(90%); mp 113–114.5 °C; TLC R_f (A) 0.50. The expected signals were seen in the NMR spectrum. Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

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Synthesis and Adrenergic Blocking Effects of 2-(Alkylamino)-3,4-dihydroquinazolines

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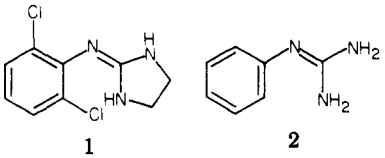
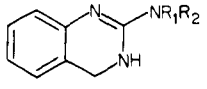
Based on the known biological activity of a variety of guanidine-containing agents, several N-substituted 3,4-dihydroquinazolines were synthesized. These compounds can be considered to be rigid analogues of phenylguanidines. In anesthetized rats the compounds decreased blood pressure and were antagonists of the pressor response to norepinephrine.

The literature is replete with examples of guanidine or guanidine-containing compounds which possess interesting pharmacological properties.[1] In addition, the number of clinically useful agents incorporating the guanidine functionality is similarly substantial.[2] Recently, interest has been stimulated in the area of arylguanidines by way of investigating the centrally active antihypertensive clonidine (1).[3] Studies have indicated that a wide variety of modifications can be made on the clonidine framework with the retention of activity.[4,5]



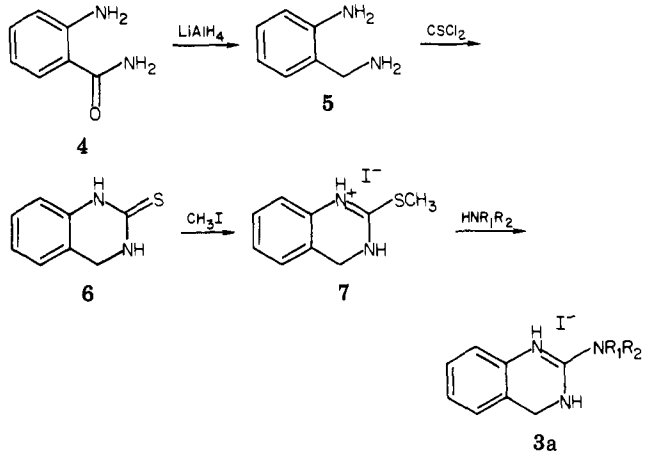
1 2



3a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = CH_3; R_2 = CH_3
d, R_1 = n-C_3H_7, R_2 = n-C_3H_7

In the course of our examination of semirigid analogues of a variety of biologically active flexible parent compounds,[6,7] it seemed of interest to prepare the conformationally defined analogue of phenylguanidine (2), 2-amino-3,4-dihydroquinazoline (3a). It was speculated that this rigid structure might exhibit significant cardiovascular activity, based upon the known activity of the parent, 2,[4] and of other multicyclic congeners.[8,9]

Scheme I



Scheme II

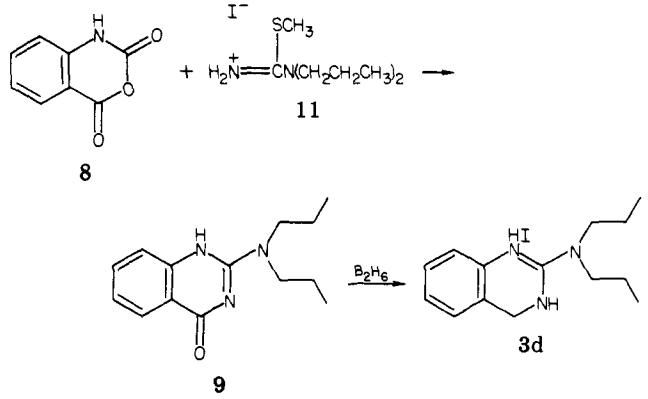


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Table I. Percent Decrease in Mean Arterial Blood Pressure in Response to Intravenous Administration of Compounds 3a–d

