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(1′*R*,2′*R*)-3-[(*cis*-2′-Cyclohexylmethylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrobromide, a hypoglycaemic semicyclic amidine

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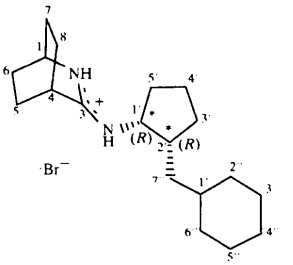
(*Received 19 May 1998; accepted 7 January 1999*)

Abstract

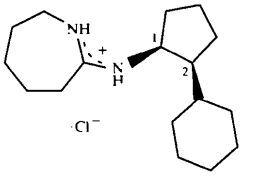
The title compound, $C_{19}H_{33}N_2^+{\cdot}Br^-$, shows dynamic equilibrium in solution between the *Z* and *E* isomers, enabled by the delocalization of the C=N double bond (C···N ~ 1.317 Å) of the amidine function. In the solid state, the absolute configuration has been determined as 1′*R*,2′*R* by X-ray analysis exploiting anomalous-dispersion effects. The double bond displays the *Z* configuration, consistent with *like-induction* in asymmetric reductive amination of prochiral cycloalkanones. Within the crystal structure the molecules are linked into chains by hydrogen bonds to the Br^- ions.

Comment

The title compound, (I), a semicyclic amidine, is a representative of an analogous series of optically pure amidines that stimulate insulin release in pancreatic B cells. The hypoglycaemic activity of racemic 2-[(*cis*-2′-cyclohexylcyclopentyl)imino]hexahydroazepine hydrochloride, (II), was first described by Grisar *et al.* (1973). Improvement of antidiabetic activity was correlated with increasing steric hindrance of the C1 atom, which is attached to the lactamimide function. Until now, however, no experiments concerning the enantiomeric differentiation of the hypoglycaemic effect have been carried out. Therefore, we synthesized two different series of optically pure amidines with variable substituents in position 2′ of the cyclopentane moiety, containing either a caprolactam or an isoquinuclidone ring system. Replacement of the seven-membered ring in compound (II) with a bicyclic ring system allows for separate investigation of the influence of increasing steric hindrance of the lactamimide moiety by itself. Substituents at position 2′ of the cyclopentane ring include isopropyl, phenyl, cyclohexyl, benzyl, cyclohexylmethyl and cyclopentyl residues.



(I)



(II)

In solution, these compounds show dynamic equilibration; their characterization by ^1H, ^{13}C and ^{15}N NMR techniques has been reported separately (Hartmann *et al.*, 1999). Here we are especially interested in establishing the *Z* configuration of the C=N double bond (relating to the position of the cyclopentane residue and the endocyclic N atom) in the solid state, and in elucidating the absolute configuration of the chiral centres C1′ and C2′.

The structure analysis of (I) (Fig. 1) shows that both the endocyclic and the semicyclic N atoms bear one H atom. Bond lengths between the atoms of the amidine function are nearly identical [N1—C3 1.316 (2) and N2—C3 1.319 (2) Å]. These values indicate delocalized bonding between 1.38 Å for an sp^2 C—N single bond and 1.28 Å for an sp^2 C=N double bond (Allen *et al.*, 1987). This partial sp^2 character of the semicyclic C···N bond allows two different configurations: the cyclopentane residue and the endocyclic-N atom located on the same side (*Z*) or on opposite sides (*E*) of the double bond. Earlier time-dependent ^1H NMR

experiments showed dynamic equilibrium of the *E* and *Z* configuration in liquid phase within 30 min, the *Z* isomer being the major component immediately after dissolving the semicyclic amidine. According to this observation, we also found the *Z* configuration in the crystal.

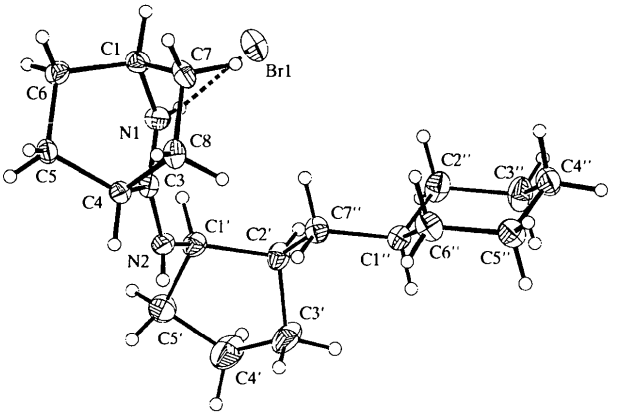


Fig. 1. Structure of (I) with 50% probability displacement ellipsoids for non-H atoms and arbitrary small displacement spheres for H atoms.

