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UNUSUAL HETISINE REARRANGEMENT PRODUCTS

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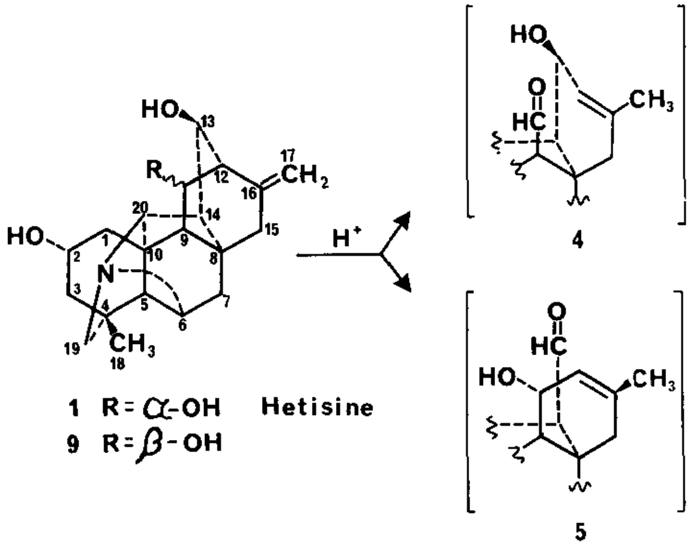
Abstract: Re-examination of an acid-catalysed hetisine rearrangement gave two, previously undetected products, whose structures were determined by X-ray crystallography. A mechanism for the formation of these products, involving an unusual epimerization of the two hydroxy groups at C(11) and C(13), is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

Recently we reported[1] 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% H_2SO_4 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 ^{13}C 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 unresolved 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-H_2O mixture. Finally, crystals, mp 272°C (corr.), enriched in compound **6** were obtained and submitted for X-ray analysis. A ^{13}C NMR spectrum (in D_2O 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 $CDCl_3$ + CD_3OD displayed signals at δ 1.00 (s, C(18)$\underline{H}_3$), 1.83 (s, C(17)$\underline{H}_3$), 5.58 (s, C(15)$\underline{H}$). The ^{13}C 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**.

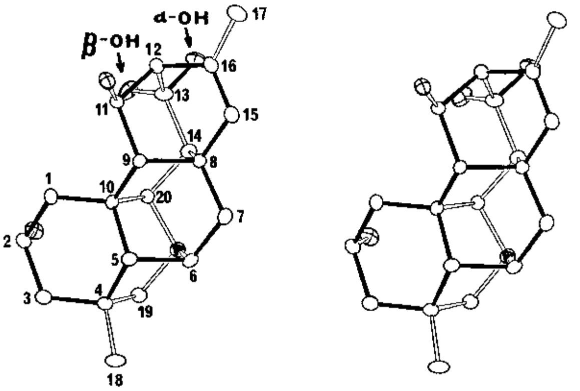
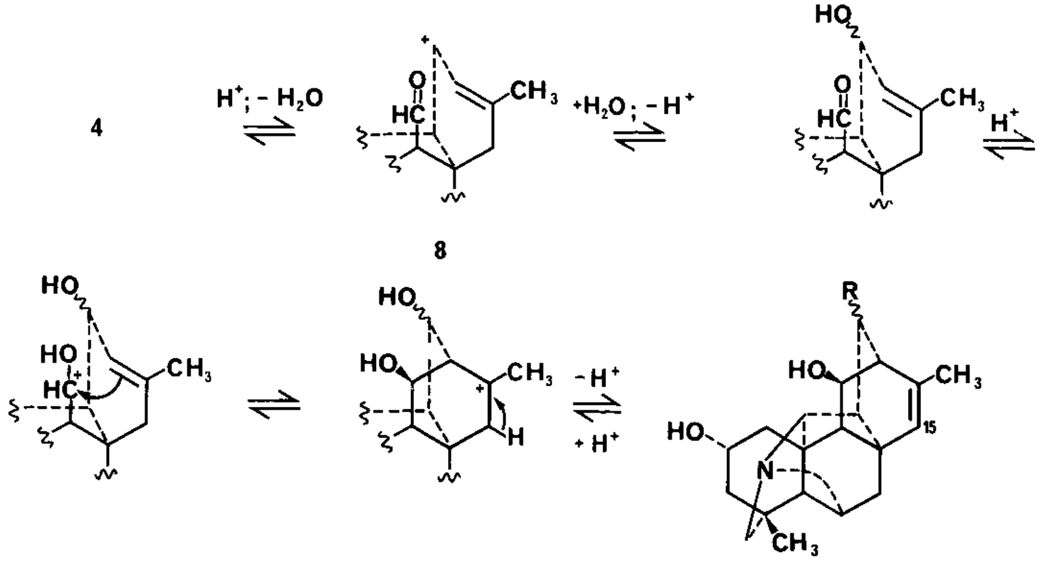


Fig. 1

Crystal data: The crystals belong to the orthorhombic space group $P2_12_12_1$ with a= 8.983(2), b= 14.868(2), c= 15.049(2)Å and z= 4. The intensity data ($2\theta \leq 150°$) 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 $|Fo| < 1.4\sigma$ (F) and hence were omitted from the least squares refinement. The structure was solved by multisolution methods[2] 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% H_2SO_4, resulting in formation of barely detectable quantities of **2** and **3**. Products of similar reactions of the intermediate **5** were not detected in the present crystal by X-ray analysis. Presumably they were eliminated as minor products during crystallization.



4

8

6 R = α-OH
7 R = β-OH

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-ketohetisine[3] with $NaBH_4$ 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 ^{13}C NMR spectrum recorded in $CDCl_3$ with a few drops of CD_3OD 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% H_2SO_4 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

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3. Unpublished results from this laboratory.

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