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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1156). Services for accessing these data are described at the back of the journal.

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Racemic Ethyl 4-(2-Fluorophenyl)-2,6,6-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

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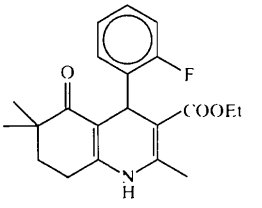
Abstract

The title compound, $C_{21}H_{24}FNO_3$, has potential calcium modulatory properties. The 1,4-dihydropyridine ring has a shallow boat conformation with the 2-fluorophenyl substituent in an axial synperiplanar orientation. The quinoline ring has a half-chair conformation. Steric interactions between the adjacent methyl and ethoxycarbonyl substituents cause local bond-angle distortions. The molecules are linked into chains by intermolecular N—H···O hydrogen bonds.

Comment

Ca^{2+} ions play a vital role in the maintenance of cardiac contractility. Calcium-channel modulators affect the passage of these ions through calcium channels and it is well established that these modulator drugs are important anti-anginal and antihypertensive agents (Janis & Triggle, 1983; Wehinger & Gross, 1986; Kendall & Luscombe, 1987; Nayler, 1988; Triggle, 1988). Those drugs that have a 1,4-dihydropyridine (1,4-DHP) moiety have been studied extensively and thoroughly reviewed (Bossert & Vater, 1989; Goldmann & Stoltefuss, 1991). Active compounds have been obtained by the introduction of the 1,4-DHP moiety to condensed systems such as acridine and quinoline. In these compounds, stereochemical differences affect their activities as an agonist and/or as an antagonist (Franckowiak *et al.*, 1985; Hof *et al.*, 1985; Rose & Dräger, 1992). Therefore, the determination of both the three-dimensional conformation of such systems and the absolute configuration of enantiomerically pure compounds, when available, is important. The structure of a racemic sample of the title compound, (I), as determined by X-ray diffraction, is reported here and corroborates the evidence obtained by IR, ^{1}H NMR, MS and elemental analyses. The calcium modulatory properties of this compound will be described in a later publication.



(I)

The 1,4-DHP ring in the structure of (I) has a shallow boat conformation, with atoms N1 and C4 0.152 (2) and 0.297 (2) Å, respectively, from the plane defined by atoms C2, C3, C4a and C8a. The maximum deviation of these latter four atoms from their mean plane is 0.0090 (6) Å for C8a. The shallowness of the boat is indicated by the puckering parameters (Cremer & Pople, 1975) Q = 0.263 (1) Å, θ = 77.3 (2) and φ_2 = 184.0 (3)°. For an ideal boat, θ and φ_2 are 90 and $n \times 60°$, respectively. The 2-fluorophenyl ring occupies an axial position and thereby lies above the 1,4-DHP boat. The plane of the 2-fluorophenyl ring is almost parallel to the N1···C4 axis [the N1···C4—C13—C18 torsion angle is 7.57 (15)°], which is sterically the most favourable

orientation. The fluoro substituent lies above the C4—H bond in a synperiplanar orientation and not over the centre of the boat.

