carbazate, 4114-31-2; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 84-58-2; 3-aminopyrazole, 1820-80-0; benzyl bromide, 100-39-0; allyl bromide, 106-95-6; iodomethane, 74-88-4; ethyl bromoacetate, 105-36-2; cyclopropanemethanol methanesulfonate, 696-77-5; ethyl 4-bromocrotonate, 6065-32-3; iodoethane, 75-03-6; propargyl bromide, 106-96-7; iodopropane, 107-08-4; 2-bromoacetic acid, 79-08-3; 3-chloro-1,2-propanediol, 96-24-2; phenacyl bromide, 70-11-1; 1-bromo-3-methylbutane, 107-82-4; ethyl 2-bromopropionate, 535-11-5; 1,4-dibromo-2-butene, 6974-12-5; *N*-methylpiperazine, 109-01-3; *N*-(diphenylmethyl)piperazine, 97763-80-9; 3-amino-2,3-dihydro-1*H*-1,2,4-triazole, 97751-70-7; 3-amino-4-phenyl-2,3-dihydropyrazole, 97763-80-9.

Synthesis, Absolute Configuration, and Conformation of the Aldose Reductase Inhibitor Sorbinil

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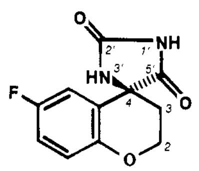
The aldose reductase inhibitor 2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione was resolved into its enantiomers. Sorbinil, the *S* isomer, was found to be a better inhibitor of the enzyme in vitro and in vivo than the corresponding *R* isomer. X-ray data on sorbinil, which were used to determine its absolute configuration, are presented. NMR studies of sorbinil in solution indicate the existence of two conformers with a low energy barrier for interconversion.

Aldose reductase inhibitors are potentially of therapeutic interest because they may play a role in preventing or treating chronic complications of diabetes mellitus. Sorbinil, the *S* isomer of 2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**1**), is an aldose

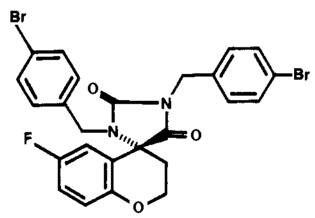


sorbinil (1)

reductase inhibitor that shows excellent in vivo activity in animal models[1,2] and is currently in clinical trials. Interestingly, sorbinil is considerably more potent than its *R* enantiomer in inhibiting aldose reductase, as shown in Table I. Analogous results were observed in an in vivo model (Table I), and this apparently highly stereospecific interaction of sorbinil with aldose reductase made it important to determine its absolute configuration and solution conformation.

Sorbinil and its enantiomer were synthesized by the reaction sequence shown in Scheme I, involving a brucine resolution of the racemic hydantoin precursor.[3] The free base of brucine forms a crystalline complex with sorbinil, whereas the enantiomer of sorbinil only forms a crystalline complex with brucine hydrochloride. Since this resolution technique does not work with certain congeners of sorbinil, a synthesis via an asymmetric induction sequence has also developed that seems generically applicable to optically active spiro hydantoins.[4]

The absolute configuration of sorbinil was established by single-crystal X-ray analyses. In an attempt to simplify the problem by the presence of a heavy atom we prepared the N_1',N_3'-bis(*p*-bromobenzyl) derivative **7** of the enantiomer of sorbinil. However, crystals of **7** proved unsuitable for X-ray analysis. On the other hand, the corresponding bis(*m*-bromobenzyl) derivative **8** yielded readily to X-ray analysis and, as depicted in Figure 1, showed that the absolute configuration of this derivative is *R* and that, therefore, the absolute configuration of sorbinil is *S*.



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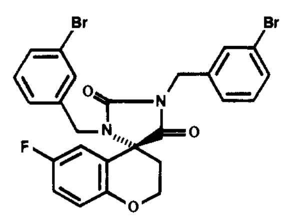

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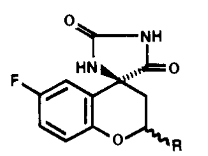

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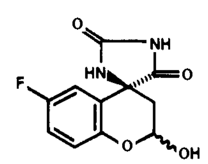

11

Subsequently, an X-ray analysis of sorbinil itself confirmed this result.

