Nuclear Magnetic Resonance and Stereochemistry of Vincamone

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The stereochemistry in solution of vincamone was deduced by proton magnetic resonance using the paramagnetic shifts reagent $Eu(fod)_3$. The lanthanide induced shift computer simulation suggests that, at room temperature, the indole group is nearly planar, the rings C and E assume the envelope conformation with N-4 and C-16 as flaps, the ring D is in the chair one and the ethyl side chain prefers a *trans* position with respect to C-15.

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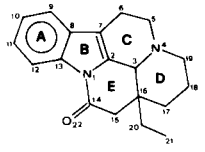
The vincamone (**1**) (1), an optical antipode of eburnamonine (2), is widely used for the treatment of cerebrovascular diseases and has a longer duration of activity and more pronounced effects than the vincamine (3).



Diffractometric data of **1** had been reported (4), but it is interesting to deduce also its stereochemistry in solution, since it can be considered as being the nearest to the form in which the drug exercises its pharmacological activity. On the other hand, the conformation in solution may be different from that present in the solid state for solute-solvent interactions. We report here the analysis by computer simulation of the ^1H nmr spectra of vincamone in order to contribute to understanding of the relationship between molecular structure and biological activity.

Results and Discussion.

The vincamone molecule consists of a pentacyclic system and an ethyl side chain. The examination of its undoped ^1H nmr spectrum (Table I) in deuteriochloroform solution at room temperature gives evidence that the aromatic proton shifts are in agreement with those reported in literature for other indole alkaloids. As regards the alicyclic portion, apart from the 3-H that shows a broad singlet at 3.78 ppm, all signals fall between 1.21 and 3.33 ppm; for accidental isocrony, the C-15 protons resonate as a singlet at 2.53 ppm. Easily discernible is the A_3X_2 system for $-CH_2-CH_3$ protons for which is observed a quartet and a triplet respectively ($J = 7$ Hz). An eventual enol form is not considered because of the absence of hydroxyl absorption in the spectrum under the adopted experimental conditions.

The analysis of the methylene region appeared very difficult because of the problem of selecting correct coupling constants from the observed and unresolved resonance pattern produced by the close proximity of the relative proton chemical shifts. An attempt to simplify the ^1H nmr absorption by lanthanide shift reagent (LSR) doping was therefore made; the ability of lanthanide derivatives to produce a notable increase in the dispersion in the nmr spectra of lone-pair-containing organic compounds is well known (5). The choice of $Eu(fod)_3$ as shift reagent used in our analysis derives from consideration of three factors: the shift towards low field, the small broadening of resonances and the negligible contact contribution.

The addition of $Eu(fod)_3$ to a deuteriochloroform solution produced the expected resonance shifts towards lower field, with an almost linear dependence of lanthanide induced shift (LIS) on lanthanide/substrate (L/S): the alicyclic pattern is simplified and the resulting spectra allow us to establish, by extrapolation, the chemical shifts of almost all methylene protons (Table I).

The C-12 and C-15 protons are the most deshielded by LSR owing to their greater proximity to the carbonyl oxygen, which represents the preferred site of complexation for Eu^{+3}, while the LIS observed for the other signals of the spectrum is not very remarkable in particular is considerably smaller for methyl protons (see table). It is interesting to see the evidence that the singlet observed for the two C-15 protons in the undoped spectrum, gradually transforms, at high L/S values, into the four line AB pattern which then became discernible. These results clearly demonstrate the validity of the additivity of the LSR, when two chemical shifts are accidentally coincident and when the resonances cannot be unambigously assigned.

It is known that the application of LSR in the nmr spectra, in addition to considerable spectra simplification, allows one to obtain configurational information and throw some light on the preferred conformation of organic molecules in solution.

In the title compound the possibility of a number of conformations has been considered. From a stereochemical standpoint the esatomic rings C, D and E can be regarded as systems able to assume intermediate configurations between two limit situations: envelope or twist for C and E, chair or boat for D, whereas the indole group can be considered nearly planar and the ethyl side chain is free to

Table I

Chemical Shifts (δ), Experimental and Calculated LIS for Vincamone Experimental Values are Eu(fod)$_3$-Induced Shift Ratios. Calculated Values are for the Structure with A (a) = 31°, B (b) = 3.5 Å and D_R (c) = 221° for which TQRF = 0.038. The Standard Nucleus is 21-Me.