Goldmann & Stoltefuss (1991) have noted that the preferred solid-state conformation for 4-aryl-1,4-DHP derivatives is a shallow boat with the aryl substituent in an axial position and, when asymmetrically substituted, in a synperiplanar orientation. The structure of (I) conforms to this pattern. Indeed, the Cambridge Structural Database (CSD, October 1997 release; Allen & Kennard, 1993) contains 71 entries with the 4-aryl-1,4-DHP moiety, excluding 4,4-disubstituted derivatives, and all of them have a shallow boat conformation with the aryl group in an axial position. The shallowness of the boat varies over a considerable range. With the exception of one nearly planar case (Pastor *et al.*, 1994), the deviations of the C4 atom from the plane defined by atoms C2, C3, C4a and C5 are in the range 0.11–0.42 Å, with the most frequently occurring values being around 0.30 Å. The deviations shown by the N1 atom are usually smaller and the range is spread fairly evenly over 0.04–0.19 Å. The full boat form, which requires deviations in the range 0.6–0.7 Å, is never attained. The CSD also indicates that other conformations, such as the envelope conformation (Huml *et al.*, 1979) or very planar systems (Beddoes *et al.*, 1996), have been observed for 1,4-DHP rings, but these occur in structures which do not possess a 4-aryl substituent or which are 4,4-disubstituted derivatives. There is no evidence for a chair-related conformation in 1,4-DHP rings. The variation in the orientation of the aryl rings is noteworthy. Of the 71 CSD entries, 55 have the aryl ring within 20° of the perfect synperiplanar orientation, while most of the remainder have twists of up to 44°. There are four reports of structures in which the substituted aryl ring adopts an antiperiplanar orientation (Tamazawa *et al.*, 1986; Rovnyak *et al.*, 1988; Sakoda *et al.*, 1992; Pastor *et al.*, 1994).

The oxocyclohexene ring in (I) has an envelope conformation in which the C7 atom is 0.614 (2) Å from the plane defined by atoms C4a, C5, C6, C8 and C8a. The maximum deviation of these latter five atoms from their mean plane is 0.0390 (9) Å for C4a. The puckering parameters are Q = 0.450 (2) Å, θ = 61.3 (1) and φ_2 = 180.3 (2)°. For an ideal envelope, θ and φ_2 are 54.7 and $n \times 60°$, respectively. The envelope flap of the ring flips up on the same side of the ring plane as the boat ends in the adjacent 1,4-DHP ring. The CSD contains 11 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.

Most of the bond lengths and angles have normal values. There are small angular distortions about the C2 and C10 atoms which result from steric interactions between the methyl substituent at C2 and the O1 atom of the ethoxycarbonyl substituent at C3 (Table 1). The presence of π-electron conjugation keeps the carboxyl group at C3 coplanar 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 CSD.

Intermolecular hydrogen bonds between the amine group and the oxo O atom of a neighbouring molecule (Table 2) link the molecules into infinite one-dimensional chains which run parallel to the z axis and have the $C(6)$ motif (Bernstein *et al.*, 1995).

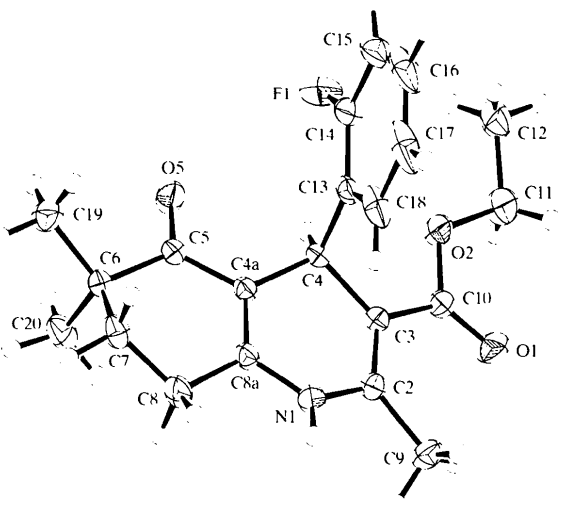


Fig. 1. View of (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary size.

Experimental

The title compound, (I), was obtained by refluxing 1 ml of ammonia solution with equimolar amounts (0.001 mol) of 4,4-dimethyl-1,3-cyclohexanedione, 2-fluorobenzaldehyde and ethyl acetoacetate in methanol for 4 h. The resultant precipitate was recrystallized from ethanol (m.p. 487 K).

