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Two carbamoyl-substituted dihydropyrimidines: potential mimics of dihydropyridine calcium channel blockers

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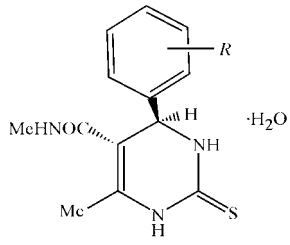
The structures of two conformationally similar 1,4-dihydropyrimidines with a novel carbamoyl substitution, *viz*. 6-methyl-5-(*N*-methylcarbamoyl)-4-phenyl-1,2,3,4-tetrahydropyrimidine-2-thione monohydrate, $C_{13}H_{15}N_3OS\cdot H_2O$, (I), and 4-(4-chlorophenyl)-6-methyl-5-(*N*-methylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-2-thione monohydrate, $C_{13}H_{14}ClN_3OS\cdot H_2O$, (II), exhibit the structural features of 1,4-dihydropyridine calcium channel blockers. In both structures, the pyrimidine ring adopts a flattened boat conformation and the carbamoyl side chain is in an extended conformation with an anticlinal orientation. The phenyl ring occupies a pseudo-axial position with respect to the pyrimidine ring in these structures. Both compounds crystallize with one molecule of water, which participates in a two-dimensional hydrogen-bonding network. The molecules are linked into dimers by N—H···S hydrogen bonds in both structures.

Comment

Pyrimidines, being critical components of naturally occurring nucleic acid, are an integral part of medically important compounds, including antiviral, antitumor and cardiovascular agents (Atwal *et al.*, 1989). Owing to their biological importance, these compounds have been the focus of synthetic activity during the past few years (Weis & van der Plas, 1986). The structural relation to and potential mimicking of the clinically important dihydropyridine (DHP) calcium channel blockers led us to study substituted 1,4-dihydropyrimidines (DHPMs). Furthermore, being inherently asymmetric, dihydropyrimidines provide an opportunity to study the effect of chirality on biological activity. To gain insight into the conformational aspect of various substitutions on the phenyl ring, as well as to obtain the possible relationship between structure and activity, an X-ray study of a series of phenyl substituted 1,4-dihydropyrimidines – having a novel carbamoyl group at atom C3 and a thione group at atom C6 of the dihydropyrimidine ring – has been undertaken. We report here the crystal and molecular structures of 6-methyl-5-(*N*-methylcarbamoyl)-4-phenyl-1,2,3,4-tetrahydropyrimidine-2-thione monohydrate, (I), and 4-(4-chlorophenyl)-6-methyl-5-(*N*-methylcarbamoyl)-1,2,3,4-tetrahydropyrimidine-2-thione monohydrate, (II).



(I) R = H
(II) R = Cl

In all essential details, the geometries of the molecules in terms of interatomic distances and angles (Figs. 1 and 2, and Tables 1 and 3) are in good agreement with those in similar structures (Kojić-Prodić *et al.*, 1976; Sulmon *et al.*, 1989; Chandra Mohan *et al.*, 2003). The two compounds are isomorphous, both crystallizing as monohydrates in the centrosymmetric space group $P\overline{1}$. An r.m.s. overlay (pyrimidine plane; r.m.s. deviation = 0.019 Å) of the two compounds shows significant similarities (Fig. 3), differing only at the periphery of the phenyl ring. The DPHM rings in both structures exist more or less in flattened boat-like conformations [DS(C4) = 0.041 (1) for (I) and DS(C4) = 0.048 (1) for (II) (Nardelli, 1983)], with atoms N1 and C4 defining the stern and bow positions. Atoms N1 and C4 lie 0.113 (1) and 0.204 (1) Å in (I), and 0.137 (2) and 0.255 (2) Å in (II), respectively, from the least-squares plane defined by the remaining four atoms (C2, C3, N5 and C6) of the DPHM ring. A similar conformation was observed in another DPHM (Atwal *et al.*, 1990; Kappe *et al.*, 1997). In both structures, the torsion angles about the C4-atom ring bonds are greater than those for the N1-atom bonds, indicating that the puckering is more influenced at atom C4. The DPHM ring exists in the

