

3.10-3.42 (m, 6), 3.58-3.64 (m, 2), 4.04-4.31 (m, 4), 7.35 (d, $J = 8.2$ Hz, 2), 7.78 (d, $J = 8.2$ Hz, 2); TLC R_f 0.48 (CHCl₃-EtOH, 9:1); MS, m/z 347 ([M - CH₂Cl]⁺, 1.0), 243 ([M + 2 - Ts]⁺, 1.6), 241 ([M - Ts]⁺, 4.3), 213 ([M + 2 - TsOCH₂]⁺, 34), 211 ([M - TsOCH₂]⁺, 100). Anal. (C₁₄H₂₂ClN₂O₅PS) C, H, N, P.

N-(2-Acetoxyethyl)-3-(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-Oxide (17). A solution of 19 (1.1 g, 5.0 mmol) in acetic acid (10 mL) was stirred at room temperature for 1 h and then concentrated under reduced pressure. The solid material was dissolved in chloroform (30 mL), and this solution was washed with 10% KHCO₃ (25 mL). The aqueous layer was extracted twice with chloroform (2 × 30 mL). The combined chloroform solutions were dried and concentrated on a rotary evaporator. TLC (CHCl₃-acetone, 1:1) revealed two compounds, unreacted 19 (R_f 0.46) and 17 (R_f 0.25). Elution of the mixture from silica gel (30 g) with CHCl₃-acetone (1:1) gave unreacted 19 (0.2 g) and 17 (0.6 g, 43%), which was subsequently purified by crystallization from acetone-*n*-pentane to give material (0.5 g) of mp 83-84 °C: ³¹P NMR (CHCl₃) δ 12.4; ¹H NMR (CDCl₃) δ 1.86-2.18 (m, 2), 2.08 (s, 3), 3.13-3.15 (m, 1), 3.16-3.32 (m, 5), 3.39-3.50 (m, 1), 3.64-3.70 (m, 2), 4.11-4.41 (m, 4); TLC R_f 0.47 (CHCl₃-EtOH, 9:1); MS, m/z 287 ([M + 3]⁺, 0.6), 285 ([M + 1]⁺, 1.3), 235 ([M - CH₂Cl]⁺, 43), 226 ([M + 3 - AcO]⁺, 66), 224 ([M + 1 - AcO]⁺, 20), 215 ([M + 2 - AcOCH₂]⁺, 60), 213 ([M - AcOCH₂]⁺, 20). Anal. (C₉H₁₈ClN₂O₄P) C, H, N, P.

N-(2-Fluoroethyl)phosphoramidic Dichloride (23). A stirred suspension of 2-fluoroethylamine hydrochloride (5.0 g, 50 mmol) in POCl₃ (25 mL) was heated under reflux for 3 h. The excess of POCl₃ was removed by rotary evaporation, and the residue was distilled under reduced pressure to give 22 (4.6 g, 50%)

as a colorless oil: bp 117-118 °C (7 Pa); ¹H NMR (CDCl₃) δ 3.0-3.9 (m, 2, NCH₂), 4.5 (m, ² $J_{HF} = 48$ Hz, ³ $J_{HH} = 6$ Hz, ⁴ $J_{HP} = 2$ Hz, 2, CH₂F), 5.8 (s, 1, NH); ³¹P NMR (CHCl₃) δ 16.6; MS, m/z 179 (M⁺, 1), 146 ([M - CH₂F]⁺, 100), 117 ([M - FCH₂CH₂NH]⁺, 28).

3-(2-Chloroethyl)-N-(2-fluoroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-Oxide (18). To a stirred solution of 23 (3.6 g, 20 mmol) in dioxane (50 mL) was added at room temperature a mixture of 3-aziridinopropanol (2.0 g, 20 mmol), triethylamine (2.2 g, 22 mmol), and dioxane (50 mL). The mixture was stirred for 18 h, then filtered, and concentrated to dryness. A solution of the residue in CHCl₃ (100 mL) was washed with water (2 × 20 mL), dried, and concentrated under reduced pressure. This material was purified by silica gel (40 g) column chromatography with CHCl₃-EtOH (18:1) as eluent and recrystallized from Et₂O. Compound 23 (1.2 g) was obtained in 30% yield: mp 56-57 °C; ³¹P NMR (CHCl₃) δ 12.2; ¹H NMR δ 1.89-2.00 (m, 2), 2.96 (s, 1), 3.16-3.36 (m, 5), 3.44-3.56 (m, 1), 3.63-3.70 (m, 2), 4.19-4.29 (m, 1), 4.34-4.44 (m, 1), 4.48 (m, $J = 48.4$ Hz, $J = 4.8$ Hz, 2); MS, m/z 195 ([M - CH₂Cl]⁺, 41), 134 (16), 83 (43), 31 (100). Anal. (C₇H₁₅ClFN₂O₂P) C, H, N, P.

Acknowledgment. This project was financially supported by the Polish National Cancer Program CPBR-11.5.110 and 11.5.112.

Registry No. 13, 104149-14-6; (R)-(+)-13, 104149-16-8; (S)-(-)-13, 104149-15-7; 14, 110971-88-5; 15, 110971-89-6; 16, 110971-90-9; 17, 110971-91-0; 18, 110971-92-1; 19, 29102-47-4; (R)-(+)-19, 72578-73-5; (S)-(-)-19, 72578-74-6; 23, 110971-93-2; 2-fluoroethylamine hydrochloride, 460-08-2; 3-aziridinopropanol, 31190-87-1.

Spiro Hydantoin Aldose Reductase Inhibitors

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Sorbitol formation from glucose, catalyzed by the enzyme aldose reductase, is believed to play a role in the development of certain chronic complications of diabetes mellitus. Spiro hydantoins derived from five- and six-membered ketones fused to an aromatic ring or ring system inhibit aldose reductase isolated from calf lens. In vivo these compounds are potent inhibitors of sorbitol formation in sciatic nerves of streptozotocinized rats. Optimum in vivo activity is reached in spiro hydantoins derived from 6-halogenated 2,3-dihydro-4H-1-benzopyran-4-ones (4-chromanones). In 2,4-dihydro-6-fluorospiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione, the activity resides exclusively in the 4S isomer, compound 115 (CP-45,634, USAN: sorbinil). This compound is currently being used to test, in humans, the value of aldose reductase inhibitors in the therapy of diabetic complications.

Aldose reductase, the NADPH-linked enzyme that reduces aldehydic substrates, converts glucose to sorbitol; sorbitol can be converted in turn by polyol dehydrogenase to fructose. Because the K_M of aldose reductase for glucose is high, the hypothesis has been put forward^{1,2} that significant flux through this "polyol pathway" occurs only at high glucose levels, for instance, in diabetics whose plasma and tissue glucose levels may often exceed the normal range.^{2e} Since sorbitol and fructose do not readily diffuse out of cells, it has been postulated that accumulation of sorbitol and fructose in tissues such as lens, nerve, or retina contributes to the development of certain chronic complications of diabetes mellitus, such as cataracts, neuropathies, or retinopathy.^{1,2} If this hypothesis were correct, inhibitors of aldose reductase should be of value in preventing or treating these diabetic complications.

The search for aldose reductase inhibitors with which to test this hypothesis has been under way for many years. In 1965 several simple C₆-C₈ fatty acids and their derivatives were disclosed as inhibitors of calf lens aldose re-

ductase.³ Tetramethyleneglutaric acid (TMG) was reported in 1968 to be an aldose reductase inhibitor which, in contrast to the C₆-C₈ fatty acids, was active and also less toxic in lens cultures,^{4a} although TMG failed to dem-

- (1) For recent reviews of the polyol pathway hypothesis, see: (a) Lipinski, C. A.; Hutson, N. J. *Annu. Rep. Med. Chem.* 1984, 19, 169. (b) Kador, P. F.; Robison, W. G.; Kinoshita, J. H. *Annu. Rev. Pharmacol. Toxicol.* 1985, 25, 691. (c) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* 1985, 28, 841. (d) Benfield, P. *Drugs* 1986, 32 (Suppl. 2), 43. (e) Sarges, R. *Trends in Medicinal Chemistry, Proceedings of the 9th International Symposium on Medicinal Chemistry*, Berlin, 1986; Mutschler, E., Winterfeldt, E., Eds.; VCH: Weinheim, 1987; pp 551-564.
- (2) (a) Van Heyningen, R. *Nature (London)* 1959, 184, 194. (b) Kinoshita, J. H. *Invest. Ophthalmol.* 1965, 4, 786. (c) Gabbay, K. H.; O'Sullivan, J. B. *Diabetes* 1968, 17, 239. (d) Beaumont, P.; Hollows, F. C.; Schofield, P. J.; Williams, J. F.; Steinbeck, W. *Lancet* 1971, 1, 579. (e) Sarges, R. *Prog. Med. Chem.* 1981, 18, 191.
- (3) Hayman, S.; Kinoshita, J. H. *J. Biol. Chem.* 1965, 240, 877.
- (4) (a) Kinoshita, J. H.; Dvornik, D.; Kraml, M.; Gabbay, K. H. *Biochim. Biophys. Acta* 1968, 158, 472. (b) Hutton, J. C.; Schofield, P. J.; Williams, J. F.; Hollows, F. C. *Biochem. Pharmacol.* 1974, 23, 2991.

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Table I. Aldose Reductase Inhibitors from the Literature

		in vitro act. reported: IC ₅₀	found activity	
			in vitro IC ₅₀ , ^a M	in vivo ED ₅₀ , ^b mg/kg
TMG (tetramethyleneglutaric acid)		10 ⁻⁵ -10 ⁻⁶ M ^c	10 ⁻⁶ -10 ⁻⁷	~500
AY-22,284 (alrestatin)		10 ⁻⁵ -10 ⁻⁶ M ^d	10 ⁻⁶	250-500
quercitrin		~10 ⁻⁷ M ^e	10 ⁻⁵ -10 ⁻⁶	>40 (11)* ^{f,g}

^a Concentration that causes a 50% inhibition of partially purified calf lens aldose reductase with glyceraldehyde as substrate. Single determination; the reproducibility of the assay did not vary by more than 10%.⁸ ^b Oral dose, given tid, that causes a 50% reduction in sorbitol levels of sciatic nerve of streptozotocinized rats.⁸ If the > or < sign is used, the percent inhibition found is shown in parentheses; in these cases, the percent inhibition produced was statistically significant (Student's *t* test) at least at the *p* < 0.05 level unless values are marked with an asterisk. Single determination. ^c Reference 4a. ^d Reference 5. ^e Reference 6a; enzyme isolated from rat lens. ^f This drug was given sc. ^g (*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

onstrate in vivo activity in an animal model.^{4b} AY-22,284 (USAN: alrestatin), developed by Ayerst, was the first aldose reductase inhibitor that exhibited in vivo activity, albeit low, in preventing polyol accumulation and cataract formation in diabetic or galactosemic rats.⁵ The flavonoid quercitrin was a very potent in vitro inhibitor of rat lens aldose reductase which delayed cataract formation in streptozotocinized degus at high doses.⁶ In our in vivo test model (streptozotocinized rats), TMG, alrestatin, and quercitrin had only weak in vivo activity as summarized in Table I.

