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Cyclohexanecarbohydroxamic Acid

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Abstract

The conformation of the hydroxamic acid moiety, O=C—N—O, of cyclohexanecarbohydroxamic acid ($C_7H_{13}NO_2$, *N*-hydroxycyclohexanecarboxamide) is synperiplanar with a torsion angle of 4.5 (2)°. The cyclohexyl ring adopts a chair conformation with the planar hydroxamic acid moiety in an equatorial position. The plane of the hydroxamic acid moiety is almost perpendicular to the cyclohexyl ring. The hydrogen bonds in the crystal form ladders of molecules which extend along the *c* axis.

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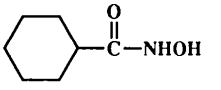
Comment

Hydroxyurea is an inhibitor of the enzyme ribonucleotide reductase (RNR), as are some other hydroxamic acids (Larsen, Sjöberg & Thelander, 1982). RNR catalyses the conversion of ribonucleotides into the corresponding deoxyribonucleotides. This is an essential step in DNA synthesis for all living cells, hence inhibitors of RNR are of interest as anticancer or antiviral drugs. The RNR enzyme of *E. coli* consists of two proteins, R1 and R2. Hydroxyurea and analogues act at the smaller R2 protein by reducing a tyrosyl free radical, which initiates the reduction process (Atkin, Thelander, Reichard & Lang, 1973; Stubbe, Ator & Krinitsky, 1983; Larsson & Sjöberg, 1986). It has been proposed that hydroxamic acids gain their activity from their ability to undergo one-electron oxidation, and that an almost planar conformation is advantageous due to steric demands at the active site (Larsen *et al.*, 1982; Lam, Fortier, Thomson & Sykes, 1990; Atta *et al.*, 1993). The X-ray structure of R2 shows that the tyrosyl radical is buried in the protein *ca* 10 Å from the nearest surface (Nordlund, Sjöberg & Eklund, 1990), and it is not yet known whether deactivators are able to penetrate to the tyrosyl radical or react *via* long-range electron transfer (Nordlund & Eklund, 1993). Cyclohexanecarbohydroxamic acid (CYCHA), with a bulky cyclohexyl substituent directly attached to the CONHOH group, has no inhibitory effect on R2 of *E. coli*, although its reducing effect is the same as that of, *e.g. n*-hexanohydroxamic acid, a weak deactivator of R2 (Larsen *et al.*, 1982). Hydroxamic acids may adopt



CYCHA

either a synperiplanar (*sp*, O=C—N—O torsion angle *ca* 0°) or an antiperiplanar (*ap*, O=C—N—O torsion angle *ca* 180°) conformation, with the *sp* conformation favoured by hydroxamic acids with a bulky substituent attached to the carbonyl group (Larsen, 1988). The hydroxamic acid moiety in CYCHA is in an equatorial position and is almost planar. The O=C—N—O torsion angle is 4.5 (2)°, the average deviation from the least-squares plane through C1, C7, O7, N8 and O9 is 0.028 Å, with a maximum deviation of 0.041 (1) Å (N8). The molecule as a whole is far from being planar. The cyclohexyl ring is in a chair conformation (*cf.* torsion angles in Table 2), and the plane of the hydroxamic acid moiety is almost perpendicular to the plane through the cyclohexyl ring atoms constituting the seat of the chair, the angle between the planes being 82.6 (1)°. Each molecule in the crystal is involved in four hydrogen bonds to three neighbouring molecules. The cyclohexyl rings are stacked in columns in the *c*

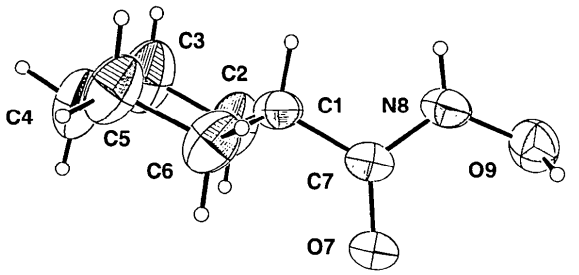


Fig. 1. Molecular structure and atomic numbering of CYCHA with displacement ellipsoids at the 50% probability level for non-H atoms.

