These were carried out by using the method of Gill and Rang.[20b] The aminotetralin hydrochloride (0.04 mmol) was dissolved in ethanol (0.5 mL) and added to buffer solution (50 mL) (10.0 mM aqueous solution of potassium dihydrogen phosphate containing ethanol (20%) and adjusted to pH 7.4 with 0.1 M sodium hydroxide solution) to give a final concentration of amine hydrochloride of 0.8 mM. The solution was kept at a constant temperature of 25 °C. The time of addition of the amine salt was noted (t = 0). Aliquots (5.0 mL) were removed at 1–2-min intervals in the early stages of the experiment and at longer time intervals as the experiment proceeded. Immediately after removal of each aliquot, the reaction was stopped by the addition of acetic acid (0.2 M, 1.0 mL), followed by sodium thiosulfate (10.0 mM, 1.0 mL). The mixture was left to stand for ca. 20 min at room temperature. Residual thiosulfate was then measured by titration with iodine solution (4.0 mM). In this manner the amount of thiosulfate consumed in reaction with the aziridinium ion could be calculated. The accuracy of this procedure was verified by repeating Gill and Rang's kinetic experiment using benzilylcholine mustard.[20b] Comparable results were obtained.

b. ^{1}H NMR Studies. These were carried out on a Bruker CXP 200 instrument using a pulse width of 45° and digital resolution of 0.648 Hz/point by following the general procedure of Levins and Papanastassiou.[21] *N*-(2-Chloroethyl)-*N*-methyl-1,2,3,4-tetrahydro-6,7-dihydroxy-2-naphthylamine hydrochloride (**10**) (ca. 10 mg) was dissolved in D_2O (0.5 mL) in an NMR tube and a solution of KOH in D_2O (10 M, >1 equiv) added to liberate the free amine. The NMR tube was placed in the probe at 25 °C and the first scan taken 30 s after mixing. Scans were then taken at 1.25-s intervals, eight scans being combined to give an averaged spectrum every 10 s. Averaged spectra were then displayed individually (Figure 4) or in a two-dimensional stacked plot (Figure 5).

Acknowledgment. We thank the M.R.C., the S.E.R.C., and the University of East Anglia for financial support (A.W.H. and S.H.S.). We are also grateful to Dr. T. A. Carpenter for carrying out the ^{1}H NMR kinetic studies (S.E.R.C. Grant GR/B/81298).

Registry No. **1**, 109529-47-7; **2**, 109529-48-8; **3**, 109529-76-2; **3**·HCl, 109529-49-9; **4**, 109529-77-3; **4**·HCl, 109529-50-2; **5**, 109529-78-4; **5**·HCl, 109529-51-3; **6**, 109529-79-5; **6**·HBr, 109529-52-4; **7**, 109529-80-8; **7**·HCl, 109529-53-5; **8**, 109529-81-9; **8**·HBr, 109529-54-6; **9**, 109529-82-0; **9**·HCl, 109529-55-7; **10**, 109529-83-1; **10**·HCl, 109529-56-8; **11**, 109529-57-9; **12**, 109529-84-2; **12**·HCl, 109529-58-0; **13**, 109529-85-3; **13**·HBr, 109529-59-1; **14**, 109529-60-4; **15**, 109529-61-5; **16**, 109529-86-4; **16**·HBr, 109529-62-6; **17**, 109529-87-5; **17**·HCl, 109529-63-7; **18**, 109529-88-6; **18**·HBr, 109529-64-8; **18**·HCl, 109529-97-7; **19**, 109529-89-7; **19**·HBr, 109529-65-9; **20**, 109529-66-0; **21**, 109529-90-0; **21**·HBr, 109529-67-1; **22**, 109529-91-1; **22**·HCl, 109529-68-2; **23**, 109529-92-2; **23**·HCl, 109529-69-3; **24**, 109529-93-3; **24**·HCl, 109529-70-6; **25**, 109529-71-7; **26**, 109529-94-4; **26**·HCl, 109529-72-8; **27**, 109529-95-5; **27**·HCl, 109529-73-9; **28**, 109529-74-0; **29**, 109529-96-6; **29**·HCl, 109529-75-1; **30**·HCl, 13917-16-3; **31**·HCl, 63307-13-1; **32**·HBr, 13575-86-5.

Evaluation of Isomeric 4-(Chlorohydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines as Dopamine D-1 Antagonists

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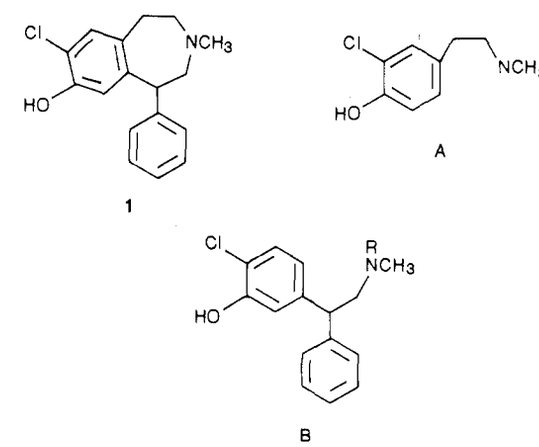
Received April 13, 1987

