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SEDUM ALKALOIDS—VI

RESOLUTION ENHANCED PROTON NMR AND ^{13}C NMR SPECTROSCOPIC STUDIES ON THE SOLUTION CONFORMATION OF *SEDUM ACRE* ALKALOIDS

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Abstract—The preferred solution conformation of 9 Sedum alkaloids and derivatives (sedinine, dihydrosedinine. 8-episedinine, diacetylsedinine, sedinone, 2-episedinone, sedacrine, 2-episedacrine and sedacryptine) was established by high resolution ^1H and ^{13}C NMR spectroscopy. These compounds may be divided into three classes based on the existence or the absence of an intramolecular hydrogen bond between the nitrogen atom and the hydroxyl group at C8 or at C10. In all of them (except sedacryptine) the N–CH_3 group was found to be axially oriented.

Recently we isolated several piperidine alkaloids from *Sedum acre*. Their structures were determined by spectroscopic methods as well as by chemical interconversions.[1-3]

We now report the results of a complete analysis of the 270 MHz proton NMR spectra of sedinine **1** and of sedacrine **2** (Fig. 1). For the former, X-ray crystallography established the position of the double bond and the conformation in the crystal.[2] Furthermore the interpretation of the ^{13}C NMR spectra of the family of alkaloids and derivatives **1** to **9** (Fig. 1) allowed us to establish their preferred solution conformation.

RESULTS AND INTERPRETATION

Proton NMR

In general the proton NMR spectra of even small alkaloids such as **1–9** are very complex due in part to spectral overlap, but mainly because of the presence of a large variety of coupling paths. The presence of unresolved small couplings results in a broadening of the signals and thus prevents the extraction of the relevant coupling data (Fig. 2a). However, the application of a digital resolution enhancement function reveals the enormous potentiality of high field proton NMR spectroscopy for structure determinations. We were thus able to resolve all the necessary transitions (Fig. 2b) and to obtain all the coupling constants after iterative spectral simulations (Fig. 2c) for the two alkaloids which were studied sedinine **1** and sedacrine **2** (Tables 1 and 2).

For sedinine **1**, the vicinal couplings between H6 and the C5 protons establish the equatorial orientation of the C6 sidechain, whereas the value of 4.0 Hz for $^3J(H2, H3)$ establishes the axial orientation[4] of the C2 sidechain. Both data are consistent with a half-chair conformation of the piperideine ring. The vicinal coupling constants between H2 and the C7 protons (10.0 and 3.3 Hz) clearly indicate a fairly rigid sidechain. On the other hand, the corresponding values of the vicinal couplings in the C6 sidechain (7.8 and 6.1 Hz) show much more averaged values, which is consistent with a greater conformational mobility. These observations indicate a solution conformation (Fig. 3) for

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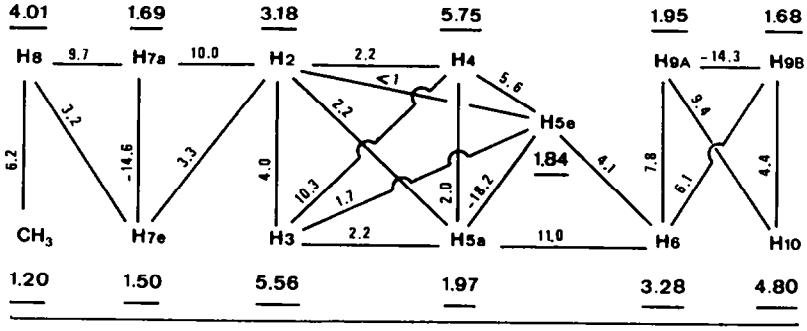
Table 1. Chemical shifts (ppm, underlined) and coupling constants (Hz) of sedinine **1**



