An *X*-Ray Study of the Aromatic Ring–Dipole Interaction in Hydantoin Crystals

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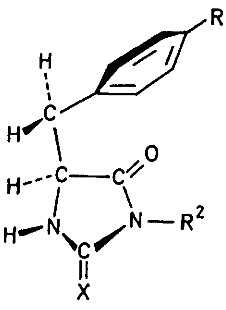
The *X*-ray crystal structures of 5-*p*-chlorobenzyl-3-(*o*-tolyl)hydantoin (1a) and 3-ethyl-5-*p*-hydroxybenzyl-2-thiohydantoin (1b) have been determined in order to explore aromatic ring–dipole interaction. A folded conformation with the aromatic ring over the amide region of the hydantoin was found in (1a) while in (1b) an extended conformation with the aromatic ring over a polar region of hydrogen bonds was found. The paper includes a description of the crystallographic solution of both compounds.

INTRAMOLECULAR attraction between aromatic rings and amide dipoles is evident in the proton and carbon-13 n.m.r. spectra of the hydantoin derivatives of aromatic α-amino acids.[1,2] In compounds containing a 5-benzyl or diphenylmethyl group there is evidence of substantial shielding of alkyl or aryl group in the 3-position. Over 35 hydantoins show evidence of a preferred folded conformation as long as there is a benzyl substituent in the 5-position. Those with a 5-phenyl or phenylethyl group do not show folding presumably, as models show, intramolecular shielding is geometrically impossible.



(1)

In order to investigate these effects in the solid phase two hydantoins (1a; $R^1 = Cl$, $X = O$, $R^2 =$ *o*-tolyl) and (1b; $R^1 = OH$, $X = S$, $R^2 = Et$) were chosen. Although several other derivatives were of potential interest, most compounds of type 1 yielded twinned or fine needle-shaped crystals.

EXPERIMENTAL

Single crystals of (1a) in the form of thin plates (0.1 mm × 0.1 mm × 0.005 mm) were obtained by slow evaporation of an acetone solution. The space group was determined to be $P2_1/c$ ($h0l$: $l = 2n + 1$ absent; $0k0$, $k = 2n + 1$ absent) from Weissenberg and precession photographs of a crystal mounted on the *b*-axis. A small crystal was mounted on a Syntex $P2_1$ diffractometer and the cell dimensions determined by centring 15 reflections in the range $20° \leqslant 2\theta \leqslant 25°$. Table 1 summarizes the cell properties of compound (1a). Integrated data was collected with monochromatic Mo-K_α radiation at a scan rate of 2°/min 3 standard reflections periodically being checked for alignment and crystal stability. There was no evidence of crystal decay over the 7 days used for data collection. Data collection was limited to the range $0 < 2\theta < 45°$ since there were few measureable reflections beyond $2\theta = 45°$. Of 2 007 collected reflections, 1 119 had intensities $I > 2\sigma$ and were classified as observed reflections.

TABLE 1

Crystal data for (1a)

Formula	$C_{17}H_{15}ClN_2O_2$
Molecular weight	314.77
Unit cell (Å)	
$a =$	12.985 ± 0.005
$b =$	7.633 ± 0.003
$c =$	17.035 ± 0.008
$\beta =$	$98.90 \pm 0.03°$
Space group	$P2_1/c$
$V =$	1 552.47 Å^3
Calculated density =	1.35 (g/cm^3)
Experimental density =	1.35

The structure was solved by direct methods using the phase program in the *X*-ray '72 system.[3] The entire molecule was visible in the first *E*-map. After 2 cycles of unweighted isotropic and one cycle of block-diagonal anisotropic refinement the agreement factor *R* † was 0.10. Further full-matrix least-squares refinement including hydrogen atoms and a weighting scheme ‡ reduced *w*R to 0.08.§ The atomic parameters are given in Table 2 using the numbering scheme shown in Figure 1.§ Bond distances and angles are listed in Table 3; observed *versus* calculated structure factors are deposited as part of the Supplementary publication.¶

Prismatic single crystals of (1b; $R = OH$, $X = S$, $R_2 = Et$) bound by 110, $1\bar{1}0$, $\bar{1}10$, $\bar{1}\bar{1}0$, 010, $0\bar{1}0$, were obtained upon recrystallization from ethanol–water. The space group was found to be $P2_1/c$ as determined from systematic absences on Weissenberg and precession photographs of a crystal mounted on the *b*-axis. There was one molecular per asymmetric unit. The cell parameters were measured on a manual *X*-ray diffractometer (GE/XRD-6) (see Table 4).

