Structure of Tiaramide

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The crystal of the title compound, $C_{15}H_{18}ClN_3O_3S$, belongs to space group $P2_1/a$ with cell dimensions $a = 12.744(5)$, $b = 8.260(2)$, $c = 15.513(5)$ Å, and $\beta = 93.42(2)^\circ$. The final R value is 0.053. The piperidine ring is almost perpendicular to the benzothiazolyl ring. The piperidine ring adopts a chair conformation in which the acetyl and ethanol groups are equatorial. There is one intermolecular O-H...N hydrogen bond that connects two molecules around the center of symmetry into a dimer.

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Tiaramide has antiallergic activity,¹ and is used as an antiasthmatic and anti-inflammatory drug. The chemical structure, 4-[(5-chloro-2-oxo-3(2*H*)-benzothiazolyl)acetyl]-1-piperazineethanol, is shown in Fig. 1. An X-ray analysis of the title compound was undertaken to disclose its inherent three-dimensional structure.

Tiaramide was purchased from Prestwick Chemical Inc. Single crystals of the molecule were grown from a water solution. A colorless platelet crystal with a size of $0.4 \times 0.3 \times 0.1$ mm was mounted on a glass fiber and used for data collection. The structure was solved by direct methods, and non-H atoms were refined by a full-matrix least-squares method with anisotropic temperature factors. The position of the H-atom of the hydroxyl group was obtained by a difference Fourier synthesis. The positions of other H-atoms were geometrically calculated. All H-atoms were included in calculations of the structure factors, but not refined. The crystal and experimental data are given in Table 1. Atomic parameters of non-H atoms are given in Table 2.

The molecular structure drawn by ORTEP-III⁴ is shown in Fig. 2. Selected bond lengths, bond angles and torsion angles are given in Table 3. The benzothiazolyl ring is almost perpendicular to the piperidine ring, with the dihedral angle between their least-squares planes being $80.6(1)^\circ$. The benzothiazolyl ring is planar, but the O1, C8 and Cl atoms are deviated significantly on the same side of the plane. The deviations are 0.080(3), 0.082(3), and 0.023(1) Å, respectively. The piperidine ring takes a chair conformation in which the

acetyl and ethanol groups are equatorial. The geometry around the N2 atom is significantly flattened, as indicated by the sum of the bond angles around N2 being 358.3° . The N1 and N2 atoms are in the *trans* position with respect to the C8-C9 bond. The ethanol group takes a *gauche* conformation with the torsion angle N3-C14-C15-O3 being $54.7(5)^\circ$. The endocyclic bond lengths around S1 and N1 in the benzothiazolyl ring are highly asymmetric. The N1-C1 bond (1.372(4) Å) is significantly shorter than the N1-C6 bond (1.399(4) Å). In contrast, it is noteworthy that the S1-C1 bond (1.782(3) Å) is markedly longer than the S1-C7 bond (1.741(3) Å). The exocyclic bond angles around N1 and N2 are also highly asymmetrical. The C6-N1-C8 angle ($124.4(2)^\circ$) is significantly larger than the C1-N1-C8 angle ($119.9(2)^\circ$). However, the C13-N2-C9 angle ($125.2(2)^\circ$) is significantly larger than the C10-N2-C9 angle ($119.8(2)^\circ$). One intermolecular hydrogen bond between N3 and O3 is observed in the crystal structure [O3...N3(-*x*, -*y*, -*z*) 2.877(4), O3-H 1.11, H...N3 1.82 Å, $\angle$ O3-H...N3 158°]. Two molecules around the center of symmetry form a dimer by this

Fig. 1 Chemical structure of Tiaramide.

