(III) respectively, in the conformations found in the crystal structures. The range can increase to 4·7 Å for (II) if the central dihedral angle is altered to a *trans* value of 180° rather than the crystallographically observed *gauche* value of *ca* 65° (Table 2). In the case of (III), the *gauche*⁻, *trans*, *gauche*⁻ conformation for the three central C—C bonds would have to be changed to *trans, trans, trans* for a maximum extended distance of 6 Å to be achieved. Even so, the potential alkylation distances are too short for the compounds to (inter-strand) span the distance between N(7) or O(6) atoms of adjacent guanosine nucleotides on opposite DNA strands. Thus, the high biological activity observed for BDMS may be due to its ability to form intra-strand rather than inter-strand cross-linking, which is geometrically quite feasible. Molecular modelling studies on these cross-linking possibilities will be reported elsewhere.

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References

ALLEN, F. H., KENNARD, O., WATSON, D. G., BRAMMER, L., ORPEN, A. G. & TAYLOR, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–S19.

BEDFORD, P. & FOX, B. W. (1983). *Biochem. Pharmacol.* **32**, 2297–2301.

FOX, B. W. (1975). *Mechanisms of Action of Methanesulfonates.* In *Antineoplastic and Immunosuppressive Agents*, Part II, edited by A. C. SARTORELLI & D. G. JOHNS, pp. 35–42. New York: Springer.

FRENZ, B. A. (1980). *Enraf–Nonius Structure Determination Packages.* Enraf–Nonius, Delft, The Netherlands.

HADDOW, A. & TIMMIS, G. M. (1951). *Acta Unio Int. Contra Cancrum*, **7**, 469–473.

HARTLEY, J. & FOX, B. W. (1986). *Cancer Chemother. Pharmacol.* **17**, 56–62.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

SAENGER, W. (1983). *Principles of Nucleic Acid Structure*, pp. 82–96. New York: Springer.

WALKER, N. & STUART, D. (1983). *Acta. Cryst.* A**34**, 158–166.

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Structure of 1-(3,4-Dichlorophenyl)-4-methylthiosemicarbazide

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Abstract. $C_8H_9Cl_2N_3S$, $M_r = 250·14$, monoclinic, $P2_1/n$, $a = 6·477$ (1), $b = 27·079$ (5), $c = 6·266$ (1) Å, $\beta = 96·84$ (2)°, $V = 1091·2$ (3) Å^3, $Z = 4$, $D_m = 1·54$, $D_x = 1·523$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 7·438$ cm^{-1}, $F(000) = 512$, $T = 293$ K, final R 0·038 with 1542 observed reflections. The molecule is in the *trans* conformation. The extent of conjugation between the phenyl ring and the thiosemicarbazide side chain is considerable. The charge density, calculated by the *CNDO*/2 method, on the hydrazinic N atom is less than in the 4-phenylthiosemicarbazides.

Introduction. The biological activities possessed by thiosemicarbazides and thiosemicarbazones (Agrawal, Cushley, Lipsky, Wheaton & Sartorelli, 1972; Nandi, Sheldrick & Ghosh, 1986; Chattopadhyay, Mazumdar, Banerjee, Ghosh & Mak, 1988; Chattopadhyay, Mazumdar, Banerjee & Mak, 1988, and references therein) are generally associated with their metal chelating ability (Umapathy, Budhkar & Dorai, 1986). Since the S and hydrazinic N atoms take part in metal chelation, the biological activity of the ligands is thought to be centred around these two atoms. The

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charge densities on these atoms, therefore, must play some important role in their reactions. Comparison of the charge densities on the atoms in a series of 4-phenylthiosemicarbazide derivatives indicates that there may be some correlation between the net negative charges on the hydrazinic terminal N atom, N(3), and the antibacterial activity of these ligands (Nandi, Chaudhuri, Mazumdar & Ghosh, 1984; Chattopadhyay, Banerjee, Mazumdar, Ghosh & Kuroda, 1987*a,b*; Chattopadhyay, Mazumdar, Banerjee, Ghosh & Mak, 1988; Chattopadhyay, Mazumdar, Banerjee & Mak, 1988). In the title compound the phenyl ring is attached to N(3) and a methyl group is attached to N(1). Nagarajan, Talwalker, Kulkarni, Venkateswarlu, Prabhu & Nayak (1984) reported antifertility activity in a series of similar compounds. The present crystal structure analysis has been carried out to study the effect of the said substitutions on the structural features and the charge density distribution in the thiosemicarbazide chain.