Data was collected photographically for the *h*0*l* to *h*7*l* layers using multiple film Weissenberg techniques (6 films) and Ni filtered Cu-K_α radiation. The intensity data along

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† $R = \dfrac{\Sigma||F_o| - |F_c||}{\Sigma|F_o|}$

‡ $1/w = \sigma^2 + 0.0025\ F_0{}^2$.

§ $wR = \Sigma w\Delta^2/w|F_{obs}|^2$.

¶ The calculated fractional co-ordinates for hydrogen atoms in (1a) assuming a C–H bond distance at 1 Å are deposited as part of Supplementary publication No. SUP 22475 (41 pp.). For details of the Supplementary Publications scheme see Notice to Authors No. 7, *J.C.S. Perkin II*, 1978, Index issue.

TABLE 2

Fractional co-ordinates for compound (1a). The e.s.d. of the last figure is indicated in parenthesis

Atom	*X*	*Y*	*Z*
N(1)	0.113 9(5)	−0.141 4(8)	0.053 2(3)
C(2)	0.084 3(6)	−0.036 4(11)	0.107 5(5)
O(2)	0.020 2(4)	0.089 4(7)	0.099 1(3)
N(3)	0.139 6(5)	−0.087 9(7)	0.182 0(3)
C(4)	0.201 1(6)	−0.237 3(10)	0.175 0(4)
O(4)	0.257 5(4)	−0.316 0(6)	0.228 7(3)
C(5)	0.192 4(6)	−0.278 7(9)	0.087(4)
C(6)	0.134 3(6)	−0.000 7(10)	0.256 5(5)
C(7)	0.183 3(6)	0.164 8(10)	0.268 7(5)
C(7A)	0.242 9(7)	0.247 1(11)	0.210 1(5)
C(8)	0.175 9(7)	0.243 1(10)	0.341 1(5)
C(9)	0.126 4(7)	0.162 9(13)	0.397 8(5)
C(10)	0.079 3(7)	−0.000 1(13)	0.383 6(5)
C(11)	0.082 8(6)	−0.081 4(10)	0.312 8(5)
C(12)	0.304 2(6)	−0.276 3(11)	0.056 8(5)
C(13)	0.368 3(6)	−0.110 5(11)	0.072 7(4)
C(14)	0.349 6(7)	0.030 5(14)	0.021 9(5)
C(15)	0.403 2(7)	0.186 5(13)	0.035 8(5)
C(16)	0.483 7(6)	0.201 7(10)	0.101 9(5)
C(17)	0.508 4(6)	0.065 0(12)	0.154 0(5)
C(18)	0.451 2(6)	−0.089 6(11)	0.138 8(4)
Cl(1)	0.556 0(2)	0.400 7(3)	0.121 8(1)

Thermal parameters and fractional co-ordinates for hydrogen atoms in (1a) are part of the Supplementary publication.

TABLE 3

(a) Bond distances for (1a). The e.s.d. of the last significant figure is in parentheses

Bond	Distance (Å)	Bond	Distance (Å)
N(1)–C(2)	1.314(10)	C(8)–C(9)	1.368(13)
N(1)–C(5)	1.471(9)	C(9)–C(10)	1.375(14)
C(2)–O(1)	1.228(10)	C(10)–C(11)	1.363(12)
C(2)–N(3)	1.395(9)	C(5)–C(12)	1.523(11)
N(3)–C(6)	1.444(10)	C(12)–C(13)	1.487(11)
N(3)–C(4)	1.378(10)	C(13)–C(14)	1.377(11)
C(4)–O(4)	1.212(9)	C(14)–C(15)	1.360(14)
C(4)–C(5)	1.512(11)	C(15)–C(16)	1.374(11)
C(6)–C(7)	1.398(11)	C(16)–C(17)	1.372(12)
C(6)–C(11)	1.362(11)	C(16)–Cl(1)	1.759(8)
C(7)–C(7A)	1.461(13)	C(17)–C(18)	1.372(12)
C(7)–C(8)	1.384(12)	C(18)–C(13)	1.395(10)

