The blood pressure was allowed to stabilize after the administration of each compound before testing for possible blockade of norepinephrine pressor responses.

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Synthesis and Aldose Reductase Inhibitory Activity of 7-Sulfamoylxanthone-2-carboxylic Acids[1,2]

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A series of xanthone-2-carboxylic acids substituted in the 7 position with sulfamoyl and other groups was synthesized and assayed in vitro for inhibition of aldose reductase isolated from rabbit lenses. At a concentration of 10^{-6} M, the *N*-methyl-*N*-(2-hydroxyethyl)sulfamoyl derivative **14** produced an 83% inhibition of aldose reductase. The structural requirements for this type of activity are discussed.

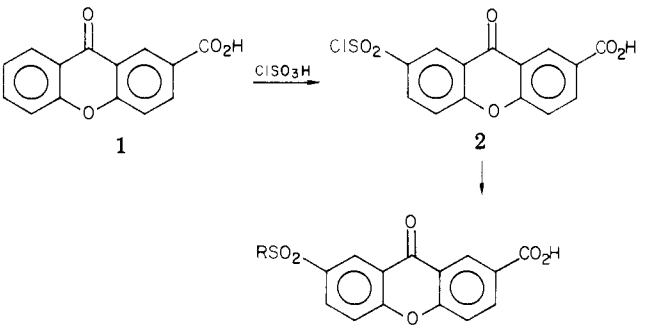
The antiallergic activity of substituted xanthone-2-carboxylic acids has been reported previously.[3,4] In the present report, evidence is presented to show that substituted xanthones can exert an entirely different kind of activity—the inhibition of aldose reductase. This enzyme catalyzes the formation of sugar alcohols from sugars and has been implicated in the development of cataracts in diabetes and galactosemia.[5] The enzyme may also be involved in other complications of diabetes, such as neuropathy and retinopathy.[6] The basis of this study was the possibility that some xanthones may be more effective than known inhibitors of aldose reductase and, therefore, could be useful in the prevention or delay of cataract formation.

Chemistry. Chlorosulfonation of xanthone-2-carboxylic acid (**1**) with excess chlorosulfonic acid at elevated temperatures readily afforded the 7-sulfo chloride **2**, which reacted in aqueous solution with NaOH or an amine to furnish the sulfonic acid **3** and the sulfonamides **4–15**, respectively (Scheme I).

The (hydroxyethyl)thio, -sulfinyl, and -sulfonyl derivatives **17**, **21**, and **22** were obtained from 7-mercaptoxanthone-2-carboxylic acid[4] (**16**) in a straightforward manner (Scheme II). Due to the low solubility of **17** in nonpolar solvents, this compound was first converted into the more soluble methyl ester **18**, with which oxidation to the desired sulfoxide **19** and sulfone **20** proceeded uneventfully.

Although it was possible to reduce the acetyl group of **25** with $NaBH_4$ in aqueous MeOH, concomitant reduction of the xanthone carbonyl could not be suppressed completely. Catalytic hydrogenation of the sodium salt of **25** over Pd/C in aqueous solution gave the desired carbinol **26** uncontaminated by the corresponding xanthydrol (Scheme III). The conversion of the glycidyl ether **28** to the known glycerol derivative **29**[7] was effected conveniently by a one-pot method involving acid-catalyzed hydrolytic epoxide opening, followed by ester hydrolysis with alkali (Scheme IV).

Scheme I



3, R = OH	**10**, R = N(Me)-*i*-Bu
4, R = NH_2	**11**, R = pyrrolidino
5, R = NHMe	**12**, R = morpholino
6, R = NMe_2	**13**, R = $NHCH_2CH_2OH$
7, R = N(Me)Et	**14**, R = $N(Me)CH_2CH_2OH$
8, R = NH-*i*-Pr	**15**, R = $N(CH_2CH_2OH)_2$
9, R = N(Me)-*i*-Pr	

Discussion and Conclusions

Several classes of compounds of diverse structure are known to inhibit the enzyme aldose reductase (EC 1.1.1.21), including acidic compounds such as tetramethylglutaric acid[8] and 1,3-dioxo-1*H*-benz[*de*]isoquinoline-2(3*H*)-acetic acid (alrestatin)[9] as well as a large number of flavonoids.[10,11] A recent report on the inhib-

