

Crystal and Molecular Structure of the Hydrochloride of the Diterpene Alkaloid Hetsine

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Abstract. The molecular and crystal structure of hetsine hydrochloride has been obtained and compared with those of the hydrobromide and perchlorate salts. These structures have been investigated as coordinatoclatrates and it has been shown that on changing from chloride to bromide and then to perchlorate a morphotropic transition is observed.

Key words. Crystal structure, X-ray crystallography, alkaloid hetsine, inclusion complexes.

Supplementary Data relevant to this article have been deposited with the British Library as Supplementary Publication No. SUB 82140 (9 pages).

1. Introduction

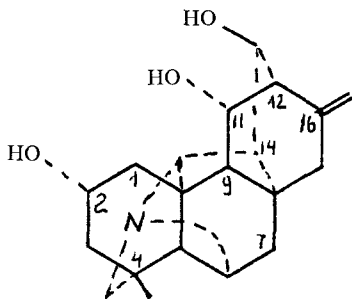
The conformation of the C₂₀-diterpene alkaloid hetsine, found in *Aconitum heterophyllum* Wall. [1], has been established by Przybylska on the basis of X-ray structure analysis of its hydrobromide (**HB**) [2]. The perchlorate (**HP**) [3] has a similar structure, both belonging to the P2₁ space group. Hetsine found in *Aconitum zeravschanicum* Steinb., allowed us to investigate the hydrochloride salt (**HC**). It was of interest to find out whether the new hetsine salt structure would have the same conformation.

2. Experimental

Hetsine hydrochloride crystals grown from ethyl alcohol solution have a prismatic form. A specimen of approximate dimensions of 0.3 × 0.4 × 0.6 mm was used for measurement on a Syntex-2₁ diffractometer. The lattice parameters were determined by a least-squares fitting of the setting angles of 15 reflections (2θ in range 25° to 30°).

The crystal data are as follows: C₂₀H₂₇O₃N·HCl, monoclinic, space group P2₁, $a = 6.474(2)$, $b = 8.148(2)$, $c = 16.915(7)$ Å, $\gamma = 100.62(2)^\circ$, $d_{\text{cal}} = 1.386$ g/cm³, $Z = 2$, $T = 295$ K.

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The intensities of the reflections were measured with graphite monochromatized $\text{CuK}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$) to $2\theta < 115^\circ$. No significant intensity variation was observed for two standard reflections. Data were corrected for Lorenz and polarization effects but not for absorption. Out of 1408 measured reflections 1351 had $I > 2\sigma(I)$. The structure was solved by direct methods with the program SHELXS-86 [4]. The structure was refined with anisotropic thermal parameters by full-matrix least-squares method with the program SHELX-76 [5]. The positions of hydrogen atoms bonded to C were calculated while the hydrogen atoms from hydroxyl groups and nitrogen atoms were localized on the ΔE maps. Hydrogen atom parameters were included in the final refinement cycles. Weighting scheme $1/[\sigma^2 + 0.001F^2]$. Final values of R and R_w are 0.033 and 0.032, respectively. The atomic parameters are given in Table I. Drawings were prepared with the program PLUTO [6]. Lists of bond lengths, bond angles and structure factors have been deposited with the British Library Lending Division, and copies may be ordered quoting Sup. No. 82140 (9 pp.).

3. Results and Discussion

The molecular structure of **HC** from X-ray analysis is shown in Figure 1, in the projection of the atom plane C(1)C(4)C(5). The three hydroxyl groups have the following orientations: α at C(2) and C(11) and β at C(13). The six-membered rings A and B are in the chair conformation. Rings C, D and E form a [2.2.2]-bicyclo-octane system, in which they are in the form of a lightly twisted boat. The mean value of the torsion angles [C(8)C(9)C(11)C(12), C(8)C(14)C(13)C(12), C(8)C(15)C(16)C(12)] defining the twisting angle and the connection in **HC**, **HB** and **HP** are similar: 10.4, 11.3 and 11.6°. The heterocyclic ring F has the ideal boat form as in **HB** and **HP**. The rings L, H and K are in the envelope conformation: the atoms C(9), C(10), C(14) and C(20) in the first are lying in the same plane to within $\pm 0.01 \text{ \AA}$, and the C(8) atom goes to -0.80 \AA , in ring H the atoms C(4), C(5), C(19) and N are lying in the same plane ($\pm 0.01 \text{ \AA}$), and then C(6) goes to -0.86 \AA . In ring K the atoms C(5), C(10), C(20) and N are coplanar, the C(6) atom goes out by 0.88 \AA . In general our data [7, 8] and those of the other workers [1, 2, 9, 10] indicate that the conformation of the hetisine nucleus is preserved independently from the position and direction of the substituents.