(b) Bond angles for (1a). The e.s.d. of the last significant figure is in parentheses

Bond	Angles (°)	Bond	Angles (°)
C(2)–N(1)–C(5)	112.6(6)	C(7A)–C(7)–C(8)	121.1(7)
N(1)–C(2)–O(2)	129.0(7)	C(7)–C(8)–C(9)	122.2(8)
N(1)–C(2)–N(3)	108.9(6)	C(8)–C(9)–C(10)	119.7(8)
O(2)–C(2)–N(3)	122.0(7)	C(9)–C(10)–C(11)	120.0(8)
C(2)–N(3)–C(4)	110.0(6)	C(6)–C(11)–C(10)	119.8(7)
C(2)–N(3)–C(6)	126.2(6)	C(5)–C(12)–C(13)	114.4(7)
N(3)–C(4)–O(4)	126.4(7)	C(12)–C(13)–C(14)	121.3(7)
N(3)–C(4)–C(5)	107.6(6)	C(12)–C(13)–C(18)	122.2(7)
O(4)–C(4)–C(5)	125.9(7)	C(14)–C(13)–C(18)	116.4(7)
N(1)–C(5)–C(4)	100.6(6)	C(13)–C(14)–C(15)	123.2(7)
N(1)–C(5)–C(12)	114.1(6)	C(14)–C(15)–C(16)	118.3(8)
C(4)–C(5)–C(12)	113.9(6)	C(15)–C(16)–C(17)	121.4(8)
N(3)–C(6)–C(7)	118.0(7)	Cl(1)–C(16)–C(15)	119.8(6)
N(3)–C(6)–C(11)	119.8(6)	Cl(1)–C(16)–C(17)	121.4(8)
C(7)–C(6)–C(11)	122.2(7)	C(16)–C(17)–C(18)	118.6(7)
C(6)–C(7)–C(7A)	122.2(7)	C(13)–C(18)–C(17)	121.9(7)
C(6)–C(7)–C(8)	116.1(7)		

the *a*-axis was collected for the 0*kl* to 2*kl* layers using another crystal measurement 0.3 mm × 0.1 mm × 0.1 mm. Optical densities were measured with an Optronics Optical Scanner interfaced to an Adage computer. The scan raster was set on a 50 μ grid but data was condensed to a 200 μ grid in the computer before recording on magnetic tape. Integrated data was extracted from the magnetic tape by using a locally modified version of R. H. Pearson's computer program [4] for Weissenberg films combined with a mapping program for determining the tilt and axial alignment parameters. The principal modification concerned using the disc on the PDP-10 computer as a direct access device for storing the film image. After data was collected within measurable ranges for each film, all the data for a layer was combined using a modified version of the Hamilton Sparks Program.[5] The data from various layers along the *a* and *b* axis were merged [5] to yield 1 929 reflections of which 1 182 were observed reflections with $I > 2\sigma$. The structure was solved manually by direct methods and the solution was then expanded using the tangent program in the *X*-ray 72 Program. All non-hydrogen atoms were located after two Fourier-structure factor cycles.

Two cycles of full-matrix anisotropic refinement with all the non-hydrogen atoms followed by 2 cycles of weighted refinement using a Hughes weighting scheme ($w = 1$ for $F_o < 4$ and $\sqrt{w} = 4/F_o$ for $F_o > 4$) reduced *wR* to 0.12.

