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Racemic isopropyl 1,4-dihydro-2,6-dimethyl-4-(6-methyl-2-pyridyl)-3-nitropyridine-5-carboxylate hemibenzene solvate

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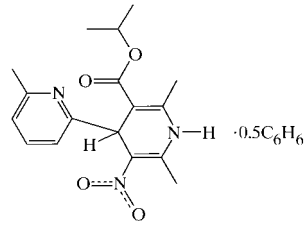
This analysis establishes the rotameric orientation of the pyridyl-ring N atom of the title compound, $C_{17}H_{21}N_3O_4{\cdot}0.5C_6H_6$, as antiperiplanar (*ap*) to the 1,4-dihydropyridine H-4, the absence of an intramolecular hydrogen bond between the 1,4-dihydropyridine NH and the pyridyl-N atom, and the unusual planarity of the 1,4-dihydropyridine ring.

Comment

The design of cardioselective Hantzsch 1,4-dihydropyridine (DHP) L-type voltage-sensitive calcium channel agonist positive inotropes has presented a significant challenge in drug design (Langs *et al.*, 1990, 1991). Although there have been extensive efforts to understand the molecular basis of action (Peterson *et al.*, 1996) and structure–activity relationships (Triggle, 1996), the development of a cardioselective calcium channel stimulant has not been reported (Rampe & Kano, 1994). Recently, we discovered a novel third generation class of isomeric alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(pyridyl)-5-pyridinecarboxylates where the 4-(2-pyridyl) isomer acted as a dual cardioselective calcium channel agonist/smooth muscle selective calcium channel antagonist (Iqbal *et al.*, 1998). ^{1}H NMR nuclear Overhauser enhancement (NOE) studies, for a group of isopropyl or phenethyl 1,4-dihydro-3-nitro-4-(3- or 6-substituted-2-pyridyl)-5-pyridinecarboxylates, clearly indicated that a significant rotamer fraction is present in which the pyridyl-N atom is antiperiplanar (*ap*) to the 1,4-DHP H-4 in all cases irrespective of whether the substituent (H, Me, Ph) is located at the C-3 or C-6 position of the 2-pyridyl moiety. In addition, variable-temperature ^{1}H NMR studies indicated the 1,4-DHP NH is hydrogen-bonded. The orientation of the 6-substituted-2-pyridyl group differs from that of an *ortho*-substituted-phenyl ring in Hantzsch 1,4-DHP calcium channel antagonists since the rotamer where the *ortho*-phenyl ring substituent is synperiplanar (*sp*) to the 1,4-DHP H-4 is generally thermodynamically more preferential (Rovnyak *et al.*, 1991).

We now describe the X-ray analysis of racemic isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(6-methyl-2-pyridyl)-pyridine-5-carboxylate, (I) (Iqbal *et al.*, 1998), to establish the rotameric orientation of the pyridyl ring unambiguously and to determine whether a potential intramolecular hydrogen-bonding interaction involving the amine NH moiety exists. These novel third generation calcium channel modulators offer a new drug-design approach directed to the treatment of congestive heart failure, and may be useful as probes to study the structure–function relationships of calcium channels.



(I)

Each unit cell contains four molecules of the title compound and two benzene molecules of crystallization. The benzene is packed between the isopropyl groups of two neighbouring molecules of the title compound, and lies on a crystallographic centre of symmetry.

The torsion angles indicate that the 1,4-DHP ring is relatively flat; however, angles of the greatest magnitude are found around the N1 and C4 atoms. The deviation from strict

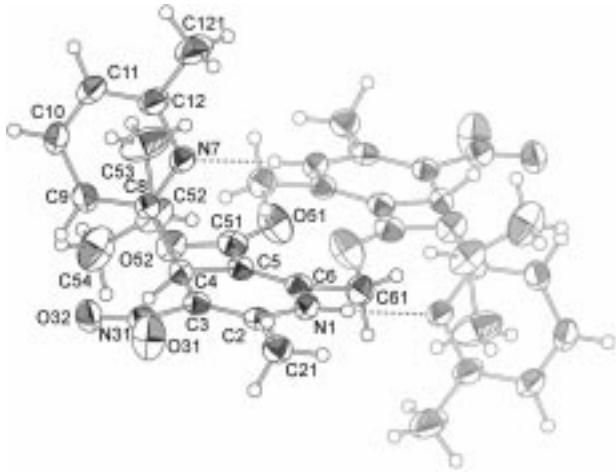


Figure 1
ZORTEP (Zsolnai & Huttner, 1994) diagram of the title compound showing the atom-labelling scheme. Two molecules are shown, with a symmetry-related molecule shown in grey. Hydrogen bonds between N7 and N1—H are shown as dotted lines. The benzene which co-crystallized is not included. Displacement ellipsoids are at the 50% probability level.

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planarity takes the form of a slight boat conformation with the N1 and C4 atoms being displaced towards the pyridyl side of the ring. The sum of the absolute values of all the torsion values around the 1,4-DHP ring is 28 (5)°, a value much smaller than the reported range of 39 to 78° for other 1,4-DHP ring structures (Langs & Triggle, 1985; Fossheim, 1987). Increased planarity of this ring has been suggested to be associated with greater pharmacological activity (Triggle *et al.*, 1980; Fossheim *et al.*, 1982).

