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Structure of Salicylaldehyde Thiosemicarbazone

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Abstract. $C_8H_9N_3OS$, monoclinic, $C2/c$, $a = 14{\cdot}206\ (3)$, $b = 14{\cdot}244\ (4)$, $c = 10{\cdot}457\ (4)$ Å, $\beta = 116{\cdot}18\ (2)°$, $V = 1898{\cdot}9\ (8)$ Å^3, $Z = 8$, $D_m = 1{\cdot}387$, $D_x = 1{\cdot}366$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, $\mu = 2{\cdot}90$ cm^{-1}, $F(000) = 816{\cdot}0$, $T = 298$ K, final $R = 0{\cdot}0429$ for 1322 observed reflections. The S and hydrazinic N atoms lie *trans*. The lowering of antibacterial activity compared to that of 4-phenylthiosemicarbazide may be correlated with the decrease in negative charge on the hydrazinic N atom. The crystal structure is stabilized by hydrogen bonding, stacking interactions and van der Waals forces.

Introduction. The wide range of biological activities possessed by substituted thiosemicarbazides and thiosemicarbazones include antitumour and antileukemic properties (French & Blanz, 1966; Agrawal, Booth & Sartorelli, 1968; Agrawal, Cushley, McMurray & Sartorelli, 1970; Agrawal, Cushley, Lipsky, Wheaton & Sartorelli, 1972), antibacterial and antiviral activity (Nandi, Chaudhuri, Mazumdar & Ghosh, 1984*a*; Chattopadhyay, Banerjee, Mazumdar, Ghosh & Kuroda, 1987*a*; Nandi, Sheldrick & Ghosh, 1986), antimalarial activity (Klayman, Scovill, Bartosevich & Mason, 1979; Klayman, Bartosevich, Griffin, Mason & Scovill, 1979) and antifertility property (Nagarajan, Talwalker, Kulkarni, Venkateswarlu, Prabhu & Nayak, 1984). Biological activities of these N,S donor ligands have been correlated with their metal-chelating abilities and reductive capacity (Kirschner, Wei, Francis & Bergman, 1966; Palenik, Rendle & Carter, 1974; Umapathy, Budhkar & Dorai, 1986, and references therein).

Salicylaldehyde thiosemicarbazone can exist in two tautomeric forms *A* and *B* (Fig. 1).

In form *A* it can act as a tridentate ligand through loss of the proton from the hydroxyl group and by coordinating through the O, imino N and thiocarbonyl S. It can also act as a doubly negatively charged tridentate ligand by losing another proton from the mercapto group of the tautomeric form *B* (Ray, 1981). A number of metal complexes of the ligand have been described (Ablov & Gerbeleu, 1965*a*,*b*) but to our knowledge no crystal structures have been reported. The *in vitro* antibacterial activity of salicylaldehyde thiosemicarbazone against *E. coli* is 8% less than that of 4-phenylthiosemicarbazide. The present crystal-structure analysis has been undertaken as part of our programme of systematic studies on the structure and activity of thiosemicarbazides and thiosemicarbazones (Chattopadhyay *et al.*, 1987*a*,*b*).

Experimental. Yellowish needle-shaped crystals from ethanol, density by flotation in benzene–chloroform. Single crystal of size $0{\cdot}30 \times 0{\cdot}28 \times 0{\cdot}22$ mm, Nicolet $R3m$ diffractometer, mean $\mu r = 0{\cdot}04$, cell parameters from 2θ values of 21 reflections with $15 \leq 2\theta \leq 25°$ (Sparks, 1976). Systematic absences: hkl with $(h + k)$ odd, $h0l$ with l odd, space group $C2/c$ favoured by intensity statistics and later confirmed by structure analysis, ω–2θ scan at 2·02–8·37° min^{-1}, scan range

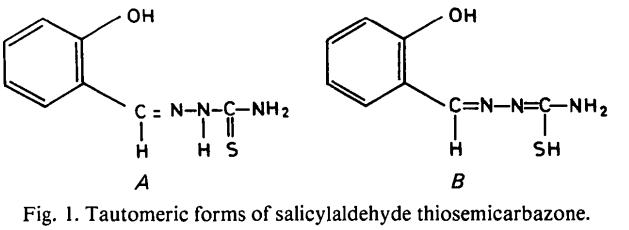

Fig. 1. Tautomeric forms of salicylaldehyde thiosemicarbazone.