The isomeric 4-(3-chloro-4-hydroxyphenyl)- and 4-(4-chloro-3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines, the *N*-methyl derivative of the 4-(4-chloro-3-hydroxyphenyl) isomer, and 4-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline were synthesized and evaluated for dopamine D-1 antagonist activity. The 4-(3-chloro-4-hydroxyphenyl) and the 4-(3-hydroxyphenyl) isomer possessed similar potencies as D-1 antagonists. Introduction of the *N*-methyl group enhanced potency about twofold. The "pharmacophore" for selective dopamine D-1 antagonist activity appears to be a tertiary 2-(3-hydroxyphenyl)-2-phenethylamine.

SCH 23390 (**1**) is a selective antagonist for central dopamine D-1 and vascular DA_1 receptors, with weak affinity for 5-HT, α_1-adrenergic and D-2 dopamine receptors.[1-4] It blocks the conditioned avoidance response in rats and squirrel monkeys in a manner similar to that of classical antipsychotics[1] such as chloropromazine and haloperidol, which have been demonstrated to block D-2 receptors. In addition, **1** has proven to be a useful pharmacological tool in discerning the functional role and location of central dopamine D-1 receptors.[5-8]

Compound **1** may bind to the D-1 receptor in one of two different modes. It may bind as a 3-chloro-4-hydroxyphenethylamine derivative as in A or as a 2-(4-chloro-3-hydroxyphenyl)-2-phenethylamine derivative as in B. For B, the hydroxy group is oriented meta to the side chain, which is generally regarded to be a critical feature of dopamine agonists.[9] However, it may be argued that replacement of the critical *m*-OH with chlorine would give an antagonist. Further, Dandrige et al.[10] have presented a dopamine-receptor model that explicitly favors fragment A, consistent with this latter argument.



[†] Purdue University.
[‡] Eli Lilly Research Laboratories.

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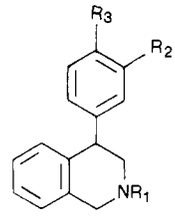
To resolve this ambiguity, it was decided to synthesize 4-phenyl-1,2,3,4-tetrahydroisoquinoline analogues **2–5** of **1**. Previously, hydroxylated derivatives of this class have shown D-1 and DA_1 agonist activity comparable to that of the phenylbenzazepine SKF 38393,[11] and a structural correspondence between the 4-phenyl-1,2,3,4-tetrahydroisoquinolines and the phenylbenzazepines has been suggested that correctly predicted the stereochemistry of the more active enantiomer of 3′,4′-dihydroxynomifensine, a 4-phenyltetrahydroisoquinoline D-1 agonist.[12] Thus, **2–5** extend D-1 antagonist structure–activity relationships into the 4-phenyl-1,2,3,4-tetrahydroisoquinoline series. Compound **2** was included to determine the necessity of the chlorine functionality for antagonist activity. The *N*-methyl derivative **5** was synthesized, since Itoh et al.[13] have shown that N-alkylation enhances D-1 antagonist properties of the phenylbenzazepines.



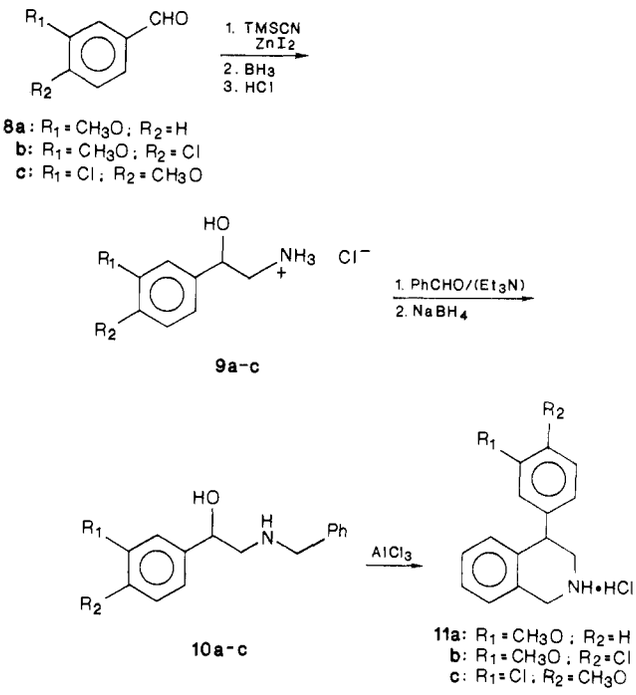
2: $R_1 = R_3 = H$; $R_2 = OH$
3: $R_1 = H$; $R_2 = OH$; $R_3 = Cl$
4: $R_1 = H$; $R_2 = Cl$; $R_3 = OH$
5: $R_1 = CH_3$; $R_2 = OH$; $R_3 = Cl$

Chemical Discussion

The key intermediates for the synthesis of the 4-(chlorohydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines were the aldehydes **8b** and **8c**. Aldehyde **8b** was synthesized from commercially available 2-chloro-5-methylphenol. Treatment with methyl iodide and potassium carbonate gave the methyl ether, which was oxidized with $KMnO_4$ to the acid **6a**.[14] The acid was reduced to benzyl alcohol **7a**, previously synthesized by Faith et al.[15] Conversion to **8b** was accomplished by treatment of **7a** with activated MnO_2.

