Acta Crystallographica Section C
**Crystal Structure Communications**
ISSN 0108-2701

# A new $\gamma$-polymorph of chlorpropamide: 4-chloro-*N*-(propylaminocarbonyl)benzenesulfonamide

**Tatiana N. Drebushchak,[a,b]* Nikita V. Chukanov[c,b] and Elena V. Boldyreva[a,b]**

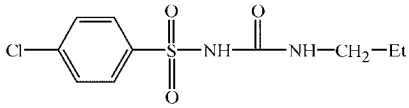
[a]Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, Kutateladze 18, Novosibirsk 128, 630128 Russian Federation, [b]REC-008, Novosibirsk State University, Pirogova 2, Novosibirsk 90, 630090 Russian Federation, and [c]Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Lavrent'ev Avenue 9, Novosibirsk 90, 630090 Russian Federation
Correspondence e-mail: tanya@xray.nsu.ru

Received 11 April 2007
Accepted 19 April 2007
Online 11 May 2007

The structure of a new polymorph of the title compound, $C_{10}H_{13}ClN_2O_3S$, known as the antidiabetic drug chlorpropamide, is monoclinic, in contrast with the two previously described orthorhombic $\alpha$- and $\beta$-forms. The molecules in the $\gamma$-polymorph are linked into bands by hydrogen bonds similar to those in the $\alpha$-polymorph. The conformation of the molecules in the $\gamma$-form is close to that in the $\beta$-polymorph.

## Comment

The existence of several polymorphs of chlorpropamide (an antidiabetic drug) has been reported (Simmons *et al.*, 1973; Burger, 1975; Al-Saieq & Riley, 1982; Ueda *et al.*, 1984; De Villiers & Wurster, 1999; Vemavarapu *et al.*, 2002), but the crystal structures of only two polymorphs have been reported so far, namely the $\alpha$-form (Koo *et al.*, 1980) and the $\beta$-form (Drebushchak *et al.*, 2006). These two polymorphs differ in the conformations and packing of the molecules in the crystal structure. In the present communication, we report the structure of the third polymorph, which we have termed the $\gamma$-polymorph, (I).




(I)

The powder diffraction pattern calculated from the single-crystal structural data of (I) using *POWDERCELL* (Version 2.4; Kraus & Nolze, 1999) has shown that this form may be present as one of the phases in the mixture, corresponding to the records 35–1969, 34–1879 and 34–1882 (not indexed) in the Powder Diffraction File (PDF-2, set 50; ICDD, 2000).

The $\gamma$-polymorph crystallized from a heptane–ethyl acetate solution on slow cooling, growing concomitantly with the $\alpha$-form. The previously described $\beta$-polymorph (Drebushchak *et al.*, 2006) was also obtained from a heptane–ethyl acetate solution, but under different crystallization conditions. In general, our numerous crystallization experiments have shown that various polymorphs can be obtained from solutions of chlorpropamide in heptane–ethyl acetate mixtures depending on the conditions.

The crystal structure of the $\gamma$-polymorph is monoclinic (space group $P2_1$, $Z = 2$), whereas the two other previously described ($\alpha$- and $\beta$-) polymorphs are orthorhombic. The $\gamma$-form is noncentrosymmetric, as is the $\alpha$-form (space group $P2_12_12_1$), whereas the $\beta$-form is centrosymmetric (space group *Pbcn*).

The asymmetric unit of the $\gamma$-polymorph contains one chlorpropamide molecule (Fig. 1). The intramolecular bond lengths and angles are in a good agreement with the statistically averaged values for organic crystal structures in general [Cambridge Structural Database, Version 5.28 (Allen, 2002) and *Mogul*, Version 1.1.1 (Bruno *et al.*, 2004)]. The C═O bond in the $\gamma$-polymorph is longer than that in the $\beta$-polymorph, and this observation is also supported by the IR spectroscopic data on the polymorphs of chlorpropamide (Drebushchak *et al.*, 2007). The torsion angles are summarized in Table 1.

