Acta Cryst. (1996). C**52**, 2377–2379

Biological Activity of 4-(4-Bromophenyl)-thiosemicarbazide

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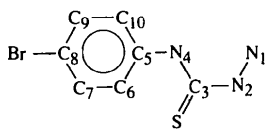
(*Received 14 September 1994; accepted 8 August 1995*)

Abstract

The two molecules (*A* and *B*) in the asymmetric unit of the title compound, $C_7H_8BrN_3S$, display different conformations. In both molecules, the S atom is *trans* to the NH_2 group. The Br atoms of the two molecules approach each other at a distance of 3.573 (2) Å. The crystal structure of the bromine compound is isomorphous with that of its chlorine analogue. In the crystal structure, intramolecular N—H···N and intermolecular N—H···S hydrogen bonds help stabilize the molecular packing. The increased antibacterial activity of the title compound compared to that of its chlorine analogue may be attributed to the increase in electron density on the hydrazinic end of the thiosemicarbazide chain.

Comment

The aim of the present work is to determine the crystal structure of 4-(4-bromophenyl)thiosemicarbazide (L_3) in order to account for its increased antibacterial (biological) activity and to compare its activity and structural features with those of 4-(4-chlorophenyl)-thiosemicarbazide (L_2) (Nandi, Chaudhuri, Mazumder & Ghosh, 1984) and 4-phenylthiosemicarbazide (L_1) (Kalman, Argay & Czugler, 1972).



L_3

The atomic coordinates and unit-cell dimensions suggest that the crystal structure of the title compound (L_3) is isomorphous with that of its chlorine analogue (L_2) and hence their molecular geometries are quite similar. A comparison of bond-length data for L_1, L_2 and L_3 shows that the N(2)—C(3) and C(3)—N(4) bond lengths in L_3 are shorter than the corresponding bonds in L_2 and are about 0.10 Å shorter than the value expected for an N—C single bond. This indicates a delocalization of electrons in this part of the molecule (Burke-Laing & Laing, 1976; Nandi *et al.*, 1984). Moreover, the N(1)—N(2) bond length is shortest in L_2 and longest in L_1, while that in L_3 is of an intermediate value. The C—Br distances [1.903 (8) and 1.901 (9) Å] agree well, within experimental error, with those of *O,O'*-dibromodibenzyl[1,2-bis(2-bromophenyl)]ethane (Corey, 1979). The values of the torsion angle S—C(3)—N(2)—N(1) [−177.8 (7) and −175.4 (8)°] imply that the S atom is *trans* to the NH_2 group in both molecules of L_3 (Fig. 1).

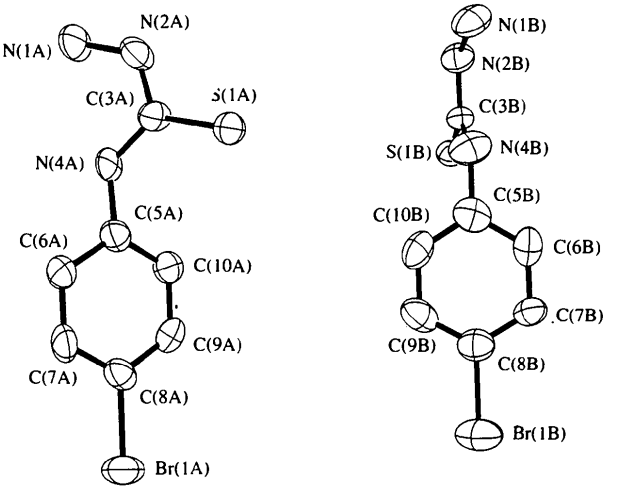


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of L_3 showing the atom-numbering scheme and 50% probability displacement ellipsoids.

