Structure Determination of Tolbutamide*

By K. A. Nirmala and D. S. Sake Gowda

Department of Physics, Central College, Bangalore University, Bangalore 560001, India

Abstract

N-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide, $C_{12}H_{18}N_2O_3S$, is an antidiabetic drug which crystallizes in the orthorhombic space group $Pn2_1a$, with $a = 20 \cdot 16$ (2), $b = 9 \cdot 05$ (1), $c = 7 \cdot 85$ (1) Å, $Z = 4$, $D_c = 1 \cdot 25$, $D_m = 1 \cdot 24$ Mg m^{-3} and μ(Cu $K\alpha$) $= 1 \cdot 968$ mm^{-1}. The structure was solved by the Patterson search method (as it could not be solved by heavy-atom techniques or direct methods) and refined to an R factor of $0 \cdot 083$ for 615 visually measured reflections. The structure is stabilized by hydrogen bonding between the polar groups and van der Waals interactions between the non-polar groups. Of the three hydrogen bonds, two are weak as they are bifurcated.

Introduction

Tolbutamide is one of the sulfonyl ureas which are an important class of compounds (Tull, O'Neill, McCarthy, Pappas & Chemerda, 1967) owing to their efficacy as oral hypoglycemic agents, which reduce the blood-sugar level without affecting glucose tolerance.

The object of the present X-ray crystallographic study of tolbutamide was to investigate the exact nature of the molecular framework, which may help to explain the compound's biological action. Tolbutamide, in the form of a white crystalline powder, was supplied by Hoechst Pharmaceuticals Ltd, Bombay. The crystals were grown from a solution of the compound in dimethyl sulfoxide mixed with alcohol. The crystals are colorless and are rectangular with pyramidal edges.

Preliminary crystal data for the compound were collected by taking Weissenberg patterns about different axes. The systematic extinctions $h00$: $h = 2n + 1$; $0k0$: $k = 2n + 1$; $00l$: $l = 2n + 1$; $0kl$: $k + l = 2n + 1$; $hk0$: $h = 2n + 1$ indicated the space group $Pn2_1a$ or $Pnma$ [successful refinement with $Pn2_1a$; the equivalent atomic positions are (1) x,y,z; (2) $-x, \frac{1}{2} + y, -z$; (3) $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} + z$ and (4) $\frac{1}{2} + x, y, \frac{1}{2} - z$].

A crystal with dimensions of about $0 \cdot 1 \times 0 \cdot 1 \times 0 \cdot 5$ mm was used for intensity data collection. Multifilm Weissenberg photographs (layers 0 to 6 down the b axis and layers 0 to 2 down the c axis) were taken using Cu $K\alpha$ radiation. The intensities of 615 reflections were estimated visually by comparison with a calibrated set of intensities. The measured intensities were corrected for Lorentz, polarization and spot-shape effects. The direct-axis data were correlated with cross-axis data, and brought to absolute scale by multiplying the layers by normalized correlated scales from an overall Wilson-plot scale.

Structure solution and refinement

Attempts were made to determine the structure using the heavy-atom method, *MULTAN* (Germain, Main & Woolfson, 1971) and *SHELX* (Sheldrick, 1976), but none was successful.

The structure was solved using a Patterson search combined with a difference electron density map phased on S and calculated by *SHELX* in the non-centrosymmetric space group $Pn2_1a$. The difference electron density map had mirror-image peaks and spurious peaks. Some spurious peaks were eliminated by checking the S-atom vectors in the Patterson map. But the mirror image of the atom also gives rise to vectors at the same positions as the real atom, and thus an atom site and its mirror-image peak were indistinguishable.

To eliminate the mirror-image peaks, intermolecular vectors with some atoms close to the S atom, and their symmetry-related images, were derived. All the calculated vectors which were not present in the Patterson map were rejected. In general, the vectors between an atom and the symmetry images of other atoms provide a more sensitive test than those between an atom and its own images. Using the located atoms together with S, structure factors were calculated and the remaining atoms were determined from a difference map. The structure-factor calculations on the basis of these atoms gave $R = 0 \cdot 22$.

Full-matrix least-squares refinement was carried out by *SHELX*. Refinement of positional parameters of 18 atoms with isotropic thermal parameters reduced R to

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* A preliminary account of this investigation was given at the National Conference on Crystallography (1978) held at Anand, India.

