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Crystal Structure of Sorbinil, $C_{11}H_9FN_2O_3$

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Abstract. $M_r = 236{\cdot}12$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}5096\ (6)$, $b = 6{\cdot}397\ (1)$, $c = 21{\cdot}018\ (3)$ Å, $V = 1009{\cdot}7\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}552$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}54178$ Å, $\mu = 4{\cdot}77$ cm^{-1}, $F(000) = 488$, $T = 293$ K, final $R = 0{\cdot}042$ for 749 unique observed reflections. The molecule contains fluorobenzene and hydantoin rings connected *via* a nonplanar pyran ring. The obtuse angle between the planes of the fluorobenzene and hydantoin rings is 98°. Bond distances and angles are normal except for CH_2–CH_2 of the pyran ring which at 1·484 (8) Å is 0·057 Å shorter than the standard value.

Introduction. The enzyme aldose reductase catalyzes the reduction of glucose to sorbitol and has been implicated in processes leading to certain complications of diabetes including cataracts and peripheral neuropathy (Kinoshita, 1974; Kinoshita, Kador & Datiles, 1981; Judzewitsch *et al.*, 1983). For this reason, inhibitors of the enzyme are of considerable medical interest.

One of the strongest known inhibitors of aldose reductase is sorbinil {(4*S*)-2,3-dihydro-6-fluorospiro-[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione} (Peterson, Sarges, Aldinger & Macdonald, 1979). The mechanism of action of sorbinil and other aldose reductase inhibitors is unknown as are the precise structural features important in their action. Examination of the molecular conformation of these compounds may allow correlation of stereochemical features with inhibitory activity and contribute to the rational design of more effective inhibitors of the enzyme. Sorbinil is of particular interest for such studies because it is a potent inhibitor of the enzyme and has a rigid molecular shape.

Experimental. Sample of sorbinil provided by Pfizer Inc. as a gift. Crystallized by slow evaporation from acetone and water solution. Crystal dimensions 0·85 × 0·65 × 0·40 mm. KRISEL Control-updated Picker FACS-1 diffractometer. Cu $K\alpha$ radiation. Cell constants determined by least squares from angular settings of 16 reflections ($22 < 2\theta < 47°$). ω–2θ scans, 2° min^{-1}. Empirical absorption correction (North, Phillips & Mathews, 1968) applied (1·02 to 1·07). Max. $(\sin\theta)/\lambda = 0{\cdot}5305$ Å^{-1} (h 0–7, k 0–6, l 0–22). 5 standard reflections showed no significant variation. 794 reflections, 768 unique, 19 unobserved ($F < 4\sigma_F$). Lorentz–polarization corrections applied. No deterioration correction. Structure solved by direct methods using *RANTAN*80 (Yao, 1981). Full-matrix least-squares refinement on F. $\sum w(||F_o| - |F_c||)^2$ minimized; $w = 1/\sigma^2 F$ based on counting statistics. Anisotropic temperature factors for non-hydrogen atoms, isotropic temperature factors for H atoms. H atoms located in a difference map. $R = 0{\cdot}042$, $wR = 0{\cdot}048$, $S = 5{\cdot}31$, mean and max. Δ/σ 0·0799 and 0·9672. Final difference map had no peaks >0·2 e Å^{-3}. Isotropic extinction parameter refined to a value of 0·0124 (3). Scattering factors for C, N and O from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965) and for F from *International Tables for X-ray Crystallography* (1974). Refinement using programs from *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. The final atomic parameters are listed in Table 1* and a view of the molecule with labeled atoms is shown in Fig. 1. Bond lengths and angles are listed in Table 2. Like other inhibitors of aldose reductase (Varma, Mikuni & Kinoshita, 1975; Kador, Sharpless & Goosey, 1982; Varughese, Przybylska, Sestani, Bellini & Humber, 1983), the sorbinil molecule contains a large planar aromatic region. The fragment of the molecule containing the phenyl ring and atoms O(1) and C(4) is essentially planar (largest deviation of an atom from the least-squares plane 0·02 Å). Atoms C(2) and C(3) deviate +0·45 and −0·31 Å respectively from the least-squares plane. The C(9)–O(1)–C(2)–C(3) dihedral angle is 51·5 (6)°; C(10)–C(4)–C(3)–C(2) is 41·7 (6)°.

