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Ethyl 5-carboxy-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate

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Key indicators

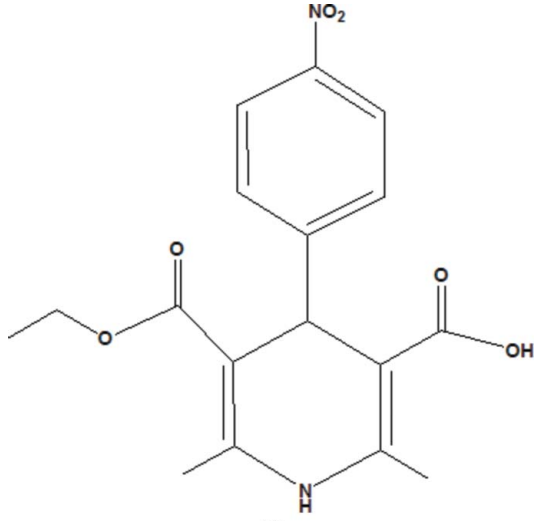
Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.004 Å
Disorder in main residue
R factor = 0.051
wR factor = 0.149
Data-to-parameter ratio = 12.7

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_{17}H_{18}N_2O_6$, is an important intermediate in the synthesis of nefidipine analogs. The crystal packing is stabilized by intermolecular N—H···O hydrogen bonds and O—H···O hydrogen bonds.

Comment

4-Aryl-1,4-dihydropyridine-3,5-dicarboxylic diesters of the nefidipine type have become almost indispensable for the treatment of cardiovascular diseases since they first appeared on the market in 1975 (Yiu & Knaus, 1999; Goldmann & Stoltefuss, 1991). The title compound, (I) (Fig. 1), is a key intermediate for the preparation of nefidipine analogs (Dagnino *et al.*, 1987).



(I)

The dihydropyridine ring has a flattened boat conformation. This compares well with the structure of 3-benzotriazol-1-yl-5-ethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and nefidipine (Sun *et al.*, 2006; Hofmann & Cimiraglia, 1990). Atoms C3 and N1 are displaced from the mean plane formed by the other atoms in the same ring by 0.389 (1) and 0.196 (1) Å, respectively. The dihedral angle between the benzene ring and the C1/C2/C4/C5 plane is 89.16°. The crystal packing is stabilized by intermolecular N—H···O hydrogen bonds and O—H···O hydrogen bonds.

Experimental

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, (II), was prepared by a Hanstzch condensation reaction (Dagnino *et al.*, 1987). The title compound, (I), was prepared by

hydrolysis of (II). Compound (II) (374 mg, 1 mmol) was dissolved in ethanol (10 ml). NaOH (320 mg, 5 mmol) in water (2 ml) was added to the solution at room temperature. The reaction mixture was stirred under reflux for a further 8 h. The solvent was removed by vacuum evaporation. Water (50 ml) was added and the solution was extracted with ethyl acetate. The organic layer contained the unreacted ester. The aqueous layer was acidified with hydrochloric acid to pH 3–4. The target compound was extracted with ethyl acetate and purified by chromatography on a silica-gel column (eluted by ethyl acetate and petroleum, 1:5) at room temperature. The product was obtained in 50% yield. Suitable crystals were obtained by slow evaporation of an ethanol solution.

Crystal data

$C_{17}H_{18}N_2O_6$
M_r = 346.33
Monoclinic, $P2_1/n$
a = 10.323 (2) Å
b = 15.590 (3) Å
c = 11.202 (3) Å
β = 108.201 (4)°
V = 1712.7 (7) Å^3
Z = 4
D_x = 1.343 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 294 (2) K
Block, yellow
0.40 × 0.28 × 0.10 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.960, T_{max} = 0.990
8538 measured reflections
3024 independent reflections
1890 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.149
S = 1.02
3024 reflections
239 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0635P)^2 + 0.8733P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^{i}	0.86	2.16	2.894 (3)	143
O6—H6···O5^{ii}	0.82	1.79	2.605 (3)	174

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$; (ii) $-x+2, -y, -z+1$.

Methyl H atoms were placed in calculated positions, with C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C); the torsion angles of the ordered methyl group were refined to fit the electron density. Other H atoms were placed in calculated positions, with C—H = 0.93–0.98 Å, N—H = 0.86 Å, O—H7 = 0.82 Å and U_{iso}(H) = xU_{eq}(C,O), where x = 1.2 or 1.5. The disordered methyl group was refined on two sites with equal occupancies. The C—C bond lengths were restrained to 1.45 (1)–1.50 (1) Å and the C···O distances restrained to 2.30 (1)–2.50 (1) Å.

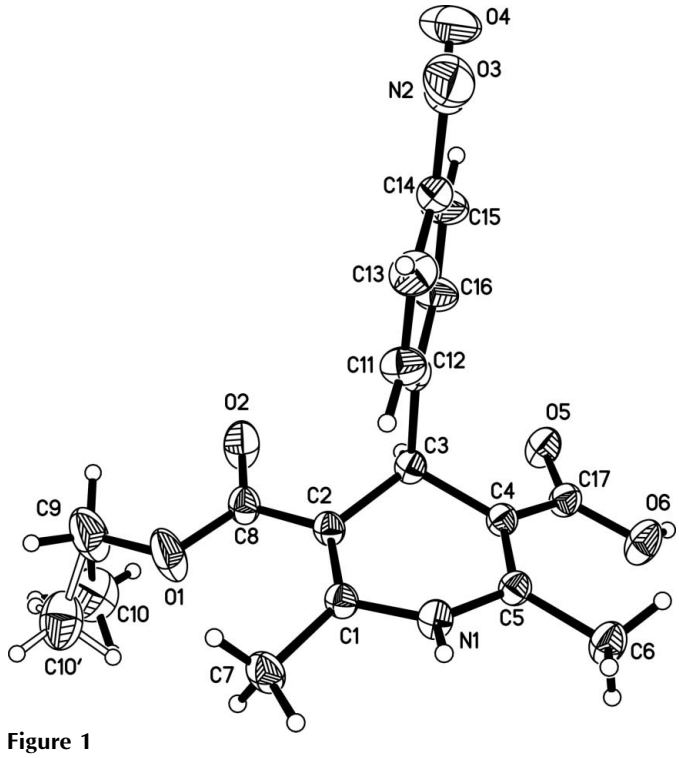


Figure 1
The molecular structure of compound (I). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

The bond angles were also restrained by restraining the 1–3 atom distances.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

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