Experimental. Colourless needle-shaped crystals from benzene, D_m measured by flotation, $P2_1/n$ (systematic absences: $0k0$, k odd; $h0l$, $h + l$ odd), crystal size: $0{\cdot}52 \times 0{\cdot}32 \times 0{\cdot}18$ mm, Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$, accurate cell parameters from 25 strong reflections with $30 \leq 2\theta \leq 40°$. 1916 reflections (of which 1774 were independent) measured with $3 \leq 2\theta \leq 50°$ in the range ($0 \leq h \leq 7$, $0 \leq k \leq 32$, $-7 \leq l \leq 7$) of which 1542 were considered observed [$I > 2{\cdot}5\sigma(I)$]. Scan mode: ω scan, scan angle $(1{\cdot}21 + 0{\cdot}35\tan\theta)°$. Intensity corrected for Lp. Intensities were corrected for variation ($< \pm$ 1%) in intensity of three standard reflections (402, 0,16,0 and 224) monitored every hour of X-ray exposure. Empirical absorption correction based on ψ scan (of nine reflections), transmission factors 0·611 to 0·911. Structure solved by direct methods (*MULTAN*78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), full-matrix least-squares refinement based on $|F|$ of the positional and isotropic thermal parameters for non-H atoms, then positional and anisotropic thermal parameters, all nine H atoms located from difference syntheses, further refinement with anisotropic thermal parameters for non-H atoms and isotropic thermal parameters for H atoms, final R (163 variables) $= 0{\cdot}038$ with 1542 observed reflections, $wR = 0{\cdot}044$, $w = 2{\cdot}5/[\sigma^2(|F_o|) + 0{\cdot}0006|F_o|^2]$, $\Delta/\sigma < 0{\cdot}4$, $\Delta\rho$ residuals $0{\cdot}33$ e Å^{-3} in final difference synthesis, atomic scattering factors from *International Tables for X-ray Crystallography* (1974), refinement program *SHELX*76 (Sheldrick, 1976).

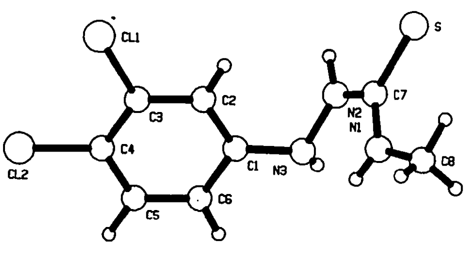

Fig. 1. Atom-labelling scheme.

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

	x	y	z	U_{eq}(Å^2)
Cl(1)	0·8632 (2)	0·81356 (4)	0·1395 (2)	0·0653 (4)
Cl(2)	0·8155 (2)	0·75763 (4)	0·5744 (2)	0·0679 (4)
S	0·2468 (1)	0·99149 (3)	−0·2622 (1)	0·0455 (3)
N(1)	0·0146 (4)	0·9247 (1)	−0·0900 (4)	0·0449 (9)
N(2)	0·2990 (4)	0·9516 (1)	0·1217 (4)	0·0424 (9)
N(3)	0·2462 (4)	0·9211 (1)	0·2856 (4)	0·0434 (9)
C(1)	0·3859 (4)	0·8824 (1)	0·3492 (4)	0·0379 (9)
C(2)	0·5395 (5)	0·8682 (1)	0·2272 (5)	0·041 (1)
C(3)	0·6706 (5)	0·8296 (1)	0·2949 (5)	0·041 (1)
C(4)	0·6482 (5)	0·8051 (1)	0·4828 (5)	0·044 (1)
C(5)	0·4922 (6)	0·8187 (1)	0·6027 (5)	0·046 (1)
C(6)	0·3622 (6)	0·8568 (1)	0·5369 (5)	0·045 (1)
C(7)	0·1794 (4)	0·9534 (1)	−0·0682 (4)	0·0358 (9)
C(8)	−0·1452 (6)	0·9246 (2)	−0·2751 (6)	0·056 (1)

