Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0437$
$wR(F^2) = 0.1163$
$S = 1.132$
3946 reflections
256 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0593P)^2 + 1.0647P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.420$ e Å^{-3}
$\Delta\rho_{min} = -0.247$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0012 (6)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
C1	0.2260 (2)	0.2506 (2)	0.41977 (7)	0.0338 (4)
C2	0.0978 (2)	0.24206 (13)	0.38140 (6)	0.0262 (3)
C3	−0.0301 (2)	0.30396 (14)	0.40934 (7)	0.0298 (3)
C4	0.0351 (2)	0.33044 (15)	0.46322 (7)	0.0334 (3)
C5	0.1414 (2)	0.4317 (2)	0.45661 (8)	0.0390 (4)
C6	0.2716 (2)	0.3773 (2)	0.42670 (7)	0.0365 (4)
C7	0.1412 (2)	0.2295 (2)	0.47087 (7)	0.0396 (4)
C8	0.0385 (2)	0.28715 (11)	0.29394 (6)	0.0234 (3)
C9	0.08702 (14)	0.34711 (11)	0.24513 (6)	0.0219 (3)
C10	0.16768 (15)	0.44910 (11)	0.24419 (5)	0.0210 (3)
C11	0.21216 (15)	0.50139 (11)	0.19867 (6)	0.0234 (3)
C12	0.1692 (2)	0.45034 (12)	0.15267 (6)	0.0246 (3)
C13	0.0901 (2)	0.34868 (13)	0.15106 (6)	0.0275 (3)
C14	0.0500 (2)	0.29782 (12)	0.19738 (6)	0.0260 (3)
N1	0.20135 (14)	0.51181 (10)	0.29229 (5)	0.0254 (3)
N2	0.20700 (15)	0.50911 (12)	0.10373 (5)	0.0304 (3)
O1	0.13831 (11)	0.29572 (8)	0.33186 (4)	0.0242 (2)
O2	−0.07677 (12)	0.23594 (10)	0.29665 (5)	0.0308 (3)
O3	0.09855 (13)	0.53387 (9)	0.32155 (5)	0.0325 (3)
O4	0.32971 (14)	0.54062 (12)	0.29909 (5)	0.0406 (3)
O5	0.29734 (14)	0.58721 (10)	0.10565 (5)	0.0383 (3)
O6	0.1451 (2)	0.47725 (14)	0.06423 (5)	0.0495 (4)

Table 2. *Selected geometric parameters* (Å, °)

C1—C2	1.526 (2)	C9—C14	1.395 (2)
C1—C7	1.541 (2)	C9—C10	1.396 (2)
C1—C6	1.544 (3)	C10—C11	1.379 (2)
C2—O1	1.465 (2)	C10—N1	1.468 (2)
C2—C3	1.542 (2)	C11—C12	1.379 (2)
C3—C4	1.536 (2)	C12—C13	1.385 (2)
C4—C7	1.533 (3)	C12—N2	1.472 (2)
C4—C5	1.533 (3)	C13—C14	1.378 (2)
C5—C6	1.544 (3)	N1—O4	1.223 (2)
C8—O2	1.204 (2)	N1—O3	1.224 (2)
C8—O1	1.333 (2)	N2—O6	1.218 (2)
C8—C9	1.502 (2)	N2—O5	1.225 (2)
C2—C1—C7	99.26 (13)	C10—C9—C8	124.35 (13)
C2—C1—C6	109.91 (13)	C11—C10—C9	122.96 (13)
C7—C1—C6	100.83 (15)	C11—C10—N1	115.68 (11)
O1—C2—C1	110.06 (12)	C9—C10—N1	121.23 (13)
O1—C2—C3	113.13 (12)	C10—C11—C12	116.97 (13)
C1—C2—C3	103.90 (12)	C11—C12—C13	122.72 (14)
C4—C3—C2	103.00 (13)	C11—C12—N2	117.73 (13)
C7—C4—C5	102.20 (15)	C13—C12—N2	119.53 (14)
C7—C4—C3	101.67 (13)	C14—C13—C12	118.57 (14)
C5—C4—C3	107.23 (14)	C13—C14—C9	121.26 (13)
C4—C5—C6	102.64 (15)	O4—N1—O3	125.30 (13)
C1—C6—C5	104.24 (14)	O4—N1—C10	117.04 (12)
C4—C7—C1	94.61 (13)	O3—N1—C10	117.63 (12)
O2—C8—O1	125.63 (14)	O6—N2—O5	124.60 (15)
O2—C8—C9	122.20 (14)	O6—N2—C12	117.56 (14)
O1—C8—C9	112.14 (12)	O5—N2—C12	117.84 (13)
C14—C9—C10	117.46 (13)	C8—O1—C2	115.68 (11)
C14—C9—C8	118.19 (12)		

