Acta Crystallographica Section E
Structure Reports
Online
ISSN 1600-5368

N-[(2′-Cyanobiphenyl-4-yl)methyl]-L-valine methyl ester hydrochloride: an intermediate in the synthesis of valsartan

Hemmige S. Yathirajan,[a] Basavegowda Nagaraj,[a] Santhosh L. Gaonkar,[a] Rajenahally S. Narasegowda,[a] Padmarajaiah Nagaraja,[a] Basappa Prabhuswamy[a] and Michael Bolte[b]*

[a]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India, and [b]Institut für Anorganische Chemie, J. W. Goethe-Universität Frankfurt, Marie-Curie-Straße 11, 60439 Frankfurt/Main, Germany

Correspondence e-mail:
bolte@chemie.uni-frankfurt.de

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.002 Å
R factor = 0.029
wR factor = 0.068
Data-to-parameter ratio = 18.7

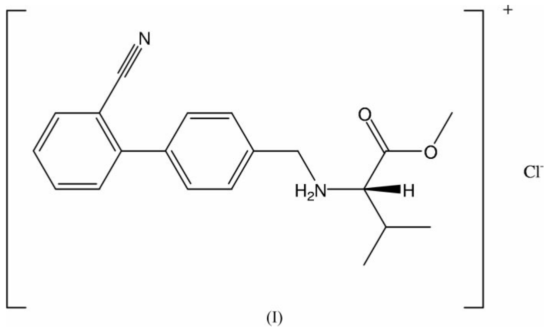
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 18 October 2004
Accepted 22 October 2004
Online 30 October 2004

The title compound {systematic name: methyl 2-[(2′-cyanobiphenyl-4-yl)methylammonio]-3-methylbutanoate chloride}, $C_{20}H_{23}N_2O_2^+\cdot Cl^-$, is a key intermediate in the synthesis of valsartan. It crystallizes with two ion pairs in the asymmetric unit, related pseudocentrosymmetrically to each other. The two cations differ only in the orientation of the isopropyl group.

Comment

The title compound, (I), $C_{20}H_{23}ClN_2O_2$, is a key intermediate for the synthesis of valsartan, which belongs to the class of angiotensin II receptor antagonists (Black *et al.*, 1997). In view of the importance of (I), a crystal structure determination has been carried out.



(I)

Perspective views of the title compound are shown in Figs. 1 and 2. Bond lengths and angles can be regarded as normal (Cambridge Crystallographic Database, Version 1.6 plus three updates; Mogul Version 1.0; Allen, 2002). The dihedral angles between the two aromatic rings are 43.27 (5) and 41.83 (5)°, respectively, for the two cations in the asymmetric unit, which are related to each other by pseudo-inversion symmetry. Bond lengths and angles in the two cations are essentially equal. The cations differ only in the orientation of the isopropyl group with respect to the amine N atom. Whereas the tertiary H atom is *anti* to the N atom in one cation, it is *gauche* in the other (Table 1). The crystal packing is stabilized by several N—H···Cl hydrogen bonds (Table 2).

The appearance of quasi-racemate crystal structures has been found previously (for example, Noguchi *et al.*, 1978; Nozaki, 1979; Giordano & Lanzetta, 1989; Kim *et al.*, 1989; Moon *et al.*, 1992; Bolte, 1996).

Experimental

An equimolar mixture of 4′-bromomethylbiphenyl-2-carbonitrile (1.36 g, 0.005 mol), L-valine methyl ester (0.655 g, 0.005 mol) and