In recent years, several additional aldose reductase inhibitors with apparently good in vivo activity have been described, including quinolineacetic acid derivatives (ICI),^{7a} phthalazinylacetic acid derivatives (ICI),^{7b} *N*-(α -naphthylthiocarbonyl)glycine derivatives (Ayerst),^{7c} and a rhodanineacetic acid derivative (Ono Pharmaceuticals).^{7d} In 1979 we presented our initial findings in the spiro hydantoin class of aldose reductase inhibitors,^{7e} and related structures have recently been disclosed by ICI,^{7f} Eisai,^{7g} and Alcon.^{7h}

Our search for aldose reductase inhibitors began in 1973 with the establishment of a high-throughput screen using isolated calf lens aldose reductase³ and the screening of structural prototypes for in vitro inhibitory activity. Agents active at 10⁻⁵ M were then further evaluated for

Table II. The Empirical Leads

no.		in vitro IC ₅₀ , ^a M	in vivo ED ₅₀ , ^b mg/kg
1 ^c		10 ⁻⁵	25-100
2 ^d		10 ⁻⁴ -10 ⁻⁵	10-25

^a See footnote a in Table I. ^b See footnote b in Table I. ^c Mylari, B. L.; Miller, M. W.; Howes, H. L., Jr.; Figdor, S. K.; Lynch, J. E.; Koch, R. C. *J. Med. Chem.* 1977, 20, 475. ^d Novelli, A. *Anales Asoc. Quim. Argentina* 1941, 29, 83; *Chem. Abstr.* 1941, 35, 6576.⁷

in vivo activity in a streptozotocinized rat model by measuring effects on sorbitol accumulation in sciatic nerve. Details of these test procedures have been published previously.⁸ One of the first leads discovered in this manner was compound 1 (Table II). SAR probes around compound 1 did not lead to greatly improved activity. However, testing of Pfizer file compounds structurally more remote relative to 1 revealed that the spiro hydantoin 2 derived from 1-tetralone had substantial in vivo activity (Table II). That finding prompted us to carry out a systematic exploration of this class of compounds.

Chemistry

The hydantoins described in this study were prepared from the corresponding ketone precursors by the Bucherer-Bergs reaction either at 55-75 °C in an open vessel or at 110 °C in a bomb (see section A of the Experimental Section). This method failed only in the preparation of the hydantoin analogue 124 of alrestatin (see section B of the Experimental Section).

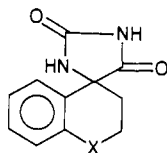
Biological Results and Discussion

Our SAR studies showed that the activity of compound 2 was shared by several spiro hydantoins derived from five- and six-membered cyclic ketones fused to a benzene ring,

- (5) Dvornik, D.; Simard-Duquesne, N.; Krami, M.; Sestan, J. K.; Gabbay, J. H.; Kinoshita, J. H.; Varma, S. D.; Merola, L. O. *Science (Washington, D.C.)* 1973, 182, 1146.
 (6) (a) Varma, S. D.; Mikuni, I.; Kinoshita, J. H. *Science (Washington, D.C.)* 1975, 188, 1215. (b) Varma, S. D.; Kinoshita, J. H. *Biochem. Pharmacol.* 1976, 25, 2505. (c) Varma, S. D.; Mizuno, A.; Kinoshita, J. H. *Science (Washington, D.C.)* 1977, 195, 205.
 (7) (a) Brittain, D. R.; Brown, E. D.; Hepworth, W.; Stacey, G. J. *Ger. Offenlegungsschrift* 2611 824, 1976. (b) Brittain, D. R.; Wood, R. *Eur. Pat. Appl.* 2895; *Chem. Abstr.* 1980, 92, 76533w. (c) Sestan, J.; Abraham, N. A.; Bellini, F.; Treasurywala, A.; Humber, L. G. *Eur. Pat.* 59-596. (d) Kikkawa, R.; Haanaka, I.; Yasuda, H.; Kobayashi, N.; Shigetani, Y.; Terashima, H.; Morimura, T.; Tsuboshima, M. *Diabetologia* 1983, 24, 290. (e) Sarges, R.; Belletire, J. L.; Schnur, R. C.; Peterson, M. J. Honolulu ACS/CSJ Chemical Congress, Medicinal Chemistry Section, April 2-6, 1979; Abstract 16. (f) Brittain, D. R.; Wood, R. E. P. 28-906. (g) Ono, H.; Nozawa, Y.; Hayano, S. *Nippon Ganka Gakkai Zasshi* 1982, 86, 253. (h) York, B. M. *Eur. Pat.* 92 385.

- (8) Peterson, M. J.; Sarges, R.; Aldinger, C. E.; MacDonald, D. P. *Metab., Clin. Exp.* 1979, 28 (Suppl. 1), 456.

Table III. Spiro Hydantoin with Modified Hydantoin-Bearing Rings



no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ ^b , M	in vivo ED ₅₀ ^c , mg/kg
2 ^d	CH ₂	240-242	C ₁₂ H ₁₂ N ₂ O ₂	A	84	10 ⁻⁴ -10 ⁻⁵	10-25
3 ^e	CH ₂ CH ₂	257-260	C ₁₃ H ₁₄ N ₂ O ₂	B	22	>10 ⁻⁴	>25 (9)* ^j
4 ^f	-	238-240	C ₁₁ H ₁₀ N ₂ O ₂	A	76	10 ⁻⁴ -10 ⁻⁵	5
5 ^g	O	236-238	C ₁₁ H ₁₀ N ₂ O ₃	A	35	10 ⁻⁵	5
6 ^g	S	225-227	C ₁₁ H ₁₀ N ₂ O ₂ S	B	53	10 ⁻⁵	5-10
7 ^h	SO ₂	280-281	C ₁₁ H ₁₀ N ₂ O ₄ S		49	10 ⁻⁵ -10 ⁻⁶	20
8 ⁱ	NMe	249 dec	C ₁₂ H ₁₃ N ₃ O ₂ ·HCl		24	10 ⁻⁴ -10 ⁻⁵	>25 (0)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSee footnote d in Table II. ^eHuisgen, R.; Ugi, I. *Justus Liebigs Ann. Chem.* 1957, 610, 57. ^fHenze, H. R.; Speer, R. J. *J. Am. Chem. Soc.* 1942, 64, 522. ^gArnold, H.; Kuehas, E.; Brock, N. German Auslegeschr. 1135915, Sept 6, 1962; *Chem. Abstr.* 1963, 58, P 3440a. ^hPrepared by oxidation of 6; for method, cf.: Sarges, R. U.S. Patent 4 117 230, Sept 26, 1978. ⁱSarges, R. U.S. Patent 4 235 911, Nov 25, 1980. ^j(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table IV. Hydantoin with Modified Relationships between the Hydantoin and the Aromatic Ring

no.	structure	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ ^b , M	in vivo ED ₅₀ ^c , mg/kg
2						10 ⁻⁴ -10 ⁻⁵	10-25
9 ^d		265-267	C ₁₂ H ₁₈ N ₂ O ₂	B	26	>10 ⁻⁴	<25 (13)* ^h
10 ^e		215-217	C ₈ H ₁₂ N ₂ O ₂	A	95	10 ⁻⁴	>25 (19)
4						10 ⁻⁴ -10 ⁻⁵	5
11 ^f		263-265	C ₁₁ H ₁₀ N ₂ O ₂	A	53	>10 ⁻⁴	>25 (9)*
12 ^g		219-221	C ₁₃ H ₁₄ N ₂ O ₂	B	22	>10 ⁻⁴	>25 (4)*
13						>10 ⁻⁴	>250 (14)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dCremlin, R. J. C.; Chisholm, M. *J. Chem. Soc. C* 1967, 2269. ^eHerbst, R. M.; Johnson, T. B. *J. Am. Chem. Soc.* 1932, 54, 2463. ^fReference 19. ^gPrepared from 2-phenylcyclopentanone. Arnold, R. T.; Buckley, J. S., Jr.; Dodson, R. M. *J. Am. Chem. Soc.* 1950, 72, 3153. ^h(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

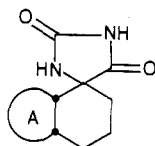
as listed in Table III. However, activity dropped off sharply as the ring bearing the hydantoin was enlarged to a seven-membered ring (compound 3). It is furthermore evident from Table IV that the proper arrangement of the aromatic ring and of the spiro hydantoin ring is critical for good activity, since hydrogenation or removal of the aromatic ring (9 and 10 vs 2) or shifting of the spiro junction from the position adjacent to the aromatic ring (11 and 12 vs 4) drastically reduced activity. Diphenylhydantoin (13), which is claimed to be a weak inhibitor of NADPH-linked brain aldehyde reductase,⁹ proved to have

no substantial activity in our test system.

The benzene ring of active agents can be replaced by other aromatic rings, such as furan, thiophene, or pyridine as shown in Table V; however, replacement by pyrrole was detrimental. Whereas the introduction of substituents into the aromatic ring of indan- or tetralin-derived hydantoin had only modest effects on activity (Tables VI and VII), halogen substitution, especially in the 6-position, dra-

(9) Erwin, V. G.; Deitrich, R. A. *Biochem. Pharmacol.* 1973, 22, 2615.

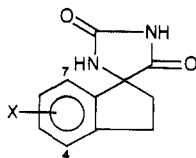
Table V. Hydantoin with Modified Aromatic Rings



no.	A	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
2						10 ⁻⁴ -10 ⁻⁵	10-25
14 ^d		245-248	C ₁₀ H ₁₀ N ₂ O ₃	B	42	10 ⁻⁴	25
15 ^e		266-268	C ₁₀ H ₁₀ N ₂ O ₂ S	B	52	10 ⁻⁴	25
16 ^f		275-277 dec	C ₁₁ H ₁₁ N ₃ O ₂	B	39	10 ⁻⁵	10
17 ^g		>300	C ₁₀ H ₁₁ N ₃ O ₂	B	26	>10 ⁻⁴	>25 (9)* ⁱ
18 ^h		>300	C ₁₂ H ₁₅ N ₃ O ₂	B	52	>10 ⁻⁴	>25 (5)*