The molecule of chlorpropamide is flexible, and all three forms ($\alpha$, $\beta$ and $\gamma$) can be classified as conformational polymorphs (Bernstein, 2002). In all three polymorphs, the atoms of the central part of the molecule (N1, C7, O3, N2 and C8) are practically in the same plane (Fig. 2), and atoms S1 and O1 are close to this plane (within 0.25 Å). The conformation of the molecule in the $\gamma$-form resembles that in the $\beta$-form: the benzene ring and the alkyl 'tail' are on the same side of the N1/C7/O3/N2/C8 plane (Fig. 2*b*,*c*), whereas in the $\alpha$-form they are on opposite sides (Fig. 2*a*). At the same time, the orientation of the benzene ring with respect to the urea group is similar in the $\alpha$- and $\gamma$-forms, but it differs noticeably from that in the $\beta$-form (Fig. 2). The angle between the plane of the benzene ring and the N1/C7/O3/N2/C8 plane is 80° in the $\alpha$-form (Koo *et al.*, 1980), 81.1 (2)° in the $\gamma$-form (present study) and 89.7 (2)° in the $\beta$-form (Drebushchak *et al.*, 2006).

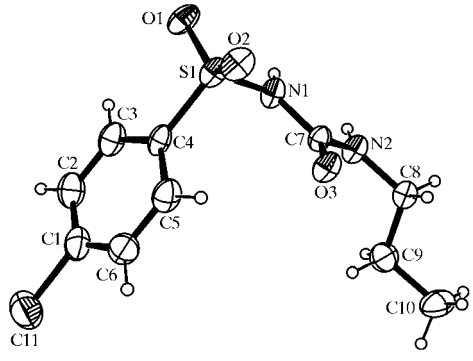



**Figure 1**
The molecular structure of $\gamma$-chlorpropamide, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

 DOI: 10.1107/S010827010701952X © 2007 International Union of Crystallography 

In all three polymorphs, intermolecular N—H···O hydrogen bonds link the molecules into infinite bands, which stretch along the *b* axis (Fig. 3). The geometric parameters of the hydrogen bonds in the $\gamma$-form are summarized in Table 2. The polymorphs differ in the orientations of the alkyl tails and the benzene rings with respect to each other and to the plane of the hydrogen-bonded bands. In the $\gamma$-form, the benzene rings in neighbouring molecules in a chain are on opposite sides of this plane, so that a zigzag pattern is seen when the chain is viewed along its axis (the *b* axis) or projected on to the (010) plane (Fig. 4*a*). The same pattern is observed in the $\alpha$-polymorph (Fig. 4*b*). In the $\beta$-polymorph, the benzene rings of all the molecules in a band are on the same side of the plane of the hydrogen-bonded 'band core', so that a 'tweezers' pattern is seen along the *b* axis/projected on to the (010) plane (Fig. 4*c*). The different packing of the molecules within a band also manifests itself in the geometric parameters of the intermolecular hydrogen bonds: they are similar in the $\alpha$- and $\gamma$-forms, but differ noticeably in the $\beta$-form, in which one of the N—H···O hydrogen bonds is shorter than in the $\alpha$- and $\gamma$-forms, while the other two bifurcated hydrogen bonds are, in contrast, much longer.

The calculated density of the $\gamma$-form is larger than that of the $\beta$-form but smaller than that of the $\alpha$-polymorph. These differences must be related to the different efficiency in the packing of the alkyl tails, depending on the molecular conformation and the mutual orientation of neighbouring molecules.

The structure quality for all three structures ($\alpha$-, $\beta$- and $\gamma$-forms) is not the best, as seen by the consistently elevated *R* factors. This can result from poor quality crystals grown under non-equilibrium conditions. As all three polymorphs give poor structures, and all three come out of the same crystallization solvent, one might also suspect that the crystals are not actually 100% pure single polymorphs, but may contain some domains of the other polymorph(s). This parallels the situation reported recently for aspirin (Bond *et al.*, 2007*a*,*b*), or postulated for the high-pressure polymorphs of L-serine (Boldyreva *et al.*, 2006), $\zeta$-glycine (Goryainov *et al.*, 2006) or L-cysteine (Moggach *et al.*, 2006). This hypothesis is

