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SEDUM ALKALOIDS. VIII. SOLUTION CONFORMATION OF SEDAMINE AND RELATED BASES.

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Abstract. The preferred solution conformation of sedamine, allosedamine, norsedamine and norallosedamine was established by high resolution proton and carbon-13 NMR spectroscopy.

In a previous communication we established, by high resolution ^{1}H and ^{13}C NMR spectroscopy, the preferred solution conformation of 2,6-dialkylpiperidine alkaloids isolated from Sedum acre[1]. We now wish to report our results concerning the favoured conformation in $CDCl_3$ of the 2-alkylpiperidine bases sedamine 1, allosedamine 2 and the corresponding nor-derivatives 3 and 4.

Sedamine was the first alkaloid isolated from Sedum acre[2,3] and has been obtained later from a number of Sedum species[4,5]; both the laevorotatory 1 and the dextrorotatory enantiomeric forms were found in all of them. The diastereoisomeric alkaloid (-)-allosedamine 2 is a long-known constituent of Lobelia inflata[6,7]. Allosedamine has been detected in S. acre[8] but the optical rotation was not recorded; during our systematic search for piperidine alkaloids we only isolated (-)-allosedamine from this species. (+)-Norallosedamine 4 is known to occur in Lobelia inflata[7,9] while norsedamine 3[10] has not yet been found in nature.

The infrared spectra of 1, 2, 3 and 4 in CCl_4 showed the presence of an intramolecularly bonded OH (broad band at 3200 cm^{-1} unaffected by dilution). The four bases may therefore exist in three interconvertible chair conformations as illustrated in figure 1.

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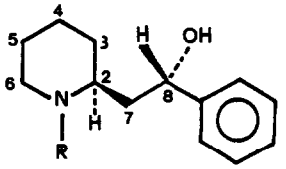
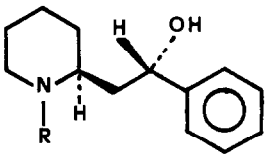


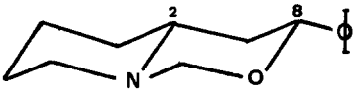
1 R = CH_3

3 R = H



2 R = CH_3

4 R = H



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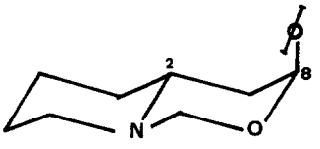

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The ^1H NMR spectra of 1 and 2 ($CDCl_3$) are largely first-order. The comparison of these spectra with those of the corresponding C7 dideuterated analogues allowed to extract the coupling constants of H2, H7 and H8. Their values were verified by iterative spectral simulations and are reported in table 1. The vicinal coupling constants between H8 and the C7 protons establish the equatorial orientation of the phenyl group in both compounds. Allosedamine 2 must therefore exist predominantly in the cis-fused conformation 2b. The observation that the H2 protons of 2 exhibits only one axial-axial coupling (with H3) substantiates this conclusion also expected on the basis of simple conformational analysis considerations. In the case of sedamine 1, the H2 proton similarly exhibits but one axial-axial coupling (with H7) thus demonstrating that this base exists predominantly in the cis-fused conformation 1c.

The ^{13}C chemical shifts of 1 and 2 are reported in table 3. The N-CH_3 group is shielded in 1c where it is axial to the piperidine ring and has therefore two γ-gauche interactions with C3 and C5 whereas only one, with C7, is present in 2b. The shielding of C6 in 1c results from the γ-gauche interaction with C7 and from the β effect of the axial methyl group. The assignments of the other carbon atoms are evident for C2, C7 and C8 and were made on the basis of the established conformations 1c and 2b for C3, C4 and C5.

The replacement of the methyl group of 1 by a hydrogen atom is expected to favour conformation 3a with a trans-ring fusion and an equatorial phenyl group in norsedamine 3. The vicinal coupling constants between H8 and the C7 protons and the presence of two axial-axial couplings for H2 (with H3a and H7a; table 2) are in agreement with this view.

The ^1H NMR spectral data for norallosedamine 4 are reported in table 2; these values were verified by decoupling experiments and iterative spectral simulations. Due to the nearly identical chemical shifts of the H3 protons, an analysis of the H2 multiplicity was impossible at 250 MHz but could be achieved at 500 MHz. This analysis was important since it allowed to determine the couplings of H2 with the H3 protons, which are essential for the determination of the conformation. It appears immediately that the vicinal coupling constants between H2, H7 and H8 are different from those expected if one of the conformations 4a, 4b or 4c predominates. On the other hand, a rapid equilibrium between conformations (e.g. 4a and 4b)

