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Methyl 4-(2-chloro-5-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

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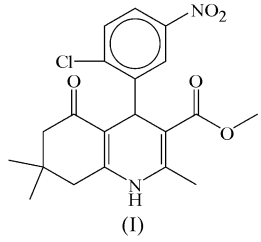
The title compound, $C_{20}H_{21}ClN_2O_5$, has potential calcium modulatory properties. The 1,4-dihydropyridine ring has the usual shallow boat conformation. The 2-chloro-5-nitrophenyl ring is oriented such that the chloro substituent is in a synperiplanar orientation with respect to the 1,4-dihydropyridine ring plane, while the nitro substituent sits over the 1,4-dihydropyridine ring. The cyclohexenone ring has a conformation that is approximately half-way between that of an envelope and that of a half-chair. The molecules are linked into chains by intermolecular N—H···O hydrogen bonds.

Comment

A wide range of chemical substances influence the flow of Ca^{2+} ions through the channels found in cell membranes. While some compounds, the calcium agonists, activate this flow, other compounds, the calcium antagonists, selectively inhibit the flow of Ca^{2+} ions through the Ca^{2+}-conducting channels (Nayler, 1988). 1,4-Dihydropyridine (1,4-DHP) derivatives have yielded many drugs that act as calcium-channel agonists. Nifedipine is the prototype of this group, and both nifedipine and its structural analogues are used as antianginal and antihypertensive drugs (Janis & Triggle, 1984). Many active derivatives have been synthesized by making various modifications to the nifedipine structure, yielding compounds with calcium agonist or antagonist properties (Rose, 1989, 1990). 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. The crystal structures of some of these derivatives have already been reported (Linden *et al.*, 1998, 2002; Şimşek *et al.*, 2000), and the title compound, (I), has been prepared as a further potentially active 1,4-DHP derivative. The structure of (I) was confirmed by IR, ^{1}H NMR and ^{13}C NMR analyses. Details of the synthesis of this compound and its antagonistic activity will be published elsewhere. The determination of its three-dimensional conformation, presented here, is important in order to obtain further insight into the structure–activity relationships of these compounds.



(I)

The 1,4-DHP ring in the structure of (I) (see Fig. 1) has a shallow boat conformation, with atoms N1 and C4 lying 0.115 (2) and 0.283 (2) Å, respectively, from the plane defined by atoms C2, C3, C4*A* and C8*A*. The shallowness of the boat is indicated by the puckering parameters (Cremer & Pople, 1975) Q = 0.2356 (15) Å, θ = 73.6 (4)° and φ_2 = 180.2 (4)° for the atom sequence N1—C2—C3—C4—C4*A*—C8*A*. 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); it is usual for the ring to have a shallow boat conformation, although considerable variation in the shallowness of the boat is evident. The deviation of atom C4 in (I) corresponds to the values of ∼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 evenly over the range 0.00–0.19 Å (Linden *et al.*, 2000, 2002). The deviation shown by atom N1 in (I) falls right in the middle of 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 was found to be completely planar (Linden *et al.*, 2002).

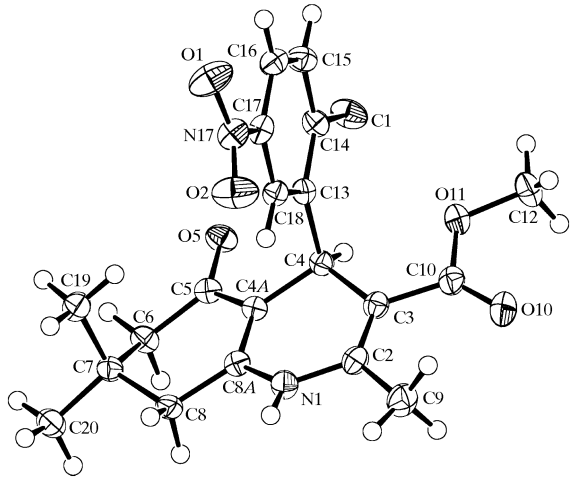


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary size.

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Another measure of the planarity of 1,4-DHP rings is the sum of the magnitudes of the six intra-ring torsion angles, *P*, around the ring (Fossheim *et al.*, 1988). For (I), *P* is 82 (1)°, which is close to the mean value of 77 (2)° 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-chloro-5-nitrophenyl ring of (I) is almost parallel to the N1···C4 axis, with an N1···C4—C13—C18 torsion angle of 2.53 (15)°. This value is normal; the corresponding torsion angle in related structures is clustered around 0° and rarely exceeds ±30° (Linden *et al.*, 2002). The chloro substituent lies above the C4—H bond in a synperiplanar orientation, while the nitro substituent sits over the 1,4-DHP ring. Examples of 2,5-disubstitution in the phenyl ring of 4-aryl-1,4-DHP compounds are rare, but the same 2-chloro-5-nitrophenyl ring appears in the analogous compound dimethyl 4-(2-chloro-5-nitrophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (Rovnyak *et al.*, 1988). The orientation of the phenyl ring in this latter compound is the same as that in (I). Such an orientation is preferred on steric grounds, since most substituents in the 2-position of the phenyl ring would not be allowed to sit directly over the 1,4-DHP ring. Thus, it is not surprising that no crystal structures of 2,6-disubstituted phenyl rings in 4-aryl-1,4-DHP compounds have been reported.

