

The Crystal and Molecular Structure of 1-(Hexahydro-1H-azepin-1-yl)-3-(p-tolylsulfonyl) Urea: Tolazamide (C₁₄H₂₁N₃O₃S)

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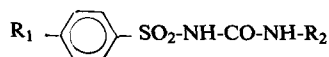
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Abstract □ Crystals of tolazamide, C₁₄H₂₁N₃O₃S, are triclinic, space group P $\bar{1}$, with cell dimensions of $a = 6.355$ (2), $b = 9.223$ (2), $c = 13.510$ (3) Å, $\alpha = 101.04$ (8), $\beta = 92.80$ (5), $\gamma = 85.72$ (6)° and $Z = 2$. Intensities were collected on an automated four-circle diffractometer using graphite-monochromated Cu K α radiations. The structure was solved by direct method and refined by full-matrix least-squares to an R factor of 0.058 for 1184 observed reflections. The molecules are dimerized by the N-H...O hydrogen bonds. There are only van der Waals interactions between these molecular dimers.

Keywords □ Crystal structure, tolazamide, hypoglycemic agent.

A number of sulfonylurea compounds exert hypoglycemic activity. All of the effective compounds hitherto reported are arylsulfonylureas which are substituted on the benzene and the urea groups. Clinical studies have demonstrated that the sulfonylureas stimulate the Langerhans' islet tissue of pancreas to secrete more insulin.

Tolazamide, tolbutamide, carbutamide and chlorpropamide are the widely used hypoglycemic agents. They have the following structural formulas;



R₁ = CH₃, R₂ = N(CH₂)₆ : tolazamide
R₁ = CH₃, R₂ = (CH₂)₃-CH₃ : tolbutamide
R₁ = NH₂, R₂ = (CH₂)₃-CH₃ : carbutamide
R₁ = Cl, R₂ = (CH₂)₂-CH₃ : chlorpropamide

Crystal structure analysis of these compounds may provide valuable information concerning the structure-activity relationship of these hypoglycemic agents. In this paper, the crystal structure of tolazamide is reported.

EXPERIMENTAL

Colorless, slightly translucent, thin crystals were obtained by recrystallization from an aqueous ethanol solution of tolazamide. Weissenberg photographs showed the crystal system is triclinic and

the distribution of the E values indicated the space group is P $\bar{1}$. Cell parameters were determined on a four-circle diffractometer by least-squares fit of the 2θ values measured for 20 strong reflections. The density was measured by flotation in a mixture of carbontetrachloride and benzene. The crystal data are given in Table I.

The intensities were measured on a Rigaku AFC four-circle diffractometer using graphite-monochromatized Cu K α radiation from a crystal with the approximate dimension of $0.2 \times 0.1 \times 0.1$ mm. The crystal was aligned with the a axis approximately parallel to the ϕ axis of the diffractometer. The intensities were recorded by the ω - 2θ scan techniques with a scan rate of 4° min^{-1} . The background was counted for 10 sec at either end of the scan range. Three reference reflections were monitored every 50 reflections and showed no variation in intensity. Of the 1696 independent reflections measured with $2\theta < 100^\circ$, 1184 were considered observed defined by $F_o > 6\sigma(F_o)$. The intensity data were corrected for Lorentz and polarization factors, but no absorption correction were made.

STRUCTURE DETERMINATION AND REFINEMENT

The structure was solved by direct method using MULTAN⁽¹⁾ with 186 E values greater than 1.35. The phase set with the best figure of merit revealed the positions of all nonhydrogen atoms, except for

Table I. Crystal data

Formula	C ₁₄ H ₂₁ N ₃ O ₃ S	Space group	P $\bar{1}$
Formula weight	311.41	F(000)	322
Melting point(K)	444-446	Z	2
Crystal system	triclinic	Dm(g cm ⁻³)	1.33
a (Å)	6.355(2)	Dc(g cm ⁻³)	1.334
b (Å)	9.223(2)	λ (Cu K α) (Å)	1.5418
c (Å)	13.510(3)	μ (cm ⁻¹)	18.67
α (°)	101.04(8)	crystal dimensions(mm)	0.2 × 0.1 × 0.1
β (°)	92.80(5)		
γ (°)	85.72(6)		

two carbon atoms in hexamethyleneimine ring. The missing atoms were located in the subsequent difference Fourier map. Initial R factor was 0.18 for 1184 observed reflections. Three cycles of full-matrix least-squares refinement using isotropic temperature factors gave the R factor of 0.097. Two cycles of anisotropic refinement reduced the R

factor to 0.068. The positions of the H atoms were either located in the difference map or geometrical-ly calculated and refined isotropically. The R factor converged at 0.058 for the 1184 observed reflections. All calculations were performed on a CYBER 73 computer using the program SHELX⁽²⁾. The final atomic coordinates and temperature factors are listed in Table II.

