HETISINE DERIVATIVES, PART 2: NOVEL REARRANGEMENT OF 11-DEHYDROHETISINE AND 2,11-DIDEHYDROHETISINE

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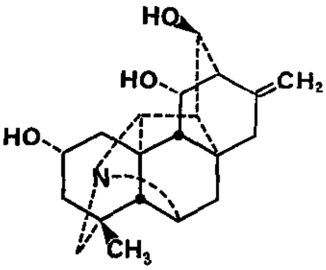
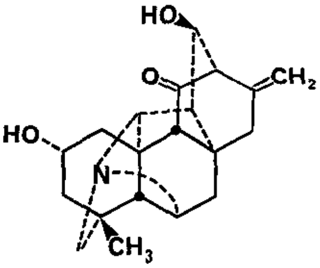
Abstract — *Heating 11-dehydrohetisine (2) with sulfuric acid gave the rearrangment product 9. Its structure was solved by an X-ray diffraction study of the perchlorate salt which belongs to the orthorhombic space group* $P2_12_12_1$. *2,11-Didehydrohetisine (3) likewise afforded the rearranged triketone (10). The structure of the latter was confirmed by oxidation of 9 with pyridinium chlorochromate to 10.*

In an earlier communication,[1] we have described the synthesis of several derivatives of hetisine (1). Thus, oxidation of 1 with chromium trioxide/pyridine (Sarett's reagent) gave a mixture of products from which 11-dehydrohetisine (2) was isolated as the major product, besides 2,11-didehydrohetisine (3). 11-Dehydrohetisine was also obtained by the alkaline hydrolysis of 13-acetyl-2,11-didehydrohetisine (4) prepared by the oxidation of 13-acetylhetisine.



1



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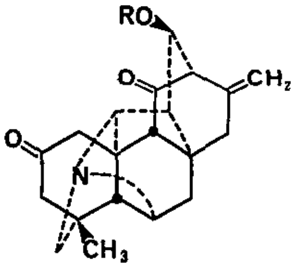
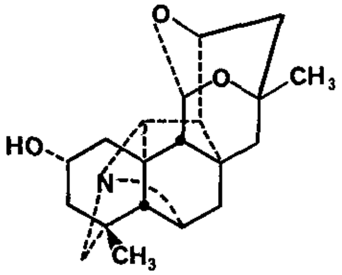


3: R = H

4: R = Ac

Acid-catalysed rearrangement of hetisine (1) to give the adamantane type products 5, 6 and a 1:1 mixture of the isomeric compounds 7 and 8 has been described in our earlier publications.[2,3]



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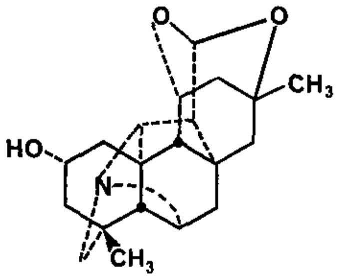

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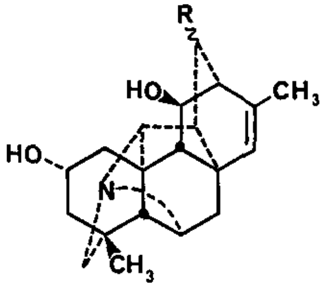


7: R = α-OH

8: R = β-OH

In the present communication, we report on the rearrangement products obtained by reaction of compounds 2 and 3 with aqueous sulfuric acid. Heating 11-dehydrohetisine (2) with 45% sulfuric acid gave a crystalline compound, mp 202-203°C. The mass spectrum showed the molecular ion peak at M^+, m/z 327 indicating that the rearrangement product is isomeric, having the same molecular formula ($C_{20}H_{25}NO_3$) as 2. The infrared spectrum showed the presence of hydroxyl (3600 cm^{-1}) and carbonyl (1710 cm^{-1}) groups. The ^{13}C nmr spectrum indicated the presence of two carbonyl groups (208.7, 210.7 ppm); the ^1H nmr spectrum showed the presence of a tertiary methyl group (δ 1.04) and the disappearance of the exocyclic methylene group present in 2. These data suggested that the rearrangement product is of a new type, not related to the rearrangement products of hetisine observed earlier.[2,3] The structure of the rearrangement product was solved by a single-crystal X-ray analysis of its perchlorate salt.

