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 ($CHCl_3$–EtOH, 9:1); MS, m/z 347 ([M – CH_2Cl]$^+$, 1.0), 243 ([M + 2 – Ts]$^+$, 1.6), 241 ([M – Ts]$^+$, 4.3), 213 ([M + 2 – $TsOCH_2$]$^+$, 34), 211 ([M – $TsOCH_2$]$^+$, 100). Anal. ($C_{14}H_{22}ClN_2O_5PS$) C, H, N, P.

***N*-(2-Acetoxyethyl)-3-(2-chloroethyl)tetrahydro-2*H*-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% $KHCO_3$ (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 ($CHCl_3$–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 $CHCl_3$–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: ^{31}P NMR ($CHCl_3$) δ 12.4; ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$–EtOH, 9:1); MS, m/z 287 ([M + 3]$^+$, 0.6), 285 ([M + 1]$^+$, 1.3), 235 ([M – CH_2Cl]$^+$, 43), 226 ([M + 3 – AcO]$^+$, 66), 224 ([M + 1 – AcO]$^+$, 20), 215 ([M + 2 – $AcOCH_2$]$^+$, 60), 213 ([M – $AcOCH_2$]$^+$, 20). Anal. ($C_9H_{18}ClN_2O_4P$) C, H, N, P.

***N*-(2-Fluoroethyl)phosphoramidic Dichloride (23).** A stirred suspension of 2-fluoroethylamine hydrochloride (5.0 g, 50 mmol) in $POCl_3$ (25 mL) was heated under reflux for 3 h. The excess of $POCl_3$ 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); ^{1}H NMR ($CDCl_3$) δ 3.0–3.9 (m, 2, NCH_2), 4.5 (m, $^2J_{HF}$ = 48 Hz, $^3J_{HH}$ = 6 Hz, $^4J_{HP}$ = 2 Hz, 2, CH_2F), 5.8 (s, 1, NH); ^{31}P NMR ($CHCl_3$) δ 16.6; MS, m/z 179 (M^+, 1), 146 ([M – CH_2F]$^+$, 100), 117 ([M – FCH_2CH_2NH]$^+$, 28).

3-(2-Chloroethyl)-*N*-(2-fluoroethyl)tetrahydro-2*H*-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 $CHCl_3$ (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 $CHCl_3$–EtOH (18:1) as eluent and recrystallized from Et_2O. Compound **23** (1.2 g) was obtained in 30% yield: mp 56–57 °C; ^{31}P NMR ($CHCl_3$) δ 12.2; ^{1}H 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 – CH_2Cl]$^+$, 41), 134 (16), 83 (43), 31 (100). Anal. ($C_7H_{15}ClFN_2O_2P$) C, H, N. P.

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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

Reinhard Sarges,* Rodney C. Schnur, John L. Belletire,† and Michael J. Peterson

Pfizer Central Research, Groton, Connecticut 06340. *Received June 8, 1987*

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-4*H*-1-benzopyran-4-ones (4-chromanones). In 2,4-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione, the activity resides exclusively in the 4*S* 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 C_6–C_8 fatty acids and their derivatives were disclosed as inhibitors of calf lens aldose reductase.[3] Tetramethyleneglutaric acid (TMG) was reported in 1968 to be an aldose reductase inhibitor which, in contrast to the C_6–C_8 fatty acids, was active and also less toxic in lens cultures,[4a] although TMG failed to dem-

† Current address: Department of Chemistry, University of Cincinnati, Cincinnati, OH 45221.

(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.

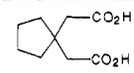
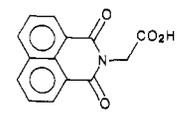
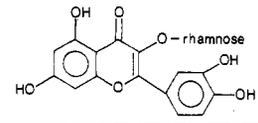
(2) (a) Van Heyningen, R. *Nature (London)* **1959**, *184*, 194. (b) Kinoshita, J. H. *Invest. Ophthalmol.* **1965**, *4*, 786. (c) Gabbay, K. H.; O'Sullivan, J. B. *Diabetes* **1968**, *17*, 239. (d) Beaumont, P.; Hollows, F. C.; Schofield, P. J.; Williams, J. F.; Steinbeck, W. *Lancet* **1971**, *1*, 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.

0022-2623/88/1831-0230$01.50/0

Table I. Aldose Reductase Inhibitors from the Literature

		in vitro act. reported: IC_{50}	found activity: in vitro IC_{50},[a] M	found activity: 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]

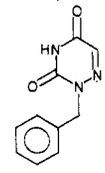
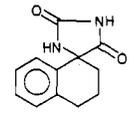
[a] Concentration that causes a 50% inhibition of partially purified calf lens aldose reductase with glyceraldehyde as substrate. Single determination; the reproducibility of the assay did not vary by more than 10%.[8] [b] Oral dose, given tid, that causes a 50% reduction in sorbitol levels of sciatic 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 reductase[3] and the screening of structural prototypes for in vitro inhibitory activity. Agents active at 10^{-5} M were then further evaluated for 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.

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]

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,

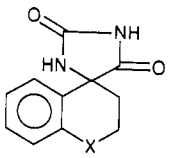
(5) Dvornik, D.; Simard-Duquesne, N.; Krami, M.; Sestanj, K.; Gabbay, J. H.; Kinoshita, J. H.; Varma, S. D.; Merola, L. O. *Science (Washington, D.C.)* **1973**, *182*, 1146.

(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. Offenlegungschrift 2611824, 1976. (b) Brittain, D. R.; Wood, R. Eur. Pat. Appl. 2895; *Chem. Abstr.* **1980**, *92*, 76533*w*. (c) Sestanj, K.; Abraham, N. A.; Bellini, F.; Treasurywala, A.; Humber, L. G. Eur. Pat. 59–596. (d) Kikkawa, R.; Haanaka, I.; Yasuda, H.; Kobayashi, N.; Shigeta, Y.; Terashima, H.; Morimura, T.; Tsobushima, 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. 92385.