The nitro group attached to C3 is almost coplanar with the 1,4-DHP ring, with a torsion of 13.4 (2)° relative to the C2═C3 bond. This rotation relieves the potential steric clash between the pyridyl group and the proximal oxygen of the nitro group. Similarly the ester group attached to C5 is rotated approximately 18 (2)° out of the plane of the 1,4-DHP ring. The shortness of the C3—N31 (nitro) bond [1.430 (2) Å] relative to the canonical length (1.471 Å) found in nifedipine structures indicates a greater degree of electron delocalization, this was previously observed in another nitro-substituted 1,4-DHP ring (Langs & Triggle, 1985). Similarly the N1—C2 bond is shorter than in nifedipine structures [1.363 (2) Å compared to 1.380 Å], but longer than that seen in methyl 2,6-dimethyl-5-nitro-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate (1.350 Å). Despite the differences, both compounds appear to share more electron delocalization over the nitro groups which may explain the greater degree of planarity of the 1,4-DHP ring.

The pyridine group is oriented approximately perpendicular to the plane of the 1,4-DHP ring, with the N atom of the pyridyl group antiperiplanar to the 1,4-DHP H4. The pyridyl-N atom is turned slightly toward C5 (approximately 3.7° relative to a line bisecting the C3—C4—C5 angle). No intramolecular hydrogen bond is formed between the NH of the 1,4-DHP ring and the pyridyl-N atom since the N—H bond vector is oriented in the same direction as the pyridyl-N atom lone pair; however, a hydrogen bond is formed between these atoms in the intermolecular packing interactions (Fig. 1). The possibility of a dimer persisting in solution similar to that found in the solid-state structure is supported by the NMR data and is worth investigating further. The *ap* orientation of the pyridyl-N atom may be due to the smaller relative size of the N atom to the C3—H atoms; alternately, there may be an electrostatic explanation because in the *sp* orientation the pyridyl-N atom lone pair would be approximately 3.0 Å from the nitro oxygen compared to 3.8 Å in the *ap* orientation.

The hydrogen positions that were defined for the methyl group attached to C2 on the 1,4-DHP ring contrast with the methyl group on C6 which does not show clearly defined H-atom positions. The explanation for this lies in the closer approach of a nitro-O atom to the methyl at C2 (2.70 Å) relative to an ester O atom to C6 methyl distance (2.85 Å); this shorter distance forces the H atoms to adopt a staggered conformation relative to the nitro-O atom.

Experimental

The title compound was dissolved in benzene and recrystallized by slow equilibration by placing the solution inside another chamber containing hexane. Yellow crystals of appropriate size were obtained after 1–2 d.

Crystal data

$C_{17}H_{21}N_3O_4\cdot0.5C_6H_6$
M_r = 370.42
Monoclinic, $P2_1/n$
a = 7.9436 (6) Å
b = 15.1440 (11) Å
c = 16.3075 (11) Å
β = 102.2083 (13)°
V = 1917.4 (2) Å^3
Z = 4
D_x = 1.283 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4348 reflections
θ = 1.85–27.49°
μ = 0.090 mm^{-1}
T = 193 (2) K
Prism, clear pale yellow
0.38 × 0.28 × 0.18 mm

Data collection

CCD area detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997*a*)
T_{min} = 0.966, T_{max} = 0.984
9844 measured reflections
4293 independent reflections
2898 reflections with $I > 2\sigma(I)$
R_{int} = 0.035
θ_{max} = 27.49°
$h = -10 \rightarrow 9$
$k = -19 \rightarrow 13$
$l = -13 \rightarrow 21$
1 standard reflection
every 1200 reflections
intensity decay: < 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.126
S = 1.003
4293 reflections
290 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0578P)^2 + 0.8765P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Methyl-H atoms on C53, C54, C61 and C121 and one of the H atoms of the benzene solvate were allowed for as riding atoms; coordinates for methyl-H atoms on C21 and other H atoms were refined; the C—H distances are in the range 0.95 (2)–1.01 (3) Å.

Data collection: *SMART* (Siemens, 1996); cell refinement: *SMART*; data reduction: *SHELXTL* (Sheldrick, 1996); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*b*); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*c*); molecular

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.3634 (19)	C6—N1	1.381 (2)
C2—C3	1.361 (2)	C3—N31	1.4297 (19)
C3—C4	1.511 (2)	N31—O31	1.2397 (17)
C4—C5	1.5263 (19)	N31—O32	1.2327 (17)
C5—C6	1.350 (2)		
C6—N1—C2	124.19 (14)	C2—C3—N31	120.58 (13)
N1—C2—C3	117.76 (14)	C4—C3—N31	114.50 (13)
C2—C3—C4	124.83 (13)	C3—C4—C8	112.59 (11)
C3—C4—C5	110.17 (12)	C5—C4—C8	112.35 (12)
C4—C5—C6	121.89 (13)	C4—C5—C51	117.34 (13)
N1—C6—C5	120.56 (14)	C6—C5—C51	120.77 (14)
N1—C2—C21	113.93 (14)	C5—C6—C61	126.63 (14)
C3—C2—C21	128.25 (14)	N1—C6—C61	112.63 (14)
C6—N1—C2—C3	−4.6 (2)	C2—C3—N31—O31	13.4 (2)
N1—C2—C3—C4	−3.0 (2)	N1—C6—C5—C51	179.05 (13)
C2—C3—C4—C5	7.4 (2)	C6—C5—C51—O51	−18.4 (2)
C3—C4—C5—C6	−5.17 (19)	C3—C4—C8—N7	65.31 (17)
C4—C5—C6—N1	−1.1 (2)	C3—C4—C8—C9	−114.88 (15)
C5—C6—N1—C2	6.7 (2)	C5—C4—C8—N7	−59.78 (17)
N1—C2—C3—N31	173.52 (12)	C5—C4—C8—C9	120.03 (15)

graphics: *XtalView* (McRee, 1998); software used to prepare material for publication: *XtalView* and *ZORTEP* (Zsolnai & Huttner, 1994).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1058). Services for accessing these data are described at the back of the journal.

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