N1—C5—C10	133.8 (2)	C16—N15—S2	126.2 (2)
C13—C10—C5	117.5 (2)	C21—C16—C17	122.5 (2)
C13—C10—C24	110.8 (2)	C17—C16—N15	107.1 (2)
C5—C10—C24	109.0 (2)	C18—C17—C16	118.5 (2)
C13—C10—C11	109.1 (2)	C16—C17—C13	107.8 (2)
C5—C10—C11	98.5 (2)	C20—C21—C16	117.3 (2)
C24—C10—C11	111.4 (2)	C26—C25—S1	119.6 (2)
C12—C11—C10	110.2 (2)	C30—C25—S1	118.8 (2)
C4—C12—C23	112.2 (2)	C32—C31—C36	120.5 (3)
C4—C12—C22	110.7 (2)	C36—C31—S2	120.1 (2)
C23—C12—C22	109.9 (2)		
O1—S1—N1—C2	158.0 (2)	C12—C4—C5—C10	−5.2 (2)
O2—S1—N1—C2	28.0 (2)	C5—C10—C11—C12	−16.8 (2)
C25—S1—N1—C2	−87.0 (2)	C3—C4—C12—C22	−56.6 (3)
N1—S1—C25—C26	53.6 (2)	C3—C4—C12—C23	66.6 (3)
O3—S2—N15—C16	−171.5 (2)	C11—C10—C13—C14	−114.8 (2)
O4—S2—N15—C16	−41.5 (2)	C10—C13—C14—N15	172.9 (2)
C31—S2—N15—C16	73.3 (2)	N1—C5—C10—C24	59.0 (2)
N15—S2—C31—C32	87.0 (2)	N1—C5—C10—C11	175.2 (2)

For both compounds, data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CELSIUS* (Svenson, 1974); data reduction: *CORINC* (Dräger & Gattow, 1971; Wiehl & Schollmeyer, 1994). Program(s) used to solve structures: *SHELXS86* (Sheldrick, 1990) for (1); *SIR92* (Altomare *et al.*, 1994) for (2). For both compounds, program(s) used to refine structures: *SHELXL93* (Sheldrick, 1993); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: CF1009). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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A Thyrotropin-Releasing Hormone Analogue: pGlu-Phe-D-Pro-Ψ [CN_4]-NMe at 293 and 107 K

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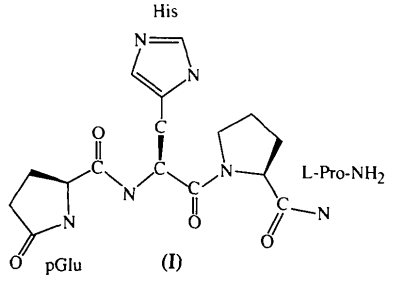
Abstract

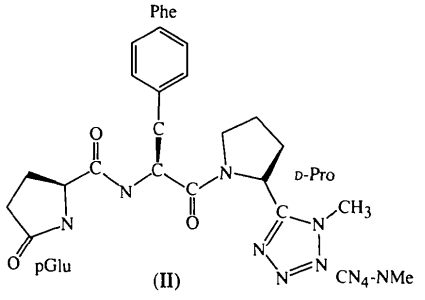
Data have been measured at two temperatures, 293 K and 107 K, for a crystal of a thyrotropin-releasing hormone analogue, pGlu-Phe-D-Pro-Ψ[CN_4]-NMe, $C_{20}H_{25}N_7O_3$, and the structures solved and refined. The tripeptide contains a tetrazole ring which mimics a *cis*-peptide bond at the C terminus. An intermolecular hydrogen bond exists between two molecules related by the twofold screw axis, resulting in infinite chains of hydrogen-bonded peptide molecules. Because of the folding and packing of the molecules, there are no intermolecular contacts of less than 4 Å to the N atom of the phenylalanine residue.

