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Effect of Phenyl Substitution on the Structure and Activity of 3-Hydroxyimino-2-butanone Thiosemicarbazone: Structure of 3-Hydroxyimino-2-butanone 4-Phenylthiosemicarbazone

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Abstract. $C_{11}H_{14}N_4OS$, $M_r = 250{\cdot}32$, monoclinic, $P2_1/n$, $a = 5{\cdot}539$ (2), $b = 22{\cdot}222$ (3), $c = 10{\cdot}074$ (1) Å, $\beta = 91{\cdot}70$ (2)°, $V = 1239{\cdot}3$ (8) Å^3, $Z = 4$, $D_m = 1{\cdot}339$ by flotation, $D_x = 1{\cdot}341$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 0{\cdot}2396$ mm^{-1}, $F(000) = 528$, $T =$ 297 K, final $R = 0{\cdot}037$ for 1869 observed reflections. The molecule is in a fully extended form. Respective centrosymmetric pairs of intermolecular N—H···S and O—H···N hydrogen bonds, characteristic of thiosemicarbazone and oxime molecules, are observed leading to chain building in the [100] direction. Intramolecular N—H···N hydrogen bonds lend extra stability to the *trans* conformation of the molecule.

Introduction. It has been established that thiosemicarbazides and thiosemicarbazones containing N—S donor chromophores exhibit a wide range of biological activity such as antibacterial, antiviral, antitumour, antimalarial and antileprotic actions (Johnson, Joyner & Perry, 1952; French & Blanz, 1965, 1966; Lewis & Shephard, 1970; Bauer, 1972; Williams, 1972; Klayman, Scovill, Bertosevich & Mason, 1981). In general, these activities are attributed to the metal chelating ability of these molecules (Sorkin, Roth & Erlenmeyer, 1952; Cymerman, Willis, Rubbo & Edgar, 1955; Kirschner, Wei, Francis & Bergman, 1966) and their reductive capacities (Palenik, Rendle & Carter, 1974). A crystal structure analysis of an antiviral and antibacterial tridentate ligand, 3-hydroxyimino-3-butanone thiosemicarbazone, (I), which contains an S—N—N chromophore, was carried out; its activity has been explained on the basis of its structure favouring chelation with both hard and soft acceptor metal ions and its reductive capacity (Nandi, Chaudhuri, Mazumdar & Ghosh, 1984*a*). A crystal structure analysis of the title compound, (II), which possesses antibacterial and antiviral activity (Ray, 1981), has been undertaken to explore the molecular geometry, the forces stabilizing the molecule, to compare and contrast the conformational difference between (I) and its phenyl-substituted derivative (II) and to throw some light on the weakening of the biological activity of this phenyl-substituted molecule compared with that of the unsubstituted one.

Experimental. Colourless transparent crystals (from methanol), symmetry from oscillation and Weissenberg photographs, $P2_1/n$ (systematic absences $0k0$, k odd, $h0l$, $h+l$ odd), crystal size: 0·16 × 0·58 × 0·49 mm, Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Mo $K\alpha$; accurate cell parameters from 25 high-angle ($15 \le \theta \le 20°$) reflections: 2186 unique reflections measured in the range $15 \le \theta \le 25°$ ($0 \le h \le 6$, $0 \le k \le 26$, $-11 \le l \le 11$), 1869 reflections with $I > 2\sigma(I)$ corrected for variation in intensity (<3%) of the standard reflections ($0\bar{1}\bar{6}$, $\bar{2}\bar{8}\bar{3}$, 402) monitored every hour of X-ray exposure, intensity corrected for Lp, absorption ignored; direct methods (*MULTAN*78, Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); a scale factor, atomic coordinates for all atoms, isotropic thermal parameters for H atoms and anisotropic thermal parameters for non-H atoms refined by full-matrix least squares based on F (*ORFLS*, Busing, Martin & Levy, 1962), H (from ΔF synthesis) isotropic, $R = 0{\cdot}037$, $wR = 0{\cdot}036$, $S = 2{\cdot}362$, $w = 1/\sigma^2(|F_o|)$ based on counting statistics, shift/e.s.d. <0·59 for H atoms, otherwise <0·01, residual electron density $< \pm 0{\cdot}20$ e Å^{-3} in final ΔF synthesis, scattering factors: non-H from Cromer & Waber (1965), H from Stewart, Davidson & Simpson

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(1965), anomalous-dispersion correction for all non-H atoms from *International Tables for X-ray Crystallography* (1974).