An intramolecular hydrogen bond is observed in the hetisine molecule. The hydrogen bond O(3)—H \cdots O(2) closes a six-membered ring formed by O(2),

Table I. Fractional atomic coordinates ($\times 10^4$) and equivalent thermal parameters with e.s.d.s in parentheses.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq.}
C(1)	2200(5)	10241(4)	-1190(2)	2.54
C(2)	0807(6)	10265(5)	-0470(2)	2.92
C(3)	1360(7)	09211(5)	0200(2)	3.24
C(4)	1699(6)	07467(4)	-0033(2)	3.07
C(5)	3206(6)	07494(4)	-0752(2)	2.58
C(6)	2605(6)	05713(4)	-1060(2)	2.70
C(7)	3590(6)	05328(4)	-1838(3)	2.91
C(8)	3337(5)	06621(4)	-2461(2)	2.34
C(9)	4106(5)	08425(4)	-2151(2)	2.37
C(10)	2506(5)	08503(4)	-1458(2)	2.27
C(11)	4212(5)	09608(4)	-2884(2)	2.62
C(12)	2790(5)	08736(5)	-3548(2)	2.83
C(13)	0616(5)	07954(4)	-3216(2)	2.53
C(14)	0968(6)	06681(4)	-2557(2)	2.19
C(15)	4346(7)	06250(5)	-3241(3)	3.51
C(16)	3763(6)	07359(5)	-3882(2)	3.29
C(17)	4010(7)	07153(7)	-4649(3)	4.10
C(18)	2541(9)	06679(6)	0701(3)	4.60
C(19)	-0321(6)	06326(4)	-0357(2)	2.86
C(20)	0448(5)	07281(4)	-1738(2)	2.13
N	0325(4)	05828(3)	-1165(2)	2.34
O(1)	-1406(4)	09727(4)	-0662(2)	3.35
O(2)	3671(5)	11203(3)	-2760(2)	3.14
O(3)	-0551(4)	09155(4)	-2936(2)	2.87
		Anion		
Cl	2172(1)	07417(1)	-6831(0)	3.70

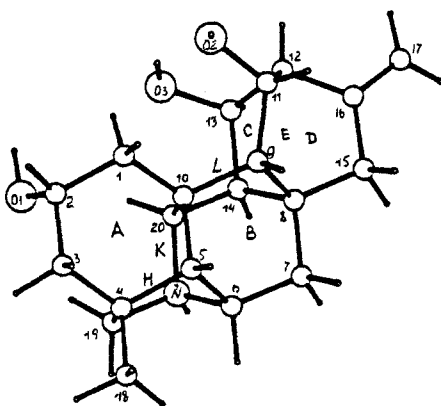


Fig. 1. Atom numbering scheme for the hetisine molecule.

C(11)—C(13), O(3) and H(O3) [distances O(2)⋯O(3) 2.94 Å, H(O3)⋯O(2) 2.27 Å, angle O(3)—H(O3)⋯O(2) 142°].

Anomalies have not been observed, in the values of bond lengths and valency angles (Table II, supplementary material) the deviation of lengths and angles are correspondingly not more than 0.006 Å and 0.4°.

In the hetisine hydrochloride crystal structure (Figure 2) channels are formed among four cations H in which chloride ions are located. All three hetisine hydroxyl groups are in the channel. But only two of them [O(1) and O(3)] form hydrogen bonds with chloride ions. Among the others the nearest oxygen atom O(2) is at 3.70 Å. The Cl⋯N electrostatic interaction is quite strong, the corresponding distance is 3.05 Å (N—H⋯Cl 2.15 Å). The hetisine molecules are not connected by hydrogen bonds. Nevertheless, chloride ions via their hydrogen bonds are connecting the molecules into a layer parallel to the *ab* plane.

In the hetisine hydrobromide crystal structure (Figure 3) bromide ions are situated in channels parallel to the (100) direction. The channels are surrounded by four cations H: H1 (*x*, *y*, *z*), H2 ($-x$, $0.5 + y$, $-z$), H3 and H4, which are formed from H1 and H2, while translating from the *y* and *x* axes, respectively. The bromide ions hydrogen bond with O(1) and O(2) of the H1 and H2 cations respectively and interact electrostatically with the nitrogen atom of the H4 molecule. The cations H interact with each other due to van der Waals forces, excluding the weak hydrogen bond N⋯O(3) (H).

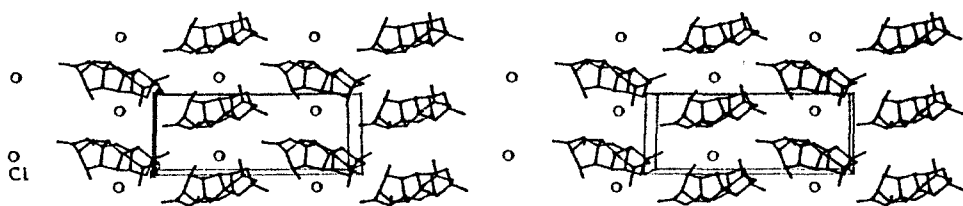


Fig. 2. Crystal structure of hetisine hydrochloride.

