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Comparative X- Ray Crystallographic Studies on $C_{10}H_{11}N_3O_3S$

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Abstract: ***Title compound $C_{10}H_{11}N_3O_3S$ belongs to the family of Sulpha drug. Its IUPAC name is 4-amino-N-(5-methyl-lisoxazole-3-yl)-benzene sulfanilamide. Single crystal X-ray diffraction study showed the unit cell parameters as a=16.0620(4), b=5.4750(1), c=25.7530(7) Å and β=96.148˚(1) with Z=8. It belongs to monoclinic crystal system with space group C2/c. In all total with 1979 unique reflections, the final R value is 0.034.***

Keywords: X-ray diffraction, Sulpha drugs, Sulfonamide, Crystal structure, Refinement

1. Introduction

Title compound is most often used these days as part of a synergistic combination with Trimethoprim in a 5:1 ratio. It is commonly used to treat urinary tract infections. Solfonamides are structural analogs and competitive antagonists of p-amino-benzoic acid (PABA).They inhibit normal bacterial utilization of PABA for the synthesis of folic acid, an important metabolite in DNA synthesis. The effect can be seen are usually bacteriostatic in nature.

In addition it can be used as an alternative to amoxicillin-based antibiotic to treat sinusitis. It can also be used to treat toxoplasmosis and is the drug of choice for *pneumocystis pneumonia* which affects primarily patients with HIV. Its chemical structure is shown in **Fig.1**.

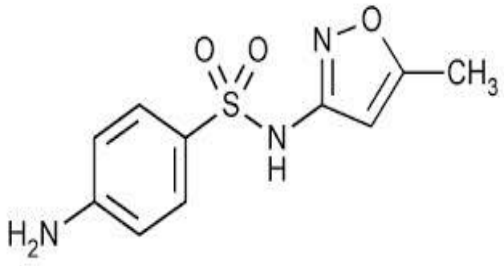

Figure 1: Chemical structure of Title Compound

2. Experimental

Colorless well formed cube shaped crystals of the title compounds were obtained by slow evaporation from a solution of methyl alcohol. The density of the crystals was measure by flotation method using a mixture of benzene and carbon tetrachloride. The crystal was placed in RD bottle half filled with carbon tetrachloride. Benzene was slowly added to the RD bottle until the crystals floated in the middle of the mixture. Thus the crystal and solution were of same density. Then the density of solution was measured with pyknometer. The measured density is 1.491 mg/m^3 and calculated density is 1.494 mg/m^3. The molecular weight of the sample is 253.28 g/mol and melting point is 169˚c. The unit cell parameters were determined by a computerized automatic Bruker Kappa apex 2 CCD diffractometer at SAIF Chennai.

3. Data collection and Structure solution

The complete three dimensional intensity data collection was done at SAIF, IIT Chennai on a computerized automatic Bruker Kappa apex 2 CCD diffractometer. The temperature of crystal during data collection was 293k. All the data were corrected for Lorentz and polarization effects and absorption corrections because the coefficient of absorption was 0.288 mm^{-1}. The data collection was done by a θ range of 2.38 to 31.26˚. The entire data were collected where h varies from -18 to 18, k from -6 to 6 and I from -30 to 30. The total number of reflection measured was 10028 out of which only 1979 were unique. Each intensity measurement involved in a scan over the reflection peak, a background measurement at each end of the scan range and a measurement of the peak height. The crystals belongs to monoclinic system with space group C2/c. the structure was solved using **SHELXS-97**.[1]

4. Refinement

The positional coordinates of non-hydrogen atoms were obtained from **SHELXS-97** and their isotropic temperature factors were subjected to refinement by **SHELXL-97** refinement program. The refinement was carried out using Full matrix block diagonal least square refinement. During refinement, calculated weighting scheme was employed. The Refinement of F^2 against all reflections. The weighted R-factor wR and goodness of fit's are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. After a few initial cycles of refinement the overall R-factor dropped to 0.0736. Further refinement of the structure was carried out with individual anisotropic temperature factor of the form:

$$\textbf{Exp. } [-(U_{11}h^2+U_{22}k^2+U_{33}l^2+2U_{12}hk+2U_{23}kl+2U_{13}hl)]$$

Reduced R-factor to 0.541. At this stage the hydrogen atoms were fixed by geometrical considerations and refined subsequently with isotropic temperature factors which were taken from the corresponding non- hydrogen atoms.

Refinement of the structure was terminated after three more cycles of refinement when all the shifts in the parameters became much smaller than the corresponding e.s.d's. The

final R-value was 0.0348 for all the 1979 observed unique reflections.

