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Stereochemical Investigation of 2,3,4,6-Tetra-*O*-acetyl-1-*S*-benzhydroximoyl-*α*-D-glucopyranose

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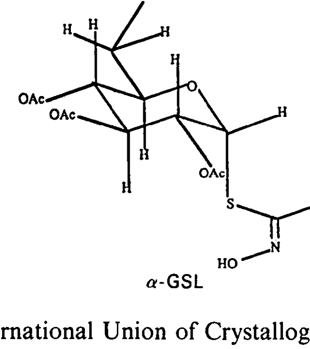
Abstract. 2,3,4,6-Tetra-*O*-acetyl-1-*S*-benzhydroximoyl-1-thio-*α*-D-glucopyranose (*α*-GSL) is the first synthetic *α*-glucosinolate. $C_{21}H_{25}NO_{10}S$, $M_r = 483.5$, monoclinic, $C2$, $a = 16.247\ (9)$, $b = 11.182\ (7)$, $c = 13.420\ (6)$ Å, $\beta = 91.62\ (4)°$, $V = 2437.33$ Å^3, $Z = 4$, $D_m = 1.309$, $D_x = 1.317$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha) = 0.711$ Å, $F(000) = 1016$, room temperature, final $R = 0.052$ for 3712 unique reflections. The stereochemistry around the C=N bond was determined. The glucose residue has the expected $^4C_1$ conformation and the hydroxyl group on the N atom is found to be *syn* to the sugar ring. The crystal structure is stabilized by packing interactions. The structural features at the glucosidic position are: C(1)—S = 1.838 (3), C(7)=N = 1.273 (5) Å, φ [O(5)—C(1)—S—C(7)] = 54.9, ψ [C(1)—S—C(7)—C(8)] = 42, C(1)—S—C(7) = 98.5 (2)°. The observed conformational behaviour has been analyzed and compared with other known structures of thiosugars.

Introduction. Natural glucosinolates (GSL) occurring mainly in the family *Cruciferae* display exclusively a *β*-D-thioglucosyl configuration at the anomeric carbon and a *syn* relationship on the aglycon between the sulfur and oxygen atoms (Kjaer, 1978; Fenwick, 1983). In the course of our studies on the elaboration of potent artificial analogues of natural GSL with aim of understanding their biosynthesis and biodegradation, we have developed the synthesis of *α*-glucosinolates.

The investigation of the crystal structure of the first member (*α*-GSL) of this new family of compounds was undertaken in order to determine the geometry around the C=N bond. It was also of interest to provide more crystallographic information on thiosugars, because few X-ray structures of these compounds are available from the literature, for example: Takagi & Jeffrey (1978), Ducruix & Pascard (1977) and see Fig. 1.



α-GSL

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Experimental. α-GSL was prepared following the method of Blanc-Muesser, Driguez, Joseph, Viaud & Rollin (1990) and crystallized in methanol. D_m was measured by flotation (Roman & Gutierrez-Zorrilla, 1985). Unit-cell parameters were refined by a least-squares fit of 25 reflections ($6.8 < \theta < 21.8°$). 3857 *hkl* intensities were collected with index range *h* 0–13, *k* 0–13, *l* 0–18, by θ–2θ scan mode to $\theta_{\max} = 30°$ on a CAD-4 X-ray diffractometer with graphite monochromated Mo *Kα* radiation. No absorption correction was applied. Four standard reflections ($\bar{2}33$, 044, 606, $4\bar{2}\bar{6}$) measured at regular intervals showed a decrease in intensity of 5.3%, and a linear decay correction [1 + 0.14exp](− 6*t*)] was applied where *t* is the exposure time in s. The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971), and refined by full-matrix least squares (Busing, Martin & Levy, 1962) on *F* with *SHELX76* (Sheldrick, 1976). Refined parameters included scale factor, positional and anisotropic thermal parameters for all non-H atoms, and positional parameters for H atoms. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1/[\sigma^2(F) + gF^2]$ and a final *g* value of 0.00164; $\sigma(F_o)$ was determined from counting statistics. All H atoms were located from difference Fourier syntheses. Minimum and maximum heights in the final $\Delta\rho$ map were -0.22 and $0.35\ \text{e Å}^{-3}$, respectively. Final values $R = 0.0517$, $wR = 0.0577$ (max. shift/e.s.d. = 0.08) for 2714 reflections with $I > 3\sigma(I)$. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). All calculations were performed on a Prime 9955 computer.

