

Article

Temperature-Dependent Ordering of the Methyl Group in the Crystal Structure of 5-(2-Chlorophenyl)-7-ethyl-1*H*-thieno [2,3-*E*][1,4]diazepin-2(3*H*)-one

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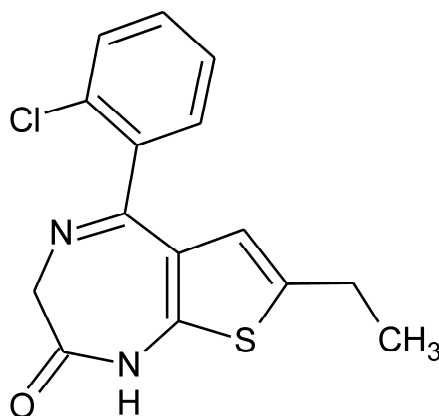
Abstract: 5-(2-Chlorophenyl)-7-ethyl-1*H*-thieno[2,3-*e*][1,4]diazepin-2(3*H*)-one, a close analogue of clotiazepam (full agonist at GABA receptor), crystallizes in monoclinic $P2_1/c$ space group with $a = 15.6941(6)$ Å, $b = 10.7909(4)$ Å, $c = 8.6586(3)$ Å, and $\beta = 102.184(4)^\circ$ (at 125 K). Seven-Membered diazepine ring has approximate mirror plane of symmetry, planar thieno and phenyl rings are almost perpendicular to one another, dihedral angle between their mean planes is $84.11(5)^\circ$. N–H \cdots O hydrogen bonds connect molecules into centrosymmetric dimers which are further expanded into 3D crystal structure with the help of weaker C–H \cdots O and C–H $\cdots\pi$ interactions. The methyl group is disordered at room temperature, but it gets gradually ordered at lower temperatures and becomes fully ordered at approximately 200 K. The changes in structure with temperature were studied between 125 and 380 K. The unit cell volume—as expected—increases almost monotonically when the temperature rises, but one of the parameters shortens significantly.

Keywords: diazepines; hydrogen bonding; disorder; structural change

1. Introduction

1,4-Benzodiazepine derivatives are widely used as daytime sedatives, tranquilizers, sleep inducers, anesthetics, anticonvulsants and muscle relaxants (e.g., [1–4]). Five-Atom heterocyclic fused benzodiazepine ring systems occupy a prominent place among drugs for the treatment of central nervous system (CNS) disorders ([5–8], and references therein).

Figure 1. Compound 1.



The title compound, (**1**, Figure 1), $C_{15}H_{13}N_2OClS$, is structurally similar to clonazepam, the only difference is the hydrogen atom on the nitrogen atom instead of the methyl group. Of similar compounds, the crystal structures of 6,7-dimethyl-5-phenyl-1*H*-thieno[2,3-*e*][1,4]diazepin-2(3*H*)-one [9] and 5-phenyl-9*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepin-8(7*H*)-one [10] as well as of the salt, (*E*)-5-(2-chlorophenyl)-7-ethyl-2-oxo-2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]-diazepin-4-ium 2,4,6-trinitrophenolate [10] have been reported. In view of the importance of heterocyclic fused benzodiazepine ring systems, the paper reports the crystal structure of 5-(2-chlorophenyl)-7-ethyl-1*H*-thieno[2,3-*e*][1,4]diazepin-2(3*H*)-one (**1**). In the course of the structural studies it turned out that the title compound is an example of the ordering of the methyl group while the temperature drops below *ca.* 200 K. Also, the changes of the unit cell parameters with the temperature show the interesting abnormality: One of the parameters shortens significantly with the rising temperature, while the unit cell volume—as expected—increases almost monotonically.

2. Results and Discussion

2.1. Molecular Structure and Crystal Packing

Over the whole range of temperatures studied there is no phase transition, the only change observed is related to the disorder of the C82 methyl group. Therefore we will describe the molecular structure and the crystal packing for one chosen temperature, 125 K—without disorder—and only add the information of the disordered structure if necessary.

