Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Trityl losartan

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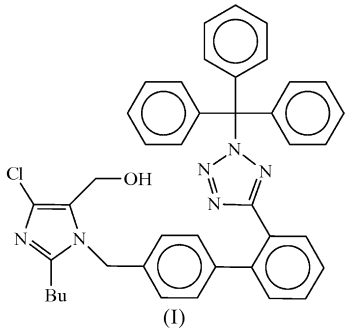
Received 1 September 2004
Accepted 24 September 2004
Online 22 October 2004

The title compound (systematic name: {2-butyl-4-chloro-1-[2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-1*H*-imidazol-5-yl}methanol), $C_{41}H_{37}ClN_6O$, crystallizes in the centrosymmetric space group $P\overline{1}$ with two independent molecules in the asymmetric unit. These molecules differ significantly only in the relative orientations of the rings in the biphenylyltetrazole moieties. One of the molecules shows disorder for three C atoms in the *n*-butyl group. Hydrogen bonds link the molecules in an infinite chain along the *a* axis.

Comment

Imidazole is a protonated five-membered ring that promotes chemical reactions at enzyme catalytic sites, depending on the specific physical conditions. Various imidazole derivatives are found to possess biological activity and are used in pharmaceuticals, agrochemicals, dyestuffs and high-temperature polymer products (Rasmussen, 1999).



(I)

The title compound, trityl losartan, (I), is used as a key intermediate in the synthesis of losartan potassium, which is a very useful antihypertensive drug in the treatment of hypertension by inhibiting angiotensin II (Campbell *et al.*, 1995). With a view to understanding the conformation of the imidazole moiety, the influence of the substituents at different positions of this five-membered ring and the effect of the trityl group on the losartan molecule as a whole, the crystal structure determination of (I) has been carried out and the results are presented here.

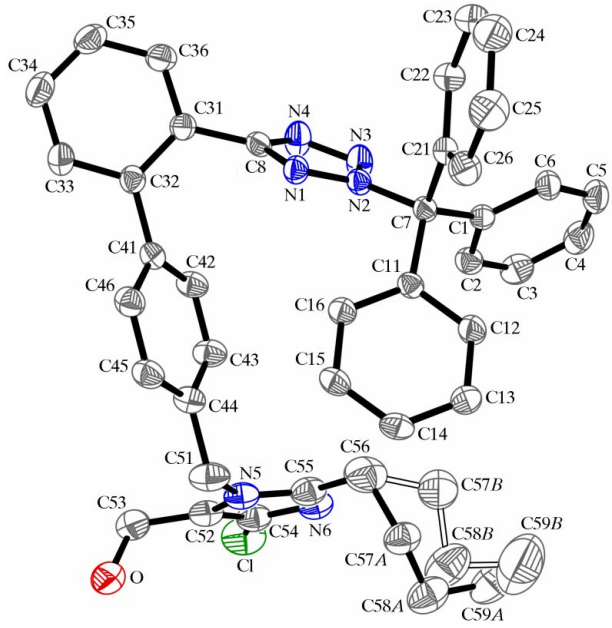


Figure 1
A view of the unprimed molecule of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity. The suffixes *A* and *B* denote the two disordered moieties.

The asymmetric unit of (I) contains two crystallographically independent molecules (Figs. 1 and 2); these are distinguished by primes on the labels for the second molecule. The corresponding bond lengths and angles of both molecules agree