The absolute configuration is found to be 1′*R* and 2′*R* according to the Cahn–Ingold–Prelog system. The chiral C1′ atom is generated by asymmetric reductive amination of the respective prochiral cyclopentanone, corresponding with the absolute configuration of the inducing agent used (*like-induction*) (Wiehl & Frahm, 1986; Knupp & Frahm, 1983). The five-membered ring displays an envelope conformation with both substituents pseudo-axial, the flexible methylene bridge (C7′′) then allowing the 2′-cyclohexyl residue to avoid the energetically unfavourable pseudo-axial position.

The crystal structure shows two weak hydrogen bonds to the bromide ion, linking two symmetrically equivalent molecules: N1—H1···Br1 3.271 (2) Å and 165 (3)°; N2—H2···Br1^{i} 3.290 (2) Å and 168 (3)° [symmetry code: (i) $1-x, y+\frac{1}{2}, \frac{1}{2}-z$]. These hydrogen bonds link the residues into chains.

Experimental

3-Ethoxy-2-azabicyclo[2.2.2]oct-2-ene (0.77 g, 5 mmol) and (1*R*,2*R*)-*cis*-2-cyclohexylmethylcyclopentaneamine hydrobromide (1.05 g, 4 mmol), prepared by asymmetric reductive amination (Wiehl & Frahm, 1986) of racemic 2-cyclohexylmethyl cyclopentanone with (1*R*)-(+)-1-phenylethylamine, were stirred for six weeks at room temperature to give the title compound, (I), in 84% yield after crystallization (1.24 g, 3.36 mmol) [m.p. 506–507 K; $[\alpha]_D^{25} = +37.9°$ (*c* = 1.0, EtOH)]. Crystals suitable for diffraction analysis were obtained by recrystallization from methanol/acetone.

Crystal data

$C_{19}H_{33}N_2^+ \cdot Br^-$
$M_r = 369.39$
Orthorhombic
$P2_12_12_1$
$a = 11.245\ (2)$ Å
$b = 11.752\ (2)$ Å
$c = 14.476\ (5)$ Å
$V = 1913.0\ (8)$ Å^3
$Z = 4$
$D_x = 1.282$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 13 764 reflections
$\theta = 3$–$25.6°$
$\mu = 2.149$ mm^{-1}
$T = 150\ (1)$ K
Approximately spherical (ground)
0.09 × 0.085 × 0.08 mm
0.0425 mm (radius)
Colourless

Data collection

MAR 180 mm image plate
Area detector scans
Absorption correction: none
24 133 measured reflections
3714 independent reflections
3706 reflections with $I > 2\sigma(I)$
$R_{int} = 0.050$
$\theta_{max} = 25.94°$
$h = -13 \rightarrow 13$
$k = -14 \rightarrow 14$
$l = -17 \rightarrow 17$
Intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.020$
$wR(F^2) = 0.051$
$S = 1.102$
3714 reflections
208 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0217P)^2 + 0.4565P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.387$ e Å^{-3}
$\Delta\rho_{min} = -0.134$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.006 (6)

Table 1. *Selected geometric parameters (Å, °)*

N1—C3	1.316 (2)	C1—C7	1.531 (3)
N1—C1	1.480 (2)	C8—C4	1.544 (2)
N2—C3	1.319 (2)	C2′—C7′′	1.525 (2)
N2—C1′	1.467 (2)	C2′—C3′	1.537 (3)
C5—C4	1.545 (2)	C2′—C1′	1.564 (2)
C3—C4	1.498 (2)	C1′′—C7′′	1.531 (2)
C6—C1	1.532 (2)	C1′—C5′	1.551 (2)
C3—N1—C1	115.20 (14)	C3—C4—C5	108.02 (13)
C3—N2—C1′	126.13 (16)	C8—C4—C5	108.45 (13)
N1—C3—N2	125.20 (16)	C7′′—C2′—C1′	114.43 (14)
N1—C3—C4	113.62 (14)	C3′—C2′—C1′	103.57 (14)
N2—C3—C4	121.18 (15)	N2—C1′—C5′	109.07 (14)
N1—C1—C6	107.54 (14)	N2—C1′—C2′	113.25 (13)
N1—C1—C7	108.23 (14)	C5′—C1′—C2′	105.58 (13)
C6—C1—C7	109.57 (14)	C2′—C7′′—C1′′	115.47 (14)
C3—C4—C8	106.93 (14)		