A view of the unit-cell contents is presented in Fig. 2. The difference between the chloro and bromo analogues is seen in the nature of the hydrogen bonding (see Table 3). All the N atoms in both molecules of L_3 take part in hydrogen bonding and atom S(*B*) accepts three intermolecular hydrogen bonds while S(*A*) accepts only two. The hydrogen bonds of N(4*A*)—H(4*A*) with N(1*A*) and S(*B*) seem to be of the bifurcated type, similar to those observed in glycylglycine hydrochloride (Parthasarathy, 1969), while they are absent in the chloro derivative (L_2). Extensive N—H···N and N—H···S hydrogen bonding helps stabilize the molecular packing. The closest Br(*A*)···Br(*B*)(x, y, $z-1$) distance is 3.573 (2) Å and the shortest intermolecular non-H-atom contact in the structure is 3.27 (1) Å [N(1*A*)···N(2*B*)($-x+1$, $-y$, $-z+1$)].

Selected atomic charges computed by the *CNDO*/2 method (Pople & Beveridge, 1970) are presented in Table 4. Molecules *A* and *B* can not be distinguished in solution and hence the magnitude of the overall activity

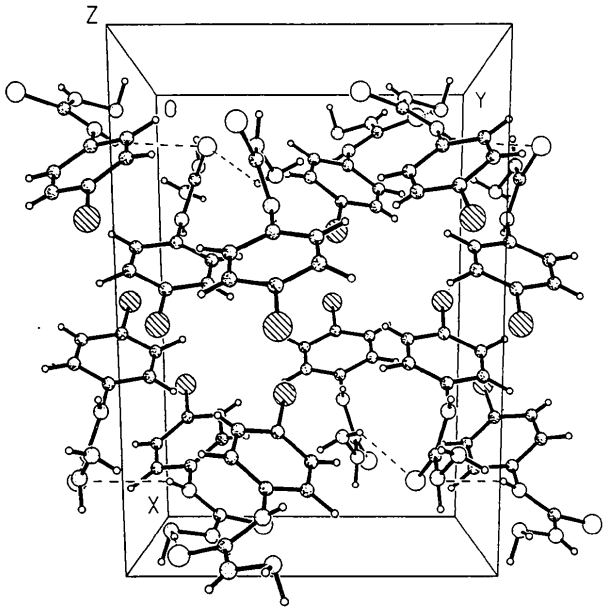


Fig. 2. Packing diagram showing the contents of one unit cell of the title compound.

of L_3 can not be related directly to either *A* or *B*. The two key atoms [N(1) and S] which actually take part in metal chelation are responsible for antibacterial activity. The higher electron density found on the N(1) atom of L_3 compared to those on the corresponding N(1) atom of both L_2 and L_1 makes it a better donor and a stronger reductant. The slight decrease of electron density on the thiocarbonyl S atom is more than compensated for by the accumulation of much greater electron density on the N(1) atom of L_3. This is also reflected in the cyclic voltammograms of L_2 and L_3. The lower electron density on the thione S atom of L_3 is evidenced by the higher value of the potential of oxidation centred on the S atom.

Experimental

The title compound was conveniently prepared from 4-bromoaniline according to the method of Sen & Sengupta (1962). The crude compound was recrystallized from hot ethanol, from which plate-shaped crystals were obtained.

Crystal data

$C_7H_8BrN_3S$
M_r = 246.12
Monoclinic
$P2_1/c$
a = 14.907 (7) Å
b = 10.506 (4) Å
c = 12.518 (3) Å
β = 104.07 (3)°
V = 1901 (1) Å^3
Z = 8
D_x = 1.719 Mg m^{-3}
D_m = 1.73 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 25.1–39.9°
μ = 7.54 mm^{-1}
T = 294 K
Plate
0.30 × 0.25 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
2235 measured reflections
1912 independent reflections
1402 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.031
θ_{max} = 52.2°
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 60 min
intensity decay: insignificant