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

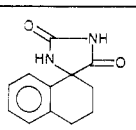
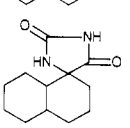
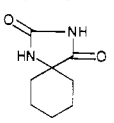
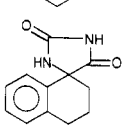
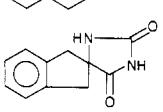
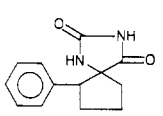
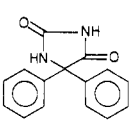
Table III. Spiro Hydantoins with Modified Hydantoin-Bearing Rings



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	$C_{12}H_{12}N_2O_2$	A	84	10^{-4}–10^{-5}	10–25
3[e]	CH_2CH_2	257–260	$C_{13}H_{14}N_2O_2$	B	22	$>10^{-4}$	>25 (9)*[j]
4[f]	–	238–240	$C_{11}H_{10}N_2O_2$	A	76	10^{-4}–10^{-5}	5
5[g]	O	236–238	$C_{11}H_{10}N_2O_3$	A	35	10^{-5}	5
6[g]	S	225–227	$C_{11}H_{10}N_2O_2S$	B	53	10^{-5}	5–10
7[h]	SO_2	280–281	$C_{11}H_{10}N_2O_4S$		49	10^{-5}–10^{-6}	20
8[j]	NMe	249 dec	$C_{12}H_{13}N_3O_2$·HCl		24	10^{-4}–10^{-5}	>25 (0)*

[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] See footnote *d* in Table II. [e] Huisgen, R.; Ugi, I. *Justus Liebigs Ann. Chem.* **1957**, *610*, 57. [f] Henze, H. R; Speer, R. J. *J. Am. Chem. Soc.* **1942**, *64*, 522. [g] Arnold, H.; Kuehas, E.; Brock, N. German Auslegeschr. 1135915, Sept 6, 1962; *Chem. Abstr.* **1963**, *58*, P 3440*a*. [h] Prepared by oxidation of **6**; for method, cf.: Sarges, R. U.S. Patent 4117230, Sept 26, 1978. [i] Sarges, R. U.S. Patent 4235911, Nov 25, 1980. [j] (*) The inhibition was not statistically significant (Student's *t* test) at the $p < 0.05$ level.

Table IV. Hydantoins 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	$C_{12}H_{18}N_2O_2$	B	26	$>10^{-4}$	<25 (13)*[h]
10[e]		215–217	$C_8H_{12}N_2O_2$	A	95	10^{-4}	>25 (19)
4						10^{-4}–10^{-5}	5
11[f]		263–265	$C_{11}H_{10}N_2O_2$	A	53	$>10^{-4}$	>25 (9)*
12[g]		219–221	$C_{13}H_{14}N_2O_2$	B	22	$>10^{-4}$	>25 (4)*
13						$>10^{-4}$	>250 (14)*

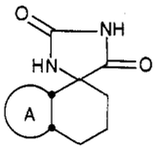
[a] All new compounds were analyzed for C, H, N. [b] See footnote *a* in Table I. [c] See footnote *b* in Table I. [d] Cremlyn, R. J. C.; Chisholm, M. *J. Chem. Soc. C* **1967**, 2269. [e] Herbst, R. M.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 2463. [f] Reference 19. [g] Prepared from 2-phenylcyclopentanone. 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 hydantoins 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.

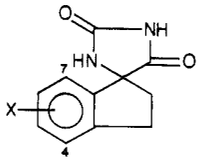
Table V. Hydantoins with Modified Aromatic Rings



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	$C_{10}H_{10}N_2O_3$	B	42	10^{-4}	25
15[e]		266–268	$C_{10}H_{10}N_2O_2S$	B	52	10^{-4}	25
16[f]		275–277 dec	$C_{11}H_{11}N_3O_2$	B	39	10^{-5}	10
17[g]		>300	$C_{10}H_{11}N_3O_2$	B	26	$>10^{-4}$	>25 (9)*[i]
18[h]		>300	$C_{12}H_{15}N_3O_2$	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(5*H*)-one. Stetter, H.; Lauterbach, R. *Justus Liebigs Ann. Chem.* **1962**, *655*, 20. [h] Prepared from 6,7-dihydro-1,2-dimethylindol-4(5*H*)-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 Hydantoins



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^{-5}	5
19[d]	6-F	255–257	$C_{13}H_9FN_2O_2$	B	5	10^{-4}–10^{-5}	5
20[d]	5-OMe	167–169	$C_{12}H_{12}N_2O_3$	B	19	10^{-5}	>25 (23)*[g]
21[d]	6-OMe	192–194	$C_{12}H_{12}N_2O_3$	B	14	10^{-5}	10
22[d]	5,6-$(OMe)_2$	246–248	$C_{13}H_{14}N_2O_4$	B	48	10^{-5}–10^{-6}	10
23[e]	5,6,7-$(OMe)_3$	196–197	$C_{14}H_{16}N_2O_5$	B	69	10^{-4}	
24[d]	5,6-OCH_2O	248–250	$C_{12}H_{10}N_2O_4$	B	29	10^{-5}–10^{-6}	>5 (9)*
25[f]	6-OH	253–255	$C_{11}H_{10}N_2O_3$		22	10^{-4}–10^{-5}	>10 (15)*

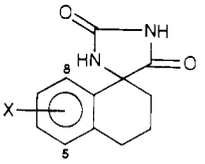
[a] All new compounds were analyzed for C, H, N. [b] See footnote *a* in Table I. [c] See footnote *b* in Table I. [d] Sarges, R. U.S. Patent 4 117 230, Sept 26, 1978. [e] Prepared from 5,6,7-trimethoxy-1-indanone. Dann, O.; Volz, G.; Huber, O. *Justus Liebigs Ann. Chem.* **1954**, *587*, 16. [f] Prepared from treatment of **21** with BBr_3; 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 hydantoins 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 hydantoins, 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 hydantoins).[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.

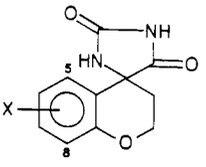
Table VII. Substituted Tetralin Hydantoins



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	$C_{13}H_{14}N_2O_3$	A	74	10^{-5}	>25 (29)
27[e]	6-OMe	219–221	$C_{13}H_{14}N_2O_3$	B	38	10^{-4}–10^{-5}	>25 (17)*[h]
28[f]	7-OMe	227–229	$C_{13}H_{14}N_2O_3$	B	59	10^{-4}	10–25
29[f]	6,7-$(OMe)_2$	238–240	$C_{14}H_{16}N_2O_4$	B	49	10^{-4}–10^{-5}	>5 (3)*
30[g]	5-OMe, 8-Cl	272–274	$C_{13}H_{13}ClN_2O_3$	B	52	$>10^{-4}$	>25 (2)*
31[g]	5-OMe, 8-F	306–308	$C_{13}H_{13}FN_2O_3$	B	31	$>10^{-4}$	>25 (−14)*

[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.; Tretter, J. R.; Tenen, S. S.; Weissman, A. *J. Med. Chem.* **1973**, *16*, 1003. [e] Fletcher, H., III; Russell, P. B.; Alburn, H. E. U.S. Patent 3 532 744, Oct 6, 1970; *Chem. Abstr.* **1971**, *74*, P 42218*k*. [f] Sarges, R. U.S. Patent 4 117 230, Sept 26, 1978. [g] See 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 Hydantoins

