Tetrahedron Letters No. 3, pp 263 - 266, 1978. Pergamon Press. Printed in Great Britain.

NON-EQUILIBRATION OF ATISINE EPIMERS - A REBUTTAL

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(Received in UK 14 November 1977; accepted for publication 24 November 1977)

Recently a paper has appeared[1] in these pages which casts doubt on our experimental findings and rejects certain aspects of our interpretation[2] pertaining to the structure of Atisine, an alkaloid of Aconitum Heterophyllum Wall.

The pertinent facts are briefly outlined here to be followed by a full paper on the intricacies of the atisine to *iso*atisine rearrangement.

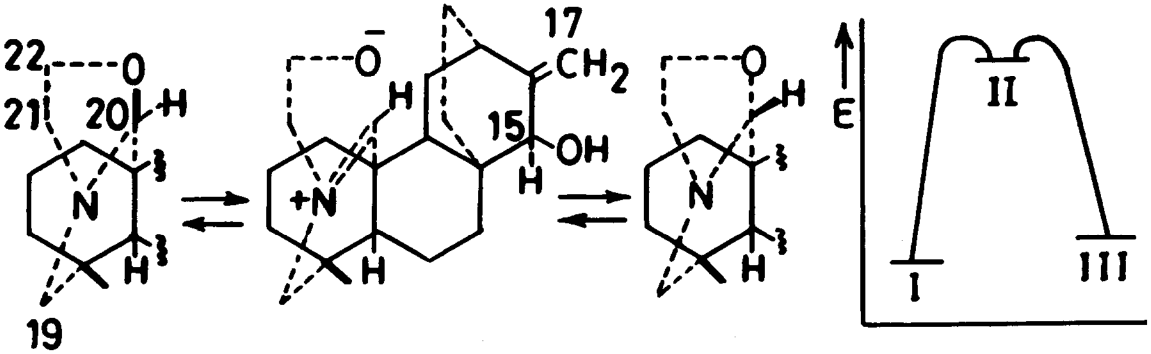
Several years of careful work on atisine[3] had failed to indicate the existence of two "isomers" until its NMR was observed[4] to contain two peaks, in the ratio of 2:1, separated by 3 Hz and together integrating for three protons in place of the expected singlet due to a methyl group attached to a tertiary carbon. The same paper[4] reports the important observation that the peaks coalesce to a singlet when the temperature is raised to 85° with benzene as solvent. This was a clear-cut demonstration of the existence of two species of almost equal energy equilibrating rapidly enough to prevent isolation of the individual species.

It was to be expected that other pairs of signals should be observable. We could locate with certainty two peaks at δ 4.28 and δ 4.00 respectively (in $CDCl_3$) which could be assigned[5] to the hydrogen at C-20. It could have been predicted that ^{13}C-NMR would also reveal duplicate peaks for several carbons in the ratio of 2:1. It was gratifying to find this expectation fulfilled with eleven out of twenty two carbons giving rise to duplicate peaks[6].

The existence of two species interconverting extremely rapidly at 85° is now being doubted by the same group who discovered it. Failure to observe coalescence of the duplicate ^{13}C-NMR signals on heating to 90° in deuterated toluene is cited[1] as evidence against the rapid interconversion. The relation[7] between T_c and frequency separation has been overlooked. In this specific case, only signals separated by less than 5 Hz could be expected to approach coalescence by 90° whereas ten of the duplicate ^{13}C peaks are separated by values ranging from 8 to 140 Hz.

Assuming the earlier conclusion of the existence of an equilibrium mixture of two species to be still valid, the question arises as to the nature of these. Existence of two conformations separated by a high energy barrier was mooted[4] earlier but has now been rejected on expert advice[8].

Because we were sceptical of the original explanation we made an alternative proposal[2] involving rapid interconversion between two epimers via a zwitterion lying near the top of the energy barrier as shown.