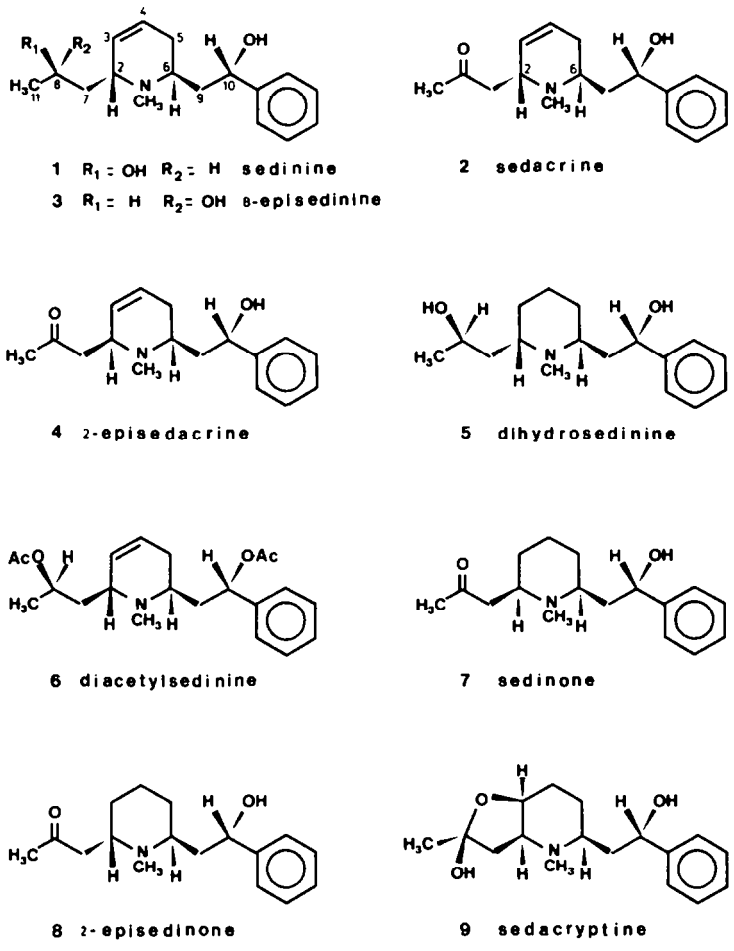
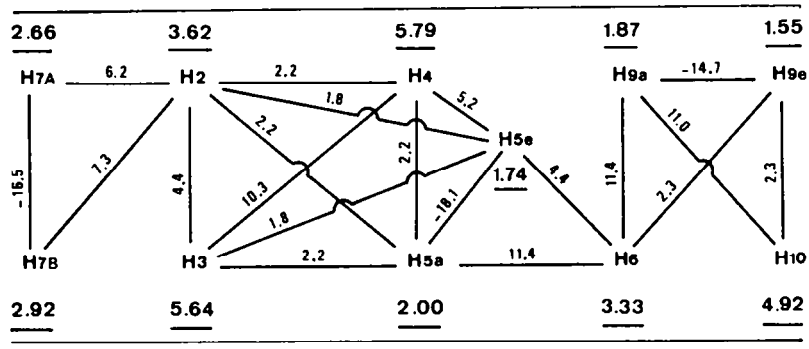


Fig. 1.

Table 2. Chemical shifts (ppm, underlined) and coupling constants (Hz) of sedacrine **2**



sedinine **1** which is identical to the one in the crystal.[2] The rigidity of the C2 sidechain is due to the formation of a pseudo-cyclic conformation through a hydrogen bond between the nitrogen atom and the C8 hydroxyl group.

For sedacrine **2** similar observations can be made with regard to the piperideine conformation: the C2 sidechain is axial and the C6 sidechain is equatorial. However, the sidechain mobilities are reversed: a mobile C2 sidechain as indicated by averaged ^3J(H2, H7A and H2, H7B), and a fixed C6 sidechain conformation as indicated by extreme ^3J(H6, H9a and H6, H9e). The proposed conformation therefore has a pseudo-cyclic conformation in which the hydrogen bond involves the C10 hydroxyl group (Fig. 3). This hydrogen bond is detected as a concentration independent absorption in the infrared spectrum of **2**.[3] The axial orientation of the N-methyl group is confirmed by the observation of a 12% NOE effect on H2 and none on H6 on irradiation of the N-methyl signal.

In both compounds it is interesting to note that homoallylic couplings over the C3–C4 double bond can be resolved. These confirm the half-chain conformation on the piperideine ring (Fig. 4a). Indeed, a boat conformation (as in Fig. 4b) would lead to a

Fig. 2. H3 and H4 signals of sedinine 1. Trace a: normal spectrum; trace b: resolution enhanced spectrum; trace c: simulated spectrum.

larger homoallylic coupling between H2 and H5e than between H2 and H5a,[5] which is contrary to our observations.

