

THE C-20 EPIMERS OF ATISINE AND BEHAVIOR OF THE OXAZOLIDINE RING

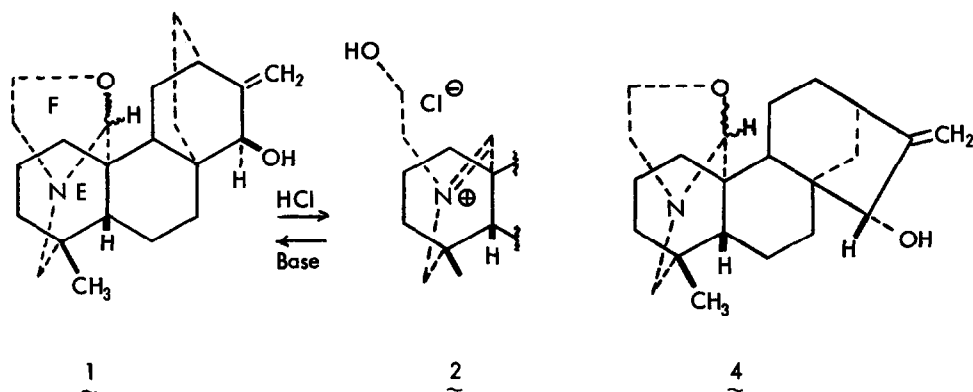
S. William Pelletier* and Naresh V. Mody

Institute for Natural Products Research and the Department of Chemistry

University of Georgia, Athens, Georgia 30602, USA

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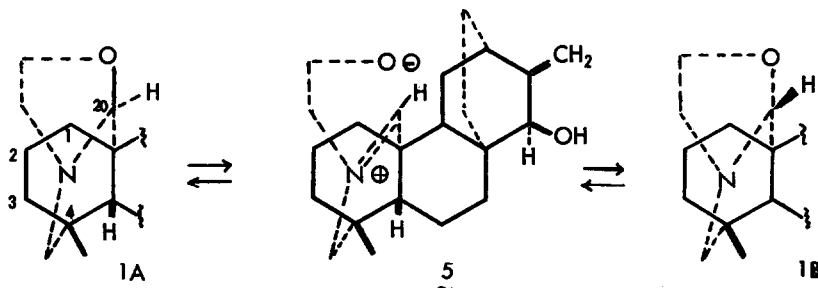
Atisine (1), an alkaloid of Aconitum heterophyllum Wall, is usually isolated¹ as the salt, atisinium chloride (2), and can be regenerated from this salt by treatment with strong base. Atisine is a very strong base (pKa 12.8) that may be isomerized easily to isoatisine (3) (pKa 10.3) by refluxing in methanol or other hydroxylic solvents.² In 1970, Pradhan and Girijavallabhan³ concluded that atisine in solution contains an



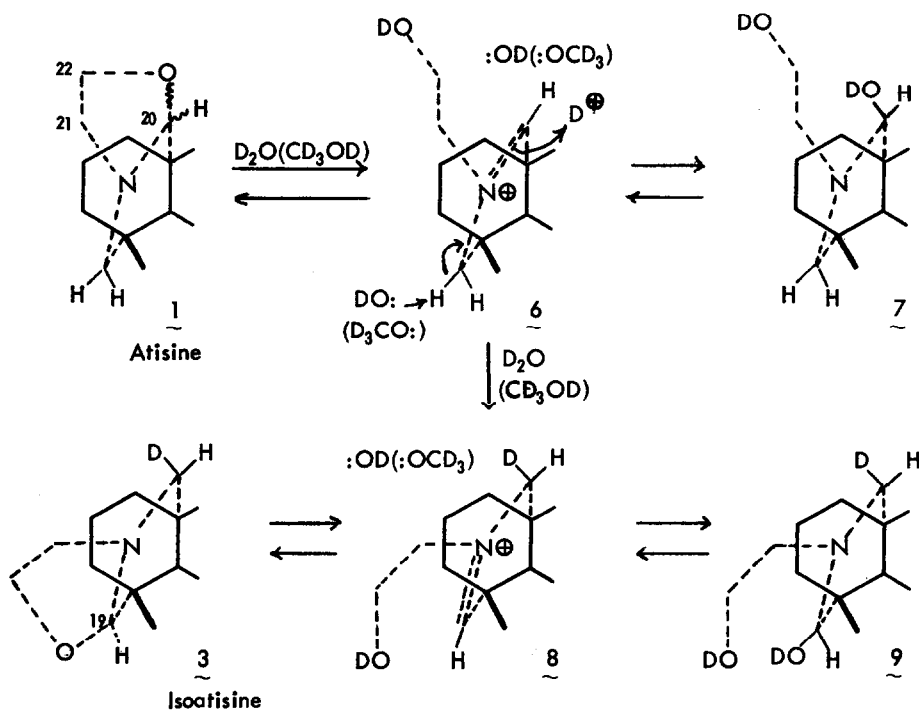
equilibrium mixture of the C-20 epimers (1A and 1B) which are interconvertible via a zwitterion (5). This conclusion appeared to be supported by a ¹H nmr study of atisine (in different polar solvents at 37° C) in which two C-4 methyl signals coalesced to a singlet and progressive broadening of the C-20 proton signals⁴ occurred during the gradual addition of D₂O to a CD₃COCD₃ solution of atisine. The extremely broad absorption due to the C-20 protons was observed also in CD₃OD at 37°. Since, ionic solvents (e.g. water and methanol) are known to stabilize ionic species, they concluded that a transition state resembling a zwitterion (5) is involved in the interconversion of the C-20 epimers.

