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Ramipril

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.008 Å
R factor = 0.064
wR factor = 0.085
Data-to-parameter ratio = 11.8

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

The crystal structure of the antihypertensive and cardiovascular protective ramipril {systematic name: 1-[2-(1-ethoxycarbonyl-3-phenylpropylamino)propionyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid}, $C_{23}H_{32}N_2O_5$, has been determined. Within the crystal structure, strong hydrogen bonds connect the molecules into chains along the [100] direction. The preferred crystal growth along these chains causes a crystal morphology of very thin needles which previously prevented the crystal structure determination.

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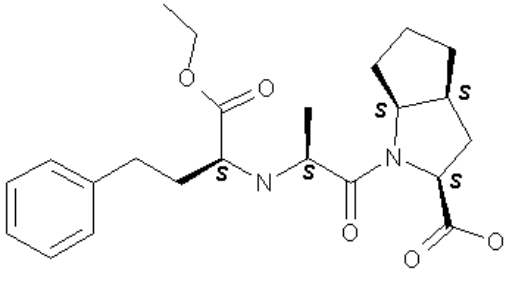
Dedicated to Professor Erich F. Paulus on the occasion of his 64 th birthday.

Comment

Ramipril, (I), is an ACE inhibitor, which can dramatically improve cardiovascular situations (Hall *et al.*, 1997; Yusuf *et al.*, 2000). The active pharmaceutical ingredient is contained in numerous drugs with trade names such as Delix, Altace, Triace, Triatec, Delmuno, Unimax, Acovil and Vesdil. Crystals of ramipril adopt the morphology of long very thin needles and, during drug development in the eighties, all attempts to determine the crystal structure remained unsuccessful. The absolute configuration (all *S*) was confirmed by structure determinations of derivatives (Paulus, Geiger *et al.*, 1987; Paulus, Henning & Urbach, 1987), taking into account that L-alanine was one of the educts. In 1987, the last attempt to determine the crystal structure failed, since the collected diffraction data of the largest crystal found (0.7 × 0.05 × 0.03 mm) was too weak. A new data collection on the same crystal applying a rotating anode operated at 50 kV and 120 mA still yielded a data set with reflections still only observed up to about 1.0 Å, but the structure was immediately solved with direct methods.



(I)

Ramipril crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit (Fig. 1). Since there are no atoms higher than oxygen present in the

crystal structure, it was not possible to reconfirm the absolute configuration (Flack & Bernadinelli, 1999) and the absolute configuration with ramipril in an all-*S* configuration was chosen for refinement. All bond lengths and angles (Table 1) are in the usual range of values (Orpen *et al.*, 1994). The first five-membered ring (N01, C01–C04) is twisted about C01—C02 and the second five-membered ring (C03–C07) is twisted about C5—C6. A Cremer & Pople puckering analysis (Cremer & Pople, 1975) yields Q = 0.275 Å and φ = 61.48°, and Q = 0.4407 Å and φ = 121.64°, respectively. Despite the coexistence of a carboxylic acid group and an amino group, the neutral molecule and not the zwitterionic tautomer is found in the crystal. The carboxylic acid group adopts the frequently observed synplanar (s-*cis*) conformation (Leiserowitz, 1976; Gandour, 1981). An intramolecular hydrogen bond between the amino hydrogen H2 and the amido oxygen O03 is formed with contact distances N02···O03 2.829 (5) Å and H2···O03 2.43 (3) Å and an angle N02—H2···O03 114 (3)°. Within the crystal structure, the molecules are connected in chains *via* strong –COOH···NH– hydrogen bonds between the carboxylic acid groups and the amino groups of adjacent molecules. The molecules within these chains are symmetry related by the 2_1 screw axis parallel to the crystallographic *a* axis. These hydrogen-bonded chains account for a preferred crystal growth in [100] direction and for the corresponding crystal morphology with the long needle axis coinciding with this direction. The intermolecular hydrogen bond exhibits distances O01···N02^{i} 2.601 (5) Å and H1···N02^{i} 1.58 (6) Å, and an angle O01—H1···N02 168 (4)° [symmetry code: (i) $x+\frac{1}{2}, \frac{1}{2}-y, -z$]. In addition, a short intermolecular distance C03—H03···O05^{ii} to the carbonyl oxygen of the ester group is found [C03···O5^{ii} 3.388 (6) Å, H03···O05 2.45 Å and C03—H03···O5^{ii} 161°; symmetry code: (ii) $\frac{3}{2}-x, -y, z+\frac{1}{2}$] which might be discussed as a weak intermolecular C—H···O hydrogen bond (Desiraju, 1996; Desiraju & Steiner, 1998).