Data were collected at 130 K using an Oxford Cryostream low-temperature cooling device. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1985). Refinement was performed by *SHELXL*93 (Sheldrick, 1993) using full-matrix least squares, with anisotropic displacement parameters for all non-H atoms. H atoms were refined without constraint. The figure was generated using *ORTEP*II (Johnson, 1976) and tables prepared using *SHELXL*93. All calculations were carried out on a VAX 4000VLC computer system.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KH1023). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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N-D-Glucopyranosyl-*S*-phenylsulfenamide: Structure and Evaluation as a Novel β-Glucosidase Inhibitor

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Abstract

The structure of 2,3,4,6-tetra-*O*-acetyl-*N*-β-D-glucopyranosyl-*S*-phenylsulfenamide, $C_{20}H_{25}NO_9S$, at low temperature is reported. The glucopyranosyl residue adopts

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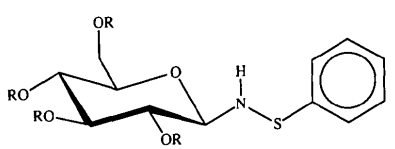
the $^4C_1$ conformation. The primary hydroxy group has a *gauche-trans* orientation with respect to O(5) and C(4). ^{1}H NMR data suggest that the solution conformation of the hydroxymethyl group is characterized by a *gg/gt* equilibrium for both the tetraacetate and the parent sulfenamide. As observed for most crystalline β-D-pyranoses, the orientation of the C(1)—N bond corresponds to the *E*1 conformer.

Comment

Glycosidase inhibitors have been instrumental in the study of glycosidase catalysed processes during biosynthesis and catabolism of saccharides, and in the study of the mechanisms of glycosidases. They have also attracted considerable interest because of the *anti*-HIV activity shown by 1-deoxynojirimycin, castanospermine and some of their derivatives (Tyms, Taylor, Sunkara & Kang, 1990; Hughes & Rudge, 1994). These inhibitors act competitively against the glycosidases governing the processing of the glycoproteins of the viral coat and thereby alter viral infectivity (Evans *et al.*, 1985; Gruters *et al.*, 1987). In an attempt to find new enzyme-activated irreversible inhibitors for glucosidases, we have synthesized *N*-β-D-glucopyranosyl-*S*-phenylsulfenamide, (1). Irreversible inhibition by *N*-glycosylsulfenamides may be triggered by protonation of the amino group. However, preliminary studies have indicated that (1) is only a weak competitive inhibitor of sweet almond glucosidases (see below). We report here the low-temperature X-ray structure of a derivative of (1), 2,3,4,6-tetra-*O*-acetyl-*N*-β-D-glucopyranosyl-*S*-phenylsulfenamide, (2).



(1) R = H
(2) R = CH_3CO

A view of (2), showing the displacement ellipsoids and the atomic numbering, is given in Fig. 1. The diagram depicts the correct absolute configuration of the molecule, which was assigned to agree with that of its known precursor and was confirmed by the X-ray analysis. Bond lengths are normal and agree well with those of β-D-glucopyranose (Ferrier, 1963) and *N*-β-D-glucopyranosylhydroxylamine (Mostad, 1978). The bond angles within the pyranosyl ring of (2), with the exception of C(1)—O(5)—C(5), are, however, generally 1–3° larger than those of these reference compounds and most pyranoses. The sulfenamide H atom does not take part in any hydrogen-bonding interactions.