dose, μmol/kg	% decrease in blood pressure[a]			
	3a	3b	3c	3d
2	6.76 ± 3.1	4.67 ± 2.23	0	3.2 ± 2.6
4	12.0 ± 0.58	7.7 ± 1.67	0	7.6 ± 4.6
8	13.3 ± 0.88	12.7 ± 0.67	5.67 ± 2.9	11.5 ± 2.7
16	15.0 ± 1.0[b]	19.7 ± 1.67[b]	7.3 ± 1.7	30.9 ± 1.98[c]
32	17.7 ± 1.2[b]	25.0 ± 1.0[c]	12.3 ± 1.2	40.0 ± 3.5[c]
64	23.3 ± 2.6[c]	33.3 ± 2.03[c]	24.7 ± 1.45[c]	

[a] $n = 3$ for each determination. [b] $p < 0.05$. [c] $p < 0.01$.

Chemistry. The target compounds (**3a–d**) were prepared by two different methods, depending upon the *N*-alkyl substitution. The primary amino (**3a**), *N*-methylamino (**3b**), and *N,N*-dimethylamino (**3c**) derivatives were synthesized by the displacement of thiomethoxide from 2-(methylthio)-3,4-dihydroquinazoline hydriodide (**7**) with the appropriate amine in a modification of the procedure described by Orth and Jones[10] (Scheme I). The yields were 67, 84, and 86%, respectively. The reaction would not proceed, even under forcing conditions, when *N,N*-di-*n*-propylamine was used. The 2-(methylthio)-3,4-dihydroquinazoline hydriodide (**7**) was obtained in 89% yield by alkylation of 3,4-dihydro-2(1*H*)-quinazolinethione (**6**) with methyl iodide in absolute ethanol. The thione, in turn, was prepared by condensation between *o*-aminobenzylamine and thiophosgene in Et_2O at −78 °C. The mild conditions for this cyclization are in contrast to an earlier report of the synthesis of the thione using carbon disulfide, which required heating in a sealed vessel for several hours.[10] *o*-Aminobenzylamine was obtained in nearly quantitative yield by reduction of commercially available *o*-aminobenzamide (**4**) with $LiAlH_4$ in refluxing tetrahydrofuran. This was preferable to an early method of preparation using reduction of *o*-nitrobenzylamine or *o*-aminobenzonitrile with tin and hydrochloric acid.[10,11]

The *N,N*-di-*n*-propylamino derivative (**3d**) was obtained by reduction of the corresponding 2-(*N,N*-di-*n*-propylamino)-4(1*H*)-quinazolinone (**9**) with diborane in refluxing tetrahydrofuran (Scheme II). This quinazolinone was synthesized in 41% yield by the reaction of commercially available isatoic anhydride **8** with *S*-methyl-*N,N*-di-*n*-propylisothiourea hydriodide (**11**) in refluxing dioxane, by a modification of the procedure described by Coppola, Hardtman, and Pfister.[12] The isothiourea hydriodide was prepared by alkylation of *N,N*-di-*n*-propylthiourea (**10**) with methyl iodide using a procedure described by Braun.[13] The thiourea **10** was obtained following the method of Hartmann and Reuther.[14]

