Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

(4*R*,1′*S*)-Diethyl 6-methyl-2-[(1′-phenylethylimino)methyl]-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate

Viktor Vrábel,[a]* Pavol Skubák,[b] Štefan Marchalín,[c] Vratislav Langer[d] and Barbora Baumlová[c]

[a]Department of Analytical Chemistry, Faculty of Chemical Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic, [b]Department of Physical Chemistry, Faculty of Chemical Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic, [c]Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic, and [d]Environmental Inorganic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-412 96 Göteborg, Sweden

Correspondence e-mail: vrabel@cvt.stuba.sk

Key indicators

Single-crystal X-ray study
T = 183 K
Mean σ(C–C) = 0.002 Å
R factor = 0.042
wR factor = 0.114
Data-to-parameter ratio = 28.6

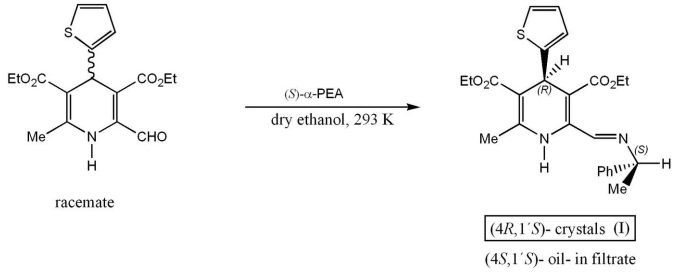
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 17 May 2006
Accepted 27 May 2006

The absolute configuration of the title compound, $C_{25}H_{28}N_2O_4S$, has been determined. The 1,4-dihydropyridine (1,4-DHP) ring has the usual shallow boat conformation. The thiophene ring is approximately perpendicular to the plane through the four atoms of the base of the boat. The two ester groups are twisted in the same direction and have a *cis*,*cis* geometry with respect to the adjacent ring double bonds.

Comment

Substituted 1,4-dihydropyridines (1,4-DHPs) are important because of their wide spectrum of biological activities. These include action against cardiovascular diseases (hypertension, angina pectoris and cardiac arrhythmias), action as calcium channel blockers (Goldmann & Stoltefuss, 1991), and neurotropic, antidiabetic, antiviral, antibacterial and anticancer properties (Klusa, 1995; Gorlitzer *et al.*, 2000; Sobolev *et al.*, 2004). Interestingly, it has now been recognized that the absolute configuration at the C4 position of the 1,4-DHP nucleus is very important for activity modulation. Indeed, enantiomerically pure versions of unsymmetrical 1,4-DHPs usually differ in their biological properties, and sometimes they can act in the opposite (calcium antagonist–calcium agonist) direction (Kongsamut *et al.*, 1985). The different biological activities of 1,4-DHP enantiomers and diastereomers can cause problems in drug development (Strong, 1999). The title compound, (I), was synthesized and its crystal structure is reported here.



The absolute configuration of the pure diastereomer, (I), was established without ambiguity from the anomalous dispersion of the S atom (Flack, 1983) and confirmed the stereochemistry of the atoms as C4 (*R*) and C22 (*S*) (Fig. 1).

There are inter- and intramolecular C—H···O hydrogen bonds in the structure (Table 1). The 1,4-dihydropyridine ring adopts a shallow boat conformation, with atoms C4 and N1 deviating by 0.414 (1) and 0.182 (1) Å, respectively, from the base of the boat. The planar thiophene ring is approximately perpendicular to the 1,4-DHP ring: the dihedral angle between

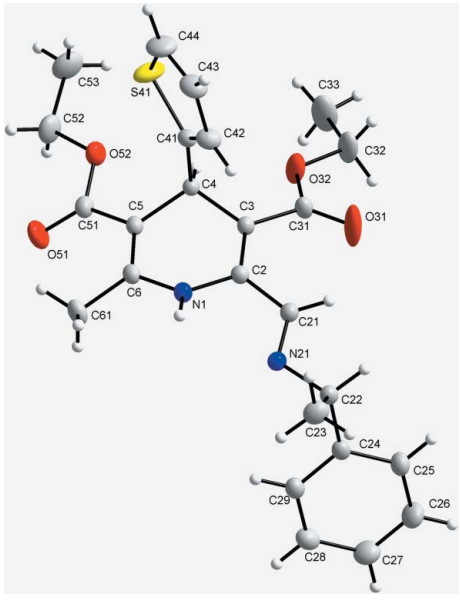


Figure 1
The molecular structure of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

the plane of the five-membered ring and the plane of the base of the boat, C2/C3/C5/C6, is 86.97 (5)° (Nardelli, 1995). The structure shows near coplanarity of the carbonyl C═O bonds with the conjugated double bonds at positions C3 and C5 in the DHP ring. The torsion angles C2—C3—C31—O31 and C6—C5—C51—O51 are −13.5 (2) and −8.7 (2)°, respectively. These torsion angles reflect the *syn*-periplanar (*sp*,*sp*) conformations of the carbonyl C═O bonds.