The hexopyranosyl ring adopts a normal $^4C_1$ conformation, with the ring distortion being greater than in methyl β-D-glucopyranoside, where the torsion angles lie in the range 52–70° (Jeffrey & Takagi, 1977). This greater distortion is also shown by the puckering parameters (Cremer & Pople, 1975): Q = 0.531 (3), q_2 = 0.096 (3), q_3 = 0.523 (3) Å, θ = 10.4 (3), φ_2 = 335 (2)°, compared with Q = 0.598 (2), q_2 = 0.072 (2), q_3 = 0.593 (2) Å, θ = 7.0 (2), φ_2 = 39 (2)° for methyl β-D-glucopyranoside. The direction of the distortion is towards the twist-boat ($^0S_2$) conformation, as indicated by the φ_2 value (Jeffrey & Yates, 1979). In methyl β-D-glucopyranoside, the distortion is in the direction of the $^3S_1$ conformation (φ_2 = 30°). The flattening of the ring at O(5) and C(2) causes the C(1)—O(5)—C(5) and C(1)—C(2)—C(3) angles to widen to >113°. Compounds (1) and (2) also exist in the $^4C_1$ conformation in solution. The ^{1}H NMR spectra of (1) and (2) show large $J_{H(1),H(2)}$, $J_{H(2),H(3)}$, $J_{H(3),H(4)}$ and $J_{H(4),H(5)}$ couplings, which are consistent with diaxial arrangements of H(1)···H(2), H(2)···H(3), H(3)···H(4) and H(4)···H(5), respectively.

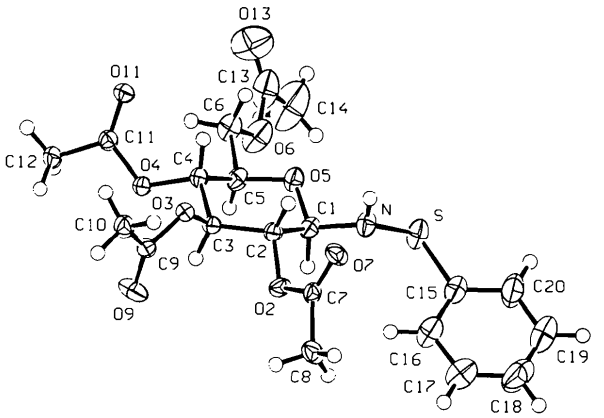
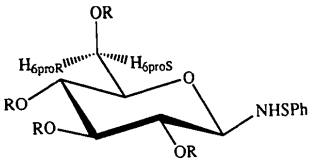


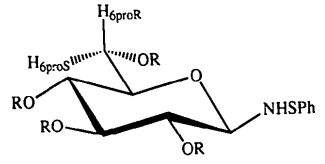
Fig. 1. View of the molecule of (2) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary radii.

The conformation of the acetoxymethyl group in (2) is *gauche-trans* (Fig. 2) [O(5)—C(5)—C(6)—O(6) = 72.4 (3) and C(4)—C(5)—C(6)—O(6) = −168.2 (3)°], as observed for β-D-glucopyranosylhydroxylamine (Mostad, 1978), β-D-glucopyranosyl-*p*-bromophenylhydrazine (Dukefos & Mostad, 1965) and methyl β-D-glucopyranoside (Jeffrey & Tagaki, 1977). The ^{1}H NMR spectra of (1) and (2), however, show small vicinal couplings between H(5) and H(6pro*R*,6pro*S*) [for (1), $J_{H(5),H(6proR)}$ = 5.2, $J_{H(5),H(6proS)}$ = 2.4 Hz; for (2), $J_{H(5),H(6proR)}$ = 3.2, $J_{H(5),H(6proS)}$ = 2.3 Hz] (*cf.* Rao & Perlin, 1983; Nishida, Hori, Ohrui & Meguro, 1988). From these spectra it can be calculated (Duus, 1993; Bock & Duus, 1994) that, in solution, there is a 56:44 *gg/gt* [(3*a*):(3*b*), R = H] rotameric distribution for (1) and a 75:25 *gg/gt* [(3*a*):(3*b*), R = Ac] rotameric distribution for (2).

The conformation of the anomeric substituent in (2) with respect to the pyranosyl ring is similar to that found in crystalline β-D-glucopyranosylhydro-



(3*a*) *gg* rotamer



(3*b*) *gt* rotamer

Fig. 2. Rotameric forms of (1) and (2).

xylamine (Mostad, 1978) and β-D-glucopyranosyl-*p*-bromophenylhydrazine (Dukefos & Mostad, 1965). The torsion angles about the C(1)—N bond describe the *E*1 conformer (de Hoog, Buys, Altona & Havinga, 1969), in which the N—S bond is *gauche* to C(1)—O(5) and *trans* to C(1)—C(2). The *E*1 conformer has been shown by Eliel and co-workers (Eliel & Giza, 1968; Eliel, 1969) to be the favoured conformation of β-D-pyranosides in the crystalline state.