Results

The effects of the compounds on rat blood pressure are shown in Table I. All compounds produced an immediate decrease in blood pressure. Blood pressure returned to preinjection control levels within 1–3 min. Pretreatment with propranolol (2 mg/kg) failed to attenuate the depressor response. The dipropyl-3,4-dihydroquinazoline hydriodide **3d** had low solubility even in a 20:10:70 mixture of polyethylene glycol, ethanol, and water. Precipitation in the intravenous cannula could not be prevented at high doses. In all rats receiving the dipropyl compound (**3d**) at a dose of 32 μmol/kg, the blood pressure remained at the initial low level following injection for approximately 10 min. The blood pressure never returned to preinjection levels, and all rats died within 25 min of injection. Therefore, the norepinephrine blocking action of **3d** was not determined. The 2-amino- (**3a**), 2-(*N*-methylamino)- (**3b**), and 2-(*N,N*-dimethylamino)-3,4-dihydroquinazoline (**3c**) decreased the pressor response to 0.3 μg/kg of norepinephrine (see Table II). This effect was transitory and lasted no longer than 15 min with **3a** and less than 10 min with **3b** and **3c**. When compared using Student's *t* test, the percent block of the norepinephrine pressor response after **3a** was not significantly different from that of **3b**. The blocking ability of phentolamine was significantly higher than all other compounds tested (**3a** vs. phentolamine, $p < 0.05$; **3b** vs. phentolamine, $p < 0.01$).

These results are interesting in light of the fact that phenylguanidine (**2**), the "open-chain" analogue of **3a**, is an α-adrenergic stimulant and increases blood pressure.[16] It is unclear why the incorporation of a flexible molecule into a rigid framework should lead to a reversal of activity. However, the hypotensive effects of **3a–d** are not unexpected, since related compounds containing an arylguanidine in a planar configuration have this action.[8,9] These results seem to support the conclusion that clonidine (**1**) acts by a different mechanism than arylguanidines in general.[9] Further, these observations are consistent with the idea that clonidine interacts with the receptor when the guanidine moiety is in a plane approximately perpendicular to the aromatic ring, as is observed in the crystal structure.[17] On the other hand, the results seem to indicate that the α-adrenergic blocking agents tolazoline and phentolamine, both of which can be considered to be chemically related to the 3,4-dihydroquinazolines, may possess active binding conformations where the imidazoline is coplanar with the aromatic ring.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries using a Mel-Temp apparatus and are corrected. IR spectra were recorded on a Beckman IR-33 instrument. The three strongest absorptions (four in the case of two being equal) are reported in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 or FT-80. Chemical shifts are reported in parts per million with Me_4Si as the internal reference. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; br, broad. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values. Thin-layer chromatography (TLC) was performed on Macherey-Nagel Polygram SIL G/UF_{254} 0.25-mm precoated plastic plates.

2-Aminobenzylamine (5). To a stirring suspension of 15.2 g (0.04 mol) of $LiAlH_4$ in 100 mL of dry THF in a 500-mL

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Table II. Antagonist Effects of 3a–c to the Pressor Response of 0.3 μg/kg of Norepinephrine Intravenously in Rats

compd	dose, μmol/kg	% block of NE[a]	n
3a	32	49.3 ± 6.5[c]	4
3b	32	37.8 ± 6.2[b]	3
3c	32	10.0 ± 3.0	3
phentolamine	32	66.2 ± 3.7[c,d]	3

[a] Values are mean plus or minus SEM. [b] $p < 0.05$. [c] $p < 0.01$. [d] The blocking effect of phentolamine was significantly greater than either 3a or 3b ($p < 0.05$ and $p < 0.001$, respectively).

round-bottom flask was added dropwise 13.6 g (0.1 mol) of 2-aminobenzamide (4), dissolved in 50 mL of dry THF. The mixture was stirred at reflux under N_2 for 52 h. The $LiAlH_4$ was decomposed by the dropwise addition of 15 mL of H_2O, 15 mL of 2 N NaOH, and then 45 mL of H_2O. An additional 50 mL of THF was added to aid in the dispersion of the aluminum salts. The suspension was filtered using suction. The solids were stirred in 400 mL of hot $CHCl_3$ and filtered. The filtrates were combined and reduced under vacuum. The resulting brown oil solidified while drying at 25 °C under high vacuum: yield 11.9 g (97.5%); a small amount of starting material remained by TLC [$CHCl_3/CH_3OH/NH_4OH$ (58%) (15:5:1)].

