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CRYSTAL STRUCTURES OF VASICINONE AND PEGANIDINE HYDROCHLORIDE

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Crystal structures of the alkaloids vasicinone and peganidine hydrochloride were studied by x-ray structure analysis. The configurations of asymmetric centers C4 and C9 in peganidine were determined. The hydroxyl and acetonyl groups were mutually syn-positioned relative to the tricyclic plane. H-bonds involving the Cl ion, which connected molecular cations transformed by 2_1 screw axes, were formed in the peganidine hydrochloride crystal. H-bonds between the C4 carbonyl and the C9 hydroxyl transformed by a glide plane were formed in the vasicinone crystal. The N1 atom was not involved in forming intermolecular H-bonds.

Keywords: quinazolines, vasicinone, peganidine, x-ray structure analysis.

Tricyclic quinazoline alkaloids with a C9 hydroxyl such as peganine, vasicinone, and peganidine, are definitely of practical interest. Peganine and peganidine exhibit high anticholinesterase activity whereas vasicinone exhibits bronchodilating activity [1, 2]. Vasicinone was isolated from *Peganum harmala* as the L-isomer [3, 4] or the racemate [5]. The latter form was also obtained by oxidation of (±)-peganine by H_2O_2 [6]. The alkaloid peganidine is a peganine derivative and contains an acetone substituent in the 4-position. It was also isolated from *P. harmala* [7] together with deoxypeganidine [8].

The structure of (–)-vasicinone hydrobromide was established by an x-ray structure analysis (XSA) and its absolute (*S*)-configuration at C9 was determined [9]. However, data from the XSA are missing from the CCDC (only the cell constants are given). The crystal structure of the racemate of this base has not been reported.

Peganidine has two asymmetric centers at C4 and C9, i.e., its molecule can theoretically exist as four diastereomers. However, the plant alkaloid was isolated only as the racemate [7]. Therefore, the stereochemical question reduces to finding the mutual (*cis*- or *anti*-) positioning of the C4 and C9 substituents relative to the plane of the tricyclic system, which has until now been unanswered.

Furthermore, an intramolecular H-bond involving the hydroxyl H atom and N1 can theoretically form in vasicinone and peganidine. The formation of such a H-bond was observed for α-hydroxymethylenedeoxyvasicinone [10].

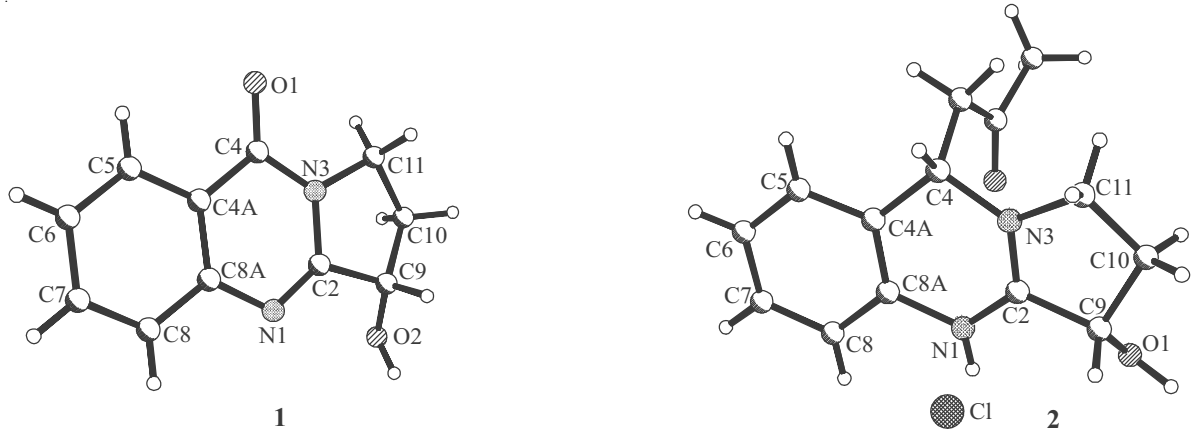

Fig. 1. Molecular structures of vasicinone (**1**) and peganidine hydrochloride (**2**).