The 3-chloro-4-methoxybenzaldehyde (**8c**) was synthesized from commercially available 3-chloro-4-hydroxybenzoic acid, which was converted to its methyl ester **12** and O-methylated with methyl iodide and potassium carbonate. The ester **13** was saponified to acid **6b**, followed by reduction to the benzyl alcohol **7b** with BH_3/THF. Oxidation to the desired aldehyde **8c** was accomplished with activated MnO_2.

Scheme I



8a: $R_1 = CH_3O$; $R_2 = H$
b: $R_1 = CH_3O$; $R_2 = Cl$
c: $R_1 = Cl$; $R_2 = CH_3O$

11a: $R_1 = CH_3O$; $R_2 = H$
b: $R_1 = CH_3O$; $R_2 = Cl$
c: $R_1 = Cl$; $R_2 = CH_3O$

Table I. Inhibitory Effects of Tetrahydroisoquinoline Derivatives on the Adenylate Cyclase Response to Dopamine

no.	R_1	R_2	R_3	concn, μM	% inhibn[a]
1				0.01	23.2 ± 3
				0.1	59.9 ± 5.2
				1.0	74.3 ± 1.5
2	H	OH	H	1	NI[b]
				10	8.8 ± 3.9
				100	22.9 ± 3.2
3	H	OH	Cl	1	NI
				10	8.9 ± 4.8
				100	26.3 ± 4.9
4	H	Cl	OH	1	NI
				10	NI
				100	NI
5	CH_3	OH	Cl	1	NI
				10	21.0[c]
				30	45.1 ± 2.8
				100	57.9 ± 2.9

[a] Values represent mean ± SEM of three determinations of the compound in the presence of 10 μM dopamine. [b] No inhibition. [c] $n = 2$ for this value.

m-Anisaldehyde (**8a**), **8b**, and **8c** were stirred with trimethylsilyl cyanide and a catalytic amount of zinc iodide. The crude trimethylsilyl ether cyanohydrins were reduced with diborane to yield **9a–c** (Scheme I). The salts of these amines were converted to **10a–c** by stirring with triethylamine and benzaldehyde in ethanol at reflux, followed by reduction of the intermediate imines with sodium borohydride. Cyclization of **10a–c** to **11a–c**, respectively, was accomplished by stirring with anhydrous aluminum chloride in dichloromethane at reflux. Conversion of **11b** to **11d** was easily carried out with excess aqueous formaldehyde and $NaCNBH_3$ in methanol. Demethylation to the target molecules was accomplished by stirring at reflux in aqueous 48% hydrobromic acid.

Results and Discussion

The chlorohydroxy compounds **3–5** were compared, together with **2**, as D-1 antagonists in inhibiting dopamine-sensitive adenylate cyclase. The data are presented in Table I. Compounds **2** and **3** had comparable, albeit weak, antagonist activity. Compound **4** was inactive at all concentrations. The *N*-methyl derivative **5** was approxi-

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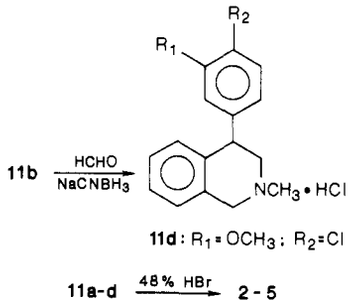

mately 2.5 times more active than either **2** or **3**. However, **1** can be estimated to be about 1000 times more potent an antagonist than **5**.

From the data it is apparent that the hydroxy group must reside in the position meta to the ethylamine side chain. Compound **4**, with the *p*-hydroxy substituent, is devoid of antagonist properties. Also, the chlorine substituent is not required for antagonist activity[13] (compare **2** to **3**). In agreement with previously known structure–activity relationships, the *N*-methyl group enhances antagonist potency approximately twofold.[13] Therefore, it would appear that the essential structural feature within **1** is the tertiary *N*-methyl-2-(3-hydroxyphenyl)-2-phenethylamine fragment.

An obvious question remains to be answered: why is **1** so much more active than **5**, its 4-phenyl-1,2,3,4-tetrahydroisoquinoline analogue? The 4-phenyltetrahydroisoquinolines are probably able to bind to the dopamine D-1 receptor in an essentially trans antiperiplanar conformation. However, the conformation of the phenethylamine fragment in the phenylbenzazepines is closer to an extended cis orientation.

Furthermore, the unsubstituted aromatic rings of both compounds can adopt approximately the same orientation with respect to the chloro–hydroxy-substituted ring. Therefore, a plausable explanation for the enhanced activity of **1** might be that the conformationally restricted, extended cis conformation of the phenylbenzazepine intrinsically increases dopamine D-1 antagonist activity.