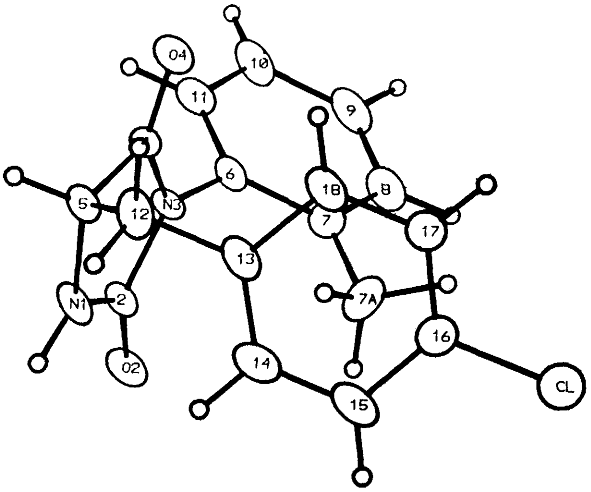


FIGURE 1 Numbering scheme and conformation of 3-(*o*-tolyl)-5-(*p*-chlorobenzyl)hydantoin (1a)

Hydrogen atom positions were calculated and after 2 further anisotropic refinement cycles with fixed hydrogen positions the final *wR* was 0.107. Atomic parameters are shown in Table 5 while structure factors and thermal parameters are deposited as part of the Supplementary publication; see footnote 91 on p. 659.

DISCUSSION

The bond distance and angles for (1a) as shown in Table 3 are within reasonable ranges for the type of bonding. It is evident that the folded structure for (1a) which was predicted from n.m.r. solution studies is also the form in the solid (Figure 1). In the solid there is no evidence of disorder and the methyl group is pointed toward the benzyl group. In solution the tolyl group is more mobile and exists in two conformations with the major conformer the same as that in the solid. The distance between the carbon atom of the *o*-methyl group in the 3-*N*-tolyl substituent and the plane of *p*-chloro-substituted benzyl ring at position 5 is 3.56 Å.

The *Z* and *P* co-ordinates [6] are 2.56 and 0.36 respectively which places the methyl in the shielding cone

TABLE 4

Crystal data for (1b)

Formula	$C_{12}H_{14}O_2N_2S$
Molecular weight	250.31
Unit cell	
a	5.488 (0.003) Å
b	15.705 (0.004)
c	14.865 (0.004)
β	101.45 (0.05)
V	1 297.98 Å
Space group $P2_1/c$	
Crystal density (g/cm³)	
Calculated (D_c)	1.31
Experimental (D_m)	1.31

TABLE 5

Fractional co-ordinates for (1b)

Atom	*x*	*y*	*z*
S(2)	−0.008 0(5)	0.083 9(2)	0.123 7(2)
C(2)	0.227 7(16)	0.018 2(5)	0.148 6(6)
N(3)	0.409 4(14)	0.206 4(5)	0.229 8(4)
C(4)	0.582 5(18)	−0.042 4(6)	0.229 0(6)
C(5)	0.521 0(18)	−0.088 1(6)	0.138 4(6)
N(1)	0.282 0(15)	−0.045 7(5)	0.098 2(5)
O(4)	0.753 3(13)	0.056 8(5)	0.292 9(4)
C(13)	0.423 7(20)	0.081 8(7)	0.302 4(6)
C(14)	0.311 8(26)	0.051 9(8)	0.381 8(8)
C(6)	0.504 4(19)	−0.182 0(6)	0.145 1(6)
C(7)	0.414 6(18)	−0.225 3(6)	0.054 9(6)
C(8)	0.537 5(18)	−0.218 1(7)	−0.019 0(6)
C(9)	0.455 6(18)	−0.256 5(6)	−0.100 8(6)
C(10)	0.234 2(18)	−0.306 9(6)	−0.115 2(5)
C(11)	0.111 7(18)	−0.314 2(7)	−0.042 1(6)
C(12)	0.198 7(18)	−0.275 0(6)	0.040 4(6)
O(10)	0.156 5(13)	−0.342 8(5)	−0.197 9(4)
H(2)	−0.667 7	−0.074 4	0.102 3
H(1)	0.162 3	−0.067 3	0.034 8
H(3)	0.612 9	0.098 5	0.329 2
H(4)	0.327 6	0.139 7	0.274 8
H(5)	0.119 4	0.034 6	0.355 7
H(6)	0.320 8	0.096 0	0.435 7
H(7)	0.404 7	0.006 7	0.410 1
H(8)	0.344 1	−0.196 7	0.189 7
H(9)	0.344 1	−0.196 7	0.189 7
H(10)	0.706 2	−0.182 1	−0.008 0
H(11)	0.552 3	−0.247 2	−0.156 3
H(12)	−0.056 4	−0.350 8	−0.051 6
H(13)	0.106 3	−0.281 7	0.095 2