The torsion angle between the C(1)—H and the N—H bonds in (2) [H(1)—C(1)—N—H(6) = −169 (3)°] indicates a diaxial arrangement of these H atoms. This is also the conformation in solution, as shown by the large $J_{H(1),NH}$ coupling constant (9.4 Hz) found in its ^1H NMR spectrum. In β-D-glucopyranosylhydroxylamine, these H atoms have a *gauche* relationship [$J_{H(1),NH}$ = 3.2 Hz] (Finch & Merchant, 1975; Mostad, 1978). The structural requirement for strong glycosidase inhibition by N-substituted β-D-glycopyranosylamines is protonation of the inhibitor at the amino group (Legler, 1978, 1990). The generally accepted mechanism proposed for glycosidase action involves general acid catalysis promoted by an acidic group in the active centre of the enzyme (Capon, 1969). The reaction proceeds *via* a cationic intermediate. Since there is a strict requirement for the correct positioning of the amino group at the active site of the enzyme, the weak inhibition by (1) (K_i = 2.3 mmol) (Lee & Vasella, 1994) suggests that the conformation adopted by the *N*-phenylsulfenamido substituent in (1) is not ideal for a favourable interaction at the active centre of the enzyme.

Experimental

Synthesis of (2). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine (Bertho & Maier, 1932; Bertho, 1949) (0.57 g, 1.65 mmol) in dry tetrahydrofuran (10 ml) was cooled to 258 K and treated with triethylamine (0.23 ml, 1.65 mmol) and phenylsulfenyl chloride (Hopkins & Fuchs, 1978) (3.31 ml of an ~0.5 *M* solution, ~1.65 mmol). The solution was stirred at 258 K for 1.5 h, poured into a saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The organic phase was concentrated and the syrupy residue was triturated with hexane (3 × 5 ml) and crystallized from *tert*-butyl methyl ether to give (2) (0.59 g, 78.9%); m.p. 374–375 K; $[\alpha]_D$ −51.5° (*c* 0.1, ethyl acetate); UV (CCl_4) λ_{max} 236.0 nm; ^1H NMR (300 MHz, $CDCl_3$) δ_H (p.p.m.) 7.2–7.3 (*m*, 5 H, Ph), 5.24 (*t*, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 9.5 Hz, H-3), 5.07 (*t*, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.97 (*t*, 1 H, $J_{1,2}$ 9.4 Hz, H-2), 4.29 (*dd*, 1 H, $J_{5,6a}$ 3.2, $J_{6a,6b}$ 12.6 Hz, H-6), 4.28 (*t*, 1 H, $J_{H(1),NH}$ 9.4 Hz, H-1), 4.08 (*dd*, 1 H, $J_{5,6b}$ 2.3 Hz, H-6*b*), 3.66 (*d*, 1 H, N-H), 3.6–3.7 (*m*, 1 H, H-5), 2.01, 2.02, 2.07, 2.08 (4 *s*, 12 H, 4 $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C (p.p.m.) 92.83 (C-1), 72.92, 72.85 (C-3,5), 71.05 (C-2), 68.37 (C-4), 61.84 (C-6); CI-MS (NH_3) *m/z* 564 (32), 457 (22), 456 (100, $[M+1]^+$), 348 (33), 331 (33), 288 (5); analysis calculated for $C_{20}H_{25}NO_9S$, C 52.75, H 5.53, N 3.08, S 7.04%; found, C 52.81, H 5.63, N 2.95, S 6.96%.