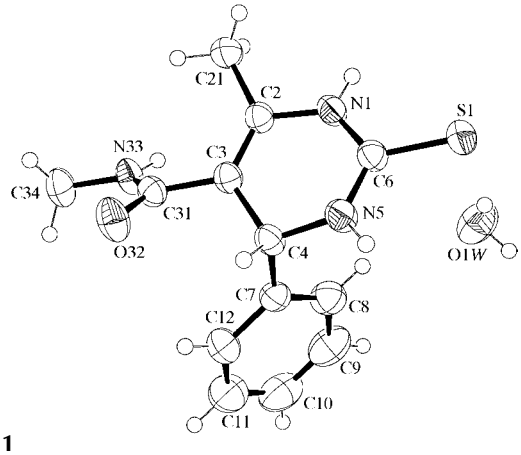


Figure 1
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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thione form; the C6═S1 distance [1.6982 (14) Å in (I) and 1.693 (2) Å in (II)] essentially has double-bond character (Trinajstic, 1968). In addition, this C═S distance in both structures is longer than 1.61 Å, the distance expected for a C═S double bond (Pauling, 1960). A similar lengthening has been reported and discussed as being due to the substantial hydrogen bonding involving the S atom (Tiekink, 1989). In both structures, the S atom participates in a network of hydrogen bonds.

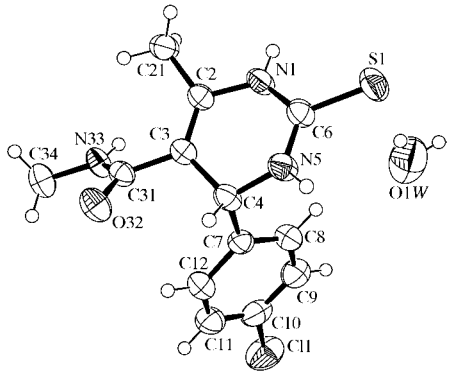

Figure 2
A view of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Figure 3
An r.m.s. overlay of (I) and (II), showing the similarities in conformation.

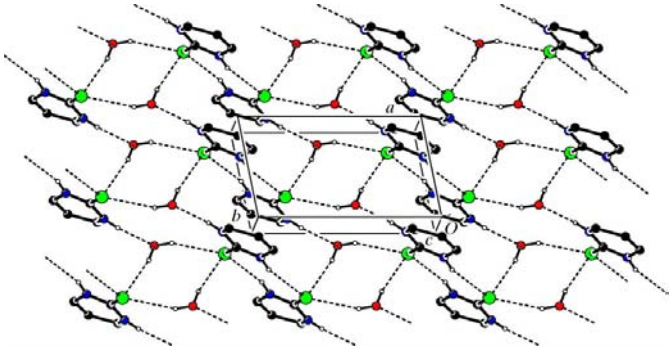

Figure 4
Part of the crystal structure of (I), showing the formation of the three-dimensional framework from the two component (001) and (110) chains built by water molecules. For clarity, the substituents on the DPHM ring have been omitted.

The carbamoyl side chain in both structures is in a fully extended conformation, with C3—C31—N33—C34 torsion angles of 179.52 (13)° for (I) and −179.9 (2)° for (II). The spatial arrangement of the carbonyl group at atom C3 adopts an anticlinal (*ac*) orientation about the C3—C31 bond in both structures [C2—C3—C31—O32 = −132.12 (15)° in (I) and −134.9 (2)° in (II)]. This orientation can probably be attributed to intermolecular N—H···O hydrogen bonding involving carbonyl atom O32.