Finally, even though **5** is weaker than **1**, the greater antagonist activity of **3** and **5**, compared with **5**, challenges the validity of the receptor model presented by Dandridge et al.[10]

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 or XL-200 instrument. Chemical shifts are reported in parts per million with TMS or DSS as the internal reference. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical-ionization (CI) mass spectra were obtained with a Finnigan 4000 quadrupole spectrometer. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values unless otherwise noted.

Methyl 3-Chloro-4-hydroxybenzoate (12). A solution of 3-chloro-4-hydroxybenzoic acid hemihydrate (Aldrich) (5 g, 27.5 mmol) in 100 mL of methanol containing 5 mL of concentrated H_2SO_4 was held at reflux for 5 h. The methanol was removed by rotary evaporation and the residue was diluted with 100 mL of ether. The ether layer was washed with 100 mL water, followed by 120 mL saturated $NaHCO_3$ solution and finally 100 mL water. The organic solution was dried ($MgSO_4$) and the solvent was removed by rotary evaporation. The residue was recrystallized from dichloromethane/hexanes: yield 5 g, 93%, mp 103–105 °C (previously synthesized by Hirai,[16] no melting point was reported); NMR ($CDCl_3$) δ 8.04 (d, 1, Ar H), 7.88 (dd, 1, Ar H), 7.05 (d, 1, Ar H), 6.14 (br s, 1, OH), 3.89 (s, 3, CH_3O).

Methyl 3-Chloro-4-methoxybenzoate (13). Ester **12** (4.5 g, 24.1 mmol) was dissolved in 80 mL of dry acetone, to which was added 4.2 g (30 mmol) of K_2CO_3. After addition of 2 mL (30 mmol) of methyl iodide, the mixture was held at reflux for 16 h. After removal of solvent by rotary evaporation, the residue was redissolved in 100 mL of ether. The ether layer was washed with 100 mL of water, followed by 100 mL of 1 N NaOH and finally 100 mL of water. After drying ($MgSO_4$), removal of solvent afforded 5 g (98%) of crude product, which was recrystallized from dichloromethane/hexanes: mp 97–99 °C (lit.[17] mp 94–94.3 °C; NMR ($CDCl_3$) δ 8.00 (m, 2, Ar H), 6.95 (d, 1, Ar H), 3.96 (s, 3, CH_3), 3.89 (s, 3, CH_3O).

4-Chloro-3-methoxybenzoic Acid (6a). A solution of 4-chloro-3-methoxytoluene (2 g, 15.1 mmol) was stirred with 5.5 g (34.8 mmol) of $KMnO_4$ in 100 mL of water at reflux for 16.0 h. MnO_2 was removed by suction filtration and washed with hot water (2 × 50 mL). The aqueous phase was then extracted with ether (2 × 50 mL) and acidified with concentrated HCl to pH 2, and the solid was collected by suction filtration. The product was recrystallized from aqueous ethanol: yield 1.45 g, 58%; mp 217–220 °C (lit.[14] mp 211 °C). Anal. ($C_8H_7ClO_3$) C, H.

3-Chloro-4-methoxybenzoic Acid (6b). Ester **13** (23.9 mmol) was suspended in 100 mL of 0.6 N NaOH. The two-phase mixture was stirred at reflux until it was homogeneous. The solution was cooled and washed with ether (2 × 100 mL) and then acidified to pH 2. The precipitated acid was obtained by suction filtration and air-dried. Recrystallization from aqueous ethanol gave a 4.29-g yield (91.8%): mp 213–215 °C (lit.[20] mp 217.5 °C); NMR ($CDCl_3$) δ 7.88 (m, 2, Ar H), 7.24 (d, 1, Ar H), 3.93 (s, 3, CH_3O).

4-Chloro-3-methoxybenzyl Alcohol (7a).[18] Acid **6a** (1.6 g, 8.6 mmol) was dissolved in 20 mL of THF. BH_3/THF (1 M, 14 mL) was added and the mixture was held at reflux under a nitrogen atmosphere for 2.0 h. The layers were separated, and the organic phase was washed with 50 mL of water and 50 mL of 5% Na_2CO_3. After drying ($MgSO_4$), the solvent was removed by rotary evaporation: yield 1.4 g, 94%; CI-MS 183 (M + 1), base peak 155; NMR ($CDCl_3$) δ 7.26 (d, 1, Ar H), 6.93 (m, 2, Ar H), 4.66 (s, 2, CH_2), 3.91 (s, 3, CH_3O), 1.71 (s, 1, OH).

3-Chloro-4-methoxybenzyl Alcohol (7b).[19] Via a procedure similar to that for **7a**, 4.29 g (21.9 mmol) of **6b** was converted to **7b**: yield 3.91 g (98%); NMR ($CDCl_3$) δ 7.37 (d, 1, Ar H), 7.22 (dd, 1, Ar H), 6.88 (d, 1, Ar H), 4.59 (s, 2, CH_2), 3.89 (s, 3, CH_3O), 1.74 (br s, 1, OH).