0·148. At this stage H atoms were calculated stereochemically and introduced in the subsequent structure-factor calculations. The phenyl ring was refined as a rigid group. Then blocked full-matrix least-squares refinement with anisotropic temperature factors for all the non-H atoms was carried out using eight blocks, of which three blocks were refined per cycle. The R index at the end of this refinement was 0·083. The molecular structure and the numbering of atoms are shown in Fig. 1.

The coordinates of all the non-H atoms at the end of the refinement with their e.s.d.'s are given in Table 1.*

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* Lists of structure factors, anisotropic thermal parameters and H positions have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36043 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
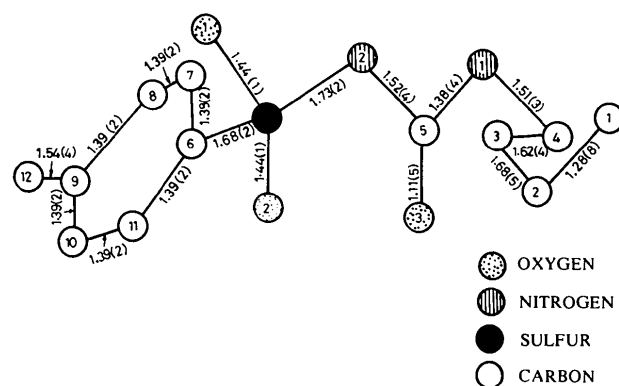

Fig. 1. A projection of the molecule showing the atom numbering and bond lengths (Å). The H atoms are excluded for clarity.

Scattering factors for non-H atoms were taken from Cromer & Waber (1965) and for H atoms from Stewart, Davidson & Simpson (1965).

Discussion

The structure consists of n-butyl, urea, sulfonyl and p-tolyl groups. One of the two N atoms of the urea is bonded to the n-butyl group while the other is bonded to the sulfonyl group which, in turn, is connected to the p-tolyl group.

The bond lengths, bond angles and torsion angles for the molecule are given in Fig. 1 and Tables 2 and 3 respectively. The bond distances involving H atoms range from 0·91 to 1·26 Å, and angles range from 92 to 129°.

The methyl-group carbon atom C(12), which is connected to the benzene ring, is bent out of the benzene plane by 0·02 Å.

The mean S—O length of 1·44 (1) Å agrees, within experimental error, with the values found in other aromatic sulfonates, sulfonamides and related species (Meyers & Trueblood, 1969; O'Connell & Maslen, 1967; Hall & Maslen, 1965; Herdklotz & Sass, 1969; Sabesan, 1970; Usha, 1980). The C—S distance of 1·68 (2) Å is shorter than the value (1·777 Å) expected of a C(sp^2)—S bond.

It has been well established that the C—S—O angle in the sulfonate group is always smaller than the tetrahedral angle, whereas the large separation between the O atoms tends to make the O—S—O angle larger than the tetrahedral value (Okaya, 1967; Herdklotz & Sass, 1969; Sabesan, 1970; Usha, 1980). In the

Table 1. *Positional and equivalent isotropic thermal parameters* $(\times 10^4)$ *of the non-H atoms with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}[U_{11} + U_{22} + U_{33}].$$

	x	y	z	U_{eq} (Å²)
S(1)	3950 (1)	7335	1579 (1)	483 (7)
O(1)	3662 (9)	8629 (12)	2350 (23)	575 (21)
O(2)	4033 (8)	5988 (11)	2531 (21)	464 (25)
O(3)	5004 (11)	5935 (26)	−337 (28)	682 (26)
N(1)	5466 (10)	8135 (26)	−1133 (23)	433 (23)
N(2)	4676 (10)	8182 (33)	907 (30)	593 (26)
C(1)	6243 (28)	7405 (88)	−6071 (59)	1854 (39)
C(2)	5831 (23)	6357 (59)	−5793 (53)	1544 (48)
C(3)	5458 (14)	7186 (50)	−4127 (35)	993 (39)
C(4)	5896 (12)	7319 (45)	−2401 (36)	988 (36)
C(5)	5075 (12)	7152 (45)	−232 (31)	452 (26)
C(6)	3539 (7)	7027 (17)	−251 (27)	535 (7)
C(7)	3580 (7)	8026 (17)	−1600 (27)	668 (6)
C(8)	3210 (7)	7791 (17)	−3078 (27)	582 (7)
C(9)	2799 (7)	6556 (17)	−3207 (27)	715 (7)
C(10)	2758 (7)	5557 (17)	−1858 (27)	825 (5)
C(11)	3128 (7)	5792 (17)	−380 (27)	717 (6)
C(12)	2443 (18)	6579 (51)	−4950 (48)	1439 (43)