Comment

The title compound was prepared by solution methods in an ongoing evaluation of the 1,5-disubstituted tetrazole ring as a surrogate for *cis*-amide bonds (Marshall, Humblet, Van Opdenbosch & Zabrocki, 1981;

Zabrocki, Smith, Dunbar, Iijima & Marshall, 1988; Smith, Zabrocki, Flak & Marshall, 1991; Zabrocki, Dunbar, Marshall, Toth & Marshall, 1992). The conformation of the peptide backbone is all *trans*. The tetrazole ring mimics a *cis*-peptide bond for atoms CA3—C3—N4—CA4. The proline residue has a D configuration with φ values of 125.9 and 124.6° for the 293 and 107 K structures, respectively. Schematic diagrams of the thyrotropin-releasing hormone, (I), and the analogue described in this paper, (II), are illustrated below.





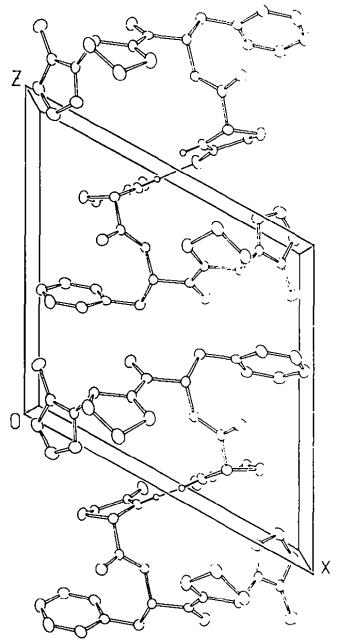


Fig. 1. Packing diagram for the 107 K structure showing the hydrogen-bond network. The packing of the molecules in the two structures is identical.

The refined N—H distances range from 0.835 to 0.861 Å, and 0.838 to 0.895 Å, while the C—H distances range from 0.889 to 1.012 Å, and 0.890 to 1.013 Å, for the 293 and 107 K structures, respectively. A complete listing of bond distances is provided in the supplementary material. No intramolecular hydrogen bonds exist and only the pGlu residue participates in the intermolecular hydrogen-bonding scheme. The H atom of N1 is donated to a symmetry-related carbonyl O atom (OE1) and because of the presence of the twofold screw axis, infinite chains of hydrogen-bonded peptide molecules are produced parallel to the *b* axis, as illustrated in Fig. 1. Donor–acceptor hydrogen-bond distances are 2.809 (2) and 2.803 (2) Å, and hydrogen–acceptor distances are 1.952 (15) and 1.912 (18) Å for the 273 and 107 K structures, respectively; the respective *D*—H···*A* angles are 174.5 (14) and 173.7 (16)°.