^a All new compounds were analyzed for C, H, N. ^b See footnote a in Table I. ^c See footnote b in Table I. ^d Kelbaugh, P. R.; Sarges, R. U.S. Patent 4 147 797, April 3, 1979. ^e Sarges, R.; Schnur, R. C. U.S. Patent 4 127 665, Nov 28, 1978. ^f Sarges, R. U.S. Patent 4 117 230, Sept 26, 1978. ^g Prepared from 6,7-dihydroindol-4(5H)-one. Stetter, H.; Lauterbach, R. *Justus Liebigs Ann. Chem.* 1962, 655, 20. ^h Prepared from 6,7-dihydro-1,2-dimethylindol-4(5H)-one. Stetter, H.; Lauterbach, R. *Justus Liebigs Ann. Chem.* 1962, 655, 20. ⁱ (*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table VI. Substituted Indan Hydantoin



no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
4	H					10 ⁻⁴ -10 ⁻⁶	5
19 ^d	6-F	255-257	C ₁₃ H ₉ FN ₂ O ₂	B	5	10 ⁻⁴ -10 ⁻⁵	5
20 ^d	5-OMe	167-169	C ₁₂ H ₁₂ N ₂ O ₃	B	19	10 ⁻⁵	>25 (23)* ^g
21 ^d	6-OMe	192-194	C ₁₂ H ₁₂ N ₂ O ₃	B	14	10 ⁻⁵	10
22 ^d	5,6-(OMe) ₂	246-248	C ₁₃ H ₁₄ N ₂ O ₄	B	48	10 ⁻⁶ -10 ⁻⁶	10
23 ^e	5,6,7-(OMe) ₃	196-197	C ₁₄ H ₁₆ N ₂ O ₅	B	69	10 ⁻⁴	
24 ^d	5,6-OCH ₂ O	248-250	C ₁₂ H ₁₀ N ₂ O ₄	B	29	10 ⁻⁵ -10 ⁻⁶	>5 (9)*
25 ^f	6-OH	253-255	C ₁₁ H ₁₀ N ₂ O ₃		22	10 ⁻⁴ -10 ⁻⁵	>10 (15)*

^a All new compounds were analyzed for C, H, N. ^b See footnote a in Table I. ^c See footnote b in Table I. ^d Sarges, R. U.S. Patent 4 117 230, Sept 26, 1978. ^e Prepared from 5,6,7-trimethoxy-1-indanone. Dann, O.; Volz, G.; Huber, O. *Justus Liebigs Ann. Chem.* 1954, 587, 16. ^f Prepared from treatment of 21 with BBr₃; see footnote d. ^g (*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

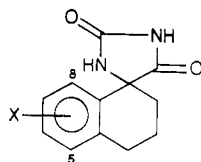
matically increased in vivo activity in the chroman and thiochroman hydantoin series (Tables VIII and IX). In general, the chroman derivatives were more potent in vivo than the corresponding thiochroman derivatives, possibly because the chromans have longer plasma half-lives in rats.¹⁰ Oxidation of certain thiochroman hydantoin to the sulfoxide or sulfone (Table X) gave compounds with slightly diminished in vivo activity. Fusion of another aromatic ring to the benzene ring of chroman hydantoin, especially in the 7,8-position, gave rise to potent in vitro inhibitors of aldose reductase, but their in vivo activity was unexpectedly low (Table XI); ring fusion to the 1,8-position of a tetrahydroquinoline hydantoin also led to moderately

potent compounds (76 and 77). Substitution in the ring bearing the hydantoin function resulted in loss of in vivo activity when tested in the tetralin series (Table XII). However, findings by Eisai workers^{7g} suggest enhanced activity in chroman derivatives such as 32 bearing a 2-methyl substituent, and researchers at Alcon have found excellent activity in the indan system fused in the 2,3-position to a benzene ring (9-fluorenyl spiro hydantoin).^{7h} Opening the ring bearing the hydantoin function abolished activity, e.g., in compound 83 (Table XIII).

Opening the hydantoin ring, for instance, by the scissions shown in Table XIV, proved also deleterious to activity. Replacement of the hydantoin ring in the tetralin, indan, and 6-chlorochroman series (Tables XV-XVII) with modified rings led generally, with the exception of the oxazolidinediones, to compounds that lack in vitro activity. Compound 87 was active in vivo, presumably because it

(10) Foulds, G. H., unpublished results. In rats, compound 117 had a plasma half-life of 0.8-1.4 h and compound 115 had a half-life of 4.9-7.6 h.

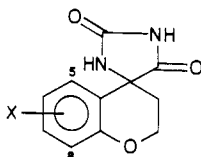
Table VII. Substituted Tetralin Hydantoin



no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
2	H					10 ⁻⁴ -10 ⁻⁵	10-25
26 ^d	5-OMe	243-243.5	C ₁₃ H ₁₄ N ₂ O ₃	A	74	10 ⁻⁵	>25 (29)
27 ^e	6-OMe	219-221	C ₁₃ H ₁₄ N ₂ O ₃	B	38	10 ⁻⁴ -10 ⁻⁵	>25 (17)* ^h
28 ^f	7-OMe	227-229	C ₁₃ H ₁₄ N ₂ O ₃	B	59	10 ⁻⁴	10-25
29 ^f	6,7-(OMe) ₂	238-240	C ₁₄ H ₁₆ N ₂ O ₄	B	49	10 ⁻⁴ -10 ⁻⁵	>5 (3)*
30 ^g	5-OMe, 8-Cl	272-274	C ₁₃ H ₁₃ ClN ₂ O ₃	B	52	>10 ⁻⁴	>25 (2)*
31 ^g	5-OMe, 8-F	306-308	C ₁₃ H ₁₃ FN ₂ O ₃	B	31	>10 ⁻⁴	>25 (-14)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSarges, R.; Tretter, J. R.; Tenen, S. S.; Weissman, A. *J. Med. Chem.* 1973, 16, 1003. ^eFletcher, H., III; Russell, P. B.; Alburn, H. E. U.S. Patent 3 532 744, Oct 6, 1970; *Chem. Abstr.* 1971, 74, P 42218k. ^fSarges, R. U.S. Patent 4 117 230, Sept 26, 1978. ^gSee footnote d for preparation of starting ketone. ^h(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table VIII. Substituted Chroman Hydantoin



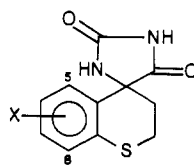
no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
5	H					10 ⁻⁵	5
32 ^d	6-F	239-241	C ₁₁ H ₉ FN ₂ O ₃	A	36	10 ⁻⁶	0.75
33 ^e	6-Cl	268-270	C ₁₁ H ₉ ClN ₂ O ₃	A	81	10 ⁻⁷	0.25-0.75
34 ^e	6-Br	266-268	C ₁₁ H ₉ BrN ₂ O ₃	A	15	10 ⁻⁶ -10 ⁻⁷	<1.5 (85)
35 ^f	8-F	203-205	C ₁₁ H ₉ FN ₂ O ₃	A	74	<10 ⁻⁴	
36 ^e	8-Cl	231-233	C ₁₁ H ₉ ClN ₂ O ₃	A	34	10 ⁻⁶	>1.5 (30)* ^s
37 ^d	6,8-Cl ₂	234-235	C ₁₁ H ₈ Cl ₂ N ₂ O ₃	A	20	<10 ⁻⁷	0.25
38 ^d	6,7-Cl ₂	263-265	C ₁₁ H ₈ Cl ₂ N ₂ O ₃	A	8	<10 ⁻⁷	<1.5 (64)
39 ^d	6-OMe	170-172	C ₁₂ H ₁₂ N ₂ O ₄	A	32	10 ⁻⁵ -10 ⁻⁶	>2.5 (24)*
40 ^g	6-SO ₂ Me	>300	C ₁₂ H ₁₂ N ₂ O ₅ S		2	10 ⁻⁴ -10 ⁻⁵	
41 ^h	6-SMe	186-187	C ₁₂ H ₁₂ N ₂ O ₃ S	B	29	10 ⁻⁶	<25 (90)
42 ^e	6-Me	242-243	C ₁₂ H ₁₂ N ₂ O ₃	B	58	10 ⁻⁵ -10 ⁻⁶	5
43 ^d	6,8-Me ₂	188-189	C ₁₃ H ₁₄ N ₂ O ₃	A	65	10 ⁻⁶	>1.5 (31)
44 ⁱ	5,8-Me ₂	228-229	C ₁₃ H ₁₄ N ₂ O ₃	A	56	10 ⁻⁶	>1.5 (12)*
45 ^j	5,7,8-Me ₃	134-135.5	C ₁₄ H ₁₆ N ₂ O ₃ ·CH ₃ OH	B	38	10 ⁻⁶	
46 ^h	6- <i>t</i> -Bu	197-198	C ₁₅ H ₁₈ N ₂ O ₃ · ¹ / ₂ C ₆ H ₆	B	11	10 ⁻⁴ -10 ⁻⁵	
47 ⁱ	6-SO ₂ NMe ₂	221-223	C ₁₃ H ₁₅ N ₃ O ₅ S		28	10 ⁻⁴	>5 (3)*
48 ^m	6-CONH ₂	318 dec	C ₁₂ H ₁₁ N ₃ O ₄ · ¹ / ₈ H ₂ O	A	8	10 ⁻⁴ -10 ⁻⁵	>100 (-1)*
49 ⁿ	6-Ph	283-285	C ₁₇ H ₁₄ N ₂ O ₃	A	27	<10 ⁻⁴	>1.5 (-3)*
50 ⁿ	8-Ph	217-218.5	C ₁₇ H ₁₄ N ₂ O ₃ · ¹ / ₈ H ₂ O	A	36	10 ⁻⁶ -10 ⁻⁷	10
51 ⁿ	6-OPh	168	C ₁₇ H ₁₄ N ₂ O ₄	A	7	10 ⁻⁵	25 (18)
52 ^o	7-CF ₃	213-215	C ₁₂ H ₉ F ₃ N ₂ O ₃	A	16	10 ⁻⁶	5
53 ^p	6-CH ₂ N ₅	232-233	C ₁₇ H ₂₁ N ₃ O ₃ · ¹ / ₈ CH ₃ OH	B	19	10 ⁻⁴	
54 ⁿ	6-Ph, 8-Cl	243-244	C ₁₇ H ₁₃ ClN ₂ O ₃	B	35	10 ⁻⁵ -10 ⁻⁶	
55 ^q	6-Cl, 8-Me	214-215	C ₁₂ H ₁₁ ClN ₂ O ₃	B	53	<10 ⁻⁷	<1.5 (70)
56 ^r	5-OMe, 8-Cl	227.5-228.5	C ₁₂ H ₁₁ ClN ₂ O ₄	B	88	>10 ⁻⁴	

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSarges, R. U.S. Patent 4 117 230, Sept 26, 1978. ^eSee ref g in Table III. ^fThis compound was prepared by R. L. Robertson of Pfizer Central Research; see Experimental Section, Section C, for preparation of 8-fluoro-2,3-dihydro-4*H*-1-benzopyran-4-one. ^gPrepared by methanesulfonylation of compound 5; see Experimental Section, Section B. ^hPrepared from 2,3-dihydro-6-(methylthio)-4*H*-1-benzopyran-4-one. Canalini, G.; Degani, I.; Fochi, R.; Spunta, G. *Ann. Chim. (Rome)* 1967, 57, 1045. ⁱPrepared from 2,3-dihydro-5,8-dimethyl-4*H*-1-benzopyran-4-one. Dann, O.; Volz, G.; Huber, O. *Justus Liebig's Ann. Chem.* 1954, 587, 16. ^jPrepared from 2,3-dihydro-5,7,8-trimethyl-4*H*-1-benzopyran-4-one. Koo, J. *J. Am. Chem.* 1953, 75, 1891. ^kPrepared from 6-*tert*-butyl-2,3-dihydro-4*H*-1-benzopyran-4-one, ref 25. ^lPrepared from the corresponding sulfonyl chloride; see Experimental Section, Section B. ^mPrepared from 6-(aminocarbonyl)-2,3-dihydro-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. ⁿSarges, R.; Belletire, J. L. U.S. Patent 4 181 729, Jan 1, 1980. ^oPrepared from 2,3-dihydro-7-(trifluoromethyl)-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. ^pPrepared from 2,3-dihydro-6-(piperidinylmethyl)-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. ^qPrepared from 6-chloro-2,3-dihydro-8-methyl-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. ^rPrepared from 8-chloro-2,3-dihydro-5-methoxy-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. ^s(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

is demethylated in the rat. Metabolic activation probably also bestows in vivo activity in compounds 91, 93, and 97. Replacement of the weakly acidic hydantoin function with

the carboxylic acid group (Table XVIII) led to a series of compounds with aldose reductase inhibitory activity that roughly paralleled that of the corresponding hydantoin.