In a recent study⁵ of the conformation of the E and F rings of atisine (1), veatchine (4) and related alkaloids by ¹³C nmr spectroscopy, we concluded that atisine and related alkaloids with a normal-type oxazolidine ring do indeed exist as a mixture of the C-20 epimers. We also indicated that the mixture of C-20 epimers results from formation of the oxazolidine ring from both sides of the trigonal C-20 carbon

during regeneration of atisine from atisinium chloride (2) by treatment with base. These results prompted us to examine whether the configurational isomers of atisine at C-20 are interconvertible in solution via a zwitterion as concluded by Pradhan and Girijavallabhan.³



The ^{13}C nmr spectrum of atisine in CD_3COCD_3 at 37° shows two different sets of signals each for the C-20 carbon, the oxazolidine ring carbons, the piperidine ring carbons, and the C-4 methyl group. Similar results also were observed in various deuterated non-ionic solvents (e. g. chloroform and toluene).⁶ This observation supports our recent findings⁵ for the existence of C-20 epimers in atisine. When the ^{13}C nmr spectrum of atisine was taken in a solution of 10% D_2O in CD_3COCD_3 , the isomerization of atisine (1) into isoatisine (3) was observed. A similar spectrum also was taken using 10% H_2O in CD_3COCD_3 instead



of D₂O to see whether deuterium exchange took place at any position in atisine. No difference between spectra taken in D₂O and H₂O was observed. When the ¹³C nmr spectrum of atisine was taken in CD₃OD, the ¹³C chemical shifts⁵ of carbons 20, 21, and 22 had moved upfield and no new downfield signals for a zwitterion were observed. This result suggests that in hydrogen-bonding type solvents atisine can exist in the form of species 6, 7, 8, and 9 and supports the early postulate of this idea, by Wiesner and Edwards.⁷ This observation accounts for the high pKa values of atisine (pKa 12.8) and veatchine (pKa 11.9) in an aqueous solution. After the ¹³C spectrum of atisine was taken in CD₃OD (one hour), the solvent was removed and the remaining material dissolved in CDCl₃ (free of CD₃OD). The ¹³C spectrum of the solution now showed the presence of isoatisine as well as the C-20 epimers of atisine. No deuterium exchange at C-20 in atisine and at C-19 in isoatisine was found. A similar effect was also observed in the ¹H nmr spectrum of atisine in a solution of 10% D₂O in CD₃COCD₃ as well as in CD₃OD.

To demonstrate further that the C-20 epimers of atisine do not exist in an equilibrium mixture in solution and are not interconvertible via a zwitterion, a temperature dependence study of atisine in deuterated toluene was carried out. At 25°C, atisine exists as the C-20 epimers, 1A and 1B, in 65% and 35%, respectively. At 40°C no significant change in the ratio of these two C-20 epimers was observed. As the temperature increased progressively from 56°C to 70°C to 90°C, new ¹³C chemical shifts due to the formation of isoatisine appeared, but the two sets of signals of both atisine epimers did not coalesce to a single resonance. Also, the ratio of both epimers at different temperatures remained constant.

The above results lead us to conclude that atisine in non-ionic solvents exists as a mixture of C-20 epimers without interconversion via a zwitterion of any type and in ionic solvents isomerizes slowly to isoatisine via the intermediate species 6 and 8. The Indian workers' interpretation of the broadening of the C-20 proton as indicating equilibration between the C-20 epimers in 10% D₂O in CD₃COCD₃ or in CD₃OD is actually due to isomerization of atisine (1) to isoatisine (3) and the formation of species 6-9. Their conclusion that these epimers are interconvertible via a zwitterion is thus in error.

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3. S. K. Pradhan and V. M. Giriavallabhan, Chem. Comm., 644 (1970).
4. The reported values for the C-20 proton shift in ref. 3 are in error. The C-20 proton signals of atisine

in CD_3COCD_3 or CDCl_3 appear between $\delta 4.0$ and $\delta 4.4$ in the ^1H nmr spectrum. Cf. S. W. Pelletier and T. N. Oeltmann, Tetrahedron, 24, 2019 (1968) and S. W. Pelletier and N. V. Mody, unpublished results.

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6. For the ^{13}C nmr spectrum of atisine see ref. 5. The pattern of ^{13}C nmr spectra of atisine in CDCl_3 and CD_3COCD_3 is the same, but the ^{13}C chemical shifts are moved downfield between 1 to 2 ppm in CD_3COCD_3 as compared to the shifts observed in CDCl_3 .
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