The title compound, C_8H_9N_3O_4S_1/2(H_2O), which is an impurity found in a drug lamivudine, crystallizes in the hexagonal space group P_6_2 with \( a = 10.208(1) \) Å and \( c = 18.073(2) \) Å. Such a rare packing is constructed by the hierarchical network of hydrogen bonds, which connect the molecules into chains, then into pairs of chains, and neighboring chains, oriented at the angle of 60°, make the final packing mode. The molecule exists in the crystal as the zwitterion, with negative charged carboxylate and positive ammonio groups. The oxathiolane ring is close to an envelope conformation, and both pyrimidine and carboxylate substituent are in the equatorial positions.

**Keywords** Oxathiolane ring · Hydrogen bonds · Crystal packing · Lamivudine

**Results and Discussion**

Lamivudine (which is a common name for 4-amino-1-(2R, 5S)-[2-(hydroxymethyl)l,3-oxathiolan-5-yl]pyrimidin-2(1H)-one) is a reverse transcriptase inhibitor used in the treatment of HIV infection alone or in combination with other class of Anti HIV drugs. It is an antiretroviral agent, which belongs to a class of drugs called “nucleoside reverse transcripts inhibitors” or “NRTIs”. The drug is marketed by GlaxoSmithKline with the brand names Zeffix, Heptovir, Epivir, and Epivir-HBV. Lamivudine and its hydrate have been studied [1]. The identification of lamivudine conformers by Raman scattering measurements and quantum chemical calculations is reported [2]. Lamivudine acid—or 5-(4-amino-2-oxopyrimidine-1(2H)-yl)-1,3-oxathioline-2-carboxylic acid is an impurity which can be present in the drug lamivudine. In view of the importance of lamivudine, the paper reports the synthesis and crystal structure of lamivudine acid, C_8H_9N_3O_4S, which turned out to crystallize in a zwitterionic form, and additionally as a hydrate (I, Scheme 1).

Figure 1 shows the perspective view of the molecule, and Table 1 lists the relevant geometrical parameters. In the crystal structure the molecule of lamivudine acid exists as the zwitterion, with carboxylate anionic and ammonio cationic groups on the opposite ends of the molecule. This is proven by the bond lengths pattern: almost equal C–O bonds, short C9–N91 bond (cf. Table 1). The bond lengths and angles pattern is similar to that found in the structure of Lamivudine saccharinate [3], which might be regarded as an additional proof for the protonation site in the six-membered ring.

The conformation of the oxathioline ring is close to an envelope, with four atoms: S1, C2, O3 and C5 almost coplanar (maximum deviation from the least-squares plane of 0.033(2) Å) while the fifth atom (C4) is significantly, by 0.608(5) Å out of this plane. Also the asymmetry parameter [4], which describes the deviation from the ideal symmetry (in this case C_s), has relatively low value of 8.8°. Similar conformation was observed in the majority of the structures with not fused oxathioline rings found in the
Cambridge Structural Database [5], however different atoms occupy the out-of-plane position. The pyrimidine substituent (which is approximately planar, within 0.010(2) Å) occupies the equatorial position with respect to the oxathiolane ring (C2–O3–C4–N6 torsion angle is 172.9 (3)°, S1–C5–C4–N6—160.8 (3)°), the position of carboxylate group is also close to the equatorial one (C4–O3–C2–C21—149.6(3)°, C5–S1–C2–C21—125.3(3)°).

Compound 1 crystallizes in a rather uncommon space group P6_2—in the CSD there are only 61 structures in either P6_2 or P6_4 space groups, of which 26 are of organic compounds. The crystal packing is determined mainly by an extensive network of hydrogen bonds (Table 2), both strong (N–H···O(carboxylate), O(water)–H···O(carboxylate)) and weak (C–H···O(water, carbonyl)). The organization of the three-dimensional network may be analyzed as the step-by-step construction of the six-fold screw symmetry. At the first level, molecules are connected by means of two different hydrogen bonds: N8–H8···O23(x, y − 1, z) and N91–H91A···O22(x, y − 1, z) into the infinite chains expanding along y direction (Fig. 2a). Using the graph-set notation [6, 7] one could find, at this level, two parallel chains C(9) and C(11) along y, which give rise to the second-order R2_1(8) ring. The neighboring chains are connected by hydrogen bonds with water molecules (which lie on the twofold axes) into the pairs of antiparallel chains; the “linking” graph symbol is R6_4(30), cf. Fig. 2b.

Then, at the next level, these double strands are linked by means of N91–H91B···O23(y, −x+y, z − 1/3) hydrogen bonds with the subsequent strands, which are oriented at the angle of 60° to the former one (Fig. 2c). At this level relatively short and directional C5–H5···O1Wiii hydrogen bonds also play their part, by linking the neighbouring chains. Altogether, all these steps lead to the hexagonal symmetry as seen in the packing diagram (Fig. 3).