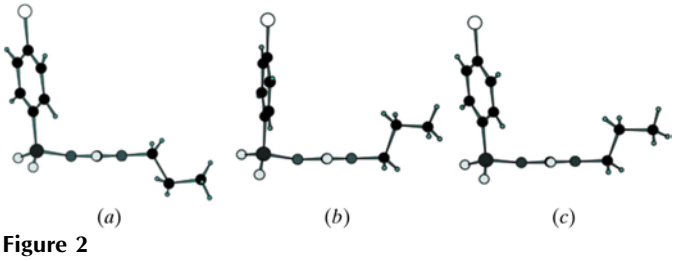



**Figure 2**
Molecules of chlorpropamide viewed along the O3—C7 bond in (*a*) the $\alpha$-form, (*b*) the $\beta$-form and (*c*) the $\gamma$-form.

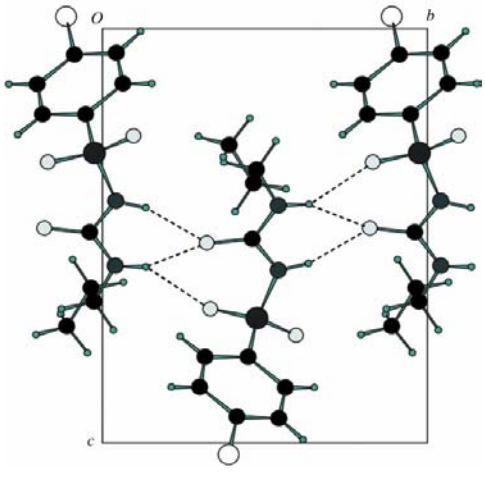



**Figure 3**
A fragment of the crystal structure of the $\gamma$-polymorph of chlorpropamide, viewed along the *a* axis. Hydrogen bonds are shown as dashed lines.

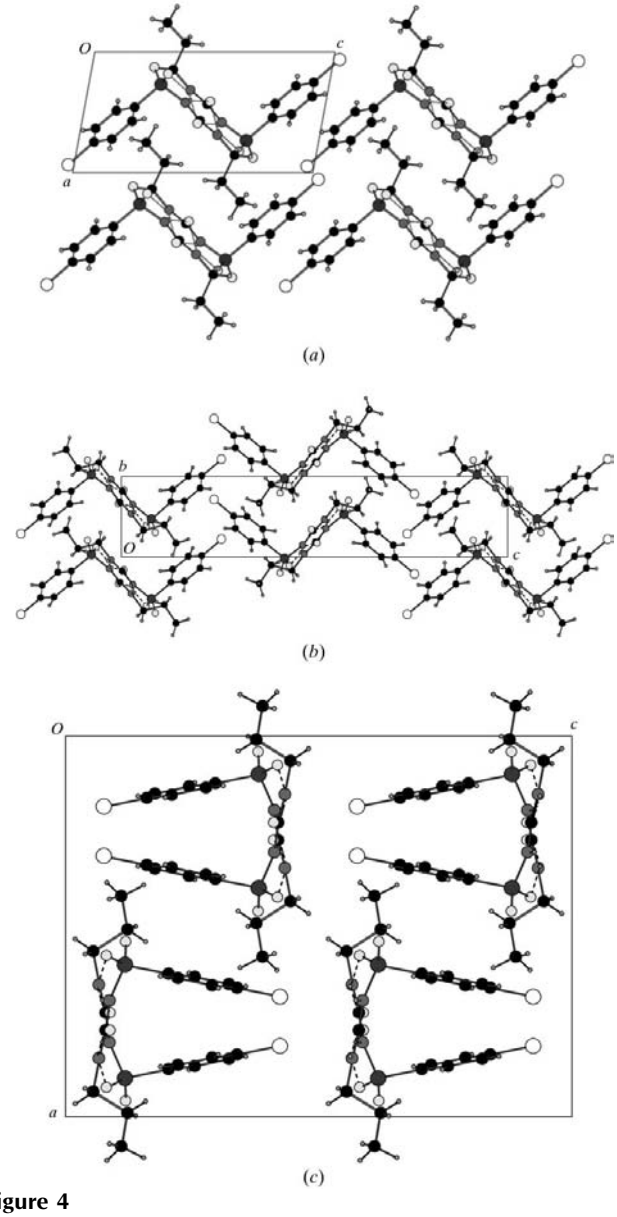



**Figure 4**
Comparative views of the crystal packing of the three polymorphs of chlorpropamide, showing (*a*) the $\gamma$-polymorph viewed along the *b* axis, (*b*) the $\alpha$-polymorph viewed along the *a* axis, and (*c*) the $\beta$-polymorph viewed along the *b* axis. Hydrogen bonds are shown as dashed lines.