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

Cl(1)–C(3)	1·727 (4)	N(3)–C(1)	1·411 (4)
Cl(2)–C(4)	1·735 (3)	C(1)–C(2)	1·379 (4)
S–C(7)	1·691 (3)	C(1)–C(6)	1·389 (4)
N(1)–C(7)	1·314 (4)	C(2)–C(3)	1·381 (4)
N(1)–C(8)	1·460 (4)	C(3)–C(4)	1·374 (4)
N(2)–C(7)	1·341 (3)	C(4)–C(5)	1·379 (5)
N(2)–N(3)	1·392 (4)	C(5)–C(6)	1·364 (4)
C(7)–N(1)–C(8)	125·0 (3)	Cl(1)–C(3)–C(4)	121·2 (2)
N(3)–N(2)–C(7)	120·6 (2)	Cl(2)–C(4)–C(3)	121·0 (2)
N(2)–N(3)–C(1)	116·3 (2)	C(3)–C(4)–C(5)	119·8 (3)
N(3)–C(1)–C(6)	118·5 (3)	Cl(2)–C(4)–C(5)	119·2 (2)
N(3)–C(1)–C(2)	122·1 (2)	C(4)–C(5)–C(6)	120·2 (3)
C(2)–C(1)–C(6)	119·3 (3)	C(1)–C(6)–C(5)	120·4 (3)
C(1)–C(2)–C(3)	119·9 (3)	N(1)–C(7)–N(2)	116·5 (2)
Cl(1)–C(3)–C(2)	118·4 (2)	S–C(7)–N(2)	119·3 (2)
C(2)–C(3)–C(4)	120·3 (3)	S–C(7)–N(1)	124·2 (2)
N(3)–N(2)–C(7)–S	179·2 (2)	C(8)–N(1)–C(7)–S	−6·1 (4)
N(3)–N(2)–C(7)–N(1)	−0·9 (4)	C(8)–N(1)–C(7)–N(2)	173·9 (3)

Discussion. The atomic labelling scheme is shown in Fig. 1. The fractional atomic coordinates are listed in Table 1.* Bond distances, bond angles and selected torsion angles are presented in Table 2.

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond distances and angles involving H atoms, and deviations from least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51315 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The thiosemicarbazide moiety is nearly planar. This group exists in its thione tautomeric form as indicated by the C—S bond length which is comparable to the length of this bond in different thione tautomers (Nandi *et al.,* 1984; Chattopadhyay *et al.,* 1987*a,b*). In accordance with the general rule for uncomplexed and neutral thiosemicarbazide and thiosemicarbazone derivatives the S and hydrazinic N atoms lie in a *trans* conformation. An intramolecular hydrogen-bond-like contact is observed between N(1) and N(3) which lie *cis* to each other [N(1)···N(3) = 2·638 (4), N(3)···H(N1) = 2·24 (3), N(1)—H(N1) = 0·88 (3) Å, ∠N(2)—H(N1)···N(3) = 107 (2)°]. Similar weak intramolecular contacts have been found in other derivatives (Chattopadhyay *et al.,* 1987*a,b*; Chattopadhyay, Mazumdar, Banerjee, Ghosh & Mak, 1988; Chattopadhyay, Mazumdar, Banerjee & Mak, 1988). The mean plane of the thiosemicarbazide side chain makes an angle of 72·08 (8)° with the planar phenyl ring.

The N(1)—C(7) bond length in the present structure is shorter than those in some 4-phenyl derivatives (Kálmán, Argay & Czugler, 1972; Nandi *et al.,* 1984; Chattopadhyay *et al.,* 1987*a*) and is comparable to those in unsubstituted thiosemicarbazide (Andreetti, Domiano, Gasparri, Nardelli & Sgarabotto, 1970), thiosemicarbazide hydrochloride (Coghi, Lanfredi & Tiripicchio, 1976) and 1-phenylthiosemicarbazide (Czugler, Kálmán & Argay, 1973). In the 4-phenyl thiosemicarbazide derivatives, the lone pair of electrons on the N(1) atom is involved in conjugation with the phenyl ring which in the absence of the phenyl ring at N(1) is available for imparting partial double-bond character to the N(1)—C(7) bond. The N(2)—N(3) bond length is similar to the corresponding bond length in 1-phenylthiosemicarbazide [1·395 (2) Å (Czugler *et al.,* 1973)]. The length of the C(1)—N(3) bond suggests considerable conjugation between the phenyl ring and the thiosemicarbazide chain. However, the substituents in the phenyl ring, the Cl atoms, have their influences on this conjugation (Chattopadhyay & Mazumdar, 1986).