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0·5° below $K\alpha_1$ to 0·5° above $K\alpha_2$, stationary background counts for half of scan time at each end, $2\theta_{max} = 55°$, $-17 \le h \le 15$, $0 \le k \le 18$, $0 \le l \le 13$, intensities of two standards monitored every 125 data measurements were within ±1%, 1924 independent reflections measured, profile fitting of raw intensities (Diamond, 1969), 1322 observed with $|I| > 2{\cdot}5\sigma(|I|)$, empirical absorption correction based on ψ scans of 16 strong reflections (North, Phillips & Mathews, 1968; Kopfmann & Huber, 1968), transmission factors 0·899 to 0·941. Structure solved by direct methods (*MULTAN*78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), full-matrix least-squares refinement based on $|F|$ for non-H atoms with isotropic thermal parameters and then with anisotropic thermal parameters, all nine H atoms located from difference syntheses, further refinement with isotropic thermal parameters for H atoms and anisotropic thermal parameters for non-H atoms, final R(154 variables) = 0·0429, $wR = 0{\cdot}0453$, $w = [\sigma^2(|F_o|) + 0{\cdot}0003\,|F_o|^2]^{-1}$, $\Delta/\sigma \le 0{\cdot}14$, $\Delta\rho$ residuals 0·49 to −0·23 e Å^{-3} in final difference synthesis, atomic scattering factors from *International Tables for X-ray Crystallography* (1974), calculations on an IRIS80 computer using *SHELX*76 (Sheldrick, 1976). The final atomic parameters are listed in Table 1,* and selected bond distances and angles in Table 2, in accordance with the atom-numbering scheme shown in Fig. 2.

Discussion. The *trans* configuration of the thiocarbonyl S atom with respect to the hydrazinic N atom as indicated by the S–C(7)–N(2)–N(3) torsion angle is in accordance with that observed in uncomplexed and unprotonated thiosemicarbazides and thiosemicarbazones (Chattopadhyay *et al.*, 1987*a*). As a result, the N(1) atom lies *cis* to N(3). The N(3) atom accepts an intramolecular hydrogen bond from O. In addition, there is an intramolecular hydrogen-bond-like contact between N(1) and N(3) through H(N1)*a* [N(3)···H(O) = 1·96 (3), N(3)···O = 2·664 (3), H(O)–O = 0·78 Å, N(3)···H(O)–O = 148 (3)°; N(3)···H(N1)*a* = 2·38 (3), N(3)···N(1) = 2·687 (3), H(N1)*a*–N(1) = 0·80 (3) Å, N(3)···H(N1)*a*–N(1) = 104 (2)°]. The presence of an N(3)···H–N(1) intramolecular hydrogen bond has been found to be a general feature in the crystal structures of thiosemicarbazides and thiosemicarbazones (Kálmán, Argay & Czugler, 1972; Nandi *et al.*, 1984*a,b*; Nandi *et al*, 1986; Chattopadhyay *et al.*, 1987*a,b*).

* Lists of structure factors, anisotropic thermal parameters, H coordinates, bond distances and angles involving H and least-squares-planes' details have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44673 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors with e.s.d.'s in parentheses*

	x	y	z	U_{eq}*(Å^2)
S	0·2994 (1)	0·8935 (1)	0·5844 (1)	0·076 (5)
O	0·4041 (2)	0·8619 (1)	0·0696 (2)	0·062 (11)
N(1)	0·3613 (2)	0·9636 (2)	0·4006 (3)	0·075 (15)
N(2)	0·3205 (2)	0·8070 (2)	0·3771 (2)	0·049 (9)
N(3)	0·3473 (2)	0·7999 (1)	0·2657 (2)	0·044 (9)
C(1)	0·3729 (2)	0·6987 (2)	0·1009 (2)	0·044 (10)
C(2)	0·4012 (2)	0·7705 (2)	0·0319 (2)	0·047 (11)
C(3)	0·4264 (2)	0·7488 (2)	−0·0796 (3)	0·062 (14)
C(4)	0·4230 (2)	0·6571 (3)	−0·1224 (3)	0·074 (17)
C(5)	0·3951 (3)	0·5860 (3)	−0·0560 (4)	0·075 (19)
C(6)	0·3706 (2)	0·6060 (2)	0·0545 (3)	0·058 (12)
C(7)	0·3295 (2)	0·8891 (2)	0·4453 (3)	0·051 (12)
C(8)	0·3461 (2)	0·7174 (2)	0·2174 (2)	0·046 (11)

* U_{eq} calculated as one third of the trace of the orthogonalized U tensor.