^{13}C NMR

The signal assignments for sedinine 1 as shown in Fig. 5, are based on the multiplicities and on selective proton decoupling experiments for every carbon, except for the phenyl carbons. In sedacrine 2, the assignments of C7 and C11 were confirmed by deuterium exchange in these positions. For all the compounds, the chemical shifts were compared throughout the series. Although some ambiguities in the assignments remain present, none of the chemical shifts that are pertinent to the following conformational considerations can be interconverted without giving an inconsistency.

The shifts are shown in Figs. 5–7, along with the preferred conformations which were deduced from them. The compounds were divided into three classes: those forming a pseudo-cyclic conformation through a hydrogen bond with the C2 sidechain (Fig. 5), with the C6 sidechain (Fig. 6), or those without the pseudo-cyclic conformation (Fig. 7).

The formation of an intramolecular hydrogen bond and the concomitant fixation of the sidechain conformation and flexibility of the other sidechain has a profound influence on the spectrum. For instance, on going from sedinine 1 to 8-episedinine 3, C2 shifts 4.7 ppm upfield, which can be ascribed to a gauche interaction with the now mobile sidechain. On the other hand, C6 experiences a 3.9 ppm downfield shift in 3 due to the fixation of its sidechain and due to the disappearance of a gauche interaction with the C8 hydroxyl group.

When both sidechains are mobile as in diacetylsedinine 6 (Fig. 7), the chemical shift of C2 is

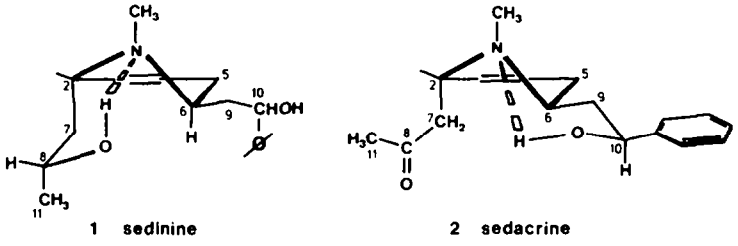


Fig. 3. Preferred solution conformation of sedinine 1 and sedacrine 2.

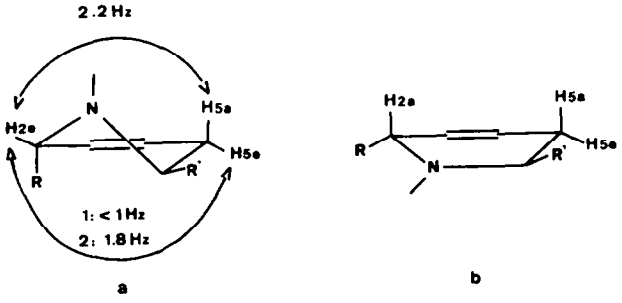


Fig. 4. Homoallylic couplings in sedinine 1 and sedacrine 2 and half-chair (a) or boat conformation (b) of the piperideine ring.

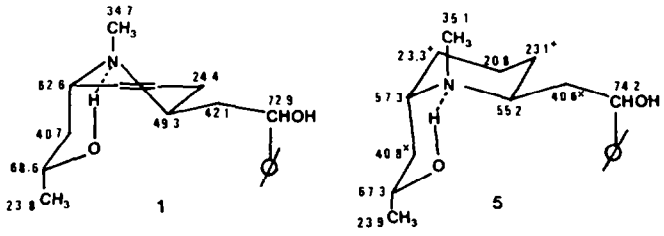


Fig. 5. ^{13}C chemical shifts of sedinine **1** and dihydrosedinine **5**.