Comparison of charge density distribution on the atoms in the present molecule as calculated by the *CNDO*/2 method (Pople & Beveridge, 1970) (Table 3) with those in ring-substituted 4-phenylthiosemicarbazide derivatives shows that the net negative charges on the N(1) and N(3) atoms decrease in the present case. The calculated distribution may be explained from the above consideration. The electron-repelling methyl group at N(1) causes an increased conjugation of the lone pair of electrons on N(1) with the adjacent C(7)=S system thereby lowering the net negative charge on N(1) and the net negative charge on N(3) decreases again due to its conjugation with the phenyl ring. The charge density on the S atom, however, does not differ significantly as compared to the 4-phenyl derivatives.

Both the C(Ph)—Cl bond distances in the present molecule are shorter than that in 4-(4-chlorophenylthiosemicarbazide) [1·749 (3), 1·751 (3) Å]. The average endocyclic valence angle and the average C—C bond distance in the phenyl ring are 119·99° and 1·377 Å respectively.

Centrosymmetrically related molecules form dimers through N(2)—H(N2)···S hydrogen bonds [N(2)—H(N2) 0·82 (3), N(2)···S 3·345 (3), H(N2)···S 2·53 (3) Å, ∠N(2)—H(N2)···S 168 (2)°]. These dimers are linked through a pair of N(3)—H(N3)···S hydrogen bonds [N(3)—H(N3) 0·84 (4), N(3)···S 3·414 (3), H(N3)···S 2·59 (3) Å, ∠N(3)—H(N3)···S 166 (3)°]. Fig. 2 shows the crystal packing arrangement.

We thank Hindustan Civa-Geigy Ltd for the generous gift of the compound.

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

Cl1	−0·1363	C(2)	−0·0412
Cl2	−0·1482	C(3)	0·1090
S	−0·4605	C(4)	0·0702
N(1)	−0·1316	C(5)	0·0275
N(2)	−0·1119	C(6)	−0·0474
N(3)	−0·1316	C(7)	0·2739
C(1)	0·1289	C(8)	0·0399

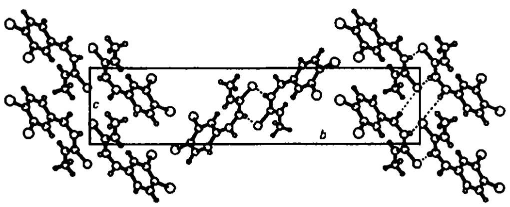

Fig. 2. View of the crystal packing in the *bc* plane. Broken lines represent hydrogen bonds.

References

AGRAWAL, K. C., CUSHLEY, R. J., LIPSKY, S. R., WHEATON, J. R. & SARTORELLI, A. C. (1972). *J. Med. Chem.* **15**, 192–195.

ANDREETTI, G. D., DOMIANO, P., GASPARRI, G. F., NARDELLI, M. & SGARABOTTO, P. (1970). *Acta Cryst.* B**26**, 1005–1009.

CHATTOPADHYAY, D., BANERJEE, T., MAZUMDAR, S. K., GHOSH, S. & KURODA, R. (1987*a*). *Acta Cryst.* C**43**, 974–977.

CHATTOPADHYAY, D., BANERJEE, T., MAZUMDAR, S. K., GHOSH, S. & KURODA, R. (1987*b*). Unpublished.

CHATTOPADHYAY, D. & MAZUMDAR, S. K. (1986). *Z. Kristallogr.* **177**, 103–106.

CHATTOPADHYAY, D., MAZUMDAR, S. K., BANERJEE, T., GHOSH, S. & MAK, T. C. W. (1988). *Acta Cryst.* C**44**, 1025–1028.

CHATTOPADHYAY, D., MAZUMDAR, S. K., BANERJEE, T. & MAK, T. C. W. (1988). *J. Cryst. Spectrosc. Res.* Submitted.

COGHI, L., LANDREDI, A. M. M. & TIRIPICCHIO, A. (1976). *J. Chem. Soc. Perkin Trans.* 2, pp. 1808–1810.

CZUGLER, M., KÁLMÁN, A. & ARGAY, GY. (1973). *Cryst. Struct. Commun.* **2**, 655–658.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

Kálmán, A., Argay, Gy. & Czugler, M. (1972). *Cryst. Struct. Commun.* **1**, 375–378.

Main, P., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1978). *MULTAN78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Nagarajan, K., Talwalker, P. K., Kulkarni, C. L., Venkateswarlu, A., Prabhu, S. S. & Nayak, G. V. (1984). *Indian J. Chem.* **23B**, 1243–1257.