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Table 1 Crystal and experimental data

Formula: $C_{15}H_{18}ClN_3O_3S$	
Formula weight = 355.84	
Crystal system: monoclinic	
Space group: $P2_1/a$	$Z = 4$
$a = 12.744(5)$ Å	
$b = 8.260(2)$ Å	$\beta = 93.42(2)^\circ$
$c = 15.513(5)$ Å	
$V = 1630.0(9)$ Å ³	
$D_x = 1.450$ g/cm ³	
No. of observations ($I > 2.00\sigma(I)$) = 2313	
$\theta_{\max} = 68.23^\circ$ with Cu K_α	
$R(I > 2.00\sigma(I)) = 0.053$	
$(\Delta/\sigma)_{\max} = 0.000$	
$(\Delta\rho)_{\max} = 0.35$ e/Å ³	
$(\Delta\rho)_{\min} = -0.36$ e/Å ³	
Measurement: Rigaku RAXIS-RAPID	
Program system: CrystalStructure 3.6.0 ²	
Structure determination: SIR92 ³	
Refinement: full-matrix	
CCDC No. 643694	

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

atom	x	y	z	$B_{eq}(\text{\AA}^2)$
Cl(1)	-0.03820(7)	0.7119(1)	0.57705(5)	5.00(2)
S(1)	0.29850(6)	0.9803(1)	0.34206(6)	4.12(2)
O(1)	0.2540(2)	0.8595(3)	0.1848(2)	5.18(6)
O(2)	0.1894(2)	0.4815(3)	0.2929(1)	4.22(5)
O(3)	-0.0381(2)	-0.1697(3)	0.0480(2)	4.93(6)
N(1)	0.1422(2)	0.7974(3)	0.2913(1)	3.19(5)
N(2)	0.0604(2)	0.4077(3)	0.1947(1)	3.00(5)
N(3)	-0.0655(2)	0.1589(3)	0.1117(2)	3.36(5)
C(1)	0.2287(3)	0.8686(4)	0.2587(2)	3.70(7)
C(2)	0.0539(2)	0.7549(4)	0.4274(2)	3.29(6)
C(3)	0.0583(2)	0.7926(4)	0.5153(2)	3.56(6)
C(4)	0.1363(3)	0.8875(4)	0.5543(2)	4.19(7)
C(5)	0.2135(3)	0.9532(4)	0.5051(2)	4.16(7)
C(6)	0.1323(2)	0.8198(3)	0.3798(2)	2.87(5)
C(7)	0.2115(2)	0.9168(4)	0.4176(2)	3.38(6)
C(8)	0.0759(2)	0.6923(3)	0.2373(2)	3.15(6)
C(9)	0.1140(2)	0.5166(3)	0.2442(2)	2.84(5)
C(10)	0.0977(3)	0.2398(4)	0.1916(2)	3.70(7)
C(11)	0.0077(3)	0.1231(4)	0.1843(2)	3.91(7)
C(12)	-0.1063(3)	0.3227(4)	0.1245(3)	4.64(8)
C(13)	-0.0193(3)	0.4463(4)	0.1262(2)	4.01(7)
C(14)	-0.1504(3)	0.0364(5)	0.1052(3)	5.09(9)
C(15)	-0.1353(3)	-0.0886(5)	0.0390(3)	5.02(9)

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha).$$

Fig. 2 Molecular structure of Tiaramide along with the labeling atoms. Thermal ellipsoids of non-H atoms are drawn at the 50% probability level.

hydrogen bond.

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Table 3 Selected bond lengths ($\text{\AA}$), bond angles ($^\circ$) and torsion angles ($^\circ$)

