An Exceptionally Ready Interconversion of Configurational Isomers in Atisine

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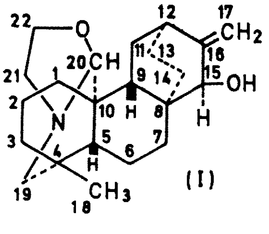
Summary Atisine in solution is shown to contain a 2 : 1 mixture of two isomeric species whose rate of interconversion is fast on the n.m.r. time scale in polar hydrogen-bonding solvents, but relatively slow in solvents which would not stabilize an ionic species, leading to the suggestion that it is a mixture of configurational isomers interconvertible *via* a zwitterion.

To account for the observation that the C-4 methyl group of atisine (I) occurs as a singlet (3H) in the 60 MHz n.m.r. spectrum in benzene solution *above* 85° but is resolved into an unequal doublet of 2 : 1 intensity at room temperature in both benzene and $CDCl_3$, conformational isomerism has recently been postulated.[1] An approximate estimate of the energy barrier could be made assuming equal population of the two species and applying the standard formulae.[2] A value of 19·7 kcal/mole was obtained from $\Delta\nu = 3$ Hz and $T_C = 85°$.

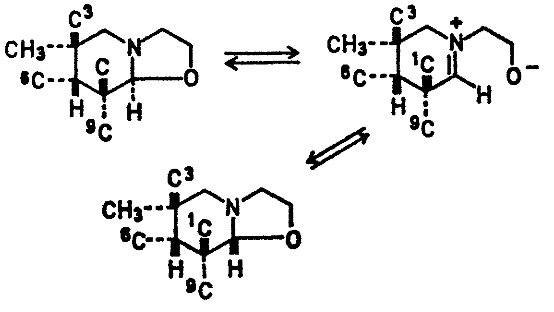


(I)

Such a high barrier is unusual[3] for the postulated chair-to-boat conversion. Dreiding models revealed that considerable steric interactions were present in the *ground states* but none of the expected magnitude in the transition states.

Hence alternative explanations had to be considered. Slow inversion at nitrogen was a possibility that could be accommodated within the framework of a single configurational description for atisine. Though high barriers to nitrogen inversion have not been observed for 1,3-oxazolidines[4] they were not less likely than the one suggested above.

The third alternative envisages the existence in solution of a mixture of configurational isomers differing in configuration at C-20 and interconvertible *via* a zwitterion as indicated (Scheme). Such ionic species have been postulated to co-exist with the closed form to account for the high pK_a of atisine,[5] *viz.* 12·2 in 50% aqueous methanol. In model compounds having the oxazolidine system[6] the pK_a is significantly lower, indicating much larger energy separation between the closed and open forms. The smaller separation in atisine is undoubtedly due to destabilization of the closed forms, primarily by steric interactions. Thus, in the configuration having a 20α-H this hydrogen is seen, in models, to be extremely close to the hydrogens at C-13 and C-14 in *all* possible conformations. Additional contribution to the strain is provided by interactions between the 20β-oxygen and hydrogens at C-1, C-2, and C-11. In the C-20 epimer the latter hydrogens are not too close to the 20β-H and hence the primary cause for destabilization is the proximity of the 20α-oxygen to hydrogens at C-13 and C-14. The overall result could be such as to render the C-20 epimers comparable in energy. Since the hydrogen at C-20 in the 20α-H epimer is subjected to a much higher degree of steric compression it would be expected[7] to be significantly deshielded as compared with its epimeric counterpart. Comparison of the n.m.r. of atisine and 19,19,20-trideuterioatisine† revealed that the hydrogen at C-20 was responsible for *two* peaks separated by 20 ± 2 Hz in $CDCl_3$, benzene, nitrobenzene, and hexadeuterioacetone. The low-field peak integrated for 0·6 to 0·7 protons, in line with the expectation that the predominant species had a 20α-H. Raising the temperature to the value required for coalescing the methyl signals led to progressive broadening of the 20-H signals.



SCHEME

Almost identical changes were noted in the n.m.r. spectrum when the temperature was kept constant at 37°, but the solvent composition was gradually changed from pure hexadeuterioacetone to one containing increasing D_2O. At 10% D_2O concentration the methyl peaks had coalesced. In the Figure the effect on the C-20 proton signals is shown. This behaviour clearly indicates a substantial lowering of the energy barrier separating the two isomeric species and is not due to preferential stabilization of *one* by change in solvent composition. In tetradeuteriomethanol at 37° the methyl was found to be a singlet but the extremely broad absorptions due to C-20 hydrogens indicated the existence of two "isomers." Resolution of the methyl peaks into a doublet was achieved by lowering the temperature below −5°. This leads to a value of approximately 14—15 kcal/mole for the energy barrier separating the two isomers. If inversion at nitrogen were involved, the barrier would have been expected to be raised on going to hydrogen-bonding solvents.[8] On the other hand, solvents such as water and methanol are known to stabilize ionic species, and hence the magnitude of stabilization observed here supports the contention that a transition state resembling a zwitterion is involved with the zwitterion itself being an intermediate on the energy profile.

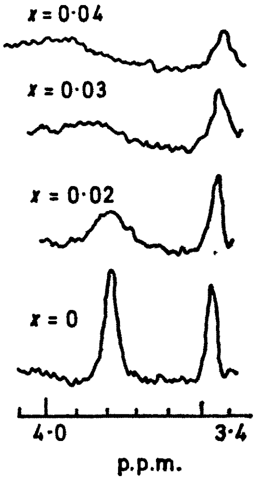


FIGURE. *N.m.r. spectra, showing the* C-20 *proton peaks of atisine* (110 *mg*) *in hexadeuterioacetone* (0·6 *ml*) + D_2O (x *ml*).

Hence it is concluded that atisine in solution contains an equilibrium mixture of C-20 epimers. This is the first case to be noted of extremely ready interconversion between configurational isomers actually involving the cleavage and re-formation of a bond attached to tetrahedral carbon.

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† Preparation and structural assignment of this will be the subject of another paper dealing with the subtler aspects of the atisine to isoatisine rearrangement.

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