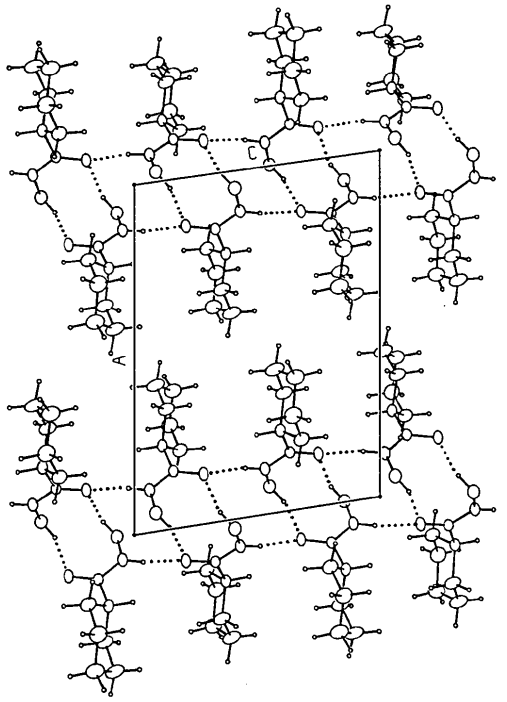


Fig. 2. The structure of CYCHA viewed along the *b* axis, with *c* horizontal and *a* vertical (displacement ellipsoids at the 20% probability level for non-H atoms). Hydrogen bonds are illustrated by dotted lines.

direction with NH···O hydrogen bonds connecting the molecules, thus forming the sides of a ladder (*cf.* Table 3 and Fig. 2). The rungs of the ladder are formed by OH···O hydrogen bonds between pairs of molecules on the same level but in different stacks.

The formation of two hydrogen bonds to the O atom of the carbonyl group weakens the C=O bond [1.247 (2) Å], which aids π-electron delocalization throughout the hydroxamic acid moiety (Taylor, Kennard & Versichel, 1984). The short C—N bond [1.322 (2) Å] reflects the high degree of delocalization of the lone-pair electrons of the N atom. The large CNO angle [121.7 (1)°] reveals that the geometry about the N atom tends toward trigonal. The sum of the valency angles at N8 is 360.01°. More or less pyramidalization of the N atom is most often observed in hydroxamic acids (Larsen, 1988).

Experimental

The compound was synthesized as described previously (Larsen *et al.*, 1982). Single crystals were obtained by slow cooling of a hot solution in ethyl acetate and chloroform. M.p. 388–391 K (decomp.). Room-temperature intensity data were used because the crystals decompose on cooling.

Crystal data

$C_7H_{13}NO_2$
M_r = 143.18
Monoclinic
$P2/c$
a = 13.044 (3) Å
b = 6.847 (2) Å
c = 9.465 (4) Å
β = 98.46 (3)°
V = 836.1 (5) Å^3
Z = 4
D_x = 1.137 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 20 reflections
θ = 15.01–18.84°
μ = 0.083 mm^{-1}
T = 294 (2) K
Needle
0.45 × 0.20 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
7143 measured reflections
3153 independent reflections
1589 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.039
θ_{max} = 32.97°
h = −19 → 19
k = 0 → 10
l = 0 → 14
3 standard reflections monitored every 600 reflections
frequency: 166 min
intensity variation: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0546
$wR(F^2)$ = 0.1446
S = 0.970
3151 reflections
92 parameters
H atoms refined isotropically using the riding model
$w = 1/[\sigma^2(F_o^2) + (0.1004P)^2 + 0.1017P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.088
$\Delta\rho_{max}$ = 0.183 e Å^{-3}
$\Delta\rho_{min}$ = −0.168 e Å^{-3}
Extinction correction: none
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)

