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A non-peptide angiotensin II receptor antagonist: 2-butyl-6-methyl-5-(1-oxopyridin-2-yl)-1-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazo[5,4-*b*]pyridine methanol solvate

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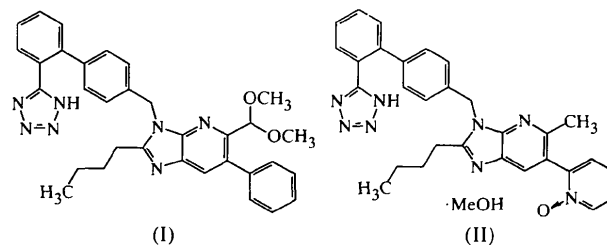
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Abstract

The title compound, C₃₀H₂₈N₈O·CH₄O, is one of a series of imidazo[5,4-*b*]pyridine-based angiotensin II receptor antagonists showing high antihypertensive activity. The overall conformation of the biphenyl-tetrazole moiety as well as its relative orientation with respect to the central fused ring is significantly different from those of related compounds, indicating that this class of compounds has considerable conformational flexibility.

Comment

Non-peptide angiotensin II (AII) receptor antagonists such as losartan are being actively investigated for treatment of hypertension in man (Duncia *et al.*, 1992). Most of them contain a biphenyltetrazole moiety linked to a heterocycle by a methylene group. We have reported the crystal structure of an imidazo[5,4-*b*]pyridine-based AII antagonist, compound (I), with a high antihypertensive activity (Shin *et al.*, 1996). The title compound (II), with an oxopyridine ring, is more potent and shows better pharmacological profile than compound (I) and is currently under clinical study. The present X-ray analysis has been performed to establish its conformational characteristics.



Molecular dimensions are normal within experimental error. The imidazopyridine ring system is planar with a maximum deviation of 0.014 (2) Å for atom C5. The three six-membered rings and the tetrazole ring are also planar, with maximum deviations of 0.006 (3),

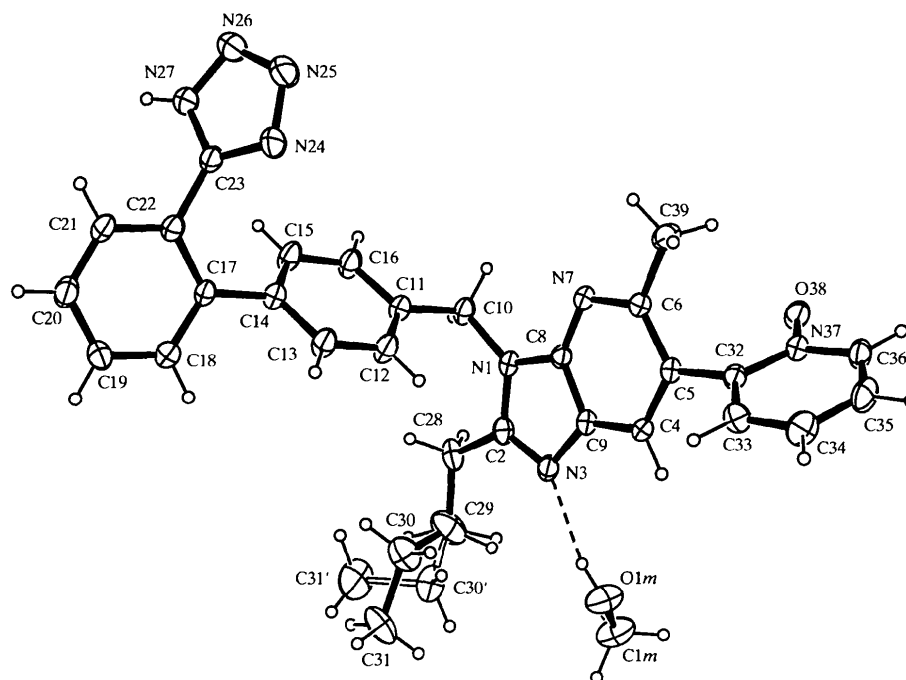


Fig. 1. ORTEP (Johnson, 1976) view of (II) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 25% level. The dashed line denotes the hydrogen bond and the atoms at the minor site are primed.