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

The bond distances and angles with the atomic numbering scheme are presented in Fig. 1. The stereoscopic ORTER⁽³⁾ drawing of the molecule is given in Fig. 2.

The benzene ring is planar with a maximum deviation of 0.007 Å (see Table III). S and C(1) lie approximately in the ring plane with displacements of -0.056 and 0.021 Å, respectively. The tetrahedral configuration around the S atom is distorted, similarly to those found in other molecules containing a -C(SO₂)N-moiety⁽⁴⁾. The O(1)-S-O(2) angle

Table II. Atomic coordinates and temperature factors in tolazamide (× 10⁴ for non-hydrogen atoms; × 10³ for hydrogen atoms). The e.s.d.'s are given in parentheses.

	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
S	4789(3)	2278(2)	2262(1)	595(13)	338(10)	388(11)	73(8)	132(9)	3(9)
O(1)	3613(8)	3422(5)	1850(3)	978(39)	411(29)	479(33)	206(25)	182(28)	145(28)
O(2)	7032(7)	2258(5)	2345(4)	535(34)	545(32)	665(36)	2(27)	155(26)	-160(26)
O(3)	5657(7)	418(5)	3827(3)	568(29)	387(26)	394(28)	66(22)	-7(22)	132(23)
N(1)	3833(8)	2453(6)	3402(4)	633(37)	335(31)	289(35)	79(26)	159(28)	94(29)
N(2)	3376(8)	1781(6)	4904(4)	611(37)	410(33)	290(34)	111(27)	99(28)	146(31)
N(3)	1849(8)	3000(6)	5099(4)	584(36)	347(32)	348(35)	67(27)	74(28)	71(30)
C(1)	2306(12)	-3657(8)	-54(6)	779(58)	608(55)	596(58)	-69(45)	198(45)	-199(47)
C(2)	2950(11)	-2175(8)	527(5)	585(46)	452(45)	320(44)	48(36)	125(36)	-61(40)
C(3)	1457(12)	-1026(9)	787(6)	440(46)	671(58)	658(58)	82(47)	-65(40)	-121(45)
C(4)	1967(11)	336(8)	1332(6)	441(47)	508(50)	708(58)	57(44)	39(40)	93(39)
C(5)	4065(9)	542(7)	1606(4)	413(38)	362(39)	284(40)	70(31)	79(31)	19(34)
C(6)	5557(11)	-590(8)	1358(5)	391(43)	508(49)	548(51)	-77(40)	24(36)	39(40)
C(7)	4998(11)	-1922(8)	814(5)	505(47)	462(48)	622(55)	-61(42)	11(40)	94(38)
C(8)	4383(10)	1466(7)	4047(4)	441(39)	372(38)	267(39)	27(31)	-45(31)	-61(32)
C(9)	2525(11)	4080(7)	5989(5)	637(50)	376(42)	556(53)	-12(37)	154(39)	-87(38)
C(10)	2708(10)	3599(8)	7000(5)	499(45)	487(46)	437(49)	-49(38)	13(37)	-89(37)
C(11)	616(12)	3716(9)	7523(5)	696(56)	829(61)	347(48)	-12(43)	70(42)	33(49)
C(12)	-1215(12)	3005(10)	6962(6)	620(56)	1010(70)	559(59)	75(53)	168(45)	-68(52)
C(13)	-859(13)	1863(10)	5986(7)	604(56)	791(64)	1080(81)	184(62)	-136(52)	-234(50)
C(14)	-274(11)	2490(9)	5127(5)	551(47)	668(51)	395(47)	136(40)	-18(37)	-52(41)

Table II. Continued

	x	y	z	U_{iso}
H(N1)	293(11)	310(8)	357(5)	75(26)
H(N2)	369(10)	120(8)	529(5)	75(26)
H(11)	91(12)	-360(8)	-39(6)	118(28)
H(12)	263(12)	-448(8)	42(6)	118(28)
H(13)	301(12)	-399(9)	-61(6)	121(28)
H(31)	0(11)	-111(8)	59(5)	109(27)
H(41)	76(9)	121(7)	156(4)	74(21)
H(61)	691(9)	-45(7)	156(4)	57(20)
H(71)	612(10)	-265(7)	59(5)	79(24)
H(91)	399(9)	434(6)	582(4)	54(19)
H(92)	140(10)	492(7)	601(4)	68(21)
H(101)	331(8)	256(6)	691(4)	50(18)
H(102)	385(7)	422(5)	750(3)	35(15)
H(111)	14(12)	486(9)	769(6)	140(30)
H(112)	89(11)	340(9)	807(5)	111(28)
H(121)	-201(12)	264(9)	728(6)	91(29)
H(122)	-217(13)	379(10)	645(6)	169(33)
H(131)	-240(10)	132(8)	575(5)	99(24)
H(132)	50(12)	103(9)	604(6)	145(30)
H(141)	-135(11)	345(9)	536(5)	93(27)
H(142)	-70(10)	199(8)	450(5)	63(23)

