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## Structure of 6-(4-Chlorobenzylidene)-2,3-dihydroimidazo[2,1-*b*]thiazol-5(6*H*)-one. Conformational Analysis of *Z* Isomers of 5-Benzylidenethiohydantoin Derivatives

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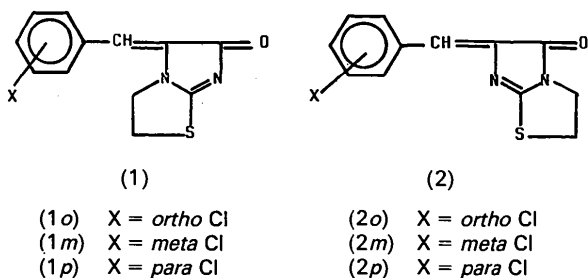
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**Abstract.** C<sub>12</sub>H<sub>9</sub>ClN<sub>2</sub>OS, *M<sub>r</sub>* = 264.73, monoclinic, *P*2<sub>1</sub>/*n*, *a* = 6.837 (2), *b* = 12.053 (1), *c* = 14.251 (10) Å, β = 96.98 (3)°, *V* = 1165.6 (2) Å<sup>3</sup>, *Z* = 4, *D<sub>x</sub>* = 1.508 Mg m<sup>-3</sup>, λ(Cu *Kα*) = 1.54178 Å, μ = 4.27 mm<sup>-1</sup>, *F*(000) = 544, room temperature. All available samples were twinned with *c'* = 28.502 (1) Å in the twin. The intensity data were collected on a twinned sample. 5044 reflections measured [*F* > 4σ(*F*)]; 1458 reflections used for structure solution. Final *R* = 0.043 for 1126 reflections with *F* > 4σ(*F*). The nearly planar molecule has a *Z* configuration. Molecular mechanics calculations for *Z* isomers of 5-(chloro-substituted)benzylidene-2-thiohydantoin derivatives with 1,2- or 2,3-dialkylation indicated some differences in the preferred orientations of the aromatic ring. These orientations depend on the Cl-substituent position and on the type of alkylation.

**Introduction.** To search for new compounds influencing the central nervous system we have examined annelated 2-thiohydantoin derivatives. Comparisons of physicochemical properties, stability and X-ray structure analysis results for 5,5-diphenyl-2-thiohydantoin (DPTH) derivatives have been performed (Kieć-Kononowicz, Zejc, Mikołajczyk, Zatorski, Karolak-Wojciechowska & Wieczorek, 1980, 1981; Kieć-Kononowicz, Zatorski & Karolak-Wojciechowska, 1989; Karolak-Wojciechowska, Mikołajczyk, Zatorski, Kieć-Kononowicz & Zejc, 1985). In the continuation of our studies we have investigated 5-(substituted)benzylidene-2-thiohydantoin derivatives of types (1) and (2) (Karakolak-Wojciechowska, Kwiatkowski & Kieć-Kononowicz, 1989; Kwiatkowski, Karolak-Wojciechowska & Kieć-Kononowicz, 1991). The derivatives of DPTH have shown sedative properties while the derivatives

of 5-(substituted)benzylidene-2-thiohydantoin of type (2) possessed analgesic, anxiolytic, antidepressant and anticonvulsant properties (Kolasa, Kleinrok, Pietrusiewicz, Czechowski, Kieć-Kononowicz & Zejc, 1989).



The aim of the present paper dealing with the structure of (2*p*) is to confirm the *Z* configuration of the molecule and to collect the data for the continuation of our studies on structure-pharmacological activity relationships. From this viewpoint the conformational analysis will also be necessary.

**Experimental.** The title compound was crystallized from five solvents, but in all cases twinned samples were obtained. It was determined from X-ray photographs obtained using a reciprocal-lattice explorer (Stoe) (Wölfel, 1971) that the twins had double unit-cell volume [ $c' = 28.502(10) \text{ \AA}$ ]. There were observed  $0k0$  reflections for  $k = 2n$ ,  $00l'$  for  $l' = 4n$  and unusual extinctions on  $h00$ ,  $h0l'$ ,  $h1l'$  ... layers. It was concluded that the two individual crystals were attached to each other with their orientation relative to the  $c$  axis turned by  $180^\circ$ . Such twinning did not allow the separation of the intensities of some reflections. A twinned crystal ( $0.3 \times 0.2 \times 0.4 \text{ mm}$ ) was used for data collection. Final cell parameters from least-squares refinement of 25 reflections with  $5 < \theta < 20^\circ$  and intensity measurements on a CAD-4 diffractometer; no absorption correction was applied;  $2\theta < 150^\circ$ ;  $h - 8/8$ ,  $k 0/14$ ,  $l' 0/35$ ;  $\omega - 2\theta$  scan mode; three standard reflections measured every 70 reflections; no decay; 5044 reflections measured, 2766 with  $F > 4\sigma(F)$ .