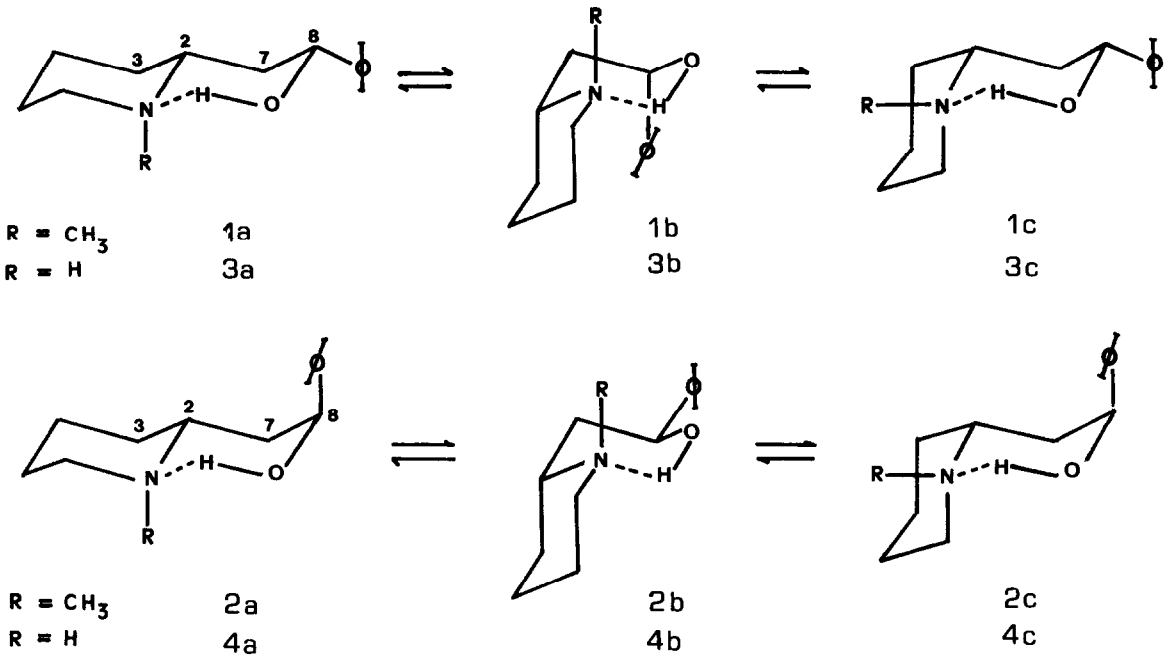

Figure 1. The chair conformations of sedamine, allosedamine, norsedamine and norallosedamine. These structures are the mirror images of 1, 2, 3 and 4 and represent respectively (+)-sedamine, (+)-allosedamine, (+)-norsedamine and (-)-norallosedamine.

can be ruled out: the ^{1}H NMR spectrum of 4 remains virtually unaltered by lowering the temperature from +30°C to -50°C. It is likely therefore that the actual conformation of the pseudo-cycle departs appreciably from a chair form. The magnitude of the vicinal couplings between H2 and H3 clearly shows that the C2 substituent of the piperidine ring is equatorially oriented. Inspection of molecular models indicates that the strong steric interaction between H2 and the axial phenyl group in 4a can be released by distorting the pseudo-cycle into a twisted conformation 4d (figure 2). In this conformation, the dihedral angle of about 20-30° between H2 and H7e and between H8 and H7a is in agreement with the observed couplings of 7.7 Hz and 7.4 Hz respectively[11].

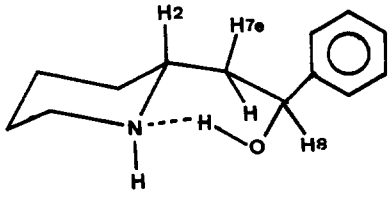

Figure 2. The twisted conformation of norallosedamine.

A comparison of the ^{13}C chemical shifts (table 3) of norallosedamine 4 relative to norsedamine 3 shows essentially a shielding of C2 and C8 in 4. This shielding is moderate ($\Delta\delta$: 3.9 ppm for C2 and 3.7 ppm for C8), compared to the values observed in the related tetrahydro 1,3-oxazines 5 and 6 ($\Delta\delta$: 4.4 ppm for C2 and

7.0 ppm for C8)[12] and is in agreement with previous observations about ring carbons in twist conformations[13].

In this series of compounds, norsedamine 3 adopts a trans-fused conformation 3a, in which the unfavourable 1,3-lone pair interactions are avoided by the axial orientation of the N-H, as is observed for tetrahydro 1,3-oxazines[14]. The replacement of the hydrogen on nitrogen in 3 by a methyl in sedamine 1, causes a conformational change to the cis form 1c. This was not anticipated but could be firmly proved by the analysis of the multiplicity of the H2 signal.

In the allo-series, a similar effect is observed: the N-methyl compound allosedamine 2 adopts the cis conformation 2b, whereas the NH compound norallosedamine 4 prefers a distorted trans conformation 4d.

