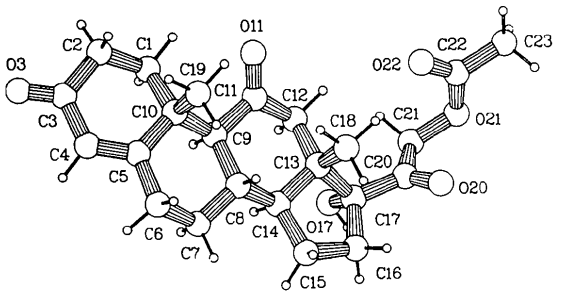

Fig. 1. Perspective view of the molecule with atom numbering.

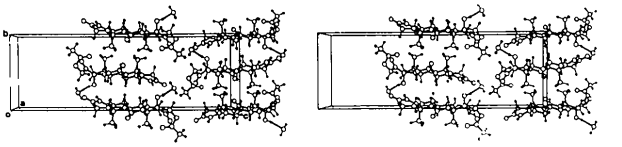

Fig. 2. Stereo packing diagram viewed down **a**. Hydrogen bonds are indicated.

these parameters were 7·9 (6) and 5·0 (5)° respectively. The conformation of the side chain of CA is given by torsion angles C(17)–C(20)–C(21)–O(21) = 166·7 (7), O(20)–C(20)–C(21)–O(21) = −14 (1), C(20)–C(21)–O(21)–C(22) = −75·8 (9), C(21)–O(21)–C(22)–C(23) = −176·2 (8), C(21)–O(21)–C(22)–O(22) = −1 (1)° and its orientation with respect to the steroid skeleton is given by the torsion angles about C(17)–C(20), *e.g.* C(13)–C(17)–C(20)–C(21) = −92·2 (9)°. The orientations of the side chains of CA V*aq* and CA IV*ac* are almost the same with the mean difference of the six C(17)–C(20) torsion angles amounting to only 1 (1)°. Fig. 2 shows a stereoview down **a**. The water molecule is an acceptor in a hydrogen bond with O(17) and a donor in a rather poor hydrogen bond to O(3{$-\frac{1}{2}+x$, $\frac{3}{2}-y$, $-z$}), with distances O(17)···O(aq) = 2·742 (9) and O(aq)···O(3) = 2·87 (1) Å and angles O(17)–H···O(aq) = 167 (8) and O(aq)–H···O(3) = 115°. This latter angle and the H···O(3) distance of 2·3 Å indicate the rather poor geometry of this H bond, but this may be due to the approximate coordinates of the H atom, which could not be refined satisfactorily. The packing is different from those of the other described modifications and can be described as $O\ b_{11}a_9c_3$ 212 (Duax & Norton, 1975), indicating that the molecules are packed two thick, one wide and two long, with the steroid length parallel to **c**.

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Absolute Configuration and Structure of Ethyl 2-(3-Methyl-1,4-dioxoperhydrocyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl)-4-phenylbutyrate

BY E. F. PAULUS, R. GEIGER, R. HENNING, V. TEETZ AND H. URBACH

Hoechst AG, D-6230 Frankfurt am Main 80, Federal Republic of Germany

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Abstract. $C_{23}H_{30}N_2O_4$, $M_r = 398·5$, orthorhombic, $P2_12_12_1$, $a = 9·145$ (2), $b = 12·602$ (1), $c = 18·782$ (3) Å, $V = 2164·5$ Å^3, $Z = 4$, $F(000) = 856$, $D_m = 1·21$ (flotation in aqueous K_2HgI_4 solution), $D_x = 1·223$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0·078$ cm^{-1}, $T = 293$ K, $R = 0·11$, $wR = 0·040$ for 2297 reflections [$F^2 > \sigma(F^2)$]. Solution of the phase problem was not straightforward; the phases of 13 reflections had to be varied systematically. The absolute configuration is all-(*S*). Both the condensed five-

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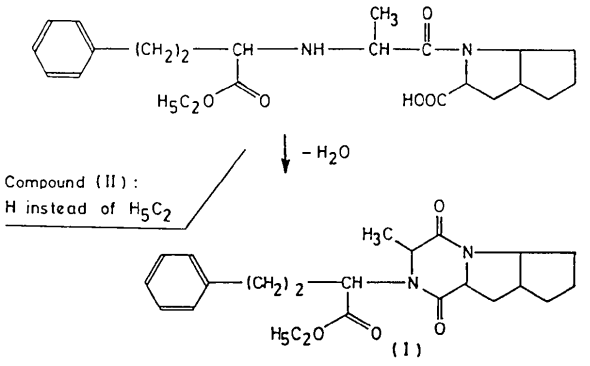
membered rings have envelope conformations and are *cis*-annulated. The compound is obtained from the highly effective angiotensin-converting enzyme inhibitor ramipril (HOE 498) by splitting off one molecule of water and forming a diketopiperazine ring.

