Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two new chiral nucleoside analogues: (4*R*,5*R*)-4-(4,6-dimethylpyrimidin-2-ylsulfanyl)-5-[(2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-2,3,4,5-tetrahydrofuran-2-one and (4*R*,5*R*)-5-[(2*S*,5*R*)-isopropyl-5-methylcyclohexyloxy]-4-(4-methyl-1,3-thiazol-2-ylamino)-2,3,4,5-tetrahydrofuran-2-one

Lan He,* Yu-Mei Liu, Wei Zhang and Qing-Hua Chen

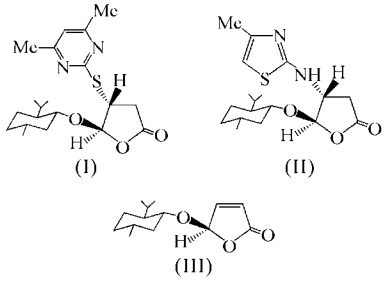
Department of Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China
Correspondence e-mail: helan1961@hotmail.com

Received 5 November 2004
Accepted 11 March 2005
Online 20 May 2005

Synthesis and X-ray structural investigations have been carried out for the two title compounds, *viz*. $C_{20}H_{30}N_2O_3S$, (I), and $C_{18}H_{28}N_2O_3S$, (II). In both molecules, the cyclohexyloxy moiety and the conjugated cyclic system are located on opposite sides of the tetrahydrofuran-2-one ring. In the crystal structure of (II), there are two types of intermolecular hydrogen bonds, *viz*. C—H···S and N—H···O, and the molecules form a three-dimensional supramolecular architecture *via* the hydrogen bonds.

Comment

The chemistry and biology of nucleoside analogues have been the subject of intensive study, since they possess many potent bioactivities, such as antiviral properties, for example against herpes simplex, AIDS-driven viral infections and the human



immunodeficiency virus (Guillarme *et al.*, 2003; Perbost *et al.*, 1992; Wang *et al.*, 2001; de Vrueh *et al.*, 2000). As part of our research work on nucleoside analogues, we synthesized the title compounds, (I) and (II), from 5-(*R*)-menthyloxyfuran-2(5*H*)-one, (III), in order to evaluate their biological activity, and we report their structures here.

Compounds (I) and (II) are both composed of three sections, namely a cyclohexyloxy moiety, a tetrahydrofuran-2-one ring and a conjugated cyclic system, of which the first two have almost the same configuration in the two compounds, with similar bond distances and angles. Compounds (I) and

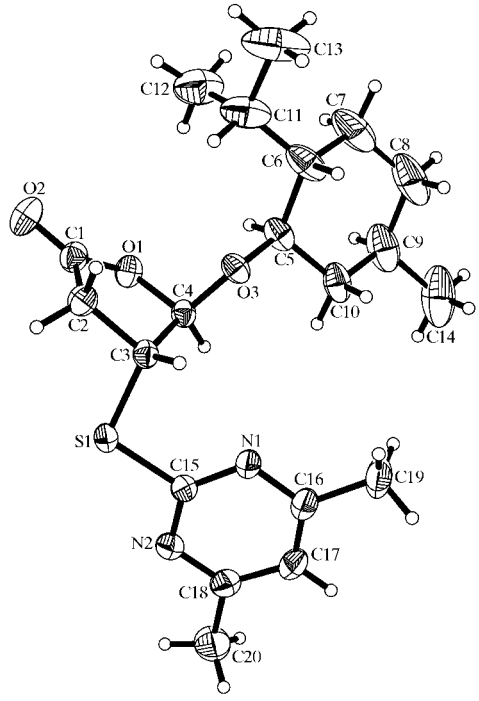


Figure 1
The structure of (I), showing 30% probability displacement ellipsoids and the atom-numbering scheme.