(1) Contribution no. 549 from the Institute of Organic Chemistry, Syntex Research.
(2) Presented in part at the 63rd Annual Meeting of the Federation of American Societies for Experimental Biology, Dallas, Texas, April 2, 1979.
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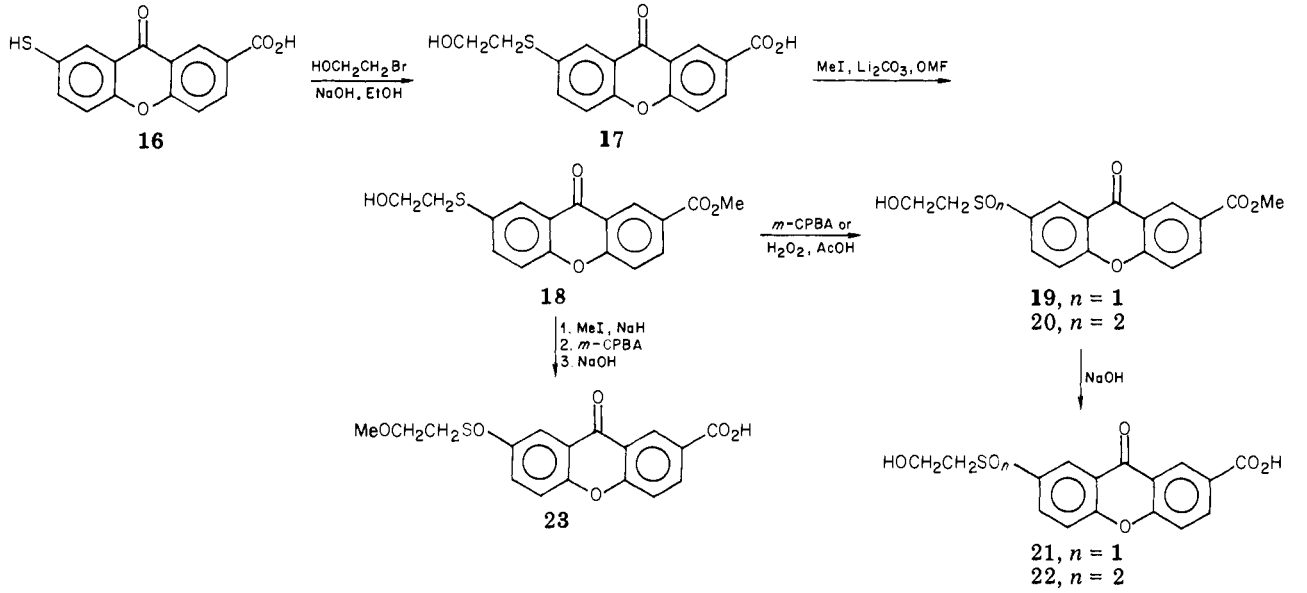
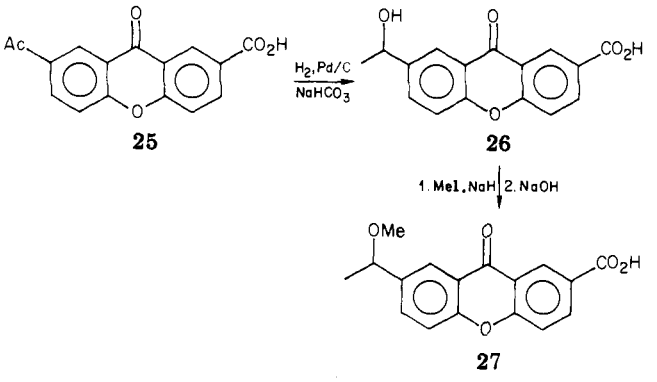
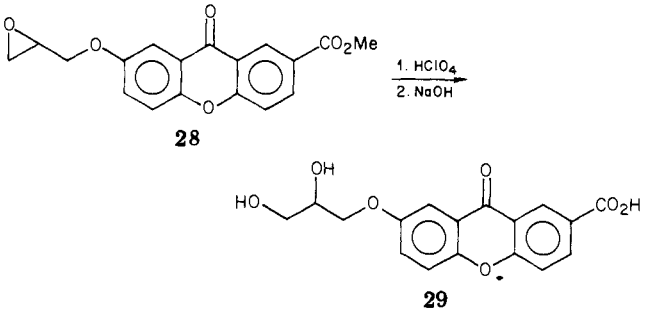
Scheme II