Crystal data

$C_{21}H_{24}FNO_3$
M_r = 357.41
Triclinic
$P\overline{1}$
a = 10.9500 (12) Å
b = 12.2333 (9) Å
c = 7.1453 (6) Å
α = 90.242 (7)°
β = 106.042 (7)°
γ = 85.257 (8)°
V = 916.55 (14) Å^3
Z = 2
D_x = 1.295 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 19.5–20.0°
μ = 0.093 mm^{-1}
T = 173 (1) K
Prism
0.50 × 0.40 × 0.25 mm
Colourless

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
Absorption correction: none
5585 measured reflections
5326 independent reflections
4309 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$
$\theta_{max} = 30.0°$
$h = 0 \rightarrow 15$
$k = -17 \rightarrow 17$
$l = -10 \rightarrow 9$
3 standard reflections
every 150 reflections
intensity decay: insignificant

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.160$
$S = 1.050$
5326 reflections
330 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0875P)^2 + 0.2634P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.96$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

F1—C14	1.332 (2)	C3—C4	1.5265 (16)
O1—C10	1.2113 (16)	C4—C4a	1.5207 (16)
O2—C10	1.3549 (16)	C4—C13	1.5260 (17)
O2—C11	1.4572 (17)	C4a—C8a	1.3619 (16)
O5—C5	1.2334 (15)	C4a—C5	1.4540 (17)
N1—C8a	1.3673 (16)	C5—C6	1.5372 (17)
N1—C2	1.3860 (17)	C6—C7	1.5326 (19)
C2—C3	1.3610 (17)	C7—C8	1.517 (2)
C3—C10	1.4745 (17)	C8—C8a	1.4986 (18)
C10—O2—C11	115.59 (11)	C5—C4a—C8a	120.19 (11)
C8a—N1—C2	122.57 (11)	C4a—C5—C6	119.62 (10)
C3—C2—N1	119.28 (11)	C5—C6—C7	111.10 (10)
C3—C2—C9	127.60 (12)	C6—C7—C8	113.32 (11)
N1—C2—C9	113.09 (11)	C7—C8—C8a	111.12 (11)
C2—C3—C10	120.83 (11)	C4a—C8a—N1	120.14 (11)
C2—C3—C4	120.84 (11)	C4a—C8a—C8	123.71 (11)
C4—C3—C10	118.24 (10)	O1—C10—O2	121.65 (12)
C3—C4—C4a	110.44 (9)	O1—C10—C3	127.48 (12)
C4—C4a—C8a	120.36 (11)	O2—C10—C3	110.85 (10)
C8a—N1—C2—C3	16.1 (2)	C5—C6—C7—C8	−48.90 (15)
N1—C2—C3—C4	4.19 (18)	C6—C7—C8—C8a	49.25 (17)
C2—C3—C4—C4a	−22.60 (16)	C7—C8—C8a—C4a	−20.8 (2)
C3—C4—C4a—C8a	24.22 (16)	C5—C4a—C8a—C8	−8.1 (2)
C4—C4a—C8a—N1	−7.44 (19)	C2—C3—C10—O1	5.7 (2)
C2—N1—C8a—C4a	−14.5 (2)	C4—C3—C10—O1	−177.78 (14)
C8a—C4a—C5—C6	8.15 (18)	C2—C3—C10—O2	−172.64 (11)
C4a—C5—C6—C7	20.24 (16)	C4—C3—C10—O2	3.92 (16)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O5^{i}	0.86 (2)	2.06 (2)	2.9012 (15)	165 (2)

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

The largest peak of residual electron density was within 0.07 Å of the H atom at C18 and attempts to refine the isotropic displacement parameter of this H atom led to a negative value. This suggests that the fluorophenyl ring might have orientational disorder caused by a 180° rotation about the C4—C13 bond, thereby leading to two sites for the F atom. However, all attempts to refine a model with a second position for the F atom, even with very low site occupancy, failed to yield chemically reasonable results. The C—F bond for the minor orientation always refined to about 1.0 Å. When appropriate bond-length restraints were imposed on this C—F bond, the displacement parameters for the F atom became unreasonable. Therefore, an ordered model was employed and the H atom at C18 was placed in a geometrically calculated position and allowed to ride on its parent atom with an isotropic displacement parameter set equal to $1.2U_{eq}$ of C18. All other H atoms were located in a difference electron-density map and their positions were refined together with individual isotropic displacement parameters.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1989). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). 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.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1427). Services for accessing these data are described at the back of the journal.