The measured reflections were divided into three sets: (A) reflections from one crystal only with indexes transformed by the matrix  $[1\ 0\ 0; 0\ 1\ 0; 0\ 0\ 0.5]$ ; (B) from the second specimen with indexes recalculated by the matrix  $[1\ 0\ 0; 0\ -1\ 0; -0.5\ 0\ -0.5]$ ; (C) the overlapping reflections. The intensities from set (B) were 2.2 times higher than from set (A). The ratio 2.2 was determined as an average value using respective unoverlapping reflections from (A) and (B). Then seven  $0k0$  reflections from set (C) and 214 reflections with identical indexes for both monocrystals were added to set (B).

The intensities of the added reflections were recalculated according to equation  $I(B) = [2.2/(2.2 + 1)]I$ , where  $I(B)$  are intensities in set (B) and  $I$  intensities in the basic set.

The structure was solved in  $P2_1$  ( $Z = 4$ ), using 1418 reflections from set (B). Direct methods in *SHELXS86* (Sheldrick, 1986) yielded the positions of 25 non-H atoms, out of 32 existing in the asymmetric unit, with  $R(E) = 0.39$ . The remaining atoms were found in the first  $\Delta\rho$  map. Statistical tests suggested a centrosymmetric space group; after isotropic refinement ( $R = 0.24$ ), the space group was changed to  $P2_1/n$ ; 40 more  $h0l$  reflections for  $h + l = 2n$  from (C), systematically absent for crystal (A), were added to (B). Finally, 1458 reflections [1127 with  $F > 4\sigma(F)$ ] were used in further refinement. H atoms, in calculated positions, were then refined in a riding model with  $B = 1.5$  times the value for the parent C atoms. Refinement by full-matrix least squares (on  $F$ ) (anisotropically for all non-H atoms) converged to  $R = 0.043$  and  $wR = 0.039$  with  $w = 1/\sigma^2(F)$  for 1126 reflections and 154 refined parameters (the 200 reflection was omitted in the last cycle due to  $\Delta/\sigma = 19.6$ );  $S = 3.03$ ; maximum parameter change in the last cycle of refinement  $\Delta/\sigma = 0.003$ ; maximum and minimum electron densities in the final  $\Delta\rho$  map were  $0.17$  and  $-0.23 \text{ e \AA}^{-3}$ . All calculations were performed on a PC computer using *SHELX76* (Sheldrick, 1976) and *SHELXTL* (Sheldrick, 1990). Atomic scattering factors from *SHELX76*.

**Discussion.** A molecular scheme for (2*p*) with atom numbering is shown in Fig. 1, while Table 1 gives the final positional parameters and equivalent temperature factors for non-H atoms.\* It is clear from Fig. 1 that the molecule has a *Z* configuration. Bond

\* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54214 (6 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

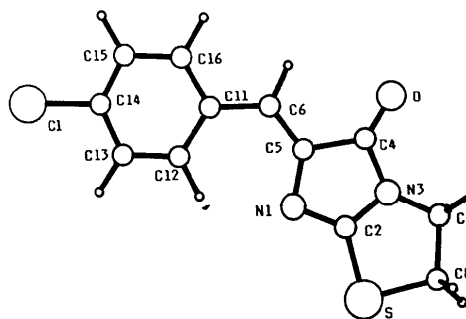


Fig. 1. Molecular structure and atomic numbering of 6-(4-chlorobenzylidene)-2,3-dihydroimidazo[2,1-*b*]thiazol-5(6*H*)-one (4*p*).

Table 1. *Non-H-atom fractional atomic coordinates* ( $\times 10^4$ ) *and equivalent temperature factors* ( $\text{\AA}^2 \times 10^3$ ) *with e.s.d.'s in parentheses*

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	$U_{eq}$
Cl	2414 (3)	-8239 (1)	1011 (1)	56.6 (4)
S	2429 (3)	-1542 (1)	-2510 (1)	69.4 (4)
O	2558 (7)	-812 (2)	870 (2)	63 (1)
N1	2568 (10)	-2870 (3)	-932 (2)	47 (1)
N3	2587 (6)	-999 (3)	-752 (2)	44 (1)
C2	2532 (10)	-1912 (4)	-1344 (3)	48 (1)
C4	2586 (8)	-1364 (3)	158 (3)	45 (1)
C5	2597 (8)	-2614 (3)	37 (3)	44 (1)
C6	2623 (7)	-3293 (3)	780 (3)	47 (1)
C7	2343 (9)	84 (4)	-1203 (3)	57 (1)
C8	2887 (9)	-82 (4)	-2192 (3)	70 (2)
C11	2598 (7)	-4503 (3)	808 (3)	42 (1)
C12	2510 (7)	-5165 (4)	3 (3)	51 (2)
C13	2458 (8)	-6312 (4)	72 (3)	51 (1)
C14	2485 (12)	-6790 (4)	950 (3)	45 (1)
C15	2572 (7)	-6173 (4)	1761 (3)	53 (1)
C16	2612 (8)	-5028 (4)	1687 (3)	51 (1)