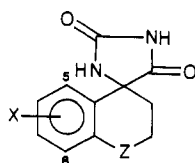
Table IX. Substituted Thiochroman Hydantoin



no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
6	H					10 ⁻⁵	5-10
57 ^d	6-F	200-202	C ₁₁ H ₉ FN ₂ O ₂ S	B	60	10 ⁻⁶ -10 ⁻⁷	1.5
58 ^d	6-Cl	244-246	C ₁₁ H ₉ ClN ₂ O ₂ S	B	53	10 ⁻⁶ -10 ⁻⁷	2.5
59 ^d	6-Br	234-236	C ₁₁ H ₉ BrN ₂ O ₂ S	B	56	10 ⁻⁶ -10 ⁻⁷	2.5
60 ^d	7-Cl	235-237	C ₁₁ H ₉ ClN ₂ O ₂ S	B	67	10 ⁻⁶	>1.5 (26)* ⁱ
61 ^d	8-Cl	265-267	C ₁₁ H ₉ ClN ₂ O ₂ S	B	66	10 ⁻⁴	>1.5 (5)*
62 ^d	6,7-Cl ₂	298-300	C ₁₁ H ₈ Cl ₂ N ₂ O ₂ S	B	49	<10 ⁻⁷	2.5
63 ^e	6,8-Cl ₂	247-248	C ₁₁ H ₈ Cl ₂ N ₂ O ₂ S ¹ / ₄ C ₆ H ₁₂ ^f	B	94	<10 ⁻⁷	
64 ^g	5,8-Cl ₂	250-252	C ₁₁ H ₈ Cl ₂ N ₂ O ₂ S ¹ / ₂ CH ₃ OH	B	24	>10 ⁻⁴	
65 ^d	6-OMe	170-172	C ₁₂ H ₁₂ N ₂ O ₃ S	B	41	10 ⁻⁵	>5 (26)
66 ^h	6- <i>t</i> -Bu	238-239	C ₁₅ H ₁₈ N ₂ O ₂ S	B	8	10 ⁻⁴ -10 ⁻⁵	

^a All new compounds were analyzed for C, H, N. ^b See footnote a in Table I. ^c See footnote b in Table I. ^d Sarges, R. U.S. Patent 4117 230, Sept 26, 1978. ^e Prepared from 6,8-chloro-2,3-dihydro-4*H*-1-benzothiopyran-4-one; see Experimental Section, Section C. ^f Cyclohexane. ^g Prepared from 5,8-dichloro-2,3-dihydro-4*H*-1-benzothiopyran-4-one; see Experimental Section, Section C. ^h Prepared from 6-*tert*-butyl-2,3-dihydro-4*H*-1-benzothiopyran-4-one; see Experimental Section, Section C. ⁱ (*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table X. Oxidized Thiochroman Hydantoin



no.	X	Z	mp, °C	formula ^a	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
6	H	S				10 ⁻⁵	5-10
7 ^d	H	SO ₂				10 ⁻⁵ -10 ⁻⁶	20
57	6-F	S				10 ⁻⁶ -10 ⁻⁷	1.5
67 ^d	6-F	SO	289-291 dec	C ₁₁ H ₉ FN ₂ O ₃ S	22	10 ⁻⁶ -10 ⁻⁷	>1.5 (35)
68 ^d	6-F	SO ₂	184-186 dec	C ₁₁ H ₉ FN ₂ O ₄ S ¹ / ₂ EtOAc	74	10 ⁻⁶ -10 ⁻⁷	2.5
63	6,8-Cl ₂	S				<10 ⁻⁷	
69 ^d	6,8-Cl ₂	SO ₂	>300	C ₁₁ H ₈ Cl ₂ N ₂ O ₄ S·H ₂ O	56	10 ⁻⁷	>1.5 (25)* ^e

^a All new compounds were analyzed for C, H, N. ^b See footnote a in Table I. ^c See footnote b in Table I. ^d Prepared by oxidation of the corresponding thiochroman derivatives; see: Sarges, R. U.S. Patent 4117 230, Sept 26, 1978. ^e (*) The inhibition was not significant (Student's *t* test) at the *p* < 0.05 level.

However, with regard to potency, the carboxylic acids were inferior to the hydantoin both in vitro and in vivo.

Resolution of compounds **32**, **57**, and **102** showed clearly that the aldose reductase inhibitory activity resides essentially in one enantiomer (Table XIX). The absolute configuration of **115**, the active enantiomer of **32**, was established as *S* by an X-ray analysis of the bis(*m*-bromobenzyl) derivative of **116**.^{11a} X-ray studies showed that the active oxazolidinedione **119** also has the *S* configuration.^{11b} The postulated absolute configuration of **117**, the active enantiomer of **57** depicted in Table XIX, is based on the known configuration of **115** and **119**. It is interesting to note that the weak anticonvulsant activity displayed by **32** is not configuration dependent.¹²

A further probe examined the effects of selective alkylation of the hydantoin ring nitrogens of compound **115**.

As shown in Table XX, methylation of either or both the 1'- and the 3'-nitrogen greatly diminished in vitro activity, the acidic compound **122** being somewhat more potent than the other derivatives. In vivo, all these methylated derivatives were active, presumably because they are metabolized to **115**.

Taken together, these results show that potent in vitro and in vivo activity is associated with spiro hydantoin derived from five- and six-membered ketones fused to certain aromatic rings or ring systems, provided the spiro junction is adjacent to the aromatic ring. Optimum activity is reached in hydantoin derived from 6-halogen-substituted 4-chromanones, and the activity seems to reside exclusively in the 4*S* enantiomer in this case. Any disturbance of these rigid systems by opening the hydantoin ring or the ring bearing the hydantoin results in loss of activity. Replacement of the hydantoin function by an oxazolidinedione leads to diminished in vivo activity, and replacement by carboxyl reduces both the in vitro and in vivo activity.

Active compounds from these hydantoin series compare very favorably in terms of in vivo potency in our rat model with other published non-hydantoin aldose reductase inhibitors.^{1e} It is tempting to speculate that the weakly

- (11) (a) Sarges, R.; Bordner, J.; Dominy, B. W.; Peterson, M. J.; Whipple, E. B. *J. Med. Chem.* 1985, 28, 1716. (b) Schnur, R. C.; Sarges, R.; Peterson, M. J. *J. Med. Chem.* 1982, 25, 1451.
 (12) Both enantiomers had ED₅₀'s of 56-100 mg/kg ip, with measurement of blockade of supramaximal electroconvulsant shock in mice after a 1-h pretreatment; Weissman, A., unpublished results.

Table XI. Systems with a Fused Aromatic Ring

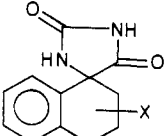
no.	structure	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
5						10 ⁻⁵	5
70 ^d		253-254	C ₁₅ H ₁₂ N ₂ O ₃ ·1/2H ₂ O	A	38	<10 ⁻⁴	>1.5 (30)
71 ^d		295 dec	C ₁₆ H ₁₂ N ₂ O ₃	B	48	10 ⁻⁵	>1.5 (-13)* ⁱ
72 ^e		305 dec	(C ₁₄ H ₁₁ N ₃ O ₃) ^f	A	21	10 ⁻⁵	>1.5 (27)
73 ^e		>330	C ₁₄ H ₁₁ N ₃ O ₃	A	64	10 ⁻⁶ -10 ⁻⁷	1.5-10
74 ^d		275 dec	C ₁₆ H ₁₄ N ₂ O ₄	B	29	10 ⁻⁷	>1.5 (1)*
33						10 ⁻⁷	0.25-0.75
75 ^d		215-217	C ₁₅ H ₁₁ ClN ₂ O ₃	B	79	<10 ⁻⁷	1.5-5
76 ^g		290-292	C ₁₄ H ₁₁ N ₃ O ₃	A	80	10 ⁻⁶ -10 ⁻⁷	2.5-5
77 ^{g,h}		199-205	C ₁₄ H ₁₀ ClN ₃ O ₃ ·H ₂ O		5	<10 ⁻⁷	>1.5 (32)

^a All new compounds were analyzed for C, H, N. ^b See footnote a in Table I. ^c See footnote b in Table I. ^d Sarges, R.; Belletire, J. L. U.S. Patent 4181728, Jan 1, 1980. ^e Schnur, R. C. U.S. Patent 4176185, Nov 27, 1979. ^f By high-resolution mass spectrometry. ^g Schnur, R. C. U.S. Patent 4193996, March 18, 1980. ^h Prepared by chlorination of 76. ⁱ (*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

acidic hydantoin are more potent in vivo than the carboxylic acids because they are better able to penetrate biological membranes. This hypothesis is supported by the data shown in Table XXI. There seems to be an inverse correlation between the acidity (low *pK_a*) and the relative potency of the carboxylic acids AY-22,284 and 108, the oxazolidinedione 119, and the hydantoin 115 in inhibiting sorbitol formation in isolated nerves incubated in

a solution containing the test drug and a high glucose concentration.⁸ The ratio of the inhibitory concentration causing a 50% reduction of sorbitol in the isolated nerve to the IC₅₀ in the isolated enzyme (A/B in Table XXI) is most likely a measure of the compound's ability to penetrate the nerve membrane; this value is highest for the hydantoin, being approximately 250 times greater than that of the carboxylic acids. The in vivo potency in the

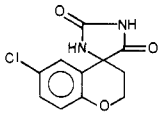
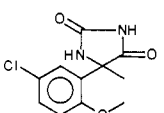
Table XII. Compounds with Substituents in the Hydantoin-Bearing Ring



no.	X	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
2	H					10 ⁻⁴ -10 ⁻⁵	10-25
78 ^d	2-Me	224-226	C ₁₃ H ₁₄ N ₂ O ₂	B	52	10 ⁻⁴	>25 (13)* ^h
79 ^e	4-Me	224-226	C ₁₃ H ₁₄ N ₂ O ₂	B	25	10 ⁻⁴	>25 (2)*
80 ^f	2-Ph	289	C ₁₈ H ₁₆ N ₂ O ₂	B	33	>10 ⁻⁴	>25 (18)*
81 ^f	4-Ph	210-212	C ₁₈ H ₁₆ N ₂ O ₂ ·1/4H ₂ O	B	47	10 ⁻⁴	>25 (2)*
82 ^g	4-CO ₂ H	289-290 dec	C ₁₃ H ₁₂ N ₂ O ₄	B	62	>10 ⁻⁴	

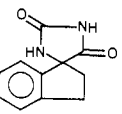
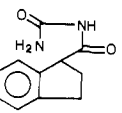
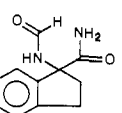
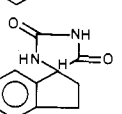
^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dPrepared from 2-methyl-1-tetralone (Aldrich). ^ePrepared from 4-methyl-1-tetralone (Aldrich). ^fSarges, R.; Belletire, J. L. U.S. Patent 4181729, Jan 1, 1980. ^gPrepared from 4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid. Horning, E. C.; Finelli, A. F. *J. Am. Chem. Soc.* 1949, 71, 3204. ^h(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table XIII. Spiro and Nonspiro Hydantoin

no.	structure	mp, °C	formula ^a	method	% yield	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
31						10 ⁻⁷	0.25-0.75
83 ^d		251-253	C ₁₁ H ₁₁ ClN ₂ O ₃	B	32	>10 ⁻⁴	

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dPrepared from 5-chloro-2-methoxyacetophenone. Wittig, G. *Ber. Dtsch. Chem. Ges.* 1924, 57, 88.