A small amount of the product was converted to its HCl salt with 5% HCl/EtOH for analysis and recrystallized from MeOH/anhydrous Et_2O, mp 197–199 °C. The pure free base was regenerated by neutralization of this salt and extraction into $CHCl_3$. The $CHCl_3$ was removed on the rotary evaporator to yield a tan powder: mp 58.5–60.5 °C (lit.[11] mp 59–60 °C); IR (KBr) 3260, 1480, 1300 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (m, 4, Ar H's), 3.90 (s, 2 Ar CH_2), 2.8 (br, 4, Ar NH_2 and NH_2).

3,4-Dihydro-2(1*H*)-quinazolinethione (6). A solution of 6.35 g (0.052 mol) of the 2-aminobenzylamine (5) and 12.24 g (0.120 mol) of Et_3N dissolved in 150 mL of dry Et_2O was cooled to −78 °C; to this was added, dropwise, a solution of 7.2 g (0.060 mol) of $CSCl_2$ dissolved in 40 mL of dry Et_2O, over a period of 1 h. The heterogeneous mixture was allowed to warm to 25 °C and was suction filtered. The filter cake was suspended in 100 mL of dry Et_2O, refiltered, and washed on the filter with 50 mL of dry Et_2O. The filter cake was then dissolved in 150 mL of MeOH and 6.72 g (0.120 mol) of KOH was stirred into the solution. The KCl precipitate was removed by gravity filtration, and the filtrate was evaporated to dryness on a rotary evaporator. The solid residue was recrystallized from EtOH/H_2O: yield 4.9 g (58%); mp 200–205 °C; trace impurities by TLC [$CHCl_3/CH_3OH/NH_4OH$ (58%) (8:2:0.3)].

An analytical sample was recrystallized from EtOH/H_2O: mp 204–207 °C (lit.[15] mp 210–212 °C); IR (KBr) 3200, 1530, 1505 cm^{-1}; NMR [Me_2SO-d_6/$CDCl_3$ (1:1)] δ 8.5 (br, 2, 2-NH), 7.05 (m, 4, Ar H's), 4.5 (s, 2, Ar CH_2).

2-(Methylthio)-3,4-dihydroquinazoline Hydriodide (7). To a suspension of 2.8 g (0.017 mol) of 3,4-dihydro-2(1*H*)-quinazolinethione (6) in 110 mL of absolute EtOH was added 9.8 g (0.069 mol) of CH_3I. The mixture was stirred at reflux for 45 min. The resulting solution was concentrated on the rotary evaporator, whereupon the product crystallized: yield 4.57 g (89%); mp 215 °C (dec); pure by TLC [$CHCl_3/CH_3OH$ (8:2)]; IR (KBr) 1620, 1545, 1250 cm^{-1}; NMR (Me_2SO-d_6/$CDCl_3$) δ 7.37 (m, 4, Ar H's), 4.91 (s, 2, Ar CH_2), 4 (br, 2, 2-NH), 2.95 (s, 3, SCH_3). Anal. ($C_9H_{11}N_2SI$) C, H, N.

General Preparation of 2-(Alkylamino)-3,4-dihydroquinazolines (3a–c). Typically, to 40 mL of a 40% (w/w) aqueous solution of the amine and 10 mL of 95% EtOH was added 0.003 mol of 2-(methylthio)-3,4-dihydroquinazoline hydriodide (7). The resulting solution was stirred at reflux for 4 h. The solvent was removed on the rotary evaporator. The residue was first dissolved in 10 mL of absolute EtOH, and this solution was reduced to dryness on the rotary evaporator. This process was repeated four times. The products recovered were tan powders, which were recrystallized from absolute EtOH/anhydrous Et_2O.