Discussion. The atomic labelling scheme is shown in Fig. 1. The atomic coordinates are listed in Table 1; the intramolecular bond distances and angles are listed in Table 2. The packing of the molecules in the unit cell is shown in Fig. 2.*

The C—S distance of 1·666 (2) Å is even shorter than that of 1·683 (2) Å found in the unsubstituted compound (I); the shortest C—S distances found in most thiosemicarbazides and thiosemicarbazones fall in the 1·687 to 1·706 Å range (Palenik, Rendle & Carter, 1974). Appreciable shortening of the C—S bond length from the normal S—C(sp^2) single-bond distance of 1·747 (7) Å (Uechi & Oniki, 1982), as well as the presence of a fairly strong band around 730 cm^{-1} in the IR spectrum, confirms the existence of the ligand in its thiocarbonyl (keto) form (Bellamy, 1975). This C—S distance is longer than the normal S—C(sp^2) double-bond distance of 1·59 Å (Domiano, Fava Gasparri, Nardelli & Sgarabotto, 1969) and indicates the presence of partial double-bond character and electron delocalization. All other bond distances are found to be similar to those in (I), with the exception of the longer C(1)—N(1) length of 1·330 (2) Å observed in the present study compared with 1·312 (3) Å in the unsubstituted compound; this may be attributed to the effect of phenyl substitution. The observed N(1)—C(11) bond length of 1·409 (3) Å is appreciably shorter than the 1·457 (3) Å found in 4-phenylthiosemicarbazide (Kálmán, Argay & Czugler, 1972). This may be attributed to the condensation of 4-phenylthiosemicarbazide with 2,3-butanedione monoxime. Whatever the causes may be, the result of this condensation is an ultimate loss of degrees of rotational freedom around the N(1)—C(11) bond.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, torsion angles, details of least-squares planes and net atomic charges have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43063 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

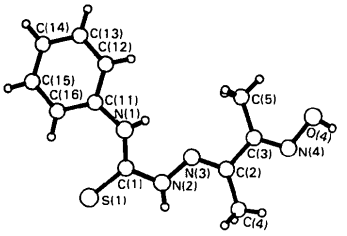

Fig. 1. A view of the molecule with atomic numbering scheme.

Table 1. *Fractional atomic coordinates for non-H atoms with e.s.d.'s in parentheses and the equivalent isotropic temperature factors B_{eq} (Hamilton, 1959) for non-H atoms*

	x	y	z	B_{eq}(Å²)
S	−0·1519 (1)	0·0850 (1)	0·5221 (1)	4·2 (1)
O(4)	0·9087 (2)	0·0638 (1)	−0·0558 (1)	4·9 (1)
N(1)	0·0022 (3)	0·1527 (1)	0·3199 (2)	4·1 (1)
N(2)	0·1855 (3)	0·0627 (1)	0·3516 (2)	3·6 (1)
N(3)	0·3203 (3)	0·0789 (1)	0·2460 (1)	3·3 (1)
N(4)	0·7929 (3)	0·0372 (1)	0·0518 (2)	3·6 (1)
C(1)	0·0130 (3)	0·1026 (1)	0·3920 (2)	3·2 (1)
C(2)	0·4898 (3)	0·0442 (1)	0·2061 (2)	3·0 (1)
C(3)	0·6174 (3)	0·0691 (1)	0·0923 (2)	3·1 (1)
C(4)	0·5586 (4)	−0·0150 (1)	0·2650 (2)	4·0 (1)
C(5)	0·5409 (4)	0·1276 (1)	0·0323 (2)	4·5 (1)
C(11)	−0·1516 (4)	0·2032 (1)	0·3179 (2)	3·4 (1)
C(12)	−0·0917 (4)	0·2489 (1)	0·2313 (2)	4·2 (1)
C(13)	−0·2358 (4)	0·2988 (1)	0·2166 (2)	5·0 (1)
C(14)	−0·4409 (4)	0·3044 (1)	0·2882 (2)	5·1 (1)
C(15)	−0·4988 (4)	0·2597 (1)	0·3749 (2)	5·1 (1)
C(16)	−0·3573 (4)	0·2088 (1)	0·3908 (2)	4·5 (1)