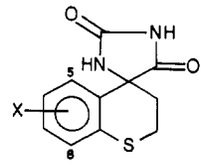


no.	X	mp, °C	formula[a]	method	% yield	in vitro IC_{50},[b] M	in vivo ED_{50},[c] mg/kg
5	H					10^{-5}	5
32[d]	6-F	239–241	$C_{11}H_9FN_2O_3$	A	36	10^{-6}	0.75
33[e]	6-Cl	268–270	$C_{11}H_9ClN_2O_3$	A	81	10^{-7}	0.25–0.75
34[e]	6-Br	266–268	$C_{11}H_9BrN_2O_3$	A	15	10^{-6}–10^{-7}	<1.5 (85)
35[f]	8-F	203–205	$C_{11}H_9FN_2O_3$	A	74	$<10^{-4}$	
36[e]	8-Cl	231–233	$C_{11}H_9ClN_2O_3$	A	34	10^{-6}	>1.5 (30)*[s]
37[d]	6,8-Cl_2	234–235	$C_{11}H_8Cl_2N_2O_3$	A	20	$<10^{-7}$	0.25
38[d]	6,7-Cl_2	263–265	$C_{11}H_8Cl_2N_2O_3$	A	8	$<10^{-7}$	<1.5 (64)
39[d]	6-OMe	170–172	$C_{12}H_{12}N_2O_4$	A	32	10^{-5}–10^{-6}	>2.5 (24)*
40[g]	6-SO_2Me	>300	$C_{12}H_{12}N_2O_5S$		2	10^{-4}–10^{-5}	
41[h]	6-SMe	186–187	$C_{12}H_{12}N_2O_3S$	B	29	10^{-6}	<25 (90)
42[e]	6-Me	242–243	$C_{12}H_{12}N_2O_3$	B	58	10^{-5}–10^{-6}	5
43[d]	6,8-Me_2	188–189	$C_{13}H_{14}N_2O_3$	A	65	10^{-6}	>1.5 (31)
44[i]	5,8-Me_2	228–229	$C_{13}H_{14}N_2O_3$	A	56	10^{-6}	>1.5 (12)*
45[j]	5,7,8-Me_3	134–135.5	$C_{14}H_{16}N_2O_3 \cdot CH_3OH$	B	38	10^{-6}	
46[k]	6-*t*-Bu	197–198	$C_{15}H_{18}N_2O_3 \cdot {}^1/_2C_6H_6$	B	11	10^{-4}–10^{-5}	
47[l]	6-SO_2NMe_2	221–223	$C_{13}H_{15}N_3O_5S$		28	10^{-4}	>5 (3)*
48[m]	6-$CONH_2$	318 dec	$C_{12}H_{11}N_3O_4 \cdot {}^1/_8H_2O$	A	8	10^{-4}–10^{-5}	>100 (−1)*
49[n]	6-Ph	283–285	$C_{17}H_{14}N_2O_3$	A	27	$<10^{-4}$	>1.5 (−3)*
50[n]	8-Ph	217–218.5	$C_{17}H_{14}N_2O_3 \cdot {}^1/_8H_2O$	A	36	10^{-6}–10^{-7}	10
51[n]	6-OPh	168	$C_{17}H_{14}N_2O_4$	A	7	10^{-5}	25 (18)
52[o]	7-CF_3	213–215	$C_{12}H_9F_3N_2O_3$	A	16	10^{-6}	5
53[p]	6-CH_2N⟨⟩	232–233	$C_{17}H_{21}N_3O_3 \cdot {}^1/_8CH_3OH$	B	19	10^{-4}	
54[n]	6-Ph, 8-Cl	243–244	$C_{17}H_{13}ClN_2O_3$	B	35	10^{-5}–10^{-6}	
55[q]	6-Cl, 8-Me	214–215	$C_{12}H_{11}ClN_2O_3$	B	53	$<10^{-7}$	<1.5 (70)
56[r]	5-OMe, 8-Cl	227.5–228.5	$C_{12}H_{11}ClN_2O_4$	B	88	$>10^{-4}$	

[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] See ref *g* in Table III. [f] This 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. [g] Prepared by methanesulfonylation of compound **5**; see Experimental Section, Section B. [h] Prepared 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. [i] Prepared from 2,3-dihydro-5,8-dimethyl-4*H*-1-benzopyran-4-one. Dann, O.; Volz, G.; Huber, O. *Justus Liebigs Ann. Chem.* **1954**, *587*, 16. [j] Prepared from 2,3-dihydro-5,7,8-trimethyl-4*H*-1-benzopyran-4-one. Koo, J. *J. Am. Chem.* **1953**, *75*, 1891. [k] Prepared from 6-*tert*-butyl-2,3-dihydro-4*H*-1-benzopyran-4-one, ref 25. [l] Prepared from the corresponding sulfonyl chloride; see Experimental Section, Section B. [m] Prepared from 6-(aminocarbonyl)-2,3-dihydro-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. [n] Sarges, R.; Belletire, J. L. U.S. Patent 4 181 729, Jan 1, 1980. [o] Prepared from 2,3-dihydro-7-(trifluoromethyl)-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. [p] Prepared from 2,3-dihydro-6-(piperidinylmethyl)-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. [q] Prepared from 6-chloro-2,3-dihydro-8-methyl-4*H*-1-benzopyran-4-one; see Experimental Section, Section C. [r] Prepared 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 hydantoins.

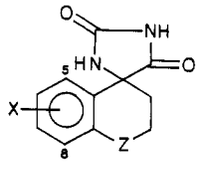
Table IX. Substituted Thiochroman Hydantoins



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	$C_{11}H_9FN_2O_2S$	B	60	10^{-6}–10^{-7}	1.5
58[d]	6-Cl	244–246	$C_{11}H_9ClN_2O_2S$	B	53	10^{-6}–10^{-7}	2.5
59[d]	6-Br	234–236	$C_{11}H_9BrN_2O_2S$	B	56	10^{-6}–10^{-7}	2.5
60[d]	7-Cl	235–237	$C_{11}H_9ClN_2O_2S$	B	67	10^{-6}	>1.5 (26)*[i]
61[d]	8-Cl	265–267	$C_{11}H_9ClN_2O_2S$	B	66	10^{-4}	>1.5 (5)*
62[d]	6,7-Cl_2	298–300	$C_{11}H_8Cl_2N_2O_2S$	B	49	$<10^{-7}$	2.5
63[e]	6,8-Cl_2	247–248	$C_{11}H_8Cl_2N_2O_2S \cdot {}^1/_4C_6H_{12}$[f]	B	94	$<10^{-7}$	
64[g]	5,8-Cl_2	250–252	$C_{11}H_8Cl_2N_2O_2S \cdot {}^1/_2CH_3OH$	B	24	$>10^{-4}$	
65[d]	6-OMe	170–172	$C_{12}H_{12}N_2O_3S$	B	41	10^{-5}	>5 (26)
66[h]	6-*t*-Bu	238–239	$C_{15}H_{18}N_2O_2S$	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 4 117 230, 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 Hydantoins



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	$C_{11}H_9FN_2O_3S$	22	10^{-6}–10^{-7}	>1.5 (35)
68[d]	6-F	SO_2	184–186 dec	$C_{11}H_9FN_2O_4S \cdot {}^1/_2EtOAc$	74	10^{-6}–10^{-7}	2.5
63	6,8-Cl_2	S				$<10^{-7}$	
69[d]	6,8-Cl_2	SO_2	>300	$C_{11}H_8Cl_2N_2O_4S \cdot H_2O$	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 4 117 230, 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 hydantoins 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 hydantion 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**.