is 119.9 (3)°, giving an O(1)⋯O(2) separation of 2.472 Å, which is comparable to the N(1)⋯O(1) and N(1)⋯O(2) separations of 2.427 and 2.515 Å.

The molecular dimensions of the sulfonylurea moiety of the relevant compounds are compared in Table IV. The S-C(5) bond distance (1.756 (6) Å) is

in good agreement with 1.752 Å observed in sulfa-guanidine monohydrate⁽⁴⁾. The S-N bond distance in the sulfonylamide and sulfonylurea compounds shows significant variations, ranging from 1.633 (2) Å in methanesulfonanilide⁽⁵⁾, 1.641 (3) Å in rasemide⁽⁶⁾ to 1.664 (6) Å in chlorpropamide⁽⁷⁾ and 1.68 (5) Å in trans-4-tert-butyl-1-(N-ethyl-N-p-toluenesulfonylamino)-1-thioniacyclohexane fluoroborate⁽⁸⁾. S-N(1) in tolazamide is 1.656 (5) Å. The S-O bond distances do not vary much in the sulfonylurea compounds with a mean value of 1.434 Å. The bond order curve given by Cruickshank⁽⁹⁾ indicates that this value corresponds to a π -bond order of 0.6.

Two C-N bonds in the urea moiety show significant differences (1.392 vs 1.322 Å) which are commonly observed in the sulfonylurea compounds where the substituents at two N atoms are different (Table IV). The angles around C(8) are in good agreement with those found in carbutamide⁽¹⁰⁾. The N(2)-N(3) bond distance of 1.423 (7) Å is somewhat shorter than pure single bond distance. The urea moiety shows a good planarity with a maximum deviation of 0.002 Å. S and N(3) directly bonded to the urea moiety also lie in the plane with deviations of -0.056 and -0.041 Å, respectively. The urea plane is almost perpendicular to the benzene ring with a dihedral angle of 71°. This conformation is similar to that of chlorpropamide (dihedral angle; 76°).

The hexamethyleneimine ring assumes a chair conformation. The molecular dimensions of the ring are in good agreement with those of bacmecillinam⁽¹¹⁾ containing the same seven-membered ring although the ring conformations are different.

Projections of the molecular packing along the a

Table III. Comparison of bond lengths(Å) and angles(°) in sulfonylurea compounds. The e.s.d.'s are omitted.

compounds	bond lengths			bond angles					
	C(ring)-S	S-O	S-N	N-C	C-O	C-N	O-S-O	R ₁ -S-R ₂	N-C-N
tolazamide	1.756	1.433, 1.423	1.656	1.392	1.213	1.322	119.9	105.3	113.5
chlorpropamide	1.758	1.419, 1.419	1.664	1.380	1.221	1.318	119.9	106.0	112.6
tolbutamide	1.757	1.424, 1.422	1.635	1.397	1.246	1.312	118.8	105.9	113.0
carbutamide	1.762	1.443, 1.451	1.642	1.414	1.267	1.319	119.1	106.7	113.5
torasemide(I) A	1.773	1.444, 1.437	1.567	1.370	1.250	1.345	114.9	105.6	111.9
torasemide(I) B	1.784	1.443, 1.450	1.562	1.381	1.244	1.342	115.3	104.7	113.4
torasemide(II) A	1.763	1.432, 1.432	1.641	1.386	1.228	1.344	118.6	106.2	113.8
torasemide(II) B	1.792	1.442, 1.438	1.574	1.345	1.272	1.348	115.7	107.4	116.2
I P S U*	1.760	1.427, 1.428	1.631	1.396	1.239	1.325	119.4	106.6	114.4