Figure 2 compares the perspective views of the molecule (together with the labeling scheme and displacement ellipsoids) at 125 K (no disorder) and at 300 K (quite pronounced disorder), and Table 1 lists some relevant geometrical parameters. In general, they are within the typical range for the similar compounds.

Figure 2. Ellipsoid representation of molecule **1** at (a) 125 K and (b) 300 K, together with the atom labeling scheme [11]. The ellipsoids are drawn at 50% probability level, hydrogen atoms are depicted as spheres with arbitrary radii. In Figure 2b the C81 hydrogen atoms are omitted for clarity.

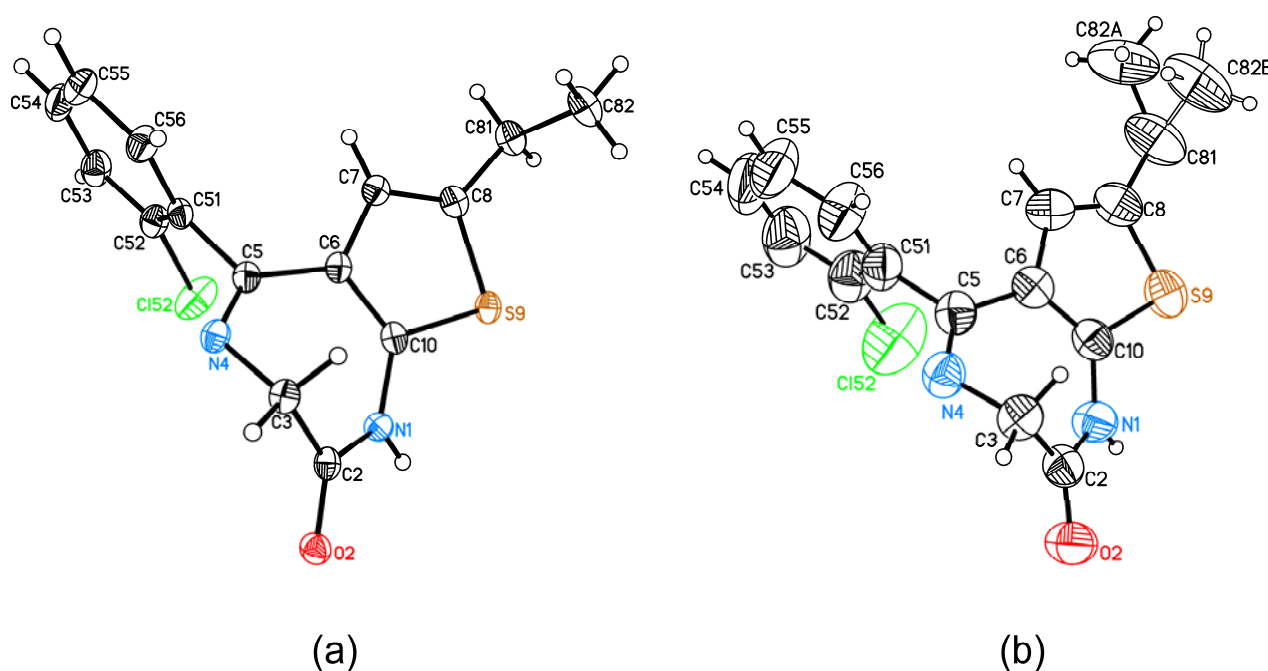


Table 1. Relevant geometrical data (Å, °) for the lowest and highest temperature. The second line, where shown, refers to the lower-occupancy position.