Table 2. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

S–C(7)	1·689 (4)	C(2)–C(3)	1·397 (4)
O–C(2)	1·356 (3)	C(3)–C(4)	1·375 (5)
N(1)–C(7)	1·317 (4)	C(4)–C(5)	1·381 (6)
N(2)–N(3)	1·380 (4)	C(5)–C(6)	1·376 (6)
N(2)–C(7)	1·346 (4)	C(6)–C(1)	1·402 (4)
N(3)–C(8)	1·276 (3)	C(8)–C(1)	1·452 (4)
C(1)–C(2)	1·409 (4)		

N(3)–N(2)–C(7)	120·9 (2)	C(3)–C(4)–C(5)	120·6 (3)
N(2)–N(3)–C(8)	116·2 (2)	C(4)–C(5)–C(6)	120·4 (4)
C(6)–C(1)–C(8)	119·2 (3)	C(1)–C(6)–C(5)	120·6 (3)
C(2)–C(1)–C(6)	118·3 (2)	S–C(7)–N(2)	119·2 (2)
O–C(2)–C(1)	121·8 (2)	S–C(7)–N(1)	122·2 (2)
O–C(2)–C(3)	118·0 (3)	N(3)–C(8)–C(1)	122·6 (3)
C(1)–C(2)–C(3)	120·2 (3)	N(1)–C(7)–N(2)	118·6 (3)
C(2)–C(3)–C(4)	119·8 (3)		

N(3)–N(2)–C(7)–S	−178·1 (2)	O–C(2)–C(1)–C(8)	−0·6 (4)
N(3)–N(2)–C(7)–N(1)	2·2 (4)	N(3)–C(8)–C(1)–C(2)	−0·6 (4)

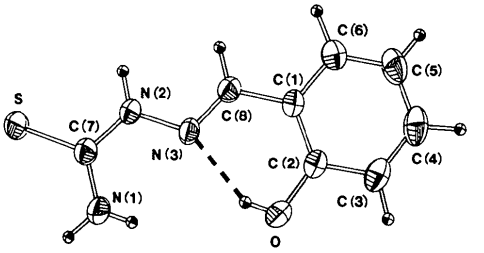

Fig. 2. Perspective view and atom labelling of the salicylaldehyde thiosemicarbazone molecule. The thermal ellipsoids are drawn (Johnson, 1965) at the 35% probability level, and the broken line represents an intramolecular hydrogen bond.

Palenik *et al.* (1974) pointed out that apparently the parent aldehyde or ketone moiety has a strong influence on the C–S bond distance. The C–S bond length in the present structure, however, does not differ significantly from the corresponding length in acetone thiosemicarbazone (Palenik *et al.*, 1974), 3-ethoxy-1,1-dihydroxy-2-butanone bis(thiosemicarbazone) (Gabe, Taylor, Glusker, Minkin & Patterson, 1969), 2-thiophenecarbaldehyde thiosemicarbazone (Mathew &

Table 3. *Net charges on the atoms in the salicylaldehyde thiosemicarbazone molecule as calculated by the CNDO/2 method (Pople & Beveridge, 1970)*

S	−0·4588	C(3)	−0·0582
O	−0·2820	C(4)	0·0375
N(1)	−0·2022	C(5)	−0·0366
N(2)	−0·0949	C(6)	0·0300
N(3)	−0·0957	C(7)	0·2815
C(1)	−0·0516	C(8)	0·0912
C(2)	0·1891		

Palenik, 1971), and 3-hydroxyimino-2-butanone thiosemicarbazone (Nandi *et al.*, 1984*b*). The mangitude of this bond length indicates that the S atom is in the thioketo form which is corroborated by the presence of a fairly strong band in the IR spectrum of this compound at 760 cm^{-1} due to the ν(C—S) modes. It may be noted that this bond length remains similar to those in various 4-phenylthiosemicarbazide derivatives (Kálmán *et al.*, 1972; Nandi *et al.*, 1984*a*; Chattopadhyay *et al.*, 1987*a*,*b*). The charge density on the S atom, calculated by the CNDO/2 method (Pople & Beveridge, 1970) (Table 3), is very close to the corresponding value of −0·4603 in 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*a*). The N(2)—N(3) and C(7)—N(2) bond lengths are comparable to those in several thiosemicarbazones (Palenik *et al.*, 1974; Brown & Agrawal, 1978). The negative charge density on N(3) decreases considerably as compared to that (−0·1385) in 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*a*).

Of the two C(7)—N bonds in the present molecule, the C(7)—N(1) bond is significantly shorter than C(7)—N(2). This is due to a greater double-bond character of the former bond and indicates an increased electron localization at this end of the molecule. The negative charge density on N(1) increases significantly as compared to that (−0·1850) in 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*a*).

The endocyclic bond angles in the phenyl ring, except that at C(1), do not deviate from the normal sp^2 value. The observed narrowing of the C(2)—C(1)—C(6) angle may be due to conjugation of the phenyl ring with the side chain (Domenicano, Vaciago & Coulson, 1975). The partial double-bond character of the C(phenyl)—O bond and the high positive charge density on C(2) indicate that there is considerable delocalization of π electrons from the benzene ring towards the —OH group, thereby imparting good electron-donor capacity to the O atom.