Table 2. *Bond lengths* ( $\text{\AA}$ ) *and bond angles* ( $^\circ$ ) *with e.s.d.'s in parentheses*

Cl—C14	1.750 (5)	C5—C6	1.337 (6)
S—C2	1.714 (5)	C6—C11	1.459 (5)
S—C8	1.835 (5)	C7—C8	1.514 (7)
O—C4	1.215 (5)	C11—C12	1.393 (6)
N1—C2	1.294 (6)	C11—C16	1.402 (6)
N1—C5	1.413 (5)	C12—C13	1.387 (7)
N3—C2	1.384 (6)	C13—C14	1.376 (6)
N3—C4	1.370 (5)	C14—C15	1.370 (6)
N3—C7	1.456 (6)	C15—C16	1.385 (7)
C4—C5	1.517 (5)		
C2—S—C8	91.4 (3)	C5—C6—C11	129.4 (4)
C2—N1—C5	104.2 (4)	N3—C7—C8	105.3 (4)
C2—N3—C4	108.6 (4)	S—C8—C7	107.6 (4)
C2—N3—C7	116.8 (4)	C6—C11—C12	123.3 (4)
C4—N3—C7	133.9 (4)	C6—C11—C16	118.5 (4)
S—C2—N1	131.9 (4)	C12—C11—C16	118.2 (4)
S—C2—N3	112.3 (4)	C11—C12—C13	120.8 (4)
N1—C2—N3	115.8 (5)	C12—C13—C14	119.0 (5)
O—C4—N3	128.1 (4)	Cl—C14—C13	117.8 (4)
O—C4—C5	129.8 (4)	Cl—C14—C15	119.9 (4)
N3—C4—C5	102.2 (4)	C13—C14—C15	122.3 (5)
N1—C5—C4	109.2 (4)	C14—C15—C16	118.4 (5)
N1—C5—C6	129.6 (4)	C11—C16—C15	121.3 (4)
C4—C5—C6	121.2 (4)		

lengths and angles are normal (Table 2). There is no conjugation between the phenyl and thiohydantoin rings [C6—C11 bond length 1.460 (5)  $\text{\AA}$ ]. The five-membered thiazole ring has a half-chair conformation with the plane of symmetry going through C2 and bisecting the C7—C8 bond [asymmetry parameter (Griffin, Duax & Weeks, 1984)  $\Delta C_m = 1.4^\circ$ ]. The molecule of (2*p*) in the crystal is planar whereas in the structure of (1*o*) (N1-atom substituted) the angle between benzene and the thiohydantoin rings is large [34.3 (2) $^\circ$ ; Kwiatkowski *et al.*, 1991]. So, as for 5-benzylidenehydantoin derivatives (Drew, Mok, Ang & Tan, 1987*a,b,c*), the planarity of the molecules in the crystal depends on the substituent present at

atom N1 of the thiohydantoin (or hydantoin) ring. If a bulky substituent is present at N1, the angle increases in the crystallographic conformation of the molecule.

The presence of a substituent at N1 and the position of the substituent in the aromatic ring are important parameters in determining the minimum-energy conformation of the molecule (corresponding to a free molecule conformation). Therefore, we decided to perform a conformational analysis for *Z* isomers (the six molecules shown in the scheme) based on molecular mechanics calculations using the *MMX* program (Burkert & Allinger, 1982) with  $\pi$  overlap taken into account. The energy of the molecules was minimized for each  $10^\circ$  rotation from 0 to  $360^\circ$  about  $\varphi = \text{C12—C11—C6—C5}$  angles with torsion angles N1—C5—C6—C11 kept with values from the X-ray analyses [ $7^\circ$  for (1*o*), (1*p*) and (1*m*) and  $2^\circ$  for (2*o*), (2*p*) and (2*m*)]. The conformational analysis of (1*o*) and (2*p*) was initiated with the crystallographic geometry of the molecules. The remaining four molecules were generated from a respective basic molecule by moving the Cl substit-