	125 K	380 K
N1-C2	1.3541(19)	1.342(4)
N1-C10	1.3905(19)	1.385(4)
C2-O2	1.2360(18)	1.234(4)
C2-C3	1.507(2)	1.487(5)
C3-N4	1.4716(19)	1.463(4)
N4-C5	1.279(2)	1.282(4)
C5-C6	1.468(2)	1.457(5)
C6-C10	1.375(2)	1.365(5)
C6-C7	1.428(2)	1.421(5)
C7-C8	1.353(2)	1.344(5)
C8-S9	1.744(2)	1.730(4)
S9-C10	1.726(2)	1.714(3)

Table 1. Cont.

C2-N1-C10	125.0(1)	125.0(3)
C3-N4-C5	117.7(1)	116.8(3)
N4-C5-C6	126.7(1)	126.9(3)
C8-S9-C10	91.60(7)	91.9(2)
N1-C2-C3-N4	67.4(2)	65.7(4)
C2-C3-N4-C5	-72.2(2)	-72.4(4)
C3-N4-C5-C6	7.9(2)	8.6(5)
N4-C5-C6-C10	32.2(2)	33.1(5)
C5-C6-C10-N1	0.6(2)	-1.6(6)
C6-C10-N1-C2	-35.3(2)	-35.3(6)
C10-N1-C2-C3	-1.2(2)	1.4(5)
N4-C5-C51-C52	-107.9(2)	-105.3(4)
N4-C5-C51-C56	71.0(2)	74.3(5)
C6-C7-C8-C81	-174.6(2)	178.6(4)
C10-S9-C8-C81	175.3(1)	-178.8(4)
C7-C8-C81-C82	97.8(2)	78.7(9)
		18(1)
S9-C8-C81-C82	-75.8(2)	-103.0(8)
		-164(1)

The seven-membered diazepine ring adopts a boat-like conformation, similar to that observed in the salt [12], and displays approximately C_s symmetry. The bond lengths pattern suggest the double-bond character for the N4=C5 bond and the significant delocalization of the C6=C10-N1-C2=O2 fragment. The asymmetry parameter ΔC_s (kind of the expansion of Duax & Norton concept [13]), which describes the deviation from the ideal symmetry, is only 4.8°. The values of Cremer and Pople puckering parameters [14, 15] are Q_2 : 0.729(2) Å, Q_3 : 0.244(2) Å, φ_2 : 157.3(1)°, and φ_3 : 51.7(4)°. The thieno and phenyl rings are planar (largest deviations from the appropriate least-squares planes are 0.0042(7) Å and 0.006(1) Å, respectively), and their planes are almost perpendicular — the dihedral angle is 84.11(5)°.

In the crystal structure the most prominent interaction is the N–H⋯O hydrogen bonding (cf. Table 2) that connects the molecules of **1** into the discrete dimers ($R^2_2(8)$ graph set, Figure 3). The dimers are connected by quite short C–H⋯O hydrogen bonds (Table 2) and by weak but directional C–H⋯ π (thieno) (Figure 4).

Figure 3. Hydrogen-Bonded $R^2_2(8)$ dimer of molecules **1** [11]. Hydrogen bonds are shown as dashed lines.