2-Amino-3,4-dihydroquinazoline Hydriodide (3a): yield 0.60 g (67%); pure by TLC [$CHCl_3$/MeOH/NH_4OH (58%) (8:2:0.3)]; mp 199–201 °C; IR (KBr) 1675, 1620, 1580 cm^{-1}; NMR (Me_2SO-d_6) δ 10.36 (br, 1, N_1 H), 9.21 (br, 1, N_3 H), 7.43 (s, 2, NH_2), 7.35–6.91 (m, 4, Ar H's), 4.50 (s, 2, Ar CH_2). Anal. ($C_8H_{10}N_3I$) C, H, N.

2-(*N*-Methylamino)-3,4-dihydroquinazoline Hydriodide (3b): yield 0.73 g (84%); pure by TLC [$CHCl_3/CH_3OH/NH_4OH$ (58%) (8:2:0.3)]; mp 204–206 °C; IR (KBr) 3180, 1665, 1620 cm^{-1}; NMR (Me_2SO-d_6) δ 10.26 (br, 1, N_1 H), 8.41 (br, 1, N_3 H), 7.71 (q, 1, $NHCH_3$), 7.31–7.08 (m, 4, Ar H's), 4.5 (s, 2, Ar CH_2), 2.88 (d, 3, $NHCH_3$). Anal. ($C_9H_{12}N_3I$) C, H, N.

2-(*N*,*N*-Dimethylamino)-3,4-dihydroquinazoline Hydriodide (3c): yield 0.77 g (86%); pure by TLC [$CHCl_3/CH_3OH/NH_4OH$ (58%) (8:2:0.3)]; mp 243–246 °C (dec); IR (KBr) 3200, 1650, 1555 cm^{-1}; NMR (Me_2SO-d_6) δ 8.5 (br, 2, 2-NH), 7.20 (m, 4, Ar H's), 4.47 (s, 2, Ar CH_2), 3.12 [s, 6, 2-$N(CH_3)_2$]. Anal. ($C_{10}H_{14}N_3I$) C, H, N.

2-(*N*,*N*-Dipropylamino)-4(1*H*)-quinazolinone (9). To 60 mL of dry dioxane was added 5.55 g (0.013 mol) of *S*-methyl-*N*,*N*-dipropylisothiourea hydriodide (11), followed by 2.14 g (0.020 mol) of Na_2CO_3. The suspension was heated until the isothiourea dissolved. To the reaction mixture was added 3.0 g (0.018 mol) of isatoic anhydride 8. The resulting suspension was heated at reflux for 14 h. The turbid solution was allowed to cool to 25 °C. Agitation caused the product to precipitate. The entire reaction was poured into 60 mL of H_2O and stirred for 15 min. The product was recovered by suction filtration. The filter cake was dried under aspirator vacuum at 50 °C for 24 h: yield 1.85 g (41%).

An analytical sample was recrystallized from dioxane/MeOH: mp 188–190 °C; IR (KBr) 1660, 1575, 1320 cm^{-1}; NMR (Me_2SO-d_6) δ 10.99 (s, 1, N_1 H), 7.4 (m, 4, Ar H's), 3.47 (t, 4, 2-NCH_2), 1.62 (sx, 4, 2-CH_2), 0.88 (t, 6, 2-CH_3). Anal. ($C_{14}H_{19}N_3O$) C, H, N.

2-(*N*,*N*-Dipropylamino)-3,4-dihydroquinazoline Hydriodide (3d). To 23.2 mL of 1 M BH_3 in THF (0.0232 mol of BH_3) was added 1.42 g (0.0056 mol) of 2-(*N*,*N*-dipropylamino)-4(1*H*)-quinazolinone (9). The resulting solution was heated at reflux under N_2 for 2 h. The borate complex and excess reagent were then hydrolyzed by the dropwise addition of 5.7 mL of 6 N HCl. The acidic suspension was basified with 22.8 mL of 6 N NaOH. The mixture was concentrated under vacuum and the residue was extracted with three 10-mL portions of hot $CHCl_3$. The combined extracts were concentrated on the rotary evaporator to yield an amber oil.

