

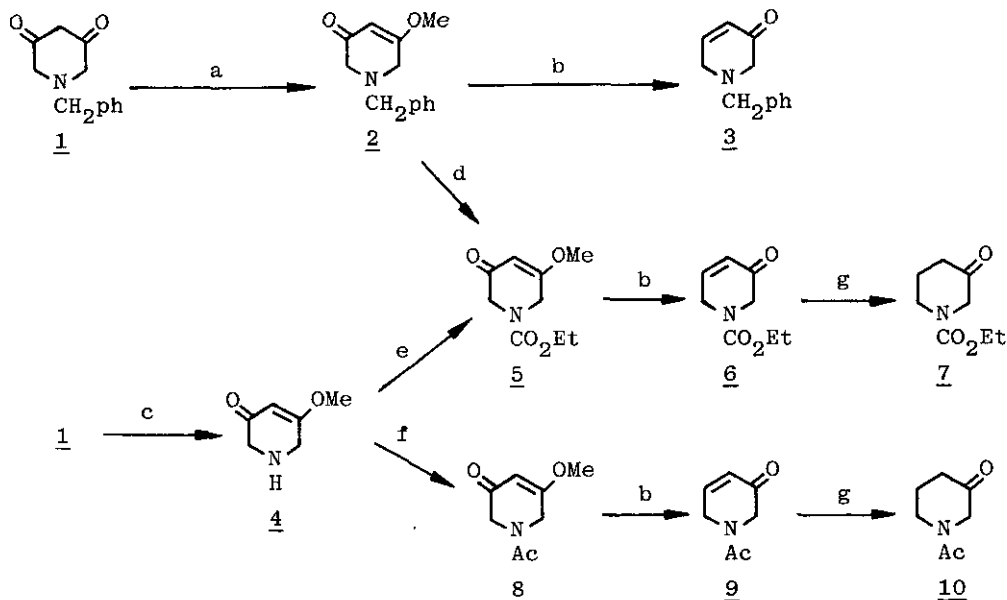
SYNTHESIS OF N-SUBSTITUTED 1,6-DIHYDRO-3(2H)-PYRIDINONES AND 1-ACYL-3-PIPERIDONES

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Abstract — Synthesis of the N-substituted 1,6-dihydro-3(2H)-pyridinones (3, 6, and 9) and 1-acyl-3-piperidones (7 and 10) is described. 1-Benzylpiperidine-3,5-dione (1) was converted into N-substituted 1,6-dihydro-3(2H)-pyridinones (3, 6, and 9) via the methyl enol ethers (2, 5, and 8). Selective reduction of 6 and 9 with Et_3SiH in the presence of TiCl_4 produced the 1-acyl-3-piperidones (7 and 10).

Recently, 1,6-dihydro-3(2H)-pyridinone system has been reported by M. Hanaoka and his co-workers¹ to be a potential synthon to many kinds of alkaloid syntheses, and 1-acyl-3-piperidone derivatives have proved to be useful intermediates for syntheses analogues of nipecotic acid and guvacine.² Hence, we have investigated the chemistry of 1,6-dihydro-3(2H)-pyridinones and wish to report herein a convenient route to the N-substituted 1,6-dihydro-3(2H)-pyridinones and 1-acyl-3-piperidones.

The synthesis of the title compounds in the Scheme 1 was achieved from the known 1-benzylpiperidine-3,5-dione (1), which was subsequently converted into 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine (2) [mp 111-112°C (lit.³ 109.5-110°C)] by treatment with dry MeOH and HCl gas in yield of 67%. Reduction of 2 using NaBH_4 in EtOH gave a 71% yield of 1-benzyl-1,6-dihydro-3(2H)-pyridinone (3) [syrup, ν_{max} 1685 cm^{-1} , m/e 187 (M^+)]. Debenzylation of 1 hydrochloride by catalytic hydrogenation on 5% Pd-C in MeOH at room temperature gave a 80% yield of 3-methoxy-5-oxo-3,4-dehydropiperidine (4) [oil, ν_{max} 1650 and 1610 cm^{-1} , m/e 127 (M^+)]. Treatment of 2 with a small excess of ClCO_2Et in boiling C_6H_6 for 2h gave 1-carboethoxy-3-methoxy-5-oxo-3,4-dehydropiperidine (5). [mp 59-60°C (n-hexane), ν_{max} 1690, 1660, 1620 cm^{-1} , m/e 199 (M^+)].⁴ Alternatively, 5 was also obtained by acylation of 4 with aqueous K_2CO_3 and ClCO_2Et in yield of 75%. Acylation of 4 using aqueous K_2CO_3 and Ac_2O gave a 70% yield of 1-acetyl-3-methoxy-5-oxo-3,4-dehydropiperidine (8) [mp 95.5-97°C (AcOEt), ν_{max} 1665, 1620 cm^{-1} , m/e 169 (M^+)]. Ethyl 1,6-dihydro-3-(2H)-pyridinone-1-carboxylate (6)⁵ and 1-acetyl-1,6-dihydro-3(2H)-pyridinone (9) were prepared in analogy with preparation of 3 described above to give 73% and 70% yields, respectively.