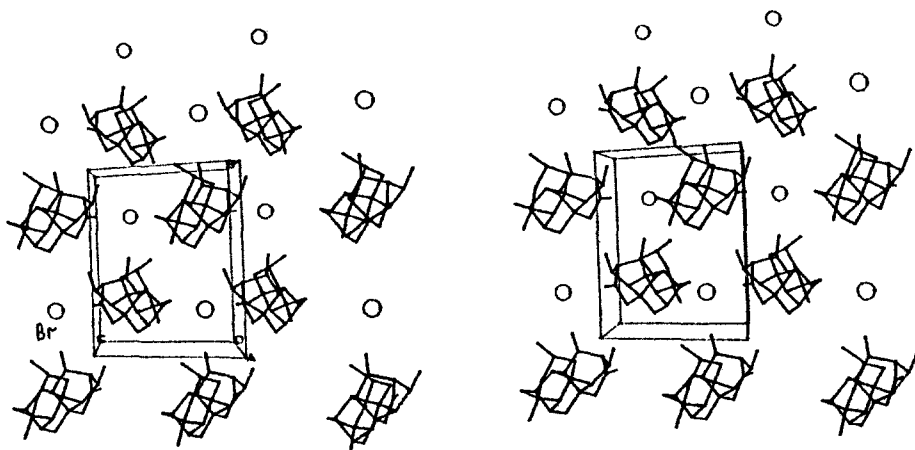


Fig. 3. Crystal structure of hetisine hydrobromide.

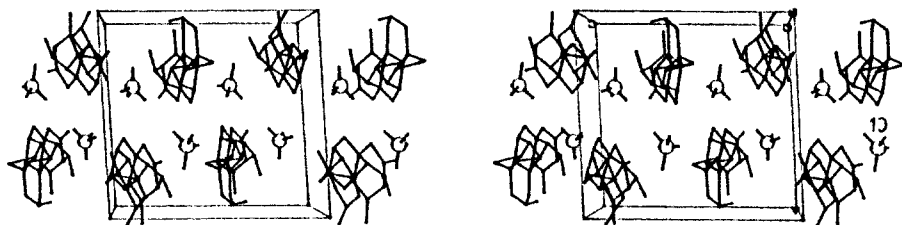


Fig. 4. Crystal structure of hetisine perchlorate.

In the hetisine perchlorate crystal structure (Figure 4) there are two hetisine molecules (H1, H2) and two perchlorate ions (P1, P2) in the independent part of the unit cell, where the cations H1 and H2 are combined into dimers by two hydrogen bonds [O(2)···O(5) 2.80 and O(3)···O(6) 2.92 Å]. The perchlorate ions are situated in the channels parallel to the monoclinic axis. The walls of the channels are formed by both H or P molecules. The ions P1 (x, y, z) form H-bonds with the molecules of H1 and H2. The oxygen atom O(7) of anion P1 (x, y, z) is in electrostatic interaction (possibly a hydrogen bond) with the nitrogen atom N(2). The oxygen atom O(10) of P1 (x, y, z) participates in two bonds: a strong one with the hydroxylic group O(2)—H of cation H1 [O(2)···O(10) 2.74 Å] and a weak hydrogen bond with group O(4)—H of cation H2 [O(4)···O(10) 3.03 Å]. The anions P2 hydrogen bond with atom O(6) of the H2 cation through the O(13) atom of the anions, the corresponding distance being 2.82 Å. Other oxygen atoms of P1 and P2 anions do not form intermolecular hydrogen bonds. Only the O(1)—H (H1) group of the hydroxyl groups of the two independent cations does not participate in hydrogen bonds. The P1 anion, via its bonds, forms columns of dimers of H1 and H2 cations, which are parallel to the x axis.

Thus, on changing the chloride anion for bromide and then for perchlorate a morphotropic transition is observed. The salt structure is very sensitive to the anion dimension. Usually in two-component crystals a small increase of ion dimensions (van der Waals radius increases 0.15 Å on interchanging Cl into Br) does not change the structure type and isostructures are observed. The above mentioned structures can be regarded on the basis of conformation preservation and of the charge condition (all through cations) as inclusion compounds (or clathrates) of one and the same host – the hetisine cation, being three channel type clathrates of the hetisine cation. It would be correct to name these structures as coordinato-clathrates [11] of the hetisine cation as there are two types of interaction, electrostatic and hydrogen bonds, between host and guest.

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