CRYSTAL STRUCTURE OF A PERINDOPRIL CYCLIZATION PRODUCT, $C_{19}H_{30}N_2O_4$

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ABSTRACT

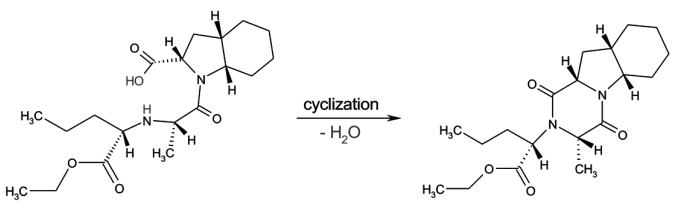
The title compound is a product of perindopril intramolecular cyclization. It crystallizes in the tetragonal, non-centrosymmetric space group $P4_12_12$ (No. 92) with a = 9.3574(2), b = 9.3574(2), c = 45.6369(9) Å, V = 3996.01(14) Å^3 and Z = 8. The crystal consists of one molecule in the asymmetric unit. The packing exhibits weak intermolecular C-H···O=C contacts forming two *C(5)* and *C(10)* chains, which together result in graph-set descriptor R^3_3 (18) motif, running along the crystallographic *a*-axis.

Keywords: crystal structure, X-ray diffraction, perindopril

INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors are used in therapy of cardiovascular disfunctions.[1] One of the most common ACE inhibitors on the market is perindopril, ((2*S*,3a*S*,7a*S*)-1- [(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2 carboxylic acid (**1**), used as an antihypertensive drug utilized in the treatment of high blood pressure and heart failure.[2] In the liver and plasma the perindopril is de-esterified by esterases to its active metabolite – the respective diacid – perindoprilat. Contrary to other ACE-inhibitors, it has a higher tissue affinity for the angiotensin-converting enzyme.[3] Clinically useful forms of perindopril are its *tert*-butylamine (perindopril erbumine) or *L*-arginine (perindopril *L*-arginine) salts, which were mentioned for the first time in respective patents a decade ago.[4,5,6] Although perindopril was first reported in 1982,[7] no details were given on its crystal structure. However, the crystal structure of perindoprilat solvate with ethanol was revealed in 1991.[8] Also three crystal structures, of a hydrate of perindoprilat, of an erbumine salt and its hydrate have been determined in our laboratory. [9,10]

The cyclization of dipeptides to diketopiperazines is a well-known phenomenon, being a major stability issue of many ACE inhibitors.[11] Perindopril may undergo the appropriate degradation reaction (Scheme) during the manufacturing and formulation processes, which is undesirable due to high toxicity of the product.[12] Now we have determined the crystal structure of the perindopril cyclization product, ethyl (2S)-2-[(3S,5aS,9aS,10aS)-3-methyl-1,4-dioxo-5a,6,7,8,9,9a,10,10a-octahydro-3H-pyrazino[1,2-a]indol-2-yl]pentanoate.



General scheme of perindopril intramolecular cyclization to **1**.

EXPERIMENTAL

Well shaped, colourless plate monocrystals suitable for X-ray analysis were grown by slow evaporation from a nitrobenzene solution of the title compound at room temperature.

The crystal structure of (**1**) was determined by single-crystal X-ray diffraction method from the data collected on the Bruker AXS Smart APEX-II CCD 3-circle diffractometer (equipped with MonoCap capillary). The absorption correction was applied using semi-empirical methods of SADABS program.[13] Data collection and reduction were done with SMART and SAINT-PLUS programs.[14,15] The structure was solved by direct methods and refined by the full-matrix least-squares methods on F^2 with anisotropic thermal parameters for all non-hydrogen atoms to R = 0.0485. All hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C-H = 0.93 – 0.97 Å and with U_{iso}(H) = 1.2 – 1.5 U_{eq}(C). The terminal methyl (C14) and ethyl (C18, C19) groups were disordered over two positions. Both parts of the disordered groups were restrained using DFIX with the C-C and C-O distances of 1.525 and 1.430 Å respectively.

A perspective view of the molecular structure of **1** with the atom labels is shown in Figure 1, while the crystal data are summarized in Table 1. The configuration of the molecule is *all-S*.[16]

For preparing figures and the geometrical calculations, Mercury and PLATON programs were used.[17,18]

Table 1. Crystal data and details of the structure determination for **1**.