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TABLE 1. Principal Crystallographic Parameters and Characteristics of X-ray Structures of **1** and **2**

Structure	**1**	**2**
Molecular formula	$C_{11}H_{10}O_2N_2$	$C_{14}H_{17}O_2N_2Cl$
MW/gmol^{-1}	202.21	280.75
System	Monoclinic	Orthorhombic
Temperature, K	293 (2)	293 (2)
Wavelength	1.54184	0.71073
Space group	P 2_1/c	Pna21
Z	4	4
a, Å	7.2142 (3)	18.136 (4)
b, Å	10.3663 (4)	13.179 (3)
c, Å	12.6175 (5)	5.796 (1)
α	90.00	90.00
β	103.771 (4)	90.00
γ	90.00	90.00
V, Å^3	916.47 (7)	1385.4 (5)
ρ, g/cm^3	1.466	1.346
Crystal size, mm	0.30 × 0.25 × 0.15	0.55 × 0.40 × 0.20
2θ scanning range	5.59 ≤ θ ≤ 75.84°	1.91 ≤ θ ≤ 25.99°
μ_{exp}, cm^{-1}	0.851	0.275
Index range	$-9 \le h \le 7$, $-13 \le k \le 13$, $-15 \le l \le 15$	$0 \le h \le 22$, $-16 \le k \le 0$, $0 \le l \le 7$
Number of reflections	1875	1499
Number of reflections with $I > 2\sigma(I)$	1354	929
R_1 ($I>2\sigma(I)$ and total)	0.0501 (0.0689)	0.0838 (0.1619)
WR_2	0.1423 (0.1533)	0.1014 (0.1276)
S	1.064	1.261
Electron density difference peaks, e Å^{-3}	0.453 and –0.212	0.351 and –0.369
CCDC	711598	711599

The structures of the racemate of vasicinone (**1**) and peganidine hydrochloride (**2**) were solved by XSA in order to answer these questions and to determine the structural features in the crystal.

Vasicinone is a planar tricyclic system with a C9 hydroxyl and a C4 carbonyl where the plane of the tricyclic system is slightly distorted (with the exception of the hydroxyl the molecule is planar within ±0.064 Å). The five-membered ring adopts a flattened envelope conformation with C10 deviating from the plane of the other atoms by 0.423 Å.

Figure 1 shows the molecular structure of peganidine hydrochloride. It can be seen that the salt is protonated on N1. The Cl anion and cation (protonated alkaloid) lie in the same plane. It can also be seen that the acetonyl substituent in the C4 position of peganidine and the C9 hydroxyl are mutually *cis*-positioned relative to the plane of the tricyclic system. The tricyclic system is almost planar within ±0.083 Å. The five-membered ring has the flattened envelope conformation, like in peganidine, with C10 deviating from the plane of the other four atoms by 0.287 Å. Therefore, the geometry of the tricyclic system in peganidine and vasicinone are practically the same, despite the fact that C4 in these alkaloids has different hybridization.

The crystal structure of the racemate of vasicinone (**1**) has intermolecular H-bonds that differ from those in the structures of its hydroxy analogs peganol and peganine. Atom N1 is not involved in forming intermolecular H-bonds (Fig. 2) although it does interact weakly with one of the C11 H atoms at a distance of 2.51 Å. H-bonds are formed between the C4 carbonyl of the starting molecule and the C9 hydroxyl transformed by a glide plane [O1...H–O2 (*x*, 0.5 - *y*, 0.5 + *z*)]. The translation results in formation of an infinite chain along the *c* axis. The parameters of the H-bond are O1...O2 2.802(2) Å, H...O1 1.98 Å, O2–H...O1 177°.

