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7-Chloro-(*R*)-3-[1-(cyclohexyl)ethylamino]-4*H*-1,2,4-benzothiadiazine 1,1-dioxide and 7-chloro-(*S*)-3-[1-(cyclohexyl)ethylamino]-4*H*-1,2,4-benzothiadiazine 1,1-dioxide

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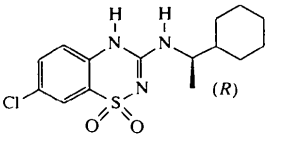
Abstract

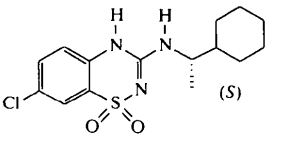
3-Alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides structurally related to diazoxide are expected to present a pharmacological profile of potassium-channel openers. The influence on biological activity of the absolute configuration of the title compounds, both $C_{15}H_{20}ClN_3O_2S$, is being studied. The crystallographic results confirm the enantiomeric characterization of each compound.

Comment

3-Alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides structurally related to diazoxide (Bandoli & Nicolini, 1977) and bearing a short branched hydrocarbon chain in the 3-position have been reported to exhibit myorelaxant properties (de Tullio *et al.*, 1996). Such an effect of the drugs should be attributed to their possible pharmacological profile as potassium-channel openers. In the search of new similar compounds expressing smooth muscle myorelaxant properties, it was of interest to study the influence on biological activity of the stereospecificity associated with the first C atom of the hydrocarbon chain linked to the exocyclic N atom in the 3-position. The (*R*)- and (*S*)-7-chloro-3-[1-(cyclohexyl)-ethylamino]-4*H*-1,2,4-benzothiadiazine 1,1-dioxides, (I) and (II), respectively, were prepared from the reaction of 7-chloro-3-methylsulfanyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide with commercially available (*R*)- and (*S*)-1-(cyclohexyl)ethylamine. The optical purity of the enantiomeric antipodes was determined by a chiral high-pressure liquid chromatography technique as previously described (Khelili *et al.*, 1999).

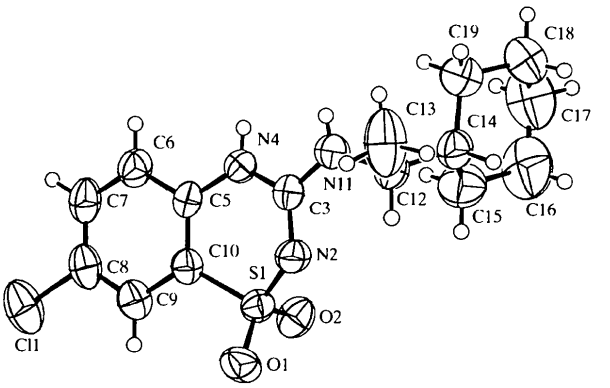


(I)

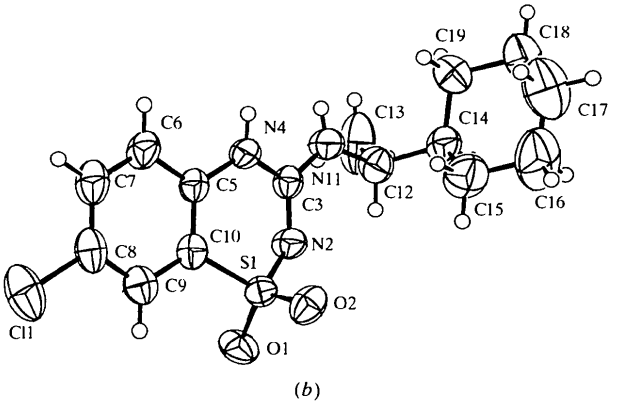


(II)

For the two compounds, the enantiomeric excess (ee) is larger than 95%. The Flack parameter of the crystal structure confirms the configuration of each enantiomer. The refinements of the inverted structures have been tested. The corresponding Flack parameters have the values of 0.94 (3) and 0.84 (4), respectively. In the two structures the geometrical parameters (cell dimensions,



(*a*)



(*b*)

Fig. 1. Molecular structure with atom-labelling scheme for the (*a*) (*R*)- and (*b*) (*S*)- enantiomers. Displacement ellipsoids are shown at 50% probability levels. H atoms are drawn as small circles of an arbitrary radius.

distances, bond and torsional angles) are comparable with each other. Many deviations between respective values in the two structures are less than 1σ. Only a few of them are equal or greater than 3σ (Tables 1 and 3). The cohesion of the crystals is the result of van der Waals interactions and of intermolecular hydrogen bonds N4—H4···O1 and N11—H11···O1 (Tables 2 and 4). These results may help to establish the important chemical and geometrical parameters required (pharmacophore) for biological activity in such molecules.

