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Cocrystals of diastereoisomers of 1,4-dihydropyridine derivatives

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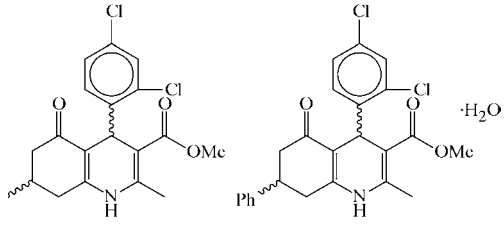
A mixture of the *RR*/*SS* and *RS*/*SR* diastereoisomeric pairs of methyl 4-(2,4-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, $C_{19}H_{19}Cl_2NO_3$, forms cocrystals in which there is one unique molecule in the asymmetric unit, but the molecule displays disorder in the region of the 7-position of the quinoline ring system as a result of the random occurrence of the diastereoisomers at the same crystallographic site. A similar arrangement exists in the monohydrate cocrystals that form from a mixture of the *RR*/*SS* and *RS*/*SR* diastereoisomeric pairs of methyl 4-(2,4-dichlorophenyl)-2-methyl-7-phenyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate monohydrate, $C_{24}H_{21}Cl_2NO_3\cdot H_2O$. These compounds belong to a class of 1,4-dihydropyridines whose members have calcium modulatory properties. The 1,4-dihydropyridine rings have the usual shallow boat conformation. In each structure, the 2,4-dichlorophenyl ring is oriented such that the 2-chloro substituent is in a synperiplanar orientation with respect to the 1,4-dihydropyridine ring plane. In each crystal structure, the molecules are linked into chains by N—H···O hydrogen-bonding interactions.

Comment

1,4-Dihydropyridine (1,4-DHP) derivatives have yielded many drugs which act as calcium channel agonists or antagonists (Rose, 1989, 1990). Nifedipine is the prototype of this group, and both it and its structural analogues are used as antianginal and antihypertensive drugs (Janis & Triggle, 1984). Our interest is in the correlation between the three-dimensional structure and calcium antagonistic behaviour of condensed derivatives of 1,4-DHP (Linden *et al.*, 1998, 2002, 2004, 2005; Şimşek *et al.*, 2000, 2003; Kısmetli *et al.*, 2004). Two new compounds have been prepared as further potentially active 1,4-DHP derivatives. These compounds differ only in the substituent at the 7-position of the cyclohexenone ring and are methyl 4-(2,4-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, (I), and methyl 4-(2,4-dichlorophenyl)-2-methyl-7-phenyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate monohydrate, (II). The syntheses are not stereospecific, so the reactions produced mixtures of the 4,7-diastereoisomers of the racemic compounds. The stereoisomers could not be separated readily and, as subsequently revealed by the crystal structure determinations, crystallization yielded cocrystals in which both diastereoisomers were incorporated, rather than crystals of a single compound forming preferentially.



Views of the asymmetric units in the structures of (I) and (II) are shown in Figs. 1 and 2, respectively. Compound (II) crystallizes as the monohydrate, in which the water molecule is disordered over two sites. The centrosymmetric space groups indicate that the compounds are racemic. Although there is only one formula unit in the asymmetric unit of each structure, the molecules are disordered at atom C7 of the oxocyclohexene rings [and at atom C6 in (II)] and the disorder extends through the substituents at C7 [methyl in (I) and phenyl in (II)]. The disorder manifests itself as alternate directions of folding of the flap of the C7-envelope [in (I)] or half-chair [in (II)] conformations of the cyclohexenone rings, but inspection of the positions of the substituents indicates that the two arrangements are related by inversion of the configuration at atom C7. As the configuration at atom C4 is constant in both of the disordered arrangements, the disorder is actually a consequence of the presence of a mixture of diastereoisomers

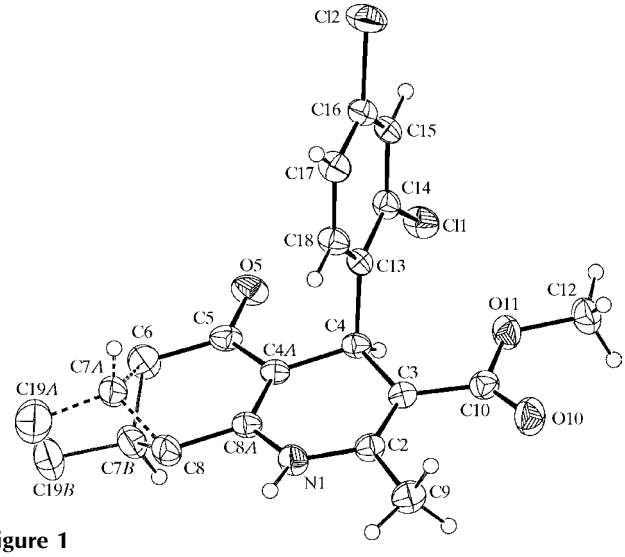


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme and the disorder resulting from the occurrence of diastereoisomers at the same crystallographic site. Displacement ellipsoids are drawn at the 40% probability level. Some of the disordered H atoms have been omitted for clarity.