The problem of solution conformations was approached by using both theoretical and NMR analyses. Molecular mechanical energy computations[5] of sorbinil yield two potential energy minima with torsion angles about the C_2–C_3 bond of approximately ±60°. These minima correspond to the pseudochair forms **9a**, with the N_3' nitrogen of the spiro hydantoin ring in a pseudoequatorial position and **9b** with a pseudoaxial N_3' nitrogen. The energy computations predict that **9a** is more stable than **9b** by 570 cal/mol^{-1}.

Inspection of the X-ray structure of 8 (figure 1) shows that this sorbinil derivative indeed crystallizes in a form corresponding to **9a**, with the N_3' nitrogen in a pseudoequatorial position. Similarly, the X-ray analysis of sorbinil itself (Figure 2) shows that the unsubstituted compound

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‡ North Carolina State University.

(1) R. Sarges, J. L. Belletire, R. C. Schnur, and M. J. Peterson, ACS/CSJ Chemical Congress, Medicinal Chemistry Section, April 22–26, 1979, Honolulu, HI; Abstract 16.
(2) M. J. Peterson, R. Sarges, C. E. Aldinger, and D. P. MacDonald, *Metab. Clin. Exp.*, *28* (Suppl. 1), 456 (1979).
(3) R. Sarges, U.S. Patent 4130714.
(4) R. Sarges, H. R. Howard, Jr., and P. R. Kelbaugh, *J. Org. Chem.*, **47**, 4081 (1982).
(5) These energy calculations were carried out by using the MMI program (N. L. Allinger, et al., *QCPE* 11, 318 (1976). The authors will provide parameters on request.

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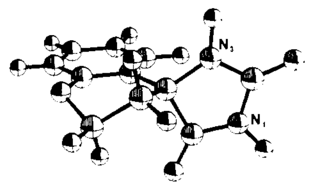
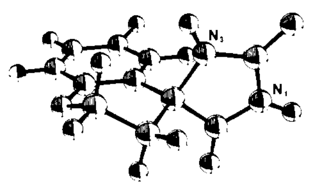


9a



9b

prefers to crystallize as **9a**, with a torsion angle about the C_2–C_3 bond of −62°. Therefore, it seemed of interest to investigate the conformation of sorbinil in solution, which may be relevant to its interaction with the enzyme aldose reductase.

Nuclear magnetic resonance studies of sorbinil in $CDCl_3$, Me_2SO-d_6, D_2O, and mixtures of these solvents[6] show that the vicinal spin coupling constants between the protons of the two adjacent methylene groups are solvent dependent (Table II), indicating that at least two conformations are significantly populated at room temperature. The ~60° torsions about the interconnecting C_2–C_3 bond that accompany the computed conformation change permute dihedral angles of ~180 and ~60° between two vicinal proton pairs, resulting in a set of $^3J_{H,H}$ coupling constants that are related, in terms of the Karplus equation[7]

$$^3J(\theta) \simeq a + b \cos \theta + c \cos (2\theta)$$

by

$$J_{AX} + J_{BY} \simeq {}^3J(180°) + {}^3J(60°) = 2a + \tfrac{1}{2}(c - b)$$

$$J_{AY} + J_{BX} \simeq 2\,{}^3J(60°) = 2a - (c - b)$$

and

$$J_{AX} - J_{BY} \simeq (2x - 1)[{}^3J(180°) - {}^3J(60°)] = \tfrac{3}{2}(2x - 1)(c - b)$$

where x is the mole fraction of one conformer. Using the sums to obtain a and $(b - c)$, values of x calculated from the differences between the larger couplings are listed in Table II.[8]

The enthalpy differences calculated on the basis of these values of x are of the order of 10^2 cal mol^{-1}, so that substituents larger than H on the 2- or 3-positions of sorbinil should force spiro hydantoins such as **10** into a single conformation dictated by the added substituent. In the most common case where R is equatorial its interaction with the spiro hydantoin ring is also small, so that the equilibrium ratio of diastereomers should reflect the conformational weighting in sorbinil itself. The sorbinil metabolite **11**,[9] which exists reversibly as a 3:2 mixture of two epimers in Me_2SO-d_6 solution, is an example. Here, with a single known (from $^3J_{H,H}$ couplings) conformation for each epimer, the relative configuration at C-2 and C-4 is determinable from nuclear Overhauser polarizations. For example, a significant NOE is observed between H-2 and the N-3′ proton only in the minor epimer of **11**, which must therefore have the 2*R* configuration and a conformation corresponding to **9b**.