5. Results and discussion

The ORTEP [2] view of the molecule the numbering scheme is shown in **Fig. 2**. The bond lengths involving non-hydrogen atoms are given in **Table 1**. The bond angles involving non-hydrogen atoms are in **Table 2**. The C(1)-N(1) distance of 1.378(3)Å is a characteristics bond length as in other sulfonamide structures [3-24]. The bond lengths and angles in the benzene ring have characteristics values. The S(1)-C(1) bond distance of 1.746(2)Å is similar to those observed in other sulfonamides [3-24]. In all these comparable structures, the S-C distance is considerably shorter than 1.82Å, which is the sum of Pauling's covalent radii [25] of carbon and sulfur atoms except in sulfamethoxypyradazine[26]. Abrahams[27] has calculated the S-C single bond distance to be 1.82Å. So in all these structures these are considerable amount of double bond nature in the S-C bond. The S(1)-N(2) distance 1.645(2)Å is however, slightly shorter than those observed in similar structures [3-24]. Sass[28] has estimated the S-N bond distance by 1.764(3) Å. So, the S-N distance in this structure is having a considerable amount of double bond character. The S(1)-O(1) and S(1)-O(2) distances of 1.434(2) and 1.429(2)Å respectively are comparable to those observed in analogues structures. The tetrahedral geometry around the Sulfur S(1) is shown in **Fig. 3**. The tetrahedral geometry around sulfur is slightly distorted from the ideal tetrahedral geometry. The largest deviations are in the angles O(1)-S(1)-O(2) 119.43˚(10), and O(1)-S(1)-N(2) 104.06˚(10) conforms to the altered-tetrahedral arrangement commonly observed in sulfonamides.

The dimensions of the Oxazole ring show good agreement with those observed in its isomer, Sulfisoxazole and 3-4-biisoxazole and they have characteristic values. The variations in bond lengths of these molecules are in the same range (sulfamoxole-1.33(2) to 1.40(2) Å, Sulfisoxazole-1.307(3) to 1.414(4) Å, 3-4 biisoxazole-1.322(3) to 1.428(4) Å, but the range of variation of bond angles is small.

The phenyl and isoxazole rings are essentially planar and oriented with respect to each other at an angle of 76.7˚. The torsional angle along the S(1)-N(2) bond is 56.89˚(18). C(10) atom is displaced from the plane of isoxazole ring by -0.07(2) Å. Some important dihedral angles are shown in **Table 3**.

6. Hydrogen bonding and Molecular packing

The hydrogen bonds in the structure are given in **Table 4**. The amide nitrogen N(1) is involved in two hydrogen bonds with symmetry related oxygen atoms (3.324(3) and 3.281(3)Å respectively. Similarly the amino nitrogen N(2) is involved in hydrogen bonding with oxygen of another symmetry related oxygen atom (3.240(2)Å). The symmetry relations are (x+½, y+½, z; x+½, y-½, z; x, y+1, z). The density of the crystals being higher in comparison to reported sulfonamides indicates that the intermolecular forces are acting very strongly to bring the molecules closer to have a compact arrangement.

7. Conclusion

The determination of structural disturbance in antibiotic derivatives and comparison of the results of their molecular collaboration with the other receptor sides by X-ray crystallography techniques will be done. In parallel with these structural investigations, the author will carry out spectroscopic studies on them. The goal is then to correlate between structural and spectroscopic studies to have more comprehensive account of the precise shape of these molecules the non covalent interactions which are likely to be involved in and the changes introduced in the molecular geometry and electric structure of these compounds as a result of their molecular interaction with other compounds.

The aim of this research work is to study the structure of variety of such medicinal compounds and more safer and effective drugs at reasonable prices can be developed.

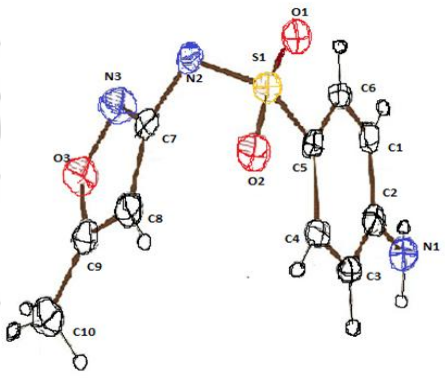

Figure 2: ORTEP view of the molecule

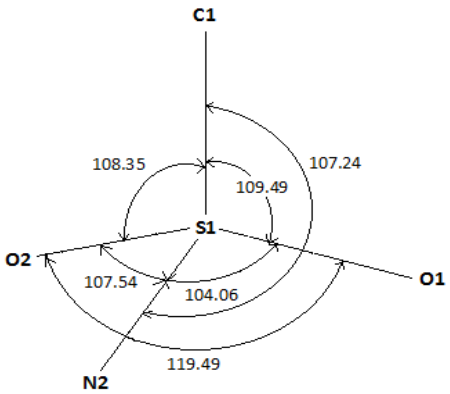

Figure 3: Tetrahedral geometry around Sulfur atom

Table 1: Bond lengths [Å] of non-hydrogen atoms. Corresponding e.s.d's are given in parenthesis

