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(±)-9-(2-Bromophenyl)-7,7-dimethyl-1,3,4,5,6,7,8,9-octahydrofuro[3,4-*b*]-quinoline-1,8-dione

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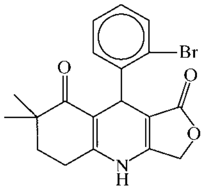
The title compound, $C_{19}H_{18}BrNO_3$, has potential calcium modulatory properties. The 1,4-dihydropyridine ring has a very shallow boat conformation and is one of the most planar examples of this moiety. The 2-bromophenyl substituent is in the axial synperiplanar orientation. The quinoline ring has a half-chair conformation, with the unusual arrangement of the out-of-plane atom being on the opposite side of the ring plane to the bromophenyl substituent. The molecules are linked into chains by intermolecular hydrogen bonds.

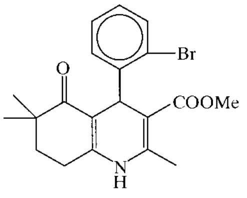
Comment

Dihydropyridine calcium entry blockers have been widely explored as cardiovascular agents. Nifedipine is the prototype of 1,4-dihydropyridine (1,4-DHP) derivatives and has been approved as a clinical agent for antianginal and anti-hypertensive therapy (Janis & Triggle, 1983; Goldmann *et al.*, 1990). It has been proposed (Fossheim, 1986; Goldmann & Stoltefuss, 1991) that the activity of ester derivatives of 1,4-DHP compounds may, in part, be associated with the orientation of the ester carbonyl groups. In order to fix these carbonyl groups in the antiperiplanar position with respect to the 1,4-DHP ring double-bond so that the activity of compounds with this arrangement can be studied, the 1,4-DHP structure can be anellated and such compounds have been obtained by the introduction of the 1,4-DHP moiety to condensed systems (Rose & Dräger, 1992). These derivatives possess similar activities to nifedipine. In addition, biotransformation studies on 1,4-DHP derivatives show that these compounds convert to lactone analogues *in vivo* and these latter compounds were also found to be active as agonists or antagonists.

The title compound, (I), has been synthesized because it is thought to be a possible metabolite of the ester, (II), which we have previously synthesized. The structure of the 2-fluorophenyl ethyl ester analogue of (II) has already been reported (Linden *et al.*, 1998). The crystal structure of (I) has now been determined in order to elucidate the specific conformational properties of the molecule.



(I)



(II)

The 1,4-DHP ring in the structure of (I) (see Fig. 1) has a very shallow boat conformation, with N1 and C4 being 0.060 (6) and 0.095 (7) Å, respectively, from the plane defined by C2, C3, C4a and C8a. The maximum deviation of these latter four atoms from their mean plane is 0.003 (2) Å for C2. The 2-bromophenyl ring occupies a pseudo-axial position and thereby lies above the 1,4-DHP boat. The plane of the 2-bromophenyl ring is almost parallel to the N1···C4 axis, with an N1···C4—C11—C16 torsion angle of −2.5 (6)°, which is sterically the most favourable orientation. The bromo substituent lies above the C4—H bond in a synperiplanar orientation and not over the centre of the boat.

The conformations of 4-aryl-1,4-DHP rings have been discussed previously (Goldmann & Stoltefuss, 1991; Linden *et al.*, 1998). The orientation of the 2-bromophenyl ring in (I) is consistent with related structures, but the 1,4-DHP ring has one of the shallowest boat conformations seen so far. The Cambridge Structural Database (CSD, April 1999 release; Allen & Kennard, 1993) contains 75 entries with the 4-aryl-1,4-DHP moiety, excluding 4,4-disubstituted derivatives, and all of them have the shallow boat conformation with the aryl group in an axial position. With the exception of one nearly planar case (Pastor *et al.*, 1994), C4 is found in the range of 0.11–0.42 Å from the plane defined by C2, C3, C4a and C8a,

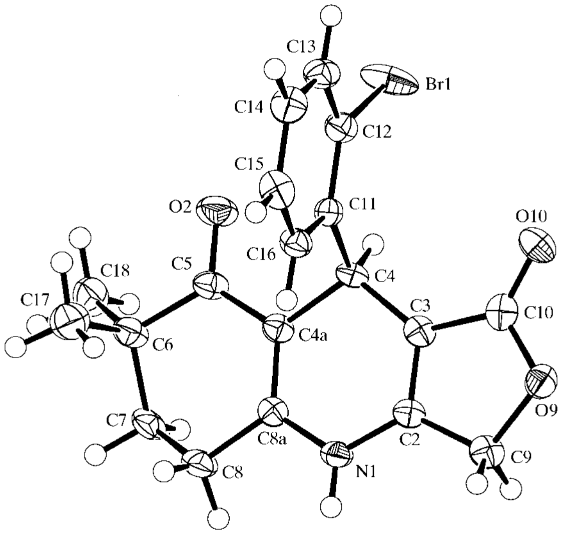


Figure 1
View of the molecule of (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by spheres of arbitrary size.