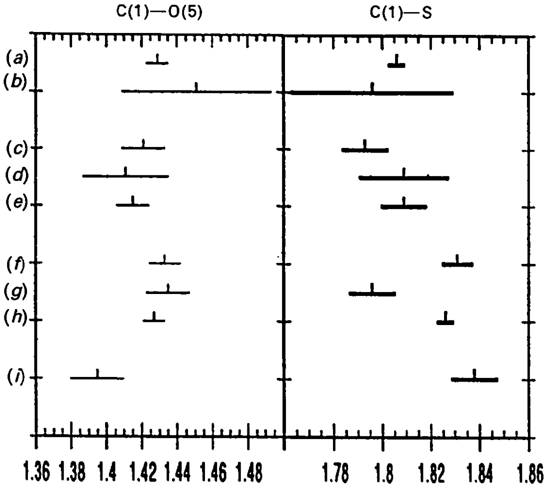

Fig. 1. C(1)—O(5) (—) and C(1)—S (—) distances (Å) in some 1-thiopyranos(id)es. The vertical bar represents the experimental value, the horizontal bar extends to ± 3σ. *Alkyl 1-thio-β-*D*-pyranoside*: (*a*) methyl 1-thio-β-D-galactopyranoside (Atkinson, Ruble & Jeffrey, 1981), (*b*) methyl 1-thio-β-D-xylopyranoside (Mathieson & Poppleton, 1966). *Conjugated 1-thio-β-*D*-pyranos(id)e*: (*c*) pyridyl 1-thio-β-D-glucopyranoside (Nordenson & Jeffrey, 1980), (*d*) allylglucosinate (Watson & Taira, 1977), (*e*) hydroximinopentyl 1-thio-β-D-glucopyranoside (Tocher & Truter, 1990). *Alkyl 1-thio-α-*D*-pyranoside*: (*f*) heptyl 1-thio-α-D-glucopyranoside (van Doren, van der Geest, van Bolhuis, Kellogg & Wynberg, 1989), (*g*) methyl 1-thio-α-D-ribopyranoside (Girling & Jeffrey, 1973), (*h*) methyl α-thiomaltoside (Perez & Vergelati, 1984). *Conjugated 1-thio-α-*D*-pyranose*: (*i*) α-GSL.

Discussion. The atomic coordinates and thermal parameters of non-H atoms are given in Table 1.* An *ORTEP* view of the molecule with the labelling scheme is shown in Fig. 2. The molecule is in the conventional $^4C_1$ chair conformation.

The bond lengths and angles given in Table 2, and torsion angles of the four acetyl groups are comparable to those found for the penta-*O*-acetyl-α-D-glucopyranose (Jones, Sheldrick, Kirby & Glenn, 1982). All atoms of one acetyl group lie in a plane formed with the adjacent atom of the glucosyl ring. The mean value of the C—O—C═O torsion angle is 3.2°.

The geometry of the glucosyl ring is similar to that observed for the α-D-glucose (Brown & Levy, 1965), except near the anomeric carbon. To understand this effect better, our results are compared with those of other 1-thiopyranos(id)es (Fig. 1). According to the anomeric effect (Tvaroska & Bleha, 1989) we expected α-GSL to have an exocyclic C(1)—S bond longer and an intracyclic C(1)—O(5) bond shorter than in β-thiopyranosides. C(1)—S is longer, as expected, but C(1)—O(5) is not significantly shorter. When compared with the α isomer, the values are close for C(1)—S and smaller for C(1)—O(5). These ambiguous results lead to the observation that when the thiosugar has π electrons in the aglycon, the C(1)—O(5) distance is short; this is more evident for the α-GSL in the α series where the values are significant. This phenomenon is important in α-GSL where the aromatic cycle is near the O(5) atom, with C(8)—O(5) = 3.2 Å and *d*[O(5)—*G*] = 41.5 (8)° (*d* is the normal to the phenyl plane and *G* is the centre of the phenyl ring). In both series, the nature of the aglycon (conjugated *vs* alkyl) seems to have no significant influence on the C(1)—S distance although C(1)—S is significantly shorter when the sugar is a ribose (*g*).