Refinement

Refinement on F
R = 0.056
wR = 0.058
S = 1.010
1401 reflections
282 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o) + 0.001215F_o^2]$
$(\Delta/\sigma)_{max}$ = 0.597
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.73 e Å^{-3}
Extinction correction: $F^* = F(1 - \chi F^2/\sin\theta)$
Extinction coefficient: χ = 0.0178 (7)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N(1*A*)	0.9395 (6)	0.0963 (8)	0.7595 (6)	0.062 (4)
N(2*A*)	0.9574 (6)	0.2105 (8)	0.7085 (6)	0.056 (4)
C(3*A*)	0.9263 (6)	0.2256 (10)	0.6006 (7)	0.043 (4)
N(4*A*)	0.8785 (6)	0.1289 (8)	0.5443 (7)	0.046 (3)
C(5*A*)	0.8355 (7)	0.1234 (10)	0.4311 (7)	0.043 (4)
C(6*A*)	0.8445 (8)	0.0122 (11)	0.3759 (8)	0.055 (5)
C(7*A*)	0.7975 (8)	0.0003 (12)	0.2676 (9)	0.056 (5)
C(8*A*)	0.7411 (7)	0.0971 (11)	0.2146 (7)	0.045 (4)
C(9*A*)	0.7335 (8)	0.2065 (12)	0.2711 (9)	0.050 (5)
C(10*A*)	0.7796 (7)	0.2203 (11)	0.3806 (8)	0.045 (5)
Br(*A*)	0.6716 (1)	0.0783 (1)	0.0664 (1)	0.0657 (5)
S(*A*)	0.9533 (2)	0.3626 (3)	0.5431 (2)	0.0561 (11)
N(1*B*)	0.2265 (8)	0.0987 (13)	0.1076 (8)	0.062 (5)
N(2*B*)	0.1752 (7)	0.1479 (9)	0.1797 (7)	0.049 (4)
C(3*B*)	0.2113 (7)	0.1445 (9)	0.2873 (7)	0.036 (4)
N(4*B*)	0.2990 (7)	0.1046 (10)	0.3201 (8)	0.064 (5)
C(5*B*)	0.3522 (7)	0.0981 (13)	0.4310 (9)	0.055 (5)
C(6*B*)	0.3641 (7)	−0.0156 (13)	0.4867 (10)	0.054 (5)
C(7*B*)	0.4144 (7)	−0.0220 (12)	0.5953 (8)	0.048 (4)
C(8*B*)	0.4539 (7)	0.0866 (13)	0.6462 (8)	0.055 (5)
C(9*B*)	0.4419 (8)	0.2026 (14)	0.5932 (10)	0.064 (5)
C(10*B*)	0.3918 (9)	0.2073 (13)	0.4847 (10)	0.062 (6)
Br(*B*)	0.5243 (1)	0.0781 (1)	0.7946 (1)	0.0799 (6)
S(*B*)	0.1502 (2)	0.1918 (3)	0.3776 (2)	0.0465 (10)

Table 2. *Selected geometric parameters (Å, °)*

N(1*A*)—N(2*A*)	1.42 (1)	N(1*B*)—N(2*B*)	1.42 (1)
C(3*A*)—S(*A*)	1.70 (1)	C(3*B*)—S(*B*)	1.69 (1)
C(8*A*)—Br(*A*)	1.903 (8)	C(8*B*)—Br(*B*)	1.901 (9)

S(*A*)—C(3*A*)—N(2*A*)—N(1*A*)	−178 (1)
C(5*A*)—N(4*A*)—C(3*A*)—S(*A*)	−5 (2)
N(4*A*)—C(3*A*)—N(2*A*)—N(1*A*)	−0 (1)
C(6*A*)—C(5*A*)—N(4*A*)—C(3*A*)	138 (1)
C(10*A*)—C(5*A*)—N(4*A*)—C(3*A*)	−48 (2)
S(*B*)—C(3*B*)—N(2*B*)—N(1*B*)	−175 (1)
C(5*B*)—N(4*B*)—C(3*B*)—S(*B*)	−1 (2)
N(4*B*)—C(3*B*)—N(2*B*)—N(1*B*)	6 (1)
C(6*B*)—C(5*B*)—N(4*B*)—C(3*B*)	100 (1)
C(10*B*)—C(5*B*)—N(4*B*)—C(3*B*)	−79 (2)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N(4*A*)—H(4*A*)···N(1*A*)	0.83 (9)	2.32 (8)	2.65 (1)	104 (7)
N(4*A*)—H(4*A*)···S(B^{i})	0.83 (9)	2.86 (9)	3.56 (1)	143 (7)
N(4*B*)—H(4*B*)···N(1*B*)	0.80 (11)	2.21 (9)	2.62 (1)	112 (8)
N(1*A*)—H(12*A*)···S(A^{ii})	0.84 (10)	2.69 (10)	3.53 (1)	174 (8)
N(2*A*)—H(2*A*)···S(B^{iii})	0.74 (7)	2.65 (7)	3.29 (1)	147 (7)
N(2*B*)—H(2*B*)···S(A^{iv})	0.89 (8)	2.48 (7)	3.34 (1)	164 (7)
N(1*B*)—H(12*B*)···S(B^{v})	0.83 (10)	2.91 (9)	3.58 (1)	141 (7)