* Isopropyl-1-[(chloro-3-phenylthio)-4-pyridyl-3 sulfonyl]-3-uree

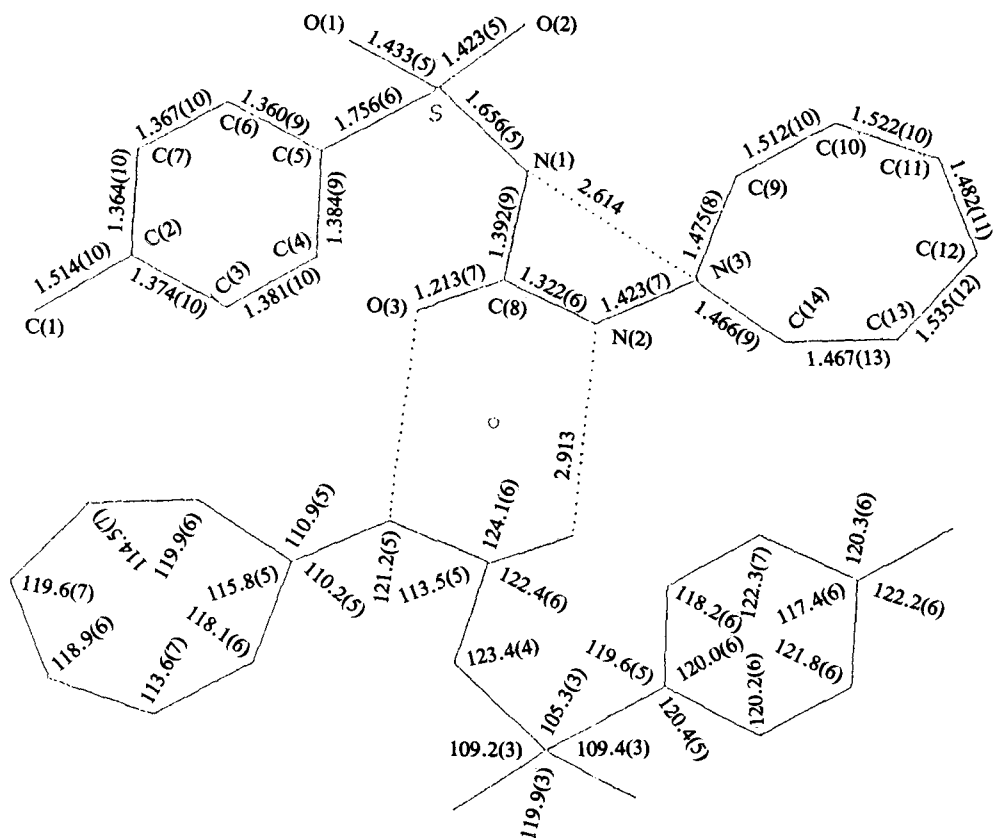


Fig. 1. The dimer, showing interatomic distances (Å; upper molecule) and angles (°; lower molecule) in tolazamide. The dashed lines indicate hydrogen bonds. The two molecules comprising the dimer are related by a center of symmetry.

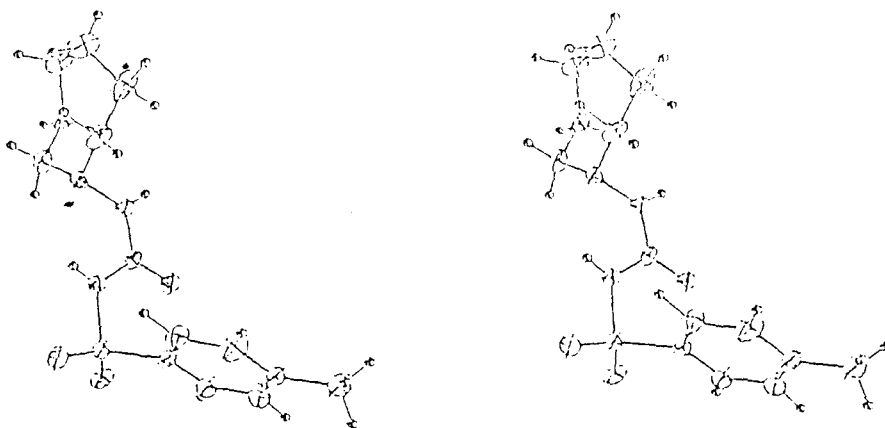


Fig. 2. Stereoscopic view of the tolazamide molecule. The non-hydrogen atoms are represented by their thermal ellipsoids, while the hydrogens are drawn with constant radii.

Table IV. Equations of the least-squares (LS) planes, and deviations (A) of the atoms from the planes in tolazamide.

The planes are expressed as $Ax + By + Cz = D$, where x , y and z are in Å relative to the axis a , b and c . The atoms indicated with asterisks were omitted from the calculations of the least-squares planes.

