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3-(Benzotriazol-1-yl) 5-ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate ethyl acetate hemisolvate

Feng-Xia Sun, De-Cai Fu* and Yi-Feng Yu

College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, People's Republic of China

Correspondence e-mail: fxsun001@163.com

Key indicators

Single-crystal X-ray study
T = 113 K
Mean σ(C–C) = 0.002 Å
Disorder in solvent or counterion
R factor = 0.044
wR factor = 0.120
Data-to-parameter ratio = 14.7

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

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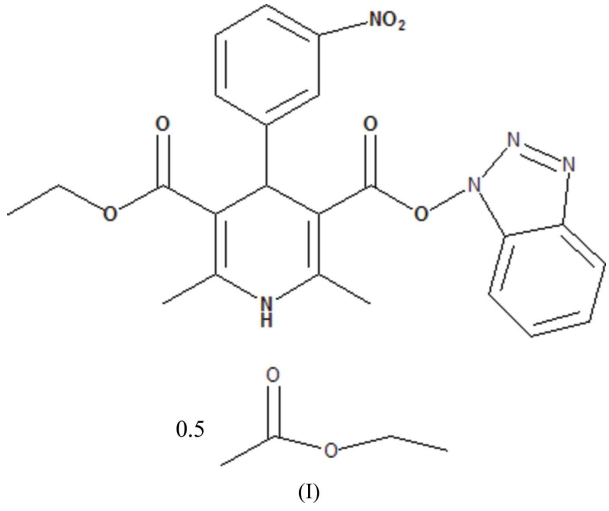
The title compound, $C_{23}H_{21}N_5O_6\cdot0.5C_4H_8O_2$, is an important intermediate in the synthesis of nefidipine-type pharmaceuticals. The crystal packing is stabilized by intermolecular N—H···O hydrogen bonds.

Comment

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



(I)

Fig. 1 shows the structure of (I). The dihydropyridine ring has a flattened boat conformation. This compares well with the structures of 3-(benzotriazol-1-yl)-5-*tert*-butyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and nefidipine (Liu *et al.*, 2006; Hofmann & Cimiraglia, 1990; Ramusino & Varì, 1999). The ethyl acetate solvent was found to be disordered across an inversion center.

The crystal packing is stabilized by intermolecular N—H···O hydrogen bonds (see Table 2), which link the molecules into chains running parallel to the *a* axis.

Experimental

The title compound was prepared by dissolving 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid monoethyl ester (346 mg, 1 mmol) in 28 ml CH_2Cl_2 with dicyclohexyl carbodiimide (206 mg, 1 mmol). Benzotriazol-1-ol (135 mg, 1 mmol) in 10 ml CH_2Cl_2 was added dropwise to this solution at 278 K. The reaction

mixture was stirred at 276–279 K for a further 6 h. The solvent, CH_2Cl_2, was removed by vacuum evaporation at 293 K. The desired compound was purified by chromatography on a silica gel column (eluted by ethyl acetate and petroleum, 1:5) at room temperature. The product (430 mg) was obtained in a yield of 93%. Suitable crystals were obtained by slow evaporation of an ethyl acetate solution.

Crystal data

$C_{23}H_{21}N_5O_6\cdot0.5C_4H_8O_2$
M_r = 507.50
Monoclinic, $P2_1/n$
a = 10.2988 (13) Å
b = 17.092 (2) Å
c = 14.2211 (17) Å
β = 90.162 (4)°
V = 2503.2 (5) Å^3
Z = 4
D_x = 1.347 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 113 (2) K
Block, colorless
0.22 × 0.18 × 0.14 mm

Data collection

Rigaku Saturn diffractometer
ω scans
Absorption correction: multi-scan (Jacobson, 1998)
T_{min} = 0.973, T_{max} = 0.986
22057 measured reflections
5438 independent reflections
4048 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 27.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.120
S = 1.02
5438 reflections
370 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0708P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0196 (16)

Table 1
Selected geometric parameters (Å, °).

O1—N1	1.3718 (14)	N2—N3	1.3113 (17)
N1—N2	1.3448 (17)		
N2—N1—O1	119.47 (11)	N3—N2—N1	106.98 (11)

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4A···O5^{i}	0.86 (2)	2.17 (2)	2.9770 (18)	157.4 (18)

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

All C-bound H atoms were positioned geometrically and refined using a riding model, with C—H = 0.97 Å and U_{iso}(H) = 1.2U_{eq}(C).

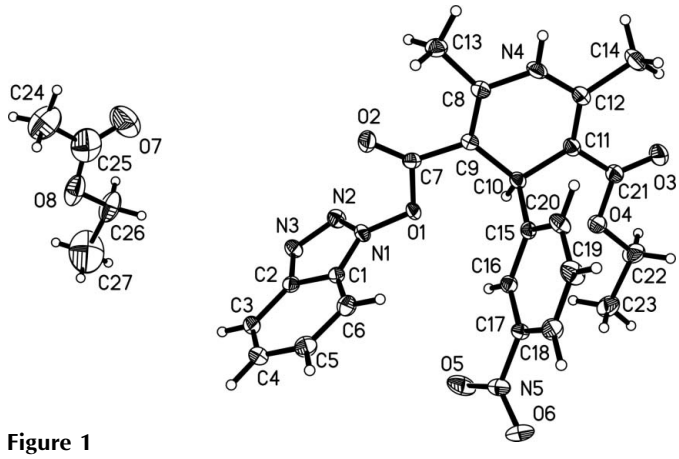


Figure 1
A view of the title compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

The H atom on N4 was located in a difference Fourier map and was refined isotropically. The disordered ethyl acetate molecule is located on an inversion center. The C═O double bond was restrained to 1.26 (1) Å, while the C—O and C—C single bonds were restrained to 1.42 (1) and 1.52 (1) Å, respectively. The bond angles were also restrained by restraining the 1–3 atom distances.

Data collection: *CrystalClear* (Rigaku, 2005); cell refinement: *CrystalClear*; data reduction: *CrystalClear*; 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: *CrystalStructure* (Rigaku/MSC, 2005).

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