Crystal and Molecular Structure of cis-(+)-3-Acetoxy-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-1-oxide

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cis-(+)-3-Acetoxy-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-1-oxide was synthesized and the crystal structure was determined at room temperature. The compound crystallizes in an orthorhombic system with space group P2₁2₁2₁ and Z = 4. The unit cell dimensions are a = 9.271(1)Å, b = 11.838(1)Å, c = 15.836(2)Å, and V = 1738.0(3)Å³. The final R value is 0.042 for 1733 observed reflections. The seven-membered ring is distorted, showing a twist boat conformation. The molecular packing is stabilized by hydrogen bonding. The amide group forms strong hydrogen bonds with the symmetrically related neighboring molecules in the crystal. The molecules are linked into an infinite chain through hydrogen bonds.

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Table 1 Crystal and structure refinement for cis-(+)-3-acetoxy-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-1-oxide

| CCDC No. | 604145 |
| Empirical formula: | C₁₈H₁₇NO₅S |
| Formula weight | 359.39 |
| Crystal system: | orthorhombic |
| Space group: | P2₁2₁2₁ |
| Z = 4 |
| Cell dimensions: |
| a = 9.271(1)Å |
| b = 11.838(1)Å |
| c = 15.836(2)Å |
| V = 1738.0(3)Å³ |
| T = 293(2)K |
| μ(Cu Kα) = 1.908 mm⁻¹, λ = 1.5418 Å |
| Dₐ = 1.373 Mg m⁻³ |
| 2θmax = 135.68 |
| Crystal size = 0.3 × 0.2 × 0.12 mm |
| F(0 0 0) = 751.9 |
| R₁ = 0.042, R₂ = 0.043 |
| Goodman-of-fit = 1.041 |
| Extinction coefficient = 0.0036 |
| No. of parameters = 227 |
| (Δ/σ)max = 0.000 |
| (Δρ)max = 0.562 e.Å⁻³ |
| (Δρ)min = -0.301 e.Å⁻³ |
| Flack parameter = 0.13(3) |
| Measurement: Enraf-Nonius CAD-4 |
| Program System: SHELXS97 and SHELXL97 |
| Structure determination: direct methods |
| Refinement: full-matrix |

The title compound is a diltiazem₁-related compound. Diltiazem, is a benzothiazepine calcium-channel blocking agent. This is a part of our work on a series of 1,5-benzothiazepine compounds²–⁴ to understand the geometrical effect and the nature of hydrogen-bonding interactions by varying the different substituents with the parent skeleton using x-ray analysis. As expected, the seven-membered ring (Fig. 1) is not planar; this trend is almost the same in all reported 1,5-benzothiazepine structures,¹,³,⁴ including its racemic form.² cis(+)–Propionic acid (5 g) was treated with acetic anhydride (3.4 g) and pyridine (2.2 g) in acetonitrile at 50°C for 4 h; the reaction mass was poured in water. The precipitated compound (4 g) was filtered and then oxidized with oxone (7.2 g) in a water and acetone mixture. The product formed was extracted with ethyl acetate, and then evaporated ethyl acetate to obtain the above mentioned compound, 3.5 g [α]RT = +322.89°.

Further, the compound was crystallized from acetone by a slow evaporation method at room temperature. The molecular structure of the title compound is shown in Fig. 2. Crystallographic data and experimental details of a structural analysis are summarized in Table 1. The structure was solved by direct methods and refined by full-matrix least-squares. All of the non-hydrogen atoms were refined anisotropically and the H atoms were geometrically fixed and constrained to ride on the parent atom in the model. The atomic coordinates and equivalent isotropic displacement parameters for non-hydrogen

Fig. 1 Chemical structure of the title compound.
Results

The interatomic distances and angles in the 1,5-benzothiazepine ring reflect the usual seven-membered ring geometry and hybridization. The conformation of the seven-membered ring was determined using a least-squares plane calculation. In this ring atoms C(2) and C(3) lie above and C(23) and N(25) below the plane of atoms S(7), C(9) and C(18). The values of the torsion angles indicate a twist-boat conformation. A similar type of confirmation has also been noticed in other analogous structures. 

As expected, the benzene ring is planar and the methoxyphenyl group is significantly deviated from planarity. The methoxyphenyl and acetoxyl groups at C(9) and C(18) are cis oriented with respect to one another, as indicated by the torsion angle C(10)–C(9)–C(18)–C(19) of –39.1(3)°. The relative orientation of the sulfoxide group to the methoxypyphenyl group is defined by the torsion angle, 69.8(2)°. However, the acetoxy group and the carbonyl O(24) atom is cis oriented as the torsion angle 24.2(5)°. The dihedral angles between the seven-membered ring and methoxyphenyl, acetoxyl, sulfoxide O(8), carbonyl O(24) are 75.2(1), 14.5(3), 12.7(1), 65.7(1)° respectively. The methoxyphenyl and carbonyl O(24) adopts a pseudo-axial position in the molecule with an acetoxyl group and a sulfoxide O(8) equatorial position.

Fig. 2 The Molecular structure of the title compound, showing a 50% probability displacement ellipsoids and arbitrary spheres for the H-atoms.

The molecular packing is stabilized by hydrogen bonding. The amide group N(25)–H(25) forms a hydrogen bond (Fig. 3) with atom O(8) of the adjacent molecule in the crystal. The distances are N(25)–H(25) 0.86, H(25)···O(8) 2.100(3)Å, N(25)···O(8) 2.948(3)Å and the angle is N(25)–H(25)···O(8) 168.9(2)° [Symmetry code: (i) –x, –1/2+y, 1/2–z]. This hydrogen bonding-interaction makes a link between the molecules and forms an infinite chain in the crystal.

Table 2  Final atomic coordinates and equivalent isotropic displacement parameters of the non-hydrogen atoms (Å²)

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<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
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Table 3  Selected bond distances (Å) and angles (°)

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<th>Angle (°)</th>
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<td>C12–C13</td>
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<td>C13–O16</td>
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<td>C2–C7</td>
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References