

Communication

The Crystal Structures of 4-(1-Methylpiperidin-1-ium-1-yl)-2,2-Diphenylbutanamide Bromide and 4-(1-Methylpiperidin-1-ium-1-yl)-2,2-Diphenylbutanamide Bromide Hemihydrate

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Abstract: Fenpiverinium is an agent which, from a medical perspective, has anticholinergic and antispasmodic properties, with applications in the treatment of smooth muscle spasm. The crystal and molecular structures of two fenpiverinium-based crystals, namely fenpiverinium bromide and fenpiverinium bromide hemihydrate, were elucidated and explored by single-crystal X-ray diffraction.

Keywords: fenpiverinium; crystal structure; intermolecular interaction

1. Introduction

Fenpiverinium [4-(1-methylpiperidin-1-ium-1-yl)-2,2-diphenylbutanamide] is an antispasmodic drug which, in practice, was marketed in conjunction with pitofenone and metamizole or nimesulide in the alleviation of menstrual and muscle pains, gastrointestinal disorders, headache, toothache and urinary infections [1–3]. The effectiveness of fenpiverinium combined with pitofenone and dipyrone was investigated and compared with that of propacetamol in patients after abdominal aortic repair [4].

The literature and the CSD database do not yet report the crystal structure of fenpiverinium and other structure-related data. The objective of the actual work was the preparation of fenpiverinium crystals in solid forms using different crystallization techniques in order to elucidate their crystalline structure. Thus, we report the crystal structures and molecular characterization of fenpiverinium bromide (denoted as Fen-brom, Figure 1a) and fenpiverinium bromide hemihydrate as well (denoted as Fen-brom-hydrate, Figure 1b).

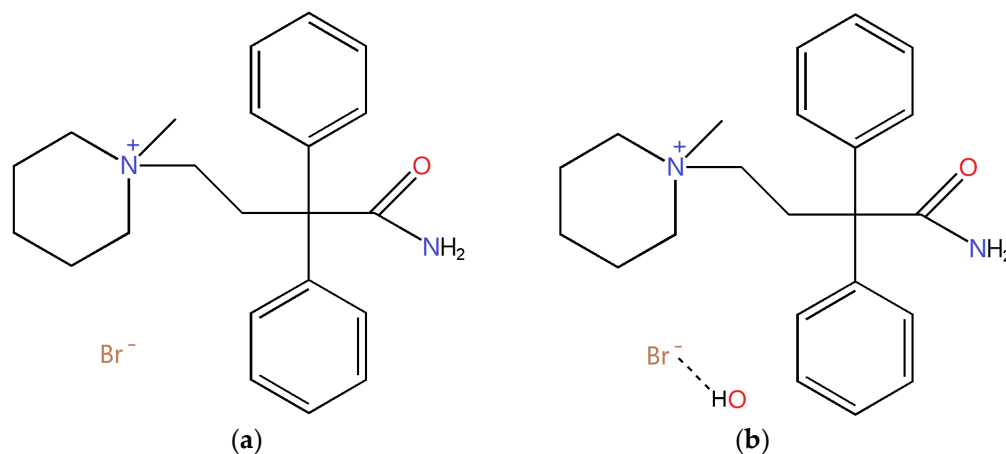


Figure 1. Molecular structure of fenpiverinium bromide (a); fenpiverinium bromide hemihydrate (b).



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2. Results

2.1. X-Ray Structure Analysis of the Crystals

The detailed crystallographic data of investigated fempiverinium-based crystals are given in Table 1.

Table 1. Crystallographic details of the investigated crystals.