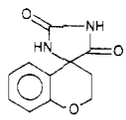
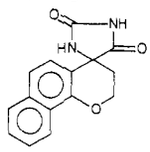
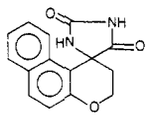
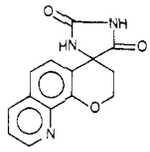
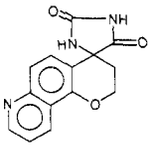
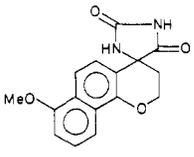
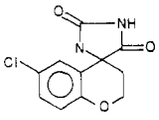
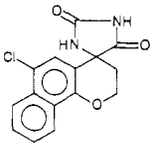
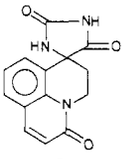
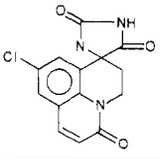
Taken together, these results show that potent in vitro and in vivo activity is associated with spiro hydantoins derived from five- and six-membered ketones fused to certain aromatic rings or ring systems, provided the spiro junction is adjacent to the aromatic ring. Optimum activity is reached in hydantoins 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 ED_{50}'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.

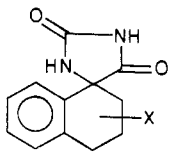
Table XI. Systems with a Fused Aromatic Ring

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	$C_{15}H_{12}N_2O_3 \cdot {}^1/_2H_2O$	A	38	$<10^{-4}$	>1.5 (30)
71[d]		295 dec	$C_{15}H_{12}N_2O_3$	B	48	10^{-6}	>1.5 (−13)*[i]
72[e]		305 dec	$(C_{14}H_{11}N_3O_3)$[f]	A	21	10^{-5}	>1.5 (27)
73[e]		>330	$C_{14}H_{11}N_3O_3$	A	64	10^{-6}–10^{-7}	1.5–10
74[d]		275 dec	$C_{16}H_{14}N_2O_4$	B	29	10^{-7}	>1.5 (1)*
33						10^{-7}	0.25–0.75
75[d]		215–217	$C_{15}H_{11}ClN_2O_3$	B	79	$<10^{-7}$	1.5–5
76[g]		290–292	$C_{14}H_{11}N_3O_3$	A	80	10^{-6}–10^{-7}	2.5–5
77[g,h]		199–205	$C_{14}H_{10}ClN_3O_3 \cdot H_2O$		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 4 181 728, Jan 1, 1980. [e] Schnur, R. C. U.S. Patent 4 176 185, Nov 27, 1979. [f] By high-resolution mass spectrometry. [g] Schnur, R. C. U.S. Patent 4 193 996, 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 hydantoins 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 IC_{50} 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

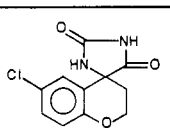
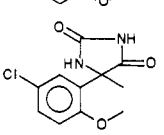
Table XII. Compounds with Substituents in the Hydantoin-Bearing Ring



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	$C_{13}H_{14}N_2O_2$	B	52	10^{-4}	>25 (13)*[h]
79[e]	4-Me	224–226	$C_{13}H_{14}N_2O_2$	B	25	10^{-4}	>25 (2)*
80[f]	2-Ph	289	$C_{18}H_{16}N_2O_2$	B	33	$>10^{-4}$	>25 (18)*
81[f]	4-Ph	210–212	$C_{18}H_{16}N_2O_2 \cdot {}^1/_4H_2O$	B	47	10^{-4}	>25 (2)*
82[g]	4-CO_2H	289–290 dec	$C_{13}H_{12}N_2O_4$	B	62	$>10^{-4}$	

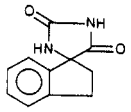
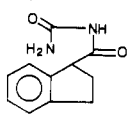
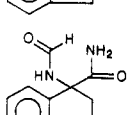
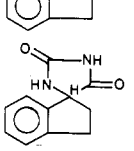
[a] All new compounds were analyzed for C, H, N. [b] See footnote *a* in Table I. [c] See footnote *b* in Table I. [d] Prepared from 2-methyl-1-tetralone (Aldrich). [e] Prepared from 4-methyl-1-tetralone (Aldrich). [f] Sarges, R.; Belletire, J. L. U.S. Patent 4 181 729, Jan 1, 1980. [g] Prepared from 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 Hydantoins

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	$C_{11}H_{11}ClN_2O_3$	B	32	$>10^{-4}$	

[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 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	$C_{11}H_{12}N_2O_2 \cdot {}^1/_4H_2O$	10^{-4}	>10 (0)*[e]
85[d]		182–186	$C_{11}H_{12}N_2O_2 \cdot {}^1/_4H_2O$	10^{-4}	>10 (−8)*
86[d]		201–203	$C_{11}H_{12}N_2O_2$	$>10^{-4}$	>10 (3)*

[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] See 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 hydantoins 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 reductase[8] with respect to the sugar aldehyde substrate (in our tests, glyceraldehyde). This suggests that the spiro hydantoins do not interact directly at the substrate binding site. Other experiments suggest that **115** is not a competitive inhibitor of the cofactor 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 hydantoins.