The perchlorate salt crystallized as a chloroform complex from a mixture of ethanol, chloroform and toluene in the orthorhombic space group $P2_12_12_1$ with a = 7.891(4), b = 11.106(1), c = 23.618(3) and z = 4. The intensity data for 2437 unique reflections ($2\theta \leq 150°$) were measured using CAD-4 diffractometer by $\omega/2\theta$ scan with CuKα (λ = 1.5418Å) radiation. The crystal disintegrated during the measurement of intensity data. These reflections were used to monitor the changes in intensity which decreased to about half of the original values towards the end of the measurement. A decay correction was applied as a function of time. Of the 2437 reflections, 348 reflections had $|Fo|$ less than 1.4 σ (F) and they were excluded from the least square calculations. The crystal structure was determined by multisolution methods[4] using the program MULTAN[5] and refined to an R of 0.104 and Rw of 0.099. Hydrogen atoms were not located and positions of the non-hydrogen atoms are listed in Table 1. Figure 1 shows a projection view of the rearrangement product 9 obtained from 11-dehydrohetisine.

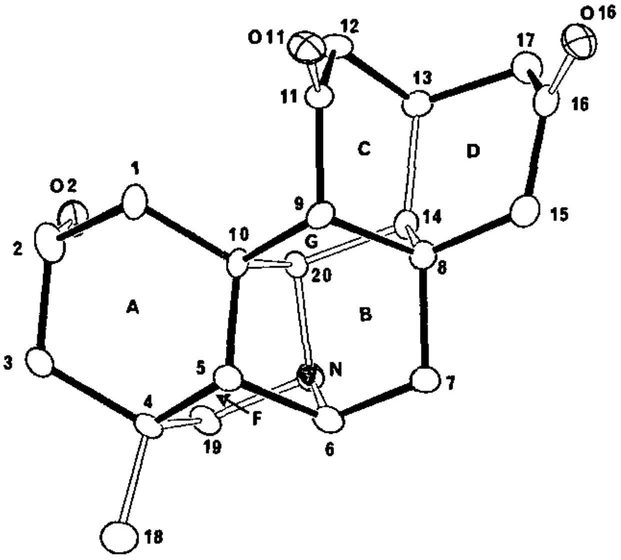
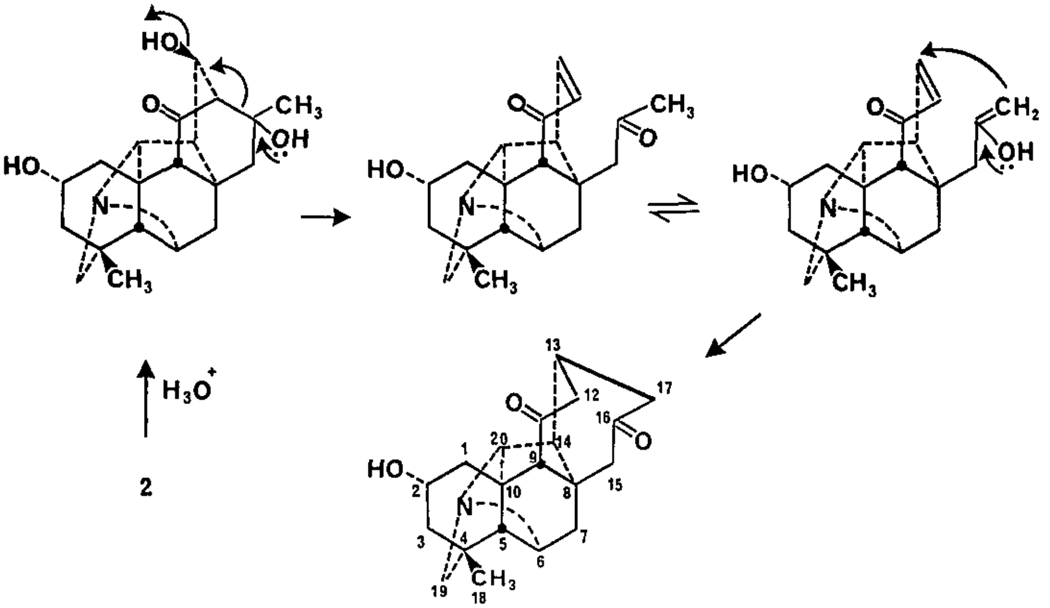