Introduction. The angiotensin-converting inhibitor ramipril (HOE 498) splits off in solution one molecule of water after a period of time to form the compound (I) which is to be investigated by X-ray diffraction. This reaction occurs at raised temperatures and the reaction product (I) crystallizes quite well (Teetz, Geiger, Henning & Urbach, 1984). Because it turned out to be difficult to get suitable crystals of the drug ramipril itself, we investigated compound (I) first to get an impression of the overall conformation of this varied molecule. The absolute configuration of compound (II) was determined recently (Paulus, Henning & Urbach, 1987) and the present study should provide further confirmation. Although ramiprilat (II) is distinguished from ramipril only by having a carboxy group instead of an ethoxycarbonyl group, its tendency to split off a water molecule in solution is much less.



Experimental. The sample was recrystallized from ethanol. A crystal of dimensions 0·5 × 0·2 × 0·15 mm was sealed in a Lindemann-glass capillary; 25 reflections with $23 > 2\theta > 10°$ used for cell refinement; one standard reflection (212); intensity variation <1·7%; 2298 of 2976 unique reflections had according to the counting statistics intensities $I > \sigma(I)$ and were used for the structure analysis; Nicolet *R*3 computer-controlled (Nova 3/12, 64 kbyte) diffractometer; $2\theta_{max} = 56°$; h 0→12, k 0→16, l 0→24; 3° min^{-1}; no corrections for absorption or extinction; the solution of the phase problem was relatively difficult and was performed by direct methods (13 variable phases) and successive difference Fourier syntheses; after refinement of the structure parameters of the non-hydrogen atoms it was not possible to find the coordinates of the hydrogens in a difference electron density synthesis; in final refinement all hydrogen atoms were inserted using a model with idealized geometry (C–H 0·96 Å) and temperature factors fixed at 1·2 times the equivalent isotropic values for the C atoms to which they were attached; all the other atoms refined anisotropically; least-squares refinement on F with 2297 reflections, 268 parameters, $w = 1/\sigma^2(F)$ and the final R values were $R = 0·11$ and $wR = 0·0450$;* $S = 1·66$; the ten largest peaks in final difference electron density synthesis were between 0·27 and 0·31 e Å^{-3}; $(\Delta/\sigma)_{max} < 0·1$; the reason for the relatively large difference between R and wR is that many reflections with small intensities were included. The weighting scheme according to the counting statistics assigned these only a small weight. All calculations and drawings were executed on a Nova 3/12 (128 kbyte) computer and with *SHELXTL* (Sheldrick, 1978); scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. The overall conformation and configuration of the molecule are shown in Fig. 1. Table 1 gives the coordinates of the non-hydrogen atoms and Table 2 the appropriate bond lengths and bond angles. Together with the relative configuration the absolute one may be determined, because (*S*)-alanine was used for the chemical synthesis and it can be accepted that this part of the molecule does not change its configuration during the synthesis. The absolute configuration is all-(*S*).

* Lists of structure factors, anisotropic temperature factors, hydrogen-atom coordinates and bond lengths and angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43623 (28 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

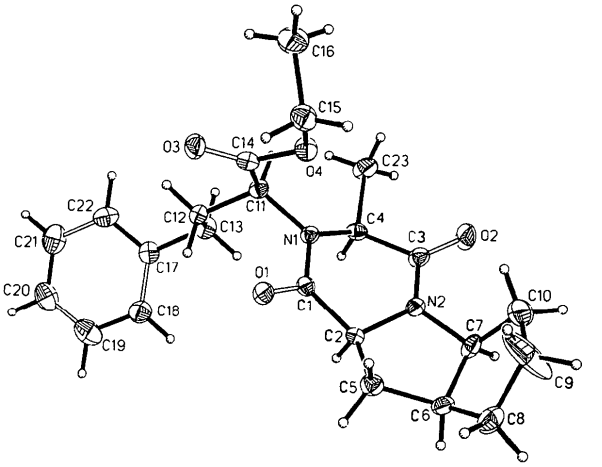


Fig. 1. Molecular structure of compound (I), showing 30% probability thermal ellipsoids for the non-hydrogen atoms and the atom-numbering scheme.

