

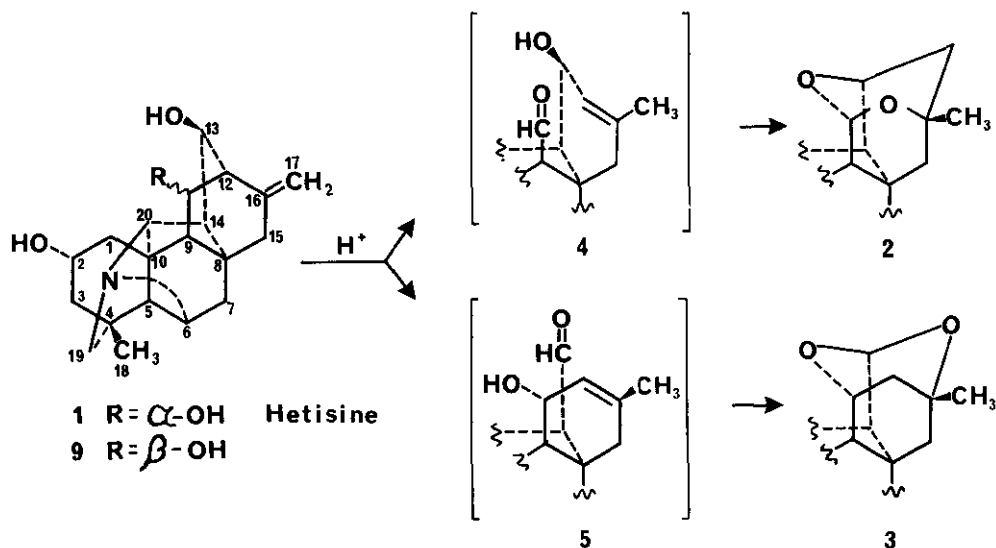
UNUSUAL HETISINE REARRANGEMENT PRODUCTS

S. William Pelletier*, Jan A. Glinski, Kottayil I. Varughese, Joseph Maddry and Naresh V. Mody

Institute for Natural Products Research and The Department of Chemistry
The University of Georgia, Athens, Georgia 30602, U.S.A.

Abstract: Re-examination of an acid-catalysed hetisine rearrangement gave two, previously undetected products, whose structures were determined by X-ray crystallography. A mechanism for the formation of these products, involving an unusual epimerization of the two hydroxy groups at C(11) and C(13), is proposed.

Recently we reported¹ an acid-catalysed rearrangement of hetisine (1) to the two adamantane-type products 2 and 3, via the intermediates 4 and 5.



Further investigation has extended some of the previously made observations. TLC analysis has shown that the rearrangement requires substantial time and moreover compounds 2 and 3 are not the only products. A sample of hetisine refluxed in 5% H₂SO₄ for 2 hrs gave a mixture of products. Routine isolation followed by chromatography over alumina afforded a mixture of compounds 2 and 3 (approx. 70%) and a new product (approx. 20%), mp 295-299°C, MW 329, plus traces of unreacted hetisine. The ¹H NMR and ¹³C NMR spectra indicate this product is a 1:1 mixture of two isomeric compounds 6 and 7, both having an endocyclic double bond. A detailed NMR study of the unre-

solved mixture of 6 and 7 was impossible because of overlapping of signals. A perchlorate salt of the mixture of 6 + 7 was prepared and then crystallized several times from a MeOH-H₂O mixture. Finally, crystals, mp 272°C (corr.), enriched in compound 6 were obtained and submitted for X-ray analysis. A ¹³C NMR spectrum (in D₂O with ext. TMS) displayed the following signals for 6: 139.0, 124.4, 72.3, 71.7, 68.0, 67.3, 66.5, 61.3, 59.7, 57.4, 56.7, 50.2, 48.5, 43.5, 38.5, 36.1, 32.4, 32.0, 29.0 and 23.6 ppm. ¹H NMR of 6, in CDCl₃ + CD₃OD displayed signals at δ 1.00 (s, C(18)H₃), 1.83 (s, C(17)H₃), 5.58 (s, C(15)H). The ¹³C NMR signals arising from the double bond of compound 7 were at 139.9 and 125.0 ppm. The ¹H NMR signals of 7 were at 1.02, 1.93 and 5.74 ppm, respectively. Figure 1 shows a stereoscopic view of the epimeric mixture of 6 and 7.