(I) Benzene ring: LS plane through C(2), C(3), C(4), C(5), C(6) and C(7)

A = -0.1978	C(2) 0.003	C(6) 0.007
B = -0.4933	C(3) -0.002	C(7) -0.005
C = 0.9376	C(4) 0.004	S* -0.056
D = 0.2832	C(5) -0.006	C(1)* 0.021

(II) Urea group: LS plane through O(3), N(1), N(2) and C(8)

A = 0.7601	O(3) -0.001	S* -0.056
B = 0.5546	N(1) -0.001	N(3)* -0.041
C = 0.2780	N(2) -0.001	
D = 4.3834	C(8) 0.002	

(III) Hexamethyleneimine ring: LS plane through N(3), C(10), C(11), C(12), C(13) and C(14)

A = -0.4704	N(3) -0.063	C(12) 0.129
B = 0.8414	C(9) 0.304	C(13) 0.294
C = -0.2234	C(10) 0.167	C(14) -0.403
D = 0.3002	C(11) -0.428	N(2)* -1.406

; continued

(IV) Six-membered ring forming hydrogen bonding: LS plane through O(3), N(2), C(8), O(3)#, N(2)# and C(8)#

A = 0.7668	O(3) 0.012	N(2)# -0.010
B = 0.5135	N(2) 0.011	C(8)# 0.016
C = 0.3190	C(8) -0.016	N(1)* -0.095
D = 4.5909	O(3)# -0.012	N(1)#* 0.095

#: The symmetry-related atoms

(V) LS plane through C(9), C(10), C(13) and C(14) in hexamethyleneimine ring

A = 0.6276	C(9) -0.047	N(3)* 0.590
B = -0.6628	C(10) 0.039	C(11)* -1.011
C = -0.2055	C(13) 0.048	C(12)* -1.151
D = -3.1032	C(14) -0.040	

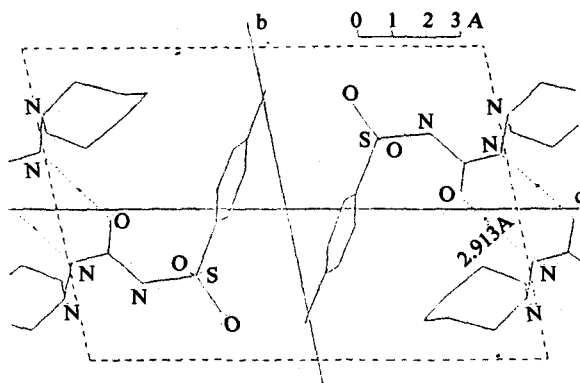


Fig. 3. Projection of the molecular packing viewed along a in tolazamide. Dotted lines are hydrogen bonds; arrows indicate donor directions.

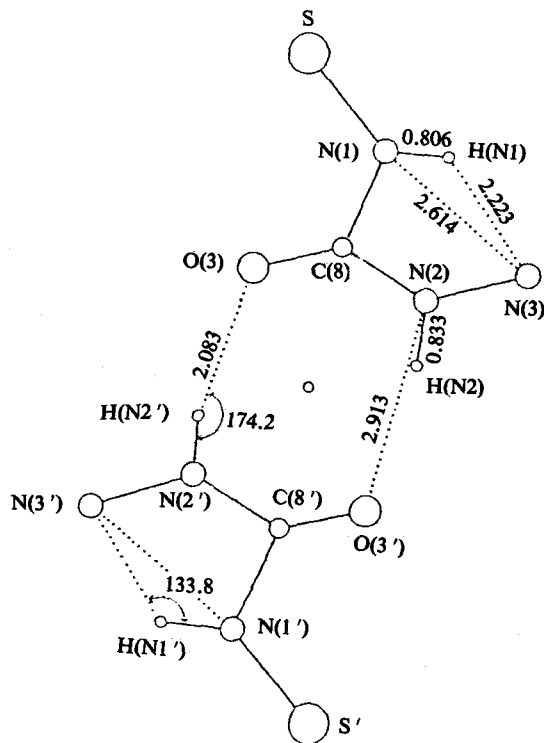


Fig. 4. Hydrogen-bonding scheme in tolazamide.

axis is shown in Fig. 3. Two molecules related by the center of symmetry are dimerized via the N(2)-H...O(3) hydrogen bonds. There is an intramolecular hydrogen bond between the imino

N(1) and N(3) in the ring, which may stabilize the conformation of the tolazamide molecule. The detailed hydrogen bonding scheme is presented in Fig. 4. There are only van der Waals interactions

between the hydrogen-bonded molecular dimers.

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