Table XIV. Compounds with Opened Hydantoin Rings

no.	structure	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
4				10 ⁻⁴ -10 ⁻⁵	5
84 ^d		217-218	C ₁₁ H ₁₂ N ₂ O ₂ ·1/4H ₂ O	10 ⁻⁴	>10 (0)* ^e
85 ^d		182-186	C ₁₁ H ₁₂ N ₂ O ₂ ·1/4H ₂ O	10 ⁻⁴	>10 (-8)*
86 ^d		201-203	C ₁₁ H ₁₂ N ₂ O ₂	>10 ⁻⁴	>10 (3)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSee Experimental Section, Section B. ^e(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

streptozotocinized rat model correlates very well with the potency of these compounds in the isolated nerve model (B/C ≈ 1).

In order to test this hypothesis further, we synthesized the hydantoin "analogue" of alrestatin, compound 124 (Table XXI), in which the acetic acid moiety of alrestatin is replaced by a hydantoin ring. Consistent with our prediction, 124 showed excellent tissue penetration in the isolated nerve, but its in vivo activity was unexpectedly

low, perhaps due to rapid metabolic inactivation.

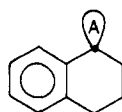
The mechanism by which the spiro hydantoin inhibit aldose reductase is not yet clear. It is apparent from Table XIX that active compounds interact with the enzyme in a highly stereospecific manner. Compound 115 is an uncompetitive inhibitor of aldose reductase⁸ with respect to the sugar aldehyde substrate (in our tests, glyceraldehyde). This suggests that the spiro hydantoin do not interact directly at the substrate binding site. Other experiments suggest that 115 is not a competitive inhibitor of the co-factor NADPH either, since the inhibition of aldose reductase by 115 cannot be overcome by the addition of excess NADPH.^{13a} Hence further experiments are needed to determine in detail the mechanism of aldose reductase inhibition by spiro hydantoin.

Our SAR exploration in the spiro hydantoin series has yielded a number of potent in vivo aldose reductase inhibitors. Of these, compound 115 (CP-45,634; USAN: sorbinil) has been extensively investigated both pharmacologically and clinically. Early results from clinical trials of sorbinil tend to confirm the validity of the aldose reductase/polyol pathway hypothesis in the development of chronic complications of diabetes mellitus.^{13b}

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by the Analytical Department of Pfizer Central Research. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements are within ±0.4% of the theoretical values. NMR spectra were recorded on

(13) (a) Kador, P. F.; Sharpless, N. E. *Mol. Pharmacol.* 1983, 24, 521. (b) Pitts, N. E.; Vreeland, F.; Shaw, G. L.; Peterson, M. J.; Mehta, D. J.; Collier, J.; Gunderson, K. *Metab., Clin. Exp.* 1986, 35 (Suppl. 1), 96.

Table XV. Tetralin-Based Compounds with Modified Hydantoin Rings

no.	A	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
2				10 ⁻⁴ -10 ⁻⁵	10-25
87 ^d		139-141	C ₁₆ H ₁₆ N ₂ O ₂	>10 ⁻⁴	25
88 ^e		251-254	C ₁₂ H ₁₂ N ₂ S ₂	>10 ⁻⁴	>25 (1)* ^j
89 ^e		219-220	C ₁₂ H ₁₂ N ₂ O _S	>10 ⁻⁴	
90 ^e		148-150	C ₁₃ H ₁₅ NO	>10 ⁻⁴	>25 (26)
91 ^{f,g}		153-156	C ₁₃ H ₁₃ N ₂ O ₂	>10 ⁻⁴	5
92 ^g		173-175	C ₁₄ H ₁₅ N ₂ O ₂	>10 ⁻⁴	>25 (23)
93 ^h		182-183	C ₁₂ H ₁₄ N ₂ O	>10 ⁻⁴	25
94 ⁱ		170-172	C ₁₃ H ₁₇ N ₂ O ₂	10 ⁻⁵	>50 (-17)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dPrepared by methylation of 2; see Experimental Section, Section B. ^eSee Experimental Section, Section B. ^fSandberg, R. V. U.S. Patent 3 507 881; *Chem. Abstr.* 1973, 78, p 15890z. ^gSarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. ^hSarges, R.; Belletire, J. L. U.S. Patent 4 283 409, Aug 11, 1981. ⁱSchnur, R. C. U.S. Patent 4 226 875, Oct 7, 1980. ^j(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

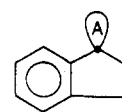
Varian T-60 and XL-100 spectrometers with TMS as internal standard; the solvent was CDCl₃ unless otherwise indicated. IR spectra were obtained on a Perkin-Elmer Model 21 spectrometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer.

Section A. Preparation of Hydantoin (Tables III-XIII).

General Method A. A mixture of 0.1 mol of ketone (e.g., 1-indanone), 9.75 g (0.15 mol) of KCN, and 28.8 g (0.3 mol) of powdered (NH₄)₂CO₃ in 200 mL of 50% aqueous EtOH was heated in an oil bath at 55-75 °C for 24 h. The reaction mixture was then diluted with 800 mL of H₂O, boiled for 15 min, cooled to room temperature, and poured into 600 mL of ice-cold 6 N HCl. The precipitate was filtered, washed with H₂O, dried, and recrystallized (e.g., from MeOH-EtOH-Et₂O) to afford the hydantoin (e.g., spiro[imidazolidine-4,1'-indan]-2,5-dione).

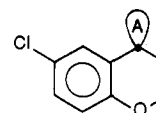
General Method B. A mixture of 0.1 mol of ketone, 0.15 mol of KCN, and 0.7 mol of (NH₄)₂CO₃ in 140 mL of EtOH was placed in a stainless steel bomb and heated at 110 °C for 20-48 h. After cooling, the mixture was poured into 700 mL of H₂O and acidified with 6 N HCl to pH 2. The precipitated product was filtered and recrystallized as described above.

Section B. Preparation of Specific Compounds in Tables VIII-XXI. 2,3-Dihydro-6-(methylsulfonyl)spiro[4*H*-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (40). A mixture of 1.22 g (5.6 mmol) of 5 and 906 mg (5.2 mmol) of methanesulfonic

Table XVI. Indan-Based Compounds with Modified Hydantoin Rings

no.	A	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
4				10 ⁻⁴ -10 ⁻⁵	10-25
95 ^d		124-126	C ₁₂ H ₁₅ N· C ₄ H ₄ O ₄ ^e	>10 ⁻⁴	>25 (-23)* ^h
96 ^d		197-199.5	C ₁₁ H ₁₂ N ₂ O	>10 ⁻⁴	
97 ^f		148-150	C ₁₂ H ₁₁ NO ₂	>10 ⁻⁴	>2.5 (28)
98 ^g		163-164.5	C ₁₁ H ₉ NO ₃	10 ⁻⁴ -10 ⁻⁶	>25 (22)*

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSee Experimental Section, Section B. ^eMaleic acid. ^fSarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. ^gSchnur, R. C. U.S. Patent 4 226 875, Oct 7, 1980. ^h(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

Table XVII. Chroman-Based Compounds with Modified Hydantoin

no.	A	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
33				10 ⁻⁷	0.25-0.75
99 ^d		222-224	C ₁₁ H ₁₁ ClN ₂ O ₂ · 1/2 H ₂ O	10 ⁻⁵	>10 (15)* ⁱ
100 ^e		107 dec	(C ₁₂ H ₉ ClN ₂ O ₄)/	10 ⁻⁴ -10 ⁻⁵	>10 (-5)*
101 ^f		225-226.5	C ₁₂ H ₁₀ ClNO ₃	<10 ⁻⁴	>5 (13)*
102 ^h		196-198	C ₁₁ H ₉ ClNO ₄	10 ⁻⁶ -10 ⁻⁷	>1.5 (28)

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dPrepared in 28% yield from 33 by the method described for 96 in the Experimental Section, Section B. ^eSee Experimental Section, Section B. ^fBy high-resolution mass spectrometry. ^gSarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. ^hSchnur, R. C. U.S. Patent 4 200 642, April 29, 1980. ⁱ(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

anhydride in 10 mL of tetrachloroethylene was refluxed for 18 h according to Gilbert.¹⁴ After cooling, 10 mL of H₂O was added and the mixture made basic with 2 N NaOH. The aqueous layer was acidified with 6 N HCl to precipitate 460 mg of 5. Extraction of the filtrate with EtOAc provided, after evaporation, 560 mg of 5 mixed with a small amount of product, which was isolated

(14) Gilbert, E. E. *J. Org. Chem.* 1963, 28, 1945.