Fig. 1 Projection view of the rearrangement product **9**

The bond lengths and angles of **9** are listed in table 2. The presence of the two keto groups is clearly shown by O(11)-C(11) and O(16)-C(16) distances 1.217(5)Å and 1.203(7)Å, respectively, and by the planarity of the bond meetings at C(11) and C(16). The only hydrogen bond donor in the molecule is O(2) and there appears to be an intermolecular hydrogen bond between O(2) and N with an O----N distance of 2.765Å. An interesting feature is the formation of an additional carbonyl group and the formation of a new ring system incorporating the methylene carbon atom C(17). The rearranged molecule **9** contains five six-membered rings and two five-membered ring fused together. All the six-membered rings are in a chair conformation. Ring A [C(1), C(2), C(3), C(4), C(5), C(10)] is a flattened distorted chair; ring B [C(5), C(6), C(7), C(8), C(9), C(10)] is also a flattened chair, ring C [C(9), C(11), C(12), C(13), C(14), C(8)] and ring D [C(8), C(14), C(13), C(17), C(16), C(15)] are in chair conformations. The piperidine ring E [C(6), C(7), C(8), C(14), C(20), N] is also a chair. The two five-membered rings F [C(4), C(5), C(6), N, C(19)] and G [C(8), C(9), C(10), C(20), C(14)] have both a distorted half-chair conformation. The carbonyls at C(11) and C(16) of the eight-membered ring [C(8), C(9), C(11), C(12), C(13), C(17), C(16), C(15)] are almost parallel.

A plausible mechanism for this rearrangement has been depicted as below, involving hydration of the exocyclic methylene group followed by dehydration and an internal Michael addition.

Similarly, refluxing 2,11-didehydrohetisine (**3**) with 45% sulfuric acid gave (**10**), mp 285-287°C. The structure of this compound was deduced from its spectral data and confirmed by the oxidation of **9** with pyridinium chlorochromate to afford **10**.



2

9

10: carbonyl at C(2)

EXPERIMENTAL

Melting points were taken on a Thomas-Kofler apparatus and are corrected. ^{1}H nmr spectra were determined in $CDCl_3$ with Me_4Si as internal reference on a Varian EM-390 spectrometer and ^{13}C nmr spectra were taken on a JEOL FX-60 spectrometer.

Rearrangement of 11-Dehydrohetisine (2) to 9 — 11-Dehydrohetisine (**2**, 150 mg) was heated on a steam bath with 45% sulfuric acid (8 ml) for 1.5 h. The mixture was cooled, made alkaline with aqueous sodium hydroxide and extracted with methylene chloride. The residue (150 mg) crystallized from methanol-hexane as colorless crystals (**9**, 130 mg), mp 202-203°C. $C_{20}H_{25}NO_3$, ms: m/z 327 (M^+, 20%), 299(100), 282(70), 271(8), 255(10), 176(15). ^{1}H nmr: δ 1.04 (3H, s, C(4)-CH_3), 3.32 (1H, s, C(6)-β-H), 3.86 (1H, s, C(20)-H), 4.23 (1H, br, C(2)-β-H). ^{13}C nmr (ppm): 32.4 C(1)^a, 70.6 C(2)^b, 38.6 C(3), 36.7 C(4), 58.7 C(5), 66.1 C(6), 34.2 C(7)^a, 46.0 C(8), 64.1 C(9), 47.8 C(10), 210.7 C(11)^c, 50.7 C(12), 40.0 C(13), 42.4 C(14), 47.2 C(15)^d, 208.7 C(16)^c, 48.7 C(17)^d, 29.3 C(18), 63.7 C(19), 70.5 C(20)^b (the assignments a, b, c, d may be interchanged). IR (nujol) ν max 3600, 1710, 1450, 1435, 1410, 1372, 1348, 1331, 1311, 1270, 1250, 1238, 1220, 1210, 1181, 1170, 1130, 1105, 1088, 1055, 1030, 1010, 992, 968, 940, 910, 892, 870, 840, 820 cm^{-1}.

Rearrangement of 2,11-Didehydrohetisine (3) to 10 — 2,11-Didehydrohetisine (3, 85 mg) was heated on a steam bath with 45% sulfuric acid (6 ml) for 1.5 h. Basification with 30% sodium hydroxide and extraction with methylene chloride gave a residue (80 mg). The rearrangement product (**10**) crystallized from methylene chloride-hexane as colorless cubes (70 mg), mp 285-287°C.