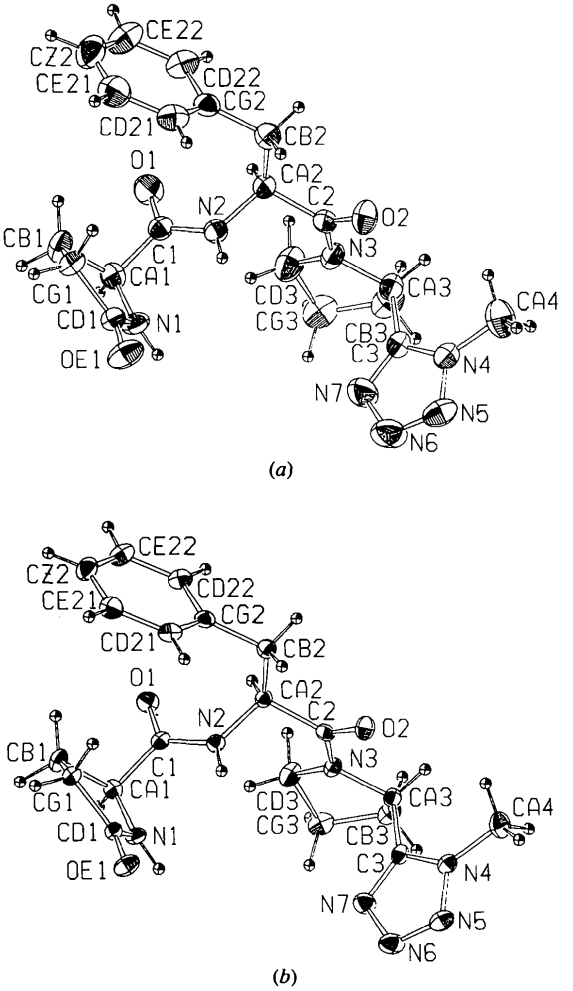


Fig. 2. *ORTEP*II drawings (Johnson, 1976) of the (*a*) 293 K and (*b*) 107 K structures with all non-H atoms labelled. Displacement ellipsoids are drawn at 50% probability, and H atoms have been assigned an isotropic temperature factor of 1.0 $Å^2$ for clarity.

An unusual situation exists in that the N atom of the phenylalanine residue does not participate in any hydrogen bonding. It makes no intramolecular contacts to a potential hydrogen-bond acceptor and the shortest distance to a symmetry-related molecule is 3.98 Å (*CD*3 of proline).

The largest r.m.s. deviation of an atom from the least-squares planes defining the phenylalanine and tetrazole rings is 0.005 at 293 K and 0.003 Å at 107 K. *ORTEP*II drawings (Johnson, 1976) of the 293 and 107 K structures are illustrated in Fig. 2.

Experimental

Single crystals of the thyrotropin-releasing hormone analogue pGlu-Phe-D-Pro-Ψ[CN_4]-NMe were grown by slow evaporation of ethanol. The same crystal was used to collect both sets of data at 293 and 107 K.

Compound at 293 K

Crystal data

$C_{20}H_{25}N_7O_3$	Mo $K\alpha$ radiation
M_r = 411.47	λ = 0.71069 Å
Monoclinic	Cell parameters from 49 reflections
$P2_1$	θ = 9.96–14.05°
a = 13.464 (1) Å	μ = 0.0905 mm^{-1}
b = 6.225 (1) Å	T = 293 K
c = 13.476 (1) Å	Plate
β = 118.52°	0.6 × 0.4 × 0.08 mm
V = 992.2 (1) Å^3	Colorless
Z = 2	
D_x = 1.377 Mg m^{-3}	

Data collection

Syntex $P3$ diffractometer	θ_{max} = 32.48°
$\theta/2\theta$ scans	$h = -20 \rightarrow 17$
Absorption correction: none	$k = 0 \rightarrow 9$
5758 measured reflections	$l = 0 \rightarrow 20$
3901 independent reflections	6 standard reflections monitored every 60 reflections
3901 observed reflections	intensity decay: 2%
R_{int} = 0.016	

Refinement

Refinement on F	$(\Delta/\sigma)_{max}$ = 0.06
R = 0.057	$\Delta\rho_{max}$ = 0.614 e Å^{-3}
wR = 0.034	$\Delta\rho_{min}$ = −0.436 e Å^{-3}
S = 1.653	Extinction correction: none
3901 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
370 parameters	
All H-atom parameters refined	
$w = 1/\sigma^2(F)$	

Compound at 107 K

Crystal data

$C_{20}H_{25}N_7O_3$	Mo $K\alpha$ radiation
M_r = 411.47	λ = 0.71069 Å
Monoclinic	Cell parameters from 49 reflections
$P2_1$	θ = 9.96–14.05°
a = 13.397 (1) Å	μ = 0.0926 mm^{-1}
b = 6.171 (1) Å	T = 107 K
c = 13.331 (1) Å	Plate
β = 118.44 (1)°	0.6 × 0.4 × 0.08 mm
V = 969.1 (3) Å^3	Colorless
Z = 2	
D_x = 1.410 Mg m^{-3}	

Data collection

Syntex $P3$ diffractometer	θ_{max} = 27.49°
$\theta/2\theta$ scans	$h = -17 \rightarrow 15$
Absorption correction: none	$k = 0 \rightarrow 8$
3042 measured reflections	$l = 0 \rightarrow 17$
2440 independent reflections	6 standard reflections monitored every 60 reflections
2440 observed reflections	intensity decay: <1%
R_{int} = 0.023	