Crystal data	
$C_{19}H_{30}N_2O_4$	Z = 8
Mr = 350.45	Cu $K\alpha$ radiation,
Tetragonal, $P4_12_12$ (No. 92)	μ = 0.659 mm^{-1}
a = b = 9.3574(2) Å	T = 291 (2) K
c = 45.6369(9) Å	colourless plate
V = 3996.01 (14) Å^3	0.5 x 0.3 x 0.2 mm
Data collection	
Bruker SMART APEX II CCD diffractometer	3549 reflections with $I > 2\sigma(I)$
37069 measured reflections	R_{int} = 0.0308
3644 independent reflections	
Refinement	
R [(F^2>2σ (F^2)] = 0.0485 wR(F^2) = 0.1529 S = 1.061 3644 reflections	255 parameters $\Delta\rho_{max}$ = 0.41 e Å^{-3} $\Delta\rho_{min}$ = -0.18 e Å^{-3}

RESULTS AND DISCUSSION

The title compound (**1**) crystallizes in the non-centrosymmetric space group $P4_12_12$ (No. 92), with one crystallographically independent molecule in the asymmetric unit. The core of the molecule consists of three fused rings, a cyclohexane ring ***a*,** a five-membered pyrrolidine ring ***b*** and a six-membered diketopiperazine ring ***c***, resulting in a rigid structure. The rest of the molecule is completed by disordered terminal methyl and ethyl groups of alkyl chains, which exist in two equally occupied conformations. Ring ***a*** (C3-C8) adopts a slightly deformed chair conformation as indicated by the Cremer and Pople puckering[19] parameters, having a total puckering amplitude Q of 0.527(3) Å with φ = 2.6(12) and θ = 165.9(3)º. Ring ***b*** (N1/C1-C3/C8) adopts a slightly deformed half-chair conformation. Its total puckering amplitude Q is 0.399(2) Å and φ = 276.0(3)º. The diketopiperazine ring ***c*** (N1/C1-C15/N2/C9-C10) is in a boat conformation with puckering amplitude Q = 0.584(2) Å, φ = 60.9(2) and θ = 92.2(2)º. The two oxygen atoms of carbonyl groups (O1) and (O4) lie on the same side of the pyrrolidine ring. Selected bond lengths and angles with their estimated standard deviations are given in Table 2.

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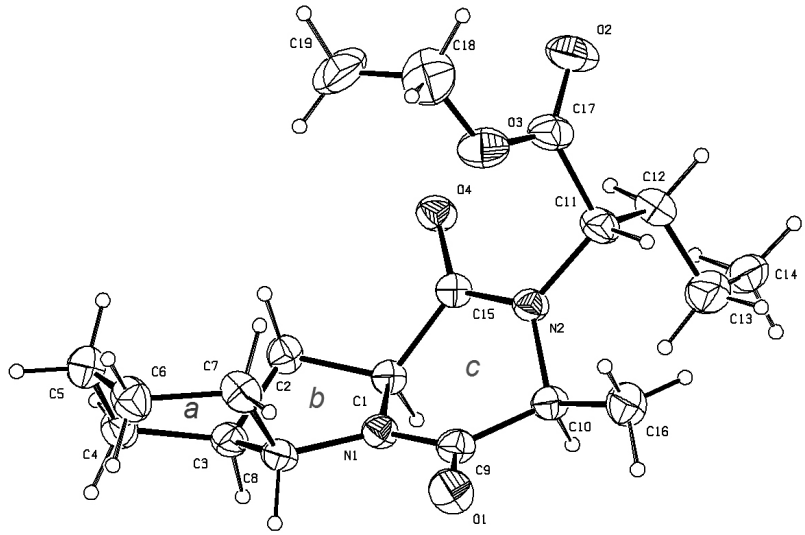

Figure 1. A view of the asymmetric unit of **1** showing the molecule and atom numbering scheme. Disorder was omitted for clarity.

Table 2. Selected geometric parameters: bond lengths [Å], bond angles and torsion angles [º].