The N-3′ proton shifts in the two epimers of **11** differ by 0.25 ppm while that in sorbinil has an intermediate value that if taken as the weighted average of the shifts in **11**, yields a mole fraction of x = 0.59 in Me_2SO-d_6 now identified with **9a**. Measurements and computations thus agree that **9a** is preferred over **9b** by amounts of the order of several hundred calories/mole in nonpolar solvents. However, this preference is reversed in D_2O.

In conclusion, the absolute configuration at C-4 of sorbinil is critically important for aldose reductase inhibition, indicating that there is a highly stereospecific binding site for spiro hydantoins at the enzyme, complementary to the *S* isomer sorbinil. On the other hand, it is not possible to discern whether conformers **9a** or **9b** interact preferentially at the enzyme, since both conformers occur in solution and since the energy barrier for this interconversion is low.

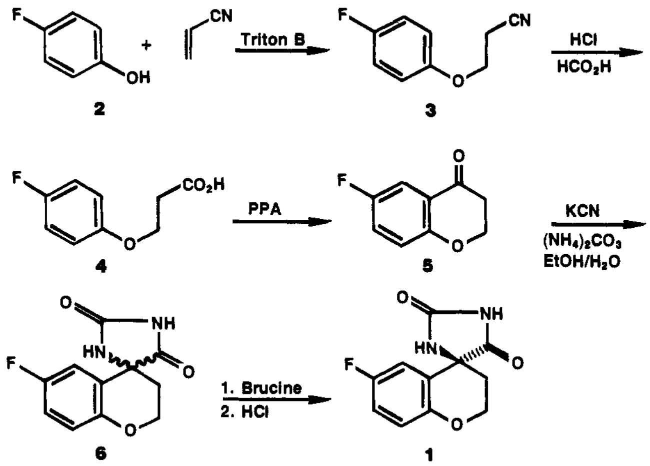
(6) Measured on 5-mm samples at 250 MHz.
(7) M. Karplus, *J. Am. Chem. Soc.*, 85, 2870 (1963).
(8) The fourth condition that J_{AY}–J_{BX} = 0 is poorly satisfied, especially in $CDCl_3$ solution. The values for a and c–b are in general accord with the theory.
(9) R. A. Ronfeld, submitted for publication.

Table I

	sorbinil (1)	enantiomer of sorbinil
IC_{50}, μM: bovine lens aldose reductase[a]	0.15	4.4
IC_{50}, μM: rat lens aldose reductase[b]	0.2	9
IC_{50}, μM: human placenta aldose reductase[b]	1	20
ED_{50},[c] mg/kg, po[a]	0.25	25

[a] See ref 2 for method. [b] Kador, P. F.; Goosey, J. D.; Sharpless, N. E.; Kolish, J.; Miller, D. D. *Eur. J. Med. Chem.-Chim. Ther.* 1981, *16*, 293. [c] Dose that inhibits sorbitol accumulation in sciatic nerves of streptozotocinized rats by 50%.

Scheme I



Experimental Section

3-(4-Fluorophenoxy)propanenitrile (3). A mixture of 475 g (4.24 mol) of 4-fluorophenol, 450 g (8.48 mol) of acrylonitrile, and 30 mL of Triton B (*N*-benzyltrimethylammonium hydroxide, 40 wt % solution in MeOH) was heated at reflux for 39 h in analogy to the method of Ricci.[10] After cooling and dilution with 1 L of EtOAc, the solution was washed with four 1-L portions of 5% aqueous NaOH 3× with 1 L of 3 N HCl, and 2× with 1 L of H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 565 g (81%) of **3** as an oil, MS *m/e* 165.

