

STUDIES ON 3,5-DIOXOPIPERIDINES:^{1,2} NOVEL AND FACILE SYNTHETIC ROUTES
TO 3-AMINO-5-HYDROXYPYRIDINE DERIVATIVES

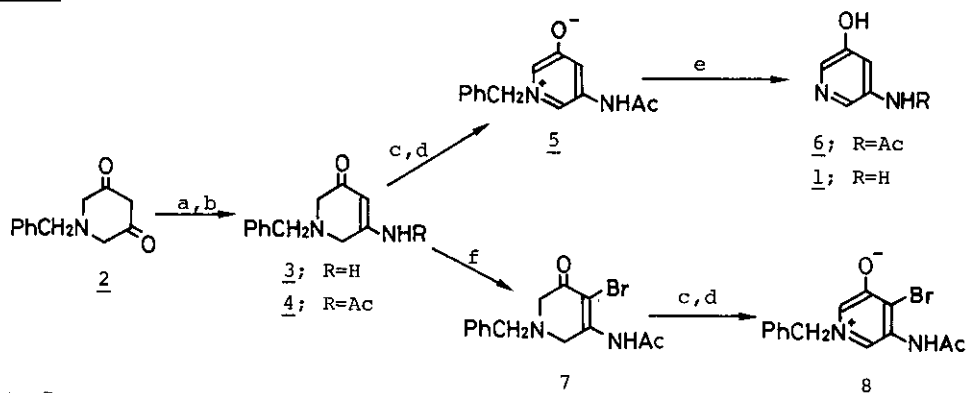
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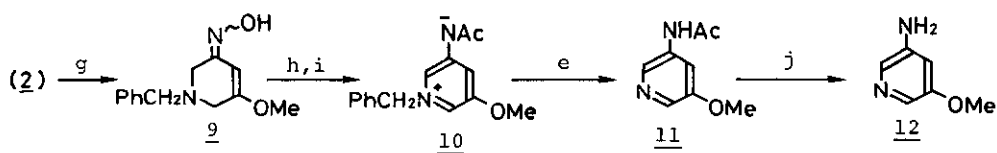
Abstract — Three novel synthetic routes to the title compounds were described. Modified Polonovski reaction of 3-acetamido-1-benzyl-5-oxo-3,4-dehydropiperidine (4) or Semmler-Wolff aromatization of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine oxime (9) followed by reductive debenzylations gave 3-acetamido-5-hydroxypyridine (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-oxidopyridiniums⁸ 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.

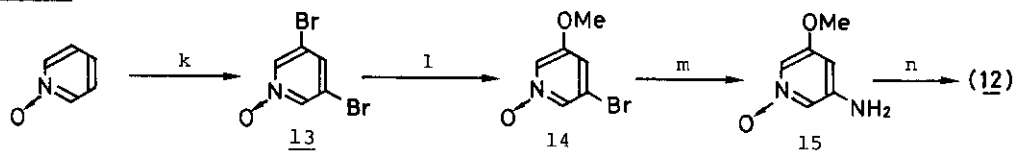
Route A



Route B



Route C



(a) $\text{NH}_3\text{-CH}_3\text{CN}$; (b) $\text{Ac}_2\text{O-pyridine}$; (c) *m*-CPBA; (d) IRA-410; (e) $\text{H}_2/\text{Pd-C}$; (f) $\text{CF}_3\text{CO}_2\text{H-NBS}$; (g) $\text{NH}_2\text{OH}\cdot\text{HCl-MeOH}$; (h) $\text{ClCO}_2\text{Et-pyridine}$; (i) AcCl ; (j) aq. NaOH ; (k) $\text{Br}_2\text{-Ac}_2\text{O-AcONa}$; (l) KOH-MeOH ; (m) $\text{aq. NH}_3\text{-CuSO}_4$; (n) $\text{H}_2/\text{Ra-Ni}$.

