Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

3-Ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-[(2-phthalimidoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate diethyl ether hemisolvate

He-Chao Liu and Ya-Qing Feng*

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

Correspondence e-mail: hechaoliu@163.com

Received 18 May 2005
Accepted 26 July 2005
Online 20 August 2005

Key indicators

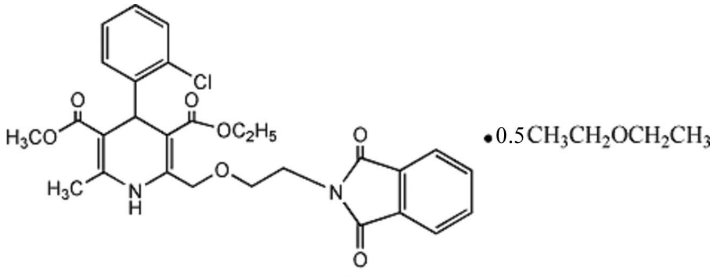
Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
Disorder in solvent or counterion
R factor = 0.047
wR factor = 0.138
Data-to-parameter ratio = 15.0

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

The title compound, $C_{28}H_{27}ClN_2O_7\cdot0.5C_4H_{10}O$, was synthesized from ethyl 3-amino-4-[2-(phthalimido)ethoxy]crotonate and methyl 2-(2-chlorobenzylidene)acetoacetate by the Hantzsch reaction. The dihydropyridine ring is not planar, but adopts a boat conformation. The dihedral angle between the phthalimide and 2-chlorophenyl ring planes is 66.0 (3)°.

Comment

Amlodipine is a 1,4-dihydropyridine derivative with potent calcium antagonist and vasodilator properties, and is an important drug in the treatment of angina and hypertension (Zanchetti *et al.*, 2001; Cross *et al.*, 1993). It can be prepared from the title compound, (I), by deprotection (Arrowsmith *et al.*, 1986). The title compound was synthesized from ethyl 3-amino-4-[2-(phthalimido)ethoxy]crotonate and methyl 2-(2-chlorobenzylidene)acetoacetate by the Hantzsch reaction (Jie, 2003), which is the usual way for preparing 1,4-dihydropyridine derivatives. The molecular structure of (I) is illustrated in Fig. 1.



(I)

The dihydropyridine ring is not planar, but adopts a boat conformation. The phthalimide unit is effectively planar, with a mean deviation of 0.0126 (2) Å of all contributing atoms from the mean plane. The dihedral angle between the phthalimide unit and the 2-chlorophenyl ring is 66.0 (3)°.

Experimental

Ethyl 3-amino-4-[2-(phthalimido)ethoxy]crotonate (1.2 g, 5 mmol) and methyl 2-(2-chlorobenzylidene)acetoacetate (1.6 g, 5 mmol) in ethanol (30 ml) were heated under reflux for 20 h. The ethanol was evaporated off and diethyl ether (30 ml) was added to the distillation residue. After stirring for 1 h, a brown solid was obtained and was recrystallized from methanol to give the title compound. ^{1}H NMR ($CDCl_3$): δ 1.16 (*t*, 3H, J = 7.25 Hz), 2.43 (*s*, 3H), 3.61 (*s*, 3H), 3.76 (*m*, 2H), 4.02 (*m*, 4H), 4.68 (*dd*, 2H, J = 16.0, 39.5 Hz), 5.37 (*s*, 1H), 7.02–7.36 (*m*, 4H), 7.76–7.90 (*m*, 4H). Recrystallization from diethyl ether over 2 d at ambient temperature gave colorless single crystals of (I) suitable for X-ray analysis.