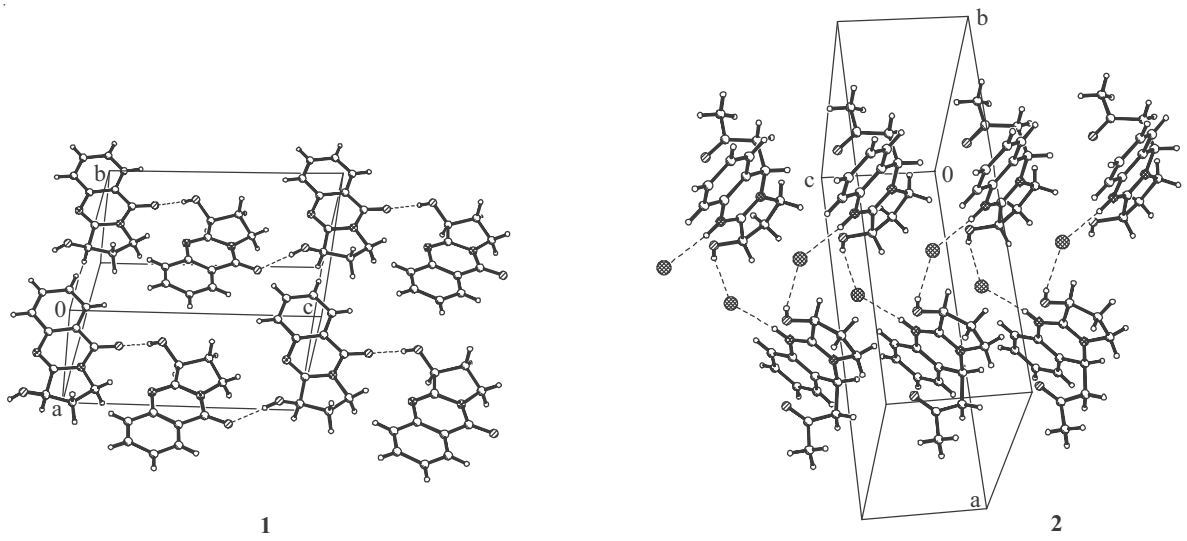

Fig. 2. Crystal packing of vasicinone (**1**) and peganidine hydrochloride (**2**).

Analysis of the crystal packing of **2** showed that the crystal has intermolecular H-bonds O1–H...Cl and N–H...Cl. The H-bonds in **2** involved the Cl ion that connects the molecular cations transformed by 2_1 screw axes passing through 0, 1/2, *z*. The parameters of these interactions are Cl...N1 3.153(7) Å, Cl...H1B 2.32 Å, Cl...H1B–N1 164°; and Cl...O1 3.052(6) Å, Cl...H1A–O1 2.27 Å, Cl...H1A–O1 159°.

EXPERIMENTAL

(±)-Vasicinone and peganidine were isolated from *P. harmala* by the literature method [5, 7]. Crystals of **1** and **2** were grown from a MeOH (dried beforehand) solution by slow evaporation at room temperature.

X-ray Structure Analysis. Unit cell constants of crystals of **1** were determined and refined on an Xcalibur CCD diffractometer (Oxford Diffraction) using CuK_α-radiation. A three-dimensional data set was collected on this same diffractometer. Absorption corrections were applied by the Multi-scan method. The corresponding experiments for a single crystal of **2** were performed on a Stoe Stadi-4 diffractometer (graphite monochromator) by the ω/2θ-scanning method using MoK_α-radiation. Absorption corrections were not applied. Table 1 lists the principal parameters of the XSA and calculations.

The structures were solved by direct methods using the SHELXS-97 program and refined using the SHELXL-97 program. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} was the equivalent isotropic thermal parameter of the corresponding C atoms. H atoms of hydroxyls were found in the structures from difference electron-density syntheses.

Structural data were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC).

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