**Experimental**

**Preparation**

L-menthyl-5-cytosin-1,3-oxathiolane-2-carboxylate (2.0 g, 5.2 mmol) was added to a solution of KOH (0.3 g, 6.0 mmol) in 20 ml of methanol (Scheme 2). The mixture was stirred for 4 h. Methanol was distilled out and the residue was diluted with water. Aqueous layer was extracted with ethyl acetate. The pH of aqueous layer was adjusted to four using acetic acid. The solid was collected by filtration and further recrystallized from water (m.p.: 311–313 K).

**Crystallography**

Colourless block-like crystal (0.2×0.1×0.1 mm) was used for data collection. Diffraction data were collected at 100(1) K.
Fig. 2 The construction of the packing motifs. a the hydrogen bonded chain along y; b the pair of antiparallel chains; c the set of strands giving the six-fold symmetry.

![Diagram](image)

Table 2 Hydrogen-bond geometry (Å, °)

| D–H...A   | D–H | H...A | D...A   | D–H...A |
|-----------|-----|------|---------|---------|
| N8–H8...O23i | 0.88 | 1.81 | 2.681(4) | 173     |
| N91–H91A...O22ii | 0.88 | 2.01 | 2.873(4) | 168     |
| N91–H91B...O23iii | 0.88 | 2.01 | 2.870(4) | 166     |
| C5–H5A...O1 Wiii | 0.99 | 2.34 | 3.202(5) | 145     |
| O1 W...H1W1...O22 | 0.85 | 2.06 | 2.885(3) | 173     |

Symmetry codes: (i) x, y – 1, z; (ii) y, –x+y, z – 1/3; (iii) –x+y+1, –x+1, z + 1/3

by the ω-scan technique up to 2θ = 60°, on an Xcalibur diffractometer [8] with graphite-monochromatized MoKα radiation (λ = 0.71073 Å). The temperature was controlled.
by an Oxford Instruments Cryosystems cooling device. The data were corrected for Lorentz-polarization and absorption effects [8]. Accurate unit-cell parameters were determined by a least-squares fit of 2307 reflections of highest intensity, chosen from the whole experiment. The structures were solved with SIR92 [9] and refined with the full-matrix least-squares procedure on F² by SHELXL97 [10]. Scattering factors incorporated in SHELXL97 were used. The function R\( = \sqrt{\sum \left( F_o^2 - F_c^2 \right)^2} \) was minimized, with w\( ^{-1} \) = [\( \sigma^2(F_o) + 0.0951F^2 + 0.2763P \)] \( P = \max (F_o^2, 0) + 2F_c^2/3 \). All non-hydrogen atoms were refined anisotropically, hydrogen atoms were put in the idealized positions (only that from water molecule was found in the difference Fourier map), and refined as riding model. Their isotropic thermal parameters were set at 1.2 times Ueq’s of appropriate carrier atoms. There are cavities on the two-fold axis which appeared to be filled by highly disordered water molecule; relatively satisfactory results were obtained with half occupancy, but the displacement parameters were very large. Therefore, we decided that the disorder is so severe that in fact it is smeared-out electron density. As an alternative strategy, the SQUEEZE function of PLATON [11] was used to eliminate the contribution of the electron density in the solvent region from the intensity data. The use of this strategy and the subsequent solvent-free model produced better refinement parameters and more precise geometric parameters, than the model with the disordered water molecule. Relevant crystal data are listed in Table 3, together with refinement details.

CCDC-753804 contains supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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Table 3 Crystal data, data collection and structure refinement

| Formula          | C₈H₉N₃O₄S · 1/2H₂O |
|------------------|----------------------|
| Formula weight   | 167.67               |
| Crystal system   | Hexagonal            |
| Space group      | P6₂                  |
| a(Å)             | 10.208(1)            |
| c(Å)             | 18.073(2)            |
| V(Å³)            | 1631.0(3)            |
| Z                 | 6                    |
| D₂(g cm⁻³)       | 1.56                 |
| F (000)          | 798                  |
| μ (mm⁻¹)         | 0.31                 |
| θ range (°)      | 3.22–24.99           |
| hkl range        | h: -10 ≤ h ≤ 12, k: -12 ≤ k ≤ 7, l: -21 ≤ l ≤ 21 |

Reflections:
- Collected 3196
- Unique (R(int)) 1715 (0.046)
- With I > 2σ(I) 1531
- Number of parameters 155
- R (F) [I > 2σ(I)] 0.056
- wR (F²) [I > 2σ(I)] 0.143
- R (F) [all data] 0.062
- wR (F²) [all data] 0.146
- Goodness of fit 1.107
- Max/min Δρ (e Å⁻³) 0.79/–0.43

Scheme 2 Synthesis of the lamivudine acid
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