Table 1. *Final atomic coordinates and equivalent isotropic temperature factors*

The atomic coordinates are given in units of the lattice constants, the isotropic temperature coefficients were calculated from the anisotropic ones after the last least-squares cycle.

$U_{eq} = \frac{1}{3}$(trace $\tilde{U}$).

	x	y	z	U_{eq}(Å^2)
O1	0·8809 (3)	0·7882 (2)	0·4713 (1)	0·051
O2	0·4266 (4)	0·9853 (3)	0·3663 (2)	0·082
O3	1·0374 (3)	0·9772 (2)	0·5638 (1)	0·059
O4	0·9279 (3)	1·0279 (2)	0·4627 (1)	0·053
N1	0·6953 (3)	0·9024 (2)	0·4912 (2)	0·038
N2	0·5749 (3)	0·8423 (2)	0·3645 (2)	0·046
C1	0·7579 (4)	0·8186 (3)	0·4582 (2)	0·039
C2	0·6609 (4)	0·7650 (3)	0·4041 (2)	0·039
C3	0·5088 (5)	0·9248 (4)	0·3959 (2)	0·052
C4	0·5426 (4)	0·9344 (3)	0·4753 (2)	0·043
C5	0·7416 (4)	0·7039 (3)	0·3461 (2)	0·053
C6	0·6377 (4)	0·7073 (3)	0·2822 (2)	0·049
C7	0·5513 (5)	0·8100 (3)	0·2903 (2)	0·056
C8	0·7159 (5)	0·7159 (3)	0·2094 (2)	0·071
C9	0·7170 (8)	0·8290 (4)	0·1937 (3)	0·203
C10	0·6142 (6)	0·8873 (4)	0·2352 (2)	0·099
C11	0·7782 (4)	0·9491 (3)	0·5504 (2)	0·042
C12	0·7848 (4)	0·8761 (3)	0·6155 (2)	0·044
C13	0·6354 (4)	0·8579 (3)	0·6496 (2)	0·057
C14	0·9320 (4)	0·9827 (3)	0·5275 (2)	0·048
C15	1·0672 (5)	1·0650 (3)	0·4354 (2)	0·065
C16	1·1009 (5)	1·1713 (3)	0·4665 (2)	0·079
C17	0·6498 (4)	0·7825 (4)	0·7128 (2)	0·053
C18	0·6346 (5)	0·6744 (4)	0·7027 (2)	0·066
C19	0·6583 (5)	0·6071 (4)	0·7597 (2)	0·090
C20	0·6966 (5)	0·6435 (4)	0·8241 (2)	0·086
C21	0·7116 (5)	0·7499 (4)	0·8352 (2)	0·089
C22	0·6866 (5)	0·8195 (4)	0·7790 (2)	0·072
C23	0·5078 (5)	1·0464 (3)	0·5002 (3)	0·077

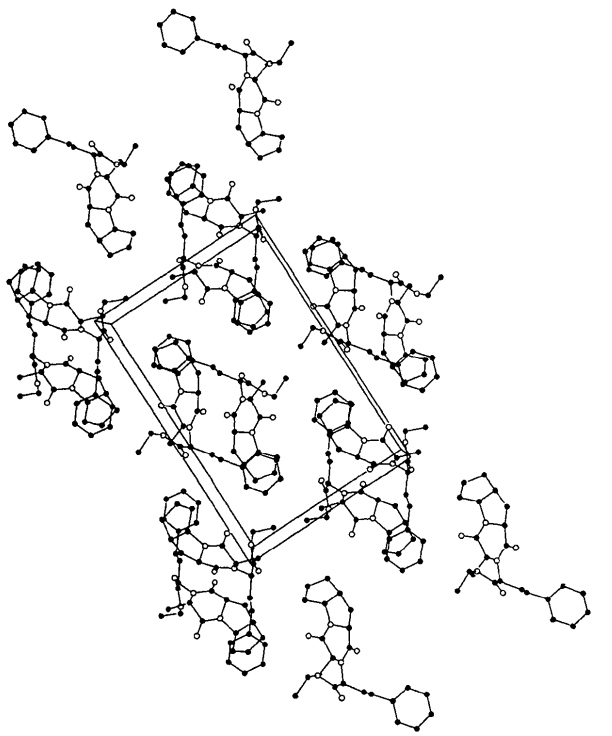


Fig. 2. Projection of the crystal structure, viewed parallel to the crystallographic *a* axis.