Table 2. *Bond lengths* (Å) *and angles* (°) *involving non-H atoms*

S—C(1)	1·666 (2)	C(2)—C(3)	1·472 (3)
C(4)—N(4)	1·406 (2)	C(2)—C(4)	1·488 (3)
N(1)—C(1)	1·330 (3)	C(3)—C(5)	1·490 (3)
N(1)—C(11)	1·409 (3)	C(11)—C(12)	1·385 (3)
N(2)—N(3)	1·366 (2)	C(11)—C(16)	1·379 (3)
N(2)—C(1)	1·374 (3)	C(12)—C(13)	1·372 (3)
N(3)—C(2)	1·288 (3)	C(13)—C(14)	1·369 (3)
N(4)—C(3)	1·280 (3)	C(14)—C(15)	1·367 (3)
		C(15)—C(16)	1·383 (3)
C(1)—N(1)—C(11)	133·8 (2)	N(3)—C(2)—C(3)	112·9 (2)
N(3)—N(2)—C(1)	117·5 (2)	C(3)—C(2)—C(4)	121·3 (2)
N(2)—N(3)—C(2)	120·4 (2)	N(4)—C(3)—C(2)	115·3 (2)
O(4)—N(4)—C(3)	112·4 (2)	C(2)—C(3)—C(5)	120·4 (2)
N(1)—C(11)—C(16)	125·0 (2)	N(4)—C(3)—C(5)	124·3 (2)
N(1)—C(11)—C(12)	115·9 (2)	C(11)—C(12)—C(13)	120·7 (2)
C(12)—C(11)—C(16)	119·1 (2)	C(12)—C(13)—C(14)	120·4 (2)
N(1)—C(1)—N(2)	113·5 (2)	C(13)—C(14)—C(15)	119·0 (2)
S—C(1)—N(2)	118·9 (2)	C(14)—C(15)—C(16)	121·7 (2)
S—C(1)—N(1)	127·5 (2)	C(11)—C(16)—C(15)	119·1 (2)
N(3)—C(2)—C(4)	125·8 (2)		

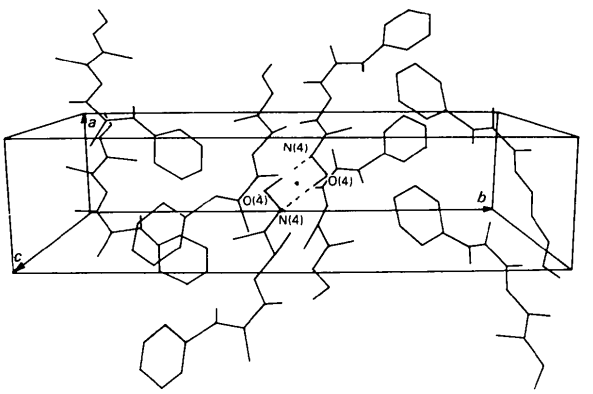

Fig. 2. Packing of the molecule in the unit cell; hydrogen-bonded dimers, O(4)—H(4)···N(4), are shown by dotted lines. The phenyl and the methyl hydrogen atoms have been omitted from the figure.