Scheme III



Scheme IV



ition of aldose reductase by a number of chromonecarboxylic acids,[12] some of which are known antiallergy agents (inhibitors of mediator release from mast cells),[13,14] prompted us to present our findings that certain substituted xanthone-2-carboxylic acids are also potent inhibitors of the enzyme aldose reductase.

This type of activity was initially encountered in a series of sulfonamides with hydrogen or lower alkyl substitution on the nitrogen atom (Table I, compounds **4**–**10**). In this group, the *N,N*-dimethylsulfonamide **6** was the most active compound, while the more hydrophilic or lipophilic analogues were invariably inferior. Interestingly, in compounds with acidic hydrogens due to the groups $-SO_3H$ and $-SO_2NHR$, aldose reductase inhibitory activity was reduced even further (compounds **3**–**5** and **8**), while the unsubstituted xanthone-2-carboxylic acid **1** showed barely any activity. The cyclic pyrrolidino and morpholino derivatives **11** and **12** were also less active than **6** and related dialkylsulfonamides.

In an attempt to improve the aqueous solubility of these compounds (lack of water solubility being a disadvantage they share with the flavonoids[10]), one of the methyl groups of **6** was replaced by 2-hydroxyethyl. Surprisingly, the resulting derivative **14** showed a higher potency than **6**. On the other hand, conversion of phenolic OH groups in the flavone series to 2-hydroxyethoxy was accompanied by a loss of potency.[10] As noted before, changing from **14** ($NMeCH_2CH_2OH$) to a compound with an acidic NH group (**13**) resulted in a decrease in activity. The same effect was seen when both methyl groups of **6** were replaced by 2-hydroxyethyl (compound **15**).

Of the sulfonamides described here, only **5** and **6** were appreciably more active as mast-cell protectors than the reference standard, disodium cromoglycate (**5**: 12 × DSCG; **6**: 10 × DSCG). In view of the structural requirements for antiallergy activity in the xanthone series, described earlier,[3,4] the lack of correlation of aldose reductase inhibition with mast-cell protective activity is not surprising.

Activity was retained when the moiety $-SO_2NMe-$ in **14** was exchanged for –S–, –SO–, and $-SO_2-$ (compounds **17**, **21**, and **22**). Converting **21** into the corresponding methyl ether **23** lowered activity, pointing out the importance of the free OH function, which possibly might act as a secondary binding site. In fact, **23** is about as weak an aldose reductase inhibitor as the methylsulfinyl analogue **24** (tixanox), a known antiallergy agent.[4] Another mast-cell protector, the glycerol ether **29**,[7] was approximately equipotent with the flavone quercetin.

Additional experiments were conducted to determine the nature of the inhibition of lens aldose reductase by the xanthones. The effect of varying substrate concentrations (D,L-glyceraldehyde) on the inhibition by dimethylsulfamoyl derivative **6**, one of the most potent xanthones, was investigated by graphing the kinetic data as a Lineweaver–Burke plot. The K_m of aldose reductase was found to be unaffected by the presence of **6** at 1.0×10^{-6} M, whereas the V_{max} decreased. The inhibition of aldose re-