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4-Cyano-4′-[(4*R*)-4,5-epoxypentyloxy]biphenyl: a Pseudosymmetry Problem Solved with Synchrotron Data

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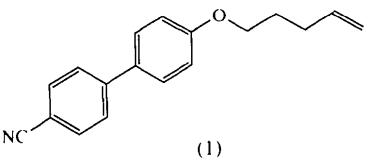
Abstract

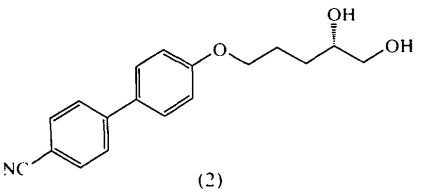
The title compound, 4′-[(4*R*)-4,5-epoxypentyloxy]-4-biphenylcarbonitrile, $C_{18}H_{17}NO_2$, crystallizes in space group $P2_1$ with two independent molecules of identical chirality. The molecules differ significantly only in the conformation of the substituent containing the epoxide ring. With the exception of this ring, the structure approximates closely to the centrosymmetric space group $P2_1/n$, in which refinement can be achieved with the assumption of twofold disorder of orientation of the epoxide ring and a racemic material. The pseudosymmetry is resolved by a weak subset of $h0l$ reflections ($h + l = 2n$), which are found to be significant in a synchrotron data set. The two rings of the biphenyl unit are essentially coplanar, in contrast to most 4-cyano-4′-(alkyloxy)biphenyl compounds.

Comment

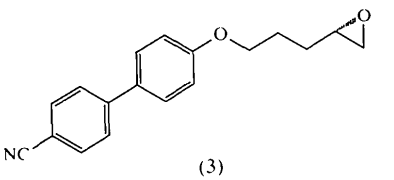
The title compound, (3), was synthesized as part of a study of chiral side-chain liquid crystalline polymers. Only very thin plate crystals could be obtained and no measurable diffraction pattern was found on an Enraf–Nonius FAST diffractometer with Mo $K\alpha$ radiation from a rotating-anode source. Satisfactory data were collected during the commissioning of the new high-flux single-crystal diffraction station 9.8 at CCLRC Daresbury Laboratory Synchrotron Radiation Source (Cernik *et al.*, 1997).



(1)



(2)



(3)

Intensity statistics strongly suggested a centrosymmetric structure, and the presence of a 2_1 axis was clearly indicated; the mean intensity for $h0l$ reflections with $h + l = 2n + 1$ was only about 10% that of the rest of the data, and they were initially taken to be systematic absences. Structure solution was possible in space group $P2_1/n$ and refinement required a twofold disorder of orientation of the epoxide ring. All other molecular features appeared normal and the final residuals were acceptable, *e.g.* R was approximately 0.07. In this case, the material must be racemic.

The 'n-glide absences' in the data set, although considerably weaker than the general reflections, were markedly more intense than the absences due to the 2_1 axis, and the mean I/σ ratio was 6.1 for this subset of data (13.4 for the complete data set and 0.4 for the screw-axis absences). There is anecdotal evidence for the overestimation of weak intensities by area-detector systems, but some of the explanations proposed do not apply for synchrotron data collected in this experiment; for example, the second-order harmonic of the selected wavelength (Kirschbaum *et al.*, 1997) is absent, corresponding to the 'forbidden' (in spherical atom terms) 222 reflection of the silicon monochromator, and higher-order harmonics should be rejected by the vertically focusing mirror.

The assumption of space group $P2_1$ led to a solution with two molecules in the asymmetric unit. In this case, apparent disorder of the epoxide rings was due to pseudosymmetry (an approximate inversion centre relating the two molecules), which could be overcome by selection of correct atom sites from the double images initially obtained in electron-density syntheses. On refinement, the second image of each ring disappeared and the molecular geometry was normal, without the need of any constraints or restraints other than the usual con-

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