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

S1—N2	1.586 (3)	N4—H4	0.81 (4)
S1—C10	1.745 (3)	N11—C12	1.459 (4)
N2—C3	1.325 (4)	N11—H11	0.75 (4)
C3—N11	1.322 (4)	C12—C13	1.519 (6)
C3—N4	1.353 (4)	C12—C14	1.520 (5)
N4—C5	1.392 (4)		
C3—N2—S1	119.6 (2)	C3—N4—H4	116 (3)
N2—C3—N11	120.1 (3)	C5—N4—H4	120 (3)
N2—C3—N4	123.4 (3)	C3—N11—C12	125.8 (3)
N11—C3—N4	116.5 (3)	C3—N11—H11	118 (3)
C3—N4—C5	124.9 (3)	C12—N11—H11	117 (3)
C10—S1—N2—C3	−34.5 (3)	N2—C3—N11—C12	4.7 (6)
S1—N2—C3—N11	−160.0 (3)	C3—N11—C12—C13	−114.7 (4)
S1—N2—C3—N4	22.1 (5)	C3—N11—C12—C14	117.8 (4)
N2—C3—N4—C5	5.1 (5)	N11—C12—C14—C15	−65.1 (5)
N11—C3—N4—C5	−172.9 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4···O1^{i}	0.81 (4)	2.17 (4)	2.935 (4)	156 (3)
N11—H11···O1^{i}	0.75 (4)	2.23 (4)	2.926 (4)	154 (4)

Symmetry code: (i) $2-x, y-\frac{1}{2}, \frac{1}{2}-z$.

Experimental

The compounds were synthesized at the Laboratory of Medicinal Chemistry of Liège (discussed in the text). Crystals were obtained by slow evaporation of a methanol solution at room temperature.

Compound (I)

Crystal data

$C_{15}H_{20}ClN_3O_2S$
$M_r = 341.85$
Orthorhombic
$P2_12_12_1$
$a = 11.2963\ (8)$ Å
$b = 11.8026\ (11)$ Å
$c = 12.8831\ (11)$ Å
$V = 1717.6\ (2)$ Å^3
$Z = 4$
$D_x = 1.322$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54180$ Å
Cell parameters from 31 reflections
$\theta = 23.93$–$27.00°$
$\mu = 3.190$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.61 × 0.38 × 0.30 mm
Colourless

Data collection

Stoe–Siemens AED four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1987*a*)
$T_{min} = 0.211$, $T_{max} = 0.384$
2366 measured reflections
2155 independent reflections

1679 reflections with $I > 2\sigma(I)$
$R_{int} = 0.014$
$\theta_{max} = 68.02°$
$h = -9 \rightarrow 13$
$k = -14 \rightarrow 9$
$l = -10 \rightarrow 15$
2 standard reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.098$
$S = 0.988$
2155 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0703P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997*a*)
Extinction coefficient: 0.0128 (8)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.03 (2)

Compound (II)

Crystal data

$C_{15}H_{20}ClN_3O_2S$
$M_r = 341.85$
Orthorhombic
$P2_12_12_1$
$a = 11.2968\ (4)$ Å
$b = 11.8091\ (7)$ Å
$c = 12.8835\ (10)$ Å
$V = 1718.72\ (18)$ Å^3
$Z = 4$
$D_x = 1.321$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54180$ Å
Cell parameters from 28 reflections
$\theta = 28.48$–$30.82°$
$\mu = 3.188$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.76 × 0.46 × 0.34 mm
Colourless

Data collection

Stoe–Siemens AED four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1987*a*)
$T_{min} = 0.161$, $T_{max} = 0.338$
1766 measured reflections
1766 independent reflections