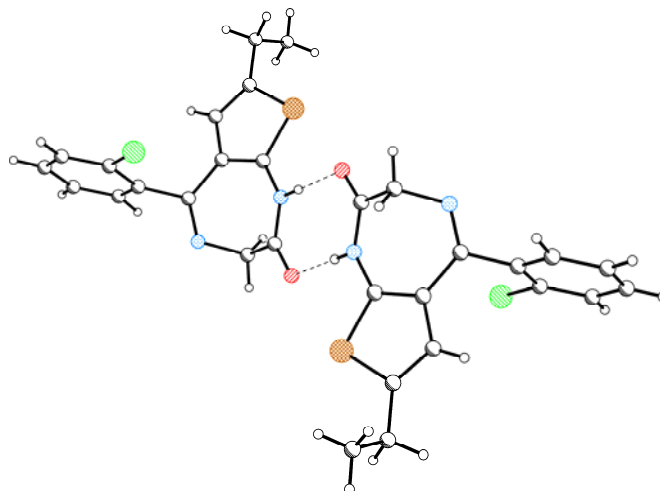
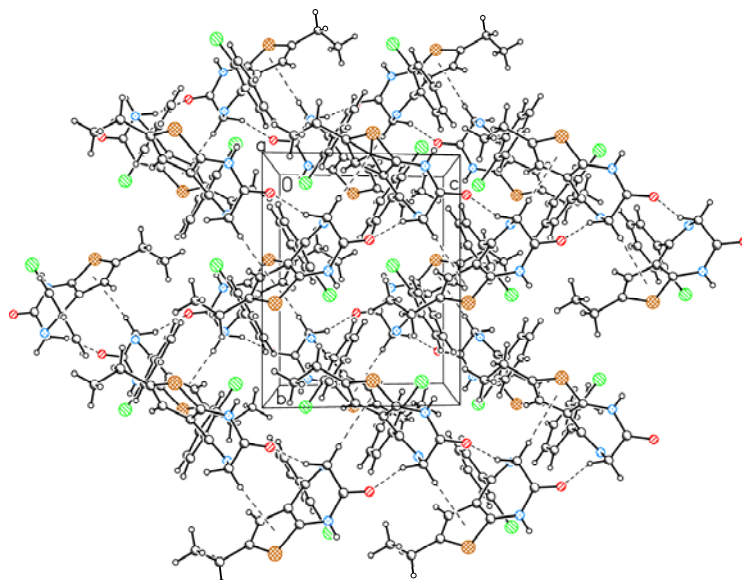


Table 2. Hydrogen bond data (Å, °). CgA denotes the centroid of the five-membered ring.

125K						
D	H	A	D–H(Å)	H···A(Å)	D···A(Å)	D–H···A(°)
N1	H1	O2 ⁱ	0.86(2)	1.94(2)	2.793(2)	178(2)
C3	H3B	O2 ⁱⁱ	1.01(2)	2.38(2)	3.316(2)	154(1)
C3	H3A	CgA ⁱⁱⁱ	0.96(2)	2.83(2)	3.637(2)	143(1)
1LT						
D	H	A	D–H(Å)	H···A(Å)	D···A(Å)	D–H···A(°)
N1	H1	O2 ⁱ	0.86	1.99	2.836(4)	167
C3	H3B	O2 ⁱⁱ	0.97	2.48	3.389(5)	155
C3	H3A	CgA ⁱⁱⁱ	0.97	3.01	3.866(5)	148

Symmetry codes: ⁱ $-x, 1 - y, 1 - z$; ⁱⁱ $x, 3/2 - y, 1/2 + z$; ⁱⁱⁱ $x, 3/2 - y, -1/2 + z$.