4-Chloro-3-methoxybenzaldehyde (8b). Alcohol **7a** (2.68 g, 15.5 mmol) was dissolved in 60 mL of benzene. Activated MnO_2 (4.1 g, 46.5 mmol) was added and the mixture was held at reflux for 9 h. The MnO_2 was removed by suction filtration and was then washed with dichloromethane (3 × 50 mL). After solvent removal, 1.95 g of a viscous oil was obtained: yield 1.95 g, 73.7%; crystallization from hexanes gave mp 41–42.5 °C (lit.[15] mp (from acetic acid) 52 °C); NMR ($CDCl_3$) δ 9.95 (s, 1, aldehyde H), 7.48 (m, 3, Ar H), 3.98 (s, 3, CH_3O).

3-Chloro-4-methoxybenzaldehyde (8c). Via a procedure similar to that for **8b**, alcohol **7b** (3.4 g, 18.7 mmol) was oxidized with MnO_2 and recrystallized from ether/hexanes to yield 2.73 g (85.5%): mp 54–56 °C (lit.[21] mp (from aqueous acetic acid) 62 °C); NMR ($CDCl_3$) δ 9.85 (s, 1, aldehyde H), 7.90 (d, 1, Ar H (J = 2 Hz)), 7.78 (dd, 1, Ar H (J = 2, 8.4 Hz)), 7.04 (d, 1, Ar H (J = 8.4 Hz)), 3.99 (s, 3, CH_3O).

1-(3-Methoxyphenyl)-2-aminoethanol Hydrochloride (9a). *m*-Anisaldehyde (**8a**) (2.5 g, 18.4 mmol) was stirred overnight with 2.0 g (20.2 mmol) of trimethylsilyl cyanide in 20 mL of dichloromethane and a catalytic amount of ZnI_2. The solvent was removed by rotary evaporation. The crude trimethylsilyl ether cyanohydrin was reduced with 1 M BH_3/THF (40 mL, 40.0 mmol), with stirring at reflux for 4 h under a nitrogen atmosphere. The THF was removed by rotary evaporation and the borane–amine

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complex was decomposed by reflux with 1 N methanolic HCl for 1.0 h. The methanol was removed by rotary evaporation and the residue was dissolved in 50 mL of dilute HCl. The acidic solution was washed with ether (2 × 50 mL). The aqueous layer was basified to pH 10 with concentrated NH_4OH and extracted with dichloromethane (3 × 30 mL), and the organic solution was dried ($MgSO_4$). The dichloromethane was removed by rotary evaporation, the crude base was converted to the HCl salt, and the salt was recrystallized from ethanol/ether: yield 2.0 g, 65%; mp 111–112 °C; NMR (D_2O) δ 7.21 (m, 1, Ar H), 6.82 (m, 2, Ar H), 4.87 (m, 1, CH), 3.70 (s, 3, CH_3O), 3.12 (m, 2, CH_2). Anal. ($C_9H_{14}ClNO_2$) C, H, N.

1-(4-Chloro-3-methoxyphenyl)-2-aminoethanol Hydrochloride (9b). Aldehyde **8b** (1.90 g, 11 mmol) was dissolved in 50 mL of dichloromethane, containing 2 mL (14.3 mmol) of trimethylsilyl cyanide and a catalytic amount of ZnI_2. The mixture was stirred at 25 °C for 2 h, washed with 25 mL of water, and dried ($MgSO_4$). After solvent removal, the residue was treated with 1 M BH_3/THF (25 mL, 25 mmol) at reflux for 16 h. After cooling, the THF was removed by rotary evaporation. The residue was stirred with 10 mL of 1 N methanolic HCl for 1.0 h. After removal of the solvents, the residue was dissolved in 10 mL of water and washed with ether (2 × 30 mL). After concentration by rotary evaporation, the residue was recrystallized from ethanol/ether: yield 0.97 g, 35.8%; mp 199–201 °C; NMR (D_2O) δ 7.48 (d, 1, Ar H (J = 8.1 Hz)), 7.19 (d, 1, Ar H (J = 8.1 Hz)), 7.07 (dd, 1, Ar H (J_1 = 1.8 Hz, J_2 = 8.1 Hz)), 5.05 (dd, 1, CH), 3.95 (s, 3, CH_3O), 3.31 (m, 2, CH_2). Anal. ($C_9H_{13}Cl_2NO_2$) C, H, N.

1-(3-Chloro-4-methoxyphenyl)-2-aminoethanol Hydrochloride (9c). Aldehyde **8c** (1.30 g, 7.6 mmol) was converted to **9c** in a manner similar to that for **9b** to afford 1.0 g (53.9%): mp 175–178 °C; NMR (D_2O) δ 6.57 (m, 3, Ar H), 4.79 (dd, 1, CH), 3.96 (s, 3, CH_3O), 3.35 (m, 2, CH_2). Anal. ($C_9H_{13}Cl_2NO_2$) C, H, N.