Crystal data

$C_{28}H_{27}ClN_2O_7\cdot0.5C_4H_{10}O$
M_r = 576.03
Monoclinic, $C2/c$
a = 32.134 (5) Å
b = 10.8983 (15) Å
c = 22.339 (3) Å
β = 132.932 (2)°
V = 5727.8 (14) Å^3
Z = 8
D_x = 1.336 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2931 reflections
θ = 2.5–22.2°
μ = 0.19 mm^{-1}
T = 293 (2) K
Block, colorless
0.26 × 0.24 × 0.20 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.947, T_{max} = 0.964
15982 measured reflections
5874 independent reflections
2970 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 26.4°
$h = -40 \rightarrow 36$
$k = -13 \rightarrow 7$
$l = -26 \rightarrow 27$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.138
S = 0.99
5874 reflections
391 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0551P)^2 + 2.3127P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

Cl1—C1	1.735 (3)	O3—C16	1.451 (3)
O1—C9	1.338 (3)	O4—C15	1.212 (3)
O1—C10	1.440 (3)	O5—C18	1.413 (3)
O2—C9	1.200 (3)	O5—C19	1.413 (3)
O3—C15	1.348 (3)	N2—C20	1.453 (3)
C9—O1—C10	116.80 (19)	C14—C7—C6	112.61 (18)
C15—O3—C16	115.86 (19)	C8—C7—C6	109.82 (18)
C18—O5—C19	113.56 (18)	N2—C20—C19	112.3 (2)
C13—N1—C11	122.8 (2)		

The diethyl ether solvent molecule exhibits orientational disorder such that the atom sites O9, C29, C30, C31 and C32 are very close to one another. The disordered diethyl ether was constrained with C—C bond lengths of 1.54 Å, C—O bond lengths of 1.45 Å, and with occupancies of 0.656 and 0.344. H atoms were positioned geometrically, with C—H = 0.93–0.98 Å, and refined as riding, with U_{iso}(H) = 1.2U_{eq}(carrier).

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*.

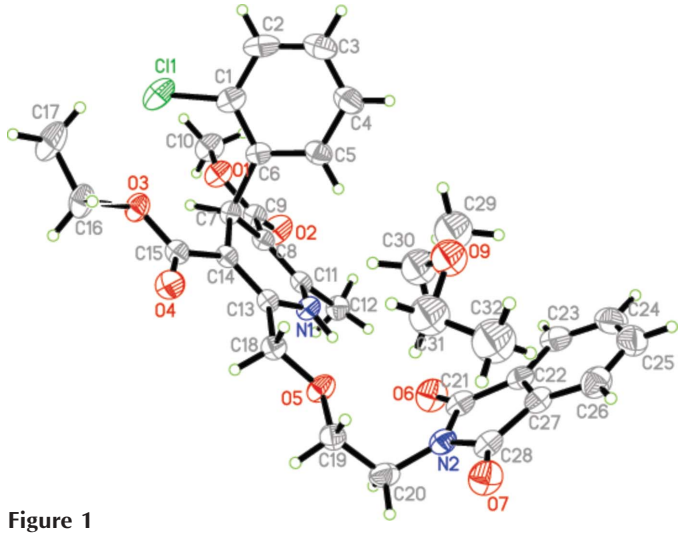


Figure 1
The molecular structure of (I), drawn with 30% probability ellipsoids. H atoms are drawn as spheres of arbitrary radius. One of the disorder components for the solvent has been omitted.

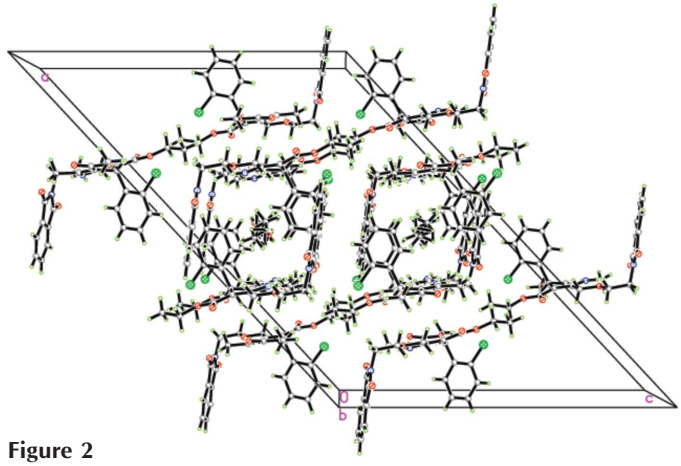


Figure 2
The crystal structure of (I), viewed along the *b* axis. One of the disorder components for the solvent has been omitted.

This work was supported by the National Natural Science Foundation (grant No. 20376059).

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