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Ethyl methyl 1,4-dihydro-4-(3-nitrophenyl)-2,6-bis(1-piperidylmethyl)-pyridine-3,5-dicarboxylate

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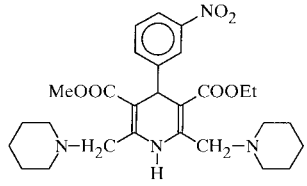
In the title compound, $C_{28}H_{38}N_4O_6$, the 4-aryl substituent occupies a pseudo-axial position approximately orthogonal to the plane of the dihydropyridine ring [88.1 (3)°]. The dihydropyridine ring adopts a flattened boat conformation. The H atom on the pyridine N atom is involved in a bifurcated intramolecular hydrogen bond, the acceptors being the N atoms of the two piperidylmethyl groups [N···N 2.629 (4) and 2.695 (4) Å].

Comment

Research on the 4-aryl-1,4-dihydropyridine (1,4-DHP) system is of current interest due to its exceptional properties as a calcium antagonist. Many 4-aryl-1,4-dihydropyridines related to nifedipine have been synthesized, and some attempts have been made to generate a quantitative structure–activity relationship (Triggle *et al.*, 1989). This type of compund is involved in the regulation of intracellular Ca^{2+} concentration, which is of fundamental significance to a host of cellular processes (Schleifer, 1999). Other important related molecules, such as nimodipine (Kazda & Toward, 1981) or amlodipine (Arrowsmith *et al.*, 1985), are chiral drugs, due to the presence of a stereogenic carbon at C4. Pharmacological studies have shown quantitative differences between enantiomers and, consequently, a large effort has been directed towards the asymmetric synthesis of 1,4-DHPs (Goldmann & Stoltefuss, 1991). However, the synthesis of racemic 1,4-DHPs bearing novel substituents is still a highly active field, leading to stronger activities and novel pharmacological effects (Ogawa *et al.*, 1993). In spite of the widely developed chemistry of the 1,4-DHP system (Kuthan & Kurfurst, 1982), much less is known about the synthesis of 1,4-DHP derivatives bearing substituents other than H atoms or alkyl groups at C2 and C6 (Guzman *et al.*, 1990). Recently, we have developed the study of 1,4-dihydropyridine derivatives of hexahydroquinoline (Dago Morales *et al.*, 1996) and of acridine (Novoa de Armas *et al.*, 1999), and the X-ray analyses show a boat conformation for the 1,4-DHP ring. In this paper, we report the crystal structure of the title compound, (I), as a contribution toward the definition of a structure–activity relationship for this important class of compounds.



(I)

In compound (I), the 4-aryl substituent occupies a pseudo-axial position, approximately orthogonal to the plane of the dihydropyridine ring [88.1 (3)°]. The 3-nitrophenyl substituent is rotated 5.1 (4)° with respect to the plane of the aromatic ring, and the nitro group adopts a synperiplanar (*sp*) arrangement, on the side opposite the H atom at C4.

Both ester groups were found to be nearly coplanar with the nearest double bond in the DHP ring. The ester group of the methoxycarbonyl substituent is rotated 22.2 (3)° with respect to the plane of the dihydropyridine ring (C2—C3···C5—C6), and the ester group of the ethoxycarbonyl substituent is twisted with respect to the plane of the dihydropyridine ring. The ester groups show a preference for the *sp* orientation, as found in the majority of the more than 30 crystal structures of the members of the nifedipine family (Triggle *et al.*, 1989).

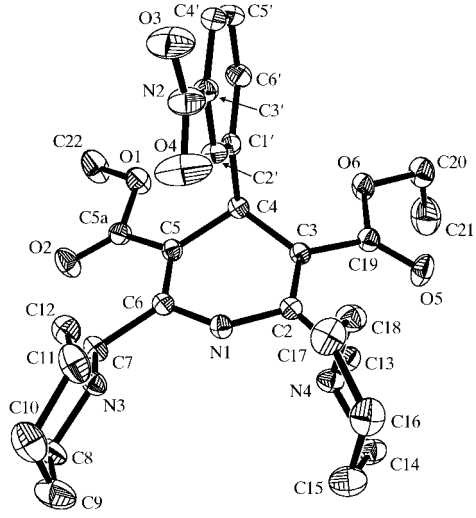


Figure 1
A perspective view of the molecule of (I) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 20% probability level and H atoms have been omitted for clarity.