3-(4-Fluorophenoxy)propanoic Acid (4). A mixture of 565 g (3.42 mol) of **3**, 1.2 L of concentrated HCl, and 1 L of 97% HCO_2H was heated at reflux for 4 h. After slight cooling, the reaction mixture was poured onto 5 L of ice water to precipitate a solid that was filtered and washed with 5 L of H_2O. After drying at 60 °C under vacuum for 17 h, there was obtained 528 g (84%) of **4**, mp 84–86 °C (lit.[11] mp 86 °C).

Attempts to convert **3** to **4** under basic conditions led to extensive decomposition. Efforts to synthesize **4** by the literature procedure[11] from 4-fluorophenol and 3-chloropropanoic acid gave very low yields (less than 10%).

(10) A. Ricci, D. Balucani, and N. P. Buu-Hoi, *Ann. Chim. (Rome)*, 58, 455 (1968).
(11) G. C. Finger, M. J. Gortatowski, R. H. Shiley, and R. H. White, *J. Am. Chem. Soc.*, 81, 94 (1959).

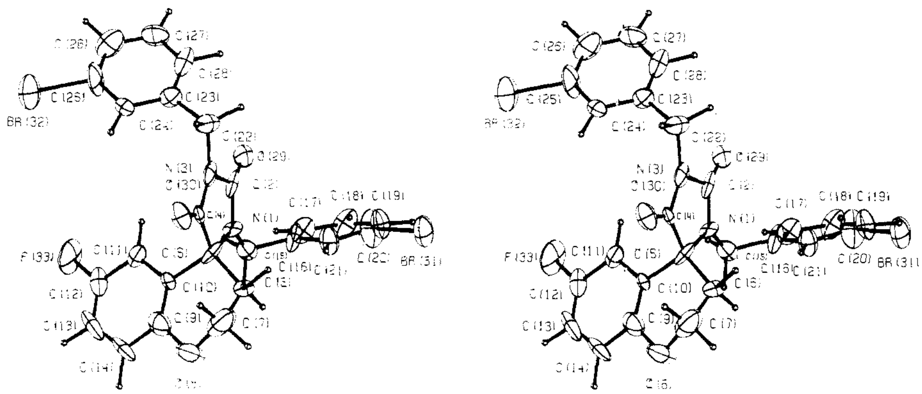


Figure 1. Stereoview of molecule 8.

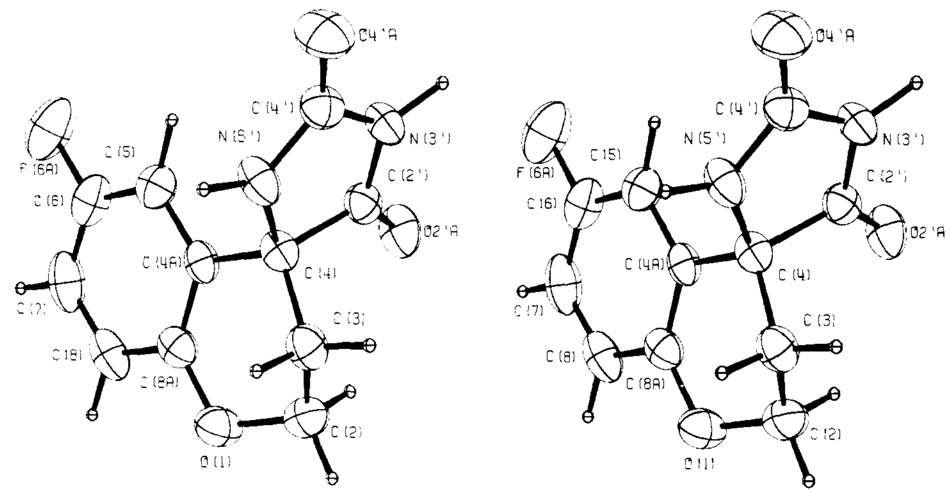
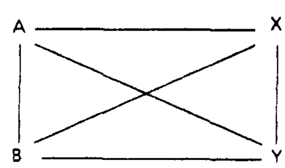
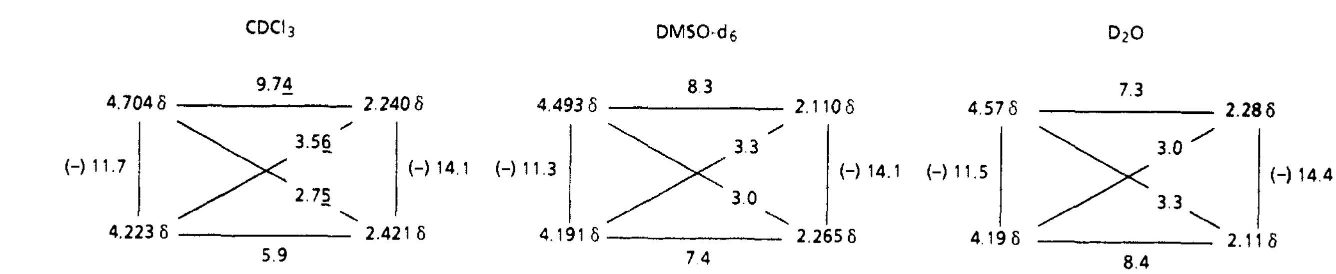