The pyrrolidine ring has an envelope conformation. C5 lies 0·476 Å above the plane of the other atoms of the ring, which have a distance from their best plane of less than 0·02 Å. At first glance the cyclopentane ring seems to have a twisted envelope form; C6 and C8 are on different sides of the plane C7C9C10 and 0·152 and 0·176 Å respectively out of the plane. However, from Fig. 1 it can be seen immediately that C9 has a huge anisotropic temperature factor with its main component approximately perpendicular to the plane of the ring. There is no doubt that the cyclopentane ring also has an envelope conformation; C9 migrates at room temperature from one side of the ring to the other. The two five-membered rings are *cis*-annulated. The two nitrogen atoms N1 and N2 lie 0·065 and 0·066 Å out of the plane of their ligands, which is quite usual for amides. The conformation of the diketopiperazine ring is boat.

Table 3 shows relevant torsion angles in the compounds (I) and (II) respectively. It can be seen that the given torsion angles for ramiprilat (II) have the effect that the carboxy group on the pyrrolidine ring is far away from the amino group, the partner for the internal

Table 2. *Bond lengths* (Å) *and bonding angles* (°) *with e.s.d.'s in parentheses*

O1–C1	1·214 (4)	C6–C7	1·524 (5)
O2–C3	1·206 (5)	C6–C8	1·547 (5)
O3–C14	1·182 (5)	C7–C10	1·532 (6)
O4–C14	1·343 (4)	C8–C9	1·455 (7)
O4–C15	1·451 (5)	C9–C10	1·425 (8)
N1–C1	1·351 (5)	C11–C12	1·532 (5)
N1–C4	1·484 (5)	C11–C14	1·531 (5)
N1–C11	1·468 (5)	C12–C13	1·526 (5)
N2–C2	1·457 (5)	C13–C17	1·526 (6)
N2–C3	1·340 (5)	C15–C16	1·494 (6)
N2–C7	1·468 (5)	C17–C18	1·382 (6)
C1–C2	1·509 (5)	C17–C22	1·370 (6)
C2–C5	1·525 (5)	C18–C19	1·383 (7)
C3–C4	1·528 (6)	C19–C20	1·340 (6)
C4–C23	1·521 (6)	C20–C21	1·365 (7)
C5–C6	1·532 (5)	C21–C22	1·390 (6)

O1–C1–N1	123·2 (3)	C2–C5–C6	104·2 (3)
O1–C1–C2	122·6 (3)	C3–N2–C7	124·5 (3)
O2–C3–N2	124·7 (4)	C3–C4–C23	109·3 (3)
O2–C3–C4	121·7 (4)	C4–N1–C11	121·9 (3)
O3–C14–O4	124·7 (4)	C5–C6–C7	105·5 (3)
O3–C14–C11	124·8 (3)	C5–C6–C8	114·0 (3)
O4–C14–C11	110·2 (3)	C6–C7–C10	106·2 (3)
O4–C15–C16	109·4 (3)	C6–C8–C9	104·5 (4)
N1–C1–C2	114·2 (3)	C7–C6–C8	105·5 (3)
N1–C4–C3	111·4 (3)	C7–C10–C9	106·8 (4)
N1–C4–C23	112·8 (3)	C8–C9–C10	112·9 (5)
N1–C11–C12	112·6 (3)	C11–C12–C13	112·9 (3)
N1–C11–C14	111·9 (3)	C12–C11–C14	110·7 (3)
N2–C2–C1	111·2 (3)	C12–C13–C17	110·0 (3)
N2–C2–C5	103·5 (3)	C13–C17–C18	119·9 (4)
N2–C3–C4	113·5 (4)	C13–C17–C22	121·0 (4)
N2–C7–C6	104·7 (3)	C14–O4–C15	115·6 (3)
N2–C7–C10	114·2 (3)	C17–C18–C19	118·9 (4)
C1–N1–C4	121·2 (3)	C17–C22–C21	121·0 (4)
C1–N1–C11	116·2 (3)	C18–C17–C22	119·0 (4)
C1–C2–C5	115·0 (3)	C18–C19–C20	122·0 (5)
C2–N2–C3	122·5 (3)	C19–C20–C21	120·0 (4)
C2–N2–C7	112·3 (3)	C20–C21–C22	119·2 (4)