TABLE 6

Least-square planes for compound (1a). The coefficients are the direction cosine relative to *a*, *b*, and *c**

o-Tolyl

$$9.811X - 3.245Y + 4.599Z = 2.525$$

Distance from mean plane

C(6)	−0.007 Å	C(9)	0.011 Å
C(7)	−0.010	C(10)	0.016
C(7A)	0.021	C(11)	−0.01
C(8)	0.025		

5-Benzyl

$$-9.593X + 2.434Y + 10.977Z = -2.984$$

C(12)	0.014 Å	C(16)	−0.006 Å
C(13)	0.009	C(17)	−0.001
C(14)	−0.028	C(18)	−0.012
C(15)	0.015	Cl(19)	0.008

Hydantoin ring

$$9.688X + 4.517Y - 3.543Z = 0.276$$

N(1)	−0.005 Å	C(5)	−0.013 Å
C(2)	0.002	O(4)	−0.014
O(2)	0.015	C(5)	0.013
N(3)	0.032		

TABLE 7

(a) Bond distances for compound (1b)

Bond	Distance	Bond	Distance
S(2)–C(2)	1.61(2)	C(6)–C(7)	1.50(3)
C(3)–N(3)	1.40(4)	C(7)–C(8)	1.40(3)
N(3)–C(4)	1.32(1)	C(8)–C(9)	1.35(2)
C(4)–C(5)	1.50(2)	C(9)–C(10)	1.42(2)
C(5)–N(1)	1.37(1)	C(10)–C(11)	1.39(3)
C(4)–O(4)	1.21(4)	C(11)–C(12)	1.37(3)
N(3)–C(13)	1.44(1)	C(7)–C(12)	1.39(2)
C(13)–C(14)	1.51(3)	C(10)–O(2)	1.34(2)
C(5)–C(6)	1.48(1)		

(b) Bond angles for compound (1b)

Bond	Angles	Bond	Angles
S(2)–C(2)–N(3)	124.5(0.6)	C(5)–C(6)–C(7)	113.9(0.7)
S(2)–C(2)–N(1)	127.3(0.6)	C(5)–C(6)–C(8)	110.0(0.8)
N(3)–C(2)–N(1)	108.1(0.7)	C(5)–C(6)–C(9)	107.0(0.7)
N(1)–C(4)–O(4)	110.0(0.7)	C(6)–C(7)–C(8)	122.9(0.9)
N(3)–C(4)–C(5)	123.5(0.8)	C(6)–C(7)–C(12)	120.6(0.9)
O(4)–C(4)–C(5)	123.8(0.7)	C(8)–C(7)–C(12)	116.5(0.8)
C(5)–N(1)–C(2)	125.5(0.8)	C(8)–C(9)–C(10)	120.2(0.9)
C(2)–N(3)–C(4)	110.0(0.7)	C(7)–C(8)–C(9)	123.1(0.9)
C(2)–N(3)–C(13)	123.5(0.8)	C(9)–C(10)–C(11)	116.9(0.8)
C(4)–N(3)–C(13)	123.8(0.7)	C(9)–C(10)–O(2)	118.3(0.8)
C(4)–C(5)–N(1)	99.6(0.7)	C(11)–C(10)–O(2)	124.7(0.9)
C(6)–C(5)–N(1)	114.5(0.8)	C(7)–C(12)–C(11)	121.4(0.9)
N(3)–C(13)–C(14)	114.5(0.9)	C(10)–C(11)–C(12)	121.9(0.9)