Figure 2. Stereoview of sorbinil (1).

Table II. Methylene Proton NMR Parameters in Sorbinil





	$CDCl_3$	DMSO-d_6	D_2O
J (180) + J (60)	15.65	15.7	15.7
2J (60)	6.31	6.3	6.3
a	6.3	6.3	6.3
3/2 (c − b)	9.3	9.4	9.4
x	0.71	0.55	0.44

2,3-Dihydro-6-fluoro-4*H*-1-benzopyran-4-one (5). A mixture of 528 g (2.87 mol) of 4 and 5.5 kg of polyphosphoric acid was heated on a steam bath for 20 min. After cooling, the reaction mixture was poured into 20 L of ice water to precipitate a gum that crystallized upon stirring. The solids were filtered, washed with H_2O, air-dried, and dissolved in $CHCl_3$. After separation of the water layer, the $CHCl_3$ solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give 397 g (83%) of 5, mp 113–116 °C. Typically, this material contains a small amount of water; an analytically pure sample was obtained by sublimation

Table III. Single-Crystal X-ray Crystallographic Analysis

A. Crystal Parameters		
formula (M_r)	$C_{28}H_{19}N_2O_8F$-Br_2 (574.26)	$C_{11}H_9O_8N_2F$ (236.20)
cryst med	ethanol	methanol
cryst size, mm	0.11 × 0.1m × 0.28	0.31 × 0.31 × 0.20
cell dimensn:		
a, Å	8.821 (2)	6.397 (1)
b, Å	8.092 (2)	7.507 (2)
c, Å	16.037 (5)	21.028 (5)
α, deg	90.0	90.0
β, deg	93.92 (2)	90.0
γ, deg	90.0	90.0
V, Å^3	1142.1 (6)	1009.9 (4)
space gp	$P2_1$	$P2_12_12_1$
Z	2	4
d(obsd), g/cm^3	1.64	1.51
d(calcd), g/cm^3	1.670	1.553
linear abs coeff, cm^{-1}	35.5	11.1
B. Refinement Parameters		
no. of reflcns	4069	1296
no. of nonzero reflcns ($I > 3.0\sigma$)	3667	1258
$R = \sum\lVert F_o\rvert - \lvert F_c\rVert / \sum\lvert F_o\rvert$	0.055	0.040
GOF = $[\sum w(F_o^2 - F_c^2)^2/(m - S)]^{1/2}$	2.68	3.56
scale factor	0.842 (2)	0.684 (4)
secondary extinc coeff (×10^{-6})	1.29 (8)	118 (3)

at 85 °C (1.1 mmHg); mp 113–115 °C. Anal. ($C_9H_7FO_2$) C, H.

Alternatively, 4 can be conveniently cyclized to 5 in 85–95% yield by treatment with concentrated H_2SO_4 at 50 °C for 15–45 min, followed by quenching into about 4 volumes of ice water.