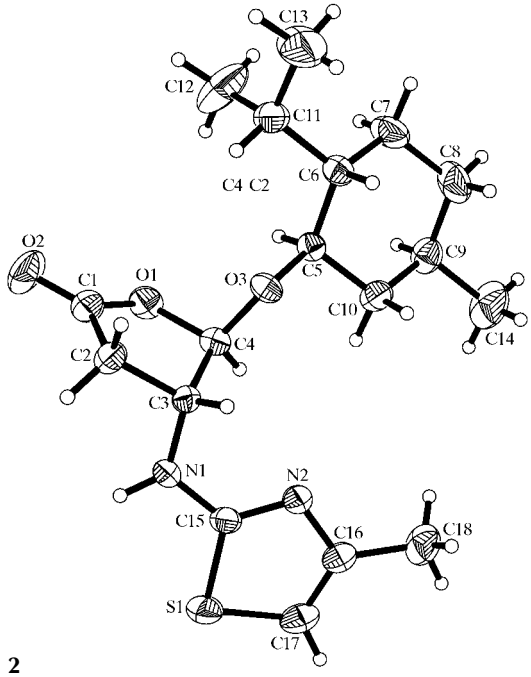


Figure 2
The structure of (II), showing 30% probability displacement ellipsoids and the atom-numbering scheme.

  DOI: 10.1107/S0108270105007833

(II) are not flat molecules (Figs. 1 and 2). The cyclohexyloxy section and the conjugated cyclic system are located on opposite sides of the tetrahydrofuran-2-one ring and the three rings are not coplanar with each other. In the cyclohexyloxy section, the six-membered ring adopts a chair conformation, with the isopropyl and methyl groups both located in the β-position, which is beneficial to the stability of the structure.

In the 4,6-dimethylpyrimidin-2-ylsulfanyl section of (I), all the non-H atoms of the group are coplanar, with a mean deviation of 0.013 (2) Å. The electrons of the ring are highly delocalized, with similar C—N and C—C bond distances (Table 1). The C15—S1 bond distance, which is shorter than C3—S1, arises from the conjugation of the electrons of atom S1 with the pyrimidinyl ring.

In the 4-methyl-1,3-thiazol-2-ylamino section of (II), all the non-H atoms of the group are coplanar, with a mean deviation of 0.009 (2) Å. The electrons on the ring are not as delocalized as those in (I). There are two obviously different C—N bond distances, *viz*. C15—N2 and C16—N2. The C16—C17 bond distance is 1.332 (3) Å, characterizing a C=C double bond (Table 2). The short bond distances of C17—S1 and C15—S1 result from the conjugation of the electrons of atom S1 with atoms C15 and C17. The N1—C15 bond distance is shorter than the single bond C3—N1, but longer than that of the double bond C15=N2 [1.291 (3) Å], which can be attributed to the conjugation of the electrons of atom N1 with atoms C15 and N2.

Compound (II) contains one S atom, two N atoms and three O atoms, which are potential hydrogen-bond acceptors. One of the two N atoms (atom N1 of the NH group) is also a strong hydrogen-bond donor. However, the present results show that only two sites, one S atom (S1) and one O atom (O2), act as hydrogen-bond acceptors, and one N atom (N1) and one C atom (C10) act as hydrogen-bond donors, forming two types of intermolecular hydrogen bonds, C—H···S and N—H···O (Table 3). The C—H, H···S and C···S distances and the C—H···S angle indicate a weak hydrogen bond, while the N—H, H···O and N···O distances and the N—H···O angle indicate a strong hydrogen bond. Each molecule is connected to four adjacent ones through four intermolecular hydrogen bonds, two C—H···S hydrogen bonds and two N—H···O hydrogen bonds (Fig. 3). Through the action of these two types of hydrogen bonds, compound (II) forms a three-dimensional supramolecular architecture.

