A Novel Rearrangement of Hetisine, and *X*-Ray Crystal Structure of the Major Product: Transformation of a Dihydroxy-bicyclo[2.2.2]-octane System to an Adamantane-type Skeleton

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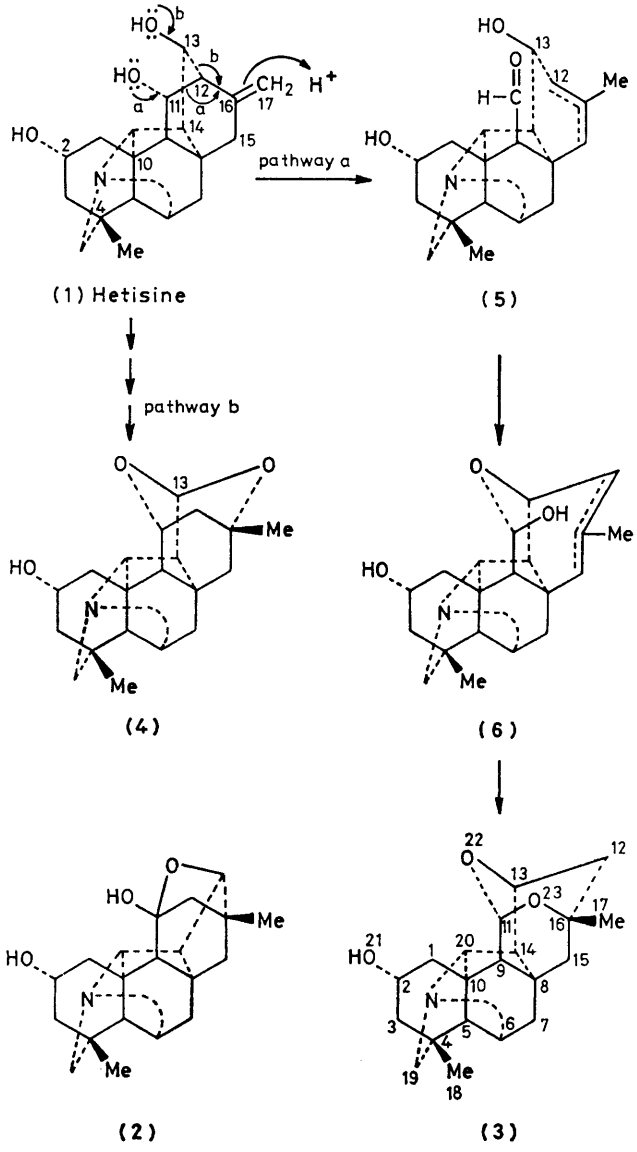
Summary Treatment of hetisine with acid leads to two unusual rearrangement products, (**3**) and (**4**), *via* a unique transformation of a dihydroxy-bicyclo[2.2.2]octane system to an adamantane-type skeleton; the structure of (**3**) has been determined by *X*-ray crystallography.

DURING the course of isolation of alkaloids from *Aconitum heterophyllum*, we encountered an alkaloid, m.p. 278—279·5 °C, with the same molecular formula ($C_{20}H_{27}NO_3$) as that of hetisine (**1**), a constituent of *A. heterophyllum*[1] and *Delphinium cardinale*.[2] Formation of the identical compound (m.p. 278—279·5 °C) by treatment of hetisine with aqueous sulphuric acid was reported in 1959.[3] After the structure of hetisine (**1**) had been established in 1962 by an *X*-ray crystallographic study,[4] Wiesner and his co-workers[5] reported work on its Hofmann degradation. They noted that their methiodide was not identical with the methiodide of hetisine prepared in 1947 by Jacobs and Huebner,[6] and concluded that the latter compound was actually the methiodide of an acid-catalysed rearrangement product of hetisine. Based on the structure of hetisine, they proposed[5] structure (**2**) for the product of a rearrangement involving a 1→2 hydride shift mechanism. However, examination of the ^1H and ^{13}C n.m.r. spectra for this compound shows that they are not compatible with the proposed structure (**2**). We now propose a new mechanism for the acid-catalysed rearrangement of hetisine and establish structures (**3**) and (**4**) for the major and minor products of the rearrangement, respectively.

Compound (**3**), $C_{20}H_{27}NO_3$, m.p. 279—279·5 °C (corr.), $[\alpha]_D^{28}$ + 9·1° (*c* 1·45, CH_2Cl_2), showed i.r. absorptions at 3150 (OH) and 1100 (ether) cm^{-1} (Nujol). Its 90 MHz ^1H

n.m.r. spectrum in $CDCl_3$ showed resonances at δ 0·97 (s, 4-Me), 1·16 (s, 16-Me), 2·88br. (s, 2α-OH), 4·02 (m, 13-H), 4·16br. (2β-H), and 4·98 (d, C-11 acetal-H), and its ^{13}C *n.m.r.* spectrum in $CDCl_3$ showed the following signals: 94·1, 71·3, 70·8, 69·6, 66·6, 64·5, 64·1, 58·8, 53·2, 51·0, 46·7, 41·3, 39·9, 38·7, 38·1, 37·9, 36·8, 31·5, 29·5, and 28·5 p.p.m.