The hydantoin ring is approximately planar [standard deviation of ring atoms from the least-squares plane through the five ring atoms is 0·018 Å; maximum

* Lists of structure factors anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42097 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final positional and equivalent isotropic thermal parameters with e.s.d.'s in parentheses* ($\times 10^4$ *for x,y,z and* $\times 10^2$ *for* U_{eq})

$U_{eq} = (U_{11} + U_{22} + U_{33})/3.$

	x	y	z	U_{eq}(Å^2)
O(1)	7743 (4)	273 (6)	5730 (1)	51
C(2)	7550 (7)	779 (10)	6399 (2)	52
C(3)	6275 (7)	−677 (10)	6707 (3)	48
C(4)	4405 (6)	−442 (7)	6414 (2)	34
C(5)	3002 (7)	−347 (8)	5323 (2)	43
C(6)	3195 (8)	−179 (8)	4677 (2)	51
C(7)	4788 (8)	87 (9)	4378 (3)	57
C(8)	6299 (8)	250 (9)	4743 (2)	52
C(9)	6163 (7)	107 (8)	5405 (2)	41
C(10)	4545 (6)	−223 (7)	5698 (2)	36
C(11)	3437 (7)	1426 (8)	6717 (2)	38
N(12)	2018 (6)	667 (7)	7051 (2)	43
C(13)	1887 (8)	−1521 (8)	6987 (2)	45
N(14)	3227 (7)	−2139 (7)	6607 (2)	43
O(15)	3853 (5)	3255 (5)	6661 (2)	52
O(16)	746 (5)	−2623 (6)	7234 (2)	61
F(17)	1658 (5)	−287 (5)	4313 (1)	71

Table 2. *Bond lengths* (Å) *and angles* (°) *for sorbinil*

O(1)–C(2)	1·450 (6)	C(9)–C(10)	1·378 (7)
C(2)–C(3)	1·484 (8)	C(9)–O(1)	1·374 (6)
C(3)–C(4)	1·540 (7)	C(4)–C(11)	1·537 (7)
C(4)–C(10)	1·516 (6)	C(11)–O(15)	1·217 (6)
C(10)–C(5)	1·403 (7)	C(11)–N(12)	1·364 (7)
C(5)–C(6)	1·370 (7)	N(12)–C(13)	1·410 (7)
C(6)–F(17)	1·386 (6)	C(13)–O(16)	1·225 (7)
C(6)–C(7)	1·362 (8)	C(13)–N(14)	1·345 (7)
C(7)–C(8)	1·374 (8)	N(14)–C(4)	1·458 (6)
C(8)–C(9)	1·398 (6)		

O(1)–C(2)–C(3)	110·3 (5)	O(1)–C(9)–C(8)	115·3 (4)
C(2)–C(3)–C(4)	110·6 (5)	C(3)–C(4)–N(14)	111·7 (4)
C(3)–C(4)–C(10)	110·1 (4)	C(3)–C(4)–C(11)	110·0 (4)
C(4)–C(10)–C(9)	121·2 (4)	C(10)–C(4)–N(14)	112·7 (4)
C(10)–C(9)–O(1)	123·4 (4)	C(10)–C(4)–C(11)	111·9 (4)
C(9)–O(1)–C(2)	114·5 (4)	C(4)–C(11)–N(12)	107·8 (4)
C(10)–C(5)–C(6)	117·7 (5)	C(11)–N(12)–C(13)	111·1 (4)
C(5)–C(6)–C(7)	124·1 (5)	N(12)–C(13)–N(14)	107·2 (4)
C(6)–C(7)–C(8)	118·5 (5)	C(13)–N(14)–C(4)	113·6 (4)
C(7)–C(8)–C(9)	119·4 (5)	N(14)–C(4)–C(11)	100·2 (4)
C(8)–C(9)–C(10)	121·3 (5)	C(4)–C(11)–O(15)	125·8 (5)
C(9)–C(10)–C(5)	119·1 (4)	N(12)–C(11)–O(15)	126·4 (5)
C(4)–C(10)–C(5)	119·7 (4)	N(12)–C(13)–O(16)	125·5 (5)
C(5)–C(6)–F(17)	117·1 (5)	N(14)–C(13)–O(16)	127·3 (5)
C(7)–C(6)–F(17)	118·9 (4)		

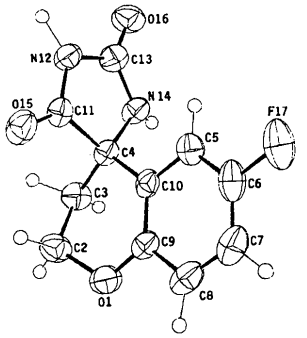

Fig. 1. View of the sorbinil molecule showing the atomic numbering scheme. The ellipsoids are drawn at the 50% probability level.

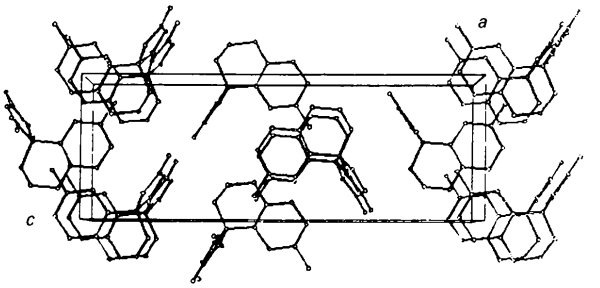

Fig. 2. Molecular packing of sorbinil. Projection is down the *b* axis. H atoms are omitted.

deviation is 0·022 Å, with O(15) and O(16) situated −0·076 and +0·031 Å respectively from the plane]. Bond distances and angles in the ring are in good agreement with the values reported for a similar hydantoin derivative, diphenylhydantoin (Camerman & Camerman, 1971). The obtuse angle between the phenyl and hydantoin rings in sorbinil is 98°.