$C_{20}H_{23}NO_3$, ms: m/z 325 (M^+, 100%), 297(55), 269(25), 254(10), 107(20), 91(30), 770(28). ^1H nmr: δ 1.18 (3H, s, C(4)-CH_3), 3.11 (1H, br s, C(6)-β-H); ^{13}C nmr (ppm): 42.9 C(1), 206.9 C(2)^a, 50.4 C(3), 42.9 C(4), 58.0 C(5), 70.0 C(6), 33.7 C(7), 46.8 C(8), 65.0 C(9), 52.9 C(10), 209.1 C(11)^a, 51.1 C(12), 38.6 C(13), 42.2 C(14), 46.7 C(15)^b, 207.9 C(16)^a, 48.6 C(17)^b, 28.3 C(18), 65.0 C(19), 72.3 C(20) (the assignments a, b may be interchanged.)

Oxidation of 9 with Pyridinium Chlorochromate to Give 10 — A solution of compound **9** (60 mg) in methylene chloride (10 ml) was added to a solution of pyridinium chlorochromate (100 mg) in methylene chloride (20 ml). The mixture was magnetically stirred at room temperature for 6 h. The reaction mixture was filtered, and extracted with water (15 ml x 2). The methylene chloride layer gave a brown gum. The aqueous layer was basified with aq. sodium hydroxide and extracted with methylene chloride (20 ml x 2). The organic layer was dried over sodium sulfate and the solvent evaporated to afford a residue (50 mg). Crystallization from methylene chloride-hexane gave colorless cubes, mp 286-287°C. This was shown to be identical (tlc, mixed mp and ir spectrum) with the rearrangement product **10** prepared from **3**.

Table 1. Fractional Coordinates* 10**4 and BEQ

N	Code	X/A	Y/B	Z/C	B(EQ)
1.	CL1	-1058 (3)	3129 (2)	11082 (1)	7.3
2.	CL2	1743 (4)	1559 (3)	11043 (2)	10.5
3.	CL3	728 (5)	2858 (4)	10047 (1)	10.2
4.	C	70 (9)	2159 (6)	10648 (3)	5.4
5.	02	5682 (4)	5385 (3)	2868 (1)	3.9
6.	011	5560 (4)	3338 (3)	4994 (1)	3.7
7.	016	6357 (6)	160 (4)	5076 (1)	4.6
8.	N	3514 (4)	2398 (3)	2766 (1)	2.8
9.	C1	4372 (6)	4865 (4)	3761 (1)	3.0
10.	C2	4293 (6)	5688 (4)	3233 (2)	3.5
11.	C3	2589 (6)	5581 (4)	2935 (2)	3.5
12.	C4	1884 (6)	4264 (4)	2858 (2)	3.3
13.	C5	2038 (5)	3497 (3)	3401 (1)	2.6
14.	C6	2036 (5)	2227 (4)	3157 (2)	3.0
15.	C7	2321 (5)	1232 (4)	3599 (2)	3.2
16.	C8	3995 (5)	1483 (3)	3919 (1)	2.7
17.	C9	3925 (5)	2778 (3)	4189 (1)	2.4
18.	C10	3826 (5)	3561 (3)	3643 (1)	2.3
19.	C11	5576 (5)	3019 (3)	4501 (1)	2.5
20.	C12	7227 (5)	2841 (4)	4182 (2)	3.0
21.	C13	7154 (5)	1710 (4)	3796 (1)	3.0
22.	C14	5420 (5)	1632 (3)	3487 (1)	2.3
23.	C15	4277 (6)	447 (4)	4356 (2)	3.6
24.	C16	6115 (7)	391 (4)	4584 (2)	3.5
25.	C17	7484 (6)	578 (4)	4143 (2)	3.5
26.	C18	45 (7)	4350 (6)	2637 (2)	4.7
27.	C19	3008 (6)	3475 (4)	2432 (1)	3.0
28.	C20	4859 (5)	2778 (3)	3178 (1)	2.5

Table 2 (a) Bond Lengths (Å)

C - Cl(1)	1.735(8)
C - Cl(2)	1.750(9)
C - Cl(3)	1.697(8)
O(2) - C(2)	1.436(7)
O(11) - C(11)	1.217(5)
O(16) - C(16)	1.203(7)
N - C(6)	1.499(6)
N - C(19)	1.487(6)
N - C(20)	1.501(6)
C(1) - C(2)	1.547(7)
C(1) - C(10)	1.537(6)
C(2) - C(3)	1.522(7)
C(3) - C(4)	1.575(7)
C(4) - C(5)	1.543(6)
C(4) - C(18)	1.545(8)
C(4) - C(19)	1.603(7)
C(5) - C(6)	1.523(6)
C(5) - C(10)	1.524(6)
C(6) - C(7)	1.536(7)
C(7) - C(8)	1.547(6)
C(8) - C(9)	1.575(6)
C(8) - C(14)	1.527(6)
C(8) - C(15)	1.562(7)
C(9) - C(10)	1.558(6)
C(9) - C(11)	1.521(6)
C(10) - C(20)	1.620(6)
C(11) - C(12)	1.518(6)
C(12) - C(13)	1.552(7)
C(13) - C(14)	1.553(6)
C(13) - C(17)	1.523(7)
C(14) - C(20)	1.532(6)
C(15) - C(16)	1.548(8)
C(16) - C(17)	1.516(7)