The structure was solved by direct methods. All non-H atoms were refined anisotropically. Atoms H1 and H2 were refined isotropically. The positions of the remaining H atoms were refined in a riding model together with the binding C atoms. The data are 99.8% complete to $2\theta = 51.2°$. The absolute configuration was determined by refining an enantiomorph-sensitive parameter (Flack, 1983) including all 1571 Friedel pairs.

Data collection: *XDS*98 (Kabsch, 1993). Cell refinement: *XDS*98. Data reduction: *XDS*98. Program(s) used to solve

structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *CRYSTAN* (Burzlaff & Rothammel, 1988). Software used to prepare material for publication: *SHELXL*97.

The authors thank the 'Fonds der chemischen Industrie' for funds. SH is grateful to the 'Dr Hilmer-Stiftung im Stifterverband für die Deutsche Wissenschaft' for a scholarship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1314). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1999). C**55**, 808–811

Imide and tribenzyl ester derivatives of Kemp's triacid

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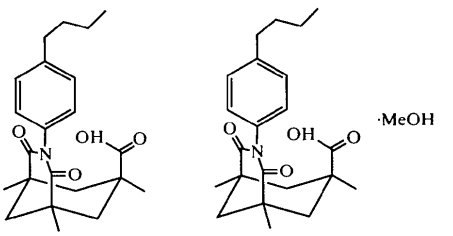
(*Received 23 September 1998; accepted 22 December 1998*)

Abstract

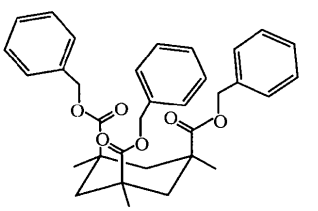
Two derivatives of Kemp's triacid (*cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid) have been structurally characterized. The imide *cis,cis*-*N*-(4-*n*-butylphenyl)-5-carboxy-1,3,5-trimethylcyclohexane-1,3-dicarboximide crystallizes either pure ($C_{22}H_{29}NO_4$) or as a methanol solvate ($C_{22}H_{29}NO_4 \cdot CH_3OH$) in which the solvent molecule is hydrogen bonded to imide and carboxyl-O atoms. The triester derivative, tribenzyl *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylate ($C_{33}H_{36}O_6$), presents the concave shape characteristic of many such derivatives.

Comment

Kemp's triacid is well known as a useful and versatile building block in systems designed for molecular recognition (Rebek, 1990) or for ion transport. The crystal structures of its pure and acetonitrile-solvate forms have been determined (Rebek *et al.*, 1985; Chan *et al.*, 1991; Hirose *et al.*, 1998). The imide derivative, *N*-(4-*n*-butylphenyl)-5-carboxy-1,3,5-trimethylcyclohexane-1,3-dicarboximide, (1), has been shown to be both an efficient alkaline-earth metal-ion transport agent with a marked selectivity for calcium ions (Hirose *et al.*, 1995), and a transition-metal-ion complexant selective for divalent mercury ions (Hirose *et al.*, 1996). Chromogenic reagents for mercury ions have been synthesized using an azobenzene moiety in place of the *n*-butyl group in the *N*-substituent (Wang *et al.*, 1997). Bis(Kemp's acid imide) compounds, where the two moieties are bridged by the *N*-substituent, have also been synthesized and their complexing properties investigated (Tanase *et al.*, 1994; Herold *et al.*, 1995; Yun *et al.*, 1995). The complexing properties of the ester derivative tribenzyl *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylate, (3), have not yet been investigated.



(1) (2)



(3)

The bond distances and angles are as expected for the three structures reported here, *i.e.* (1), its methanol solvate (2), and (3). The chair cyclohexane skeleton is rigid and prevented from epimerization and