The oil was dissolved in 10 mL of absolute EtOH and titrated to pH ~3 with 50% aqueous HI. The EtOH was removed on the rotary evaporator. The residue was dissolved in 10 mL of absolute EtOH and concentrated to dryness under vacuum. This process was repeated three more times. The oily residue was then recrystallized from absolute EtOH/anhydrous Et_2O: yield 1.455 g (72%) as the ethanol solvate.

An analytical sample was recrystallized from absolute EtOH/anhydrous Et_2O and dried under aspirator vacuum at 100 °C for 48 h: mp 158–160 °C; IR (KBr) 3180, 1620, 1530 cm^{-1}; NMR (Me_2SO-d_6) δ 10.20 (s, 1, N_1 H), 8.52 (s, 1, N_3 H), 7.40 (m, 4, Ar H's), 4.45 (s, 2, Ar CH_2), 3.52 (t, 4, 2-NCH_2), 3.27 (OH), 1.60 (sx, 4, 2-CH_2), 0.91 (t, 6, 2-CH_3). Anal. ($C_{14}H_{22}N_3I \cdot 0.375CH_3CH_2OH$) C, H, N.

***S*-Methyl-*N*,*N*-di-*n*-propylisothiourea Hydriodide (11).** To 11.3 g (0.071 mol) of *N*,*N*-di-*n*-propylthiourea (10)[14] was added 5 mL of absolute EtOH. Through the top of a long water-cooled condenser was added 11.1 g (0.077 mol) of CH_3I in a single addition. As the evolution of heat became apparent, the reaction was externally cooled in an ice/H_2O bath. Shortly thereafter (~3 min) the solution solidified. The solid mass was broken up in 25 mL of anhydrous Et_2O. The solid was collected by suction filtration and washed on the filter with 25 mL of anhydrous Et_2O: yield 21.4 g (quantitative); mp 137–139 °C; IR (KBr) 3040, 1614, 1572 cm^{-1}; NMR (Me_2SO-d_6) δ 8.90 (br, 2, NH_2), 3.60 (t, 4, 2-NCH_2), 2.78 (s, 3, SCH_3), 1.14 (sx, 4, 2-CH_2), 0.90 (t, 6, 2-CH_3). Anal. ($C_8H_{19}N_2SI$) C, H, N.

Pharmacology. Male Sprague–Dawley rats weighing 300–350 g were used. The rats were anesthetized with pentobarbital sodium, 40 mg/kg, given intraperitoneally. Tracheal cannulation was performed to ensure adequate ventilation. Drugs were dissolved in 0.9% saline and administered in a volume of 0.1 to 0.15 mL through a cannulated external jugular vein. The carotid artery was cannulated and connected to a Statham P23 pressure transducer for recording of blood pressure on a Grass polygraph.

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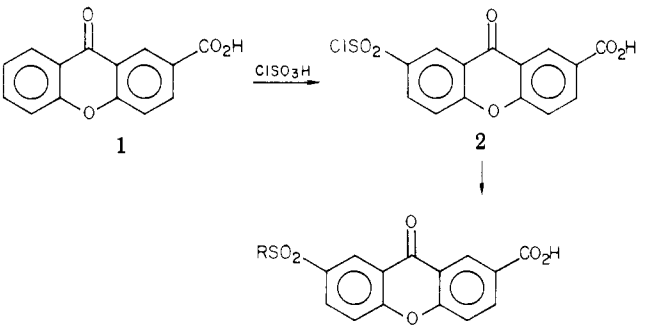
A series of xanthone-2-carboxylic acids substituted in the 7 position with sulfamoyl and other groups was synthesized and assayed in vitro for inhibition of aldose reductase isolated from rabbit lenses. At a concentration of 10^{-6} M, the *N*-methyl-*N*-(2-hydroxyethyl)sulfamoyl derivative **14** produced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

Scheme I



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

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).

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-

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