Cl(1)—C(3)	1.736(3)	S(1)—C(1)	1.782(3)
S(1)—C(7)	1.741(3)	O(1)—C(1)	1.212(4)
O(2)—C(9)	1.221(3)	O(3)—C(15)	1.408(5)
N(1)—C(1)	1.372(4)	N(1)—C(6)	1.399(4)
N(1)—C(8)	1.444(4)	N(2)—C(9)	1.342(3)
N(2)—C(10)	1.467(4)	N(2)—C(13)	1.461(4)
N(3)—C(11)	1.450(4)	N(3)—C(12)	1.467(4)
N(3)—C(14)	1.480(4)		
Cl(1)—C(3)—C(2)	117.7(2)	Cl(1)—C(3)—C(4)	119.5(2)
S(1)—C(1)—O(1)	124.7(3)	S(1)—C(1)—N(1)	109.4(2)
C(7)—S(1)—C(1)	91.3(2)	S(1)—C(7)—C(5)	128.2(2)
O(2)—C(9)—C(8)	111.4(2)	O(1)—C(1)—N(1)	125.9(3)
O(3)—C(15)—C(14)	120.2(2)	O(2)—C(9)—N(2)	123.3(3)
C(8)—N(1)—C(1)	114.5(3)	C(6)—N(1)—C(1)	115.2(2)
N(1)—C(6)—C(2)	119.9(2)	N(1)—C(6)—C(2)	125.6(2)
N(1)—C(6)—C(7)	112.6(3)	C(8)—N(1)—C(6)	124.4(2)
N(1)—C(8)—C(9)	110.9(2)	N(2)—C(9)—C(8)	116.5(2)
C(10)—N(2)—C(9)	119.8(2)	C(13)—N(2)—C(9)	125.2(2)
N(2)—C(10)—C(11)	111.3(3)	C(13)—N(2)—C(10)	113.3(2)
N(2)—C(13)—C(12)	110.1(3)	N(3)—C(11)—C(10)	112.5(3)
C(14)—N(3)—C(11)	110.4(3)	C(12)—N(3)—C(11)	107.4(3)
C(14)—N(3)—C(12)	112.1(3)	N(3)—C(12)—C(13)	111.2(3)
N(3)—C(14)—C(15)	113.6(3)		
C(7)—S(1)—C(1)—O(1)	-177.9(3)	C(7)—S(1)—C(1)—N(1)	2.9(2)
C(1)—S(1)—C(7)—C(5)	179.1(3)	C(1)—S(1)—C(7)—C(6)	-1.7(2)
C(6)—N(1)—C(1)—S(1)	-3.5(3)	C(6)—N(1)—C(1)—O(1)	177.3(3)
C(8)—N(1)—C(1)—S(1)	-176.5(2)	C(8)—N(1)—C(1)—O(1)	4.3(5)
C(1)—N(1)—C(6)—C(2)	-177.6(3)	C(1)—N(1)—C(6)—C(7)	2.3(3)
C(8)—N(1)—C(6)—C(2)	-5.0(4)	C(8)—N(1)—C(6)—C(7)	174.9(2)
C(1)—N(1)—C(8)—C(9)	89.6(3)	C(6)—N(1)—C(8)—C(9)	-82.6(3)
C(10)—N(2)—C(9)—O(2)	-5.7(4)	C(10)—N(2)—C(9)—C(8)	174.4(2)
C(13)—N(2)—C(9)—O(2)	-170.0(3)	C(13)—N(2)—C(9)—C(8)	10.1(4)
C(9)—N(2)—C(10)—C(11)	144.2(3)	C(13)—N(2)—C(10)—C(11)	-49.7(3)
C(9)—N(2)—C(13)—C(12)	-143.3(3)	C(10)—N(2)—C(13)—C(12)	51.5(3)
C(12)—N(3)—C(11)—C(10)	-59.8(3)	C(14)—N(3)—C(11)—C(10)	177.6(2)
C(11)—N(3)—C(12)—C(13)	61.6(4)	C(14)—N(3)—C(12)—C(13)	-177.0(3)
C(11)—N(3)—C(14)—C(15)	-100.3(3)	C(12)—N(3)—C(14)—C(15)	140.0(3)
C(6)—C(2)—C(3)—Cl(1)	-179.5(2)	C(3)—C(2)—C(6)—N(1)	-179.8(3)
Cl(1)—C(3)—C(4)—C(5)	-179.7(3)	C(4)—C(5)—C(7)—S(1)	-179.3(3)
N(1)—C(6)—C(7)—S(1)	0.0(2)	N(1)—C(6)—C(7)—C(5)	179.4(3)
C(2)—C(6)—C(7)—S(1)	180.0(2)	N(1)—C(8)—C(9)—O(2)	2.1(4)
N(1)—C(8)—C(9)—N(2)	-178.0(2)	N(2)—C(10)—C(11)—N(3)	54.5(4)
N(3)—C(12)—C(13)—N(2)	-58.0(4)	N(3)—C(14)—C(15)—O(3)	54.7(5)

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