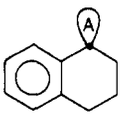
Our SAR exploration in the spiro hydantoin series has yielded a number of potent in vivo aldose reductase inhibitors. Of these, compound **115** (CP-45,634; USAN: sorbinil) has been extensively investigated both pharmacologically and clinically. Early results from clinical trials of sorbinil tend to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

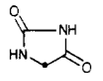
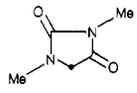
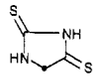
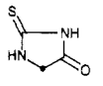
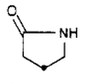
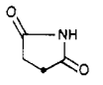
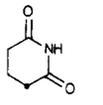
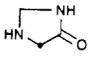
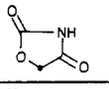
Experimental Section

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	$C_{16}H_{16}N_2O_2$	$>10^{-4}$	25
88[e]		251–254	$C_{12}H_{12}N_2S_2$	$>10^{-4}$	>25 (1)*[j]
89[e]		219–220	$C_{12}H_{12}N_2OS$	$>10^{-4}$	
90[e]		148–150	$C_{13}H_{15}NO$	$>10^{-4}$	>25 (26)
91[f,g]		153–156	$C_{13}H_{13}NO_2$	$>10^{-4}$	5
92[g]		173–175	$C_{14}H_{15}NO_2$	$>10^{-4}$	>25 (23)
93[h]		182–183	$C_{12}H_{14}N_2O$	$>10^{-4}$	25
94[i]		170–172	$C_{13}H_{17}NO_2$	10^{-5}	>50 (−17)*

[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 methylation of **2**; see Experimental Section, Section B. [e] See Experimental Section, Section B. [f] Sandberg, R. V. U.S. Patent 3 507 881; *Chem. Abstr.* **1973**, *78*, *p* 15890*z*. [g] Sarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. [h] Sarges, R.; Belletire, J. L. U.S. Patent 4 283 409, Aug 11, 1981. [i] Schnur, 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.

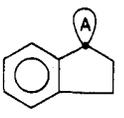
Varian T-60 and XL-100 spectrometers with TMS as internal standard; the solvent was $CDCl_3$ unless otherwise indicated. IR spectra were obtained on a Perkin-Elmer Model 21 spectrometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer.

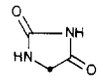
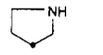
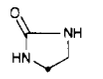
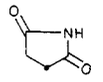
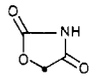
Section A. Preparation of Hydantoins (Tables III–XIII). General Method A. A mixture of 0.1 mol of ketone (e.g., 1-indanone), 9.75 g (0.15 mol) of KCN, and 28.8 g (0.3 mol) of powdered $(NH_4)_2CO_3$ in 200 mL of 50% aqueous EtOH was heated in an oil bath at 55–75 °C for 24 h. The reaction mixture was then diluted with 800 mL of H_2O, 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 H_2O, dried, and recrystallized (e.g., from MeOH–EtOH–Et_2O) 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 $(NH_4)_2CO_3$ 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 H_2O 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 anhydride in 10 mL of tetrachloroethylene was refluxed for 18 h according of Gilbert.[14] After cooling, 10 mL of H_2O 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

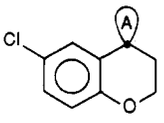
Table XVI. Indan-Based Compounds with Modified Hydantoin Rings

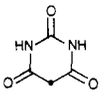


no.	A	mp, °C	formula[a]	in vitro IC_{50},[b] M	in vivo ED_{50},[c] mg/kg
4				10^{-4}–10^{-5}	10–25
95[d]		124–126	$C_{12}H_{15}N \cdot C_4H_4O_4$[e]	$>10^{-4}$	>25 (−23)*[h]
96[d]		197–199.5	$C_{11}H_{12}N_2O$	$>10^{-4}$	
97[f]		148–150	$C_{12}H_{11}NO_2$	$>10^{-4}$	>2.5 (28)
98[g]		163–164.5	$C_{11}H_9NO_3$	10^{-4}–10^{-6}	>25 (22)*

[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] See Experimental Section, Section B. [e] Maleic acid. [f] Sarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. [g] Schnur, 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 Hydantoins

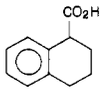
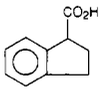
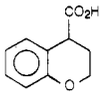
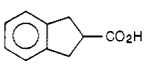
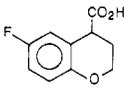
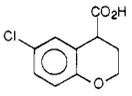
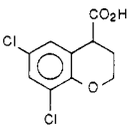
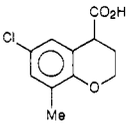
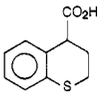
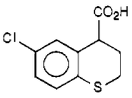
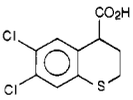
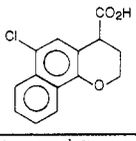


no.	A	mp, °C	formula[a]	in vitro IC_{50},[b] M	in vivo ED_{50},[c] mg/kg
33				10^{-7}	0.25–0.75
99[d]		222–224	$C_{11}H_{11}ClN_2O_2 \cdot {}^1/_2H_2O$	10^{-5}	>10 (15)*[i]
100[e]		107 dec	$(C_{12}H_9ClN_2O_4)$[f]	10^{-4}–10^{-5}	>10 (−5)*
101[g]		225–226.5	$C_{12}H_{10}ClNO_3$	$<10^{-4}$	>5 (13)*
102[h]		196–198	$C_{11}H_8ClNO_4$	10^{-6}–10^{-7}	>1.5 (28)

[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 in 28% yield from **33** by the method described for **96** in the Experimental Section, Section B. [e] See Experimental Section, Section B. [f] By high-resolution mass spectrometry. [g] Sarges, R.; Belletire, J. L. U.S. Patent 4 307 108, Dec 22, 1981. [h] Schnur, 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.

(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	$C_{10}H_9FO_3$	10^{-4}–10^{-6}	>25 (11)*[j]
108[h]	33		90–90.5	$C_{10}H_9ClO_3$	10^{-5}–10^{-6}	>25 (28)
109[h]	37		124.5–126	$C_{10}H_8Cl_2O_3$	10^{-5}	
110[h]	55		95–96	$C_{11}H_{11}ClO_3$	10^{-5}–10^{-6}	
111[i]	6		78–80	$C_{10}H_{10}O_2S$	10^{-4}	
112[h]	58		153–154	$C_{10}H_9ClO_2S$	$<10^{-4}$	
113[h]	62		157–161	$C_{10}H_8Cl_2O_2S$	10^{-5}	
114[h]	75		141–142	$C_{14}H_{11}ClO_3$	10^{-6}	>25 (12)

[a] All new compounds were analyzed C, H. [b] See footnote *a* in Table I. [c] See footnote *b* in Table I. [d] *Beilstein, 4th ed.* **1927**, *9*, 625. [e] *Beilstein, 4th ed.* **1949**, *9*, II, 411. [f] Prepared in 33% yield from 2,3-dihydro-4*H*-1-benzopyran-4-one by the method described in ref *h*; G. Fontaine noted mp 66 °C: *Chem. Abstr.* **1968**, *69*, 106536*v*. [g] *Beilstein, 4th ed.* **1927**, *9*, 620. [h] Belletire, J. L. U.S. Patent 4 210 663, July 1, 1980. [i] Prepared from 2,3-dihydro-4*H*-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. ($C_{12}H_{12}N_2O_5S$) C, H, N.