Identification Code	Fen-Brom	Fen-Brom-Hydrate
Empirical formula	C ₂₂ H ₂₉ N ₂ OBr	C ₂₂ H ₃₀ BrN ₂ O _{1.5}
Formula weight	417.38	426.39
Temperature/K	293 (2)	293 (2)
Crystal system	monoclinic	monoclinic
Space group	P2 ₁ /c	C2/c
a/Å	14.3432 (3)	37.375 (2)
b/Å	9.8420 (2)	6.4573 (2)
c/Å	15.1183 (3)	20.1608 (11)
α/°	90	90
β/°	104.135 (2)	117.321 (8)
γ/°	90	90
Volume/Å ³	2069.58 (8)	4322.9 (5)
Z	4	8
ρ _{calc} g/cm ³	1.340	1.310
μ/mm ^{−1}	2.792	1.917
F (000)	872.0	1784.0
Radiation	CuKα (λ = 1.54184)	MoKα (λ = 0.71073)
2θ range/°	10.828 to 141.35	6.08 to 58.512
Index ranges	−17 ≤ h ≤ 17, −11 ≤ k ≤ 6, −18 ≤ l ≤ 18	−49 ≤ h ≤ 49, −8 ≤ k ≤ 8, −27 ≤ l ≤ 25
Reflections collected	7232	24810
Independent reflections	3897 [R _{int} = 0.0298, R _{sigma} = 0.0384]	5310 [R _{int} = 0.0391, R _{sigma} = 0.0328]
Data/restraints/parameters	3897/0/351	5310/9/264
Goodness of fit on F ²	1.053	1.025
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0382, wR ₂ = 0.1055	R ₁ = 0.0456, wR ₂ = 0.0976
Final R indexes [all data]	R ₁ = 0.0420, wR ₂ = 0.1105	R ₁ = 0.0742, wR ₂ = 0.1096
Largest diff. peak/hole/ e Å ^{−3}	0.39/−0.46	0.61/−0.63

2.1.1. Fen-Brom

The start compound crystallized in the centrosymmetric P2₁/c space group of the monoclinic crystal system. It is found in the form of bromide salt, with the asymmetric unit composed of one bromide anion (Br[−]) and one fempiverinium cation (Figure 2a).

The piperidine ring depicts a chair configuration, while the phenyl rings are twisted one with respect to the other, and the two planes that characterize them form an angle of 58°. The carbon atoms C8, C9, C10, C11, and C17 adopt a slightly distorted tetrahedral geometry with the central atom C9, and also, C1, C5, C6, C7, N1 are found to be tetrahedral with central N1.

In the formation of supramolecular architectures the bromide anion bridges the amide group of fempiverinium molecules via N-H⋯Br interactions (2.740 Å and 2.781 Å). Further, the bromide participates as well in C-H⋯Br intercontacts (2.826 Å, 2.865 Å, 2.900 Å, and 2.928 Å) with the methylpiperidin moiety. The oxygen of the carbonyl group connects a neighboring piperidine ring via the C-H⋯O interaction (2.596 Å). The packing perspective seen along

the *a*-axis is depicted in Figure 2b. In Figure 2c, it can be seen that the Fen-brom structure possesses voids; the voids are generated with the Mercury software [5] and are located in the *boc* plane and repeated on the *oc* axis at distances of $c/2$. Their volume relative to the unit cell is 6.1%, considering a sample radius of 1.2 Å with a grid spacing of 0.3 Å.