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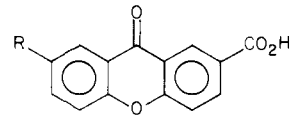
Table I. Aldose Reductase Inhibitory Activity of 7-Substituted Xanthone-2-carboxylic Acids[a]



compd	R	mp, °C	formula[b]	recrystn solvent	% inhibn[c] 10^{-4} M	% inhibn[c] 10^{-5} M	% inhibn[c] 10^{-6} M
1	H[d]				20	10	0
3	SO_3H	>400	$C_{14}H_8O_7S\cdot H_2O$	AcOH-H_2O	70	43	0
4	SO_2NH_2	338	$C_{14}H_9NO_6S$	DMF-H_2O	70	20	10
5	SO_2NHMe	>300	$C_{15}H_{11}NO_6S$	DMF-AcOH	75	40	25
6	SO_2NMe_2	290-292	$C_{16}H_{13}NO_6S$	DMF-H_2O	94	87	67
7	$SO_2N(Me)Et$	285	$C_{17}H_{15}NO_6S$	THF-EtOH	92	81	23
8	SO_2NH-*i*-Pr	>300	$C_{17}H_{15}NO_6S$	DMF-H_2O	72	30	0
9	$SO_2N(Me)$-*i*-Pr	285-286	$C_{18}H_{17}NO_6S$	EtOH-H_2O	89	69	17
10	$SO_2N(Me)$-*i*-Bu	301-302	$C_{19}H_{19}NO_6S$	EtOH-H_2O	95	75	25
11	$SO_2NC_4H_8$[e]	292-293	$C_{18}H_{15}NO_6S$	DMF-H_2O	85	46	0
12	$SO_2NC_4H_8O$[f]	307-308	$C_{18}H_{15}NO_7S$	DMF-AcOH	76	6	0
13	$SO_2NHCH_2CH_2OH$	317-318	$C_{16}H_{13}NO_7S$	$MeOCH_2CH_2OH$	79	38	0
14	$SO_2N(Me)CH_2CH_2OH$	277-278	$C_{17}H_{15}NO_7S$	THF-EtOH	100	96	83
15	$SO_2N(CH_2CH_2OH)_2$	262-263	$C_{18}H_{17}NO_8S$	AcOH-H_2O	89	49	2
17	SCH_2CH_2OH	>400	$C_{16}H_{12}O_5S$	DMF-AcOH	93	65	7
21	$SOCH_2CH_2OH$	>400	$C_{16}H_{12}O_6S$	AcOH	87	50	17
22	$SO_2CH_2CH_2OH$	278-279	$C_{16}H_{12}O_7S$	AcOH-H_2O	96	77	50
23	$SOCH_2CH_2OMe$	>400	$C_{17}H_{14}O_6S$	EtOH-H_2O	65	12	4
24	SOMe[g]				63	20	0
26	CH(OH)Me	245-247	$C_{16}H_{12}O_5$	EtOH-H_2O	50	10	10
27	CH(OMe)Me	256-257	$C_{17}H_{14}O_5$	THF-EtOH	70	6	0
29	$OCH_2CHOHCH_2OH$[h]				88	46	8
quercetin						52	9

[a] All compounds exhibited IR and NMR spectra consistent with the assigned structures. [b] All compounds were analyzed at least for C and H. [c] Percent inhibition of rabbit lens aldose reductase in vitro as described under Experimental Section. [d] Reference 3. [e] NC_4H_8 is pyrrolidino. [f] NC_4H_8O is morpholino. [g] Reference 4. [h] Reference 7.

ductase by **6** is thus of the noncompetitive type. The K_i for **6** was determined graphically to be 4×10^{-7} M, and the K_m of rabbit lense aldose reductase was 3×10^{-5} M.

In summation, we describe here a series of potent, noncompetitive inhibitors of rabbit lense aldose reductase, which, being colorless substances, would be more suitable for topical application to the eye than the characteristically yellow flavonoids. Moreover, compounds **6** and **14** were also active in vitro against human placental aldose reductase,[15] and **6** was effective either topically or orally in delaying the occurrence of cataracts in rats receiving a diet containing 35% galactose.[16]

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. The IR spectra were measured on a Perkin-Elmer Model 267 grating infrared spectrophotometer as Nujol mulls. The UV spectra were recorded in methanol solution with a Perkin-Elmer UV-visible spectrophotometer. The NMR spectra were measured with a Varian T-60 NMR spectrometer in $CDCl_3$ or Me_2SO-d_6 solutions, using Me_4Si as internal standard. Silica gel GF plates (0.25 mm; Analtech, Inc.) were used for thin-layer chromatography, eluting with a toluene–THF–AcOH (30:3:1) mixture. The plates were visualized with UV light.