Route A — Heating of 2 with ammonia bubbling through a CH_3CN solution for 4 h gave 3-amino-1-benzyl-5-oxo-3,4-dehydropiperidine (3) [mp. $86\text{--}87^\circ$ (CHCl_3), ν_{max} 1505 and 1275 cm^{-1} , m/e 202 (M^+)] in 57% yield. Acetylation of 3 using $\text{Ac}_2\text{O-pyridine}$ provided the acetate (4) [mp. $152\text{--}154^\circ$ (CH_3COCH_3), ν_{max} 1720, 1620, 1540, and 1525 cm^{-1}] in 45% yield, which was aromatized by the previously reported method⁸ using *m*-CPBA to give a 95% yield of the betaine (5) (syrup, ν_{max} 1615, 1575, and 1490 cm^{-1}). Debenzoylation 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. $275\text{--}276^\circ$ (MeOH), ν_{max} 1660, 1620, 1580, and 1430 cm^{-1}]. Bromination of 4 using $\text{CF}_3\text{CO}_2\text{H-NBS}$ gave the bromide (7) [mp. $148\text{--}149^\circ$ (AcOEt),

$\nu_{\max}$ 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, $\nu_{\max}$ 3390, 1690, 1550, 1480, and 1390 cm^{-1} , m/e 321 (M^+)] in 87% yield.

Route B — Oximation of the diketone (2) by the previously reported method¹⁰ using $\text{NH}_2\text{OH}\cdot\text{HCl}$ 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), $\nu_{\max}$ 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, $\nu_{\max}$ 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 reported¹¹ 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 13¹² and KOH for 30 min gave a 79% yield of 3-bromo-5-methoxypyridine *N*-oxide (14) [mp. 200-201° (MeOH), $\nu_{\max}$ 1580, 1550, and 1410 cm^{-1}]. Conversion of 14 to 3-amino-5-methoxypyridine *N*-oxide (15) (syrup, 95%, $\nu_{\max}$ 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.
- 2 Y. Tamura, L.C. Chen, M. Fujita, H. Kiyokawa, and Y. Kita, Chem. & Ind., 1979, 668. Y. Tamura, L.C. Chen, M. Fujita, and Y. Kita, J. Het. Chem., 17, 1 (1980).
- 3 In the case of some antihistamines, a benzene ring can be often replaced by a pyridine ring with full retention of biological activity [A. von Schlichtergroll, Arzneimittel Forsch., 8, 489 (1958), Anon., French Patent 1,173,134 (1958), W. A. Schuler and H. Klebe, Ann., 653, 172 (1962)], and we have recently prepared the 7-aza analogue of 5-(3-tert-butylamino-2-hydroxy)propoxy-3,4-dihydrocarbo-
styryl hydrochloride, which is clinically used as a β -receptor blocking agent [K. Nakagawa, N. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuuchi, and S. Shintani, J. Med. Chem., 17, 529 (1974)]; Y. Tamura, L.C. Chen, M. Fujita, H. Kiyokawa, and Y. Kita, Chem. Pharm. Bull., in preparation.
- 4 H.J. den Hertog, A.W.M. Falter, and A. van der Linde, Rec. Trav. chim., 67, 377 (1948) [Chem. Abstr., 43, 641e (1949)], W. Czuba, Roczniki Chem., 34, 1639 (1960) [Chem. Abstr., 56, 3445h (1962)], M.J. Piterse and H.J. den Hertog, Rec. Trav. chim., 80, 1376 (1961) [Chem. Abstr., 58, 5625e (1963)].
- 5 R. Urban and O. Schinider, Helv., 47, 363 (1964).
- 6 Some bromination methods of pyridine were reported under the extremely vigorous and tedious conditions; E.E. Garcia, J. Am. Chem. Soc., 82, 4430 (1960), T. Batkowski, D. Tomasik, and P. Tomasik, Rocz. Chem., 41, 2101 (1967) [Chem. Abstr., 69 18984h (1968)], H.J. den Hertog, Rec. Trav. chim., 81, 864 (1962) [Chem. Abstr., 58, 11323d (1963)]. In spite of our efforts to obtain 3,5-dibromopyridine in a laboratory scale according to the Hertog's method, it is quite difficult to prepare it and less than 10% yield of the bromide was obtained in every runs.
- 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)].
- 8 Y. Tamura, T. Saito, H. Kiyokawa, L.C. Chen, and H. Ishibashi, Tetrahedron Lett., 1977, 4075.
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- 11 C.D. Johnson, A.R. Katritzky, and M. Viney, J. Chem. Soc. B, 1967, 1211.
- 12 3,5-Dibromopyridine N-oxide (13) was prepared by the bromination of pyridine N-oxide in a considerable yield [M. Yamazaki, Y. Chono, K. Noda, and M. Hamana, Yakugaku Zasshi, 85, 62 (1965)] [Chem. Abstr., 62, 10409e (1965)].
- 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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