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(±)-Methyl and (±)-ethyl 4-(2,3-difluorophenyl)-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

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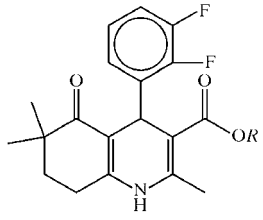
The title compounds, $C_{20}H_{21}F_2NO_3$ and $C_{21}H_{23}F_2NO_3$, respectively, belong to a class of 1,4-dihydropyridines whose members sometimes display calcium modulatory properties. The 1,4-dihydropyridine rings have the usual shallow boat conformation. In each structure, the 2,3-difluorophenyl ring is oriented such that the fluoro substituents are in a synperiplanar orientation with respect to the 1,4-dihydropyridine ring plane and the oxocyclohexene ring has a slightly distorted envelope conformation. Both structures exhibit the same intermolecular N—H···O hydrogen-bonding motif, in which the molecules are linked into chains by interactions involving the carbonyl O atom of the oxocyclohexene ring.

Comment

1,4-Dihydropyridine (1,4-DHP) derivatives have yielded many drugs that act as calcium channel agonists and antagonists. Nifedipine is the prototype of this group, and both it and its structural analogues are used as anti-anginal and antihypertensive drugs (Janis & Triggle, 1984). Many active derivatives have been synthesized by making various modifications to the nifedipine structure, which yield compounds with calcium agonistic or antagonistic properties (Rose, 1989, 1990). It is thought that the activity displayed by these compounds may be influenced by their stereochemistry (Langs & Triggle, 1985). Our interest is in the structure and calcium antagonistic behaviour of condensed derivatives of 1,4-DHP (Şimşek *et al.*, 2003; Kısmetli *et al.*, 2004). The crystal structures of some of these derivatives have already been reported (Linden *et al.*, 1998, 2002, 2004; Şimşek *et al.*, 2000), and the title compounds, (±)-methyl 4-(2,3-difluorophenyl)-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, (I), and the (±)-ethyl analogue, (II), respectively, have been prepared as further potentially active 1,4-DHP derivatives. Their structures were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra, mass spectrometry and elemental analyses. Details of the antagonistic activities of these and related compounds will be published elsewhere (Şimşek *et al.*, 2006). The determination of the three-dimensional conformations of the title compounds, presented here, is important in order to obtain further insight into the structure–activity relationships of these compounds.



(I) R=Me
(II) R=Et

The switch from the methyl ester in (I) to the corresponding ethyl ester in (II) has no major influence on the conformations of the molecules. The 1,4-DHP rings (Figs. 1 and 2) have shallow boat conformations. In (I), atoms N1 and C4 lie 0.159 (2) and 0.348 (2) Å, respectively, from the plane defined by atoms C2, C3, C4*A* and C8*A*. The corresponding displacements in compound (II) are 0.142 (1) and 0.287 (1) Å, respectively. The shallowness of the boat is indicated by the ring-puckering parameters (Cremer & Pople, 1975). For compound (I), Q is 0.2986 (15) Å, θ is 75.4 (3)° and φ_2 is 183.5 (3)° for the atom sequence N1—C2—C3—C4—C4*A*—C8*A*. For the corresponding atom sequence in compound (II), Q is 0.2507 (13) Å, θ is 76.7 (3)° and φ_2 is 182.8 (3)°. For an ideal boat, θ and φ_2 are 90° and $n \times 60°$, respectively. The conformations of 4-aryl-1,4-DHP rings have been discussed previously (Goldmann & Stoltefuss, 1991; Linden *et al.* 1998, 2002; Şimşek *et al.*, 2000) and it is usual for the ring to have a shallow boat conformation, although considerable variation in the shallowness of the boat is evident. The displacement of atom C4 from the base of the boat in (I) and (II) corresponds to the values of around 0.30 Å found most frequently for this atom in 1,4-DHP rings (Şimşek *et al.*, 2000). The deviations shown by atom N1 are generally smaller and spread fairly

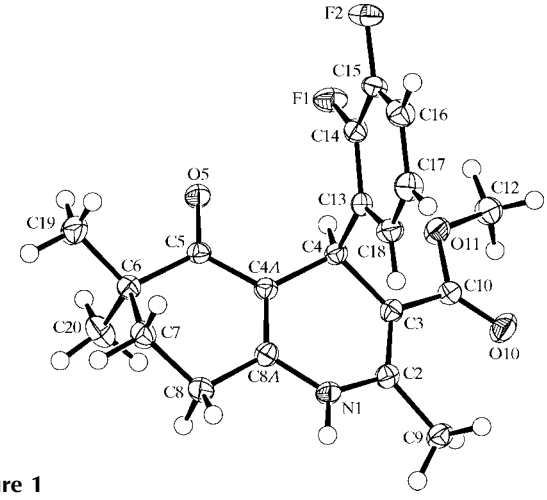


Figure 1
View of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

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evenly over the range 0.00–0.19 Å (Şimşek *et al.*, 2000; Linden *et al.*, 2002). The deviations shown by atom N1 in (I) and (II) fall well within this range. In contrast, the 1,4-DHP ring in *N*,*N*-diethyl-2,6,6-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide is completely planar (Linden *et al.*, 2002).