The experimentally determined powder diffraction pattern of the sample agrees with the one calculated from the crystal structure model, which proves that the crystal structure determined here represents the crystalline phase of the bulk sample.

Experimental

The sample was recrystallized several times from ethanol–diisopropyl ether for further purification. In the final crystallization step, an ethanolic solution, which was almost saturated at 313 K, was slowly cooled to room temperature.

Crystal data

$C_{23}H_{32}N_2O_5$
M_r = 416.51
Orthorhombic, $P2_12_12_1$
a = 7.4845 (11) Å
b = 13.937 (2) Å
c = 22.012 (3) Å
V = 2296.0 (6) Å^3
Z = 4
D_x = 1.205 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2316 reflections
θ = 2.4–18.2°
μ = 0.09 mm^{-1}
T = 293 (2) K
Needle, colourless
0.70 × 0.05 × 0.03 mm

Data collection

Bruker SMART diffractometer
ω scans
15 851 measured reflections
3291 independent reflections
1640 reflections with $I > 2\sigma(I)$
R_{int} = 0.166
θ_{max} = 23.3°
$h = -4 \rightarrow 8$
$k = -15 \rightarrow 15$
$l = -24 \rightarrow 24$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.064
$wR(F^2)$ = 0.085
S = 0.92
3291 reflections
279 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0263P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −2.0 (19)

Table 1
Selected geometric parameters (Å, °).

O01—C08	1.311 (5)	C03—C04	1.546 (6)
O01—H1	1.04 (6)	C04—C07	1.523 (6)
O02—C08	1.202 (5)	C05—C06	1.513 (6)
O03—C09	1.226 (5)	C06—C07	1.505 (6)
O04—C13	1.334 (5)	C09—C10	1.529 (5)
O04—C14	1.463 (4)	C10—C11	1.532 (5)
O05—C13	1.194 (5)	C12—C13	1.513 (5)
N01—C09	1.347 (4)	C12—C16	1.527 (5)
N01—C01	1.466 (4)	C14—C15	1.485 (6)
N01—C04	1.467 (5)	C16—C17	1.524 (4)
N02—C10	1.472 (5)	C17—C18	1.506 (5)
N02—C12	1.482 (5)	C18—C19	1.374 (6)
N02—H2	0.77 (3)	C18—C23	1.381 (6)
C01—C08	1.518 (5)	C19—C20	1.378 (6)
C01—C02	1.534 (5)	C20—C21	1.365 (7)
C02—C03	1.515 (6)	C21—C22	1.378 (7)
C03—C05	1.537 (6)	C22—C23	1.371 (7)
C13—O04—C14	116.1 (4)	O03—C09—C10	119.9 (4)
C09—N01—C01	126.3 (4)	N01—C09—C10	117.3 (4)
C09—N01—C04	120.2 (4)	N02—C10—C09	113.1 (4)
C01—N01—C04	113.4 (4)	N02—C10—C11	109.0 (3)
C10—N02—C12	116.0 (3)	C09—C10—C11	107.6 (3)
N01—C01—C08	111.5 (4)	N02—C12—C13	107.4 (4)
N01—C01—C02	103.2 (3)	N02—C12—C16	117.1 (3)
C08—C01—C02	113.5 (4)	C13—C12—C16	108.3 (3)
C03—C02—C01	104.9 (4)	O05—C13—O04	125.2 (5)
C02—C03—C05	117.6 (5)	O05—C13—C12	125.2 (5)
C02—C03—C04	107.1 (4)	O04—C13—C12	109.6 (5)
C05—C03—C04	102.8 (5)	O04—C14—C15	110.5 (4)
N01—C04—C07	115.1 (4)	C18—C17—C16	112.3 (3)
N01—C04—C03	103.5 (4)	C19—C18—C23	117.9 (5)
C07—C04—C03	106.9 (4)	C19—C18—C17	121.5 (5)
C06—C05—C03	105.0 (5)	C23—C18—C17	120.6 (6)
C07—C06—C05	101.7 (5)	C18—C19—C20	121.5 (5)
C06—C07—C04	105.9 (4)	C21—C20—C19	120.1 (6)
O02—C08—O01	124.8 (4)	C20—C21—C22	119.0 (7)
O02—C08—C01	124.0 (5)	C23—C22—C21	120.8 (6)
O01—C08—C01	111.2 (4)	C22—C23—C18	120.6 (6)
O03—C09—N01	122.6 (4)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O01—H1···N02^{i}	1.04 (6)	1.58 (6)	2.601 (5)	168 (4)
N02—H2···O03	0.78 (3)	2.43 (3)	2.829 (5)	114 (3)
C03—H03···O05^{ii}	0.98	2.45	3.388 (6)	161