O1-C9	1.212(3)	C9-C10-C16	110.28(19)	C1-N1-C9-O1	-179.19(19)
O2-C17	1.207(4)	N2-C11-C17	111.2(2)	C9-N1-C1-C15	-41.0(2)
O3-C17	1.329(4)	C1-N1-C8	112.86(15)	C8-N1-C1-C15	131.98(16)
O4-C15	1.220(2)	C1-N1-C9	121.73(17)	C8-N1-C9-C10	-172.70(17)
N1-C1	1.469(3)	C8-N1-C9	124.99(18)	C15-N2-C10-C16	-168.3(2)
N1-C9	1.344(3)	C10-N2-C11	122.44(17)	C10-N2-C15-O4	-176.59(19)
N2-C11	1.471(3)	C10-N2-C15	120.28(16)	C10-N2-C11-C17	-135.7(2)
N2-C15	1.339(3)	C11-N2-C15	116.70(17)	C11-N2-C10-C9	144.7(2)
C1-C15	1.517(3)	N1-C1-C15	110.72(15)	C11-N2-C15-C1	174.66(18)
C9-C10	1.530(3)	O4-C15-N2	123.44(18)	N1-C1-C15-O4	-141.46(19)
C10-C16	1.513(3)	O4-C15-C1	121.72(17)	N1-C1-C15-N2	38.8(2)
C11-C17	1.511(4)	N2-C15-C1	114.84(16)	O1-C9-C10-N2	-139.4(2)
		O2-C17-O3	123.9(3)	N1-C9-C10-C16	168.10(19)
		O2-C17-C11	124.8(3)	N1-C9-C10-N2	42.0(2)
		O3-C17-C11	111.2(2)	N2-C11-C17-O2	-143.2(3)
		O1-C9-N1	123.5(2)	N2-C11-C17-O3	40.5(3)

A similar geometry is observed in (3*S*-(2(*R**),3α,5αβ,9αβ,10αβ))-decahydro-3-methyl-1,4-dioxo-α-(2-phenylethyl)pyrazino(1,2-α)indole-2(1H)-acetic acid ethyl ester methanol solvate (**2**), which was obtained by cyclization of an other angiotensin-converting enzyme inhibitor - indolapril.[20] The slight difference is visible from superposition of the two structures (Figure 2).

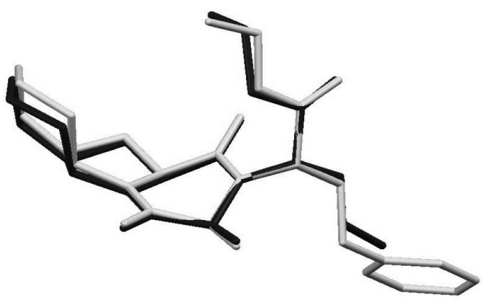

Figure 2. Superposition of molecules of known cyclization products of ACE inhibitors, the title compound **1** (black) and that of indolapril **2** (grey).

The crystal packing of (**1**) shows two weak intermolecular C-H…..O contacts (Table 3), C10–H10···O4 [½-x,-1/2+y] and C19A-H19C···O1 [x,1+y,z] which link molecules into 5- and 10-membered chains, respectively, with graph-set notations *C(5)*, *C (10)* and 18-membered rings as viewed along the *a*-axis (Figure 3).[21]

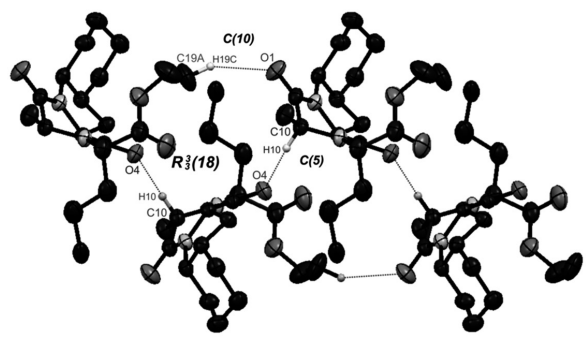

Figure 3. A packing view of **1** in the crystal: the intermolecular C-H···O contacts forming infinite chains running along the [100] direction. Disordered atoms have been omitted for clarity.

Table 3. Intermolecular contacts (Å, º).

D-X...A	d(D-X)	d(X···A)	d(D···A)	<(DXA)
C10–H10···O4^{i}	0.98	2.34	3.267(3)	157
C19A–H19C···O1^{ii}	0.96	2.41	3.284(10)	151

Symmetry codes: (i) ½-x,- ½+y,¼-z, (ii) x,1+y,z.

Supplementary Information: Crystallographic data for the structural analysis have been deposited in the Cambridge Crystallographic Data Centre CCDC 853460. Data Acquisition - the Cambridge Crystallographic Data Centre deposit@ccdc.cam.ac.uk Telephone: (44) 01223 762910 Facsimile: (44) 01223 336033 Postal Address: CCDC, 12 Union Road, CAMBRIDGE CB2 1EZ, UK (http://www.ccdc.cam.ac.uk/).

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