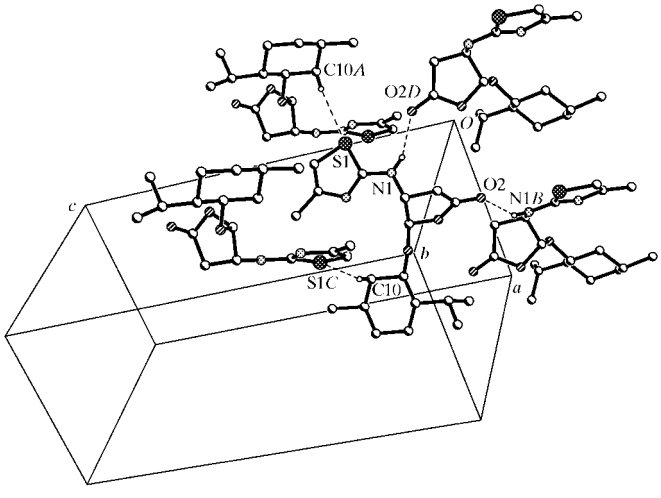


Figure 3
A packing view for (II), showing the hydrogen bonding. Atoms labelled with the suffixes *A*–*D* are at the symmetry positions $(-x, y-\frac{1}{2}, \frac{1}{2}-z)$, $(\frac{1}{2}+x, \frac{1}{2}-y, -z)$, $(-x, \frac{1}{2}+y, \frac{1}{2}-z)$ and $(x-\frac{1}{2}, \frac{1}{2}-y, -z)$, respectively.

The crystal analysis shows the configuration of C3, C4, C5, C6 and C9 to be *R*, *R*, *R*, *S* and *R* in both compounds.

Experimental

For the preparation of (I), triethylamine (404 mg, 4 mmol) was added at 298 K under nitrogen to a stirred mixture of 4,6-dimethylpyrimidine-2-thiol (280 mg, 2 mmol) and (III) (476 mg, 2 mmol; see scheme) (Huang & Chen, 1999) in dimethylformamide (8 ml). The mixture was stirred at room temperature. The completion of the reaction was monitored using thin-layer chromatography. CH_2Cl_2 was added to the mixture, which was then filtered. The filtrate was washed with H_2O, dried and condensed *in vacuo* to give the crude product. Column chromatography gave colourless crystals of (I) (417 mg, 55%; m.p. 415.8–416.2 K). Recrystallization from petroleum–AcOEt (5:1) yielded crystals of (I) suitable for X-ray analysis. For the preparation of (II), to a mixture of 2-amino-4-methylthiazole (484 mg, 2 mmol), K_2CO_3 (1.11 g, 8 mmol) and tetrabutylammonium bromide (322 mg, 1 mmol) was added CH_3CN (6 ml) and (III) (476 mg, 2 mmol). The reaction solution was stirred at room temperature for 2 d. AcOEt was added and the resulting mixture was washed with water and condensed *in vacuo* to provide the crude product, which was purified by flash chromatography, giving (II) as light-yellow crystals (359 mg, 51%; m.p. 466.5–468 K). Recrystallization from petroleum–AcOEt (3:1) yielded crystals suitable for X-ray analysis.

Compound (I)

Crystal data

$C_{20}H_{30}N_2O_3S$
$M_r = 378.52$
Orthorhombic, $P2_12_12_1$
$a = 8.825$ (4) Å
$b = 14.401$ (6) Å
$c = 17.033$ (7) Å
$V = 2164.5$ (15) Å^3
$Z = 4$
$D_x = 1.162$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 956 reflections
$\theta = 2.7$–25.5°
$\mu = 0.17$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.42 × 0.32 × 0.26 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.977$, $T_{max} = 0.996$
12 564 measured reflections
4425 independent reflections
3686 reflections with $I > 2\sigma(I)$
$R_{int} = 0.029$
$\theta_{max} = 26.5^\circ$
$h = -11 \rightarrow 10$
$k = -17 \rightarrow 17$
$l = -21 \rightarrow 10$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.097$
$S = 1.06$
4425 reflections
242 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0476P)^2 + 0.2336P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.15$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.033 (2)
Absolute structure: Flack (1983), with 2547 Friedel pairs
Flack parameter: 0.00 (7)

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

S1—C15	1.759 (2)	N1—C16	1.342 (3)
S1—C3	1.809 (2)	N2—C18	1.330 (3)
N1—C15	1.328 (2)	N2—C15	1.331 (2)
C4—C3—C2	101.90 (15)	C2—C3—S1	108.79 (13)
C4—C3—S1	111.50 (13)		
C1—C2—C3—S1	−94.25 (16)	S1—C3—C4—O1	87.14 (15)
C15—S1—C3—C4	69.56 (14)	C3—S1—C15—N1	8.52 (18)
C15—S1—C3—C2	−178.84 (13)	C3—S1—C15—N2	−170.76 (15)
S1—C3—C4—O3	−156.00 (12)		

Table 2
Selected geometric parameters (Å, °) for (II).