Synthesis of *N*-β-D-glucopyranosyl-*S*-phenylsulphenamide, (1). A solution of (2) (0.45 g) in methanol (10 ml) was treated with 1 *M* sodium methoxide (pH 9) at room temperature for 0.5 h. The solution was neutralized with Amberlite MB resin, filtered and concentrated. The syrupy residue was purified by HPLC [using a Knauer Eurospher 100–5 C-18 (5 μm) column (250 × 20 mm ID), eluting with acetonitrile–water (5:1), flow rate 12 ml min^{-1}] to give pure (1) (0.27 g, 87%); $[\alpha]_D$ −28.0° (*c*, 0.13, ethyl acetate); UV (CH_3OH) λ_{max} 205, 240 nm; ^1H NMR (300 MHz, CD_3OD) δ_H (p.p.m.) 7.27 (*t*, 1 H, Ph), 7.25 (*t*, 2 H, Ph), 7.44 (*dd*, 2 H, Ph), 3.94 (*d*, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 3.79 (*dd*, 1 H, $J_{5,6a}$ 2.4, $J_{6a,6b}$ 11.8 Hz, H-6*a*), 3.64 (*dd*, 1 H, $J_{5,6b}$ 5.2 Hz, H-6*b*), 3.37 (*t*, 1 H, $J_{3,4} = J_{4,5}$ 8.7 Hz, H-4), 3.30 (*t*, 1 H, $J_{2,3}$ 8.7 Hz, H-3), 3.24 (*t*, 1 H, H-2), 3.2–3.3 (*m*, 1 H, H-5); analysis calculated for $C_{12}H_{17}NO_5S$, C 50.16, H 5.96, N 4.87, S 11.16%; found, C 50.46, H 6.21, N 4.91, S 11.38%.

Suitable crystals of (2) were grown from *tert*-butyl methyl ether.

Crystal data

$C_{20}H_{25}NO_9S$
M_r = 455.48
Orthorhombic
$P2_12_12_1$
a = 13.782 (1) Å
b = 29.581 (2) Å
c = 5.502 (3) Å
V = 2243 (1) Å^3
Z = 4
D_x = 1.349 Mg m^{-3}
Mo *Kα* radiation
λ = 0.71073 Å
Cell parameters from 22 reflections
θ = 11.5–18.5°
μ = 0.194 mm^{-1}
T = 173 (1) K
Prism
0.40 × 0.26 × 0.10 mm
Colourless

Data collection

Rigaku AFC-5*R* diffractometer
ω scans
Absorption correction: none
7392 measured reflections
5143 independent reflections
3817 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.034
θ_{max} = 27.5°
h = −17 → 17
k = −38 → 38
l = −7 → 7
3 standard reflections monitored every 150 reflections
intensity decay: insignificant

Refinement

Refinement on *F*
R = 0.0452
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

$wR = 0.0416$
$S = 1.505$
3817 reflections
320 parameters
$w = 1/[\sigma^2(F_o) + (0.005F_o)^2]$
$(\Delta/\sigma)_{max} = 0.001$

Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å²)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
S	0.43109 (5)	0.93166 (3)	0.0424 (2)	0.0405 (2)
O(2)	0.4653 (1)	0.82631 (6)	0.5941 (4)	0.0274 (6)
O(3)	0.6363 (1)	0.76718 (5)	0.5820 (3)	0.0234 (5)
O(4)	0.8036 (1)	0.82687 (6)	0.5978 (3)	0.0269 (6)
O(5)	0.6342 (1)	0.88227 (6)	0.1764 (4)	0.0301 (6)
O(6)	0.8057 (2)	0.93695 (7)	0.1198 (5)	0.0513 (9)
O(7)	0.3700 (1)	0.78769 (6)	0.3336 (4)	0.0312 (6)
O(9)	0.6307 (2)	0.77097 (7)	0.9886 (4)	0.0451 (7)
O(11)	0.9042 (1)	0.79454 (7)	0.3265 (4)	0.0313 (6)
O(13)	0.9104 (2)	0.92622 (9)	−0.1880 (6)	0.080 (1)
N	0.4650 (2)	0.88007 (8)	0.1438 (5)	0.0318 (8)
C(1)	0.5450 (2)	0.87579 (9)	0.3072 (6)	0.0275 (8)
C(2)	0.5432 (2)	0.82808 (9)	0.4185 (6)	0.0239 (8)
C(3)	0.6353 (2)	0.81591 (8)	0.5543 (5)	0.0224 (7)
C(4)	0.7262 (2)	0.82948 (9)	0.4194 (6)	0.0241 (8)
C(5)	0.7193 (2)	0.87785 (9)	0.3230 (6)	0.0281 (9)
C(6)	0.8053 (2)	0.8890 (1)	0.1631 (7)	0.034 (1)
C(7)	0.3821 (2)	0.80428 (9)	0.5303 (5)	0.0246 (8)
C(8)	0.3119 (2)	0.8045 (1)	0.7360 (6)	0.033 (1)
C(9)	0.6342 (2)	0.74914 (9)	0.8080 (5)	0.0263 (8)
C(10)	0.6370 (2)	0.69856 (9)	0.7962 (6)	0.0303 (8)
C(11)	0.8897 (2)	0.80836 (9)	0.5291 (5)	0.0254 (8)
C(12)	0.9585 (2)	0.8091 (1)	0.7349 (6)	0.0321 (9)
C(13)	0.8638 (3)	0.9513 (1)	−0.0628 (9)	0.058 (1)
C(14)	0.8648 (3)	1.0018 (1)	−0.073 (1)	0.098 (2)
C(15)	0.3071 (2)	0.9335 (1)	0.1392 (6)	0.038 (1)
C(16)	0.2759 (2)	0.9140 (1)	0.3527 (8)	0.050 (1)
C(17)	0.1793 (3)	0.9165 (1)	0.4163 (8)	0.056 (1)
C(18)	0.1142 (3)	0.9393 (2)	0.2740 (9)	0.069 (2)
C(19)	0.1447 (3)	0.9593 (2)	0.061 (1)	0.079 (2)
C(20)	0.2423 (2)	0.9566 (1)	−0.0097 (8)	0.058 (1)