As in the crystal structure of 4-phenylthiosemicarbazide (Kálmán *et al.*, 1972) and 4-(4-chlorophenyl)thiosemicarbazide (Nandi, Chaudhuri, Mazumdar & Ghosh, 1984*b*), the S atom and the hydrazinic $-NH_2$ group, N(3), assume a *trans* configuration. This is the general conformation found in uncomplexed thiosemicarbazide and thiosemicarbazones (Palenik, Rendle & Carter, 1974) and this has been proposed as a general rule (Fava Gasparri, Mangia, Musatti & Nardelli, 1968). Similar conformations are observed in 4-phenylthiosemicarbazide (Kálmán *et al.*, 1972). The torsion angles S–C(1)–N(2)–N(3) of −178·9 (2) and N(3)–C(2)–C(3)–N(4) of 177·7 (2)° indicate the *trans* conformation of the ligand. The torsion angles C(1)–N(2)–N(3)–C(2) = 177·9 (2), N(2)–N(3)–C(2)–C(3) = −179·4 (2), C(2)–C(3)–N(4)–O(4) = −179·3 (2), S–C(1)–N(1)–C(11) = −6·1 (4) and N(2)–C(1)–C(1)–C(11) = 175·0 (2)° show that the molecule is in a fully extended conformation. Dihedral angles between planes 1 and 2, 1 and 3, 2 and 3 are 8·48 (5), 10·55 (7) and 2·51 (7)°, respectively, where the planes, 1 [C(11), C(12), C(13), C(14), C(15), C(16)], 2 [C(2), C(3), C(4), N(3), N(4), O(4)] and 3 [N(1), N(2), N(3), C(1)], are defined by the atoms in the square brackets.

Charge densities calculated using the CNDO/2 technique (Pople & Beveridge, 1970) for some selected atoms, which are primarily responsible for both the reductive capacity and the coordinating ability of compounds (I) and (II) respectively, are shown in square brackets as follows: S [−0·4591, −0·4255], O(4) [−0·2105, −0·2222], N(1) [−0·2147, −0·1547], N(2) [−0·1198, −0·1085], N(3) [−0·0919, −0·0414], N(4) [−0·0653, −0·0242]. The reversal of the order of negative charge density on the O(4) atom in compounds (I) and (II) does not affect biological activity because O(4) is not involved either in reduction or in coordination to metal ions. The amounts of negative charge on the above atoms in (II) are comparatively less than the negative charges on the corresponding atoms in (I), indicative of a decrease in reductive capacities as well as donor capacities in (II).

The bond distances, bond angles and torsion angles of the common part of molecules (I) and (II) are similar; but some differences are observed in hydrogen-bonding patterns adopted by the molecules in the solid state. In the unsubstituted (I) a pair of hydrogen bonds is observed *via* N(1)–H(1)···S across a centre of inversion forming hydrogen-bonded dimers, a general characteristic of thiosemicarbizides and thiosemicarbazone molecules (Andreetti, Domiano, Fava Gasparri, Nardelli & Sparabotto, 1970; Restivo & Palenik, 1970); a short contact of the type N(2)–H(2)···S was also present. The molecules in the present compound (II), however, form hydrogen-bonded dimers across a centre of inversion *via* N(2)–H(2)···S. Such characteristic dimerization has also been observed in other compounds (Restivo & Palenik, 1970; Mathew & Palenik, 1971; Brown & Agrawal, 1978). The O–H···N hydrogen bonds observed for the oxime moiety in dimethylglyoxime (Hamilton, 1961) as well as in the phenyl substituted compound (II) are absent in the unsubstituted compound (I). Packing of the molecules in the unit cell (Fig. 2) shows that the molecule (II) builds a hydrogen-bonded 'dimer' *via* O(4)–H(4)···N(4) across a centre of inversion. The intramolecular hydrogen bond, namely N(1)–H(1)···N(3), similar to that found in (I), is also observed. All these appear to stabilize the *trans* conformation of the molecule. The details of hydrogen-bond geometries (Å and °) are as follows:

A–H···B	d_{A-H}	$d_{A\cdots B}$	$d_{H\cdots B}$	A–H···B
N(1)–H(1)···N(3)	0·79 (2)	2·535 (3)	2·06 (2)	118 (1)
N(2)–H(2)···S^{i}	0·87 (2)	3·527 (3)	2·67 (2)	168 (1)
O(4)–H(4)···N(4)^{ii}	0·80 (2)	2·787 (2)	2·01 (2)	162 (2)

Symmetry codes: (i) $-x, -y, -z+1$, (ii) $-x+2, -y, -z$.