Nandi, A. K., Chaudhuri, S., Mazumdar, S. K. & Ghosh, S. (1984). *J. Chem. Soc. Perkin Trans.* 2, pp. 1729–1733.

Nandi, A. K., Sheldrick, W. S. & Ghosh, S. (1986). *Acta Cryst.* C**42**, 1570–1573.

Pople, J. A. & Beveridge, D. L. (1970). In *Approximate Molecular Orbital Theory.* New York: McGraw-Hill.

Sheldrick, G. M. (1976). *SHELX76.* Program for crystal structure determination. Univ. of Cambridge, England.

Umapathy, P., Budhkar, A. P. & Dorai, S. (1986). *J. Indian Chem. Soc.* **63**, 714–721.

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Structure of Ethyl (3a*RS*,4a*SR*,5*RS*,6a*SR*,7a*SR*)-7-Benzyl-3-(*p*-chlorophenyl)-6-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[*b*]isoxazolo[4,5-*e*]pyridine-4a-carboxylate: a New Heterocyclic System

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Abstract. $C_{25}H_{24}ClN_3O_3$, $M_r = 449\cdot84$, monoclinic, $P2_1/a$, $a = 17\cdot021\ (4)$, $b = 11\cdot100\ (3)$, $c = 12\cdot177\ (3)$ Å, $\beta = 93\cdot86\ (4)°$, $V = 2295\ (1)$ Å^3, $Z = 4$, $D_x = 1\cdot30$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0\cdot71069$ Å, $\mu = 1\cdot57$ cm^{-1}, $F(000) = 944$, $T = 293$ K, final conventional R is $0\cdot055$ for 1675 unique observed reflections. The *exo* configuration between the cyclobutane and the isoxazoline ring, as well as the *trans* configuration between the ethoxycarbonyl and the cyano group, supposed on the basis of NMR data, are confirmed. The piperidine ring adopts a twist-boat conformation.

Introduction. Our studies on the photocycloaddition of acrylonitrile on 1-benzyl-1,4-dihydronicotinamide (Adembri, Donati, Fusi & Ponticelli, 1985) and on ethyl 1-benzyl-1,4-dihydronicotinate (Adembri, Donati, Fusi & Ponticelli, 1987*a*) showed the site- and stereoselectivity of the reaction. Subsequent 1,3-dipolar addition of *p*-chlorobenzonitrile oxide on the two regioisomers obtained led, in high yield with stereo- and regioselectivity, to a new class of heterocyclic systems (Adembri *et al.*, 1987*a*). Some derivatives of these compounds show activity as non-competitive inhibitors of lactoperoxidase (Adembri *et al.*, 1987*b*). The X-ray crystallographic analysis of one of these compounds was undertaken in order to confirm the stereochemical assignments made in the preceding papers. The knowledge of the stereochemistry should be of interest both from an organic and from a pharmacological point of view.

Experimental. Colourless prismatic crystals were obtained by slow hydration of an Me_2SO solution. Philips PW 1100 diffractometer, lattice parameters determined using 25 reflections with $5 \leq \theta \leq 9°$, $2\theta < 50°$, ω–2θ scan technique, $-20 \leq h \leq 20$, $0 \leq k \leq 13$, $0 \leq l \leq 14$, 1675 unique reflections with $I \geq 3\sigma(I)$, three standard reflections (203, $1\bar{1}3$, 123), no significant variation of their intensity, Lp correction, no absorption correction, parallelepipedal crystal, $0\cdot2 \times 0\cdot3 \times 0\cdot15$ mm. Structure solved by direct methods with *MULTAN*80 system (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); subsequent calculations by *SHELX*76 system programs (Sheldrick, 1976) on the IBM 3081 at CNUCE (Pisa). The locations of all the H except those of the ethyl group were found by subsequent difference Fourier maps. The H atoms of the ethyl group were located geometrically before the refinement. Non-H atoms were refined with anisotropic thermal parameters, H atoms with a common isotropic temperature factor, $U = 0\cdot073\ (4)$ Å^2; the methyl group refined as a rigid body; refinement by full-matrix least squares minimizing $\sum w(F_o - F_c)^2$, 356 parameters, $R = 0\cdot055$, $wR = 0\cdot060$, $w^{-1} = \sigma^2(F) + 0\cdot00394F^2$, $S = 1\cdot06$, $(\Delta/\sigma)_{\max} = 0\cdot17$ for non-H atoms. Max. and min. heights in the final

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