Table XVIII. Carboxylic Acids

no.	no. of corresponding hydantoin	structure	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
103 ^d	2		82-84	C ₁₁ H ₁₂ O ₂	>10 ⁻⁴	
104 ^e	4		51-53	C ₁₀ H ₁₀ O ₂	>10 ⁻⁴	
105 ^f	5		90-91.5	C ₁₀ H ₁₀ O ₃	10 ⁻⁴	
106 ^g	11		128-130	C ₁₀ H ₁₀ O ₂	10 ⁻⁴	
107 ^h	32		118-119	C ₁₀ H ₉ FO ₃	10 ⁻⁴ -10 ⁻⁶	>25 (11)* ^j
108 ^h	33		90-90.5	C ₁₀ H ₉ ClO ₃	10 ⁻⁵ -10 ⁻⁶	>25 (28)
109 ^h	37		124.5-126	C ₁₀ H ₈ Cl ₂ O ₃	10 ⁻⁵	
110 ^h	55		95-96	C ₁₁ H ₁₁ ClO ₃	10 ⁻⁵ -10 ⁻⁶	
111 ⁱ	6		78-80	C ₁₀ H ₁₀ O ₂ S	10 ⁻⁴	
112 ^h	58		153-154	C ₁₀ H ₉ ClO ₂ S	<10 ⁻⁴	
113 ^h	62		157-161	C ₁₀ H ₈ Cl ₂ O ₂ S	10 ⁻⁵	
114 ^h	75		141-142	C ₁₄ H ₁₁ ClO ₃	10 ⁻⁶	>25 (12)

^aAll new compounds were analyzed C, H. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dBeilstein, 4th ed. 1927, 9, 625. ^eBeilstein, 4th ed. 1949, 9, II, 411. ^fPrepared in 33% yield from 2,3-dihydro-4H-1-benzopyran-4-one by the method described in ref h; G. Fontaine noted mp 66 °C: Chem. Abstr. 1968, 69, 106536v. ^gBeilstein, 4th ed. 1927, 9, 620. ^hBelletire, J. L. U.S. Patent 4 210 663, July 1, 1980. ⁱPrepared from 2,3-dihydro-4H-1-benzothiopyran-4-one in 26% yield by the method described in ref h. ^j(*) The inhibition was not statistically significant (Student's *t* test) at the *p* < 0.05 level.

by silica gel chromatography with EtOAc-hexane, 1:3. After recrystallization from MeOH, 34 mg (2%) of **40** was obtained: mp >300 °C; MS, *m/e* 296; NMR (DMSO-*d*₆) δ 2.3 (m, 2 H), 3.15 (s, 3 H), 4.2-4.8 (m, 2 H), 7.15 (d, *J* = 9 Hz, 1 H), 7.65 (d, *J* = 3 Hz, 1 H), 7.8 (d of d, *J* = 3, 9 Hz, 1 H), 8.6 (s, 1 H). Anal. (C₁₂H₁₂N₂O₅S) C, H, N.

2,3-Dihydro-6-[(dimethylamino)sulfonyl]spiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (47). Compound **5** (760 mg, 3.5 mmol) was added slowly to 5 mL of chlorosulfonic acid, and the resultant yellow solution was stirred at room temperature for 30 min and then poured over 100 mL of ice. The mixture was extracted with EtOAc to give, after drying over MgSO₄ and evaporation, 770 mg (71%) of the crude 6-chlorosulfonyl derivative, mp 260-265 °C dec, which was used as such. Heating the reaction mixture to 80 °C for 2 h gave the 6,8-bis(chlorosulfonyl) derivative.

The chlorosulfonyl compound (140 mg, 0.44 mmol) was suspended in 5 mL of CHCl₃ and treated with dimethylamine gas. After the reaction mixture was stirred at room temperature for 1 h, the solution was evaporated and the residue dissolved in 2 N NaOH. After extraction with EtOAc, the aqueous layer was acidified with 6 N HCl and extracted with EtOAc. The organic layer gave, after drying, evaporation, and recrystallization of the residue from EtOH, 40 mg (28%) of **47**, mp 221-223 °C. Anal. (C₁₃H₁₅N₃O₅S) C, H, N.

N-(Aminocarbonyl)-2,3-dihydro-1H-indene-1-carboxamide (84). 1-Indancarboxylic acid¹⁶ (2 g, 0.0124 mol) and 5 mL of SOCl₂ were refluxed in 5 mL of CH₂Cl₂ for 5 h. The reaction mixture

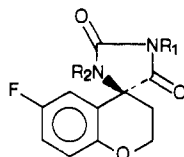
(15) Knowles, W. S.; Kuck, J. A.; Elderfield, R. C. *J. Org. Chem.* 1942, 7, 374.

Table XIX. Enantiomers of Key Compounds

no.	structure	$[\alpha]_D$	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
32		±			10 ⁻⁶	0.75
115 ^d		+54 (MeOH)	241-243	C ₁₁ H ₉ FN ₂ O ₃	2.6 × 10 ⁻⁷	0.25
116 ^d		-54.8 (MeOH)	241-243	C ₁₁ H ₉ FN ₂ O ₃	10 ⁻⁵ -10 ⁻⁶	25
57		±			10 ⁻⁶ -10 ⁻⁷	1.5
117 ^d		+71.8 (MeOH)	224-226	C ₁₁ H ₉ FN ₂ O ₂ S	<10 ⁻⁷	0.75
118 ^d		-73.8 (MeOH)	223-225	C ₁₁ H ₉ FN ₂ O ₂ S	10 ⁻⁵ -10 ⁻⁶	
102		±			10 ⁻⁶ -10 ⁻⁷	>1.5 (28)
119 ^e		-61.6 (EtOH)	200-200.5	C ₁₁ H ₈ ClNO ₄	10 ⁻⁷	2.5
120 ^e		+60.5 (EtOH)	200-201.5	C ₁₁ H ₈ ClNO ₄	10 ⁻⁴ -10 ⁻⁵	

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I. ^cSee footnote b in Table I. ^dSarges, R. U.S. Patent 4 130 714, Dec 19, 1978. ^eSchnur, R. C. U.S. Patent 4 200 642, April 29, 1980.

Table XX. N-Methylated Derivatives of Sorbinil



no.	R ₁	R ₂	mp, °C	formula ^a	in vitro IC ₅₀ , ^b M	in vivo ED ₅₀ , ^c mg/kg
115	H	H	241-243	C ₁₁ H ₉ FN ₂ O ₃	5 × 10 ⁻⁷	0.25
121 ^d	Me	H	220-224	C ₁₂ H ₁₁ FN ₂ O ₃	>10 ⁻⁴	<10 (89)
122 ^d	H	Me	142-143	C ₁₂ H ₁₁ FN ₂ O ₃	10 ⁻⁴	<10 (96)
123 ^d	Me	Me	^e	C ₁₃ H ₁₃ FN ₂ O ₃	>10 ⁻⁴	<10 (74)

^aAll new compounds were analyzed for C, H, N. ^bSee footnote a in Table I; the values in this table were obtained with aldose reductase isolated from human placenta. ^cSee footnote b in Table I. ^dSee Experimental Section, Section B. ^eOil, bp 110 °C (0.1 mmHg).

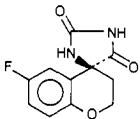
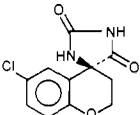
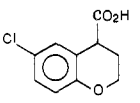
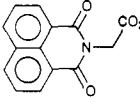
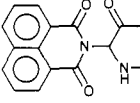
was distilled in vacuo to give an oil, 1.72 g (78%), bp_{0.02} 95-105 °C, which was added to a solution of urea (1.4 g, 0.19 mol) in 5 mL of dry DMF. After being heated for 12 h at 30 °C, the mixture was partitioned between 100 mL of CH₂Cl₂ and 50 mL of H₂O. The organic phase was washed with 50 mL of H₂O, 3 × 50 mL of 5% NaHCO₃, and 50 mL of brine, dried (Na₂SO₄), treated with decolorizing carbon, filtered, and evaporated in vacuo to yield a residue, which was crystallized from dimethoxyethane to give 0.22 g (11%) of 84: mp 217-218 °C; IR (cm⁻¹) 1675; NMR δ, 2.2-2.5 (m, 2 H), 2.7-3.3 (m, 2 H), 4.04 (m, 1 H), 7.1-7.4 (m, 4 H); MS, *m/e*, 204. Anal. (C₁₁H₁₂N₂O₂) C, H, N.

2,3-Dihydro-1-(formylamino)-1H-indene-1-carboxamide (85). 1-Amino-2,3-dihydro-1H-indene-1-carboxylic acid (2.00 g, 0.0113 mol), prepared from compound 4 by the method of Connors,¹⁶ was esterified by heating it at reflux in 50 mL of HCl-

saturated MeOH for 72 h, using 3A molecular sieves (~100 g, Linde) in a Soxhlet extractor to remove H₂O. The cooled reaction mixture was diluted with 150 mL of MeOH and 150 mL of Et₂O, filtered, and evaporated in vacuo to an oil, which crystallized from acetone to give 2.27 g (88%) of product, mp 203-204 °C dec. The crude ester hydrochloride (1.8 g, 7.91 mmol) was dissolved in 10 mL of MeOH and 10 mL of liquid NH₃ at -33 °C. After 4 h, the mixture was evaporated and the residue triturated with pentane to give 243 mg (17%) of the amino amide, mp 121-122 °C, which was sufficiently pure for the formylation step. This amino amide (0.1 g, 0.57 mmol) was dissolved in 1.4 mL of formic acid and treated with 0.5 mL of acetic anhydride. After heating at 60 °C for 2 h, the mixture was evaporated in vacuo and the oily residue crystallized from Et₂O to give 100 mg (86%) of compound 85: mp 182-186 °C dec; IR (cm⁻¹) 1690, 1660; NMR δ 2.2-2.5 (m, 1 H), 2.8-3.2 (m, 3 H), 7.1-7.5 (m, 4 H, aromatic), 8.01 (s, 1 H); MS, *m/e* 204. Anal. (C₁₁H₁₂N₂O₄·0.5H₂O) C, H, N.

1-(2,3-Dihydro-1H-inden-1-yl)-3-formylurea (86). 1-(2,3-

Table XXI. Correlation of pK_a and Biological Activity

no.	structure	A: isolated enzyme $IC_{50},^a$ M	B: isolated nerve $IC_{50},^b$ M	C: in vivo $ED_{50},^c$ moles/kg, tid	A/B: "tissue penetration"	pK_a in 30% DMF-H ₂ O
115		1.5×10^{-7}	10^{-6}	10^{-6}	0.15	8.7
119		10^{-7}	10^{-5}	10^{-5}	0.01	5.6
108		10^{-5} - 10^{-6}	10^{-2} - 10^{-3}	$>10^{-4}$	~ 0.001	4.9
alrestatin		10^{-6}	10^{-3}	10^{-3}	0.001	4.8
124 ^d		$8 \times 10^{-6}^e$	$\sim 10^{-5}$	$>10^{-4}$	~ 0.8	9.5

^a Molar concentration that causes a 50% inhibition of isolated calf lens aldose reductase.⁸ ^b Molar concentration that causes a 50% decrease in sorbitol accumulation in isolated sciatic nerves incubated in the presence of high (50 mM) glucose concentration.⁸ ^c Dose (expressed in moles/kilogram, tid) that causes a 50% decrease in sorbitol accumulation in sciatic nerve of streptozotocinized rats.⁸ ^d See Experimental Section, Section B. ^e This value was determined against human placenta aldose reductase. The IC_{50} against calf lens aldose reductase would be expected to be somewhat lower; consequently, the A/B ratio might be somewhat lower as well.

Dihydro-1*H*-inden-1-yl)urea¹⁷ (1 g, 5.67 mmol) was dissolved in 14 mL of HCO₂H, and 5 mL of Ac₂O was added. After the reaction mixture was heated at 60 °C for 2 h, the cooled mixture was filtered, diluted with H₂O, and refiltered. The combined solids (0.867 g) were crystallized from toluene to give 504 mg (44%) of **86**: mp 201–203 °C; IR (cm⁻¹) 1770, 1690; NMR δ 1.5–2.2 (m, 1 H), 2.3–3.1 (m, 3 H), 5.25 (q, $J = 8$, 1 H, methine), 7.27 (s, 4 H), 8.87 (s, 1 H); MS, m/e 204. Anal. (C₁₁H₁₂N₂O₄) C, H, N.