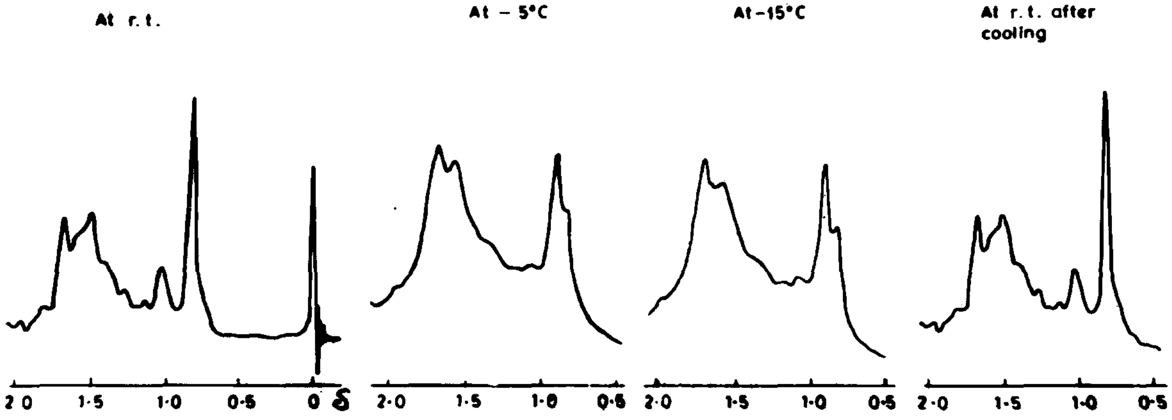
I II III

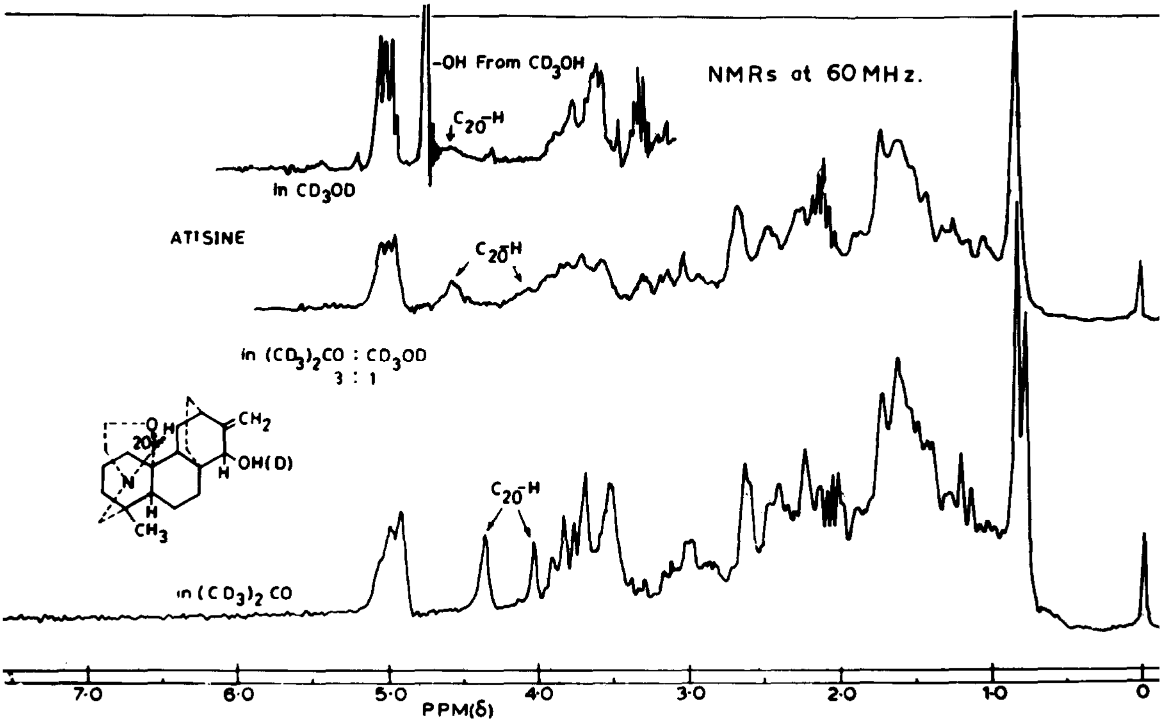
Such zwitterion would be present in too small a concentration to be detectable and hence the failure to detect ^{13}C-NMR signals corresponding to the same[1] cannot be construed as evidence against this pathway. Strong support for this proposal was obtained[2] when use of CD_3OD as a solvent increased the rate of interconversion of I and III to such an extent that the coalescence temperature (for the methyl) was reduced to -5°. At room temperature, the methyl is a singlet and evidence for two rapidly interconverting epimers was seen in a broad signal due to the C-20 hydrogen at δ 4.6. This disappears after a short time as the hydrogen gets replaced by deuterium. In a number of experiments, we never failed to observe deuterium exchange[9]. That it occurs at C-19 and C-20 in atisine could be checked by NMR examination of a $CDCl_3$ solution as well as of a D_2O solution of the corresponding hydrochloride. The latter is an excellent method for determining deuterium exchange at 19 and 20 positions as well as detecting isomerization to *iso*atisine. The NMR of atisine hydrochloride (O-protonated II) has signals due to twenty-two protons confined to the region δ 0.5 to 2.6. This leaves a singlet at 8.65 due to vinylic 20 H and multiplets at δ 5.14 (2H), 4.12 (4H) and 3.70 (3H). These can be assigned to protons at 17, 21 + 22 and 19 + 15 respectively[10]. The methyl is at δ 1.05. Any *iso*atisine hydrochloride present is detected by its methyl signal at δ 1.34 and the vinylic 19 H at δ 8.52.