Most of the bond lengths and angles in (I) have normal values. There are small angular distortions about atoms C2 and C10 (Table 1), which result from steric interactions between the methyl substituent at atom C2 and atom O10 of the ester substituent at atom C3 [O10···C9 = 2.829 (2) Å]. The presence of π-electron conjugation keeps the ester group at atom C3 almost coplanar [C2═C3—C10═O10 = 9.0 (3)°] with the endocyclic double bond and prevents the ester group from rotating into a sterically more amenable orientation. These properties are consistent with those of the many other 2-methyl-3-carboxy-4-aryl-1,4-DHP compounds archived in the Cambridge Structural Database (Allen, 2002).

The cyclohexenone ring in (I) has a conformation that is approximately half-way between that of a C7-envelope and that of a half-chair twisted around the C6—C7 bond. This conformation is demonstrated by the puckering parameters Q = 0.4641 (16) Å, θ = 53.8 (2)° and φ_2 = 165.5 (2)° for the atom sequence C4*A*—C5—C6—C7—C8—C8*A*. The φ_2 value, in particular, lies almost exactly half-way between the nearest ideal values that would correspond to an envelope and to a half-chair conformation. Atoms C6 and C7 lie −0.176 (3) and 0.520 (3) Å, respectively, from the plane defined by atoms C4*A*, C5, C8 and C8*A*. The maximum deviation of these latter four atoms from their mean plane is 0.0134 (9) Å for both C4*A* and C8*A*. Atom C7 of the ring lies on the same side of the cyclohexenone ring plane as the 2-chloro-5-nitrophenyl 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 quinolin-5-one or dioxoacridine-1,8-dione moiety, and that the side of the cyclohexenone ring to which atom C7 deviates is, in the majority but not all of these structures, the same as that in (I) (Linden *et al.*, 2002).

An intermolecular 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 that run parallel to the [010] direction and have 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 1,4-DHP compounds (Linden *et al.*, 1998, 2002; Şimşek *et al.*, 2000).

Experimental

For the synthesis of the title compound, (I), equimolar amounts of 2-chloro-5-nitrobenzaldehyde, 5,5-dimethylcyclohexane-1,3-dione and methyl acetoacetate plus ammonia (1 ml) were refluxed in methanol for 4 h. The solution was then poured into water, and the precipitate that formed was filtered off, dried and recrystallized from ethanol (m.p. 513 K).

Crystal data

$C_{20}H_{21}ClN_2O_5$
M_r = 404.85
Orthorhombic, *Pbca*
a = 14.8737 (2) Å
b = 14.3865 (2) Å
c = 17.6287 (3) Å
V = 3772.20 (10) Å^3
Z = 8
D_x = 1.426 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 33 903 reflections
θ = 2.0–30.0°
μ = 0.24 mm^{-1}
T = 160 (1) K
Prism, yellow
0.27 × 0.22 × 0.10 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans with κ offsets
Absorption correction: multi-scan (Blessing, 1995)
T_{min} = 0.845, T_{max} = 0.981
68 164 measured reflections
5520 independent reflections
4106 reflections with $I > 2\sigma(I)$
R_{int} = 0.069
θ_{max} = 30.0°
h = −20 → 20
k = −20 → 20
l = −24 → 24

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.129
S = 1.03
5517 reflections
261 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0606P)^2 + 1.849P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.47 e Å^{-3}
$\Delta\rho_{min}$ = −0.44 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O10—C10	1.211 (2)	C3—C10	1.473 (2)
O11—C10	1.349 (2)	C3—C4	1.524 (2)
N1—C8*A*	1.372 (2)	C4—C4*A*	1.516 (2)
N1—C2	1.387 (2)	C4*A*—C8*A*	1.356 (2)
C2—C3	1.355 (2)		
C2—N1—C8*A*	122.15 (14)	C4—C4*A*—C8*A*	121.71 (13)
N1—C2—C3	119.94 (14)	N1—C8*A*—C4*A*	119.97 (14)
C3—C2—C9	126.05 (15)	O10—C10—O11	122.40 (15)
N1—C2—C9	114.01 (14)	O10—C10—C3	127.60 (16)
C2—C3—C4	121.28 (13)	O11—C10—C3	110.00 (13)
C4*A*—C4—C3	109.77 (12)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O5^{i}	0.84 (2)	2.12 (2)	2.9076 (18)	156 (2)

Symmetry code: (i) $\frac{3}{2}-x, y-\frac{1}{2}, z$.

The position of the amine H atom was determined from a difference Fourier map and refined freely along with its isotropic displacement parameter. The methyl H atoms were constrained to an ideal geometry [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 idealized positions (C—H = 0.95–1.00 Å) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C)]. Three low-angle reflections were omitted from the refinement because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); structure solution: *SIR*92 (Altomare *et al.*, 1994); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2004).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1759). Services for accessing these data are described at the back of the journal.

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