0.013 (2), 0.023 (2) and 0.004 (2) Å for atoms C14, C22, N37 and N27, respectively. The dihedral angle between the imidazopyridine and the C5-oxopyridine rings is 62.5 (1)°. The dihedral angles between the two phenyl rings and between the tetrazole and its bonded phenyl ring are 48.8 (1) and 54.6 (1)°, respectively. Part of the *n*-butyl side chain (the C30 and C31 atoms) is disordered with an occupancy of 0.65 (2) for the major site.

The methanol solvent molecule is hydrogen-bonded to N3 [O1 m ··N 2.847 (4), H··N 2.04 Å, O—H··N 167°]. An intermolecular N27—H··O38 hydrogen bond [N··O(1 + *x*, 0.5 - *y*, 0.5 + *z*) 2.633 (4), H··O 1.78 Å, N—H··O 172°] links the molecules to form a hydrogen-bonded molecular chain. Otherwise there are no unusually close contacts.

It has been pointed out that the crystal conformations of the compounds related to (I) reported thus far are very similar in terms of the relative orientation of the biphenyltetrazole moiety with respect to the central heterocyclic ring as well as the conformation of the biphenyltetrazole moiety itself (Shin *et al.*, 1996; Bradbury *et al.*, 1993; Kubo *et al.*, 1993; Ellingboe *et al.*, 1994). However, the present study shows that the overall conformation of the title compound is significantly different from others. Superimposed structures of compounds (II) and (I) are shown in Fig. 2. The C8—N1—C10—C11, N1—C10—C11—C12, C13—C14—C17—C22 and C17—C22—C23—N27 torsion angles that determine the overall conformation are ∓ 94.0 (4), ± 6.7 (5), ± 133.5 (4) and ± 130.9 (4)° for the compound (II) and ∓ 88.3 , ± 67.4 , ∓ 133.5 and ± 57.8 ° for (I), respectively. The largest differences in the conformations are manifested in the last three torsion angles.

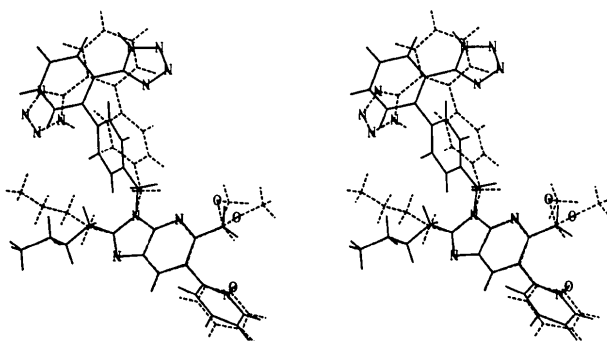


Fig. 2. Stereoscopic view of the superimposed structures of compounds (I) (dotted line) and (II) (solid line).

We have reported previously a relaxed two-dimensional potential-energy map of thiamin, showing that there is conformational flexibility about the C—C bonds in the methylene bridge linking the two aromatic ring systems (Shin *et al.*, 1993). The energy map of

the title compound (II) is essentially similar to that of thiamin, although details in the low-energy region are slightly different. The low-energy regions are continuously interconnected with energy barriers lower than 3 kcal mol⁻¹ (1 cal = 4.184 J) and thereby interconversions of the various conformations can occur easily through a concerted rotation of the two torsion angles. Thus variations in the N1—C10—C11—C12 torsion angles in the crystal structures merely reflect the presence of many local minima.

The conformation of the biphenyltetrazole moiety in (II) is enantiomeric to that of (I). It has been proposed, from molecular mechanics calculations, that the biphenyltetrazole moiety can assume two enantiomeric minimum-energy conformations with the planes of the phenyl rings twisted by $\pm 61^\circ$ and a barrier to planarity of 6.7 kcal mol⁻¹ (Bradbury *et al.*, 1992, 1993). The enantiomeric conformation is observed in this structure although the twist angle between the phenyl rings is *ca* 49 rather than 61°. The orientation of the tetrazole ring with respect to the phenyl ring in (II) is also different from others. The protonated N27 atom is situated close to the phenyl ring with a dihedral angle of *ca* 58° in all related structures, but it is directed in the opposite direction in the title compound.