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in the crystal. The diastereoisomers with the same configuration at atom C4 have been inserted randomly and in almost equal quantities in the crystal lattice and the centrosymmetric space group accommodates the enantiomers of the diastereoisomeric pair. If the diastereoisomers were incorporated into the crystal lattice in a regular sequence, one would find two molecules (at least) in the asymmetric unit. That a random distribution of diastereoisomers occurs in the crystal suggests that the shape of the volume occupied by the diastereoisomeric molecules is very similar.

Despite the disorder, most of the bond lengths and angles in (I) and (II) have normal values. There are small angular distortions about atoms C2 and C10 (Tables 1 and 3), which result from steric interactions between the methyl substituent at C2 and atom O10 of the ester substituent at C3 [O10$\cdots$C9 = 2.790 (4) and 2.814 (5) Å for (I) and (II), respectively]. The presence of π-electron conjugation keeps the ester group at C3 almost coplanar with the endocyclic double bond [C2═C3—C10═O10 = −2.7 (4) and 0.6 (5)° for (I) and (II), respectively] and prevents the ester group from rotating into a sterically more amenable orientation. These properties are consistent with those of related compounds (Linden *et al.*, 2005).

The switch from the 7-methyl substituent in compound (I) to the 7-phenyl substituent in compound (II) has no major influence on the conformations of the molecules. The 1,4-DHP rings have the shallow boat conformation generally observed for 4-aryl-1,4-DHP derivatives (Linden *et al.*, 2005), although the conformations in (I) and (II) are among the shallowest examples. In compound (I), atoms N1 and C4 are 0.035 (2) and 0.115 (2) Å, respectively, from the plane defined by atoms C2, C3, C4*A* and C8*A*. The deviation of atom N1 from this plane is so small that the ring could almost be described as having a shallow envelope conformation. The corresponding displacements in compound (II) are 0.058 (3) and 0.200 (3) Å, respectively. The shallowness of the boat conformations is indicated by the small values of the total puckering amplitudes, *Q* (Cremer & Pople, 1975), of 0.090 (3) and 0.141 (3) Å for compounds (I) and (II), respectively. Three structures of 1,4-DHP derivatives with similarly shallow boat conformations were reported recently (Quesada *et al.*, 2006) and several examples containing a planar ring are also known (Pastor *et al.*, 1994; Duque *et al.*, 2000; Low *et al.*, 2001; Linden *et al.*, 2002; Mahendra *et al.*, 2003).

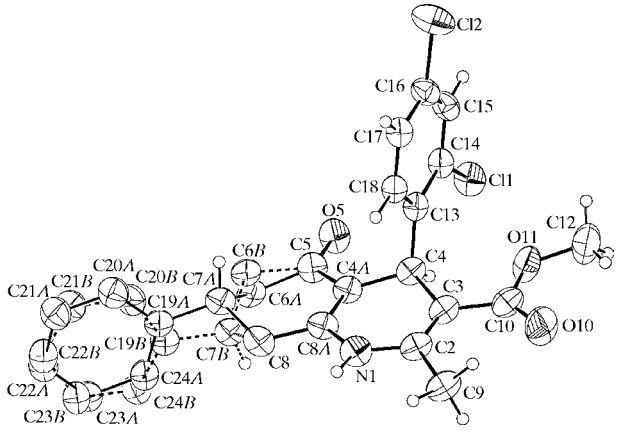

Figure 2
A view of the molecule of (II), showing the atom-labelling scheme and the disorder resulting from the occurrence of diastereoisomers at the same crystallographic site. Displacement ellipsoids are drawn at the 40% probability level. Some of the disordered H atoms have been omitted for clarity.