TABLE 8

Least-square planes for (1b)

The coefficients are the direction cosine relative to *a*, *b*, and *c**
Asterisk denote atoms defining the planes

Aromatic ring

$$-0.4816x + 0.8103 - 0.3273z - 4.2080 = 0$$

Distance from the plane (Å)

C(7) *	0.001	C(11) *	−0.001
C(8) *	−0.001	C(12) *	−0.002
C(9) *	0.002	O(10)	0.023
C(10) *	−0.001		

Thiohydantoin ring

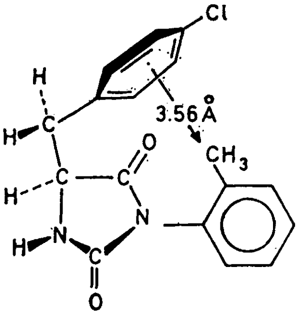
$$0.6431x + 0.6228y - 0.0446z - 0.2636 = 0$$

Asterisk denote atoms defining the plane

Distance from the plane (Å)

S(2)	0.015	C(4) *	0.003
C(2) *	0.005	C(5)	0.098
N(3) *	−0.005	O(4) *	0.003

of the phenyl ring. Calculations of the *Z* and *P* co-ordinates from the solution n.m.r. data yielded values of 2.50 and 1.00 respectively. The two aromatic rings



and the five-membered hydantoin ring in compound (1a) are essentially planar, as is shown in Table 8. The torsional angle between the *ortho*-tolyl ring and the hydantoin ring is 68.6°. Thus the results from solid and solution are in reasonable agreement. There is also an intermolecular hydrogen bond between the amide proton on N(1) and the carbonyl oxygen O(2) of length 2.83 Å (see Figure 2).

Somewhat surprisingly, the conformation of (1b) (Figure 3) has an extended rather than the folded form expected from the solution n.m.r. data. The bond distances and angles are all in the normal ranges and are shown in Table 7. The molecular packing diagram of (1b) is also shown in Figure 4. The aromatic ring is essentially planar. However, the C(5) atom in the thiohydantoin ring is 0.1 Å above the plane formed by C(2)-N(3)-C(4)-N(1). The equations for the mean planes in (1b) are given in Table 8.

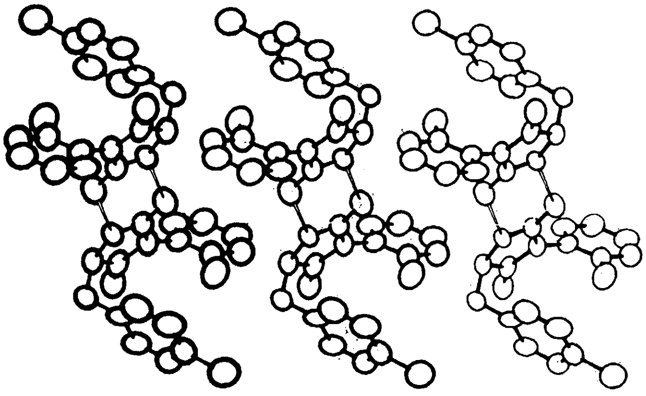


FIGURE 2 Hydrogen bonding in compound (1a)

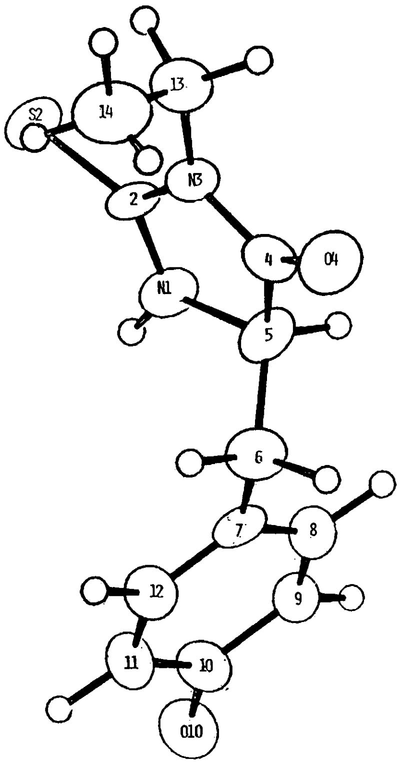


FIGURE 3 Numbering scheme and conformation of 3-ethyl-5-(*p*-hydroxybenzyl)hydantoin (1b)