indirectly supported by the fact that the powder diffraction patterns measured for several crystallites from the same crystallization batch often indicated the presence of the $\alpha$-form as an admixture to the $\gamma$-form of chlorpropamide. Although there was no difficulty indexing the reflections or initially determining the unit cell in collecting data for the $\beta$- and $\gamma$-polymorphs, we cannot exclude the presence of the domains of another form, as the data were collected with a point detector only. Further experiments using a CCD or area detector would be helpful.

## Experimental

Chlorpropamide (280 mg; Sigma Chemical Co., batch No. 31H0722) was dissolved in a boiling mixture of heptane (2 ml) and ethyl acetate (3 ml). The hot solution was filtered on a glass filter. On slow cooling, crystals suitable for X-ray crystallographic analysis were obtained. A kinetic phase transition and melting was observed in the range 383–403 K (Drebushchak *et al.*, 2007).

*Crystal data*

$C_{10}H_{13}ClN_2O_3S$
$M_r$ = 276.74
Monoclinic, $P2_1$
$a$ = 6.126 (2) Å
$b$ = 8.941 (6) Å
$c$ = 12.020 (4) Å
$\beta$ = 99.68 (3)°
$V$ = 649.0 (5) Å$^3$
$Z$ = 2
Mo $K\alpha$ radiation
$\mu$ = 0.45 mm$^{-1}$
$T$ = 295 (2) K
0.42 × 0.15 × 0.04 mm

*Data collection*

Stoe Stadi-4 four-circle D094 diffractometer
Absorption correction: $\psi$ scan (*X-RED*; Stoe & Cie, 1997)
$T_{min}$ = 0.833, $T_{max}$ = 0.978
3354 measured reflections
2961 independent reflections
1674 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.050
2 standard reflections
frequency: 240 min
intensity decay: 5.7%

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.075
$wR(F^2)$ = 0.163
$S$ = 1.17
2961 reflections
157 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.22 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.28 e Å$^{-3}$
Absolute structure: Flack (1983), with 1385 Friedel pairs
Flack parameter: 0.11 (16)

**Table 1**
Selected torsion angles (°).

| | | | |
|---|---|---|---|
| O2—S1—C4—C3 | 150.4 (5) | O2—S1—N1—C7 | 44.3 (5) |
| O1—S1—C4—C3 | 18.2 (5) | O1—S1—N1—C7 | 174.2 (5) |
| N1—S1—C4—C3 | −92.7 (5) | C4—S1—N1—C7 | −71.7 (5) |
| O2—S1—C4—C5 | −30.1 (5) | O3—C7—N2—C8 | 1.1 (9) |
| O1—S1—C4—C5 | −162.3 (5) | N1—C7—N2—C8 | −179.7 (5) |
| N1—S1—C4—C5 | 86.8 (5) | C9—C8—N2—C7 | 87.1 (7) |
| O3—C7—N1—S1 | −7.3 (8) | N2—C8—C9—C10 | −177.8 (5) |
| N2—C7—N1—S1 | 173.5 (4) | | |

**Table 2**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1$A$···O3$^{i}$ | 0.86 | 1.97 | 2.796 (6) | 161 |
| N2—H2$A$···O2$^{i}$ | 0.86 | 2.26 | 2.948 (6) | 136 |
| N2—H2$A$···O3$^{i}$ | 0.86 | 2.30 | 3.047 (6) | 145 |

Symmetry code: (i) $-x+1, y+\frac{1}{2}, -z+1$.