The plane of the 2,4-dichlorophenyl ring in each of the title compounds is, as frequently observed (Linden *et al.*, 2005), essentially parallel to the N1$\cdots$C4 axis. Compound (I) has a N1$\cdots$C4—C13—C18 pseudo-torsion angle of 2.6 (3)°, while the corresponding torsion angle in compound (II) is 1.8 (3)°. The 2-chloro substituent lies above the C4—H bond in the sterically most favourable synperiplanar orientation. The Cambridge Structural Database (Release 5.27, with January 2006 updates; Allen, 2002) contains five examples of 4-aryl-1,4-DHP compounds with 2,4-disubstitution in the phenyl ring. Three of these compounds are 3,5-dicarboxy-4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-DHP derivatives (Mehdi & Ravikumar, 1992; Sagar *et al.*, 1999; Caignan & Holt, 2000), while there is one 4-(2-chloro-4-nitrophenyl)- (Rovnyak *et al.*, 1988) and one 4-(2,4-dinitrophenyl)- analogue (Fossheim *et al.*, 1982). In each of these compounds, the 2,4-disubstituted phenyl ring has a synperiplanar orientation with respect to the 1,4-DHP ring, although with the 4-(2,4-dinitrophenyl)- derivative and one of the 4-(2,4-dichlorophenyl)- derivatives (Sagar *et al.*, 1999), the plane of the phenyl ring is rotated slightly to make angles of about 16 and 31°, respectively, with the N1$\cdots$C4 axis.

The use of geometric restraints to handle the disordered atoms in the structures of (I) and (II) makes it unwise to analyse the conformations of the cyclohexenone rings in any detail. It suffices to say that the cyclohexenone ring in each diastereoisomer of compound (I) has a C7-envelope conformation, while the corresponding conformation in each diastereoisomer of compound (II) is that of a slightly distorted half-chair twisted about the C6—C7 bond. It has been noted previously that atom C7 is the atom that deviates most from the ring plane in structures involving the quinolin-5-one or acridine-1,8-dione moiety (Linden *et al.*, 2005).

In compound (I), an intermolecular N—H$\cdots$O hydrogen bond between the amine group and the carbonyl O atom of the cyclohexenone ring of a neighbouring molecule (Table 2) links the molecules into extended chains which run parallel to the [101] direction and can be described by a graph-set motif of $C(6)$ (Bernstein *et al.*, 1995). The same $C(6)$ motif has been observed in the crystal structures of several other closely related 1,4-DHP compounds (Linden *et al.*, 1998, 2002, 2004, 2005; Şimşek *et al.*, 2000). In compound (II), the major site of the disordered water molecule accepts the N—H$\cdots$O hydrogen bond from the 1,4-DHP molecule and, in turn, forms another intermolecular hydrogen bond with the carbonyl O atom of the cyclohexenone ring of a neighbouring 1,4-DHP molecule (Table 4). These interactions link the 1,4-DHP and water molecules alternately into extended chains which run parallel to the [100] direction and can be described by a binary graph-set motif of $C_2^2(8)$. The minor site of the water molecule (12% occupancy) has not been considered in this analysis.

Experimental

For the synthesis of compounds (I) and (II), equimolar amounts of 2,4-dichlorobenzaldehyde and 5-methylcyclohexane-1,3-dione for (I) or 5-phenylcyclohexane-1,3-dione for (II), together with methyl aminocrotonoate, were refluxed in methanol for 8 h. Each solution was poured into water and the precipitate which formed was filtered off, dried, and recrystallized from ethanol. The melting points for the crystals containing the diastereoisomeric mixtures were 523 and 421 K, respectively.

Compound (I)

Crystal data

$C_{19}H_{19}Cl_2NO_3$
M_r = 380.27
Monoclinic, $P2_1/n$
a = 11.6670 (3) Å
b = 13.7746 (4) Å
c = 11.8897 (4) Å
β = 105.4328 (19)°
V = 1841.88 (10) Å^3
Z = 4
D_x = 1.371 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 13345 reflections
θ = 2.0–25.0°
μ = 0.37 mm^{-1}
T = 160 (1) K
Tablet, pale yellow
0.22 × 0.22 × 0.07 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω scans with κ offsets
Absorption correction: multi-scan (Blessing, 1995)
T_{min} = 0.871, T_{max} = 0.979
23780 measured reflections
3252 independent reflections
2469 reflections with $I > 2\sigma(I)$
R_{int} = 0.072
θ_{max} = 25.0°
$h = -13 \rightarrow 13$
$k = -16 \rightarrow 16$
$l = -14 \rightarrow 14$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.139
S = 1.04
3252 reflections
254 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.073P)^2 + 1.1256P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.71 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.011 (2)