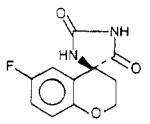
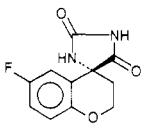
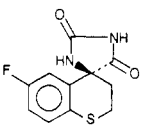
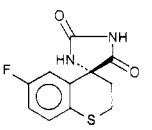
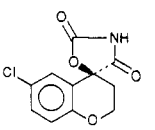
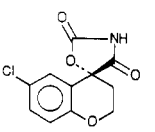
2,3-Dihydro-6-[(dimethylamino)sulfonyl]spiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (47). Compound **5** (760 mg, 3.5 mmol) was added slowly to 5 mL of chlorosulfonic acid, and the resultant yellow solution was stirred at room temperature for 30 min and then poured over 100 mL of ice. The mixture was extracted with EtOAc to give, after drying over $MgSO_4$ 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 $CHCl_3$ 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. ($C_{13}H_{15}N_3O_5S$) C, H, N.

***N*-(Aminocarbonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (84).** 1-Indancarboxylic acid[15] (2 g, 0.0124 mol) and 5 mL of $SOCl_2$ were refluxed in 5 mL of CH_2Cl_2 for 5 h. The reaction mixture

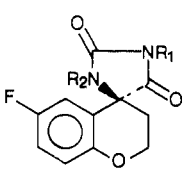
(15) Knowles, W. S.; Kuck, J. A.; Elderfield, R. C. *J. Org. Chem.* **1942**, *7*, 374.

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	$C_{11}H_9FN_2O_3$	2.6×10^{-7}	0.25
116[d]		−54.8 (MeOH)	241–243	$C_{11}H_9FN_2O_3$	10^{-5}–10^{-6}	25
57		±			10^{-6}–10^{-7}	1.5
117[d]		+71.8 (MeOH)	224–226	$C_{11}H_9FN_2O_2S$	$<10^{-7}$	0.75
118[d]		−73.8 (MeOH)	223–225	$C_{11}H_9FN_2O_2S$	10^{-5}–10^{-6}	
102		±			10^{-6}–10^{-7}	>1.5 (28)
119[e]		−61.6 (EtOH)	200–200.5	$C_{11}H_8ClNO_4$	10^{-7}	2.5
120[e]		+60.5 (EtOH)	200–201.5	$C_{11}H_8ClNO_4$	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 4 130 714, Dec 19, 1978. [e] Schnur, 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	$C_{11}H_9FN_2O_3$	5×10^{-7}	0.25
121[d]	Me	H	220–224	$C_{12}H_{11}FN_2O_3$	$>10^{-4}$	<10 (89)
122[d]	H	Me	142–143	$C_{12}H_{11}FN_2O_3$	10^{-4}	<10 (96)
123[d]	Me	Me	*e*	$C_{13}H_{13}FN_2O_3$	$>10^{-4}$	<10 (74)

[a] All new compounds were analyzed for C, H, N. [b] See footnote *a* in Table I; the values in this table were obtained with aldose reductase isolated from human placenta. [c] See footnote *b* in Table I. [d] See Experimental Section, Section B. [e] Oil, bp 110 °C (0.1 mmHg).

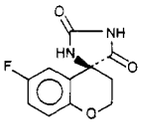
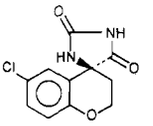
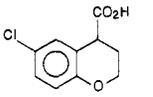
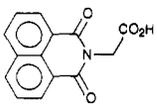
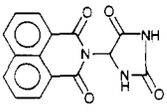
was distilled in vacuo to give an oil, 1.72 g (78%), $bp_{0.02}$ 95–105 °C, which was added to a solution of urea (1.4 g, 0.19 mol) in 5 mL of dry DMF. After being heated for 12 h at 30 °C, the mixture was partitioned between 100 mL of CH_2Cl_2 and 50 mL of H_2O. The organic phase was washed with 50 mL of H_2O, 3 × 50 mL of 5% $NaHCO_3$, and 50 mL of brine, dried (Na_2SO_4), 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. ($C_{11}H_{12}N_2O_2$) C, H, N.

2,3-Dihydro-1-(formylamino)-1*H*-indene-1-carboxamide (85). 1-Amino-2,3-dihydro-1*H*-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 H_2O. The cooled reaction mixture was diluted with 150 mL of MeOH and 150 mL of Et_2O, 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 NH_3 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 Et_2O to give 100 mg (86%) of compound **85**: mp 182–186 °C dec; [R (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. ($C_{11}H_{12}N_2O_4 \cdot 0.5H_2O$) C, H, N.

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

(16) Connors, T. A.; Ross, W. C. J. *J. Chem. Soc.* **1960**, 2119.

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_2O
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]		8×10^{-6} [e]	~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)urea[17] (1 g, 5.67 mmol) was dissolved in 14 mL of HCO_2H, and 5 mL of Ac_2O was added. After the reaction mixture was heated at 60 °C for 2 h, the cooled mixture was filtered, diluted with H_2O, 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. ($C_{11}H_{12}N_2O_4$) 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 H_2O. After extraction with Et_2O, drying ($MgSO_4$), 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. ($C_{14}H_{16}N_2O_2$) 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. ($C_{12}H_{12}N_2S_2$) 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. ($C_{12}H_{12}N_2OS$) 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 × 50 mL of H_2O, dried ($MgSO_4$), 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 H_2O, 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. ($C_{13}H_{15}NO$) 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 H_2O, then 0.5 mL of 15% NaOH, and then 1.5 mL of H_2O 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 Et_2O, 1 equiv of maleic acid dissolved in Et_2O was added slowly, and the precipitated solids were collected and recrystallized from MeOH–Et_2O to give 183 mg (25%) of **95** as the maleate, mp 124–126 °C. Anal. ($C_{12}H_{15}N{\cdot}C_4H_4O_4$) 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 Et_2O 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 H_2O, 3.5 mL of 15% NaOH, and 10.5 mL of H_2O, diluted with 300 mL of hot EtOH, and filtered. The filtrate was concentrated to a residue, which was recrystallized from EtOH–H_2O 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.; Vejdelek, Z.; Jilek, J. O. *Collect. Czech. Chem. Commun.* **1951**, *16*, 331; *Chem. Abstr.* **1953**, *47*, 8057*b*.
(21) Marshall, F. *J. Am. Chem. Soc.* **1956**, *78*, 3696.