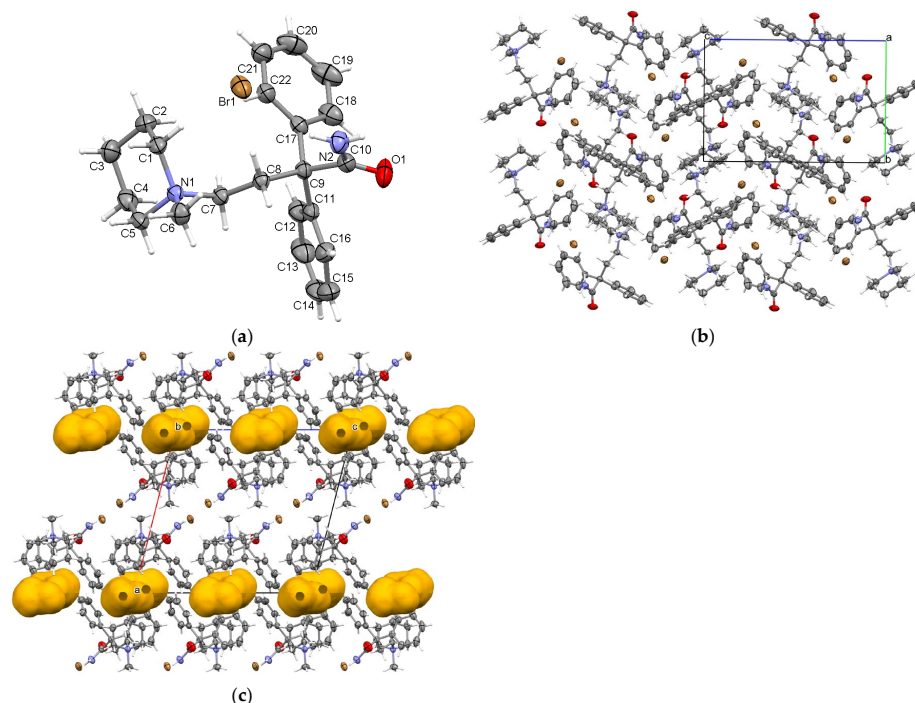


Figure 2. Asymmetric unit of Fen-brom presenting the atoms as thermal ellipsoids at a 50% probability level (a); crystal packing along *a*-axis (b); crystal voids (c).

2.1.2. Fen-Brom-Hydrate

The hemihydrate form of fempiverinium bromide was found to be centrosymmetric monoclinic as well but crystallized in the $C2/c$ space group. The asymmetric unit is illustrated in Figure 3a, and similar to Fen-brom, it contains one bromide anion and one fempiverinium cation but exhibits an extra half molecule of water, which is located on a 2-fold rotoinversion axis and a glide plane.

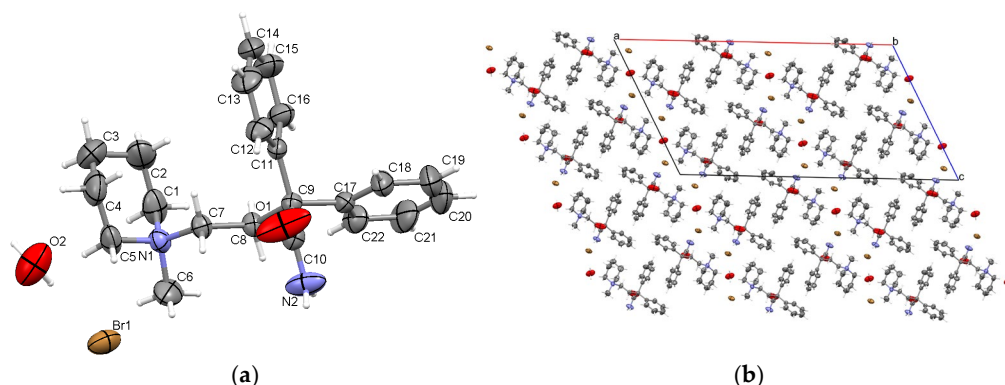


Figure 3. Asymmetric unit of Fen-brom-hydrate presenting the atoms as thermal ellipsoids at a 50% probability level (a); crystal packing along *b*-axis (b).

Also, the piperidine ring has a chair configuration, while the phenyl rings are twisted to each other, forming an angle of 85.7° . As in the previous crystal, the distorted tetrahedral geometry is maintained for the C8, C9, C10, C11, and C17 atoms, with the central C9 atom and C1, C5, C6, C7, and N1 with the central N1 nitrogen.

Once again, the bromide anion bridges the gap between the fempiverinium molecules via the N-H...Br interaction with the amide group (2.753 Å) and C-H...Br interactions (2.950 Å, 2.958 Å, 3.020 Å, and 3.841 Å) and is connected to the water molecule as well via O-H...Br (2.466 Å). In the direction of the *b*-axis, fempiverinium molecules are interconnected via trifurcated C-H...O hydrogen bonds (2.336 Å, 2.276 Å, and 2.552 Å) involving the carbonyl group as the acceptor. The crystal packing diagram seen in the direction of the *b*-axis is presented in Figure 3b.

The molecular overlay of the two fempiverinium ions show that with the inclusion of water molecules in the lattice, the amide, piperidine and phenyl rings adopt totally different configurations compared with the starting form (Figure 4). The CIF files of both investigated fempiverinium based crystals were deposited as Supplementary Materials.

