

A FACILE SYNTHESIS OF dl-SEDAMINE AND dl-ALLOSEDAMINE

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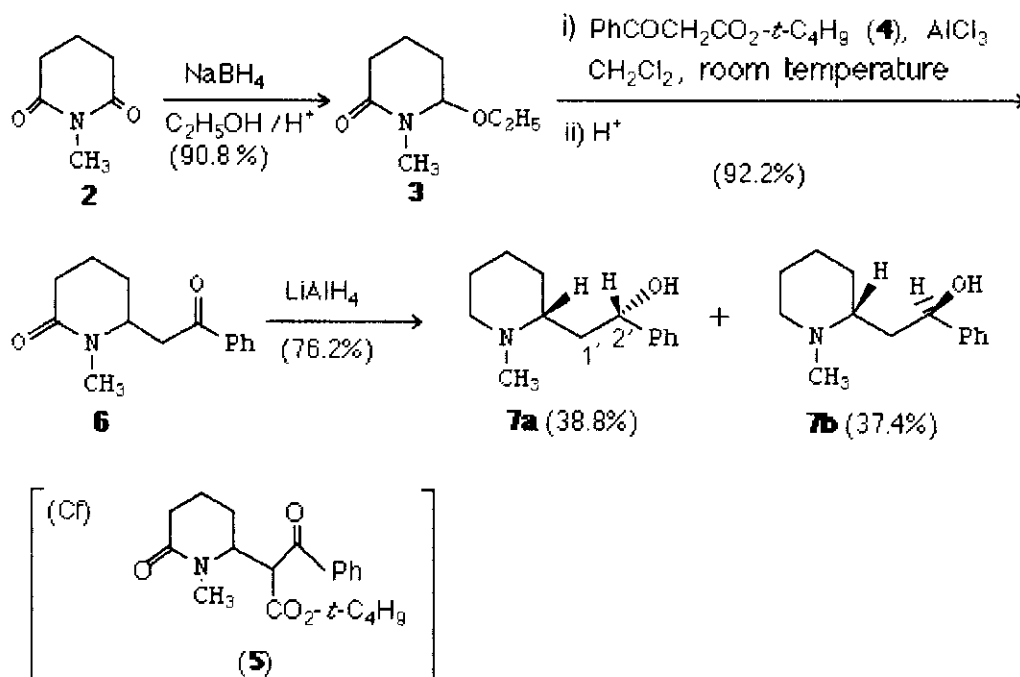
Abstract --- Racemic sedamine and dl-allosedamine were easily synthesized from the intermediate (3) using a cyclic acyliminium salt by the addition-elimination reaction sequence.

Our earlier studies^{1a,1b} on the sodium borohydride reduction of succin- and glutarimides served as a basis for the convenient synthesis of synton, α -hydroxy- or α -alkoxy-lactam, for pyrrolidine alkaloid syntheses, by Speckamp et al.^{2a,2b}

Pyrolysis of methylammonium glutarate gave *N*-methylglutarimide (2) in 94.4% yield. Reduction of 2 with sodium borohydride at -20 °C and subsequent esterification below 0 °C (Speckamp's Method (B)(acidic)^{2a}) produced 3 as an oil in 90.8% yield. Carbon-carbon bond formation between C(2) of 2-ethoxy-6-piperidone (3) and carbon with active hydrogen (4) was brought about in the presence of two equivalents of aluminum chloride as a Lewis acid at room temperature. It is a significant finding that an equimolar aluminum chloride was not sufficient for this process, as evident from Table 1. Two equivalents of aluminum chloride gave adduct (5) in good yield, almost all amount of which was subsequently hydrolyzed and spontaneously decarboxylated through the work-up after the reaction to give 6 in 92.2% yield.

Table 1		Acidolysis of a trace amount of 5 contained was readily completed by heating the crude mixture of 5 and 6 with 10% hydrochloric acid for 20 min at 80 °C. Reduction of 6
AlCl ₃ (eq.)	6(%)	with lithium aluminum hydride (LiAlH ₄) in ether at reflux for
-----		4 hours gave a mixture of 7a and 7b. The components of both of
2	92.2	these could be readily separated by column chromatography on
1.5	71.8	silica gel (see EXPERIMENTAL). Both 7a and 7b were identical
1	48.4	in all respects with the authentic samples of (±)-allosedamine ^{3b} and (±)-sedamine ^{3b,3d}
		described in the literature, respectively.

Scheme 1



EXPERIMENTAL

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep blue solution resulting from benzophenone and sodium. All other reagents and solvents were obtained commercially and used without further purification.