3',4'-Dihydro-1,3-dimethylspiro[imidazolidine-4,1'-(2*H*)-naphthalene]-2,5-dione (87). Compound **2** (0.5 g, 2.3 mmol) was dissolved in 10 mL of dry DMF and heated with 220 mg (4.6 mmol) of 50% NaH. After the gas evolution ceased, 652 mg (4.6 mmol) of MeI was added, and the mixture was stirred at room temperature for 1 h and then poured into 100 mL of H₂O. After extraction with Et₂O, drying (MgSO₄), and evaporation, there was obtained 490 mg (87%) of crude **87**, mp 136–138 °C. Recrystallization from benzene-hexane gave material of mp 139–141 °C: MS, m/e 244. Anal. (C₁₄H₁₆N₂O₂) C, H, N.

3',4'-Dihydrospiro[imidazolidine-4,1'-(2*H*)-naphthalene]-2,5-dithione (88). This compound was prepared in 4% yield from 3,4-dihydro-1(2*H*)-naphthalenone according to the method of Carrington:¹⁸ mp 251–254 °C after recrystallization from aqueous MeOH. Anal. (C₁₂H₁₂N₂S₂) C, H, N.

3',4'-Dihydro-5-thioxospiro[imidazolidine-4,1'-(2*H*)-naphthalen]-5-one (89). 1-Amino-3,4-dihydro-(2*H*)-naphthalene-1-carboxylic acid (5.25 g, 0.027 mol); prepared from compound **2** by the method of Connors,¹⁶ was treated with 6.15 g (0.081 mol) of thiourea at 210 °C for 3 h according to the method of Faust.¹⁹ After addition of 3 N HCl to pH 5.5, a tan solid (1.6 g) was obtained, which was purified by silica gel chromatography (benzene-EtOAc, 3:1) to give 628 mg (10%) of **89**: mp 219–220 °C after crystallization from EtOAc-hexane; MS, m/e 232. Anal. (C₁₂H₁₂N₂OS) C, H, N.

3,4-Dihydrospiro[(2*H*)-naphthalene-1,3'-pyrrolidin]-5'-one (90). A solution of 0.5 g (3.2 mmol) of 1,2,3,4-tetrahydro-1-naphthalenecarbonitrile, prepared by the procedure of Protiva,²⁰

in 20 mL of DMF was added to a suspension of 0.16 g of 50% NaH in 3 mL of DMF. After the reaction mixture was heated for 45 min to 50 °C, 0.4 mL of ethyl bromoacetate was added and the mixture stirred at 40 °C for 45 min and at room temperature for 1 h. After dilution with 500 mL of EtOAc, the mixture was washed with 10 \times 50 mL of H₂O, dried (MgSO₄), and evaporated in vacuo to give a residual light yellow oil (m/e 243), which was dissolved in 15 mL each of EtOH, EtOAc, and H₂O, treated with 2 mL of a Raney Ni suspension, and hydrogenated in a Parr apparatus at 50 psi for 16 h. After filtration, evaporation, and recrystallization from EtOAc-hexane, there was obtained 0.5 g (78%) of **90**: mp 148–150 °C; MS, m/e 201. Anal. (C₁₃H₁₅NO) C, H, N.

2,3-Dihydrospiro[1*H*-indene-1,3'-pyrrolidine] (95). A solution of 0.5 g (2.5 mmol) of compound **97** in 75 mL of THF was treated with 0.5 g of lithium aluminum hydride (LAH) and heated under reflux for 16 h. With cooling in an ice bath, 0.5 mL of H₂O, then 0.5 mL of 15% NaOH, and then 1.5 mL of H₂O were added dropwise and the mixture was stirred at room temperature for 30 min. After filtration and washing of the filter cake with hot THF, the organic layers were combined and evaporated in vacuo. The residue (436 mg) was dissolved in Et₂O, 1 equiv of maleic acid dissolved in Et₂O was added slowly, and the precipitated solids were collected and recrystallized from MeOH-Et₂O to give 183 mg (25%) of **95** as the maleate, mp 124–126 °C. Anal. (C₁₂H₁₅N-C₄H₄O₄) C, H, N.

2',3'-Dihydrospiro[imidazolidine-4,4'-[1*H*]inden]-2-one (96). Compound **4** (6 g, 0.030 mol) was added to a mixture of LAH (3.38 g, 0.089 mol) in 200 mL of Et₂O at 0 °C, and the mixture was warmed at reflux for 48 h according to the procedure of Marshall.²¹ The cooled reaction mixture was cautiously quenched with 3.5 mL of H₂O, 3.5 mL of 15% NaOH, and 10.5 mL of H₂O, diluted with 300 mL of hot EtOH, and filtered. The filtrate was concentrated to a residue, which was recrystallized from EtOH-H₂O to give 1.4 g (25%) of **96**: mp 197–199.5 °C; IR (cm⁻¹) 1965; NMR δ 1.9–2.5 (m, 2 H), 2.7–3.0 (m, 2 H), 3.31 (br AB q, $J = 9$ Hz, 2 H), 7.2–7.5 (m, 4 H); MS, m/e 188. Anal.

(17) Takahashi, T.; Fujimura, H.; Okamura, K. *Yakugaku Zasshi* 1962, 82, 1597.

(18) Carrington, H. C. *J. Chem. Soc.* 1947, 681.

(19) Faust, J. A.; Jules, L. H.; Yee, L.; Sahyun, M. *J. Am. Pharm. Assoc.* 1957, 46, 118.

(20) Protiva, M.; Vejdeck, Z.; Jilek, J. O. *Collect. Czech. Chem. Commun.* 1951, 16, 331; *Chem. Abstr.* 1953, 47, 8057b.

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(C₁₁H₁₂N₂O) H, N; C: calcd, 70.19; found, 69.75. Decoupling experiments showed that the broad AB quartet was coupled to only one N-H absorbance.

6-Chloro-2,3-dihydrospiro[4H-1-benzopyran-4,5'-[2H]pyrimidine]-2',4',6'(1'H,3'H)-trione (100). This compound was prepared in three steps from compound 108 by carboxylation according to the procedure of Ivanoff,²² esterification with diazomethane, and treatment of the malonate with urea using the method of Dickey.²³ Compound 108 (2.125 g, 10 mmol) in 70 mL of Et₂O was treated with 3.33 mL of 3 M ethylmagnesium bromide in THF. The heterogeneous mixture was perfused with CO₂ for 10 min. The mixture was then heated, and 35 mL of Et₂O was distilled off along with excess CO₂ and ethane. The mixture was cooled to 0 °C, and 3.33 mL of 3 M ethylmagnesium bromide in THF was added. The solution became homogeneous and was heated at reflux until no further ethane gas evolution occurred. During this heating period a precipitate formed. The reaction mixture was diluted with 100 mL of Et₂O, washed with 100 mL of 1 N H₂SO₄ (all solids dissolved) and 2 × 50 mL of brine, and evaporated in vacuo. The residue was taken up in CHCl₃, and the precipitated crystalline 108 (0.551 g, 22%) was removed by filtration. Addition of CCl₄ to the mother liquor gave 0.4 g (16%) of the desired malonic acid, mp 155–157 °C dec. A second crop of malonic acid (0.363 g, 14%) was obtained from this mother liquor. The malonic acid (0.5 g, 1.95 mmol) was converted to the dimethyl ester by treatment with a 5-fold excess of diazomethane in 30 mL of Et₂O at 0 °C. After 10 min, HOAc was added to remove the excess diazomethane, and the solution was washed with 5 × 50 mL of 5% NaHCO₃ and 2 × 50 mL of brine. The crude solid dimethyl ester (0.425 g, 77%), obtained after evaporation of the dried (MgSO₄) Et₂O solution, was reacted without further purification (spectral analyses corroborated the proposed structure) with potassium *tert*-butoxide (0.167 g, 1.493 mmol) and urea (0.09 g, 1.493 mmol) in 15 mL of Et₂O at reflux for 16 h. After cooling and dilution with Et₂O, the mixture was extracted with 5% NaHCO₃, the aqueous phase was acidified with 6 N HCl and extracted with EtOAc, and the EtOAc layer was concentrated to give 63 mg (12%) of 100: mp 107 °C dec; IR (cm⁻¹) 1709; NMR δ 2.3–2.7 (m, 2 H), 4.2–4.4 (m, 2 H), 6.89 and 7.26 (AB q, *J* = 8 Hz, 2 H), 7.31 (s, 1 H); MS, *m/e* 280.02.

(4S)-6-Fluoro-2,3-dihydro-1'-methylspiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (121) and (4S)-6-Fluoro-2,3-dihydro-1',3'-dimethylspiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (123). A solution of 2.36 g (10 mmol) of 115 in 30 mL of DMF was treated in portions with 960 mg (20 mmol) of 50% NaH. The mixture was stirred at room temperature for 30 min, 1.2 mL (20 mmol) of MeI was added, and stirring was continued for 1 h. After being poured over ice-water, the mixture was extracted with EtOAc. Drying (MgSO₄) and evaporation of the EtOAc extract gave a residue, which yielded, by crystallization from EtOAc-hexane, 550 mg (23%) of 121: mp 220–224 °C; NMR δ 2.0–2.5 (m, 2 H), 3.1 (s, 3 H), 4.0–5.0 (m, 2 H), 6.6–7.0 (m, 3 H), 8.8 (br s, 1 H). Anal. (C₁₂H₁₁FN₂O₃) C, H, N. The mother liquor of 121 was purified by chromatography on SiO₂ with CHCl₃ to give 1.4 g (53%) of 123 as an oil: bp 110 °C (0.1 mmHg); NMR δ 2.0–2.6 (m, 2 H), 2.8 (s, 3 H), 3.1 (s, 3 H), 4.0–5.0 (m, 2 H), 6.6–7.0 (m, 3 H). Anal. (C₁₃H₁₃FN₂O₃) C, H, N.

(4S)-6-Fluoro-2,3-dihydro-3'-methylspiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (122). A solution of 3.7 g (14 mmol) of 123 in 20 mL of EtOH was heated with 40 mL of 20% NaOH in a bomb at 120–130 °C for 2 days. After cooling, the bomb contents were concentrated in vacuo, acidified with HCl, washed with EtOAc, and concentrated to dryness. The residue was triturated with MeOH to give 1.8 g (57%) of (4S)-6-fluoro-4-(methylamino)-4H-1-benzopyran-4-carboxylic acid: mp 259–261 °C; MS, *m/e* 225. A 500-mg (2.2 mmol) portion of this material was suspended in 5 mL of H₂O, 286 mg (4.4 mmol) of NaOCN was added, and the mixture was refluxed for 45 min. After the addition of 2 mL of 12 N HCl, the mixture was heated for 1 h, allowed to cool, diluted with H₂O, and extracted with EtOAc.

After drying (MgSO₄) and evaporation, the residue was crystallized from Et₂O-cyclohexane to give 180 mg (33%) of 122: mp 142–143 °C; NMR δ 2.0–2.5 (m, 2 H), 2.8 (s, 3 H), 4.0–5.0 (m, 2 H), 6.6–7.0 (m, 3 H), 9.7 (br s, 1 H). Anal. (C₁₂H₁₁FN₂O₃) C, H, N.