In CD_3OD, atisine is slowly converted to deuterated *iso*atisine. This is easily detected by appearance of a new methyl singlet 11 Hz downfield of the atisine one at δ 0.55. The isomerisation is so slow[11] at 37° that the possibility[1] that it is responsible for the broad signal seen at δ 4.6 can be rejected outright. The broadening is typical of a "slow" process on the NMR time-scale but it has to be realized that such processes are very fast by ordinary standards.

Another objection[1] raised against our proposal was that "the ratio of the two epimers at different temperatures remained constant". Two compounds of closely related structures in equilibrium with each other need not differ, in their relative proportions over a small range of 40 to 90°C, to an extent that is detectable by a semi-quantitative technique.

The effect on the methyl signal of atisine on cooling a CD_3OD solution is seen below and that of adding this solvent to a hexadeuterioacetone solution is shown on the next page leaving no doubt about the correctness of our claim[2].





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2. S.K. Pradhan and V.M. Girijavallabhan, Chem. Comm., 644 (1970).
3. S.W. Pelletier, Quart. Rev. (London), **21**, 525 (1967) cites several references.
4. S.W. Pelletier and T.N. Oeltmann, Tetrahedron, **24**, 2019 (1968).
5. V.M. Girijavallabhan, Ph.D. Thesis, Keral University, 1969. In our communication (Ref.2) these values have not been specifically cited. In the reproduction of a portion of the NMR in deuterated acetone an offset of 30 Hz has been left out by oversight.
6. S.W. Pelletier and N.V. Mody, J. Am. Chem. Soc., **99**, 284 (1977).
7. W.A. Thomas, Ann. Rev. NMR Spectroscopy, 1, 44 (1968).
8. N.L. Allinger, cited in ref. 6.
9. For these experiments Atisine was O-deuterated prior to use and freshly opened CD$_3$OD was used after checking its CD$_3$OH content. Failure to observe these precautions could result in lack of exchange.
10. NMRs of these have been reported earlier (Ref. 4). Their assignment of the signals at δ 3.75 and 4.12 to the methylenes at 22 and 19 respectively are obviously in error.
11. S.W. Pelletier, K.W. Gopinath and K. Kawazu, Chem. and Ind. (London), 28 (1968) report a pseudo first order rate constant of 4.1 x 10^{-4} at 64°C in methanol.