S1—C17	1.715 (3)	N2—C15	1.291 (3)
S1—C15	1.732 (2)	N2—C16	1.392 (3)
N1—C15	1.363 (3)	C16—C17	1.332 (3)
N1—C3	1.439 (3)		
N1—C3—C2	110.78 (18)	C2—C3—C4	102.12 (17)
N1—C3—C4	110.69 (17)		
C15—N1—C3—C4	73.2 (2)	N1—C3—C4—O3	−151.98 (16)
C1—C2—C3—C4	24.1 (2)	C2—C3—C4—O3	90.1 (2)
C5—O3—C4—C3	164.24 (15)	N1—C3—C4—O1	90.43 (18)
C1—O1—C4—C3	21.5 (2)	C2—C3—C4—O1	−27.5 (2)

Compound (II)

Crystal data

$C_{18}H_{28}N_2O_3S$
M_r = 352.48
Orthorhombic, $P2_12_12_1$
a = 8.841 (3) Å
b = 11.203 (3) Å
c = 19.692 (6) Å
V = 1950.3 (10) Å^3
Z = 4
D_x = 1.200 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 826 reflections
θ = 3.1–23.1°
μ = 0.18 mm^{-1}
T = 293 (2) K
Prism, yellow
0.34 × 0.22 × 0.18 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.913, T_{max} = 0.970
11 333 measured reflections
3997 independent reflections
2992 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 26.5°
$h = -7 \rightarrow 11$
$k = -13 \rightarrow 14$
$l = -24 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.099
S = 1.06
3997 reflections
221 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0472P)^2 + 0.1182P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.013
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: none
Absolute structure: Flack (1983), with 2315 Friedel pairs
Flack parameter: −0.03 (8)

H atoms were generated goemetrically and allowed to ride on their parent C atoms, with C—H distances of 0.96 (CH_3), 0.97 (CH_2), 0.98 (CH) or 0.93 Å (unsaturated CH) and N—H distances of 0.86 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N). The absolute structure was determined by reference to the known chirality of the cyclohexyloxy moiety.

For both compounds, data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

Table 3
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^{i}	0.86	2.13	2.898 (2)	149
C10—H10B···S1^{ii}	0.97	2.81	3.751 (3)	163

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

This project was supported by the Key Project of the Chinese Ministry of Education (grant No. 03013), the National Natural Science Foundation of China (grant No. 20372010) and the Trans-Century Training Programme Foundation for Talents of the Chinese Ministry of Education.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1224). Services for accessing these data are described at the back of the journal.

References

Bruker (1997). *SHELXTL*. Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (1999). *SMART* and *SAINT*. Versions 6.02a. Bruker AXS Inc., Madison, Wisconsin, USA.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Guillarme, S., Legoupy, S., Aubertin, A. M., Olicard, C., Bourgoufnon, N. & Huet, F. (2003). *Tetrahedron*, **59**, 2177–2184.
Huang, H. & Chen, Q. (1999). *Tetrahedron: Asymmetry*, **10**, 1295–1307.
Perbost, M., Lucas, M., Chavis, C. & Imbach, J. L. (1992). *Nucleosides Nucleotides*, **11**, 1529–1537.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Vrueh, R. L. A. de, Rump, E. T., van de Bilt, E., van Veghel, R., Balzarini, J., Biessen, E. A. L., van Berkel, T. J. C. & Bijsterbosch, M. K. (2000). *Antimicrob. Agents Chemother.* **44**, 477–483.
Wang, L.-J. & Hosmane, R. S. (2001). *Bioorg. Med. Chem. Lett.* **11**, 2893–2896.