The reasons for the preference of the cis conformation in sedamine 1 are not clear to us. However, since the difference between the cis and trans conformations amounts to only one gauche-butane interaction[15], this small energy difference cannot be easily evaluated without a detailed study of the geometry and the interactions which are present in the pseudo-cycle.

Table 1. ^{1}H-NMR data ($CDCl_3$) of sedamine 1 and allosedamine 2.

Proton	Sedamine 1 (250 MHz)		Allosedamine 2 (250 MHz)	
	δ	J Hz (coupled proton)	δ	J Hz (coupled proton)
H8	4.90	2.8(H7e), 10.5(H7a)	5.12	3.5(H7e), 10.6(H7a)
H2	2.86	9.7(H7a), 6(H3a), 4(H7e,H3e)	2.26	10.3(H3a), 3.5(H7a,H7e,H3e)
NCH_3	2.49		2.43	
H7a	2.12	-14.4(H7e), 10.5(H8), 9.7(H2)	2.16	-14.9(H7e), 10.6(H8), 3.5(H2)
H7e	1.46	-14.4(H7a), 4(H2), 2.8(H8)	1.63	-14.9(H7a), 3.5(H8,H2)
H6	3.07		2.95	
H6'	2.56		2.04	
H3	1.72		1.84	
H3'	1.36		1.62	

Table 2. ^{1}H-NMR data ($CDCl_3$) of norsedamine 3 and norallosedamine 4.

Proton	Norsedamine 3 (250 MHz)		Norallosedamine 4 (500 MHz)	
	δ	J Hz (coupled proton)	δ	J Hz (coupled proton)
H8	4.92	2.7(H7e), 10.5(H7a)	5.05	3.8(H7e), 7.4(H7a)
H2	2.87	2.6(H3e,H7e), 10.5(H3a,H7a)	2.79	2.8(H3'), 2.9(H7a), 10.5(H3), 7.7(H7e)
H7a	1.55		1.73	2.9(H2), 7.4(H8),-14.5(H7e)
H7e	1.69	2.7(H2, H8), -14.3(H7a)	1.88	7.7(H2), 3.8(H8),-14.5(H7a)
H6e	3.05		3.08	
H6a	2.63		2.57	
H3	not determined		1.40	
H3'	not determined		1.38	

Table 3. ^{13}C Chemical shifts ($CDCl_3$) of compounds 1-4.

Carbon	C2	C3	C4	C5	C6	C7	C8	NCH_3
1	61.0	26.1	20.8	22.6	51.7	40.0	74.6	40.1
2	62.6	29.3	24.3	25.4	56.9	39.6	72.0	43.8
3	58.2	34.3	24.5	27.4	46.0	45.3	75.4	-
4	54.3	32.2	24.6	26.4	46.6	44.4	71.7	-

EXPERIMENTAL

The NMR spectra were recorded on Bruker WM 250 and AM 500 apparatus, working in the FT mode and equipped with an Aspect 2000 and Aspect 3000 computer respectively. Sample concentration was 2-3 mg/0.5 mL $CDCl_3$ for ^{1}H spectra and 20-30 mg/0.5 mL $CDCl_3$ for ^{13}C cpectra. Spectra simulations were performed with the PANIC program. Signal assignment in the ^{13}C NMR spectra was aided by the DEPT pulse sequence and single frequency decoupling experiments.

The IR spectra were recorded in CCl_4 on a Perkin-Elmer 237 apparatus; sample concentration was varied from 10 mg/mL to 1 mg/mL.

Sedamine, allosedamine, norsedamine and norallosedamine used in this study are racemic samples of synthetic origin; their physical properties are in agreement with the values given in the literature[10,16].

7,7-d_2-Sedamine and 7,7-d_2-allosedamine from sedaminone.

Sedaminone[17] (506 mg) was dissolved in dioxane (10 mL) and D_2O (10 mL) and potassium carbonate (750 mg) was added; the mixture was left at room temperature for two days and then extracted with $CHCl_3$. After evaporation of the solvent, the treatment was repeated to yield 7,7-d_2-sedaminone ($M^{+\cdot}$ at m/z 219). Treatment of this ketone with $LiAlH_4$ (300 mg) in THF (30 mL) for five hours yielded after the usual workup a 1:1 mixture (390 mg) of 7,7-d_2-sedamine and 7,7-d_2-allosedamine. The mixture was subjected to a counter-current distribution (trichloroethylene/McIlvaine buffer pH 7.2). Tubes 5-13 contained pure 7,7-d_2-allosedamine (70 mg) and tubes 18-23 contained pure 7,7-d_2-sedamine (140 mg). The two bases were crystallized from petroleum ether before use (MS: $M^{+\cdot}$ at m/z 221).

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