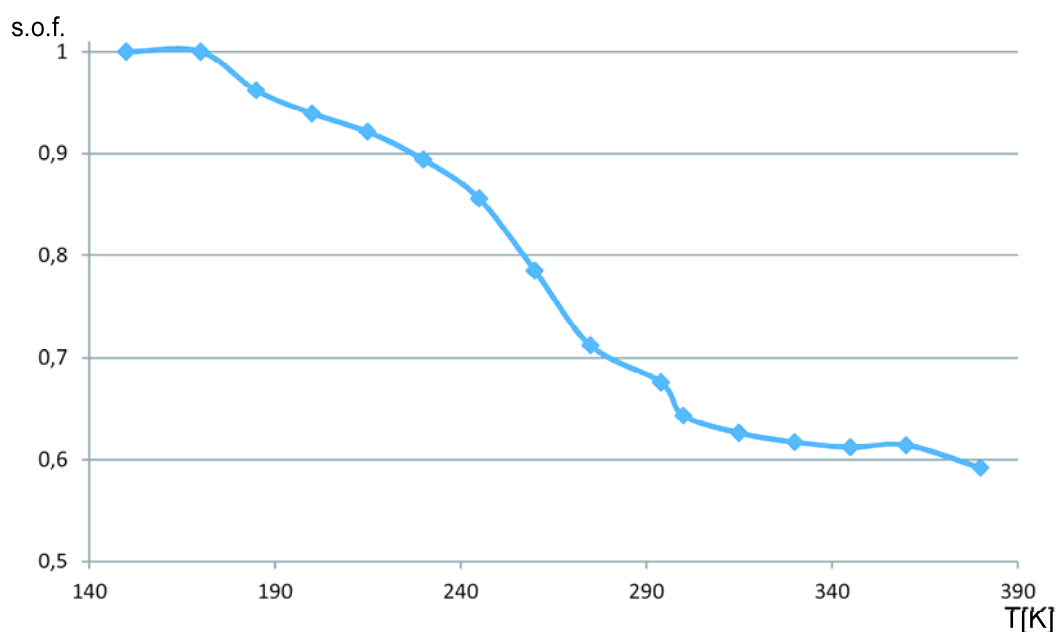
Figure 4. Crystal packing of **1** as seen approximately along [100] direction [11]; hydrogen bonds and C–H··· π interactions are drawn as dashed lines.