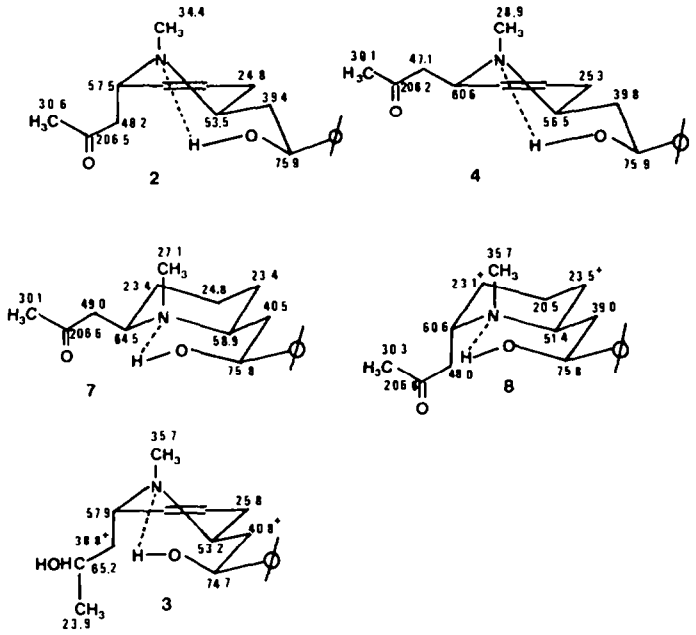


Fig. 6. ^{13}C chemical shifts of sedacrine **2**, 8-episedinine **3**, 2-episedacrine **4**, sedinone **7** and 2-episedinone **8**.

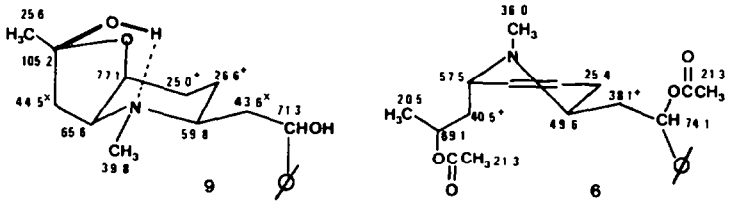


Fig. 7. ^{13}C chemical shifts of diacetylsedinine **6** and sedacryptine **9**.

similar to the one in **3** and that of C6 is similar to the one in **1**.

The change from an axial towards an equatorial orientation of the C2 sidechain results in a smaller downfield shift for C2 and C6 in the unsaturated compounds (**2**→**4**) than in the dihydroderivatives (**8**→**7**). This is as expected for the flattened half-chair form in the former compounds. In the latter compounds the chemical shift of C4 (20.5 ppm in **8** vs 24.8 ppm in **7**) is characteristic for the C2 configuration.

The chemical shift of the N-methyl group in those compounds having an axial C2 sidechain is close to the value for an axial N-methyl group in perhydroquinolines ($\delta_a = 33.1$ ppm).[6] When the C2 configuration is changed, the additional gauche interaction shifts the N-methyl signal to 27 ppm (**7**). Even on acetylation of both hydroxyl groups (diacetylsedinine **6**), the N-methyl group remains mainly axial. Only in sedacryptine **9** (Fig. 7) its position is equatorial; the same orientation was observed in the crystal.[1]

DISCUSSION

Some remarkable features can be observed in the conformations adopted by these 1,2,6-substituted piperidines. Two of the three substituents prefer a trans-diaxial arrangement. The equatorial orientation of the N-methyl group would however give rise to gauche interactions with the 2 and 6 substituents which are less easy to relieve by ring deformation than those for the axial orientation. It would also not allow the formation of an intramolecular hydrogen

bond, unless the substituent of the pseudo-cyclic conformation is in an axial position.

In sedinine **1** and dihydrosedinine **5**, the molecules also prefer to form an intramolecular hydrogen bond which leads to a cis fused ring system over that leading to a trans fused system. This can probably be explained by the fact that on formation of a hydrogen bond, the sidechain is fixed into a pseudo-cyclic conformation. As a result the steric interactions of the secondary carbinol substituent (methyl or phenyl) with the piperidine ring are reduced since the substituent is oriented away from the ring. The steric interactions of a freely rotating axial C2 substituent being larger than those of a freely rotating equatorial C6 substituent, the molecule prefers to fix the C2 substituent into the pseudo-cyclic conformation.

EXPERIMENTAL

NMR spectra were recorded on a Bruker HX270 apparatus, working in the FT mode and equipped with an Aspect 2000 computer. The ^1H spectral width was 3000 Hz, the interferogram was stored in 16 K data points. For resolution enhancement, the lorentian to gaussian transformation function was used, supplied by standard Bruker software. Spectra simulations were performed with the PANIC program, to within a r.m.s. error of 0.25 Hz. Sample concentration was 2–3 mg/0.5 mL $CDCl_3$ for ^1H spectra and 20–30 mg/mL for ^{13}C spectra.

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