When the aglycon is conjugated, the C_{sp^2}—S [C(7)—S] distance is similar in the α and β series: 1.758 (5) in α-GSL, 1.759 (3) in (*c*), 1.746 (6) in (*d*) and 1.763 (3) Å in (*e*). The relative orientation of the

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* Lists of structure factors, anisotropic thermal parameters, bond lengths and angles involving H atoms, and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55135 (21 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates* (× 10^4) *and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

	x	y	z	B_{eq} (Å^2)
S	2662 (1)	37	1686 (1)	5.21
O(2)	3780 (2)	− 1835 (3)	2444 (2)	6.31
O(3)	4005 (1)	− 1298 (3)	4447 (2)	3.79
O(4)	3227 (1)	1079 (3)	4910 (2)	4.57
O(5)	3928 (1)	1417 (3)	2387 (2)	3.92
O(31)	2814 (2)	− 1528 (3)	5219 (3)	6.51
O	1310 (2)	1492 (5)	1562 (3)	6.80
O(6)	4655 (2)	3059 (3)	3618 (2)	5.39
O(41)	4156 (2)	582 (3)	6105 (2)	5.89
O(61)	4573 (3)	5026 (4)	3695 (4)	8.83
O(21)	4945 (2)	− 2029 (4)	1651 (3)	9.60
N	1861 (2)	1883 (5)	847 (3)	5.46
C(1)	3756 (2)	278 (4)	2011 (3)	4.23
C(2)	4028 (2)	− 655 (4)	2773 (3)	4.75
C(6)	3777 (2)	2997 (4)	3526 (4)	4.38
C(3)	3630 (2)	− 446 (3)	3767 (2)	3.50
C(41)	3478 (2)	890 (4)	5862 (3)	5.34
C(5)	3545 (2)	1721 (4)	3300 (3)	3.35
C(4)	3779 (2)	819 (3)	4114 (3)	3.87
C(31)	3529 (2)	− 1784 (4)	5146 (3)	5.91
C(21)	4299 (3)	− 2436 (4)	1867 (3)	4.49
C(32)	4001 (4)	− 2621 (6)	5781 (5)	5.20
C(61)	4986 (3)	4143 (4)	3560 (3)	5.59
C(7)	2515 (2)	1256 (5)	873 (3)	4.50
C(62)	5899 (3)	4116 (6)	3640 (5)	7.21
C(42)	2778 (3)	1100 (6)	6550 (4)	7.04
C(22)	3952 (5)	− 3605 (6)	1554 (5)	7.84
C(8)	3153 (2)	1558 (6)	135 (3)	3.42
C(9)	3512 (3)	627 (7)	− 413 (3)	6.09
C(10)	4088 (4)	906 (10)	− 1101 (4)	7.58
C(11)	4318 (4)	2082 (10)	− 1235 (5)	4.53
C(12)	3964 (4)	3002 (10)	− 696 (6)	3.23
C(13)	3374 (3)	2736 (7)	6 (5)	3.84

Table 2. *Interatomic distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

S	C(1)	1.838 (3)	S	C(7)	1.758 (5)
N	C(7)	1.273 (5)	O	N	1.401 (5)
C(1)	C(2)	1.519 (6)	C(2)	C(3)	1.517 (4)
C(3)	C(4)	1.508 (4)	C(4)	C(5)	1.527 (5)
C(5)	C(6)	1.504 (6)	C(7)	C(8)	1.492 (5)
C(8)	C(9)	1.411 (8)	C(9)	C(10)	1.369 (7)
C(10)	C(11)	1.380 (15)	C(11)	C(12)	1.391 (13)
C(12)	C(13)	1.396 (9)	C(8)	C(13)	1.377 (10)
O(5)	C(1)	1.395 (5)	C(2)	O(2)	1.445 (5)
C(3)	O(3)	1.442 (4)	C(4)	O(4)	1.444 (4)
C(5)	O(5)	1.431 (4)	C(6)	O(6)	1.430 (4)
O(2)	C(21)	1.341 (5)	O(3)	C(31)	1.347 (4)
O(4)	C(41)	1.347 (4)	O(6)	C(61)	1.326 (5)
C(21)	O(21)	1.187 (6)	C(31)	O(31)	1.203 (4)
C(41)	O(41)	1.191 (4)	C(61)	O(61)	1.196 (6)
C(21)	C(22)	1.480 (8)	C(31)	C(32)	1.467 (7)
C(41)	C(42)	1.503 (6)	C(61)	C(62)	1.484 (6)