The phenyl ring in both structures is significantly planar within experimental limits. It is oriented perpendicular to the DHPM ring system [C3—C4—C7—C8 = 91.62 (16)° in (I) and 99.5 (2)° in (II)]. Furthermore, the phenyl ring is positioned pseudo-axially [107.2 (1)° in (I) and 103.2 (2)° in (II), as defined by the average magnitude of the C2—C3—C4—C7 and C6—N5—C4—C7 torsion angles] with respect to the C4 position of the DPHM ring.

Triggle *et al.* (1989), on the basis of three-dimensional structural characteristics important for calcium channel antagonist activity in DPH, proposed that a flattened boat conformation of the DHP ring, with the phenyl ring in a pseudo-axial position and a near perpendicular orientation of the phenyl ring with respect to the DHP ring, corresponds to high activity. Viewing the DHPM structures of (I) and (II), a striking similarity in conformational features is observed, suggesting that these compounds may be potential mimics of prototypical DHP calcium channel blockers. Owing to a lack of pharmacological data, such a conclusion is speculation at this stage.

A packing diagram of (I) only is shown in Fig. 4, since the compounds are isostructural. The molecules exist as dimers utilizing N—H···S hydrogen bonds (Tables 2 and 4) between centrosymmetrically related molecules described by an $R_2^2(8)$ ring motif. The most striking feature in the crystal packing is the hydrogen-bonding network formed by the water molecules, which is present in both structures. The water molecules link the dimers into infinite chains along the *a* axis *via* O*W*—H···S and N—H···O*W* hydrogen bonds, thereby acting as donors and acceptors. Furthermore, the water molecule interlinks the dimer chain along the *b* axis *via* O*W*—H···S hydrogen bonds. Interestingly, the water molecule also forms a dimer with its centrosymmetric counterpart *via* an O*W*—H···O*W* hydrogen bond running parallel to the *a* axis. The carbamoyl side chains are self-linked through N—H···O hydrogen bonds. In addition, a possible bifurcated hydrogen bond is observed in (I) between the water molecule and the S atom, while in (II), the distance between the S atom and the water molecule is 3.818 (3) Å. The hydrogen-bond networks thus formed facilitate alternate hydrophobic and hydrophilic environments in the crystal packing. Possible weak C—H···O and C—H···N interactions are also seen in both structures.

Experimental

Compounds (I) and (II) were prepared by known synthetic methods (Sadanandam *et al.*, 1992) and were recrystallized from methanol/water (90:10) solutions.

Compound (I)

Crystal data

$C_{13}H_{15}N_3OS\cdot H_2O$
M_r = 279.36
Triclinic, $P\overline{1}$
a = 5.0116 (3) Å
b = 8.9507 (6) Å
c = 16.0882 (11) Å
α = 86.095 (1)°
β = 84.841 (1)°
γ = 78.241 (1)°
V = 702.75 (8) Å^3
Z = 2
D_x = 1.32 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5613 reflections
θ = 2.3–28.0°
μ = 0.23 mm^{-1}
T = 273 (2) K
Needle, colorless
0.20 × 0.15 × 0.10 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
8102 measured reflections
3227 independent reflections
2971 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 28.0°
$h = -6 \rightarrow 6$
$k = -11 \rightarrow 11$
$l = -21 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.115
S = 1.05
3227 reflections
182 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0601P)^2 + 0.1834P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

N1—C6	1.3422 (18)	C31—O32	1.2326 (16)
N1—C2	1.4008 (16)	C31—N33	1.3299 (18)
C2—C3	1.3358 (18)	C4—N5	1.4657 (16)
C3—C4	1.5137 (18)	N5—C6	1.3252 (18)
C6—N1—C2—C3	−13.9 (2)	C3—C4—N5—C6	−20.12 (19)
C2—C3—C4—N5	13.51 (18)	C2—N1—C6—N5	8.3 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1W···S1	0.88 (3)	2.45 (3)	3.2868 (18)	157 (3)
O1W—H2W···O1W^{i}	0.84 (2)	2.60 (3)	3.014 (3)	112 (3)
O1W—H2W···S1^{ii}	0.84 (2)	2.70 (2)	3.4708 (15)	153 (3)
N1—H1N···S1^{iii}	0.86	2.62	3.4499 (12)	164
N5—H5N···O1W^{iv}	0.86	2.03	2.8791 (19)	171
N33—H33N···O32^{v}	0.86	2.04	2.8788 (15)	164
C8—H8···O1W	0.93	2.53	3.391 (2)	153
C21—H21A···N33	0.96	2.56	3.138 (2)	119