***N*-Benzyl-1-(3-methoxyphenyl)-2-aminoethanol Hydrochloride (10a).** The salt **9a** was converted to the free base; 1.5 g (8.97 mmol) was dissolved in 20 mL of absolute ethanol and 9.9 mmol of benzaldehyde was added. The solution was held at reflux for 1.0 h under a nitrogen atmosphere. The reaction mixture was cooled and 0.5 g (13.2 mmol) of $NaBH_4$ was added. The reaction mixture was stirred for 2.0 h, the solvent was removed by rotary evaporation, and 30 mL of dilute HCl was added. The salt precipitated, and after collection by filtration, the crude salt was recrystallized from ethanol/ether: yield 1.0 g, 37.9%; mp 159–162 °C; NMR ($CDCl_3$) δ 7.29 (s, 5, Ar H), 6.9 (m, 4, Ar H), 4.74 (dd, 1, CH) 3.81 (s, 2, CH_2), 3.79 (s, 3, CH_3O), 2.86 (m, 2, CH_2), 2.43 (s, 3, NH_2, OH). Anal. ($C_{16}H_{20}ClNO_2$) C, H, N.

***N*-Benzyl-1-(4-chloro-3-methoxyphenyl)-2-aminoethanol Hydrochloride (10b).** Amine salt **9b** (0.90 g, 3.8 mmol) was dissolved in 10 mL of anhydrous ethanol. Triethylamine (0.45 g, 4.2 mmol) and 0.45 g (4.2 mmol) of benzaldehyde were added. The mixture was stirred at reflux for 1.0 h and cooled, and sodium borohydride (200 mg, 5.2 mmol) was added. After the mixture was stirred for 45 min, the ethanol was removed by rotary evaporation, and 100 mL of 1 N HCl was added to the residue. The precipitate was collected by suction filtration, dried, and recrystallized from ethanol/ether: yield 0.84 g, 67.3%; mp 193–196 °C; NMR ($CDCl_3$) δ 7.29 (m, 6, Ar H), 6.88 (m, 2, Ar H), 4.67 (dd, 1, CH), 3.88 (s, 3, CH_3O), 3.81 (s, 2, CH_2), 2.84 (m, 2, CH_2), 2.63 (br s, 2, NH, OH). Anal. ($C_{16}H_{19}Cl_2NO_2$) C, H, N.

***N*-Benzyl-1-(3-chloro-4-methoxyphenyl)-2-aminoethanol Hydrochloride (10c).** Amine salt **9c** (0.34 g, 1.41 mmol) was converted to the *N*-benzyl hydrochloride salt in a procedure similar to that for compound **10b**. The crude salt was recrystallized from ethanol/ether: yield 0.29 g, 63%; mp 206–208 °C; NMR (free base; $CDCl_3$) δ 7.32 (m, 6, Ar H), 7.16 (d, 1, Ar H) 6.87 (d, 1, Ar H), 4.73 (dd, 1, CH), 3.82 (s, 3, CH_3O), 3.83 (s, 2, CH_2), 2.78 (m, 2, CH_2), 2.07 (br s, 2, NH, OH). Anal. (free base) ($C_{16}H_{18}ClNO_2$) C, H, N.

4-(3-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11a). Amine salt **10a** was converted to the free base, and 0.91 g (3.11 mmol) was dissolved in 20 mL of dichloromethane. The amine solution was dripped slowly into a suspension of 1.35 g (10.1 mmol) of $AlCl_3$ in 20 mL of dichloromethane. The mixture was held at reflux for 2.0 h and then poured over ice and basified to pH 9.5 with concentrated NH_4OH. The layers were separated, and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with saturated sodium chloride solution and dried ($MgSO_4$). The solvent was removed by rotary evaporation. The crude free base (670 mg) was converted to the HCl salt and recrystallized from ethanol/ether; yield 665 mg, 77.5%; mp 188–192 °C; CI-MS 240 (M + 1); NMR ($CDCl_3$) δ 6.9 (m, 8, Ar H), 4.11 (br s, 2, CH_2), 4.10 (m, 1, CH), 3.77 (s, 3, CH_3O), 3.29 (m, 2, CH_2). Anal. ($C_{16}H_{18}ClNO$) C, H, N.

4-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11b). *N*-Benzylamine salt **10b** (0.50 g, 1.7 mmol) was converted to **11b** following the procedure for **11a**. After removal of the solvent, 200 mg of free base was obtained. The free base was pure by TLC ($CHCl_3$, NH_3 atmosphere) and was converted to the HCl salt and recrystallized from ethanol/ether: yield 200 mg, 43%; mp 242–245 °C; CI-MS 274 (M + 1); NMR ($CDCl_3$) (free base) δ 7.19 (m, 4, Ar H), 6.90 (m, 1, Ar H), 6.68 (m, 2, Ar H), 4.11 (s + dd, 3, CH_2, CH), 3.82 (s, 3, CH_3O), 3.18 (m, 2, CH_2), 1.96 (s, 1, NH). Anal. ($C_{16}H_{17}Cl_2NO$) C, H, N.