Procedures. The reactions were routinely conducted under a dry argon atmosphere with magnetic stirring. Organic solutions of the products were dried with anhydrous magne-

sium sulfate and then concentrated in vacuo. The crude products were purified by preparative tlc or column chromatography on silica gel. No corrections were made for all temperatures. Elemental analyses were performed using a Perkin-Elmer CHN-O-Rapid Analyzer. ^1H - And ^{13}C -nmr spectra were recorded on a Varian EM 390 or Bruker AM 400. Low-resolution mass spectra (ms) were taken in the electron-impact mode on a Hitachi M-80 spectrometer. All data were obtained at an electron energy of 70 eV, using the expression, ms (m/z , relative intensity). All the titled compounds were established as >90% by inspection of ^1H - and ^{13}C -nmr spectra unless otherwise specified. Infra-red (ir) spectra were obtained on a Hitachi 260-30 spectrophotometer in prominent and diagnostic phases.

N-Methylglutarimide (2) --- A mixture of 40% aqueous methylamine (12 ml, 0.076 mol) and glutaric acid (10 g, 0.076 mol) was evaporated to dryness to give 12.36 g of the methylammonium salt of 1 as a white powder, which was then introduced into a 100 ml Claisen flask equipped with a sabel. Heating the flask in an oil bath at 140-160 °C, caused the powder to melt. After a gas smelling like ammonia ceased to evolve after several min, the content was cooled to room temperature. The oily liquid thus obtained was purified by distillation under reduced pressure to give 9.117 g (94.4%) of 2 as a colorless oil (bp 85-90 °C, 5 mmHg). Ir (NaCl, neat) cm^{-1} : 2900 (N-CH₃), 1660 (C=O). ^1H -Nmr (CDCl₃) δ (ppm): 1.95 (2H, quintet, $J=7$ Hz, C(3)H₂), 2.67 (4H, t, $J=7$ Hz, C(2)-H₂, C(4)H₂), 3.10 (3H, s, N-CH₃). Ms (m/z): 127 (M^+ , 100), 98 (M-CO, 9.3).

1-Methyl-2-ethoxy-6-piperidone (3) --- To a stirred emulsion of NaBH₄ (3.87 g, 0.09 mol) in ethanol (200 ml) cooled to 0 - -20 °C with ice-salt was added dropwise a solution of 2 (6.35 g, 0.05 mol) in ethanol (5 ml) for 15 min. The reaction mixture was then stirred for 1 h. To bring about reduction, one or two drops of ethanol saturated with hydrogen chloride gas (C₂H₅OH-HCl) were added as proton sources every 15 min. After reduction, the reaction mixture was made acidic by adding dropwise C₂H₅OH-HCl to a pH of 3, and stirring was continued for more 1 h at -10-0 °C. After being neutralized with 10% potassium hydroxide solution in ethanol, the reaction mixture was concentrated under reduced pressure to dryness to give 3 as a crude white powder, which was purified by chromatography on silica gel using a mixture of hexane and ethyl acetate (5:3) as the eluent to give 3 (7.07 g, 90.8%) as a colorless oil. ^1H -Nmr (CDCl₃) δ (ppm): 1.15 (3H, t, $J=7$ Hz, -OCH₂CH₃), 1.50-2.10 (4H, m, C(3)H₂, C(4)-H₂), 2.20-2.55 (2H, m, C(5)H₂), 2.80 (3H, s, N-CH₃), 3.55 (2H, q, $J=7$ Hz, OCH₂), 4.65 (1H, m, C(2)H₂).

Ir (NaCl, neat) cm^{-1} : 2900, 1640. Ms (m/z): 157 (M^+ , 0.02), 112 ($\text{M}-\text{OC}_2\text{H}_5$, 100). This component was used for the next preparation without further purification.^{2a}

t-Butyl Benzoylacetate (4) --- A solution of t-butyl acetate (4.18 g, 0.036 mmol) in dry THF (5 ml) was added dropwise at -78°C to excess LDA prepared from dry diisopropylamine (7.27 g, 0.072 mol), $n\text{-C}_4\text{H}_9\text{Li}$ (48.6 ml of a 1.48 M solution in hexane, 0.072 mol) and dry THF (15 ml) at -78°C for 20 min. After allowing the solution to stand for 1 h at -78°C , freshly distilled benzoyl chloride (5.40 g, 0.036 mol) in dry THF (15 ml) was added over a period of 40 min. The reaction mixture was warmed to 0°C in 2 h, quenched with water and extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated to give 7.048 g (89.0%) of 4 as a colorless oil (bp 130°C , 4 mmHg; reported⁵ bp $115\text{--}116^\circ\text{C}$, 0.5 mmHg). Ir (NaCl, neat) cm^{-1} : 1730, 1680, 760, 705 (phenyl). $^1\text{H-Nmr}$ (CDCl_3) δ (ppm): 1.35 (9H, s, $\text{t-C}_4\text{H}_9$), 3.80 (2H, s, CH_2), 7.30 -7.60 (3H, m, aromatic $\text{H} \times 3$), 7.80 -8.20 (2H, m, aromatic $\text{H} \times 2$). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found: C, 70.95; H, 6.95. Ms (m/z): 206 ($\text{M}^+ - \text{CH}_3$ + H, 8.3), 105 ($\text{C}_6\text{H}_5\text{CO}^+$, 100).