5-Naphthalimidoimidazolidine-2,4-dione (124). 5-Chlorohydantoin was prepared according to the method of Abblard et al.²⁴ by reduction of parabanic acid with KBH₄ (NaBH₄ gave unsatisfactory results) and treatment of the resultant 5-hydroxyhydantoin with SOCl₂. Efforts to obtain 124 directly by reaction of 5-chlorohydantoin with naphthalimide failed. However, when 5-hydroxyhydantoin (2.57 g, 0.022 mol) was refluxed with 30 mL of SOCl₂ and 3 drops of DMF overnight, the mixture evaporated to dryness, and the residue slurried in 30 mL of nitromethane and warmed to 50 °C for 3 h after addition of 3.3 g (0.022 mol) of benzyl carbamate in 50 mL of nitromethane, there was obtained, after evaporation and crystallization of the residue from hot H₂O, 1.97 g (36%) of 5-[(benzyloxycarbonyl)amino]-hydantoin: mp 178–180 °C dec; MS, *m/e* 249. Anal. (C₁₁H₁₁N₃O₄) C, H, N.

Removal of the amine-protecting group was best accomplished by HBr-AcOH cleavage, since catalytic hydrogenation attempts led to precipitation of the poorly soluble 5-aminohydantoin onto the catalyst. Thus was obtained, by treating 100 mg (0.4 mmol) with 1 mL of 30% HBr in AcOH for 30 min at room temperature, followed by precipitation with Et₂O, 72 mg (92%) of 5-aminohydantoin hydrobromide: mp >250 °C; MS, *m/e* 115. Anal. (C₇H₅N₃O₂·HBr) C, H, N. Reaction of 250 mg (1.3 mmol) of this compound with 200 mg (1 mmol) of naphthalic anhydride in 12.5 mL of pyridine at 40 °C for 8 h and at 120 °C for 1 h gave, after evaporation, trituration with EtOH, and recrystallization from THF, 160 mg (54%) of 124: mp 290–292 °C dec; MS, *m/e* 295. Anal. (C₁₅H₉N₃O₄·1/2H₂O) C, H, N.

Section C. Preparation of Starting Materials (SM). **8-Fluoro-2,3-dihydro-4H-1-benzopyran-4-one (SM for 35).** The procedure of Ricci et al.²⁵ was used to convert 2-fluorophenol to 3-(2-fluorophenoxy)propanenitrile (oil, 52% yield), 3-(2-fluorophenoxy)propanoic acid (mp 109–111 °C; 59%; anal. (C₉H₉FO₃) C, H), and ultimately to the title compound, mp 84–87 °C, in 86% yield. Anal. (C₉H₇FO₂) C, H.

6-(Aminocarbonyl)-2,3-dihydro-4H-1-benzopyran-4-one (SM for 48). To a refluxing solution of 25 g (0.21 mol) of 4-cyanophenol in 105 mL of 2 N NaOH was added dropwise over 15 min an ice-cold solution of 45.6 g (0.42 mol) of 3-chloropropanoic acid in 210 mL of 2 N NaOH. The pH was then kept at 10.0 by the periodic addition of 5 N NaOH while the reaction mixture was kept at reflux for 1 h. After cooling, the mixture was washed with EtOAc, acidified with 3 N HCl, and extracted with EtOAc. The EtOAc layer was extracted with aqueous NaHCO₃, the aqueous phase was acidified with 3 N HCl, and the precipitated solids were collected by filtration to give 13 g (32%) of 3-(4-cyanophenoxy)propanoic acid (mp 138–142 °C dec; MS, *m/e* 191; contaminated with some of the 4-aminocarbonyl acid). The filtrate upon standing gave 1.7 g (4%) of 3-[4-(aminocarbonyl)phenoxy]propanoic acid: mp 218–220 °C; MS, *m/e* 209. Anal. (C₁₁H₁₁NO₄) C, H, N. Cyclization of 12 g of the mixture of nitrilo and aminocarbonyl acids with polyphosphoric acid (PPA) at 100 °C for 15 min gave, after workup and two crystallizations from EtOH, 4.9 g of the title compound: mp 224–226 °C; MS, *m/e* 191. Anal. (C₁₀H₉NO₃) C, H, N.

2,3-Dihydro-7-(trifluoromethyl)-4H-1-benzopyran-4-one (SM for 52). 3-(Trifluoromethyl)phenol was reacted with 3-chloropropanoic acid as described above to give in 31% yield 3-[3-(trifluoromethyl)phenoxy]propanoic acid, mp 84–86 °C after crystallization from hexane: MS, *m/e* 215. Anal. (C₁₀H₇F₃O₃) C, H. Cyclization in PPA at 100 °C for 5 min gave in 80% yield a mixture of the 5- and 7-substituted ketones, which was separated by silica gel chromatography with hexane-CHCl₃, 4:1, to give ultimately, after sublimation, the clean 7-isomer: mp 60–63 °C; MS, *m/e* 216; NMR δ 2.8 (t, *J* = 8 Hz, 2 H), 4.6 (t, *J* = 8 Hz, 2 H), 7.1–7.3 (m, 2 H), 7.95 (d, *J* = 9 Hz, 1 H). Anal. (C₁₀H₇F₃O₂·1/8H₂O) C, H.

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2,3-Dihydro-6-(piperidinylmethyl)-4H-1-benzopyran-4-one (SM for 53). A mixture of 12.8 g (0.08 mol) of 3-(4-methylphenoxy)propanenitrile,²⁶ 14.5 g of *N*-bromosuccinimide, and 0.5 g of benzoyl peroxide in 200 mL of CCl₄ was refluxed for 48 h, filtered hot, and allowed to cool. The precipitated solids (14.6 g; NMR consistent with bromomethyl derivative) were collected, and 10 g of them were dissolved in 30 mL of CH₂Cl₂ and 30 mL of piperidine. After 3 days at room temperature, the precipitated solids were removed by filtration, the filtrate was evaporated in vacuo, and the residue (20 g) was purified by silica gel chromatography with EtOAc and the with toluene-MeOH, 4:1, to give, after crystallization from hexane, 5.4 g of 3-[4-(piperidinylmethyl)phenoxy]propanenitrile: mp 56–58 °C; IR (cm⁻¹) 2250. Anal. (C₁₅H₂₀N₂O) C, H, N. Hydrolysis of the nitrile (2 g, 8 mmol) with 20 mL of formic acid and 20 mL of 12 N HCl at reflux for 3 h gave 2.4 g (98%) of 3-[4-(piperidinylmethyl)phenoxy]propanoic acid hydrochloride: mp 187–190 °C; IR (cm⁻¹) 1720. Anal. (C₁₅H₂₁NO₃·HCl) C, H, N. This compound, after cyclization in anhydrous HF, gave 2.2 g of the title compound as an oil: MS, *m/e* 245; IR (cm⁻¹) 1720; NMR δ 1.4 (br s, 6 H), 2.1–2.4 (m, 4 H), 2.6 (t, *J* = 7 Hz, 2 H), 3.3 (s, 2 H), 4.4 (t, *J* = 8 Hz, 2 H), 6.8 (d, *J* = 9 Hz, 1 H), 7.4 (d of d, *J* = 9 Hz, 1 H), 7.65 (d, *J* 2 Hz, 1 H).

6-Chloro-2,3-dihydro-8-methyl-4H-1-benzopyran-4-one (SM for 55). The method of Ricci²⁵ was used to convert 2-methyl-4-chlorophenol to 3-(2-methyl-4-chlorophenoxy)propanenitrile (mp 57–59 °C from EtOH-H₂O; 72% yield; anal. (C₁₀H₁₀ClNO) C, H, N) and 3-(2-methyl-4-chlorophenoxy)propanoic acid (mp 103–105 °C from EtOH-H₂O; 98% yield; anal. (C₁₀H₁₂ClO₃) C, H). Cyclization in anhydrous HF gave the title compound in 81% yield: mp 53–54 °C from hexane. Anal. (C₁₀H₉ClO₂) C, H.

8-Chloro-2,3-dihydro-8-methoxy-4H-1-benzopyran-4-one (SM for 56). The method of Ricci²⁵ was used to convert 2-chloro-5-methoxyphenol to 3-(2-chloro-5-methoxyphenoxy)propanoic acid in 21% yield: mp 105–106.5 °C from cyclohexane. Anal. (C₁₀H₁₁ClO₄) C, H. Cyclization in anhydrous HF afforded the title compound in 79% yield: mp 143.5–144.5 °C from *i*-PrOH. Anal. (C₁₀H₉ClO₃) C, H.

6,8-Dichloro-2,3-dihydro-4H-1-benzothiopyran-4-one (SM for 63). 2,4-Dichlorobenzene²⁷ (prepared from 2,4-dichloroaniline) was converted by the method of Ricci²⁵ to 3-[(2,4-dichlorophenyl)thio]propanoic acid: mp 117.5–118.5 °C from EtOAc-hexane. Anal. (C₉H₆Cl₂O₂S) C, H. Then this compound was cyclized with concentrated sulfuric acid (3 h, room temperature) to give in 72% yield the title compound: mp 83.5–84.5 °C from cyclohexane. Anal. (C₉H₆Cl₂OS) C, H.

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Registry No. 1, 5991-46-8; 2, 57998-96-6; SM for 2, 529-34-0; 3, 109402-17-7; SM for 3, 826-73-3; 4, 6252-98-8; SM for 4, 83-33-0; 5, 66892-54-4; 5 (6-chlorosulfonyl deriv.), 11140-82-0; 5 (6,8-bis(chlorosulfonyl deriv.)), 11141-08-3; SM for 5, 491-37-2; 6, 66892-42-0; SM for 6, 3528-17-4; 7, 66892-64-6; 8, 11140-42-2; SM for 8, 1198-15-8; 9, 11140-43-3; SM for 9, 4832-16-0; 10, 702-62-5; SM for 10, 108-94-1; 11, 27473-61-6; SM for 11, 615-13-4; 12, 5007-34-1; SM for 12, 1198-34-1; 13, 57-41-0; 14, 70585-42-1; SM for 14, 16806-93-2; 15, 69300-50-1; SM for 15, 13414-95-4; 16, 66892-50-0; SM for 16, 53400-41-2; 17, 11140-44-4; SM for 17, 13754-86-4; 18, 11140-45-5; SM for 18, 11141-07-2; 19, 66892-38-4; SM for 19, 1481-32-9; 20, 66892-41-9; SM for 20, 5111-70-6; 21, 66892-37-3; SM for 21, 13623-25-1; 22, 66892-39-5; SM for 22, 2107-69-9; 23, 11140-46-6; SM for 23, 38472-90-1; 24, 66892-40-8; SM for 24, 6412-87-9; 25, 66892-53-3; 26, 66892-59-9; SM for 26, 33892-75-0; 27, 30265-10-2; SM for 27, 1078-19-9; 28, 66892-51-1; SM for 28, 6836-19-7; 29, 66892-52-2; SM for 29, 13575-75-2; 30, 11140-47-7; SM for 30, 34910-81-1; 31, 11140-48-8; SM for 31,

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