Table 2 (b) Bond Angles (DEC)

Cl(1) - C - Cl(2)	107.9(7)
Cl(1) - C - Cl(3)	111.6(8)
Cl(2) - C - Cl(3)	112.9(8)
C(6) - N - C(19)	102.7(6)
C(6) - N - C(20)	100.8(6)
C(19) - N - C(20)	107.9(6)
C(2) - C(1) - C(10)	113.5(7)
O(2) - C(2) - C(1)	108.4(7)
O(2) - C(2) - C(3)	112.2(7)
C(1) - C(2) - C(3)	111.2(7)
C(2) - C(3) - C(4)	116.0(7)
C(3) - C(4) - C(5)	112.9(7)
C(3) - C(4) - C(18)	108.2(7)
C(3) - C(4) - C(19)	112.6(7)
C(5) - C(4) - C(18)	112.9(7)
C(5) - C(4) - C(19)	100.1(6)
C(18) - C(4) - C(19)	110.0(7)
C(4) - C(5) - C(6)	101.4(6)
C(4) - C(5) - C(10)	111.0(6)
C(6) - C(5) - C(10)	100.7(6)
N - C(6) - C(5)	96.6(6)
N - C(6) - C(7)	113.3(6)
C(5) - C(6) - C(7)	114.1(7)
C(6) - C(7) - C(8)	109.1(6)
C(7) - C(8) - C(9)	109.4(6)
C(7) - C(8) - C(14)	108.8(6)
C(7) - C(8) - C(15)	108.2(6)
C(9) - C(8) - C(14)	101.4(6)
C(9) - C(8) - C(15)	114.2(6)
C(14) - C(8) - C(15)	114.6(6)
C(8) - C(9) - C(10)	100.1(5)
C(8) - C(9) - C(11)	109.1(6)
C(10) - C(9) - C(11)	110.2(6)
C(1) - C(10) - C(5)	111.8(6)
C(1) - C(10) - C(9)	111.2(6)
C(1) - C(10) - C(20)	119.2(6)
C(5) - C(10) - C(9)	109.3(6)
C(5) - C(10) - C(20)	100.8(5)
C(9) - C(10) - C(20)	103.7(5)
O(11) - C(11) - C(9)	120.4(7)
O(11) - C(11) - C(12)	121.5(7)
C(9) - C(11) - C(12)	118.1(6)
C(11) - C(12) - C(13)	111.4(6)
C(12) - C(13) - C(14)	110.7(5)
C(12) - C(13) - C(17)	110.3(6)
C(14) - C(13) - C(17)	110.9(6)
C(8) - C(14) - C(13)	109.9(6)
C(8) - C(14) - C(20)	101.3(6)
C(13) - C(14) - C(20)	115.6(6)
C(8) - C(15) - C(16)	113.2(7)
O(16) - C(16) - C(15)	119.6(8)
O(16) - C(16) - C(17)	125.4(8)
O(15) - C(16) - C(17)	115.0(7)
C(13) - C(17) - C(16)	111.1(7)
N - C(19) - C(4)	104.8(6)

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REFERENCES

1. J.A. Glinski, B.S. Joshi, Q.P. Jiang, and S.W. Pelletier, *Heterocycles*, 27, (1988).
2. S.W. Pelletier, N.V. Mody, J. Finer-Moore, A.M.M. Ateya, and L.C. Schramm, *J. Chem. Soc., Chem. Comm.*, 327 (1981).
3. S.W. Pelletier, J.A. Glinski, K.I. Varughese, J.A. Maddry, and N.V. Mody, *Heterocycles*, 20, 413 (1983).
4. G. Germain, P. Main, and M.M. Woolfson, *Acta Cryst.*, A27, 368 (1971).
5. P. Main, "A computer program to solve the crystal structure by multisolution methods," University of York (1980).

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