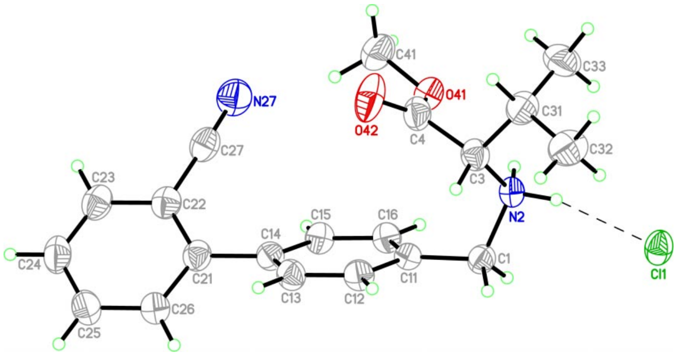


Figure 1
Perspective view of the asymmetric unit of title compound, with the atom numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

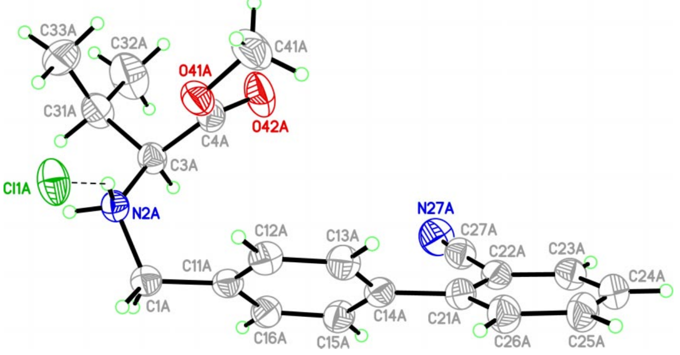


Figure 2
Perspective view of the asymmetric unit of the title title compound, with the atom numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

anhydrous K_2CO_3 (0.745 g, 0.0054 mol) in DMF (3.0 ml) was stirred at room temperature for 6 h. The product formed was filtered, dried and converted to hydrochloride by adding isopropyl alcohol–hydrochloric acid. The product was then recrystallized from ethanol to give colourless prisms of the title compound, which melts at 459 K (Buhlmayer, 1991). Analysis calculated: C 66.93, H 6.46, N 7.81%; found: C 66.82, H 6.49, N 7.85%.

Crystal data

$C_{20}H_{23}N_2O_2^+ \cdot Cl^-$
$M_r = 358.85$
Monoclinic, $P2_1$
$a = 15.6095$ (8) Å
$b = 6.8297$ (4) Å
$c = 18.6854$ (9) Å
$\beta = 103.739$ (4)°
$V = 1935.02$ (18) Å^3
$Z = 4$

$D_x = 1.232$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 43 202 reflections
$\theta = 2.6$–$27.3°$
$\mu = 0.21$ mm^{-1}
$T = 173$ (2) K
Block, colourless
0.33 × 0.27 × 0.19 mm

Data collection

Stoe IPDS II two-circle diffractometer
ω scans
Absorption correction: multi-scan (*MULABS*; Spek, 2003; Blessing, 1995)
$T_{\min} = 0.871$, $T_{\max} = 0.981$
56 436 measured reflections

8739 independent reflections
7170 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.075$
$\theta_{\max} = 27.4°$
$h = -20 \rightarrow 20$
$k = -8 \rightarrow 8$
$l = -22 \rightarrow 24$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.029$
$wR(F^2) = 0.068$
$S = 0.90$
8739 reflections
467 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0376P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.14$ e Å^{-3}
$\Delta\rho_{\min} = -0.21$ e Å^{-3}
Absolute structure: Flack (1983), 3990 Friedel pairs
Flack parameter = −0.06 (3)

Table 1
Selected geometric parameters (Å, °).