C(1)	S	C(7)	98.5 (2)	C(2)	O(2)	C(21)	117.3 (3)
C(3)	O(3)	C(31)	117.8 (2)	C(41)	O(4)	C(4)	119.5 (3)
C(1)	O(5)	C(5)	116.0 (3)	C(6)	O(6)	C(61)	116.7 (4)
O	N	C(7)	111.0 (4)	S	C(1)	O(5)	113.7 (2)
S	C(1)	C(2)	108.7 (3)	O(5)	C(1)	C(2)	109.4 (3)
O(2)	C(2)	C(1)	110.4 (3)	O(2)	C(2)	C(3)	106.7 (3)
C(1)	C(2)	C(3)	111.3 (3)	O(6)	C(6)	C(5)	107.9 (3)
O(3)	C(3)	C(2)	105.8 (3)	O(3)	C(3)	C(4)	111.3 (3)
C(2)	C(3)	C(4)	110.3 (3)	O(4)	C(41)	O(41)	123.9 (3)
O(4)	C(41)	C(42)	110.1 (3)	O(41)	C(41)	C(42)	125.9 (4)
O(5)	C(5)	C(6)	106.6 (3)	O(5)	C(5)	C(4)	110.5 (3)
C(6)	C(5)	C(4)	115.2 (3)	O(4)	C(4)	C(3)	108.7 (3)
O(4)	C(4)	C(5)	104.4 (3)	C(3)	C(4)	C(5)	111.4 (3)
O(3)	C(31)	O(31)	122.4 (4)	O(3)	C(31)	C(32)	111.2 (4)
O(31)	C(31)	C(32)	126.5 (4)	O(2)	C(21)	O(21)	121.6 (4)
O(2)	C(21)	C(22)	111.5 (5)	O(21)	C(21)	C(22)	127.0 (5)
O(6)	C(61)	O(61)	121.9 (5)	O(6)	C(61)	C(62)	112.7 (4)
O(61)	C(61)	C(62)	125.4 (5)	S	C(7)	N	122.9 (3)
S	C(7)	C(8)	120.2 (3)	N	C(7)	C(8)	116.9 (5)
C(7)	C(8)	C(9)	119.0 (6)	C(7)	C(8)	C(13)	119.2 (5)
C(9)	C(8)	C(13)	121.8 (5)	C(8)	C(9)	C(10)	119.0 (7)
C(9)	C(10)	C(11)	119.8 (8)	C(10)	C(11)	C(12)	121.3 (7)
C(11)	C(12)	C(13)	119.7 (9)	C(8)	C(13)	C(12)	118.4 (7)

benzhydroximoyl in this artificial compound was found to be identical to the one in the natural glucosinolate (*d*): the hydroxyl group is *syn* to the thiosugar with S—C(7)—N—O = 1.9°, the N—O bond length is similar [1.401 (5) *vs* 1.433 (8) Å (*d*)].

Crystal packing (Fig. 3) involves hydrogen bonds and interactions between aromatic groups. Hydrogen bonds are formed between the free hydroxyl group of one molecule and the O(21) O atom of another molecule with H···O(21) = 2.194 Å. The connectivities are: (x, y, z) and 3(x + 0.5, y + 0.5, z); 2(1 − x, y,