Another measure of the planarity of 1,4-DHP rings is the sum of the magnitudes of the six intraring torsion angles, *P*, around the ring (Fossheim *et al.*, 1988). For compounds (I) and (II), *P* is 101.8 (5) and 85.5 (5)°, respectively, which demonstrates that the boat conformations are somewhat deeper than usual. A mean value of 77 (2)° was found previously for reported 1,4-DHP rings (Linden *et al.*, 2002), although the *P* values generally vary over a wide range from 4 to 130°. For nifedipine itself, *P* is 72° (Miyamae *et al.*, 1986).

The plane of the 2,3-difluorophenyl ring in each of the title compounds deviates just slightly from being parallel to the N1···C4 axis. Compound (I) has an N1···C4—C13—C18 torsion angle of 12.19 (16)°, while the corresponding torsion angle in compound (II), N1···C4—C14—C19, is 14.26 (15)°. These values are normal. The corresponding torsion angle in related structures is clustered around 0° and rarely exceeds ±30° (Linden *et al.*, 2002). The fluoro substituents lie above the C4—H bond in a synperiplanar orientation and not over the 1,4-DHP ring; because of the substituent in the 2-position of the benzene ring, the latter configuration would be sterically unfavourable.

The Cambridge Structural Database (CSD; Release 5.26 with August 2005 updates; Allen, 2002) contains only five examples of 4-aryl-1,4-DHP compounds with 2,3-disubstitution in the benzene ring. Three of these compounds are 4-(2,3-dichlorophenyl)-2,6-dimethyl-3,5-dicarboxy-1,4-DHP derivatives (Fossheim, 1986; Lamm *et al.*, 1989; Caignan & Holt, 2000), while there is one 4-(2-chloro-3-nitrophenyl) (Rovnyak *et al.*, 1988) and one 4-(2,3-methylenedioxyphenyl) analogue (Fonseca *et al.*, 1986). In each of these compounds, the 2,3-disubstituted benzene ring has a synperiplanar orientation, similar to that found in compounds (I) and (II), and the 1,4-DHP ring has a shallow boat conformation. The 1,4-DHP ring in compound (I) actually has the most pronounced boat conformation of all of these compounds.

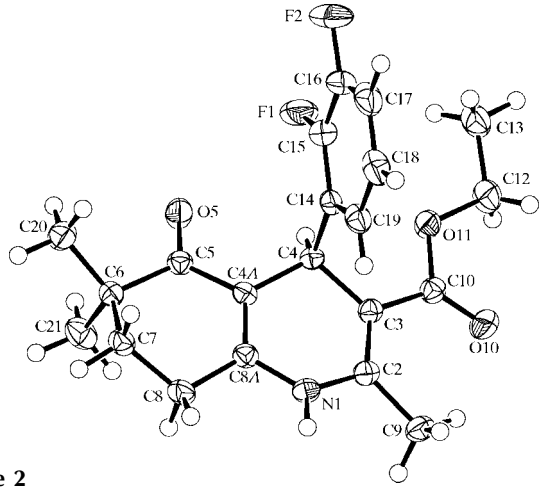

Figure 2
View of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

The oxocyclohexene ring in each of the title compounds has a slightly distorted C7-envelope conformation, as demonstrated by the ring puckering parameters (Cremer & Pople, 1975). For compound (I), *Q* is 0.4832 (17) Å, θ is 59.10 (19)° and φ_2 is 173.9 (2)° for the atom sequence C4*A*—C5—C6—C7—C8—C8*A*. Atom C7 lies 0.658 (2) Å from the plane defined by atoms C4*A*, C5, C6, C8 and C8*A*. The maximum deviation of these latter five atoms from their mean plane is 0.043 (1) Å for atom C8*A*. For the corresponding atom sequence in compound (II), *Q* is 0.4448 (15) Å, θ is 62.18 (18)° and φ_2 is 185.2 (2)°, atom C7 lies 0.606 (1) Å from the plane defined by the remaining ring atoms, and the maximum deviation of these latter five atoms from their mean plane is 0.051 (1) Å for atom C5. In both structures, atom C7 of the ring flips up on the same side of the oxocyclohexene ring plane as the 2,3-difluorophenyl substituent of the adjacent 1,4-DHP ring. It has been found that atom C7 is always the out-of-plane atom in structures involving the 5-oxoquinoline or 1,8-dioxoacridine moiety, and that the side of the oxocyclohexene ring to which C7 deviates is, in the majority, but not all, of these structures, the same as that in (I) and (II) (Linden *et al.*, 2002).

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 atom C2 and atom O10 of the ester substituent at C3 [O10···C9 = 2.8248 (19) and 2.8736 (19) 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 = −10.6 (2) and 4.4 (2)° 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 the related compound methyl 4-(2-chloro-5-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Linden *et al.*, 2004) and the many other 2-methyl-3-carboxy-4-aryl-1,4-DHP compounds archived in the CSD.

