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STEREOCHEMISTRY OF THE ASYMMETRIC REDUCTION OF (1'S)-1,3-DIMETHYL-4-(1'-PHENYLETHYLIMINO)PIPERIDINE

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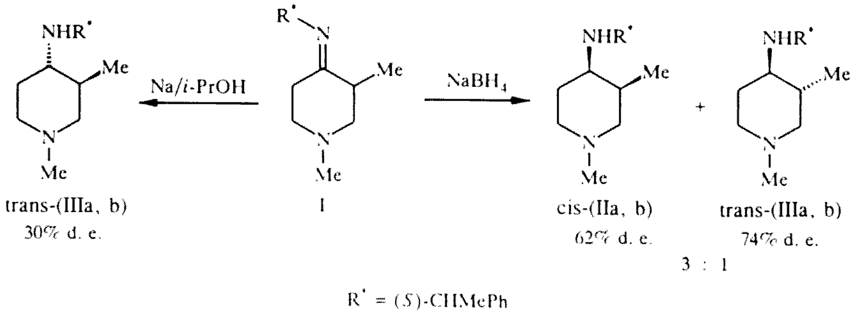
The stereochemistry of the asymmetric reduction of the imine obtained from 1,3-dimethylpiperidin-4-one and (S)-α-phenylethylamine has been studied. It is shown that hydride reduction of imine I by sodium borohydride in methanol is asymmetric and gives the cis and trans diastereomeric pair 1,3-dimethyl-4-(α-phenylethylamino)piperidine in the ratio 3:1. Using sodium in isopropanol gives only one trans diastereomeric pair. ^{1}H NMR has been used to identify the stereochemical structure and diastereomer excess of the cis and trans isomers of 1,3-dimethyl-4-(α-phenylethylamino)piperidine which had been separated by column chromatography.

4-Aminopiperidines show a very broad spectrum of biological activity. A large number of medicines have been based upon them, amongst which highly active analgesics occupy a special place.

There are no reports in the literature concerning the asymmetric synthesis of optically active 4-aminopiperidines. However, there is evidence for different analgesic effects in the optical isomers of 4-aminopiperidines. Hence (+)-cis-(3R,4S)-1-(2-phenylethyl)-3-methyl-4-(N-phenyl-N-propionylamino)-piperidine is 100 times more active than the (−)-cis-(3S,4R)-enantiomer [1].

We have discovered a stereoselective reduction of the prochiral azomethine group of (1'S)-1,3-dimethyl-4-(1'-phenylethylimino)piperidine (I) which has an asymmetric α-phenylethyl substituent with S-configuration.



Reduction of chiral imine I with sodium borohydride in methanol gives an 80% yield of (1'S)-1,3-dimethyl-4-(1'-phenylethylamino)piperidine as a mixture of the cis (IIa, b) and trans (IIIa, b) diastereomer pairs in the ratio 3:1. These diastereomer pairs were separated using column chromatography on aluminium oxide. According to ^{1}H NMR spectroscopy, in the cis pair the ratio of diastereomers IIa:IIb is 81:19 and in the trans pair IIIa:IIIb is 87:13. Thus the diastereomer excesses (d.e.) for the cis and trans pairs are 62 and 74% respectively.

Reduction of I with sodium in isopropanol gives a 70% yield of just the trans diastereomer pair (1'S)-1,3-dimethyl-4-(1'-phenylethylamino)piperidine (IIIa, b). The IIIa:IIIb ratio is 35:65 corresponding to an optical purity of 30%. It was found that predominating in this pair is diastereomer IIIb which is the minor one for hydride reduction of chiral imine I.

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The stereochemical structures of the cis and trans isomers of (1'S)-1,3-dimethyl-4-(1'-phenylethylamino)piperidine were derived from ^{1}H NMR spectroscopy. The predominantly cis II is conformationally heterogeneous, existing principally in the (1e,3a,4e) conformer, whereas in the minor trans III the conformational equilibrium is shifted completely to the form with equatorial orientations of the 3-methyl and 4-phenylethylamino groups.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer. ^{1}H NMR spectra were taken on Varian XL-300 and Bruker WM-400 instruments for solutions in $C_6D_5CD_3$ at room temperature with TMS internal standard. Chemical shifts are reported on the δ scale. Mass spectra were obtained on an MX-1321 spectrometer with direct introduction of the sample into the ionization source at 150-200°C and ionization energy of 70 eV. Specific rotations were measured on an EPO-1 polarimeter in 0.25 dm length cuvettes at 20°C. Thin layer chromatography was carried out on Merck DC-Alufolien aluminium oxide 60 F_{254} plates using ethyl acetate and heptane (5:1) eluting solvent.

(1'S)-(−)-1,3-Dimethyl-4-(1'-phenylethylimino)piperidine (I) was obtained by [2].