Refinement

Refinement on F	$(\Delta/\sigma)_{max}$ = 0.05
R = 0.033	$\Delta\rho_{max}$ = 0.550 e Å^{-3}
wR = 0.032	$\Delta\rho_{min}$ = −0.410 e Å^{-3}
S = 1.828	Extinction correction: none
2440 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
370 parameters	
All H-atom parameters refined	
$w = 1/\sigma^2(F)$	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *at* 293 *and* 107 K

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
293 K				
N1	0.38806 (12)	0.3552	−0.10802 (11)	0.0339 (5)
*CA*1	0.30619 (13)	0.1991 (4)	−0.18180 (13)	0.0309 (6)
*CB*1	0.19348 (14)	0.3249 (4)	−0.23223 (18)	0.0394 (7)
*CG*1	0.22868 (13)	0.5598 (4)	−0.21487 (14)	0.0330 (6)
*CD*1	0.34935 (12)	0.5573 (4)	−0.12122 (13)	0.0311 (6)
*OE*1	0.40382 (10)	0.7143 (4)	−0.06772 (11)	0.0505 (5)
C1	0.32875 (12)	0.1112 (4)	−0.27443 (12)	0.0287 (5)
O1	0.27076 (10)	−0.0340 (3)	−0.33542 (10)	0.0427 (5)
N2	0.41506 (10)	0.2001 (4)	−0.28442 (10)	0.0298 (5)
*CA*2	0.44294 (12)	0.1336 (4)	−0.37231 (12)	0.0295 (6)
*CB*2	0.39539 (14)	0.2859 (4)	−0.47334 (15)	0.0395 (7)
*CG*2	0.27086 (13)	0.3248 (4)	−0.51944 (13)	0.0330 (6)
*CD*21	0.23130 (16)	0.5162 (4)	−0.49868 (16)	0.0432 (8)
*CE*21	0.11636 (18)	0.5472 (5)	−0.53617 (18)	0.0511 (9)
*CZ*2	0.04014 (17)	0.3888 (5)	−0.59553 (18)	0.0542 (9)
*CE*22	0.07853 (16)	0.1995 (5)	−0.61815 (18)	0.0556 (8)
*CD*22	0.19268 (15)	0.1672 (4)	−0.58053 (15)	0.0447 (7)
C2	0.57183 (12)	0.1101 (4)	−0.31993 (13)	0.0314 (6)
O2	0.62785 (9)	0.2380 (3)	−0.34166 (11)	0.0461 (5)
N3	0.61945 (10)	−0.0563 (4)	−0.24992 (11)	0.0348 (5)
*CA*3	0.74122 (14)	−0.0981 (4)	−0.20287 (15)	0.0368 (7)
*CB*3	0.75192 (16)	−0.3319 (4)	−0.1637 (2)	0.0495 (8)
*CG*3	0.65971 (18)	−0.3571 (5)	−0.13085 (19)	0.0504 (9)
*CD*3	0.56297 (16)	−0.2251 (5)	−0.2181 (2)	0.0517 (9)
C3	0.81055 (13)	0.0515 (4)	−0.10825 (14)	0.0333 (6)
N5	0.94282 (12)	0.2779 (4)	−0.00248 (13)	0.0480 (6)
N6	0.88790 (14)	0.2176 (4)	0.04932 (13)	0.0577 (8)
N7	0.80511 (14)	0.0759 (4)	−0.01431 (13)	0.0523 (7)
N4	0.89425 (10)	0.1749 (4)	−0.10261 (11)	0.0355 (5)
*CA*4	0.93656 (**22**)	0.2020 (6)	−0.1828 (2)	0.0615 (12)