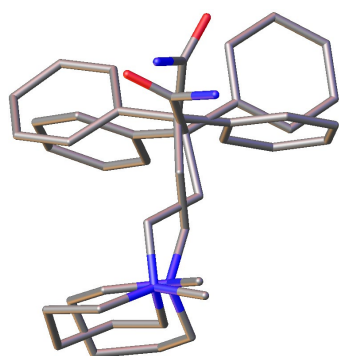


Figure 4. Molecular overlay of the two fempiverinium ions.

3. Materials and Methods

3.1. General and Sample Preparations

A white powder of fempiverinium bromide was purchased from AHH Chemical Co., Ltd., China. The solvents in which the crystal growth experiments were conducted were purchased from Sigma Aldrich and were used without further purification.

Suitable single crystals with a needle shape for X-ray analysis were successfully obtained using the platform for polymorphism and crystallization studies—CRISSY/Zinsser Analytic—in the cooling crystallization mode. Moreover, 20 mg of fempiverinium bromide was weighted in 4 mL vials, and the solvents were added in five steps of 200 µL, totalling 1 mL. The vials were heated up to 60 °C and slowly cooled to 15 °C in 24 h and further aged at 4 °C. After five days, the experiments led to single-crystal formations. The analyzed crystals were grown as follows:

- i. Fempiverinium bromide (Fen-brom) from a solution of 1,2 dichloromethane;
- ii. Fempiverinium bromide hemihydrates (Fen-brom-hydrate) from a mixture of 2-butanone with water in a volumetric ratio of 1:1.

3.2. X-Ray Diffraction and the Refinement of Crystal Structures

The experimental diffraction data were collected at ambient room temperature using a SuperNova diffractometer, which was equipped with a dual X-ray source (Mo and Cu), an Eos CCD detector and an X-ray tube set to operate at 50 kV and 0.08 mA. The collection, correction for Lorentz, absorption and polarization effects of crystallographic data were achieved in the CrysAlis PRO program [6]. The crystal structure of Fen-brom was solved with Direct Methods with the SHELXS solution program [7], while Fen-brom-hydrate was solved by SHELXT using Intrinsic Phasing [8]. Both models were further refined with ShelXL [9] via least squares minimization, all programs being included in the Olex2 interface (version Olex2-1.5-alpha) [10].

Hydrogen on carbons atoms were located and treated by the standard riding procedure, with the isotropic displacement parameter $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ for ternary CH groups [C-H = 0.93 Å], secondary CH₂ groups [C-H = 0.97 Å], and $1.5U_{\text{eq}}(\text{C})$ considered for all

methyl CH₃ groups [C-H = 0.96 Å]. The hydrogen atoms located on water molecules were located from Fourier maps and refined with a restrained distance of 0.84 Å.

4. Conclusions

Two fempiverinium bromide and fempiverinium bromide hemihydrates crystals were obtained by controlled slow heating and cooling, and their crystal structures were determined. Both were found to be centrosymmetric crystals, which belonged to the monoclinic crystal system. The cohesion and stability in the solid state is assured by combinations of C-H...Br, N-H...Br and C-H...O interactions.

Supplementary Materials: The CIF files of investigated compounds are included in the Supplementary Materials.

Author Contributions: Conceptualization: I.-G.G. and M.-O.M.; methodology: M.-O.M.; X-ray crystal structure: A.T. and G.B.; investigation: I.-G.G., M.-O.M., A.T. and G.B.; writing—original draft preparation: I.-G.G., M.-O.M., A.T. and G.B.; writing—review and editing: I.-G.G., M.-O.M., A.T. and G.B. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The CIF files of the compounds were deposited via the Cambridge Crystallographic Data Centre with the 2385930 deposit number for Fen-brom and 2385931 for Fen-brom-hydrate. They can be obtained free of charge via a written application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033); upon request via e-mail to maria.miclaus@itcm-cj.ro; or by accessing <http://www.ccdc.cam.ac.uk> (accessed on 25 September 2024).

Conflicts of Interest: The authors declare no conflicts of interest.

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