Table 2. *Selected geometric parameters* (Å, °)

S—N	1.691 (3)	O(6)—C(6)	1.438 (3)
S—C(15)	1.791 (3)	N—C(1)	1.428 (4)
O(2)—C(2)	1.445 (3)	C(1)—C(2)	1.539 (4)
O(3)—C(3)	1.450 (3)	C(2)—C(3)	1.516 (4)
O(4)—C(4)	1.452 (3)	C(3)—C(4)	1.511 (4)
O(5)—C(1)	1.437 (3)	C(4)—C(5)	1.529 (4)
O(5)—C(5)	1.430 (3)	C(5)—C(6)	1.513 (4)
N—S—C(15)	101.1 (1)	O(3)—C(3)—C(4)	107.9 (2)
C(1)—O(5)—C(5)	114.0 (2)	C(2)—C(3)—C(4)	112.9 (2)
S—N—C(1)	120.1 (2)	O(4)—C(4)—C(3)	105.2 (2)
O(5)—C(1)—N	109.5 (2)	O(4)—C(4)—C(5)	109.3 (2)
O(5)—C(1)—C(2)	109.6 (2)	C(3)—C(4)—C(5)	111.5 (2)
N—C(1)—C(2)	108.6 (2)	O(5)—C(5)—C(4)	109.4 (2)
O(2)—C(2)—C(1)	108.2 (2)	O(5)—C(5)—C(6)	107.2 (3)
O(2)—C(2)—C(3)	106.5 (2)	C(4)—C(5)—C(6)	110.9 (2)
C(1)—C(2)—C(3)	113.6 (2)	O(6)—C(6)—C(5)	108.3 (2)
O(3)—C(3)—C(2)	107.2 (2)		
S—N—C(1)—O(5)	−74.7 (3)	N—C(1)—O(5)—C(5)	−178.9 (2)
S—N—C(1)—C(2)	165.7 (2)	N—C(1)—C(2)—C(3)	168.1 (2)
O(5)—C(1)—C(2)—C(3)	48.5 (3)	C(1)—O(5)—C(5)—C(4)	63.8 (3)
O(5)—C(5)—C(4)—C(3)	−55.2 (3)	C(1)—N—S—C(15)	−122.4 (3)
O(5)—C(5)—C(6)—O(6)	72.4 (3)	C(1)—C(2)—C(3)—C(4)	−43.9 (3)
O(6)—C(6)—C(5)—C(4)	−168.2 (3)	C(2)—C(1)—O(5)—C(5)	−59.9 (3)
N—S—C(15)—C(16)	35.0 (3)	C(2)—C(3)—C(4)—C(5)	46.7 (3)
N—S—C(15)—C(20)	−146.3 (3)		

The data collection included the measurement of the intensities of the Friedel opposites of all reflections in the unique octant. Friedel pairs were not averaged during the data reduction so that the effects of anomalous dispersion could be used for the determination of the absolute configuration. For this purpose the *CRYSTALS* program system (Watkin, Carruthers & Betteridge, 1985) was used to refine the final atomic coordinates together with the enantiopole parameter (Flack, 1983). The refined value of the enantiopole parameter was 0.09 (12), which has a large uncertainty, but suggests that the atomic coordinates represent the correct enantiomorph. This indication is in agreement with the absolute configuration expected from the synthetic route to (2).