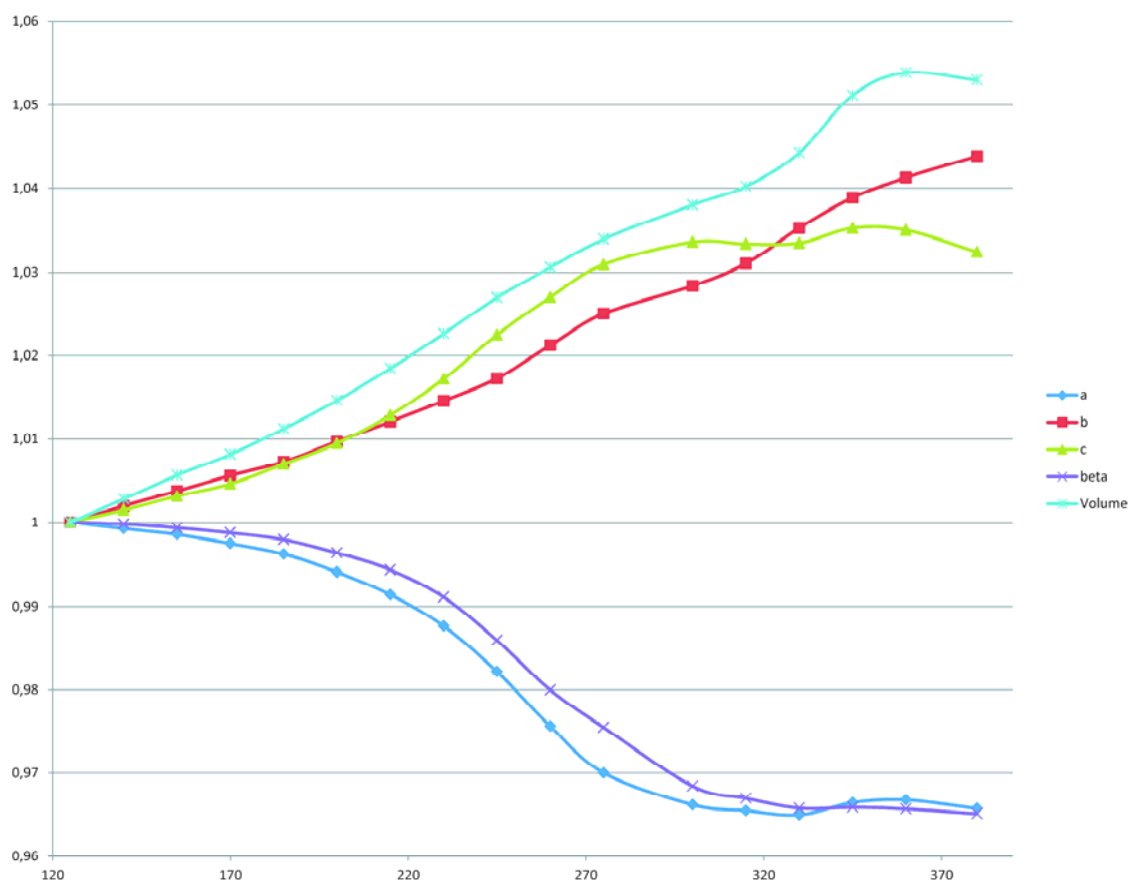
2.2. The Structural Changes

When the temperature rises, the thermal (or displacement) parameters generally increase, and these changes are of course especially significant for the terminal atoms. In the case of **1** the displacement parameters of methyl carbon atom C82 grow much faster than those of the other atoms and at approximately 200 K the description of this group as the disordered between two positions starts to be more appropriate (cf. Experimental Section). Figure 5 shows the temperature dependence of the site occupation factor of the more occupied position as a function of temperature. The contribution of the less-occupied part grows approximately linearly to the room temperature when it reaches the plateau at the value of *ca.* 40%.

Figure 5. Temperature dependence of the site occupation factor of the higher-occupied methyl group (cf. Experimental Section).



The unit-cell parameters of course do change with the changing temperature. Usually, they decrease on cooling, in the case of **1** however the situation is not straightforward (Figure 6). The unit-cell volume, the most important characteristics, behaves typically and it expands almost linearly with temperature (R^2 correlation factor is 0.993); similarly linear temperature dependence has been found for *b*-parameter. Other unit-cell edges need at least third-order polynomial to reach similar level of correlation, what's more, the *a*-axis displays the reverse thermal behavior and it shrinks while the temperature rises. We have not found clear structural reasons for such behavior, it might be partially connected with the above mentioned ordering of the methyl groups, as the non-linearity of the thermal expansion is especially prominent when the occupancy of two alternative positions of the methyl groups reach the plateau.

Figure 6. Temperature dependence of unit cell parameters and unit cell volume.

3. Experimental Section

The title compound was obtained as a gift sample from R. L. Fine Chem., Bengaluru, India. The crystals appropriate for X-ray diffraction studies were obtained by slow evaporation from toluene solution (m.p. 438–440 K). Sixteen sets of diffraction data were collected for temperatures ranging from 125 to 380 K on Agilent Technologies Xcalibur diffractometer (Eos detector) with graphite-monochromatized MoK α radiation ($\lambda = 0.71073\text{\AA}$). The temperature was controlled by an Oxford Instruments Cryosystems cooling device. The data were corrected for Lorentz-polarization effects as well as for absorption [16]. Accurate unit-cell parameters were determined by a least-squares fit of reflections of highest intensity reflections, chosen from the whole experiment. The calculations were mainly performed within the WinGX program system [17]. The structures were solved with SIR92 [18] and refined with the full-matrix least-squares procedure on F^2 by SHELXL97 [11]. Scattering factors incorporated in SHELXL97 were used. The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o^2) + (AP)^2 + BP]$, where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$. All non-hydrogen atoms were refined anisotropically, in the low temperature structure all hydrogen atoms were found in the difference Fourier maps and isotropically refined, with raising temperature some hydrogen atoms have to be placed in calculated positions (above RT–all), and were refined as “riding” on their parent atoms; the U_{iso} 's of hydrogen atoms were set as 1.2 (1.5 for methyl groups) times the U_{eq} value of the appropriate carrier atom. The refinement procedure related to the disordered methyl group is similar to that adopted in our previous paper [19]. For the disordered fragment the s.o.f. (with constraint of

adding up to unity) and one common isotropic displacement parameter were initially refined. Then the refined value of s.o.f. was fixed and the individual isotropic and subsequently anisotropic displacement parameters were refined. The soft constraints for the anisotropic parameters have to be applied (ISOR). Relevant crystal data for some chosen temperatures (125 K, 230 K for both ordered and disordered model, and 380 K) are listed in Table 3, together with refinement details. The full data (16 temperatures) are available on request.

