), bp. 185°/18 mmHg (lit.[5] 166-168°/15 mmHg)].

Katritzky has reported[11] the preparation of 3,5-dimethoxypyridines by nucleophilic replacement of 3,5-dichloropyridine N-oxides and subsequent reduction. The use of 3,5-dibromopyridine N-oxide (13) was found to provide a more convenient and high-yield route (Route C) for functionalizing C-3 and C-5 of pyridines.

Route C —— Refluxing a methanolic solution of 13[12] and KOH for 30 min gave a 79% yield of 3-bromo-5-methoxypyridine N-oxide (14) [mp. 200-201° (MeOH), ν_{max} 1580, 1550, and 1410 cm^{-1}]. Conversion of 14 to 3-amino-5-methoxypyridine N-oxide (15) (syrup, 95%, ν_{max} 1640, 1605, 1585, and 1210 cm^{-1}, m/e 140 (M^+)] was effected by the treatment with aqueous ammonia-$CuSO_4$ in a sealed tube at 130° for 5h. When 3-chloro-5-methoxypyridine N-oxide was treated with aqueous ammonia under the similar conditions, the yield of 15 never exceeded 10%. Deoxygenation of 15 by the catalytic hydrogenation on Raney-Ni in methanol at room temperature for 1h gave a 95% yield of 12.

Route C is the most suitable for the preparation of 12 itself, whose diazonium salt is known to be a versatile intermediate for other 3-substituted compounds.[13] It is worthy to note that Route A provides a useful intermediate for C-4 functionalized pyridine derivatives, 4-bromobetaine (8) in good yield, although functionalizing C-4 of 1 and its derivatives is quite troublesome by Route C.[14]

The microanalyses of all crystal new compounds (4, 6, and 14) were in satisfactory agreement with the calculated values (C, ±0.27; H, ±0.11; N, ±0.20).

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References and Notes

1 We wish to dedicate this paper to Professor Tetsuji Kametani on the occasion of his retirement.

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7 The extremely vigorous conditions required to effect substitution into the pyridine ring are well known [K. Thomas and D. Jerchel, Ang. Chem., 70, 719 (1958)].

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13 The preparation of 3-fluoro and 3-hydroxy compounds has been reported; K. Krowicki, Rocz. Chem., 49, 2085 (1975) [Chem. Abstr., 85, 21035k (1976)], K. Krowicki, ibid., 50, 1785 (1976)] [Chem. Abstr., 86, 171200v (1977)].

14 Thus, bromination of 15 gave a mixture of 2,6-dibromo and 2,4,6-tribromo compounds.

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