C1—N2	1.509 (2)	C1*A*—N2*A*	1.499 (2)
N2—C3	1.5005 (19)	N2*A*—C3*A*	1.4926 (19)
C4—O42	1.193 (2)	C4*A*—O42*A*	1.199 (2)
C4—O41	1.327 (2)	C4*A*—O41*A*	1.333 (2)
O41—C41	1.445 (2)	O41*A*—C41*A*	1.446 (2)
C22—C27	1.441 (3)	C22*A*—C27*A*	1.444 (2)
C27—N27	1.148 (2)	C27*A*—N27*A*	1.140 (2)
C3—N2—C1	115.09 (12)	C3*A*—N2*A*—C1*A*	117.04 (12)
N2—C3—C31—H31	169.99	N2*A*—C3*A*—C31*A*—H31*A*	−52.69

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*B*···Cl1	0.920 (19)	2.243 (19)	3.1199 (13)	159.0 (15)
N2—H2*A*···Cl1$^{\rm i}$	0.91 (2)	2.28 (2)	3.1168 (14)	153.1 (18)
N2*A*—H2*C*···Cl1*A*	0.96 (2)	2.19 (2)	3.0700 (14)	151.1 (16)
N2*A*—H2*D*···Cl1*A*$^{\rm ii}$	0.901 (19)	2.185 (19)	3.0676 (14)	166.0 (15)

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

H atoms bonded to C atoms were refined with fixed individual displacement parameters [$U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}({\rm C})$ or $U_{\rm iso}({\rm H}) = 1.5U_{\rm eq}({\rm C_{methyl}})$] using a riding model, with C—H = 1.00, 0.99, 0.98 and 0.95 Å, for tertiary CH, secondary CH, methyl and aromatic CH, respectively. H atoms bonded to N atoms were refined freely. A check for overlooked symmetry with *PLATON* (Spek, 2003) produces the warning that 88% of the structure can be described in $P2_1/c$. The reflections that should be unobserved if a *c* glide plane were present are significantly weaker [mean $I = 1.2$, mean $I/\sigma(I) = 2.7$] than the reflections indicating a possible *a*-glide plane [mean $I = 10.1$, mean $I/\sigma(I) = 13.0$]; for comparison the values for the 2_1 screw axis are mean $I = 0.2$, mean $I/\sigma(I) = 0.4$. However, since both chiral C atoms (C31 and C31*A*) have the same absolute configuration, *viz*. *S*, the space group must be $P2_1$.

Data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2003).

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Black, H. R., Graff, A., Shute, D., Stoltz, R., Ruff, D. & Levine, J. (1997). *J. Hum. Hypertens.* **11**, 483–489.
Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.
Bolte, M. (1996). *Acta Cryst.* C**52**, 1985–1987.
Buhlmayer, P. (1991). EP Patent No. 443983, Ciba-Geigy.

Acta Cryst. (2004). E**60**, o2160–o2162 Hemmige S. Yathirajan *et al.* • $C_{20}H_{23}N_2O_2^+ \cdot Cl^-$ **o2161**

Flack, H. D. (1983), *Acta Cryst.* A**39**, 876–881.

Giordano, F. & Lanzetta, R. (1989). *Acta Cryst.* C**45**, 1603–1606.

Kim, Ch.-H., Rothman, R. B., Jacobson, A. E., Mattson, M. V., Bykov, V., Streaty, R. E., Klee, W. A., George, C., Long, J. B. & Rice, K. C. (1989). *J. Med. Chem.* **32**, 1392–1398.

Moon, M. W., Morris, J. K., Heier, R. F., Chidester, C. G., Hoffmann, W. E., Piercey, M. F., Althaus, J. S., VonVoigtlander, P. F., Evans, D. L., Figur, L. M. & Lahti, R. A. (1992). *J. Med. Chem.* **35**, 1076–1092.

Noguchi, H., Sankawa, U. & Iitaka, Y. (1978). *Acta Cryst.* B**34**, 3273–3276.

Nozaki, H. (1979). *J. Chem. Soc. Perkin Trans.* 2, pp. 514–518.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1991). *SHELXTL-Plus.* Release 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Stoe & Cie (2001). *X-AREA*. Stoe & Cie, Darmstadt, Germany.

o2162 Hemmige S. Yathirajan *et al.* • $C_{20}H_{23}N_2O_2^+\cdot Cl^-$ *Acta Cryst.* (2004). E**60**, o2160–o2162