Symmetry codes: (i) $1-x,-y,1-z$; (ii) $x,\frac{1}{2}-y,\frac{1}{2}+z$; (iii) $1+x,\frac{1}{2}-y,\frac{1}{2}+z$; (iv) $x-1,\frac{1}{2}-y,z-\frac{1}{2}$; (v) $x,\frac{1}{2}-y,z-\frac{1}{2}$.

Table 4. *Comparison of net charge (e) on the S and amine N atoms in different thiosemicarbazides*

	S	N(1)
4-Phenylthiosemicarbazide (L_1)	−0.4603	−0.1385
4-(4-Chlorophenyl)thiosemicarbazide (L_2)	−0.4639	−0.1633
4-(4-Bromophenyl)thiosemicarbazide (L_3)	−0.4535	−0.2403

Direct-methods analysis revealed the positions of the 14 non-H atoms. The model was completed by successive weighted Fourier syntheses. Anisotropic displacement parameters were refined for C, N, S and Br atoms. H atoms bonded to C atoms were included in calculated positions using a riding model, while H atoms bonded to N atoms were located from a difference map and finally refined. Owing to the high atomic number of the Br atom, refinement of the lighter atoms in the title compound was not as satisfactory as in the case of the chlorine analogue. Again, as the intensities were recorded only up to $\theta = 55.2°$, the e.s.d.'s of the atomic coordinates, bond lengths and angles are rather large. The thermal motion of the molecules is strongly anisotropic, with one component larger than the other components for most of the atoms (U_{11} for molecule *A* and U_{22} for molecule *B*). Anomalous dispersion corrections for Br were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). As the actual aim of the study was to compare the structure and biological activity of the title bromo compound with its chloro analogue and no emphasis was placed on small variations in bond lengths, we did not apply an absorption correction.

The *in vitro* antibacterial activities of 4-(4-bromophenyl)-thiosemicarbazide and 4-(3,4-dibromophenyl)thiosemicarbazide against *Escherichia coli* were determined by the following technique. A culture was grown from a single colony of *E. coli* in a medium containing 2 g NH_4Cl, 6 g NaH_2PO_4, 3 g KH_2PO_4, 3 g NaCl, 0.01 g $MgCl_2$, 0.026 g Na_2SO_4 per litre, supplemented with Ca^{2+} (1×10^{-4} *M*), Fe^{2+} (2.5×10^{-6} *M*), 0.2% glucose and 0.4% casamino acid placed in an Erlenmeyer flask and incubated in a BOD incubator/shaker at 310 K. 1% NaCl mixtures of the two compounds were prepared separately by careful grinding of the components in a metal capsule containing stainless-steel balls with the help of a vibromill and 1 mg to 200 mg of these mixtures were added to 10 ml of the medium described above in 20 ml sterilized test tubes, 0.1 ml of the *E. coli* culture was added and the test tubes were incubated at 310 K for 24 h. The results of their minimum inhibitory concentrations (mic in $\mu g\ ml^{-1}$) were found to be 20.2 and 21.1, respectively.

All computations were carried out using the MicroVAXII system of the DIC Bose Institute, Calcutta. The programs used were *EXFFT* and *SEARCH* of *MULTAN*78 (Main *et al.*, 1978) for weighted Fourier syntheses, *SHELX*76 (Sheldrick, 1976) for the refinement and *PARST* (Nardelli, 1983) for the geometrical parameters of the molecule.

The authors thank Miss M. Pramanik of ICAS, Department of Inorganic Chemistry, for providing the sample used in this investigation and Professor T. C. W. Mak, Chinese University of Hong Kong, for the preparation of the *ORTEP* diagram.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry, least-squares-planes data and torsion angles have been deposited with the IUCr (Reference: PT1014). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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