Protons	δ (ppm)	Exp. LIS	Calcd. LIS
3H	3.78 s	6.50	5.76
9H			
10H	7.30 m		
11H		3.32	3.34
12H	8.33	17.50	17.68
15H	2.53 s	16.50	16.67
15H'		15.80	15.85
17H	1.38 t	5.70	5.85
17H'			
18H	2.08-2.70 m	3.80	3.11
18H'			3.80
19H	2.83-3.33 m		
19H'			
20H	1.8 q (J = 7 Hz)	3.50	3.59
20H'			2.91
21Me	0.91 t (J = 7 Hz)	1	

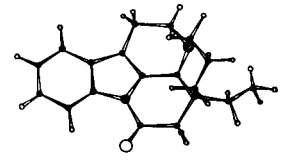
(a) A = Ln-O-C_{14} angle supplement. (b) B = Ln-O bond length. (c) D_R = Dihedral angle about C_{16}-C_{20} bond, which defines the orientation of side chain with respect C_{16}-C_{15} bond.

assume the position which is sterically less hindered. Furthermore the possibility of a nitrogen inversion cannot be ruled out.

Taking into account the above condiserations the simulation of the observed LIS using computational procedures appeared to us a valuable method for the elucidation of the vincamone molecular structure in solution.

The stereochemistry of the lanthanide-substrate complex may be achieved according to the McConnell-Robertson equation (6) $\Delta\nu = K[(3\cos^2\chi - 1)r^{-3}]$ which correlates the LIS($\Delta\nu$) to the geometric parameters of various protons: the term $(3\cos^2\chi - 1)r^{-3}$ represents the geometrical factor which can be calculated for each proton once the O-Ln-H internuclear angle (χ) and the corresponding Ln-H distance (r) are known, while K is the pseudo-contact constant.

The theoretical LIS of the protons in several model structures, intermediate between the possible limiting situations, were computer simulated, using the LISCA (Lanthanide Induced Shift Conformational Analysis) program (7). The substrate was considered as a set of rigid units connected to one another by rotatable bonds and the lanthanide atom as connected to the co-ordinating atom present in the first unit. In the title compound the lanthanide is bound to the carbonyl group present in the pentacyclic skeleton and the ethyl side chain, which represents the second unit, is connected to the first one by the C_{16}-C_{20} single bond. By setting up different structures having intermediate stereochemistry various hypotheses on the nature of the lanthanide substrate complex could be tested. The definitive molecular geometry was assumed to be the one which best fit the observed and calculated LIS. The acceptability of the results was evaluated in terms of Hamilton (8) agreement factor (AF) defined in the LISCA program as the total quasi-R-factor (TQRF) (7). The minimum TQRF (0.038) corresponds to the stereochemistry depicted in figure 1 in which, the indole group is nearly



planar, the rings C and E have the envelope conformation with N-4 and C-6 as flaps, the ring D is in the chair one and the ethyl side chain is in a preferential trans position with respect to C-15.

EXPERIMENTAL

The compound under investigation was extracted from the corresponding drug, Eburnal® with chloroform in a Soxhlet apparatus and crystallized.

The ^{1}H nmr spectra were obtained at 60 MHz on a Varian T-60A spectrometer at probe temperature of 34°, for a solution ca 0.3*M* in deuteriochloroform. All chemical shifts values are given in (δ) ppm related to TMS as internal standard. The Eu(fod)$_3$, [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)europium] was added stepwise from a stock solution (ca 300 mg/ml) using a 50 μl syringe, up to a value of 0.4 moles of ligand (L) per mole of substrate (S). Each signal was followed in the spectra and the LIS were found to be directly proportional to the L/S ratio present. At least-squares fit for the experimental points used to obtain the observed molar LIS. Calculations relative to the simulation of the experimental LIS data were carried out on an IBM 370/115 computer using the LISCA program (7) for the LSR interaction with the carbonyl group. The interatomic distances, bond angles and dihedral angles were taken from Dreiding molecular models and from the available crystallographic data.

Methyl group was treated as twelve equivalent points, on the locus of rotation of the methyl hydrogens, over which the calculated LIS are averaged.

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