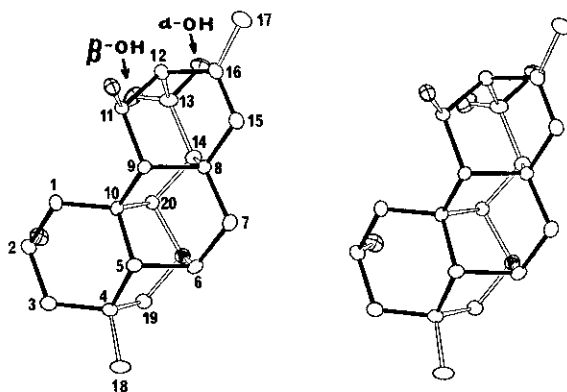


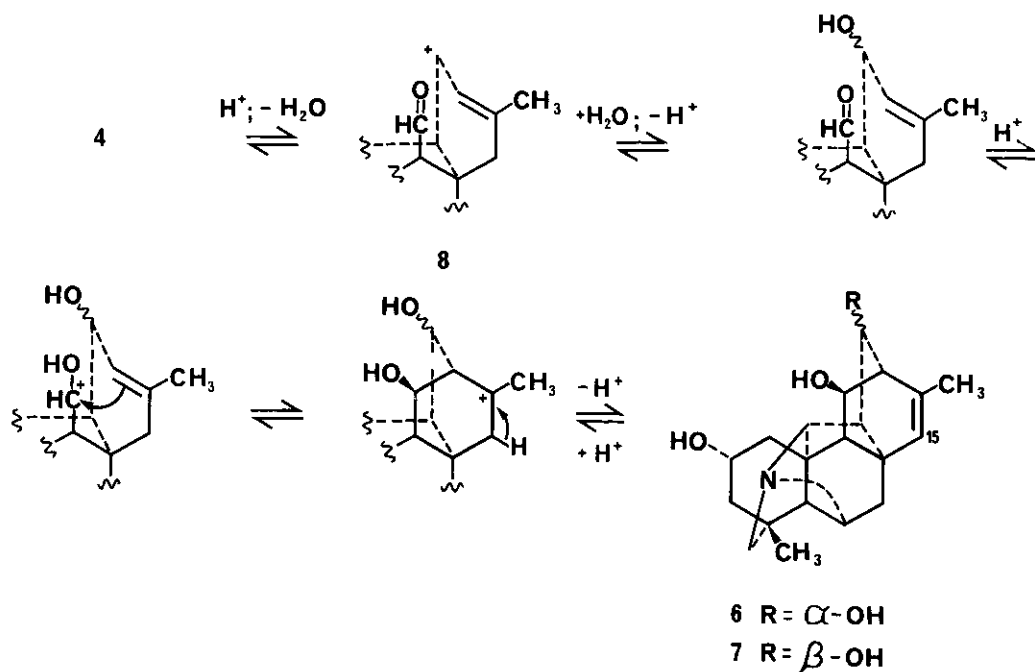
Fig. 1

Crystal data: The crystals belong to the orthorhombic space group P2₁2₁2₁ with a = 8.983(2), b = 14.868(2), c = 15.049(2)Å and z = 4. The intensity data (2θ < 150°) were measured using an Enraf-Nonius CAD-4 diffractometer by ω-2θ scans with CuKα (λ = 1.5418Å) radiation. Out of the 2270 unique reflections 79 of them had |F_o| < 1.4σ (F) and hence were omitted from the least squares refinement. The structure was solved by multiresolution methods² and refined to an R of 0.072. The hydrogen atoms were not located. An examination of the electron density map revealed the coexistence of the C(13) epimers in the crystal. The occupancies of the C(13)-α OH in 6 and the C(13)-β OH in 7 positions were adjusted to 0.83 and 0.17, respectively, such that the temperature factors became approximately equal in the least squares refinement.

Cleavage of the C(11)-C(12) bond in hetisine leads to the intermediate 4. Cleavage of the C(12)-C(13) bond and formation of the intermediate 5 is less favorable, a fact demonstrated by the 2 to 3 ratio of 95:5. A possible mechanism that accounts for the origin of isomers 6 and 7 from intermediate 4 is illustrated.

The configuration of the C(11)-β OH bond in 6 and 7 is identical, while the configuration of the C(13)-OH bond may be α or β, as a result of the isomerization taking place on the well stabilized allyl carbocation 8. The above reactions are reversible, which was observed by prolonged (6 hrs) refluxing of the mixture of 6 and 7 in 5% H₂SO₄, resulting in formation of barely detectable quantities of 2 and 3. Products of similar reactions of the intermedi-

ate 5 were not detected in the present crystal by X-ray analysis. Presumably they were eliminated as minor products during crystallization.



In order to establish the influence of the configuration of the hydroxy groups on the course of the rearrangement, the C(11)- β OH epimer of hetisine, 9, was synthesized. Reduction of 11-ketohetisine³ with NaBH₄ in MeOH for 4 hrs, followed by purification on a short alumina column afforded the desired product. Epimer 9 showed mp 268-71°C, MW 329. A ¹³C NMR spectrum recorded in CDCl₃ with a few drops of CD₃OD displayed the signals: 143.5, 111.4, 69.0, 68.0; 66.3, 64.4, 64.3, 63.5, 60.4, 60.4, 51.5, 50.0, 46.8, 41.6, 39.2, 36.6, 36.1, 33.5, 31.6, and 29.6 ppm. A ¹H NMR spectrum revealed the following signals: 1.00 (s, Me), 4.12 (m, 3p), and 4.85 (d, 2p, J=3 Hz) ppm. Compound 9, when refluxed in 5% H₂SO₄ rearranged to give 2 and 3, in the ratio of 1:3 (determined by ¹H NMR), as well as products with structures similar to those of 6 and 7. This ratio differs greatly from that given by hetisine, suggesting that a change of the C(11)-OH configuration from α to β makes cleavage of the C(11)-C(12) bond more difficult.

REFERENCES

1. S. W. Pelletier, N. V. Mody, J. Finer-Moore, A. M. M. Ateya and L. C. Schramm, *J. Chem. Soc., Chem. Comm.*, **1981**, 327.
2. G. Germain, P. Main and M. M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).
3. Unpublished results from this laboratory.

Received, 8th November, 1982