(a) HCl-MeOH; (b) NaBH₄-EtOH; (c) H₂/Pd-C; (d) ClCO₂Et-C₆H₆;
 (e) ClCO₂Et-K₂CO₃; (f) Ac₂O-K₂CO₃; (g) Et₃SiH-TiCl₄.

Scheme I

Selective reduction of 6 and 9 with Et₃SiH in the presence of TiCl₄ produced the ethyl 3-oxo-piperidine-1-carboxylate (7) [colorless liquid, ν_{\max} 1730 and 1705 cm⁻¹, m/e 171 (M⁺)] in 80% yield and 1-acetyl-3-piperidone (10) [colorless liquid, ν_{\max} 1725 and 1640 cm⁻¹, m/e 141 (M⁺)] in 76% yield.⁶ The microanalyses of all crystalline new compounds (5 and 8) were in satisfactory agreement with the calculated values (C, ± 0.13 ; H, ± 0.11 ; N, ± 0.15). Thus, a convenient route to the title compounds has been achieved.

EXPERIMENTAL

All melting points are uncorrected. The infrared (IR) absorption spectra were recorded on a Shimadzu IR-27G spectrometer, and nuclear magnetic resonance (¹H-NMR) spectra on a Hitachi EPI G-2 spectrophotometer. Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Chemical shifts and coupling constants were measured in ppm (δ) and (Hz) with respect to TMS.

1-Benzyl-1,6-dihydro-3(2H)-pyridinone (3): A mixture of 2 (300 mg, 1.38 mmol), ethanol (5 ml) and NaBH₄ (22 mg, 0.58 mmol) was stirred at room temperature for 2 hours. Removal of ethanol in vacuo, 10% sodium hydroxide solution (5 ml) was added, and extracted with chloroform (5 ml \times 3). After washing and drying of the

extract, evaporation of solvent gave a syrup. Then, 10% hydrochloric acid (3 ml) was added, stirred for 1 hour, neutralized with 10% potassium carbonate solution, and extracted with chloroform (5 ml x 3). The extract was washed with brine and dried. Evaporation of the solvent left an oily residue, which was purified by column chromatography on silica gel with benzene-ethyl acetate (1:5) as eluting solvents to give 184 mg (71%) of 3 as a syrup. $^1\text{H-NMR}$ (CDCl_3): 3.27 (s, 2H, 2-H), 3.27-3.32 (m, 2H, 6-H), 3.72 (s, 2H, CH_2ph), 6.25 (dt, $J=10$, 2.5Hz, 4-H), 7.20 (dt, $J=10$, 3Hz, 5-H), 7.50 (s, 5H, ArH); Exact mass calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}$: 187.2404. Found : 187.2409.

3-Methoxy-5-oxo-3,4-dehydropiperidine (4): Through a stirred suspension of 1 (2 g, 9.84 mmol) in dry ether (40 ml), hydrogen chloride gas was bubbled for 1 hour, giving 1 hydrochloride (2.23 g, mp 170-173°C). Crude 1 hydrochloride (2.23 g, 9.30 mmol) was submitted to the standard catalytic hydrogenolysis over 5% palladium-carbon (1.55 g) in methanol (20 ml) at room temperature for several hours, neutralized with 10% sodium hydroxide solution (15 ml), and extracted with chloroform (10 ml x 4). The extract was washed with brine, dried, and concentrated to give 993 mg (80%) of 2 as a yellow oil. $^1\text{H-NMR}$ (CDCl_3) : 3.25 (s, 1H, NH), 3.47 (s, 2H, NCH_2), 3.80 (s, 3H, OMe), 3.87 (s, 2H, NCH_2), 5.53 (s, 1H, CH=); Exact mass calcd. for $\text{C}_6\text{H}_9\text{NO}_2$: 127.1415. Found : 127.1412.

1-Carboethoxy-3-methoxy-5-oxo-3,4-dehydropiperidine (5): To a solution of 2 (800 mg, 3.68 mmol) and potassium carbonate (886 mg) in water (5 ml), ethyl chloroformate (688 mg, 6.34 mmol) was added under ice-cooling. After stirring at room temperature for 3 hours, the reaction mixture was extracted with chloroform (5 ml x 3). The extract was concentrated in vacuo to give a syrup, which was purified by column chromatography on silica gel with chloroform-methanol (1:1) as eluting solvents to give 516 mg (75%) of 3. The analytical sample of 5 was obtained by recrystallization from n-hexane, mp 59-60°C, $^1\text{H-NMR}$ (CDCl_3) : 1.30 (t, 3H, $J=7\text{Hz}$, $\text{NCO}_2\text{CH}_2\text{CH}_3$), 3.90 (s, 3H, OMe), 4.22 (s, 2H, NCH_2), 4.32 (q, 2H, $J=7\text{Hz}$, $\text{NCO}_2\text{CH}_2\text{CH}_3$), 5.73 (s, 1H, CH=); Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{NO}_4$: C, 54.27; H, 6.58 ; N, 7.03. Found : C, 54.16 ; H, 6.49 ; N, 7.18.