Symmetry codes: (i) $2-x, 1-y, 1-z$; (ii) $1-x, 1-y, 1-z$; (iii) $1-x, 2-y, 1-z$; (iv) $x-1, y, z$; (v) $1+x, y, z$.

Table 3
Selected geometric parameters (Å, °) for (II).

Cl1—C10	1.742 (2)	C3—C4	1.510 (3)
N1—C6	1.340 (3)	C31—O32	1.235 (2)
N1—C2	1.402 (3)	C31—N33	1.325 (3)
C2—C3	1.336 (3)	C4—N5	1.462 (2)
C6—N1—C2—C3	−16.4 (3)	C3—C4—N5—C6	−25.1 (3)
C2—C3—C4—N5	17.3 (3)	C2—N1—C6—N5	9.9 (3)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1W···S1	0.86	2.47	3.321 (3)	177
O1W—H2W···O1W^{i}	0.86	2.30	2.764 (4)	114
N1—H1···S1^{iii}	0.86	2.63	3.457 (2)	161
N5—H5···O1W^{iv}	0.86	2.14	2.990 (4)	167
N33—H33···O32^{v}	0.86	2.00	2.824 (2)	161
C8—H8···O1W	0.93	2.55	3.397 (4)	151
C21—H21A···N33	0.96	2.55	3.116 (3)	118

Symmetry codes: (i) $2-x, 1-y, 1-z$; (iii) $1-x, 2-y, 1-z$; (iv) $x-1, y, z$; (v) $1+x, y, z$.

Compound (II)

Crystal data

$C_{13}H_{14}ClN_3OS\cdot H_2O$
M_r = 313.8
Triclinic, $P\overline{1}$
a = 4.8853 (3) Å
b = 9.7093 (7) Å
c = 16.0343 (11) Å
α = 79.506 (1)°
β = 84.792 (1)°
γ = 82.834 (1)°
V = 740.18 (9) Å^3
Z = 2
D_x = 1.408 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4058 reflections
θ = 2.3–29.4°
μ = 0.40 mm^{-1}
T = 273 (2) K
Plate, colorless
0.18 × 0.15 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
8550 measured reflections
3391 independent reflections
2988 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 28.0°
$h = -6 \rightarrow 6$
$k = -12 \rightarrow 12$
$l = -21 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.150
S = 1.09
3391 reflections
183 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0789P)^2 + 0.4380P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.68 e Å^{-3}
$\Delta\rho_{min}$ = −0.46 e Å^{-3}

After location of the H atoms in difference density maps, all C- and N-bound H atoms were positioned using *SHELXL*97 HFIX instructions (Sheldrick, 1997) and treated as riding atoms, with C—H distances in the range 0.93–0.98 Å and an N—H distance of 0.86 Å, and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for other H atoms. Water H atoms (H1W and H2W) for (I) were refined with an O—H distance restraint (Table 2). In (II), only one H atom of the water molecule was located. Since (I) and (II) are isomorphous, the positions of the water H atoms in (I) were utilized in (II). However, attempts to refine the coordinates of these H atoms were unsuccessful, and hence the positional and displacement parameters of the water H atoms in (II) were constrained. Examination of both structures with *PLATON* (Spek, 2003) showed that there were no solvent-accessible voids in the crystal lattices.

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1782). Services for accessing these data are described at the back of the journal.

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