C(1)-C(2)	1.387(3)
C(1)-C(6)	1.388(3)
C(1)-S(1)	1.746(2)
C(2)-C(3)	1.378(2)
C(3)-C(4)	1.388(3)
C(4)-N(1)	1.378(3)
C(4)-C(5)	1.390(3)
C(5)-C(6)	1.377(3)
C(7)-N(3)	1.293(3)
C(7)-C(8)	1.397(3)
C(7)-N(2)	1.404(3)
C(8)-C(9)	1.343(3)
C(9)-O(3)	1.345(3)
C(9)-C(10)	1.468(3)
N(2)-S(1)	1.6450(19)
N(3)-O(3)	1.408(3)
O(1)-S(1)	1.4343(15)
O(2)-S(1)	1.4286(15)

Table 2: Bond angles [˚] of non-hydrogen atoms. Corresponding e.s.d's are given in paranthesis

C(2)-C(1)-C(6)	120.37(19)
C(2)-C(1)-S(1)	120.40(15)
C(6)-C(1)-S(1)	119.20(15)
C(3)-C(2)-C(1)	119.59(19)
C(2)-C(3)-C(4)	120.78(19)
N(1)-C(4)-C(3)	120.8(2)
N(1)-C(4)-C(5)	120.3(2)
C(3)-C(4)-C(5)	118.89(19)
C(6)-C(5)-C(4)	121.00(19)
C(5)-C(6)-C(1)	119.35(18)
N(3)-C(7)-C(8)	112.7(2)
N(3)-C(7)-N(2)	118.24(19)
C(8)-C(7)-N(2)	129.02(19)
C(9)-C(8)-C(7)	104.60(19)
C(8)-C(9)-O(3)	109.2(2)
C(8)-C(9)-C(10)	133.9(2)
O(3)-C(9)-C(10)	116.9(2)
O(2)-S(1)-O(1)	119.49(10)
O(2)-S(1)-N(2)	107.54(10)
O(1)-S(1)-N(2)	104.06(10)
O(2)-S(1)-C(1)	108.35(9)
O(1)-S(1)-C(1)	109.49(9)
N(2)-S(1)-C(1)	107.24(9)
C(7)-N(2)-S(1)	120.54(14)
C(7)-N(3)-O(3)	104.71(18)
C(9)-O(3)-N(3)	108.72(17)

Table 3: Torsion angles [deg]. Corresponding e.s.d's are given in paranthesis.

C(6)-C(1)-C(2)-C(3)	1.4(3)
S(1)-C(1)-C(2)-C(3)	179.36(15)
C(1)-C(2)-C(3)-C(4)	-1.1(3)
C(2)-C(3)-C(4)-N(1)	177.2(2)
C(2)-C(3)-C(4)-C(5)	0.2(3)
N(1)-C(4)-C(5)-C(6)	-176.61(19)
C(3)-C(4)-C(5)-C(6)	0.4(3)
C(4)-C(5)-C(6)-C(1)	-0.1(3)
C(2)-C(1)-C(6)-C(5)	-0.8(3)
S(1)-C(1)-C(6)-C(5)	-178.82(15)
N(3)-C(7)-C(8)-C(9)	-0.8(3)
N(2)-C(7)-N(3)-O(3)	-177.03(17)
C(8)-C(9)-O(3)-N(3)	0.7(3)
C(10)-C(9)-O(3)-N(3)	179.8(2)
C(7)-N(3)-O(3)-C(9)	-1.2(3)
C(7)-N(2)-S(1)-O(2)	-59.45(18)
C(7)-N(2)-S(1)-O(1)	172.86(16)
C(7)-N(2)-S(1)-C(1)	56.89(18)
C(2)-C(1)-S(1)-O(2)	14.21(19)
C(6)-C(1)-S(1)-O(2)	-167.77(15)
C(2)-C(2)-S(1)-O(1)	146.09(17)
C(6)-C(1)-S(1)-O(1)	-35.89(18)
C(2)-C(1)-S(1)-N(2)	-101.60(17)
C(6)-C(1)-S(1)-N(2)	76.42(17)

Table 4: Hydrogen bonds [Å and deg.]. Corresponding e.s.d's are given in paranthesis.

D-H…A	d(D-H)	d(H…A)	d(D…A)	<(DHA)
N(1)-H(1A)…O(1)#1	0.828(16)	2.64(2)	3.324(3)	141(2)
N(1)-H(1B)…O(1)#2	0.819(16)	2.493(17)	3.281(3)	162(3)
N(2)-H(2A)…O(2)#3	0.818(17)	2.458(18)	3.240(2)	160(2)

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,y+1/2,z #2 x+1/2,y-1/2,z #3 x,y+1

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