7-(Chlorosulfonyl)xanthone-2-carboxylic Acid (2). Xanthone-2-carboxylic acid[3] (**1**; 17.5 g, 72.9 mmol) was added to freshly distilled chlorosulfonic acid (70 mL, 1.05 mol), and the resulting solution was heated for 2 h in an oil bath at 120–130 °C. The dark reaction mixture was cooled in an ice bath and slowly poured into a stirred mixture of 420 mL of AcOH and 280 mL of H_2O (external cooling). After the mixture was diluted with 700 mL of H_2O, the precipitate was filtered off, washed with H_2O, and dried: yield 15.5 g (71%); mp 232–236 °C (dec). This crude material was used for the following preparations. An analytical sample was obtained by recrystallization from AcOH (charcoal) and then from dioxane, mp 334 °C (dec). Anal. ($C_{14}H_7O_6SCl$) C, H, S.

7-Sulfoxanthone-2-carboxylic Acid (3). A solution of 2.1 g (6.2 mmol) of the sulfo chloride **2** in 20 mL of 1 N NaOH was kept on a steam bath for 15 min. The cooled solution was acidified with concentrated HCl, and the reesulting precipitate was filtered off and washed with cold water and ethanol. Recrystallization from AcOH–H_2O gave 1.47 g (70%) of **3** as the monohydrate, mp >400 °C. Anal. ($C_{14}H_8O_7S\cdot H_2O$) C, H, S.

Sulfonamides 4–15. The sulfonamides **4–15** (Table I) were easily obtained by brief refluxing of 7-(chlorosulfonyl)-xanthone-2-carboxylic acid (**2**) with an excess of the requisite amine in aqueous solution. Yields were in the range of 47 to 79%. As an example, the preparation of 7-(*N*-ethyl-*N*-methylsulfamoyl)xanthone-2-carboxylic acid (**7**) is given: To a suspension of 1.1 g (3.25 mmol) of (**2**) in 10 mL of H_2O was added 2.0 g (33.9 mmol) of *N*-methylethylamine. The resulting mixture was refluxed for 5 min, acidified with AcOH, diluted with H_2O, and cooled. The white precipitate was filtered off, washed with H_2O, and dried to give 850 mg (73%) of **7**, mp 274–277 °C. Recrystallization from THF–EtOH provided an analytical sample, mp 285 °C.

7-[(2-Hydroxyethyl)thio]xanthone-2-carboxylic Acid (17). To a solution of 6.6 g (24.3 mmol) of 7-mercaptoxanthone-2-carboxylic acid[4] (**16**) and 4.0 g (71.4 mmol) of KOH in 160 mL of EtOH and 40 mL of H_2O, cooled to 0 °C, was added 10 mL (0.22 mol) of 2-bromoethanol. After stirring under N_2 for 2 h at ambient temperature, the reaction mixture was acidified with 60 mL of 2 N HCl. The resulting precipitate was washed first with EtOH–H_2O (1:1) and then with H_2O and dried to give 7.3 g (95%) of **17**, mp >400 °C. An analytical sample from AcOH had mp >400 °C. Anal. ($C_{16}H_{12}O_5S$) C, H, S.

Methyl 7-[(2-Hydroxyethyl)thio]xanthone-2-carboxylate (18). A mixture of 7.3 g (23.1 mmol) of **17**, 3.6 mL (57.75 mmol) of MeI, 4.27 g (57.75 mmol) of Li_2CO_3, and 150 mL of DMF was stirred at room temperature for 24 h. The reaction mixture was

(15) Personal communication from Dr. Jin Kinoshita, Laboratory of Vision Research, National Eye Institute, Bethesda, Md.
(16) See ref 2. A detailed account of our in vivo studies will be published later.

poured into 800 mL of H_2O containing 50 mL of 2 N HCl. Extraction with CH_2Cl_2 and filtration of the dried ($MgSO_4$) extracts through a short column of alumina (Woelm, activity III) gave a crude product (6.8 g), which was recrystallized from acetone–hexane to give 6.35 g (93.3%) of **18**, mp 123–124 °C. Anal. ($C_{17}H_{14}O_5S$) C, H, S.