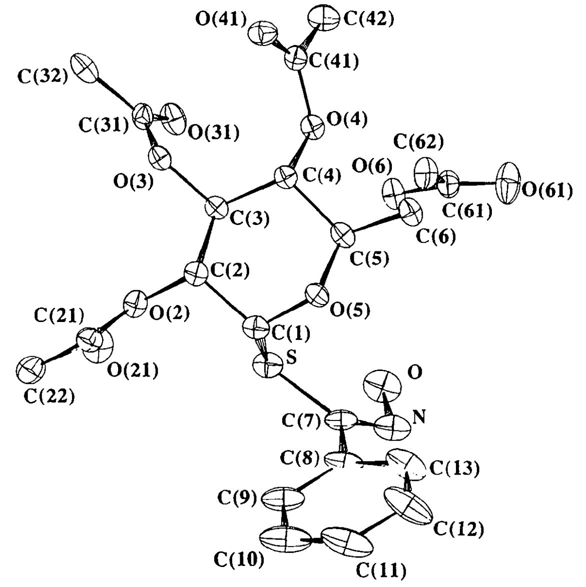

Fig. 2. Thermal ellipsoid plot of the molecule showing the atom-labelling scheme.

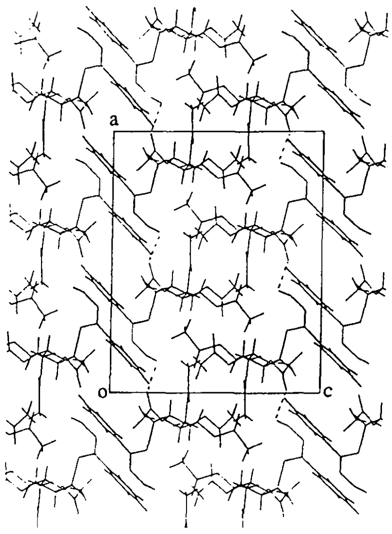

Fig. 3. Packing diagram of the molecule projected down **b** showing hydrogen bonds in the cell.

$1 - z$); and $4(0.5 - x, 0.5 + y, 1 - z)$. Short contacts are seen on phenyl groups between two positions. In each pair, the distance between the centres of gravity is 4.71 Å.

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Structures and Absolute Configurations of Enantiomers of Two Local Anaesthetics: (2*S*)-1-Methyl- and (2*R*)-1-Butyl-2′,6′-pipecoloxylidide Hydrochlorides

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Abstract. (2*S*)-2-(2,6-Dimethylphenylaminocarbonyl)-1-methylpiperidinium chloride (mepivacaine hydrochloride), $C_{15}H_{23}N_2O^+.Cl^-$, $M_r = 282.81$, orthorhombic, $P2_12_12_1$, $a = 9.777\,(1)$, $b = 10.628\,(1)$, $c = 15.316\,(1)$ Å, $V = 1591.4\,(3)$ Å^3, $Z = 4$, $D_x = 1.1804\,(1)$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1.54183$ Å, $\mu = 2.09$ mm^{-1}, $F(000) = 608$, $T = 291$ K, $R = 0.037$ for 1340 observed reflections. (2*R*)-1-Butyl-2-(2,6-dimethylphenylaminocarbonyl)piperidinium chloride (bupivacaine hydrochloride), $C_{18}H_{29}N_2O^+.Cl^-$, $M_r = 324.89$, monoclinic, $P2_1$, $a = 9.702\,(1)$, $b = 10.922\,(1)$, $c = 9.952\,(1)$ Å, $\beta = 114.38\,(6)°$, $V = 960.5\,(2)$ Å^3, $Z = 2$, $D_x = 1.1234\,(2)$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1.54183$ Å, $\mu = 1.79$ mm^{-1}, $F(000) = 352$, $T = 291$ K, $R = 0.040$ for 1626 observed reflections. The absolute configurations were determined by Bijvoet ratio measurements of selected Friedel-pair reflections. Although the absolute configurations at C(2) are different, the two compounds have very similar molecular conformations. The amide plane is twisted through about 70° with respect to the benzene ring, and the amide group and the *N*-alkyl substituent of the chair-shaped piperidine ring are in *cis* position and are equatorially oriented in both compounds. Moreover, the protonated drug molecules in both cases are linked together by hydrogen bonds *via* the chloride anions so as to form parallel endless hydrogen-bonded chains in the crystals.

Introduction. Different 1-alkyl-2′,6′-pipecoloxylidides possess varying degrees of local anaesthetic activity. Mepivacaine with an *N*-methyl-substituted piperidine ring is a rather short-time anaesthetic agent, whereas the *N*-butyl-substituted derivative, bupivacaine, has

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