2,3-Dihydro-6-fluorospiro[4*H*-1benzopyran-4,4′-imidazolidine]-2′,5′-dione (6). A mixture of 397 g (2.39 mol) of **5**, 233 g (3.58 mol) of KCN, and 917 g (9.56 mol) of powdered $(NH_4)_2CO_3$ in 3 L of 50% aqueous EtOH was heated at 65 °C for 63 h. After cooling and dilution with 2 L of H_2O, the mixture was carefully acidified with 6N HCl. The precipitate was filtered, washed with H_2O, dissolved in 2 N NaOH, and washed 3× with 1 L of EtOAc. Acidification of the aqueous phase with 6 N HCl gave a solid that was washed with H_2O, air-dried, and recrystallized from 9 L of MeOH to give, after concentration to a volume of 5 L, 276 g (49%) and a second crop of 82 g (15%) of **6**, mp 239–241 °C. Anal. ($C_{11}H_9FN_2O_3$) C, H, N.

Resolution of 6 with Brucine. A mixture of 120 g (0.508 mol) of **6** and 237 g (508 mol) of brucine tetrahydrate was heated in 1.8 L of EtOH until dissolution occurred and then allowed to cool slowly. The precipitated solids were filtered and the filtrate (A) saved. The solids were recrystallized twice from EtOH to give 121 g (68%) of 1 as the brucine adduct, mp 114–118 °C. Anal. ($C_{11}N_9FN_2O_3$·$C_{23}H_{26}N_2O_4$·C_2H_5OH) C, H, N. This material was treated with 1 L of EtOAc and 1 L of 1 N HCl; the organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from 1 L of EtOH to give 45 g of crude 1. A recrystallization from 0.3 L of EtOH gave 37 g (62%) of pure 1: mp 241–243 °C; $[\alpha]^{25}_D$ +54.0° (c 1, MeOH). Anal. ($C_{11}H_9FN_2O_3$) C, H, N. Crystals for the X-ray analysis of 1 were obtained by a slow crystallization from MeOH.

The original filtrate A was concentrated in vacuo and treated with 75 mL of 10% aqueous HCl to precipitate 118 g of the brucine hydrochloride adduct of the *R* isomer of 1, mp 172–174 °C. Anal. ($C_{11}H_9FN_2O_3$·$C_{23}H_{26}N_2O_4$·HCl·$2H_2O$) C, H, N. This material was shaken with 1 L of EtOAc and 600 mL of 10% aqueous H_2SO_4. The organic layer was collected, dried over $MgSO_4$, and filtered and the filtrate evaporated in vacuo to give 41 g (68%) of crude product. A recrystallization from 400 mL of EtOH gave 34 g (57%) of pure *R* isomer of 1: mp 241–243 °C; $[\alpha]^{25}_D$ -54.8° (c 1, MeOH). Anal. ($C_{11}H_9FN_2O_3$) C, H, N.

(*R*)-N_1′,N_3′-Bis(4-bromobenzyl)-2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (7). A solution of 1.1 g (5 mmol) of the *R* isomer of 1 and 15 mL of dried DMF was treated with 460 mg (10 mmol) of 50% NaH and mixture stirred at room temperature for 15 min. A solution of 2.5 g (10 mmol) of 4-bromobenzyl bromide in 10 mL of dried DMF was added dropwise. The mixture was kept at room temperature for 17 h, poured into 200 mL of H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was crystallized from EtOH to give 2.27 g (79%) of 7, mp 147–149 °C. Anal. ($C_{25}H_{19}Br_2FN_2O_3$) C, H, N. Recrystallization from several solvent systems failed to give crystals suitable for X-ray analysis.