During the refinement, the large displacement parameters of the acetyl group attached to C(6) indicated that it is either slightly disordered or undergoing strong thermal motion. A disordered model could not be refined satisfactorily. Some of the atoms of the phenyl ring also show evidence of thermal motion. An ordered model was employed for the final refinement and the enlarged displacement ellipsoids for some of the atoms of these groups reflect the 'smeared-out' electron density in these regions.

The H atoms of the glucopyranose ring and the amide N atom were located from a difference electron-density map and refined isotropically. All of the remaining H atoms were fixed in geometrically calculated positions and, except for those bonded to C(14), individual isotropic displacement parameters were refined for these atoms. The H atoms bonded to C(14) were assigned fixed isotropic displacement parameters with a value of $1.2U_{eq}$ of C(14).

MSC/AFC Diffractometer Control Software (Molecular Structure Corporation, 1991) was used for data collection and cell determination, and *TEXSAN* software (Molecular Structure Corporation, 1989) was used for data reduction, structure refinement and the preparation of publication material. The structure was solved using *SHELXS*86 direct methods (Sheldrick, 1990). Molecular graphics were produced using *ORTEP*II (Johnson, 1976).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1001). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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4-(Acetylamino)-3-hydroxy-5-nitrobenzoic Acid

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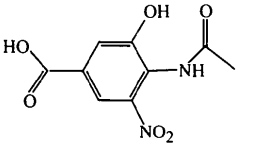
Abstract

The 4-(acetylamino)-3-hydroxy-5-nitrobenzoic acid molecule, $C_9H_8N_2O_6$, a designed inhibitor for the influenza virus neuraminidase protein, crystallizes as hydrogen-bonded dimers. The dihedral angles of the substituent groups with respect to the planar phenyl moiety are 5.0 (3)° for the carboxyl group, 45.0 (2)° for the nitro group and 37.3 (1)° for the acetylamino substituent. The crystal structure is stabilized by intermolecular hydrogen bonding.

Comment

The current X-ray diffraction study establishes the structure of the benzoic acid derivative 4-(acetylamino)-3-hydroxy-5-nitrobenzoic acid, (I). This structure and those of similar compounds are of importance both for their application in structure-based drug design and in structure–activity studies of the influenza virus neuraminidase protein (Jedrzejas *et al.*, 1995). The structure of benzoic acid has been well established by both X-ray and neutron studies (Sim, Robertson & Goodwin, 1955; Bruno & Randaccio, 1980; Feld, Lehman, Muir & Speakman, 1981). However, further details concerning the conformation of the carboxyl, *N*-acetyl and nitro substituents of the title compound were needed for the purpose of further characterization.



(I)

The benzene ring atoms are planar to within 0.026 (2) Å, with C—C bond lengths varying from 1.377 (3) to 1.408 (3) Å and endocyclic C—C—C bond angles varying from 118.7 (2) to 122.2 (2)°, which agrees with accepted values (Bruno & Randaccio, 1980; Karle, 1952*a*,*b*). The carboxyl, nitro and *N*-acetyl groups are rotated with respect to the benzene ring by 5.0 (3), 45.0 (2) and 37.3 (1)°, respectively. The acetylamino group (N4, C7, O7 and C8) is planar to within 0.0009 (2) Å, with a C—O distance of 1.209 (3) Å. The two C—O bond distances of the carboxyl group are 1.290 (3) (C9—O9) and 1.224 (3) Å (C9—O9′), and the corresponding angles are 115.6 (2) (C1—C9—O9) and 120.2 (2)° (C1—C9—O9′). The nitro group N—O distances are, as expected, almost equal: 1.231 (3) (N5—O5) and 1.198 (3) Å (N5—O5′), with corresponding angles of 117.0 (2) (C5—N5—O5) and 118.5 (2)° (C5—N5—O5′).

Fig. 1 presents an *ORTEP*II (Johnson, 1976) drawing of the title molecule together with the atomic labelling scheme. The title compound crystallizes in a dimeric form. The molecules involved in this dimer interact through hydrogen bonds between their carboxyl groups (see Fig. 2) (Benghiat & Leiserowitz, 1972). A second intermolecular hydrogen bond is present between atom O7 of the *N*-acetyl group and the HO3 atom of the hydroxyl group. Appropriate distances and angles for the

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