Methyl 7-[(2-Hydroxyethyl)sulfinyl]xanthone-2-carboxylate (19). To a stirred solution of 2.5 g (7.58 mmol) of **18** in 250 mL of CH_2Cl_2, cooled to 0 °C, was added dropwise a solution of *m*-chloroperoxybenzoic acid (85%, 1.53 g, 7.58 mmol) in 50 mL of CH_2Cl_2. After stirring for an additional 30 min at ambient temperature, the reaction mixture was washed with $NaHCO_3$ and H_2O and dried ($MgSO_4$). Trituration of the residue obtained after evaporation with a few milliliters of AcOEt gave 2.4 g (91.6%) of the sulfoxide **19**, mp 198–199 °C. An analytical sample, recrystallized from THF–*i*-PrOH, showed no change in melting point. Anal. ($C_{17}H_{14}O_6S$) C, H, S.

Methyl 7-[(2-Hydroxyethyl)sulfonyl]xanthone-2-carboxylate (20). A mixture of **18** (1.0 g, 3.03 mmol), 30% H_2O_2 (1.5 mL, 13.2 mmol), and AcOH (30 mL) was kept on a steam bath for 1 h. The resulting hot solution was diluted with 30 mL of hot water and cooled slowly. Suction filtration, followed by recrystallization from THF–EtOH, furnished 800 mg (73%) of the sulfone **20**, mp 214–215 °C. Anal. ($C_{17}H_{14}O_7S$) C, H, S.

7-[(2-Hydroxyethyl)sulfinyl]xanthone-2-carboxylic Acid (21). Ester **19** (2.3 g, 6.65 mmol) was refluxed with KOH (500 mg, 8.93 mmol) in 100 mL of EtOH–H_2O (4:1) for 30 min. Acidification with excess AcOH and cooling gave 2.08 g (44%) of **21**, mp >400 °C. Anal. ($C_{16}H_{12}O_6S$) C, H, S.

7-[(2-Hydroxyethyl)sulfonyl]xanthone-2-carboxylic Acid (22). Hydrolysis of **20** (750 mg, 2.07 mmol) with 200 mg (3.57 mmol) of KOH in a manner similar to **19** → **21** furnished 665 mg (92%) of acid **22**, mp 278–279 °C (from AcOH–H_2O). Anal. ($C_{16}H_{12}O_7S$) C, H, S.

7-[(2-Methoxyethyl)sulfinyl]xanthone-2-carboxylic Acid (23). A mixture of **18** (1.3 g, 3.94 mmol), MeI (2 mL, 32 mmol), NaH (50% in oil, 200 mg, 4.16 mmol), and DMF (30 mL) was stirred under N_2 at room temperature for 3 h and then drowned in 150 mL of H_2O containing 2 N HCl (2 mL). Extraction with CH_2Cl_2, filtration of the dried ($MgSO_4$) extracts through a short column of alumina (Woelm, activity II), and crystallization from acetone–hexane gave 900 mg of the methoxy derivative, mp 81–83 °C. This material was treated with *m*-CPBA (85%, 530 mg, 2.62 mmol) as described for **18** → **19**, to provide the desired sulfoxide (780 mg from acetone–cyclohexane, mp 149–150 °C), 750 mg (2.00 mmol) of which was saponified with NaOH (150 mg, 3.75 mmol) in aq. EtOH (30 min reflux). Two crystallizations from aqueous EtOH gave 570 mg (45.6% overall yield) of **23**, mp >400 °C. Anal. ($C_{17}H_{14}O_6S$) C, H, S.

7-(1-Hydroxyethyl)xanthone-2-carboxylic Acid (26). A mixture of 1.5 g (5.32 mmol) of 7-acetylxanthone-2-carboxylic acid[4] (**25**), 500 mg (5.95 mmol) of $NaHCO_3$, and 90 mL of a THF–EtOH–H_2O mixture (1:1:1) was refluxed on a steam bath for 15 min, and the resulting solution was concentrated on a rotary evaporator to a volume of ~70 mL. Hydrogenation of this solution over 10% Pd/C (250 mg) at room temperature and normal pressure (uptake 130 mL of hydrogen) gave 1.4 g (92.7%) of **26**, mp 245–247 °C after recrystallization from EtOH–H_2O. Anal. ($C_{16}H_{12}O_5$) C, H.