1426 reflections with $I > 2\sigma(I)$
$\theta_{max} = 68.01°$
$h = 0 \rightarrow 13$
$k = -14 \rightarrow 0$
$l = 0 \rightarrow 15$
2 standard reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.112$
$S = 1.035$
1766 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0771P)^2 + 0.1196P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997*a*)
Extinction coefficient: 0.0069 (8)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.01 (3)

Table 3. *Selected geometric parameters (Å, °) for (II)*

S1—N2	1.575 (3)	N4—H4	0.83 (4)
S1—C10	1.751 (3)	N11—C12	1.466 (5)
N2—C3	1.325 (5)	N11—H11	0.77 (5)
C3—N11	1.325 (5)	C12—C13	1.520 (7)
C3—N4	1.368 (4)	C12—C14	1.524 (6)
N4—C5	1.389 (5)		
C3—N2—S1	120.4 (3)	C3—N4—H4	114 (3)
N2—C3—N11	121.3 (3)	C5—N4—H4	121 (3)
N2—C3—N4	122.8 (3)	C3—N11—C12	124.8 (4)
N11—C3—N4	115.9 (3)	C3—N11—H11	119 (4)
C3—N4—C5	124.0 (3)	C12—N11—H11	116 (4)
C10—S1—N2—C3	34.7 (4)	N2—C3—N11—C12	−4.9 (6)
S1—N2—C3—N11	159.9 (3)	C3—N11—C12—C13	115.4 (5)
S1—N2—C3—N4	−21.9 (5)	C3—N11—C12—C14	−117.9 (5)
N2—C3—N4—C5	−6.0 (6)	N11—C12—C14—C15	65.7 (6)
N11—C3—N4—C5	172.3 (4)		

Table 4. *Hydrogen-bonding geometry (Å, °) for (II)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4···O1^{i}	0.83 (4)	2.15 (5)	2.935 (4)	158 (4)
N11—H11···O1^{i}	0.77 (5)	2.22 (4)	2.928 (4)	151 (5)

Symmetry code: (i) $-x, \frac{1}{2}+y, \frac{3}{2}-z$.

H atoms were restrained (included as riding atoms) except for atoms H4 and H11 which were refined with isotropic displacement parameters fixed at $1.2U_{eq}$ of the parent atom ($1.5U_{eq}$ for the methyl-H atoms).

For both compounds, data collection: *DIF*4 (Stoe & Cie, 1987*b*); cell refinement: *DIF*4; data reduction: *REDU*4 (Stoe & Cie, 1987*c*); program(s) used to solve structures: *SHELXS*97 (Sheldrick, 1997*b*); program(s) used to refine structures: *SHELXL*97 (Sheldrick, 1997*a*); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1050). Services for accessing these data are described at the back of the journal.

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The anomers of 8-aza-7-deaza-2′-deoxyadenosine

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Abstract

The structures of 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, (I), and 4-amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, (II), both $C_{10}H_{13}N_5O_3$, have been determined. The sugar puckering of both compounds is C-2′-*endo*–C-3′*exo* ($^{2}T_{3'}$) (*S*-type sugar). The *N*-glycosidic torsion angle χ^1 is in the *anti* range [−106.3 (2)° for (I) and 111.5 (3)° for (II)] and the crystal structure is stabilized by hydrogen bonds.

Comment

Oligonucleotides containing 8-aza-7-deaza-2′-deoxyadenosine, (I) (Seela & Kaiser, 1988), or C-7-modified 8-aza-7-deazapurine β-D-nucleosides (purine skeleton numbering is used throughout) show enhanced stability of duplexes with antiparallel (aps) chain orientation (Seela *et al.*, 1997; Seela & Becher, 1998; Seela, Becher & Zulauf, 1999; Seela & Zulauf, 1999). The X-ray structures of 7-substituted 8-aza-7-deazaguanine 2′-deoxynucleosides show that, apart from anomeric and *gauche* effects, the steric and stereoelectronic effects of the nucleobase are responsible for the high-*anti* conformation (Seela, Becher, Rosemeyer *et al.*, 1999). In this context, it was of interest to evaluate the crystal structure of 8-aza-7-deaza-2′-deoxyadenosine, (I), not carrying a substituent at C7. As duplexes with parallel (ps) chains can be formed when one oligonucleotide strand contains the sugar in an α-D-configuration (Im-