Table IV. Atomic Coordinates (×10^4) of 8 and Their Standard Deviations

	x/*a*	*y*/*b*	*z*/*c*
	Non-Hydrogen Coordinates		
N(1)	6961 (5)	−1500 (6)	7515 (2)
C(2)	7461 (6)	−141 (7)	7907 (3)
N(3)	7665 (5)	1055 (6)	7292 (3)
C(4)	7355 (6)	442 (7)	6505 (4)
C(5)	6911 (5)	−1350 (9)	6598 (3)
C(6)	5330 (6)	−1695 (8)	6197 (4)
C(7)	5380 (8)	−2037 (10)	5288 (5)
O(8)	6247 (6)	−3509 (7)	5166 (3)
C(9)	7669 (8)	−3472 (8)	5541 (4)
C(10)	8075 (6)	−2476 (7)	6222 (3)
C(11)	9579 (6)	−2482 (9)	6555 (4)
C(12)	10595 (7)	−3504 (10)	6206 (5)
C(13)	10204 (9)	−4518 (10)	5543 (5)
C(14)	8736 (10)	−4512 (9)	5219 (5)
C(15)	6823 (7)	−3049 (8)	7959 (4)
C(16)	5636 (7)	−3002 (7)	8601 (3)
C(17)	5957 (7)	−3788 (8)	9362 (4)
C(18)	4875 (10)	−3819 (11)	9943 (4)
C(19)	3483 (7)	−3061 (8)	9786 (4)
C(20)	3180 (6)	−2304 (8)	9036 (3)
C(21)	4244 (6)	−2258 (8)	8427 (3)
C(22)	8066 (6)	2767 (8)	7497 (4)
C(23)	9677 (6)	2981 (7)	7853 (4)
C(24)	10875 (6)	2751 (8)	7352 (4)
C(25)	12322 (7)	2975 (9)	7693 (5)
C(26)	12623 (8)	3419 (9)	8521 (5)
C(27)	11443 (9)	3620 (12)	9016 (4)
C(28)	9967 (7)	3404 (9)	8685 (4)
O(29)	7697 (5)	87 (6)	8652 (2)
O(30)	7415 (5)	1204 (6)	5863 (3)
Br(31)	1280 (1)	−1250 (0)	8832 (0)
Br(32)	13959 (1)	2736 (2)	6998 (1)
F(33)	12059 (5)	−3464 (7)	6527 (4)
	Hydrogen Coordinates[a]		
H(C6)	4634	−626	6243
H(C6)	4899	−2751	6443
H(C7)	5852	−931	5005
H(C7)	4202	−2142	5052
H(C11)	9958	−1798	7119
H(C13)	11006	−5338	5299
H(C14)	8300	−5234	4667
H(C15)	7895	−3377	8235
H(C15)	6451	−3982	7482
H(C17)	7035	−4466	9518
H(C18)	5088	−4464	10555
H(C19)	2572	−3268	10233
H(C21)	3879	−1743	7806
H(C22)	7284	3272	7928
H(C22)	7919	3555	6919
H(C24)	10692	2515	6669
H(C26)	13727	3803	8751
H(C27)	11565	3852	9705
H(C28)	8990	3689	8982

[a] Temperature factors fixed at 3.70 Å^2.

Analogously was prepared from the *R* isomer of 1 the bis(3-bromobenzyl) derivative 8, mp 127–129 °C. Anal. C, H, N. A slow crystallization of 8 from EtOH gave crystals suitable for X-ray analysis.

Single-Crystal X-ray Analyses. Representative crystals were surveyed for both compounds, and data sets were collected on a Syntex P$\bar{1}$ diffractometer. The diffractometer was equipped with a graphite monochromator. Molybdenum radiation (λ = 0.71069 Å) was used for compound 8 to a maximum 2θ of 50° and copper radiation (λ = 1.5418 Å) for compound 1 to a maximum

2θ of 100°. Atomic scattering factors were taken from ref 12 except hydrogen which was taken from Stewart, Davidson and Simpson[13] and Br which was taken from Cromer and Mann.[14] All calculations were facilitated by the CRYM system.[15] All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table III.

A trial structure was obtained by conventional Patterson and Fourier techniques for compound 8. An isomorphous structure solved earlier in our laboratory (not compound 8) served as the initial trial structure for compound 1. A difference Fourier was used to complete the trial structure for compound 1. Both trial structures refined routinely. Hydrogen positions were calculated wherever possible. The hydrogen on the nitrogens of compound 1 were located by using difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The final cycles of full-matrix least-squares refinement contained the scale factor, coordinates, and anisotropic temperature factors in a single matrix. The shifts calculated in the final cycle were all less than 0.1 of their corresponding standard deviation. The final R index was 0.055 for compound 8 and 0.040 for compound 1. A final difference Fourier revealed no missing or misplaced electron density. The absolute configuration of the molecules was determined by the method of Ibers and Hamilton[16] and was plotted by the ORTEP computer program of Johnson[17] (Figures 1 and 2). This configuration was established as correct at the 0.5% level of significance (i.e., with 99.5% confidence).[18] The data set for both compounds contained a complete set of Friedel's pairs to ensure the determination of its absolute configuration. This variation is similar to a method described by Subramanian and Hunt.[19] The atomic coordinates for compounds 8 and 1 are given in Tables IV and V. Anisotropic temperature factors, distances, and angles are available as supplementary material from J.B.