Table 3. Crystal data, data collection and structure refinement.

Compound	125 K	230 K (D)	230 K (No_D)	380 K
Formula	C ₁₅ H ₁₃ ClN ₂ OS			
Formula weight	304.78			
Crystal system	monoclinic			
Space group	P2 ₁ /c			
<i>a</i> (Å)	15.6941(6)	15.5187(8)		15.177(2)
<i>b</i> (Å)	10.7909(4)	10.9358(5)		11.281(1)
<i>c</i> (Å)	8.6586(3)	8.8141(4)		8.933(1)
β (°)	102.184(4)	101.245(5)		98.73(1)
<i>V</i> (Å ³)	1433.33(9)	1467.1(1)		1511.7(4)
<i>Z</i>	4			
<i>D_x</i> (g·cm ⁻³)	1.41	1.38		1.34
<i>F</i> (000)	632			
μ (mm ⁻¹)	0.41	0.40		0.39
Crystal size (mm)	0.25 × 0.15 × 0.1			
No. of reflections used for unit cell determination	2249	1661		
Θ range (°)	3.06–28.89	3.00–28.91		2.93–25.99
hkl range	–20 ≤ <i>h</i> ≤ 18	–19 ≤ <i>h</i> ≤ 18		–17 ≤ <i>h</i> ≤ 18
	–14 ≤ <i>k</i> ≤ 9	–14 ≤ <i>k</i> ≤ 9		–12 ≤ <i>k</i> ≤ 13
	–11 ≤ <i>l</i> ≤ 11	–11 ≤ <i>l</i> ≤ 11		–11 ≤ <i>l</i> ≤ 9
Reflections:				
collected	6034	6177		6031
unique (<i>R</i> _{int})	3218 (0.024)	3286 (0.024)		2942 (0.023)
with <i>I</i> > 2σ(<i>I</i>)	2723	2393		1625
Number of parameters	233	222	222	192
Weighting scheme:				
<i>A</i>	0.0405	0.0483	0.0483	0.0976
<i>B</i>	0.3247	0.3847	0.3847	0.3814
<i>R</i> (<i>F</i>) [<i>I</i> > 2σ(<i>I</i>)]	0.034	0.045	0.046	0.065
<i>wR</i> (<i>F</i> ²) [<i>I</i> > 2σ(<i>I</i>)]	0.083	0.105	0.105	0.176
<i>R</i> (<i>F</i>) [all data]	0.043	0.068	0.069	0.116
<i>wR</i> (<i>F</i> ²) [all data]	0.088	0.119	0.120	0.207
Goodness of fit	1.032	1.030	1.018	0.993
max/min Δρ (e Å ⁻³)	0.32/–0.33	0.37/–0.26	0.34/–0.29	0.32/–0.30

Crystallographic data (excluding structure factors) for the structural analyses at 125 K, 185 K (for ordered and disordered models), 300 K and 380 K have been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC-873580 (125 K), CCDC-881359 and 881360 (185 K), CCDC-873581 (300 K) and CCDC-881361 (380 K). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk, or www: www.ccdc.cam.ac.uk.

4. Conclusions

The crystal structure of the close analogue of clonazepam, 5-(2-chlorophenyl)-7-ethyl-1*H*-thieno[2,3-*e*][1,4]diazepin-2(3*H*)-one, has been studied at 16 different temperatures covering the range 125–380 K. The methyl group, which is disordered at room temperature, undergoes the ordering process and below 200 K it is fully ordered. The hydrogen bonds and weaker interaction of C–H···O and C–H··· π type connect molecules into a three dimensional structure.

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Conflict of Interest

The authors declare no conflict of interest.

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