4-(3-Chloro-4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride 11c. The free base of **10c** (0.2 g, 0.69 mmol) was converted to **11c** with 0.37 g (2.8 mmol) of $AlCl_3$ following the procedure for the cyclization of **10b** to **11b**. The crude free base was pure by TLC and was converted to the HCl salt and recrystallized from ethanol/ether: yield 132 mg, 70%; mp 181–183 °C; CI-MS 274 (M + 1); ($CDCl_3$) (HCl salt) δ 7.12 (m, 4, Ar H), 7.00 (m, 1, Ar H), 6.87 (m, 2, Ar H), 4.46 (br s + m, 3, NH_2^+, CH), 3.89 (s, 3, CH_3O), 3.88 (s, 2, CH_2), 3.12 (m, 2, CH_2). Anal. ($C_{16}H_{17}Cl_2NO$) C, H, N.

***N*-Methyl-4-(4-chloro-3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11d).** Amine salt **11b** (0.180 g, 0.58 mmol) was dissolved in 5 mL of methanol. Formalin solution (0.3 mL of 37%, 3.7 mmol) and 150 mg (2.4 mmol) sodium cyanoborohydride were added. The mixture was stirred for 16 h at 25 °C. The methanol was removed by rotary evaporation and 10 mL of 1 N HCl was added to the residue. The aqueous layer was washed with ether (2 × 10 mL), basified to pH 10 with concentrated NH_4OH, and extracted with dichloromethane (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to afford the crude free base, which was converted to its HCl salt and recrystallized from ethanol/ether: yield 0.179 g, 95%; mp 226–229 °C; CI-MS 288 (M + 1); NMR ($CDCl_3$) δ 7.20 (m, 4, Ar H), 6.79 (m, 3, Ar H), 4.22 (m, 1, CH), 3.83 (s, 3, CH_3O), 3.68 (s, 2, CH_2), 2.81 (m, 2, CH_2), 2.43 (s, 3, NCH_3). Anal. ($C_{17}H_{19}Cl_2NO$) C, H, N.

4-(3-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (2). Amine salt **11a** (80 mg, 0.29 mmol) was dissolved in 1.0 mL of 48% HBr and held at reflux for 1.25 h under a nitrogen atmosphere. After removal of the HBr by rotary evaporation, residual water was azeotropically removed with absolute ethanol by rotary evaporation. The residue was recrysallized from ethanol/ether: yield 65 mg, 65.6%; mp 255–260 °C; CI-MS 226 (M + 1); NMR ($CDCl_3$) δ 6.98 (m, 8, Ar H), 6.45 (s, 1, Ar OH), 4.05 (s, 2, CH_2), 4.00 (m, 1, CH), 3.60 (br s, 1, NH), 3.30 (m, 2, CH_2). Anal. ($C_{15}H_{16}BrNO$) C, H, N.

4-(4-Chloro-3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (3). In a manner similar to that for **2**, 0.165 g (0.53 mmol) of **11b** was converted to **3**: yield 117 mg, 65%; mp 248–252 °C; CI-MS 260 (M + 1); NMR (DMSO-d_6) (HBr salt) δ 10.17 (s, 1, Ar OH), 9.20 (br s, 2, NH_2^+), 7.22 (m, 4, Ar H), 6.89 (m, 3, Ar H), 4.40 (s + m, 3, CH_2, CH), 3.54 (m, 2, CH_2). Anal. ($C_{15}H_{15}BrClNO$) C, H, N.

4-(3-Chloro-4-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (4). Amine salt **11c** (0.105 g, 0.34 mmol) was converted to **4** following the procedure for **2**: yield 77 mg, 66.4%; mp 247–249 °C; CI-MS 260 (M + 1); NMR (DMSO-d_6) (HBr salt) δ 10.14 (s, 1, Ar OH), 9.26 (br s, 2, NH_2^+), 7.30 (m, 4, Ar H), 6.83 (m, 3, Ar H), 4.43 (s + m, 3, CH_2, CH), 3.58 (m, 2, CH_2). Anal. ($C_{15}H_{15}BrClNO$) C, H, N.

***N*-Methyl-4-(4-chloro-3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (5).** Amine salt **11d** (0.1 g, 0.31 mmol) was converted to **5** by using the procedure for **2**. The residue was recrystallized with difficulty from aqueous ethanol: yield 55 mg, 50%; mp 280–284 °C; CI-MS 274 (M + 1); NMR ($CDCl_3$, free base) δ 7.11 (m, 4, Ar H), 6.81 (m, 3, Ar H), 4.20 (m,

1, CH), 3.68 (s, 2, CH_2), 3.48 (s, 1, Ar OH), 2.96 (m, 1, C_3H_a), 2.61 (m, 1, C_3H_b), 2.42 (s, 3, NCH_3), 1.25 (s, 1, NH). Anal. ($C_{16}H_{17}BrClNO$) C, H, N.