Most bond lengths and angles in the molecule do not differ significantly from standard values with the exception of C(2)–C(3) which is significantly shorter (0·057 Å) than the standard value.

The molecular packing in the crystal is shown in Fig. 2. The molecules form intercalated stacks with the benzopyran ring systems parallel to the *ac* face. The molecules in each stack are connected by hydrogen bonds along the direction of the *b* axis [N(14)···O(15) 2·986 (6), H(14)···O(15) 2·18 (7) Å, ∠N(14)–H(14)···O(15) 161 (7)°]. Hydrogen bonds also form between pairs of adjacent stacks [N(12)···O(16) 2·787 (6), H(12)···O(16) 1·73 (5) Å, ∠N(12)–H(12)···O(16) 167 (4)°]. This hydrogen-bonding scheme is the same as that found in the crystal packing of diphenylhydantoin (Camerman & Camerman, 1971). Van der Waals interactions between the molecules of adjacent stacks presumably complete the stabilization of the crystal.

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Structures of Strychnine (I), $C_{21}H_{22}N_2O_2$, and a Solvate of Brucine (II), $C_{23}H_{26}N_2O_4.C_2H_6O.2H_2O$

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Abstract. (I): $M_r = 334{\cdot}41$, $P2_12_12_1$, $a = 11{\cdot}267$ (2), $b = 11{\cdot}892$ (11), $c = 12{\cdot}105$ (4) Å, $V = 1622$ Å^3, $Z = 4$, $D_x = 1{\cdot}369$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}83$ cm^{-1}, $F(000) = 712$, $T = 290$ K, $R = 0{\cdot}037$, 1195 unique data. (II): $M_r = 476{\cdot}53$, $P2_12_12_1$, $a = 7{\cdot}723$ (1), $b = 12{\cdot}337$ (1), $c = 25{\cdot}212$ (2) Å, $V = 2403$ Å^3, $Z = 4$, $D_x = 1{\cdot}317$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}90$ cm^{-1}, $F(000) = 1024$, $T = 290$ K, $R = 0{\cdot}039$, 1684 unique data. Strychnine and brucine are related indole alkaloids. The molecular connectivities differ only in the OMe groups present in brucine. The molecular structures show significant conformational variations in the indole rings and in the six-membered ring containing the amide group, which is affected by hydrogen bonding in brucine, the latter crystallizing as a solvate.

Introduction. Strychnine and brucine are indole alkaloids isolated from the seeds of *Strychnos nux vomica* and related plants. The molecular connectivities are shown in Fig. 1 and differ only in the methoxy substituents [O(3), C(22), O(4) and C(23)] found only in brucine. A major use of strychnine and brucine has been the resolution of racemic mixtures of amino acids. The small chemical difference of the presence or absence of methoxy groups has a profound effect on the preferred crystal formed. For example, from a mixture of *N*-benzoyl-D,L-alanine, brucine preferentially crystallizes with the D-enantiomer, while strychnine crystallizes with the L-enantiomer. The methoxy groups also produce a marked reduction of physiological activity where the principal mode of action by both strychnine and brucine is by overstimulation of the central nervous system.

Although the structure of the cation of strychnine was reported in 1951 (Robertson & Beevers, 1951; Bokhoven, Schoone & Bijvoet, 1951) the free bases were considered too difficult for the methods then available. Crystals of strychnine are included in the compilation of Groth (1919) where the reported axial ratios 0·9827 and 0·9309 are clearly those of our crystals [0·9824 (4) and 0·9308 (10)]. The form of brucine reported by Groth is a tetrahydrate, different in structure from the form reported here.

Experimental. The strychnine crystals were obtained as well formed prisms from an aqueous solution of an equimolar mixture of strychnine and *N*-acetyl-L-phenylalanine. Similar deposition of strychnine crystals occurred from several mixtures of strychnine with *N*-acyl amino acids. Brucine crystals were obtained as colourless needles by recrystallizing commercial

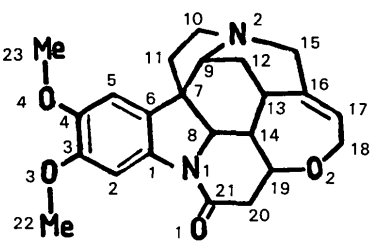

Fig. 1. Numbering scheme for atoms in (I) and (II).

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