Ethyl 1,6-dihydro-3(2H)-pyridinone-1-carboxylate (6): A mixture of 5 (300 mg, 1.51 mmol), ethanol (5 ml), and NaBH_4 (24 mg, 0.63 mmol) was carried out as described for 3 above. After the reduction was completed, an oily residue was purified by column chromatography on silica gel with acetone as eluting solvents to give 186 mg (73%) of a colorless oil. IR (CHCl_3) ν_{max} 1690 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) : 1.30 (t, 3H, $J=7\text{Hz}$, OCH_2CH_3), 4.17 (s, 2H, 2-H), 4.21 (q, 2H, $J=7\text{Hz}$, OCH_2CH_3), 4.30 (dd, 2H, $J=3$, 2.5Hz, 6-H), 6.20 (dt, 1H, $J=10.5$, 2.5Hz, 4-H), 7.03 (dt, 1H, $J=10.5$, 3Hz, 5-H); m/e 169 (M^+); Exact mass calcd. for $\text{C}_8\text{H}_{11}\text{NO}_3$: 169.1825. Found : 169.1858.

Ethyl 3-oxopiperidine-1-carboxylate (7): A stirred solution of 6 (169 mg, 1 mmol) in dry dichloromethane (10 ml), was treated with 1M TiCl_4 (1.2 ml) in dichloromethane (3 ml) under argon atmosphere. After stirring the solution for about 10 min, triethylsilane (140 mg, 1.20 mmol) was added. When the reduction was completed, ice was added to the reaction mixture and the dichloromethane layer was washed with brine, saturated aqueous sodium bicarbonate, and dried. Evaporation of the solvent left an oily residue, which was subjected to column chromatography on silica gel with ethyl acetate to give 137 mg (80%) of 5 as a colorless liquid. $^1\text{H-NMR}$ (CDCl_3): 1.30 (t, 3H, $J=7\text{Hz}$, OCH_2CH_3), 1.70-2.20 (m, 2H, 5-H), 2.20-2.60 (m, 2H, 4-H), 3.65 (t, 2H, $J=6\text{Hz}$, 6-H), 4.08 (s, 2H, 2-H) 4.17 (q, 2H, $J=7\text{Hz}$, OCH_2CH_3); Exact mass calcd. for $\text{C}_8\text{H}_{13}\text{NO}_3$: 171.1925. Found: 171.1912.

1-Acetyl-3-methoxy-5-oxo-3,4-dehydropiperidine (8): To a solution of 2 (800 mg, 3.68 mmol) and potassium carbonate (866 mg) in water (5 ml), acetic anhydride (650 mg, 6.37 mmol) was added under ice-cooling. After stirring at room temperature for 3 hours, it was extracted with chloroform (5 ml \times 3). The extract was washed with brine, dried, and concentrated to give 453 mg (70%) of 6. The analytical sample of 8 was obtained by recrystallization from ethyl acetate, mp 95.5-97°C, $^1\text{H-NMR}$ (CDCl_3): 2.13 (s, 3H, Ac), 3.77 (s, 3H, OMe), 4.06 (s, 2H, NCH_2), 4.35 (s, 2H, NCH_2), 5.51 (s, 1H, CH=); Anal. Calcd for $\text{C}_8\text{H}_{11}\text{NO}_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.93; H, 6.66; N, 8.22.

1-Acetyl-1,6-dihydro-3(2H)-pyridinone (9): A mixture of 8 (300 mg, 1.78 mmol), ethanol (5 ml), and NaBH_4 (28 mg, 0.74 mmol) was also carried as described for 3 above. After the reduction was completed, an oily residue was purified by column chromatography on silica gel with chloroform-methanol (10:1) as eluting solvents to give 147 mg (70%) of a colorless oil. IR (CHCl_3) ν_{max} 1655, 1695 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): 2.30 (s, 3H, Ac), 4.38 (s, 2H, 2-H), 4.38-4.75 (m, 2H, 6-H), 6.52 (dt, $J=10$, 2.5Hz, 4-H), 7.42 (dt, $J=10$, 3Hz, 5-H); m/e 139 (M^+); Exact mass calcd. for $\text{C}_7\text{H}_9\text{NO}_2$: 139.1520. Found: 139.1565.

1-Acetyl-3-piperidinone (10): 10 was prepared in analogy with the preparation of 7 described above by using 9 (139 mg, 1 mmol), dry dichloromethane (10 ml), 1M TiCl_4 (1.2 ml), and triethylsilane (140 mg, 1.20 mmol). After the reduction was completed, an oily residue was chromatographed on silica gel with chloroform to give 107 mg (76%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3): 1.70-2.25 (m, 5H, 5-H and NAc), 2.40-2.70 (m, 2H, 4-H), 3.65, 3.70 (each t, total 2H, $J=6\text{Hz}$, 6-H), 4.05, 4.17 (each s, total 2H, 2-H); Exact mass calcd. for $\text{C}_7\text{H}_{11}\text{NO}_2$: 141.1685. Found: 141.1681.

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