SCHEME. The atom numbering in compound (**3**) corresponds to the crystallographic numbering in the deposited data.

The doublet at 94·1 p.p.m. and the singlet at 69·6 p.p.m. [tertiary oxygenated C(16)] cannot be accommodated by the earlier proposed structure (**2**). The mechanism we propose for the rearrangement of hetisine is shown in the Scheme and would be expected to yield structures (**3**) and (**4**), each of which is compatible with the above spectral data. We found that treatment of hetisine with 10% hydrochloric acid or 5% aqueous sulphuric acid at reflux temperature for 10 min, indeed, afforded exclusively two compounds in 95 and 5% yields. The major product of this reaction is identical with the compound, m.p. 278—279·5 °C, isolated from *A. heterophyllum* (see above). The structure of the major product was confirmed as (**3**) by single-crystal *X*-ray diffraction.

Crystal data: compound (**3**), $C_{20}H_{27}NO_3$, orthorhombic, space group $P2_12_12_1$ with $a = 8·161(2)$, $b = 9·088(2)$, $c = 22·511(2)$ Å, $D_m = 1·32$, $D_c = 1·31$ g cm^{-3} for $Z = 4$. One octant of data on a crystal of dimensions *ca.* 0·30 × 0·30 × 0·20 mm was collected† to a maximum 2θ of 120° using the ω–θ scan technique and Cu-K_α radiation (λ = 1·5418 Å), and after Lorentz and polarization corrections, 1379 (98%) of the reflections with $|F| \geq 3\sigma(F)$ were used in the structure solution.

The structure was solved by direct methods[7] and refined by a blocked least-squares program[8] where data were weighted by the function $\{1·0 + [(|F| - 6·0)/12·0]^2\}^{-1}$. Hydrogen atoms, which were all located in difference maps,[8] were included in the refinement with isotropic temperature factors. The maximum shift to error ratio in the final refinement cycle was 0·79 and the weighted and unweighted *R* factors were 0·046 and 0·039, respectively.‡ One exceptionally long bond, C(10)—C(20) = 1·591(4) Å, is the only evidence for significant ring strain in the molecule, all other bond distances and angles having typical values.

Compound (**4**), $C_{20}H_{27}NO_3$, m.p. 288—290 °C (corr.), $[\alpha]_D^{30}$ + 10·5° (*c* 0·37, CH_2Cl_2), showed i.r. absorptions at 3200 (OH) and 1130 (ether) cm^{-1} in chloroform. Its 90 MHz ^1H n.m.r. spectrum in $CDCl_3$ showed resonances at δ 0·98 (s, 4-Me), 1·17 (s, 16-Me), 4·1 (m, 11-H), 4·23br. (m, 2β-H), and 4·96 (d, C-13 acetal-H). Its ^{13}C n.m.r. in $CDCl_3$ showed the following signals: 94·6, 69·4, 68·8, 68·4, 67·0, 64·8, 63·7, 58·5, 53·0, 51·1, 47·2, 41·2, 39·8, 38·6 37·9, 37·9, 36·8, 32·3, 29·5, and 28·5 p.p.m. These are in agreement with the assigned structure (**4**).

The acid-catalysed rearrangement of hetisine into compounds (**3**) and (**4**) represents a unique transformation of a dihydroxy-bicyclo[2.2.2]octane system to an adamantane-type skeleton through a facile cleavage of the C(11)–C(12) and C(12)–C(13) bonds, respectively, in hetisine. When hetisine was heated at reflux temperature with 10% DCl in D_2O under a nitrogen atmosphere compound (**3**), deuterated at C(12), C(15), and C(17), was formed as the major product, a result which supports the proposed mechanism. Formation of (**3**) probably involves the intermediate (**6**) rather than a dihydroxy-aldehyde [resulting from addition of water to (**6**) at C(16)] because of the ease of formation of the acetal (**3**), and because hydration of (**5**) to a dihydroxy-aldehyde would not be expected to proceed stereospecifically to form a single isomer which could cyclize subsequently to (**3**). The arrows labelled b in the Scheme show the pathway for the rearrangement of hetisine into compound (**4**) *via* the same mechanism considered for compound (**3**). Since the

† This data set was collected by the crystallographic staff of the Molecular Structure Corporation, College Station, Texas.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

dihydroxy-bicyclo[2.2.2]octane system is symmetrical, both compounds (**3**) and (**4**) would be expected to be formed in equal amounts, in contrast with the observed proportions of 95 and 5%, respectively.

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