Cis and Trans Diastereomeric Pairs of (1'S)-1,3-dimethyl-4-(1'-phenylethylamino)piperidine (IIa, b and IIIa, b). Sodium borohydride (0.60 g, 15.79 mmole) was added in small portions over 15 min to a solution of (−) I (3.0 g, 13.04 mmole) in methanol (30 ml) cooled in a mixture of ice and salt to 0°C. The product was warmed to room temperature for 30 min and stirred for a further 2 h. Methanol was evaporated *in vacuo* and water (15 ml) was added to dissolve the salt, followed by addition of aqueous NaOH solution (5 N, 2 ml) to pH 10. It was extracted with ether (4 × 10 ml) and the combined organic extracts successively washed with water (5 ml) and saturated NaCl solution (5 ml) and then dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue (3.07 g) chromatographed on an aluminium oxide column using ethyl acetate and heptane (5:1). The chromatographically homogeneous fractions were combined to give the cis II diastereomer pair (1.81 g) as a colorless oil with R_f 0.6 and the trans III diastereomer pair (0.61 g) as a colorless oil with R_f 0.25. The overall yield of IIa, b and IIIa, b was 80% and the ratio of the cis:trans isomers (II:III) 3:1.

Cis Diastereomer Pair (IIa, b): $[\alpha]_D^{20}$ 56.2° (c 7.2 in benzene). Mass spectrum: M^+ 232. M_{calc} 232. PMR spectrum: 0.94 (3H, d, J = 7 Hz, 3-$\underline{CH_3}$), 1.03 (3H, d, J = 7 Hz, 3-$\underline{CH_3}$), 1.20 (3H, d, J = 7 Hz, $CH(\underline{CH_3})C_6H_5$), 1.22 (3H, d, J = 7 Hz, $CH(\underline{CH_3})C_6H_5$), 2.01 (3H, s, $\underline{N\text{-}CH_3}$), 2.06 (3H, s, N-$\underline{CH_3}$), 3.72 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_5$), 3.90 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_5$), 7.05-7.25 ppm (5H, m, $CH(CH_3)\underline{C_6H_5}$). Dipicrate mp 210-211°C (from ethanol). Found, %: C 46.37, 46.23; H 4.47, 4.45; N 16.42, 16.45. $C_{15}H_{24}N_2 \cdot 2C_6H_3N_3O_7$. Calculated, % C 46.96, H 4.38, N 16.23. Diastereomer ratio IIa:IIb 81:19. Diastereomer excess 62%.

Trans Diastereomer Pair (IIIa, b): $[\alpha]_D^{20}$ 10.8° (c 5.1 in benzene). Mass spectrum: M^+ 232. M_{calc} 232. PMR spectrum: 0.89 (3H, d, J = 7 Hz, 3-$\underline{CH_3}$), 0.96 (3H, d, J = 7 Hz, 3-$\underline{CH_3}$), 1.20 (3H, d, J = 7 Hz, $CH(\underline{CH_3})C_6H_5$), 1.21 (3H, d, J = 7 Hz, $CH(\underline{CH_3})C_6H_5$), 2.03 (3H, s, N-$\underline{CH_3}$), 2.07 (3H, s, N-$\underline{CH_3}$), 3.76 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_5$), 3.87 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_5$), 7.00-7.32 ppm (5H, m, $CH(CH_3)\underline{C_6H_5}$). Diastereomer ratio IIIa:IIIb 87:13. Diastereomer excess 74%.

Trans Diastereomer Pair (IIIa, b). A solution of I (3.0 g, 13.04 mmole) in a mixture of isopropanol and dry benzene (60 ml, 1:1) was added dropwise over 20 min to a vigorously stirred suspension of finely dispersed metallic sodium (1.05 g, 45.65 mmole) in dry benzene (40 ml). The reaction mixture was refluxed for 3 h, isopropanol (10 ml) added, and reflux continued for a further 1 h. After cooling, the solvent was removed *in vacuo*. Water (15 ml) was added to the residue which was then extracted with ether (4 × 10 ml). The combined organic extracts were washed with water (5 ml) and saturated aqueous NaCl (5 ml) and dried with Na_2SO_4. Ether was removed *in vacuo*. The dry product was then chromatographed on aluminum oxide to give the trans diastereomer pair (IIIa, b, 2.12 g, 70%) as a colorless oil with R_f 0.25. IR spectrum (thin layer): 3300 cm^{-1} (N−H). $[\alpha]_D^{20}$ 66.1° (c 6.8 in benzene). Mass spectrum: M^+ 232. M_{calc} 232. PMR spectrum: 0.90 (3H, d, J = 7 Hz, 3-$\underline{CH_3}$), 0.97 (3H, d, J = 7 Hz, 3-CH_3), 1.20 (3H, d, J = 7 Hz, $CH(\underline{CH_3})C_6H_5$), 1.22 (3H, d, J = 7 Hz, $CH(CH_3)C_6H_5$), 2.03 (3H, s, N-CH_3), 2.07 (3H, s, N-CH_3), 3.87 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_5$), 3.94 (1H, q, J = 7 Hz, $\underline{CH}(CH_3)C_6H_6$), 7.20-7.40 ppm (5H, m, $CH(CH_3)\underline{C_6H_5}$). Diastereomer ratio IIIa:IIIb 35:65. Diastereomer excess 30%.

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