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

O5—C5	1.242 (3)	C2—C3	1.359 (4)
O10—C10	1.208 (3)	C3—C10	1.458 (4)
O11—C10	1.355 (3)	C3—C4	1.530 (4)
N1—C8*A*	1.367 (3)	C4—C4*A*	1.515 (4)
N1—C2	1.377 (3)	C4*A*—C8*A*	1.356 (3)
C2—N1—C8*A*	123.3 (2)	C3—C4—C4*A*	110.7 (2)
N1—C2—C3	120.1 (2)	C4—C4*A*—C8*A*	122.7 (2)
N1—C2—C9	113.1 (2)	N1—C8*A*—C4*A*	120.3 (2)
C3—C2—C9	126.8 (2)	O10—C10—O11	120.8 (3)
C2—C3—C10	119.8 (2)	O10—C10—C3	128.0 (3)
C2—C3—C4	122.1 (2)	O11—C10—C3	111.2 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5^{i}	0.88 (3)	1.96 (3)	2.835 (3)	173 (3)

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

Compound (II)

Crystal data

$C_{24}H_{21}Cl_2NO_3 \cdot H_2O$
M_r = 460.35
Triclinic, $P\overline{1}$
a = 9.4543 (5) Å
b = 9.7947 (6) Å
c = 13.4460 (9) Å
α = 76.436 (3)°
β = 89.268 (4)°
γ = 69.471 (3)°
V = 1130.23 (12) Å^3
Z = 2
D_x = 1.353 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 24569 reflections
θ = 2.0–25.0°
μ = 0.32 mm^{-1}
T = 160 (1) K
Tablet, pale yellow
0.22 × 0.22 × 0.10 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω scans with κ offsets
Absorption correction: multi-scan (Blessing, 1995)
T_{min} = 0.822, T_{max} = 0.977
14667 measured reflections
3980 independent reflections
3043 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 25.0°
$h = -11 \rightarrow 11$
$k = -11 \rightarrow 11$
$l = -15 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.150
S = 1.05
3980 reflections
376 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0709P)^2 + 0.6095P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.026 (6)

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

O5—C5	1.240 (3)	C2—C3	1.348 (4)
O10—C10	1.210 (3)	C3—C10	1.460 (4)
O11—C10	1.337 (3)	C3—C4	1.533 (3)
N1—C8*A*	1.367 (3)	C4—C4*A*	1.511 (4)
N1—C2	1.379 (4)	C4*A*—C8*A*	1.355 (3)
C2—N1—C8*A*	122.6 (2)	C3—C4—C4*A*	110.3 (2)
N1—C2—C3	120.2 (2)	C4—C4*A*—C8*A*	122.1 (2)
N1—C2—C9	112.6 (2)	N1—C8*A*—C4*A*	120.6 (3)
C3—C2—C9	127.2 (3)	O10—C10—O11	121.0 (3)
C2—C3—C10	120.5 (2)	O10—C10—C3	127.7 (3)
C2—C3—C4	122.2 (2)	O11—C10—C3	111.3 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*A*—H11···O5	0.79 (3)	1.96 (4)	2.718 (3)	159 (6)
N1—H1···O1*A*^{i}	0.88 (4)	1.97 (4)	2.854 (4)	176 (3)

Symmetry code: (i) $x + 1, y, z$.

For (I), the methyl-substituted atom of the cyclohexenone ring and its associated methyl group are disordered as a result of the occurrence of diastereoisomeric molecules at the same crystallographic site. Two sets of positions were defined for these atoms and the site-occupation factor for the atoms corresponding to the major isomer refined to 0.512 (6). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C atoms, while neighbouring atoms within and between each conformation of the disordered groups were restrained to have similar atomic displacement parameters.

For (II), the disorder of the phenyl-substituted atom of the cyclohexenone ring and its associated phenyl group, as well as an adjacent methylene group, was treated exactly as described above. The site-occupation factor for the atoms corresponding to the major isomer refined to 0.505 (7). The asymmetric unit also contains a water molecule disordered over two adjacent positions and the site-occupation factor of the more occupied site refined to 0.879 (6). The H atoms of the lesser occupied site were not included in the model.

The position of the amine H atom for each structure and the positions of the H atoms of the major occupied site of the water molecule in (II) were determined from a difference Fourier map and refined freely with individual isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry, with C—H = 0.98 Å and U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about their C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent C atoms at distances of 0.95, 0.99 or 1.00 Å for phenyl, methylene or methine groups, respectively, and with U_{iso}(H) = 1.2U_{eq}(C).

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3008). Services for accessing these data are described at the back of the journal.

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