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

	x	y	z	U_{eq}
C1	0.78083 (12)	0.6408 (3)	0.1113 (2)	0.0470 (4)
C2	0.80963 (15)	0.8289 (3)	0.1911 (2)	0.0614 (5)
C3	0.7316 (2)	0.9896 (3)	0.1454 (3)	0.0777 (6)
C4	0.6232 (2)	0.9270 (3)	0.1601 (3)	0.0828 (7)
C5	0.5938 (2)	0.7399 (4)	0.0827 (4)	0.0904 (8)
C6	0.67115 (14)	0.5788 (3)	0.1296 (3)	0.0697 (6)

C7	0.85508 (11)	0.4782 (2)	0.15986 (14)	0.0408 (3)
O7	0.87533 (8)	0.4285 (2)	0.28766 (10)	0.0486 (3)
N8	0.89618 (10)	0.3890 (2)	0.05777 (13)	0.0458 (3)
O9	0.95877 (9)	0.2264 (2)	0.08540 (13)	0.0545 (3)

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

C1—C2	1.512 (3)	C4—C5	1.497 (3)
C1—C6	1.526 (2)	C5—C6	1.517 (3)
C1—C7	1.502 (2)	C7—O7	1.247 (2)
C2—C3	1.517 (3)	C7—N8	1.322 (2)
C3—C4	1.504 (3)	N8—O9	1.383 (2)
C1—C2—C3	111.6 (2)	C2—C1—C7	112.14 (13)
C1—C6—C5	111.0 (2)	C3—C4—C5	112.1 (2)
C1—C7—O7	122.27 (13)	C4—C5—C6	111.6 (2)
C1—C7—N8	115.56 (12)	C6—C1—C7	109.39 (14)
C2—C3—C4	111.6 (2)	C7—N8—O9	121.71 (12)
C2—C1—C6	110.4 (2)	O7—C7—N8	122.16 (15)
C1—C2—C3—C4	54.6 (3)	C6—C1—C2—C3	−55.4 (2)
C2—C3—C4—C5	−54.0 (3)	C1—C7—N8—O9	−174.40 (12)
C3—C4—C5—C6	54.7 (3)	C3—C2—C1—C7	−177.6 (2)
C4—C5—C6—C1	−55.5 (3)	C5—C6—C1—C7	179.6 (2)
C5—C6—C1—C2	55.7 (2)	O7—C7—N8—O9	4.5 (2)

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N8—H8···O7^{i}	1.973 (2)	2.822 (2)	169.17 (5)
O9—H9···O7^{ii}	1.917 (2)	2.697 (2)	158.87 (4)

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

Data reduction: *DREADD* (Blessing, 1987, 1989). Program(s) used to solve structure: *SHELXS*90 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1191). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Securinine, an Alkaloid from *Fluggea virosa*

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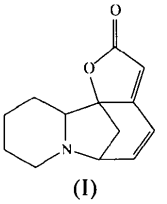
Abstract

Securinine, $C_{13}H_{15}NO_2$, is an alkaloid obtained from the leaves of the Vietnamese plant *Fluggea virosa* (*Roxb. ex Willd.*) Voigt. Its molecular structure differs markedly from the previously determined structure of its hydrobromide in that the piperidine ring has a regular chair conformation in the title compound but has a boat conformation in the protonated form.

Comment

Securinine (I) was isolated in 1.07% yield from the leaves of the Vietnamese plant *Fluggea virosa* (*Roxb. ex Willd.*) Voigt. The biological activity of securinine is well known. It stimulates the central nervous system in a manner similar to strychnine but is less toxic. It is useful in the treatment of paralysis following infectious disease and also in the treatment of psychological disorder (Do Tat Loi, 1986). So far, only the crystal structure of the hydrobromide dihydrate of securinine is known (Imado, Shiro & Horii, 1965).



(I)