N-Methyl-2-phenacyl-6-piperidone (6) --- A solution of 3 (1.2 g, 0.0076 mol) and 4 (1.672 g, 0.0076 mol) in dichloromethane (10 ml) was added to a rapidly stirred suspension of anhydrous aluminum chloride (2.02 g, 0.0152 mol) and dry dichloromethane (50 ml). The mixture was stirred for 40 min and concentrated. The residue was added into ice-water (10 ml) and extracted with dichloromethane (40 ml $\times$ 2). The dichloromethane layer was dried and concentrated to give a mixture (2.84 g) of 5 and 6. The mixture was warmed in 10% HCl (10 ml) at 80°C for 20 min. After cooling, the solution was extracted with a mixture of dichloromethane and ether (2:1) (40 ml $\times$ 2). The combined organic extracts were washed with water, dried, and concentrated. Purification of the residue by flash column chromatography [silica gel, hexane-acetone (5:3)] gave 1.618 g (92.2%) of 6 as colorless needles with mp $91\text{--}92^\circ\text{C}$ (reported^{3a} mp $90\text{--}91^\circ\text{C}$). 6: Ir (KBr) cm^{-1} : 1690, 1660, 750, 700 (phenyl). $^1\text{H-Nmr}$ (CDCl_3) δ (ppm): 1.60 -2.05 (4H, m, $\text{C}(3)\text{H}_2$, $\text{C}(4)\text{H}_2$), 2.20 -2.60 (2H, m, $\text{C}(5)\text{H}_2$), 2.95 (3H, s, N-CH_3), 3.25 (2H, d, $\text{J}=6.6$ Hz, $\text{C}(1')\text{H}_2$), 3.95 -4.03 (1H, m, $\text{C}(2)\text{H}$), 7.35 -7.70 (3H, m, aromatic $\text{H} \times 3$), 7.85 -8.05 (2H, m, aromatic $\text{H} \times 2$). Ms (m/z): 231 (M^+ , 67), 112 ($\text{M}^+ - \text{CH}_2\text{-C(=O)Ph}$, 100). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.27; H, 7.48; N, 5.98.

dl-Sedamine (7a) and dl-Allosedamine (7b) --- A solution of 5 (333 mg, 1.44 mmol) and

dry ether (5 ml) was added to a rapidly stirred suspension of LiAlH_4 (328 mg, 8.64 mmol) and dry ether (40 ml). The resulting mixture was heated at reflux for 4 h. After cooling to room temperature, ice-water (5 ml) was added slowly, the organic layer was separated and the aqueous layer was extracted with a mixture of dichloromethane and ether (2:1) (40 ml x 2). The organic extracts were dried and concentrated to give a mixture of 7a and 7b (272 mg). The crude products were separated by chromatography on a silica gel column using a mixture of hexane and acetone (4:1) as an eluent to give pure 7a (122.3 mg, 38.8%) as white needles and 7b as colorless needles (118 mg, 37.4%). 7a: mp 67–68 °C (reported^{3a} mp 67–68 °C), ir (KBr) cm^{-1} : 3250, 3060, 3040, 3010, 2930, 2800 (N-CH_3), 750, 700 (phenyl). $^1\text{H-Nmr}$ (CDCl_3) δ (ppm): 1.40–1.90 (6H, m, C(3)H_2 , C(4)H_2 , C(5)H_2), 1.90–2.30 (4H, m, C(6)H_2 , C(1')H_2), 2.35 (3H, s, N-CH_3), 2.80–3.05 (1H, m, C(2)H), 5.04 (1H, dd, $J=4$ Hz, 10 Hz, C(2')H), 7.22–7.51 (5H, m, aromatic H x 5). Ms (m/z): 219 (M^+ , 23), 98 ($\text{M}^+-\text{CH}_2\text{CH(OH)Ph}$, 100). Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.46; H, 9.62; N, 6.31. 7b: mp 90–91 °C (reported^{3b} mp 90–91 °C), ir (KBr): 3150, 3050, 3030, 2850, 2800 (N-CH_3), 750, 700 (aromatic). $^1\text{H-Nmr}$ (CDCl_3) δ (ppm): 1.20–1.70 (6H, m, C(3)H_2 , C(4)H_2 , C(5)H_2), 1.80–2.20 (2H, m, C(1')H_2), 2.25–2.55 (2H, m, C(6)H_2), 2.45 (3H, s, N-CH_3), 2.80–3.00 (1H, m, C(2)H), 4.87 (1H, dd, $J=10.42$ and 2.80 Hz, C(2')H-OH), 7.20–7.50 (5H, m, aromatic). Ms (m/z): 219 (M^+ , 13), 98 ($\text{M}^+-\text{CH}_2\text{CH(OH)Ph}$, 100). Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.33; H, 9.66; N, 6.31.

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