107 K				
N1	0.38697 (13)	0.3552	−0.10768 (12)	0.0178 (5)
CA1	0.30434 (14)	0.1973 (4)	−0.18197 (14)	0.0167 (6)
CB1	0.19123 (15)	0.3247 (4)	−0.23200 (17)	0.0205 (7)
CG1	0.22704 (14)	0.5626 (4)	−0.21723 (15)	0.0177 (6)
CD1	0.34819 (14)	0.5604 (4)	−0.12187 (14)	0.0163 (6)
OE1	0.40287 (10)	0.7188 (4)	−0.06859 (11)	0.0255 (5)
C1	0.32729 (13)	0.1103 (4)	−0.27595 (14)	0.0156 (6)
O1	0.26817 (11)	−0.0339 (3)	−0.33878 (10)	0.0217 (5)
N2	0.41509 (11)	0.1986 (4)	−0.28488 (12)	0.0164 (5)
CA2	0.44347 (13)	0.1305 (4)	−0.37320 (13)	0.0160 (6)
CB2	0.39616 (15)	0.2849 (4)	−0.47536 (15)	0.0206 (7)
CG2	0.27078 (15)	0.3240 (4)	−0.52140 (14)	0.0185 (6)
CD21	0.23140 (16)	0.5166 (4)	−0.49920 (15)	0.0221 (7)
CE21	0.11606 (16)	0.5478 (4)	−0.53612 (16)	0.0253 (7)
CZ2	0.03898 (16)	0.3865 (4)	−0.59659 (17)	0.0275 (8)
CE22	0.07762 (16)	0.1947 (5)	−0.62011 (16)	0.0277 (7)
CD22	0.19240 (15)	0.1632 (4)	−0.58300 (15)	0.0230 (7)
C2	0.57290 (14)	0.1076 (4)	−0.31992 (14)	0.0170 (6)
O2	0.62988 (10)	0.2381 (3)	−0.34071 (11)	0.0231 (5)
N3	0.62002 (11)	−0.0612 (4)	−0.24932 (12)	0.0176 (5)
CA3	0.74227 (15)	−0.1038 (4)	−0.20133 (15)	0.0185 (6)
CB3	0.75314 (15)	−0.3390 (4)	−0.16128 (17)	0.0244 (7)
CG3	0.65914 (17)	−0.3628 (4)	−0.12827 (18)	0.0260 (7)
CD3	0.56169 (15)	−0.2333 (4)	−0.22006 (17)	0.0252 (7)
C3	0.81194 (14)	0.0481 (4)	−0.10585 (15)	0.0177 (6)
N5	0.94432 (13)	0.2770 (4)	−0.00040 (13)	0.0242 (6)
N6	0.89088 (13)	0.2145 (4)	0.05397 (13)	0.0279 (6)
N7	0.80763 (13)	0.0710 (4)	−0.00956 (13)	0.0258 (6)
N4	0.89471 (11)	0.1744 (4)	−0.10155 (12)	0.0182 (5)
CA4	0.93568 (18)	0.2036 (5)	−0.18413 (18)	0.0294 (8)