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The dihydropyridine ring in (I) adopts a flattened boat conformation. The ring puckering (Cremer & Pople, 1975) parameters are ΔC_s(N1) = 0.004 (2) and Δ_s(C3—C2) = 0.057 (2). The deviations from the least-squares plane through C2, C3, C5 and C6 are C2 0.003 (4), C3 −0.003 (4), C5 0.003 (4), C6 −0.003 (4), C4 −0.437 (4) and N1 −0.175 (3) Å (Duax *et al.*, 1976). The H atom on N1 is involved in a bifurcated intramolecular hydrogen bond, the acceptor atoms being N3 and N4 of the two piperidylmethyl groups.

Experimental

A mixture of (I) (2.4 mmol) and bromine (10 mmol) in acetic acid (10 ml) was heated at reflux for 2 h and then poured over ice–water. The solid that precipitated was collected by filtration. The bromide derivative, (II), was obtained in 72% yield after recrystallization from ethanol (m.p. 470–471 K). A mixture of ethyl methyl 2,6-dibromomethylene-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, (II) (0.5 mmol), and piperidine (1.5 mmol) in ethanol (10 ml) was heated at reflux for 6 h. The reaction mixture was cooled to 273 K and the solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol–water (2:1) (yield 52%; m.p. 504–506 K). Crystals of (I) suitable for X-ray analysis were obtained by slow evaporation from an ethanol solution. The IR, and ^{1}H and ^{13}C NMR data are available in the CIF.

Crystal data

$C_{28}H_{38}N_4O_6$
M_r = 526.62
Monoclinic, $P2_1/c$
a = 8.9714 (6) Å
b = 11.7112 (11) Å
c = 26.7180 (23) Å
β = 97.271 (5)°
V = 2784.6 (4) Å^3
Z = 4
D_x = 1.256 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 38 reflections
θ = 21.48–53.81°
μ = 0.73 mm^{-1}
T = 296 (2) K
Prismatic, light yellow
0.28 × 0.24 × 0.20 mm

Data collection

Siemens $P4$ four-circle diffractometer
$2\theta/\omega$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.725, T_{max} = 0.864
6839 measured reflections
4939 independent reflections
2435 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
θ_{max} = 69.13°
$h = -1 \rightarrow 10$
$k = -1 \rightarrow 14$
$l = -32 \rightarrow 32$
3 standard reflections
every 100 reflections
frequency: 60 min
intensity decay: <1.7%

Refinement

Refinement on F^2
$R(F)$ = 0.054
$wR(F^2)$ = 0.270
S = 1.205
4939 reflections
346 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1088P)^2 + 2.85P]$ where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

Table 1
Selected geometric parameters (Å).

O4—N2	1.216 (6)	N1—C2	1.372 (5)
O3—N2	1.203 (5)	N2—C3′	1.469 (6)
O2—C5*A*	1.207 (6)	N3—C7	1.462 (5)
O5—C19	1.197 (5)	N3—C12	1.466 (5)
O1—C5*A*	1.364 (5)	N3—C8	1.450 (6)
O1—C22	1.460 (7)	N4—C13	1.467 (5)
O6—C19	1.356 (5)	N4—C18	1.457 (5)
O6—C20	1.440 (6)	N4—C14	1.459 (5)
N1—C6	1.371 (5)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···N3	0.86	2.20	2.629 (4)	110
N1—H1···N4	0.86	2.30	2.695 (4)	108

All H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms with isotropic displacement parameters fixed to $1.3U_{eq}$ of the parent atoms. C—H distances were in the range 0.93–0.98 Å.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *PARST* (Nardelli, 1983, 1995) and *PARSTCIF* (Nardelli, 1991).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1242). Services for accessing these data are described at the back of the journal.

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