In compounds (I) and (II), an intermolecular hydrogen bond between the amine group and the carbonyl O atom of the oxocyclohexene ring of a neighbouring molecule (Tables 2 and 4) links the molecules into extended chains that run parallel to the [100] 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; Şimşek *et al.*, 2000).

Experimental

For the synthesis of the title compounds, equimolar amounts of 2,3-difluorobenzaldehyde, 4,4-dimethylcyclohexanedione and methyl acetoacetate [for (I)] or ethyl acetoacetate [for (II)], together with ammonia (1 ml), were refluxed in methanol for 6 h. The resulting solution was, in each case, poured into water and the precipitate filtered off, dried and recrystallized from ethanol (m.p. 519 and 484 K, respectively).

Compound (I)

Crystal data

$C_{20}H_{21}F_2NO_3$
M_r = 361.39
Triclinic, $P\overline{1}$
a = 7.2055 (2) Å
b = 9.6702 (4) Å
c = 12.9606 (6) Å
α = 93.9639 (19)°
β = 92.624 (2)°
γ = 107.904 (2)°
V = 855.15 (6) Å^3
Z = 2
D_x = 1.403 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4905 reflections
θ = 2.0–30.0°
μ = 0.11 mm^{-1}
T = 160 (1) K
Prism, colourless
0.27 × 0.22 × 0.20 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
21670 measured reflections
4980 independent reflections
3409 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 30.0°
$h = 0 \rightarrow 10$
$k = -13 \rightarrow 12$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.137
S = 1.05
4976 reflections
243 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0583P)^2 + 0.1694P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

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

O10—C10	1.2155 (17)	C3—C10	1.470 (2)
O11—C10	1.3474 (16)	C3—C4	1.5253 (19)
N1—C8*A*	1.3651 (18)	C4—C4*A*	1.5234 (19)
N1—C2	1.3878 (18)	C4*A*—C8*A*	1.3570 (19)
C2—C3	1.3537 (19)		
C8*A*—N1—C2	122.11 (12)	C4—C4*A*—C8*A*	119.69 (12)
N1—C2—C3	119.21 (13)	C4*A*—C8*A*—N1	120.38 (13)
N1—C2—C9	113.94 (12)	O10—C10—O11	121.76 (13)
C3—C2—C9	126.83 (13)	O10—C10—C3	126.97 (13)
C2—C3—C4	120.62 (12)	O11—C10—C3	111.28 (12)
C3—C4—C4*A*	109.74 (11)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5^{i}	0.92 (2)	2.04 (2)	2.9456 (15)	168 (2)

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

Compound (II)

Crystal data

$C_{21}H_{23}F_2NO_3$
M_r = 375.41
Triclinic, $P\overline{1}$
a = 7.0677 (2) Å
b = 11.2167 (4) Å
c = 12.1844 (4) Å
α = 83.6482 (15)°
β = 86.333 (2)°
γ = 73.2481 (18)°
V = 918.74 (5) Å^3
Z = 2
D_x = 1.358 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5288 reflections
θ = 2.0–30.0°
μ = 0.10 mm^{-1}
T = 160 (1) K
Plate, colourless
0.22 × 0.17 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
25434 measured reflections
5368 independent reflections
3911 reflections with $I > 2\sigma(I)$
R_{int} = 0.055
θ_{max} = 30.1°
$h = 0 \rightarrow 9$
$k = -14 \rightarrow 15$
$l = -16 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.143
S = 1.04
5366 reflections
252 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0643P)^2 + 0.1979P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

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

O10—C10	1.2092 (16)	C3—C10	1.4706 (18)
O11—C10	1.3528 (16)	C3—C4	1.5236 (17)
N1—C8*A*	1.3664 (17)	C4—C4*A*	1.5210 (17)
N1—C2	1.3819 (17)	C4*A*—C8*A*	1.3572 (17)
C2—C3	1.3592 (17)		
C8*A*—N1—C2	122.71 (11)	C4—C4*A*—C8*A*	120.26 (11)
N1—C2—C3	119.50 (12)	C4*A*—C8*A*—N1	120.28 (12)
N1—C2—C9	112.95 (11)	O10—C10—O11	121.63 (12)
C3—C2—C9	127.53 (12)	O10—C10—C3	127.76 (12)
C2—C3—C4	120.62 (11)	O11—C10—C3	110.59 (11)
C3—C4—C4*A*	110.81 (10)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5^{ii}	0.93 (2)	1.99 (2)	2.8712 (14)	159 (2)

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

For each structure, the position of the amine H atom was determined from a difference Fourier map and refined freely along with its isotropic displacement parameter. 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 the C—C bonds. All remaining H atoms were placed in geometrically idealized positions (C—H = 0.95–1.00 Å) and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C). For (I) and (II), four and two low-angle reflections, respectively, were omitted from the final cycles of refinement because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop.

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: SK1884). Services for accessing these data are described at the back of the journal.

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