Table 2. *Selected geometric parameters* (Å, °) *at* 293 *and* 107 K

	293 K	107 K
CA1—N1	1.450 (2)	1.453 (2)
N1—CD1	1.340 (2)	1.347 (2)
CD1—OE1	1.228 (3)	1.225 (3)
CD1—CG1	1.508 (2)	1.512 (2)
CG1—CB1	1.520 (3)	1.528 (3)
CB1—CA1	1.547 (3)	1.548 (3)
CA1—C1	1.521 (3)	1.523 (3)
C1—O1	1.221 (3)	1.220 (3)
C1—N2	1.351 (3)	1.352 (2)
N2—CA2	1.463 (3)	1.461 (3)
CA2—CB2	1.526 (3)	1.530 (3)
CB2—CG2	1.504 (2)	1.508 (3)
CG2—CD21	1.387 (3)	1.389 (3)
CD21—CE21	1.393 (3)	1.394 (3)
CE21—CZ2	1.372 (4)	1.384 (3)
CZ2—CE22	1.378 (4)	1.386 (4)
CE22—CD22	1.384 (3)	1.387 (3)
CD22—CG2	1.386 (3)	1.393 (3)
CA2—C2	1.537 (2)	1.526 (2)
C2—O2	1.224 (3)	1.228 (3)
C2—N3	1.340 (3)	1.343 (3)
N3—CD3	1.476 (4)	1.477 (3)
CD3—CG3	1.514 (3)	1.523 (3)
CG3—CB3	1.513 (4)	1.526 (4)
CB3—CA3	1.531 (4)	1.529 (4)
CA3—N3	1.471 (2)	1.471 (2)
CA3—C3	1.492 (3)	1.496 (3)
C3—N4	1.336 (3)	1.334 (3)
N4—CA4	1.452 (4)	1.456 (3)
N4—N5	1.348 (2)	1.345 (2)
N5—N6	1.291 (3)	1.296 (3)
N6—N7	1.357 (3)	1.358 (3)
N7—C3	1.311 (3)	1.320 (3)
CA1—N1—CD1	114.7 (1)	114.6 (1)
N1—CD1—OE1	125.7 (1)	125.8 (2)
N1—CD1—CG1	108.4 (1)	108.3 (1)
OE1—CD1—CG1	125.9 (1)	125.9 (2)
CD1—CG1—CB1	104.5 (1)	104.2 (2)
CG1—CB1—CA1	104.5 (2)	104.5 (2)
CB1—CA1—N1	103.1 (1)	103.0 (1)
CB1—CA1—C1	111.1 (1)	111.4 (2)
N1—CA1—C1	114.8 (1)	114.2 (1)
CA1—C1—O1	120.3 (1)	120.2 (2)
CA1—C1—N2	116.9 (1)	117.1 (2)
O1—C1—N2	122.7 (1)	122.8 (2)
C1—N2—CA2	122.0 (1)	121.7 (2)
N2—CA2—CB2	112.7 (1)	112.4 (2)
N2—CA2—C2	109.0 (1)	108.9 (2)
CB2—CA2—C2	111.7 (1)	111.5 (2)
CA2—CB2—CG2	112.2 (2)	111.8 (2)
CB2—CG2—CD21	121.0 (2)	120.8 (2)
CG2—CD21—CE21	120.9 (2)	120.9 (2)
CD21—CE21—CZ2	120.3 (2)	120.0 (2)
CE21—CZ2—CE22	119.2 (2)	119.4 (2)
CZ2—CE22—CD22	120.8 (2)	120.6 (2)
CE22—CD22—CG2	120.7 (2)	120.5 (2)
CD22—CG2—CD21	118.2 (2)	118.6 (2)
CD22—CG2—CB2	120.8 (2)	120.5 (2)
CA2—C2—O2	121.2 (1)	121.4 (2)
O2—C2—N3	121.9 (1)	122.1 (2)
CA2—C2—N3	116.9 (1)	116.5 (2)
C2—N3—CA3	120.0 (1)	119.9 (2)
C2—N3—CD3	128.0 (2)	127.7 (2)
N3—CA3—CB3	102.6 (2)	102.9 (2)
CA3—CB3—CG3	104.1 (2)	103.8 (2)
CB3—CG3—CD3	103.8 (2)	103.1 (2)
CG3—CD3—N3	103.9 (2)	103.3 (2)
CD3—N3—CA3	111.8 (2)	112.1 (2)
N3—CA3—C3	111.8 (2)	111.8 (2)
CB3—CA3—C3	112.4 (2)	112.4 (2)
CA3—C3—N4	125.0 (2)	124.9 (2)
CA3—C3—N7	126.6 (2)	126.6 (2)
C3—N4—CA4	130.1 (2)	130.2 (2)
CA4—N4—N5	121.0 (2)	121.0 (2)
C3—N4—N5	108.9 (1)	108.8 (2)
N4—N5—N6	105.9 (1)	106.2 (2)
N5—N6—N7	110.9 (2)	110.7 (2)
N6—N7—C3	106.1 (2)	105.8 (2)
N7—C3—N4	108.2 (1)	108.4 (2)