During the review process, one reviewer challenged the absolute molecular structure of compound 8 on the basis that an absorption correction had not been done. This reviewer cited very spectacular differences in minimum and maximum transmission factors for a crystal of the size used. Consequently, the analysis of compound 8 was redone, using an absorption correction based on Gaussian quadrature.[20] Transmission factors after correction were t_{min} = 0.84 and t_{max} = 0.87. The crystallographic data reported in this paper for molecular structure 8 are based on these corrected data. However, the absorption corrections did not make any difference in the absolute molecular structure. To be sure, the R index was slightly better (improvement of 1.5%), but from the point of view of the absolute molecular structure the absorption correction proved useless. During the review process it was pointed out that another X-ray analysis of sorbinil has been recently reported at the Lexington meeting of the American Crystallographic Association.[21]

Table V. Atomic Coordinates ($\times 10^4$) of 1 and Their Standard Deviations

	x/a	y/b	z/c
	Non-Hydrogen Coordinates		
O(1)	2208 (4)	15 240 (3)	3230 (1)
C(2)	1748 (6)	15 060 (4)	3891 (1)
C(3)	3194 (5)	13 752 (4)	4206 (1)
C(4)	2946 (5)	11 908 (4)	3917 (1)
C(4A)	2711 (4)	12 033 (4)	3195 (1)
C(5)	2854 (5)	10 514 (4)	2819 (1)
C(6)	2697 (5)	10 680 (5)	2176 (2)
F(6A)	2808 (3)	9 175 (3)	1813 (1)
C(7)	2433 (6)	12 282 (5)	1882 (1)
C(8)	2247 (5)	13 788 (5)	2246 (2)
C(8A)	2379 (5)	13 669 (4)	2906 (1)
C(2′)	1065 (5)	10 927 (4)	4215 (1)
O(2′A)	−759 (3)	11 355 (3)	4162 (1)
N(3′)	1842 (4)	9 529 (3)	4547 (1)
C(4′)	4029 (5)	9 403 (5)	4488 (1)
O(4′A)	5087 (4)	8 244 (3)	4731 (1)
N(5′)	4632 (4)	10 727 (4)	4115 (1)
	Hydrogen Coordinates[a]		
H(C2)	274	14 544	3954
H(C2)	1797	16 227	4121
H(C3)	3024	13 732	4674
H(C3)	4719	14 219	4120
H(C5)	3127	9 265	3023
H(C7)	2330	12 381	1405
H(C8)	2056	15 004	2032
H(N3′)	1015	8 754	4846
H(N5′)	6076	10 959	3990

[a] Temperature factors fixed at 1.60 Å^2.

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(12) "International Tables for X-ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1962, pp 204, 214.
(13) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 42, 3175 (1965).
(14) D. Cromer and J. B. Mann Report LA-3816, Los Alamos Scientific Laboratory, Los Alamos, NM, 1967.
(15) D. J. Duchamp, *Am. Crystallogr. Assoc. Meeting*, Bozeman, MO, 1964, Paper B-14, p 29.
(16) J. Ibers and W. C. Hamilton, *Acta Crystallogr.*, 17, 781 (1964).
(17) C. K. Johnson, "ORTEP, Report ORNL-3794", Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
(18) W. C. Hamilton, *Acta Crystallogr.*, 18, 502 (1965).
(19) E. Subramanian and D. J. Hunt, *Acta Crystallogr.*, **B26**, 303 (1970).
(20) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, 10, 180 (1957).
(21) C. R. Kissinger, E. T. Adman, J. I. Clark, and R. E. Stenkamp, *Am. Crystallogr. Assoc. Meeting*, Lexington, KY, 1984 Paper PC22, p 55.