Experimental

The synthesis and biological evaluation of (II) were carried out at the Korea Research Institute of Chemical Technology. Crystals were obtained from a methanol solution. The density D_m was measured by flotation in an *n*-hexane/carbon tetrachloride solution.

Crystal data

C₃₀H₂₈N₈O·CH₄O

$M_r = 548.65$

Monoclinic

$P2_1/c$

$a = 12.235$ (4) Å

$b = 13.719$ (7) Å

$c = 16.974$ (7) Å

$\beta = 92.45$ (5)°

$V = 2847$ (2) Å³

$Z = 4$

$D_x = 1.280$ Mg m⁻³

$D_m = 1.28$ (2) Mg m⁻³

D_m measured by flotation

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 32 reflections

$\theta = 6.7$ – 13.8°

$\mu = 0.084$ mm⁻¹

$T = 293$ (2) K

Block

$0.70 \times 0.40 \times 0.40$ mm

Colourless

Data collection

Rigaku AFC-4 diffractometer

ω - 2θ scans

Absorption correction: none

5316 measured reflections

5307 independent reflections

2777 reflections with

$I > 2\sigma(I)$

$R_{int} = 0.053$

$\theta_{max} = 25.88^\circ$

$h = 0 \rightarrow 14$

$k = 0 \rightarrow 16$

$l = -20 \rightarrow 20$

3 standard reflections

every 100 reflections

intensity decay: 2%

*Refinement*Refinement on F^2

$$R[F^2 > 2\sigma(F^2)] = 0.069$$

$$wR(F^2) = 0.194$$

$$S = 1.022$$

5307 reflections

395 parameters

H-atom parameters

constrained

$$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\max} = 0.001$$

$$\Delta\rho_{\max} = 0.242 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.245 \text{ e } \text{\AA}^{-3}$$

Extinction correction:

SHELXL97 (Sheldrick, 1997)

Extinction coefficient:

0.0111 (16)

Scattering factors from

International Tables for Crystallography (Vol. C)Table 1. Selected torsion angles ($^\circ$)

C8—N1—C10—C11	-94.0 (4)	C2—C28—C29—C30	80.7 (6)
N1—C10—C11—C12	6.7 (5)	C28—C29—C30—C31	165.7 (10)
C17—C22—C23—N27	130.9 (4)	C28—C29—C30'—C31'	87.2 (14)
N1—C2—C28—C29	-175.9 (3)	C4—C5—C32—N37	115.0 (3)
C2—C28—C29—C30'	62.6 (10)		

Data collection: local program (Yoon *et al.*, 1994). Cell refinement: local program. Data reduction: local program. Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1305). Services for accessing these data are described at the back of the journal.

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(1*S*,2*S*,5*S*,6*S*)-5,6-Dihydroxy-6-methylcyclohex-3-en-1,2-diyl diacetate

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Abstract

The title compound, C₁₁H₁₆O₆, has been synthesized and isolated as the major product of the osmylation of (5*S*,6*R*)-5,6-diacetoxy-1-methyl-1,3-cyclohexadiene. The molecule crystallizes in the monoclinic space group *P2*₁. The hexene ring exhibits a puckered distorted half-chair conformation, with all the chiral centres (C3, C4, C5 and C6) in the *S* configuration. One intramolecular and two intermolecular hydrogen bonds stabilize the molecule by the formation of infinite chains along *b*.

Comment

The use of *cis*-cyclohexadienediols has become relevant in organic synthesis because of their rich functionality and highly selective reactivity. The dihydroxylation of chiral *cis*-cyclohexadienediols is usually used in the synthesis of a wide variety of biologically active products. These dienes are produced by microbial oxidation of aromatic substrates with enzymes from a mutant strain of *Pseudomonas*, *P. putida* 39D. Osmylation of (5*S*,6*R*)-5,6-diacetoxy-1-methyl-1,3-cyclohexadiene was performed to synthesize the title compound, (I), as the major product of the reaction. The compound was isolated and spectroscopically characterized by Brovetto *et al.* (1999). It was determined that C5 and C6 kept the same configurations as in the parent compound. The assignments for C3 and C4 were made by comparing the relative configurations with respect to the known configurations of C5 and C6 (Hudlicky *et al.*, 1988).