Symmetry codes: (i) $\frac{1}{2}+x, \frac{1}{2}-y, -z$; (ii) $\frac{3}{2}-x, -y, \frac{1}{2}+z$.

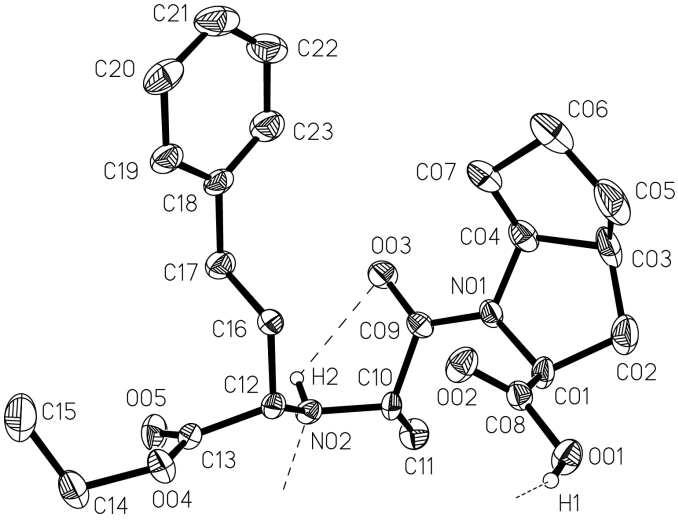


Figure 1
The molecular structure of ramipril (most H atoms omitted) showing anisotropic displacement ellipsoids at the 20% probability level and the atom-numbering scheme. The dashed lines indicate hydrogen bonds.

Data were originally collected to 54° 2θ with a SMART 1 K CCD area detector, but reflections were observed only up to about 1 Å/45° 2θ. Refinement was therefore performed with data up to 0.9 Å/47° 2θ. All H atoms were found in the electron-density difference map, but most of them were placed in idealized geometry with fixed isotropic displacement parameters. Only the coordinates and isotropic displacement parameters of the H atom of the carboxylic acid group (H1) and of the H atom of the amino group (H2), which are involved in hydrogen bonds, were refined.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SAINT*+ (Bruker, 1999); data reduction: *SAINT*+; program(s) used to solve structure: *SHELXS*94 (Sheldrick, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-PC XP* (Bruker, 1998); software used to prepare material for publication: *SHELXL*97.

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