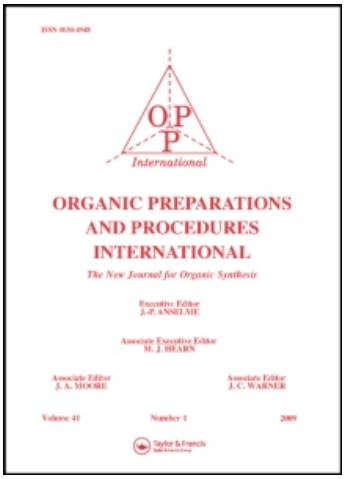

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(±)-SEDAMINE AND (±)-ALLOSEDAMINE BY REDUTION OF N-METHYL-2-PHENACYLIDENEPIPER1DINE

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(±)-SEDAMINE AND (±)-ALLOSEDAMINE BY REDUTION OF N-METHYL-2-PHENACYLIDENEPIPERIDINE

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Sedamine (**4**) is one of a series of α- and α,α'-substituted piperidine derivatives found in various *sedium* species.[1] Sedamine was the first of these alkaloids to be characterized and elucidated structurally.[2] Pyne and coworkers[3] have used the strategy of addition of nucleophiles to chiral vinyl sulfoxides for the asymmetric synthesis of chiral molecules and natural products such as sedamine. Vaultier and coworkers[4] have reported a stereoselective one-pot synthesis of γ-aminoalcohols and applied it in the synthesis of (±)-norsedamine and its pyrrolidino analogue. Stereoselective nucleophilic substitution of 6-methoxy-1-methoxycarbonylpipecolate also leads to an enantioselective route to (+)-sedamine.[5] We now report a novel approach for the synthesis of (±)-sedamine (**4**) and (±)-allosedamine (**5**) by reduction of N-methyl-2-phenacylidenepiperidine (**2**).

Thiolactam (**1**), readily prepared in 85% yield from the corresponding lactam and P_4S_{10}, was subjected to alkylative coupling *via* sulfide condensation[6] with phenacyl bromide to give (**2**) in 75% yield.

Reduction of **2** with LAH, i-Bu_2AlH and $NaCNBH_3$ gave **3** while hydrogenation in acidic medium or reduction by $NaBH_4$ in protic solvent (EtOH-H_2O) gave a 1:1 mixture of (±)-sedamine (**4**) and (±)-allosedamine (**5**) easily distinguished by ^1H nmr and separated by column chromatography. On the other hand, reduction of **3** with LAH and i-Bu_2AlH gave a mixture of **4** and **5** with the ratio of 70:30 and 0:100, respectively (Table 1).

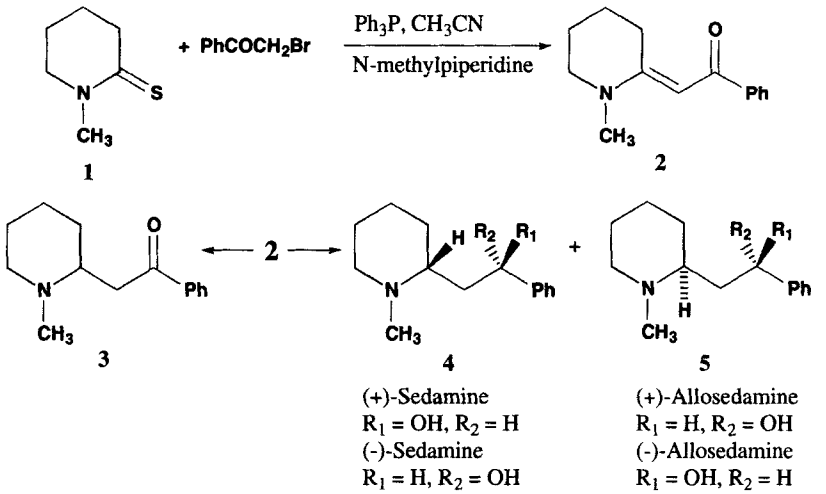

TABLE 1. Reduction of **2** and **3** under Different Conditions.

Entry	Reducing Agent	Reducing agent to substrate	Solvent	Temp (°C)	Time (hrs)	Yield (%)	Product[d] **3**	Ratio of products **4:5**[d]
1	$NaBH_3CN$[a]	1:1	MeOH-HCl	25	16	96	100	–
2	DIBAL[a]	1:1	toluene	0	12	85	100	–
3	DIBAL[a]	1:1	toluene	-64	12	85	100	–
4	$LiAlH_4$[a]	0.25:1	Et_2O	0	7	80	100	–
5	H_2 (PH_2=50 psi)[a] 10% Pt-C, CF_3CO_2H	–	EtOAc	25	2	95	–	50:50
6	$NaBH_4$[a]	1:2	EtOH-H_2O	25	2	88	–	50:50
7	$NaBH_4$[b]	1:2	EtOH-H_2O	25	2	97	–	50:50
8	DIBAL[b]	3:1	toluene	0	12	90	–	0:100
9	$LiAlH_4$[b]		Et_2O	0	10	87	–	70:30

a) Reduction of **2** . b) reduction of **3**. c) isolated yield. d) determined by ^1H NMR.