($C_{11}H_{12}N_2O$) 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[4*H*-1-benzopyran-4,5′-[2*H*]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 Et_2O was treated with 3.33 mL of 3 M ethylmagnesium bromide in THF. The heterogeneous mixture was perfused with CO_2 for 10 min. The mixture was then heated, and 35 mL of Et_2O was distilled off along with excess CO_2 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 Et_2O, washed with 100 mL of 1 N H_2SO_4 (all solids dissolved) and 2 × 50 mL of brine, and evaporated in vacuo. The residue was taken up in $CHCl_3$, and the precipitated crystalline **108** (0.551 g, 22%) was removed by filtration. Addition of CCl_4 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 Et_2O 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% $NaHCO_3$ and 2 × 50 mL of brine. The crude solid dimethyl ester (0.425 g, 77%), obtained after evaporation of the dried ($MgSO_4$) Et_2O 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 Et_2O at reflux for 16 h. After cooling and dilution with Et_2O, the mixture was extracted with 5% $NaHCO_3$, 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.

(4*S*)-6-Fluoro-2,3-dihydro-1′-methylspiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (121) and (4*S*)-6-Fluoro-2,3-dihydro-1′,3′-dimethylspiro[4*H*-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 ($MgSO_4$) 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. ($C_{12}H_{11}FN_2O_3$) C, H, N. The mother liquor of **121** was purified by chromatography on SiO_2 with $CHCl_3$ 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. ($C_{13}H_{13}FN_2O_3$) C, H, N.

(4*S*)-6-Fluoro-2,3-dihydro-3′-methylspiro[4*H*-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 (4*S*)-6-fluoro-4-(methylamino)-4*H*-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 H_2O, 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 H_2O, and extracted with EtOAc. After drying ($MgSO_4$) and evaporation, the residue was crystallized from Et_2O–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. ($C_{12}H_{11}FN_2O_3$) 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 KBH_4 ($NaBH_4$ gave unsatisfactory results) and treatment of the resultant 5-hydroxyhydantoin with $SOCl_2$. 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 $SOCl_2$ 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 H_2O, 1.97 g (36%) of 5-[(benzyloxycarbonyl)amino]-hydantoin: mp 178–180 °C dec; MS, m/e 249. Anal. ($C_{11}H_{11}N_3O_4$) 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 Et_2O, 72 mg (92%) of 5-aminohydantoin hydrobromide: mp >250 °C; MS, m/e 115. Anal. ($C_3H_5N_3O_2$·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. ($C_{15}H_9N_3O_4 \cdot {}^1/_2H_2O$) C, H, N.

Section C. Preparation of Starting Materials (SM). **8-Fluoro-2,3-dihydro-4*H*-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. ($C_9H_9FO_3$) C, H), and ultimately to the title compound, mp 84–87 °C, in 86% yield. Anal. ($C_9H_7FO_2$) C, H.

6-(Aminocarbonyl)-2,3-dihydro-4*H*-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 $NaHCO_3$, 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. ($C_{11}H_{11}NO_4$) 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. ($C_{10}H_9NO_3$) C, H, N.

2,3-Dihydro-7-(trifluoromethyl)-4*H*-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. ($C_{10}H_9F_3O_3$) 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–$CHCl_3$, 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. ($C_{10}H_7F_3O_2 \cdot {}^1/_8H_2O$) C, H.

(22) Ivanoff, D. *Bull. Soc. Chim. Fr.* **1931**, *49*, 19.
(23) Dickey, J. B.; Gray, A. R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 60.
(24) Abblard, J.; Meynaud, A. *Bull. Soc. Chim. Fr.* **1971**, 942.
(25) Ricci, A.; Balucani, D.; Buu-Hoi, N. P. *Ann. Chim. (Rome)* **1968**, *58*, 455.

2,3-Dihydro-6-(piperidinylmethyl)-4*H*-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 CCl_4 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 CH_2Cl_2 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. ($C_{15}H_{20}N_2O$) 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. ($C_{15}H_{21}NO_3$·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-4*H*-1-benzopyran-4-one (SM for 55). The method of Ricci[25] was used to convert 2-methyl-4-chlorophenol to 3-(2-methyl-4-chlorophenoxy)-propanenitrile (mp 57–59 °C from EtOH–H_2O; 72% yield; anal. ($C_{10}H_{10}ClNO$) C, H, N) and 3-(2-methyl-4-chlorophenoxy)-propanoic acid (mp 103–105 °C from EtOH–H_2O; 98% yield; anal. ($C_{10}H_{22}ClO_3$) C, H). Cyclization in anhydrous HF gave the title compound in 81% yield: mp 53–54 °C from hexane. Anal. ($C_{10}H_9ClO_2$) C, H.

8-Chloro-2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4-one (SM for 56). The method of Ricci[25] 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. ($C_{10}H_{11}ClO_4$) C, H. Cyclization in anhydrous HF afforded the title compound in 79% yield: mp 143.5–144.5 °C from *i*-PrOH. Anal. ($C_{10}H_9ClO_3$) C, H.

6,8-Dichloro-2,3-dihydro-4*H*-1-benzothiopyran-4-one (SM for 63). 2,4-Dichlorobenzenethiol[27] (prepared from 2,4-dichloroaniline) was converted by the method of Ricci[25] to 3-[(2,4-dichlorophenyl)thio]propanoic acid: mp 117.5–118.5 °C from EtOAc–hexane. Anal. ($C_9H_8Cl_2O_2S$) 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. ($C_9H_6Cl_2OS$) C, H.