Thus the typical dimerization through intermolecular as well as intramolecular hydrogen bonds is responsible for locking the S atom in the *trans* configuration and the N(4) atom *trans* to N(3) in the space lattice. This factor, along with π conjugation extended along the central chain of the molecule, hinder free rotation around C(1)–N(2) and C(2)–C(3) and stabilize the *trans* conformation in the uncomplexed ligand. As observed recently in the case of a Co^{III} complex of the unsubstituted ligand (I) (Gerasimov, Biyushkin, Belichuk & Belov, 1979), some conformational changes like 180° rotation around C(1)–N(2) and C(2)–C(3) are expected during metal complexation which will orient N(4) *cis* to N(3) and S *cis* to N(3) facilitating the formation of two five-membered chelate rings. This favourable conformation, which transforms the ligand into a tridentate chelating one, is expected to be generated at the expense of the chelation, packing and hydrogen-bond energies. The lengthening of the C(1)–N(2) bond compared with C(1)–N(1) in (II) indicates lesser electron delocalization towards the thiosemicarbazide side chain in comparison with that found in (I) and leads to the prediction that the rotation barrier around C(1)–N(2) is smaller than around C(1)–N(1).

The slight decrease in the antibacterial activity of (II) may be attributed to the substitution of one hydrogen atom of the free $-NH_2$ group of (I) by the hydrophobic and non-reducing phenyl group which leads to the decrease of the hydrophillic and reducing character of the molecules. Decrease of reductive capacity of this compound is clearly reflected in its reactions with some reducible metal ions in solution. It has been found that (II) does not reduce Fe^{3+} to Fe^{2+} and Cu^{2+} to Cu^{1+} at ordinary temperatures, but forms stable Fe^{3+} and Cu^{2+} complexes. But the unsubstituted ligand (I) invariably reduces Fe^{3+} to Fe^{2+} and Cu^{2+} to Cu^{1+} under identical

conditions (Ghosh, Ray, Saha & Kolay, 1984). CNDO/2 results, as discussed earlier, also support such a decrease in reductive power. Such a substitution thus decreases the reductive capacity as well as the hydrophilic character of the molecule and these two factors probably act together, leading to a slight decrease of its antibacterial activity.

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Structure of Ethyl 4-Acetyl-5-methyl-3-trifluoromethylpyrrole-2-carboxylate

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Abstract. $C_{11}H_{12}F_3NO_3$, $M_r = 263{\cdot}22$, triclinic, $P\bar{1}$, $a = 13{\cdot}584$ (2), $b = 11{\cdot}696$ (2), $c = 10{\cdot}268$ (3) Å, $\alpha = 64{\cdot}29$ (2), $\beta = 70{\cdot}40$ (2), $\gamma = 57{\cdot}45$ (1)°, $V = 1227{\cdot}6$ Å^3, $Z = 4$, $D_x = 1{\cdot}424$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}743$ mm^{-1}, $F(000) = 544$, $T = 293$ K. $R(F) = 0{\cdot}064$ for 3026 observed reflections with $F_o > 3\sigma(F_o)$. The two independent molecules are in a similar conformation and form a hydrogen-bonded dimer; they are stacked along the $[1\bar{1}\bar{1}]$ direction. Short intermolecular F···CH_3 contacts are 3·279 (7) Å for F(3′)···C(10′) and 3·302 (6) Å for F(2′)···C(10).

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