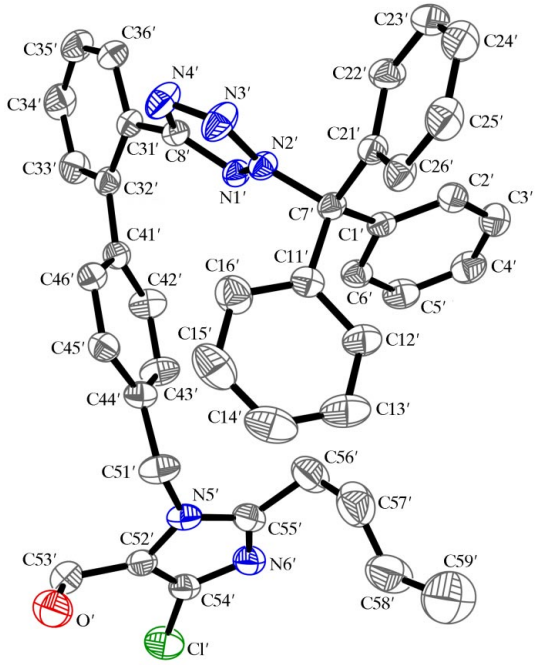


Figure 2
A view of the primed molecule of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity.

 DOI: 10.1107/S0108270104024096

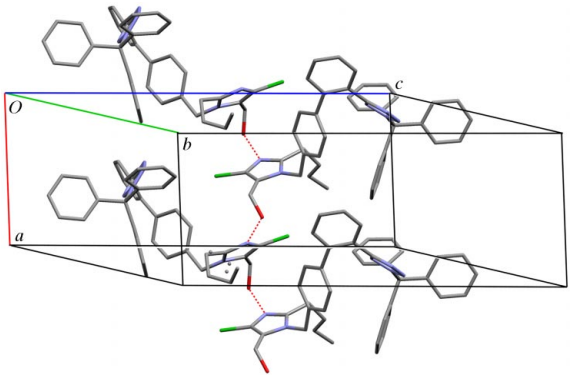


Figure 3
The packing of the molecules of (I) in the unit cell, showing the intermolecular hydrogen bonds (dashed lines) along the *a* axis. H atoms have been omitted for clarity.

with each other (Table 1), but the orientations of the phenyl rings of the biphenyl moieties, and of the phenyl rings C41–C46 and C41′–C46′, with respect to the tetrazole moieties is different in the unprimed molecule from that in the primed one. This can be seen from the C31—C32—C41—C42 and N1—C8—C31—C32 torsion angles of −52.0 (3)° [−128.7 (2)° in the primed molecule] and −61.4 (3)° [50.5 (3)° in the primed molecule], respectively. Part of the *n*-butyl side chain of the unprimed molecule (atoms C57, C58 and C59) is disordered, with equal site-occupancy factors.

The crystal structure of (I) is stabilized by two intermolecular O—H···N hydrogen bonds linking different molecules alternately along the *a* axis, to form an infinite chain (Fig. 3). The same hydrogen-bond interaction was reported previously in the structure of losartan potassium (Fernández *et al.*, 2002). Intramolecular C—H···N, C—H···O and C—H···π hydrogen bonds are observed and these have an influence on the conformation of the molecules and the crystal packing. The C14—H14···*Cg*($x+1$, y, z) (*Cg* denotes the centroid of the C1–C6 ring) interaction involves two phenyl rings of the trityl groups to form an infinite chain along the *a* direction. Details of the hydrogen-bonding geometry are given in Table 2.

Experimental

The title compound was synthesized by condensing an equimolar mixture of (2-butyl-5-chloro-3*H*-imidazol-4-yl)methanol and 5-(4′-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole with potassium carbonate in dimethylformamide with stirring at room temperature for 10 h (80% yield). The compound was recrystallized from acetonitrile.

Crystal data

$C_{41}H_{37}ClN_6O$
M_r = 665.22
Triclinic, $P\overline{1}$
a = 8.6962 (3) Å
b = 20.5493 (6) Å
c = 21.7392 (5) Å
α = 69.597 (2)°
β = 88.587 (2)°
γ = 78.962 (3)°
V = 3570.0 (2) Å^3
Z = 4
D_x = 1.238 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 13 199 reflections
θ = 2.9–30.0°
μ = 0.15 mm^{-1}
T = 293 (2) K
Prism, colourless
0.55 × 0.23 × 0.16 mm