The *in vitro* antibacterial activity of salicylaldehyde thiosemicarbazone towards *E. coli* is found to be slightly less than that of 4-phenylthiosemicarbazide. Compared to 4-phenylthiosemicarbazide, the negative charge density on N(1) in the present molecule increases while that on N(3) decreases. It is well known that N(1) does not take part either in metal complexation or in the reduction process (Campbell, 1975; Ghosh, Ray, Saha & Kolay, 1984). As one or both of these processes are thought to be responsible for the biological activity of this group of compounds (Kirschner *et al.*, 1966; Palenik *et al.*, 1974; Umapathy *et al.*, 1986, and references therein), localization of electron density on the N(1) atom cannot be expected to affect the biological activity of this compound. Since N(3) and S are the key atoms for metal chelation (Campbell, 1975), a decrease of charge density on N(3), compared to that on the corresponding atom of 4-phenylthiosemicarbazide, may be responsible for the observed lowering of activity of the present compound.

One obviously new feature of the present compound is the presence of the phenolic OH group in a position suitable for participation in metal chelation. Introduction of this O donor may also be responsible for the deactivation of this N,S donor ligand.

The thiosemicarbazide side chain is nearly coplanar with the phenyl ring; the plane comprising N(3), N(2), S, C(7) and N(1) makes an angle of 5·9 (1)° with the plane of the phenyl ring. The crystal structure (Fig. 3) is stabilized by hydrogen bonding, stacking interactions and van der Waals forces. A pair of molecules related by a centre of symmetry dimerize by forming S···H(N2)—N(2) hydrogen bonds [H(N2)···S = 2·56 (3), N(2)···S = 3·439 (3), N(2)—H(N2) = 0·89 (3) Å, S···H(N2)—N(2) = 169 (2)°]. Dimeric units generated by the *c* glide are further interlinked by hydrogen bonds of the type O···H(N1)—N(1) [O···H(N1)*b* = 2·02 (3), N(1)···O = 2·956 (3), N(1)—H(N1)*b* = 0·93 (3) Å, O···H(N1)*b*—N(1) = 173 (3)°], thereby giving rise to a stacking of the thick layers at $z = \frac{1}{4}$ and $\frac{3}{4}$ in the crystal lattice (Fig. 3).

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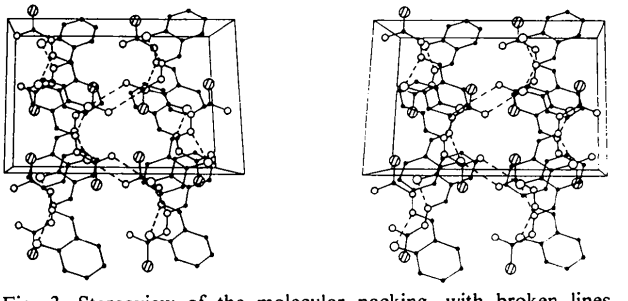

Fig. 3. Stereoview of the molecular packing, with broken lines representing O···N hydrogen bonds. The origin of the unit cell lies at the lower left corner, with *a* pointing towards the reader, *b* from left to right, and *c* upwards. The N···S hydrogen bonds formed between molecules across a centre of symmetry have been omitted.

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Structure of a Synthetic Hexahydrobenzofuran Subunit, $C_{16}H_{22}O_7$, Related to the Avermectins

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Abstract. Methyl 6,7-diacetoxy-6-methyl-3-methyleneperhydrobenzofuran-4-carboxylate, $C_{16}H_{22}O_7$, $M_r = 326{\cdot}35$, monoclinic, $P2_1$, $a = 7{\cdot}5763\ (18)$, $b = 10{\cdot}2792\ (14)$, $c = 11{\cdot}3512\ (16)$ Å, $\beta = 108{\cdot}23\ (2)°$, $V = 839{\cdot}64$ Å^3, $D_x = 1{\cdot}29$ Mg m^{-3}, $Z = 2$, $\lambda(\text{Cu } K\bar{\alpha}) = 1{\cdot}54178$ Å, $T = 293$ K, $\mu(\text{Cu } K\bar{\alpha}) = 0{\cdot}813$ mm^{-1}, $F(000) = 348$, $R = 0{\cdot}064$ for 1322 observed reflections. The title compound is constituted of a five-membered ring of the envelope type containing an O atom. To this ring is fused a cyclohexane ring in the chair conformation. There are four substituents attached to the six-membered ring: a methoxycarbonyl group in equatorial position at C(2), an axial methyl and an equatorial acetoxy group at C(4) and another acetoxy also in axial position at C(5).

Introduction. The avermectin group of macrolide antiparasitic agents contains a hexahydrobenzofuran ring system with an unusual substitution pattern (Davies & Green, 1986). Several synthetic approaches to this subunit have been reported recently (Jung & Street, 1984; Prashad & Fraser-Reid, 1985; Kozikowski & Maloney Huss, 1985; Grimmins & Lever, 1986; Ireland & Obrecht, 1986; Jung, Street &

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