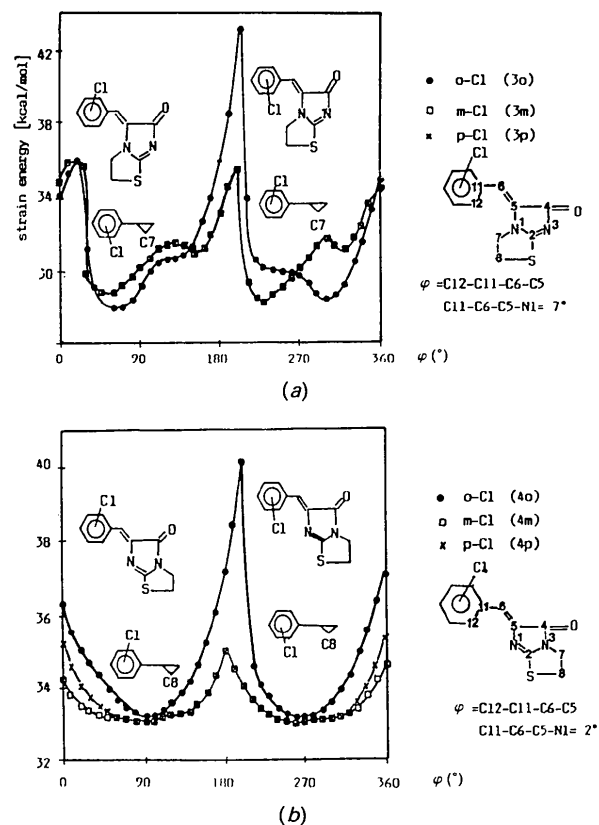


Fig. 2. Strain energy for *Z* isomers of (a) 1,2-dialkylated-5-(chloro)benzylidene-2-thiohydantoin and (b) 2,3-dialkylated-5-(chloro)benzylidene-2-thiohydantoin as a function of the torsion angle C12—C11—C6—C5.

uent to the desired position in the benzene ring. The results of the calculations are depicted in Figs. 2(a) and 2(b) for compounds (1) and (2), respectively.

Independent of the alkylation position, the general profiles of the  $E=f(\varphi)$  curves are similar in both diagrams. Therefore, the conformers corresponding to a planar arrangement of the benzene and thiohydantoin rings ( $\varphi$  about 0 and 180°) are in energy maxima. The two absolute minima-energy conformations are those in which the benzene ring is inclined to the thiohydantoin ring at almost 90° for all analyzed compounds. As is clearly visible, the effect of *para* and *meta* substitution is similar and both energy minima have similar heights. The heights of maxima in *ortho*-substituted compounds are different; those at  $\varphi$  about 180° being much greater. The corresponding planar arrangement of both molecules with an *ortho* substituent is especially unfavourable.

The differences in the conformational analysis results also depend on the dialkylation position (1,2- or 2,3-). The energy differences in 1,2-dialkylation products (Fig. 2a) are much bigger and also the positions of the extremes are slightly shifted in comparison with 2,3-analogues (Fig. 2b).

Summarizing, the energy differences between the conformers and the profiles of the curves suggest that the non-planar conformations for free molecules are preferred for all 1,2-dialkylated compounds. The *para* and *meta* substitutions in 2,3-dialkylated compounds generate no restrictions in the preferences of the conformations while for *ortho* substitution a planar molecule ( $\varphi = 180^\circ$ ) is not favoured. The planar conformation for (2*p*) in the solid state should therefore be a consequence of molecular packing in the crystal.

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## Structure of a Carcinogenic Agent: 1-Formyl-3-thiosemicarbazide

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**Abstract.** C<sub>2</sub>H<sub>6</sub>N<sub>3</sub>OS,  $M_r = 120.15$ , monoclinic,  $P2_1/c$ ,  $a = 7.261$  (1),  $b = 7.428$  (2),  $c = 9.589$  (2) Å,  $\beta = 98.62$  (1)°,  $V = 511.3$  (2) Å<sup>3</sup>,  $Z = 4$ ,  $D_m = 1.544$  (2),  $D_x = 1.560$  (2) Mg m<sup>-3</sup>,  $\lambda(\text{Cu } K\alpha) = 1.5418$  Å,  $\mu(\text{Cu } K\alpha) = 4.61$  mm<sup>-1</sup>,  $F(000) = 252$ ,  $T = 298$  K,  $R = 0.077$  for 946 observed reflections [ $I \geq 3\sigma(I)$ ]. The thiosemicarbazide moiety of the molecule is planar with N—C—N—N in a *cis* and S—C—N—N in a

*trans* conformation. The conformation of the thiosemicarbazide moiety is similar in thiosemicarbazide and its derivatives but is reversed in its metal complexes.

**Introduction.** Thiosemicarbazides, thiosemicarbazones, and their derivatives have shown metal-complexing ability in various oxidation states