Data collection

Kuma KM4 CCD area-detector diffractometer
ω scans
48 342 measured reflections
12 560 independent reflections
9584 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 25.0°
$h = -10 \rightarrow 10$
$k = -24 \rightarrow 24$
$l = -25 \rightarrow 25$

Refinement

Refinement on F^2
$R(F)$ = 0.048
$wR(F^2)$ = 0.143
S = 1.13
12 560 reflections
909 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0744P)^2 + 0.3025P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}
Extinction correction: *SHELXTL/PC* (Sheldrick, 1990)
Extinction coefficient: 0.0032 (6)

Table 1
Selected geometric parameters (Å, °).

Cl—C54	1.715 (2)	Cl′—C54′	1.720 (2)
O—C53	1.393 (3)	O′—C53′	1.415 (3)
N1—C8	1.327 (2)	N1′—C8′	1.330 (2)
N1—N2	1.335 (2)	N1′—N2′	1.328 (2)
N2—N3	1.316 (2)	N2′—N3′	1.327 (2)
N2—C7	1.514 (2)	N2′—C7′	1.500 (2)
N3—N4	1.320 (2)	N3′—N4′	1.319 (2)
N4—C8	1.346 (3)	N4′—C8′	1.347 (2)
N5—C51	1.467 (3)	N5′—C51′	1.461 (3)
N5—C52	1.382 (3)	N5′—C52′	1.388 (3)
N5—C55	1.359 (3)	N5′—C55′	1.362 (3)
N6—C54	1.363 (4)	N6′—C54′	1.365 (3)
N6—C55	1.328 (3)	N6′—C55′	1.318 (3)
N1—N2—N3	113.10 (13)	N1′—N2′—N3′	113.30 (15)
N2—N1—C8	102.27 (14)	N2′—N1′—C8′	102.06 (14)
N1—N2—C7	123.07 (14)	N1′—N2′—C7′	124.70 (14)
N3—N2—C7	123.56 (13)	N3′—N2′—C7′	121.84 (15)
N2—N3—N4	106.39 (14)	N2′—N3′—N4′	106.25 (15)
N3—N4—C8	106.39 (15)	N3′—N4′—C8′	106.21 (16)
N1—C8—C31—C32	−61.4 (3)	N1′—C8′—C31′—C32′	50.5 (3)
C31—C32—C41—C42	−52.0 (3)	C31′—C32′—C41′—C42′	−128.7 (2)

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

Cg is the centroid of the C1–C6 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O—H1···N6^{i}	0.82	2.04	2.775 (3)	149
O′—H1′···N6	0.82	2.02	2.832 (3)	170
C16—H16···N1	0.93	2.28	2.945 (2)	128
C16′—H16′···N3′	0.93	2.49	3.124 (3)	126
C51—H52···O	0.97	2.56	3.240 (3)	127
C51′—H52′···O′	0.97	2.52	3.218 (3)	129
C14—H14···*Cg*^{i}	0.93	2.67	3.518 (2)	152

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

A free refinement of the site-occupancy factors for the disordered *n*-propyl group (atoms C57, C58 and C59) of the unprimed molecule gave values very close to 0.5, and these values were constrained. Atom C57*B* was refined isotropically because of unsatisfactory anisotropic behaviour. Most of the H atoms were located in difference Fourier syntheses and all were included at geometrically idealized positions and refined as riding, with C—H = 0.93, 0.96 and 0.97 Å, and O—H = 0.82 Å. The U_{iso}(H) values were set at 1.2 (1.5 for hydroxy groups) times U_{eq} of the atoms to which they were bonded.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2004); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2004); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXTL*/*PC* (Sheldrick, 1990); program(s) used to refine structure: *SHELXTL*/*PC*; molecular graphics: *SHELXTL*/*PC* and *MERCURY* (Version 1.2.1; Bruno *et al.*, 2002); software used to prepare material for publication: *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1772). Services for accessing these data are described at the back of the journal.

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