

ON THE STRUCTURE OF CATALINE

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Abstract- A pmr study of the 4-hydroxyaporphine cataline in the presence of $\text{Eu}(\text{fod})_3$ further supports structure I proposed for this alkaloid. This was confirmed by an X-Ray analysis.

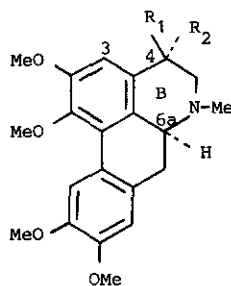
5-Hydroxyberberines and 4-hydroxyaporphines present an interesting problem concerning the biogenetical origin of the benzylic hydroxy group. To find out the configuration of these alkaloids at the hydroxylated center is in this sense of utmost importance¹.

Regarding the 4-hydroxyaporphines, Ribas et al.² have proposed the absolute stereochemistry of cataline as indicated in the structural formula I, in which the hydroxy group is pseudoaxial and the configuration of the hydrogens at C-4 (pseudoequatorial) and C-6a is *cis*. Cataline has later been taken as a reference compound in proposing the configuration at the benzylic hydroxy center of other 4-hydroxyaporphines³.

Nevertheless, Cassels et al.⁴ found the assignment of the configuration at C-4 proposed by Ribas et al. for cataline(I) highly speculative, so that the stereostructures of other 4-hydroxyaporphines would also be dubious. The proposal by Ribas' group² was based mainly on the appearance of the proton at C-4 in the pmr spectrum of cataline and its O-acetyl derivative as a poorly resolved triplet with half-band width 4Hz. According to Cassels' group, Dreiding models built in the 4(S):6a(S) and 4(R):6a(S) configurations with pseudoequatorial C-4 protons do not suggest any clear differences as far as potential energy is concerned. Therefore, any of these two stereostructures could be suggested for cataline from the above mentioned pmr data.

Since C-4 and C-6a protons must be *cis* in the 4(R):6a(S) configuration and *trans* in the 4(S):6a(S), a pmr study has now been carried out on cataline in the presence of an Europium shift reagent. This forms a complex with the C-4 hydroxyl and therefore must affect the chemical shift of the C-6a proton only in the case of the 4(S):6a(S) configuration.

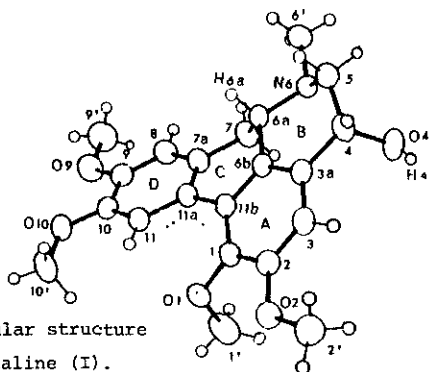
The pmr spectrum of cataline(I) in the presence of $\text{Eu}(\text{fod})_3$ ⁵ revealed the most significant displacements to low field, apart from the expected strong shift of the C-4 proton, two broad doublets (slopes: $m=9.0$ and 5.0). They were proved to be strongly coupled together ($J=12\text{Hz}$) by spin decoupling experiments. Cataline- d_3 (deuterated at C-6a and C-7)⁶, in the presence of $\text{Eu}(\text{fod})_3$ showed the same two doublets, thus proving that those signals correspond to C-5 protons. The absence of any other signal moving downfield which could be due to H-6a rules out in the case of cataline the 4(S):6a(S) configuration which has a half-boat conformation of ring B. Furthermore, high temperature pmr spectra of cataline gave no evidence of a conformational change in ring B. This would convert the C-4 proton of cataline from pseudoequatorial to pseudoaxial and would result in a shift and a change of the multiplicity of its signal which consequently would be identical to that of epicataline(II) where C-4 proton is pseudoaxial. We have found that C-4 proton in epicataline(II) resonates at δ 4.90 ppm⁷ as a doublet of doublets while in cataline



I R₁=OH R₂=H

II R₁=H R₂=OH

Fig.1: Molecular structure of cataline (I).



appears at 4.47 ppm as a poorly resolved triplet. Therefore, these results confirm the 4(R):6a(S) configuration for cataline.

This conclusion is also supported by comparison of the nmr data for C-4 and C-3 protons and C-3 carbon (¹³Cnmr) of cataline and epicaline with the corresponding values that were reported for the other known 4-hydroxyaporphines^{9,10}, 5-hydroxyberberines¹ and benzylisoquinolines¹¹. This shows a good correlation. The shift values of the C-4 proton signals for cataline and epicaline on acetylation (1.37 and 1.12 ppm, respectively)⁸ agree also with the configuration proposed by Ribas' group. This structure was confirmed by an X-Ray analysis.

Cataline (C₂₁H₂₅O₅N) crystallizes in space group P2₁2₁2₁, Z=4, with a=7.3558(9), b=14.869(3), c=17.410(4) Å, D_c=1.2994 g.cm⁻³. Intensities of 1989 independent Friedel pairs were measured up to θ=68° on an automatic four-circle diffractometer. Graphite-monochromated CuKα radiation (1.5418 Å) and ω/2θ scan technique were used. 1822 Friedel pairs were considered as observed according to the criterion I>2σ(I). The absorption effect was ignored and the Lorentz and polarization factors were applied as usual. After these corrections were made the above 1822 mentioned Friedel pairs were used in the calculations¹². The structure was solved by direct methods and the hydrogen atoms were located on a difference map. An appropriate weighting scheme¹³ was selected in order not to give any trends of <wΔ²F> vs. <F_o> and <sinθ/λ>. These weights were applied on several cycles of block-diagonal matrix mixed refinement including both hkl and h̄k̄l̄ reflexions, which converged for the right enantiomer to the discrepancy indices R=0.036 and R_w=0.045. The anomalous effect of the oxygen atoms was used to confirm the absolute configuration of the molecule, shown in Fig. 1.

The values of bond distances and bond angles are in good agreement with those expected for this kind of compounds. Ring B presents half-chair conformation at C(3a)-C(6b) and ring C a diplanar one at C(6b)-C(11b) and C(7a)-C(11a) respectively. The O(4) and H(6a) atoms are placed in trans position. The torsion angle through the ideal bond C(4)...C(6a) being -161(2)°.

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5. Pmr spectra (80MHz) were taken in CDCl₃ as solvent and TMS as internal reference. The lanthanide induced shifts show also the existence of a weak complexation center at C₉ and C₁₀ methoxy groups while the nitrogen atom seems not to be able to form an effective complex with the metal.
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