All H atoms were positioned geometrically and refined using a riding model, with C—H distances of 0.93 (aromatic), 0.96 ($CH_3$) or 0.97 Å ($CH_2$) and N—H distances of 0.86 Å, and with $U_{iso}$(H) = 1.2$U_{eq}$(C,N), or 1.5$U_{eq}$(methyl C).

Data collection: *STADI4* (Stoe & Cie, 1997); cell refinement: *STADI4*; data reduction: *X-RED* (Stoe & Cie, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *POWDER-CELL* (Kraus & Nolze, 1999); software used to prepare material for publication: *SHELXL97*, *X-RED*, *WinGX* (Farrugia, 1999) and *publCIF* (Westrip, 2007).

This work was supported by grant No. 05-03-32468 from RFBR, grants from BRHE (Nos. RUX0-008-NO-06 and Y3-C-08-01), a grant from the Russian Ministry of Education and Science (grant No. 2.2.2.3.2007), and Integration Projects Nos. 49 and 110 of the Siberian Branch of the RAS.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3052). Services for accessing these data are described at the back of the journal.

## References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Al-Saieq, S. S. & Riley, G. S. (1982). *Pharm. Acta Helv.* **57**, 8–11.
Bernstein, J. (2002). *Polymorphism in Molecular Crystals*. Oxford: Clarendon Press.
Boldyreva, E. V., Sowa, H., Seryotkin, Yu. V., Drebushchak, T. N., Ahsbahs, H., Chernyshev, V. V. & Dmitriev, V. P. (2006). *Chem. Phys. Lett.* **429**, 474–478.
Bond, A. D., Boese, R. & Desiraju, G. R. (2007*a*). *Angew. Chem. Int. Ed.* **46**, 615–617.
Bond, A. D., Boese, R. & Desiraju, G. R. (2007*b*). *Angew. Chem. Int. Ed.* **46**, 618–622.
Bruno, I. J., Cole, J. C., Kessler, M., Luo, J., Motherwell, W. D. S., Purkis, L. H., Smith, B. R., Taylor, R., Cooper, R. I., Harris, S. E. & Orpen, A. G. (2004). *J. Chem. Inf. Comput. Sci.* **44**, 2133–2144.
Burger, A. (1975). *Sci. Pharm.* **43**, 152–161.
De Villiers, M. M. & Wurster, D. E. (1999). *Acta Pharm.* **49**, 79–88.
Drebushchak, T. N., Chukanov, N. V. & Boldyreva, E. V. (2006). *Acta Cryst.* E**62**, o4393–o4395.
Drebushchak, V. A., Drebushchak, T. N., Chesalov, Yu. A. & Boldyreva, E. V. (2007). In preparation.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Goryainov, S. V., Boldyreva, E. V. & Kolesnik, E. N. (2006). *Chem. Phys. Lett.* **419**, 496–500.
ICDD (2000). PDF-2. International Centre for Diffraction Data, 12 Campus Boulevard, Newtown Square, PA 19073-3273, USA.
Koo, C. H., Cho, S. I. & Yeon, Y. H. (1980). *Arch. Pharm. Res.* **3**, 37–49.
Kraus, W. & Nolze, G. (1999). *POWDERCELL*. Version 2.4. Federal Institute for Materials Research and Testing, Berlin, Germany.
Moggach, S. A., Allan, D. R., Clark, S. J., Gutmann, M. J., Parsons, S., Pulham, C. R. & Sawyer, L. (2006). *Acta Cryst.* B**62**, 296–309.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Simmons, D. L., Ranz, R. J. & Guanchandani, N. D. (1973). *Can. J. Pharm. Sci.* **8**, 125–127.
Stoe & Cie (1997). *STADI4* and *X-RED*. Stoe & Cie, Darmstadt, Germany.
Ueda, H., Nambu, N. & Nagai, T. (1984). *Chem. Pharm. Bull.* **32**, 244–250.
Vemavarapu, C., Mollan, M. J. & Needham, T. E. (2002). *Am. Assoc. Pharm. Sci. PharmSciTech*, **3**, 29. URL: http://www.aapspharmscitech.org
Westrip, S. P. (2007). *publCIF*. URL: http://journals.iucr.org/services/cif/publcif