Table 2. *Bond angles* (°) *with e.s.d.'s in parentheses*

O(1)—S—O(2)	121 (1)	O(3)—C(5)—N(2)	125 (3)
O(1)—S—N(2)	96 (1)	N(1)—C(5)—N(2)	102 (3)
O(1)—S—C(6)	107 (1)	S—C(6)—C(7)	120 (1)
O(2)—S—N(2)	115 (1)	S—C(6)—C(11)	120 (2)
O(2)—S—C(6)	111 (1)	C(7)—C(6)—C(11)	120 (2)
N(2)—S—C(6)	103 (1)	C(6)—C(7)—C(8)	120 (2)
C(4)—N(1)—C(5)	110 (2)	C(7)—C(8)—C(9)	120 (2)
S—N(2)—C(5)	110 (2)	C(8)—C(9)—C(10)	120 (2)
C(1)—C(2)—C(3)	95 (4)	C(8)—C(9)—C(12)	109 (2)
C(2)—C(3)—C(4)	116 (2)	C(10)—C(9)—C(12)	130 (2)
N(1)—C(4)—C(3)	105 (2)	C(9)—C(10)—C(11)	120 (2)
O(3)—C(5)—N(1)	132 (3)	C(6)—C(11)—C(10)	120 (2)

Table 3. *Torsion angles* (°) *with e.s.d.'s in parentheses*

O(1)—S—N(2)—C(5)	−171 (2)	N(2)—S—C(6)—C(11)	148 (1)
O(2)—S—N(2)—C(5)	59 (2)	C(5)—N(1)—C(4)—C(3)	88 (3)
C(6)—S—N(2)—C(5)	−62 (2)	C(4)—N(1)—C(5)—O(3)	−4 (4)
O(1)—S—C(6)—C(7)	65 (2)	C(4)—N(1)—C(5)—N(2)	−178 (2)
O(2)—S—C(6)—C(7)	−159 (1)	S—N(2)—C(5)—O(3)	−16 (4)
N(2)—S—C(6)—C(7)	−35 (2)	S—N(2)—C(5)—N(1)	157 (2)
O(1)—S—C(6)—C(11)	−110 (1)	C(1)—C(2)—C(3)—C(4)	−70 (4)
O(2)—S—C(6)—C(11)	23 (2)	C(2)—C(3)—C(4)—N(1)	178 (3)

present structure also, the same trend is observed with an average value of 109·0 (9)° for the C—S—O angle and 121·1 (9)° for the O—S—O angle.

The S—N length, 1·73 (2) Å, agrees with the values estimated by Schomaker & Stevenson (1941) (S—N single-bond distance is 1·74 Å) and Sass (1960) in sulfonic acid [which exists in the crystalline state as the N has no orbital available for π-bonding and the S—N length is 1·764 (2) Å]. It is also observed that the mean N—S—O angle is 105·5° which is markedly less than the tetrahedral value 109·28°.

The average length of C—N, 1·47 (4) Å, is in agreement with the C(sp³)—N(sp³) single-bond length, 1·48 (2) Å. The observed bond length of C=O, 1·11 (5) Å, is slightly shorter than the standard C=O bond length. The average N—C—O angle is 128·5 (3·0)°, which is slightly large as it has to compensate for the angle N—C—N, 102·0 (3·0)°.

The terminal atoms of the N-butyl group have large deviations in their bond lengths and angles, which may be due to the low accuracy of the intensity data and to the very high temperature factors.

The packing of the molecules in the crystal lattice is depicted in Fig. 2. Since the H atoms could not be located in the difference Fourier map (as the intensity data were measured visually), the hydrogen-bonding scheme is based on the intermolecular distances: O(2)···H(10)—N(1ⁱ) 2·98 (3), O(3)···H(10)—N(1ⁱ) 2·94 (4), and O(3)···H(11)—N(2ⁱ) 2·61 (3) Å (where i refers to the second equivalent position).

The first and second hydrogen bonds are weak as they are bifurcated. The crystal structure on the whole is stabilized by hydrogen bonding between the polar groups and van der Waals interactions between the non-polar groups.

The hydrogen-bond network and the dynamics of the protons are of great importance in explaining the properties of the crystals and their phase transitions. Tolbutamide has a dual action, *i.e.* it stimulates the release of insulin from the pancreas, and also increases the rate of utilization of circulatory insulin.

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Fig. 2. Packing of the molecules viewed down **c**.