Table 3. *Torsion angles* (°) *in the title compound* (I) *and ramiprilat* (II)

	(I)	(II)
C1–C2–N2–C3	−43·1	−81·4
C2–N2–C3–C4	4·6	−175·1
N2–C3–C4–N1	35·7	130·8
C3–C4–N1–C11	149·7	−56·6
C4–N1–C11–C12	101·6	157·6
N1–C11–C12–C13	−65·4	66·6
C11–C12–C13–C17	178·6	173·4

condensation. There seems to be no opportunity for easy condensation to occur as apparently happens in ramipril. Because the differences in the structural formulae are quite small, the influence of the only group which is different between the molecules is promoting the dramatic changes. Ramipril has a betaine structure: the ammonium group and the carboxylate group are then 'predestined' to approach each other and split off a water molecule. The situation is different in ramiprilat (II): there is now an additional carboxy group quite near to the amino group. It is not so easy for the carboxy group at the pyrrolidine ring to react with the amino group, because it is far away and rejected by the other carboxy group which is not esterified in ramiprilat (II). Nevertheless this reaction is possible by refluxing in toluene and removing the produced water out of equilibrium.

The crystal structure of (I) is represented in Fig. 2, which is a projection of the structure along the *a* axis. The screw axes parallel to the three crystallographic directions can be recognized quite well. The intermolecular distances between non-hydrogen atoms are greater than 3·3 Å.

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Structure of the Angiotensin-Converting Enzyme Inhibitor Ramiprilat (HOE 498 Diacid)

BY E. F. PAULUS, R. HENNING AND H. URBACH

Hoechst AG, D-6230 *Frankfurt am Main* 80, *Federal Republic of Germany*

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Abstract. HOE 498 diacid, 2-{*N*-[(*S*)-1-carboxy-3-phenylpropyl]-L-alanyl}-(1*S*,3*S*,5*S*)-2-azabicyclo-[3.3.0]octane-3-carboxylic acid, $C_{21}H_{28}N_2O_5$, M_r = 388·47, crystallizes with 4·7 molecules of methanol in the orthorhombic space group $P2_12_12_1$ (M_r of complex = 539·07), a = 10·529 (1), b = 12·147 (2), c = 22·240 (3) Å, V = 2844·4 Å^3, Z = 4, D_x = 1·28 Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ = 0·079 mm^{-1}, T = 295 K, R = 0·112, wR = 0·042, 2794 observed reflections [$F^2 > \sigma(F^2)$]. It was possible to determine the given absolute configuration because L-alanine was one of the components of the synthesis [Teetz, Geiger, Henning & Urbach (1984). *Arzneim. Forsch. Drug Res.* **34**(11), 1399–1401]. The pyrrolidine and the cyclopentane rings of the bicyclooctane ring system have an envelope and a twist conformation respectively. The consequence of the *endo* position of the carboxyl group at C1 is that the methylene group C6 is forced to assume an *exo* conformation. To a large extent, the crystal structure is influenced by the non-stoichiometric content of methanol molecules in channels. Proof of the mobility of these molecules is given by the extremely large temperature coefficients (as large as 1·38 Å^2) and the rapid crystal decomposition in a methanol-free atmosphere.

Introduction. The inhibition of angiotensin-converting enzyme (ACE, kininase II, EC 3.4.15.1) represents a new therapeutical principle for the treatment of hypertension and cardiac insufficiency (Stumpe, Overlack & Kolloch, 1984).

As a peptidyl dipeptide carboxyhydrolase ACE hydrolyses the *C*-terminal dipeptide from the angiotensin 1 decapeptide to yield the potent vasopressor octapeptide angiotensin II (Petrillo & Ondetti, 1982). It also destroys the blood-pressure-lowering effect of the hypotensive nonapeptide bradykinin by splitting off the *C*-terminal dipeptide to a biologically inactive heptapeptide (Petrillo & Ondetti, 1982). Inhibitors of ACE consequently will have an antihypertensive effect. The

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