Experimental

The title compound was prepared by the reaction of the racemic aldehyde 2-formyl-3,5-dietoxycarbonyl-4-(2-thienyl)-6-methyl-1,4-DHP and chiral (*S*)-α-phenylethylamine [(*S*)-α-PEA] in dry ethanol. Compound (I) precipitated as crystals, while the diastereomer diethyl (4*S*,1′*S*)-6-methyl-2-[(1′-phenylethylimino)-methyl]-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate remained in the filtrate. Full details of the synthetic procedure have been published by Marchalín *et al.* (2004). Yellow prism-like single crystals were prepared by recrystallization from an ethanol–water solution (1:1) .

Crystal data

$C_{25}H_{28}N_2O_4S$
M_r = 452.55
Monoclinic, $P2_1$
a = 10.3270 (2) Å
b = 8.2051 (1) Å
c = 14.3630 (2) Å
β = 90.424 (1)°
V = 1217.00 (3) Å^3
Z = 2
D_x = 1.235 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.17 mm^{-1}
T = 183 (2) K
Prism, yellow
0.58 × 0.32 × 0.10 mm

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.905, T_{max} = 0.984
21382 measured reflections
8386 independent reflections
7930 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.025
θ_{max} = 32.9°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.114
S = 1.04
8386 reflections
293 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0718P)^2 + 0.1736P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983), with 3568 Friedel pairs
Flack parameter: −0.02 (5)

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

D—H···A	D—H	H···A	D···A	D—H···A
C22—H22···O51^{i}	1.00	2.42	3.409 (2)	171
C21—H21···O31	0.95	2.32	2.904 (2)	120
C4—H4···O32	1.00	2.27	2.705 (1)	105
C4—H4···O52	1.00	2.32	2.677 (1)	100
C61—H61*A*···O51	0.98	2.35	2.909 (2)	116

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

The majority of the H atoms were discernible in the difference Fourier map, including the methyl H atoms, which were not disordered. During the refinement, H atoms were placed in idealized positions (N—H = 0.88 Å, and C—H = 0.98 Å for methyl H, 0.99 Å for methylene H, 1.00 Å for methine H and 0.95 Å for aromatic H). All H atoms were treated as riding, with U_{iso}(H) = 1.2U_{eq} of the parent atom.

Data collection: *SMART* (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg, 2002); software used to prepare material for publication: *SHELXL97*.

This work was supported by the Grant Agency of the Slovak Republic (grant Nos. 1/2456/05 and 1/2449/05).

References

Brandenburg, K. (2002). *DIAMOND*. Version 2.1e. Crystal Impact GbR, Bonn, Germany.
Bruker (2001). *SHELXTL*. Version 6.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Goldmann, S. & Stoltefuss, J. (1991). *Angew. Chem. Int. Ed.* **30**, 1559–1578.
Gorlitzer, K., Kramer, C. & Boyle, C. (2000). *Pharmazie*, **55**, 651–658.
Klusa, V. (1995). *Drugs Future*, **20**, 135–138.
Kongsamut, S., Kamp, T. J., Miller, R. J. & Sanguinetti, M. C. (1985). *Biochem. Biophys. Res. Commun.* **130**, 141–148.
Marchalín, Š., Cvopová, K., Kríž, M., Baran, P., Oulyadi, H. & Daich, A. (2004). *J. Org. Chem.* **69**, 4227–4237.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Sheldrick, G. M. (2002). *SADABS*. Version 2.03. University of Göttingen, Germany.
Siemens (1995). *SMART* and *SAINT*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sobolev, A., Franssen, M. C. R., Duburs, G. & de Groot, A. (2004). *Biocatal. Biotransform.* **22**, 231–252.
Strong, M. (1999). *Food Drug Law J.* **54**, 463–487.