The variance of each structure factor was calculated according to the method of Blessing (1987). The structure was solved in each case by direct methods using *MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Following anisotropic refinement of all non-H atoms by full-matrix least squares, minimizing $\Sigma w(F_o-F_c)^2$, the positions of all protons were determined from a difference map. Positional parameters were refined for all atoms; anisotropic displacement parameters were refined for all non-H atoms while isotropic displacement parameters were refined for all H atoms. A $\delta(R)$ plot was calculated for both data sets and was linear (Howell & Smith, 1992). The slope and intercept of the least-squares line were calculated to be 1.558 and 0.1729, respectively, for the 293 K data and 1.682 and 0.0441, respectively, for the 107 K data. Minimum and maximum difference peaks were reported as the fraction of a peak corresponding to an H atom which had been excluded from the structure-factor calculation. The appearance of the final difference maps were similar in many respects to maps obtained from highly accurate electron-density studies.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1090). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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trans-3-(*p*-Chlorophenylthio)-1,4,6-trimethylpiperazine-2,5-dione

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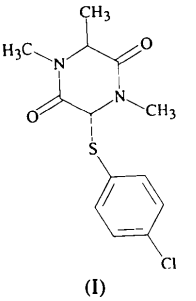
Abstract

The title compound, $C_{13}H_{15}ClN_2O_2S$, assumes a shallow boat conformation where the methyl and 4-chlorothiophenyl substituents in the α-positions are situated *trans* to one another, and the latter is folded across the piperazinedione ring.

Comment

As part of our continuing studies on piperazinediones (Chai & Page, 1993; Chai, King & Hockless, 1995), the structure of the title compound (I) was undertaken to establish the relative stereochemistry of the substituents at the C^{α} positions. The crystal structure reveals a shallow boat conformation [$\beta = -10.95°$ in the Hooker notation, defined as the dihedral angle between the two amide planes C(3)—C(2)—N(1)—C(6) and C(3)—N(4)—C(5)—C(6)] (Hooker, Bayley, Radding & Schellman, 1974) with the thiophenyl ligand occupying a pseudo-axial position, and the methyl C atom pseudo-equatorial.



(I)

Conformational parameters (in accord with the IUPAC–IUB Commission on Biochemical Nomenclature, 1970) were calculated as follows: ω_1 [C(3)—C(2)—N(1)—C(6)] = 8.1 (4), ψ_1 [N(1)—C(6)—C(5)—N(4)] = 5.5 (3), φ_1 [C(2)—N(1)—C(6)—C(5)] = 0.0 (4), ω_2 [C(6)—C(5)—N(4)—C(3)] = −20.1 (3), ψ_2 [N(4)—C(3)—C(2)—N(1)] = −20.8 (3), φ_2 [C(5)—N(4)—C(3)—C(2)] = 27.7 (3)°. Although bond lengths and angles are generally as expected, the significant differences in equivalent torsion angles suggest a substantial twist in conformation, which presumably reflects some flexibility in the molecule, enabling it to rotate and deform in order to minimize any unfavourable intramolecular interactions. Like other compounds of this type containing phenyl substituent side chains

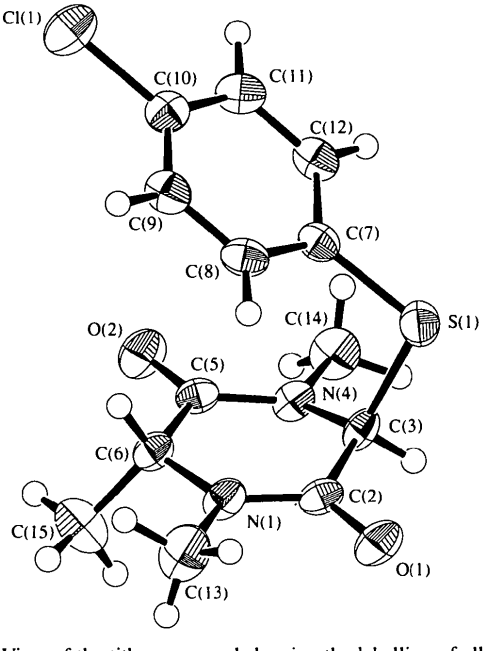


Fig. 1. View of the title compound showing the labelling of all non-H atoms. Displacement ellipsoids are shown at 50% probability levels. H atoms are drawn as circles of arbitrary radii.