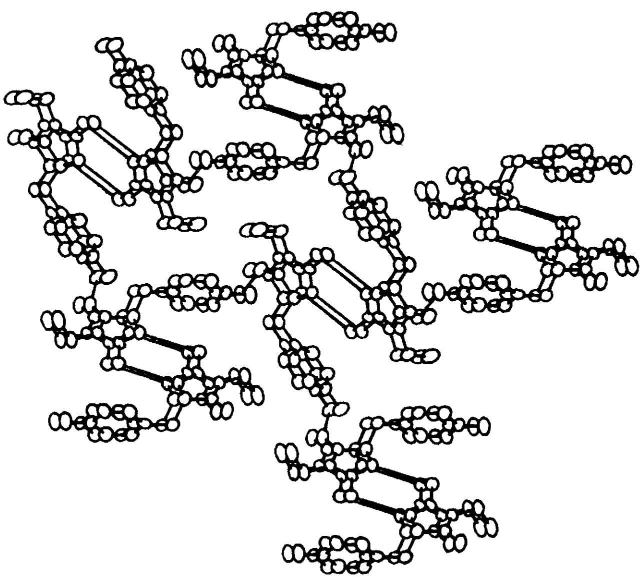


FIGURE 4 Hydrogen bonding in compound (1b)

The torsional angle associated with C(7)-C(6) C(5)-N(1) is 59.2° which is compatible with a *gauche* configuration and an unfolded structure. The torsional angle C(4)-N(1)—C(13)-C(14) is 84.5° and thus nearly perpendicular to this hydantoin ring. The C(8)-C(7)—C(6)-C(5) torsional angle of 59.9° is an indication of a less-stable eclipsed configuration between the phenyl ring and the benzyl proton H(8) (see Figure 5) which may be the result of non-bonded attraction between the aromatic ring and an intermolecular hydrogen bond N(1)-H(1) · · · S=C(2) of 3.39 Å (Figure 6). The solid structure of the simple 2-thiohydantoin [7] does not show -NH · · · S=C hydrogen bonds.

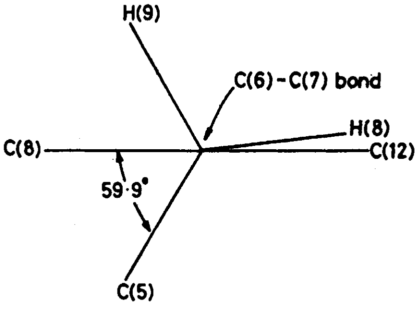


FIGURE 5 View along the C(6)-C(7) bond showing the eclipsed conformation of H(8) and C(12)

The most interesting feature of this molecule is that the hydrogen bonding site -NH · · · S=C faces the aromatic ring (see Figure 6). The distances from the phenyl plane are 2.52, 2.75, 3.50 Å for N(1), H(1), and S(2). The S · · · N axis is 17° from the axis of the aromatic ring. The polarized π-electrons of the aromatic ring may have an attraction for the hydrogen bond. This preference of the phenyl ring for the polar regions of the crystal structure has important implications for the maintenance of the preferred conformation in aromatic rings containing peptides and proteins. The effect has also been observed in other systems such as diketopiperazines,[8-11] and DL-peptides.[12-15] An n.m.r. study of hypothalamic thyrotropin releasing factor suggested similar effects due to the imidazole ring in histidine.[16]

The crystal structure of (1b) also has another intermolecular hydrogen bond –OH ··· O=C, 2.685 Å (Figure 4). This intermolecular hydrogen bond could cause the phenyl ring to assume an extended conformation in the solid rather than the folded conformation evidence by ^{1}H n.m.r. and ^{13}C n.m.r. solution studies.

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