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with the most frequently occurring values being around 0.30 Å (Linden *et al.*, 1998). The deviations shown by N1 are generally smaller and the range is spread fairly evenly over 0.04–0.19 Å. While the deviation of N1 from the above-defined plane in (I) is within the normal range, the deviation of C4 is well outside the range and indicates the near planarity of this end of the 1,4-DHP ring. Another measure of the shallowness of the boat conformation in 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 (I), *P* is only 29 (2)°, compared with a range for *P* of 51–122° found for the structures of 25 1,4-DHP compounds (Fossheim *et al.*, 1988). Such a severe flattening might have significant implications for the calcium modulatory properties of (I), as it has been suggested (Fossheim *et al.*, 1982, 1988) that the most active compounds in the nifedipine and nisoldipine series possess the shallowest boat conformations. The calcium modulatory and biotransformation properties of (I) are being studied and will be reported later.

The oxocyclohexene ring in (I) has an envelope conformation, in which C7 is 0.581 (8) Å from the plane defined by C4a, C5, C6, C8 and C8a. The maximum deviation of these latter five atoms from their mean plane is 0.033 (4) Å for C5. The puckering parameters (Cremer & Pople, 1975) are Q = 0.423 (6) Å, θ = 50.5 (8)° and φ_2 = 112.8 (10)°. For an ideal envelope, θ and φ_2 are 54.7 and $n \times 60°$, respectively. The envelope flap of the ring flips down on the opposite side of the ring plane to the 2-bromophenyl substituent of the adjacent 1,4-DHP ring. The CSD contains 16 entries for structures involving the 5-oxoquinoline or 1,8-dioxoacridine moieties and it is found that C7 is always the out-of-plane atom. This is a consequence of the π-electron conjugation between the oxo group and the cyclohexene double bond, which constrains all other atoms in the cyclohexene ring to a planar conformation. However, in 13 of these structures, C7 lies on the same side of the ring plane as the substituent at C4 of the 1,4-DHP ring, so the arrangement in (I) is uncommon in this respect.

Most of the bond lengths and angles in (I) have normal values. The only irregularity is an enlarged angle for O10—C10—C3 and a correspondingly smaller angle for O9—C10—O10 (Table 1). The lactone ring has a very shallow envelope conformation, with C9 acting as the envelope flap but lying only 0.092 (7) Å from the plane defined by C2, C3, O9 and C10. The maximum deviation of these latter four atoms from their mean plane is 0.012 (3) Å for C10. Intermolecular hydrogen bonds between the amine group and the lactone carbonyl O atom, O10, of a neighbouring molecule (Table 2) link the molecules into infinite one-dimensional zigzag chains which run parallel to the *y* axis and have the graph-set motif of *C*(6) (Bernstein *et al.*, 1995).

Experimental

Compound (I) was obtained by stirring equimolar amounts of 4-(2-bromophenyl)-1,4,5,6,7,8-hexahydro-3-methoxycarbonyl-5-oxo-2,6,6-trimethylquinoline, (II), with pyridinium bromide perbromide in chloroform for 1 h at 273 K. The mixture was then refluxed for 24 h. The solvent was removed *in vacuo* and the precipitate was recrystallized from ethanol (m.p. 575 K). The product was characterized by IR, ^{1}H and ^{13}C NMR, mass spectroscopic and elemental analyses. Single crystals were obtained by recrystallization from dimethyl sulfoxide.

Crystal data

$C_{19}H_{18}BrNO_3$
M_r = 388.26
Monoclinic, $P2_1/c$
a = 11.724 (5) Å
b = 10.911 (4) Å
c = 14.218 (6) Å
β = 113.11 (4)°
V = 1672.9 (12) Å^3
Z = 4
D_x = 1.541 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 23 reflections
θ = 18.5–20.0°
μ = 2.481 mm^{-1}
T = 180 (1) K
Irregular prism, pale yellow
0.30 × 0.30 × 0.21 mm

Data collection

Rigaku AFC-5*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ-scan (North *et al.*, 1968)
$T_{\rm min}$ = 0.536, $T_{\rm max}$ = 0.609
4239 measured reflections
3842 independent reflections
2018 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.091
$\theta_{\rm max}$ = 27.54°
$h = 0 \rightarrow 15$
$k = 0 \rightarrow 14$
$l = -18 \rightarrow 17$
3 standard reflections every 150 reflections intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.165
S = 0.967
3842 reflections
220 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0831P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max}$ = 0.001
$\Delta\rho_{\rm max}$ = 0.87 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.74 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O9—C10	1.357 (6)	C3—C10	1.439 (7)
O9—C9	1.451 (6)	C4—C4a	1.533 (6)
O10—C10	1.231 (6)	C4a—C8a	1.366 (6)
N1—C2	1.365 (6)	C4a—C5	1.463 (7)
N1—C8a	1.381 (6)	C5—C6	1.537 (7)
C2—C3	1.347 (6)	C6—C7	1.533 (7)
C2—C9	1.483 (7)	C7—C8	1.519 (7)
C3—C4	1.510 (7)	C8—C8a	1.493 (7)
O10—C10—O9	118.9 (4)	O10—C10—C3	130.2 (5)
C8a—N1—C2—C3	6.2 (7)	C4—C4a—C8a—N1	−1.8 (7)
N1—C2—C3—C4	0.8 (7)	C4a—C8a—N1—C2	−5.5 (7)
C2—C3—C4—C4a	−7.1 (6)	C4a—C5—C6—C7	−29.2 (6)
C3—C4—C4a—C8a	7.6 (6)	C4a—C8a—C8—C7	23.5 (7)

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1$\cdots$O10$^{\rm i}$	0.88	2.07	2.864 (5)	149

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

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1350). Services for accessing these data are described at the back of the journal.

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