Pharmacology. The procedure for the dopamine-stimulated rat retinal adenylate cyclase assay was as follows: Rat retinas were homogenized in 150 vol/wt of 2.0 mM Tris·HCl, pH 7.4, with 2 mM EDTA with a Teflon–glass homogenizer. Each reaction mixture contained the following final concentrations in a volume of 0.2 mL: 2 mM $MgSO_4 \cdot 7H_2O$, 0.5 mM EGTA, 1 mM IBMX, 0.01 mM GTP, 80 mM Tris·HCl (pH 7.4), 0.5 mM ATP with approximately 5×10^6 dpm [^{32}P]ATP and 20–30 μg of retinal homogenate protein. Following an incubation of 20 min at 30 °C, the reaction was terminated by adding 200 μL of a solution containing 1% SDS, 20 mM ATP, 0.7 mM cyclic AMP with 1.0×10^4 dpm [^{3}H]cyclic AMP in 80 mM Tris·HCl pH 7.4 and heating to 85 °C for 2 min. Cyclic AMP was isolated from the mixture by using the column chromatographic technique of Salomon.[22]

Acknowledgment. This work was supported by NIH Grants HL-31106 and MH-42705.

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Prodrugs of L-Cysteine as Protective Agents against Acetaminophen-Induced Hepatotoxicity. 2-(Polyhydroxyalkyl)- and 2-(Polyacetoxyalkyl)thiazolidine-4(*R*)-carboxylic Acids

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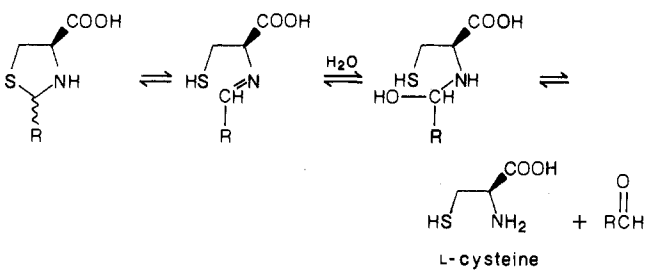
Eight prodrugs of L-cysteine (**1a–h**) were synthesized by the condensation of the sulfhydryl amino acid with naturally occurring aldose monosaccharides containing three, five, and six carbon atoms. The resulting 2-(polyhydroxyalkyl)thiazolidine-4(*R*)-carboxylic acids (TCAs) are capable of releasing L-cysteine and the sugars by nonenzymatic ring opening and hydrolysis. Thus, when added to rat hepatocyte preparations in vitro, these TCAs (1.0 mM) raised cellular glutathione (GSH) levels 1.2–2.1-fold relative to controls. On the basis of this finding, the cysteine prodrugs were tested as protective agents against acetaminophen-induced hepatotoxicity in a mouse model. The TCA derived from D-ribose and L-cysteine (RibCys, **1d**) showed the greatest therapeutic promise of the series, with a 100% (12/12) survival profile compared to 17% without treatment. However, the degree of stimulation of GSH production in rat hepatocytes by these prodrugs did not correlate with the extent of protection afforded in mice, suggesting that pharmacokinetic parameters must supervene in vivo. To evaluate the effect of increased lipid solubility, we prepared prodrugs **2a–c** by using peracetylated aldehydic sugars in the condensation reaction. These compounds, however, displayed acute toxicity to mice, possibly due to liberation of the acetylated sugars themselves. Nevertheless, the efficacy of the unacetylated TCAs, and RibCys (**1d**) in particular, suggests that the prodrug approach for the delivery of L-cysteine to the liver represents a viable means of augmenting existing detoxication mechanisms in protecting cells against xenobiotic substances that are bioactivated to toxic, reactive metabolites.

In previous studies,[1] it was shown that 2-substituted thiazolidine-4(*R*)-carboxylic acids (TCAs) can protect against the hepatotoxicity elicited by high doses of acetaminophen in mice. These TCAs function as prodrug forms of L-cysteine, liberating this sulfhydryl amino acid by nonenzymatic ring opening and hydrolysis (Scheme I). It was hypothesized that delivery of L-cysteine to the liver would elevate the intracellular levels of glutathione (GSH) by supplying this biochemical amino acid precursor of GSH to the cell. GSH is the coenzyme that mediates the protection against the reactive electrophilic species generated during the oxidative metabolism of acetaminophen by the hepatic cytochrome P-450 system.[2]

The TCAs alluded to were prepared by condensation of L-cysteine with aliphatic or aromatic aldehydes.[3] Thus, the release of an equimolar quantity of the aldehyde used in prodrug synthesis would be expected by dissociation, along with the desired therapeutic agent, L-cysteine. To avoid any possible toxicity associated with the liberation in vivo of potentially reactive aldehydes, albeit in small amounts, the present study utilized naturally occurring aldose monosaccharides of three, five, and six carbon atoms as the aldehyde moiety in thiazolidine construction.[4] The

Scheme I



aldoses used for synthesis were glyceraldehyde (Glyc), arabinose (Ara), lyxose (Lyx), ribose (Rib), xylose (Xyl),

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