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SM for **22**, 2107-69-9; **23**, 111140-46-6; 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**, 111140-47-7; SM for **30**, 34910-81-1; **31**, 111140-48-8; SM for **31**, 49800-59-1; **32**, 67146-05-8; SM for **32**, 66892-34-0; **33**, 66892-58-8; SM for **33**, 37674-72-9; **34**, 66892-61-3; SM for **34**, 49660-57-3; **35**, 111140-49-9; SM for **35**, 111141-00-5; **36**, 66892-60-2; SM for **36**, 49701-11-3; **37**, 66892-57-7; SM for **37**, 49660-60-8; **38**, 66892-56-6; SM for **38**, 27407-06-3; **39**, 66892-55-5; SM for **39**, 5802-17-5; **40**, 111140-50-2; **41**, 87058-36-4; SM for **41**, 18385-67-6; **42**, 95197-72-1; SM for **42**, 39513-75-2; **43**, 66892-66-8; SM for **43**, 15773-95-2; **44**, 111140-51-3; SM for **44**, 21875-91-2; **45**, 111140-52-4; SM for **45**, 3649-05-6; **46**, 111140-53-5; SM for **46**, 23067-77-8; **47**, 111140-54-6; **48**, 111140-55-7; SM for **48**, 111141-01-6; **49**, 73316-13-9; SM for **49**, 73316-17-3; **50**, 73316-14-0; SM for **50**, 73316-18-4; **51**, 73316-15-1; SM for **51**, 73316-19-5; **52**, 111140-56-8; SM for **52**, 111141-02-7; **53**, 111140-57-9; SM for **53**, 111141-03-8; **54**, 73316-16-2; SM for **54**, 73316-20-8; **55**, 111159-41-2; SM for **55**, 76301-90-1; **56**, 111140-58-0; SM for **56**, 111141-04-9; **57**, 66892-47-5; SM for **57**, 21243-18-5; **58**, 66892-44-2; SM for **58**, 13735-12-1; **59**, 66892-45-3; SM for **59**, 13735-13-2; **60**, 66892-49-7; SM for **60**, 13735-14-3; **61**, 66892-48-6; SM for **61**, 60639-20-5; **62**, 66892-46-4; SM for **62**, 66892-36-2; **63**, 111140-59-1; SM for **63**, 111141-05-0; **64**, 111140-60-4; SM for **64**, 13539-49-6; **65**, 66892-43-1; SM for **65**, 13735-11-0; **66**, 111140-61-5; SM for **66**, 6612-47-1; **67**, 66892-62-4; **68**, 66892-63-5; **69**, 111140-62-6; **70**, 73284-33-0; SM for **70**, 16563-51-2; **71**, 73268-52-7; SM for **71**, 4707-36-2; **72**, 72791-38-9; SM for **72**, 72791-37-8; **73**, 72806-14-5; SM for **73**, 72806-13-4; **74**, 73268-50-5; SM for **74**, 73268-56-1; **75**, 73284-32-9; SM for **75**, 73284-35-2; **76**, 74277-68-2; SM for **76**, 37012-96-7; **77**, 111140-63-7; **78**, 111140-64-8; SM for **78**, 1590-08-5; **79**, 111140-65-9; SM for **79**, 19832-98-5; **80**, 73316-11-7; SM for **80**, 7498-87-5; **81**, 73316-12-8; SM for **81**, 14578-68-8; **82**, 111140-66-0; SM for **82**, 3123-46-4; **83**, 111140-67-1; **84**, 111140-68-2; **85**, 111140-69-3; **86**, 111140-70-6; **87**, 111140-71-7; **88**, 111140-72-8; **89**, 111140-73-9; **90**, 111140-74-0; **91**, 3464-23-1; **92**, 17516-17-5; **93**, 79025-19-7; **94**, 76311-49-4; **95**, 16976-98-0; **95**·maleate, 111140-86-4; **96**, 111140-75-1; **97**, 81402-16-6; **98**, 76311-46-1; **99**, 111140-76-2; **100**, 111159-42-3; **101**, 81402-18-8; **102**, 74187-53-4; **103**, 1914-65-4; **104**, 14381-42-1; **105**, 20426-80-6; **106**, 25177-85-9; **107**, 111140-77-3; **108**, 76301-94-5; **108** (malonic acid deriv.), 111140-87-5; **108** (dimethyl malonate deriv.), 111140-88-6; **109**, 76301-92-3; **110**, 76301-91-2; **111**, 80858-99-7; **112**, 76301-97-8; **113**, 76301-89-8; **114**, 76301-96-7; **115**, 68367-52-2; **116**, 69881-27-2; **117**, 69627-83-4; **118**, 69627-84-5; **119**, 74187-84-1; **120**, 74187-85-2; **121**, 111140-78-4; **122**, 111140-79-5; **123**, 111140-80-8; **124**, 111140-81-9; 1-indancarboxylic acid, 14381-42-1; 1-indancarbonyl chloride, 19156-10-6; 1-amino-2,3-dihydro-1*H*-indene-1-carboylic acid, 3927-71-7; methyl 1-amino-2,3-dihydro-1*H*-indene-1-carboxylate, 111140-83-1; methyl 1-amino-2,3-dihydro-1*H*-indene-1-carboxylate, 111140-84-2; 1-amino-2,3-dihydro-1*H*-indene-1-carboxamide, 111140-85-3; 1-(2,3-dihydro-1*H*-inden-1-yl)urea, 6520-67-8; 1-amino-3,4-dihydro-(2*H*)-naphthalene-1-carboxylic acid, 30265-11-3; 1,2,3,4-tetrahydro-1-naphthalenecarbonitrile, 56536-96-0; (4*S*)-6-fluoro-4-(methylamino)-4*H*-1-benzopyran-4-carboxylic acid, 111140-89-7; benzyl carbamate, 621-84-1; 5-[(benzyloxycarbonyl)amino]hydantoin, 111140-90-0; 3-(2-fluorophenoxy)propanenitrile, 111140-91-1; 3-(2-fluoropohenoxy)propanoic acid, 2967-72-8; 3-(4-cyanophenoxy)propanoic acid, 58228-89-0; 3-[4-(aminocarbonyl)phenoxy]propanoic acid, 111140-92-2; 3-[3-(trifluoromethyl)phenoxy]propanoic acid, 111140-93-3; 3-(4-methylphenoxy)propanenitrile, 25268-01-3; 3-[4-(bromomethyl)phenoxy]-propanenitrile, 111140-94-4; 3-[4-(piperidinylmethyl)phenoxy]-propanenitrile, 111140-95-5; 3-[4-(piperidinylmethyl)phenoxy]-propanoic acid, 111140-96-6; 3-[4-(piperidinylmethyl)phenoxy]-propanoic acid hydrochloride, 111141-10-7; 2-methyl-4-chlorophenol, 1570-64-5; 3-(2-methyl-4-chlorophenoxy)propanenitrile, 111140-97-7; 3-(2-methyl-4-chlorophenoxy)propanoic acid, 2307-66-6; 3-(2-chloro-5-methoxyphenoxy)propanoic acid, 111140-98-8; 3-[(2,4-dichlorophenyl)thio]propanoic acid, 111140-99-9; 2,3-dihydro-5-(trifluoromethyl)-4*H*-1-benzopyran-4-one, 111141-06-1; 5-aminohydantoin hydrobromide, 111141-09-4; ethyl bromoacetate, 105-36-2; parabanic acid, 120-89-8; 5-hydroxyhydantoin, 29410-13-7; 5-chlorohydantoin, 32282-43-2; 5-aminohydantoin, 24764-63-4; naphthalic anhydride, 81-84-5; 2-fluorophenol, 367-12-4; 4-cyano phenol, 767-00-0; 3-(trifluoromethyl)phenol, 98-17-9; 3-chloropropanoic acid, 107-94-8; piperidine, 110-89-4; 2-chloro-5-methoxyphenol, 18113-04-7; 2,4-dichlorobenzenethiol, 1122-41-4; 5-chloro-2-methoxyacetophenone, 6342-64-9; aldose reductase, 9028-31-3.

(26) Cologne, J.; Guyot, A. *Bull. Soc. Chim. Fr.* **1957**, 1228.
(27) Sparke, M. B.; Camero, J. L.; Kharasch, N. *J. Am. Chem. Soc.* **1953**, *75*, 4907.