7-(1-Methoxyethyl)xanthone-2-carboxylic Acid (27). To a solution of **26** (400 mg, 1.4 mmol) in dry DMF (15 mL) were added 205 mg (4.2 mmol) of NaH (50% in oil) and 0.5 mL (8 mmol) of MeI. After the solution was stirred for 16 h at ambient temperature, a solution of NaOH (400 mg, 9.8 mmol) in H_2O (4 mL) and EtOH (10 mL) was added, and stirring was continued for another 6 h. The reaction mixture was diluted with H_2O (60 mL) and extracted with ether (2 × 30 mL). Acidification of the aqueous phase with 2 N HCl gave a precipitate, which was filtered off, washed with H_2O, dried, and recrystallized twice from THF–EtOH to provide 290 mg (70%) of **27**, mp 256–257 °C. Anal. ($C_{17}H_{14}O_5$) C, H.

7-(2,3-Dihydroxypropoxy)xanthone-2-carboxylic Acid (29). A solution of methyl 7-(2,3-epoxypropoxy)xanthone-2-carboxylate[7] (**28**; 2.3 g, 7.055 mmol) in THF (80 mL), H_2O (20 mL), and 70% $HClO_4$ (1 mL) was refluxed for 2 h. KOH (2.0 g, 35.7 mmol) and EtOH (50 mL) were added, and refluxing was continued for 30 min. After acidification (2 N HCl), volatile solvents were boiled off on a hot plate until some crystals started to appear. The crystalline material separating on cooling was isolated by suction filtration and purified by recrystallization from DMF–xylene to give **29** (55.8%), mp 272–274 °C (lit.[7] mp 270–273 °C). Anal. ($C_{17}H_{14}O_7$) C, H.

Biological Assay. Aldose reductase was prepared from lenses of mature, New Zealand albino rabbits. The lenses were obtained frozen on dry ice from Pel-Freez Biologicals, Inc. The enzyme was isolated and assayed by methods similar to those employed by Hayman and Kinoshita,[17] who obtained the enzyme from calf lens. Lenses (50) were homogenized in 33 volumes of distilled water, followed by centrifugation at 10000*g* for 15 min to remove insoluble material. Saturated ammonium sulfate was added to the supernatant fluid to 40% saturation. The suspension was centrifuged after 15 min and the supernatant recovered. Additional protein was removed by increasing the ammonium sulfate concentration to 50% and recentrifuging. Aldose reductase was precipitated from the 50% saturated solution by the addition of powdered ammonium sulfate to 75% saturation and was isolated by centrifugation.

The precipitated enzyme was assayed by following the UV absorbance at 340 nm with a Beckman DB-GT grating spectrophotometer attached to a recorder after dissolving the enzyme in 0.05 M sodium chloride. The enzyme (0.50 mL) is added to a quartz cuvette containing phosphate buffer (0.067 M, pH 6.0), NADPH (2×10^{-5} M), and water to a volume of 2.9 mL, and the cuvette is inserted into the spectrophotometer. The reaction is started by the addition of D,L-glyceraldehyde (5×10^{-4} M, final concentration) to the cuvette and is followed by the determination of loss of absorbance at 340 nm for 2 min at 37 °C. The reaction rate observed was usually linear for at least 5 min. Xanthones to be tested were dissolved in a minimal amount of 0.1 N NaOH and diluted with water so that 0.10 mL added to the cuvette would equal the desired final concentration. All results are shown in Table I as percent inhibition, i.e., based on a noninhibited control sample as 0%. At 10^{-6} M, the following standard errors were calculated: compound **6**, 67 ± 9.5% (n = 4); compound **14**, 83 ± 2.03% (n = 3).

Acknowledgment. The authors thank Dr. Jin Kinoshita of the National Eye Institute for testing compounds **6** and **14**.

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