The use of DIBAL as the reducing agent, might lead to a chelated type structure in which the substituent groups are arranged on the aluminum in such a way that the hydride atom attacks the carbonyl group from one side and produces allosedamine selectively. In the case of $LiAlH_4$, the possibility of formation a chelated structure by lithium ion is also reasonable, due to the oxophilic character of the lithium ion. But in this case, because of the size of the hydride donor (AlH_4^-), attack at the carbonyl group from the less hindered side would be favored, to some extent, thus producing sedamine and allosedamine in the ratio of 70:30.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Brucker-300 MHz Fourier transform NMR spectrometer and the chemical shifts are reported in from δ TMS. Solvents were dried using standard methods. Column chromatography was performed on silica gel (0.063-0.2mm, Merck). Thin-layer chromatography (TLC) was carried out on aluminum backed silica gel plates.

N-methyl-2-piperidinethione.- N-Methyl-2-piperidone (1.13 g, 0.01 mol) was dissolved in 70 mL THF in a 250ml Morton flask equipped with vigorous mechanical stirrer. The mixture was kept in an oil bath at 32° under N_2. Then P_4S_{10} (1.34 g, 3 mmol) was added. Three additional portions of P_4S_{10}, (0.45 g, 1 mmol each) was added at intervals of 1 hr. After the last addition of P_4S_{10}, the mixture was stirred for another 10 hrs, and then filtered through a bed of Celite (1.5 cm x 4 cm). The filter cake was washed with eight 15 mL portions of CH_2Cl_2. The THF solution was taken to dryness *in vacuo* and the residue dissolved in the combined CH_2Cl_2 washes. The CH_2Cl_2 solution was washed with sat. $NaHCO_3$ (2x30 mL), the aqueous phase was reextracted with 50 mL CH_2Cl_2 and the combined organic phase dried over Na_2SO_4. Evaporation gave 1.1 g (85%, yield) of crude product as a yellowish oil. The sample was distilled by bulb-to-bulb technique to give a white crystalline solid, mp. 31-32°. ^1H NMR ($CDCl_3$): δ 1.7- 2.0 (m, 4H), 2.95 (t, 2H, 6.4Hz), 3.47 (s, 3H), 3.5 (t, 2H, 6.3Hz).
Anal. Calcd. for $C_6H_{11}NS$: C, 58.81; H, 8.53; N, 10.85. Found: C, 58.88; H, 8.61; N, 10.81

N-Methylpiperidine-2-ylideneacetophenone.- Phenacyl bromide (1.59 g, 8 mmol) was dissolved in CH_3CN (10 mL) and N-methyl-2-piperidinethione (0.55 g, 4.26 mmol) was added. The mixture was stirred at room temperature under Ar overnight. After dilution with dry CH_2Cl_2 (35 mL), the solution was cooled to -20°, triphenylphosphine (1.04 g, 4.2 mmol) was added, the mixture was stirred for 45 min, and then N-methylpiperidine (1.46 mL, 12 mmol) was added by means of a syringe at a rate of 0.39 mL min^{-1}. Stirring was continued for 6 hrs, and allowing the bath temperature finally to reach 0°. The solution was then washed with 1M KH_2PO_4 (2x15 mL) and saturated $NaHCO_3$ (15 mL). Drying, filtering, and evaporation gave the crude product which was purified by chromatography on SiO_2 eluting with *n*-hexane and then 15% EtOAc in *n*-hexane. The separated product was recrystallized from hexane-EtOAc (78:22), to give 0.6 g. (65%) of a colorless solid, mp. 68-70°. ^1H NMR ($CDCl_3$): δ 1.70 (m, 2H), 1.82 (m, 2H), 2.98 (s, 3H), 3.32 (m, 4H), 5.65 (s, 1H), 7.3 (m, 3H), 7.84 (m, 2H).
Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.00; H, 8.20; N, 6.27

(±)-Sedamine and (±)-Allosedamine.- To a solution of N-methylpiperidine-2-ylideneacetophenone (50 mg, 0.23 mmol) in 10 mL EtOAc was added trifluoroacetic acid (0.8 g, or 20 drops). The solution was degassed (N_2) and 10% Pt/C was added (10 mg) and the mixture hydrogenated in a Parr shaker (pH_2 = 50 psi) at room temperature for 2 hrs. The TLC of the reaction mixture showed one spot and the nmr spectrum of the residue was consistent with a mixture of approximately 50:50 of sedamine and allosedamine. (±)-Sedamine and (±)-allosedamine were separated by column chromatography on SiO_2 (MeOH as eluent) to yield after chromatography 25 mg (49%) of (±)-sedamine, mp.87-88°, lit.[7] 88-89° and 23 mg (45%) of (±)-allosedamine, mp. 68-69°, lit.[7] 67-68° as colorless solids.

(±)-Allosedamine.- A dry 100 mL flask equipped with a magnetic stirring bar, septum inlet and mercury bubbler is flashed with nitrogen and then maintained under a static nitrogen pressure. The flask is charged with 50 mL of dry toluene and 30 mg (0.14 mmol) of the compound **3** and then cooled to 0 with an ice-water bath. Reduction is achieved by the addition of 0.7 mL (4.9 mmol) of 1.00M diisobutyl aluminum hydride in hexane. The solution is stirred for 1 hr at 0° and 5 hrs at 25°. Then 5 mL methanol is added to destroy traces of residual hydride. The reaction flask is then placed in a water bath at 20-25°, and the reaction mixture is treated with 20 mL diethyl ether, 5 mL water. The organic layer is separated from the aqueous layer. After drying the organic layer over anhydrous magnesium sulfate, the solvents are removed on a rotary evaporator, providing 27 mg, 90% of (±)-allosedamine, mp. 68-69° as a colorless solid.

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