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Absolute Configuration of Glycerol Derivatives. 4.[1] Synthesis and Pharmacological Activity of Chiral 2-Alkylaminomethylbenzodioxans, Competitive α-Adrenergic Antagonists[2]

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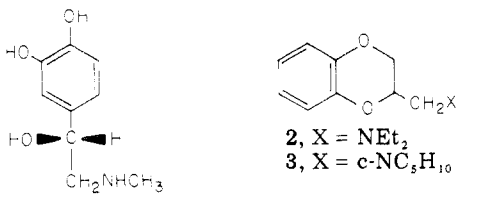
The optical isomers of α-adrenergic receptor antagonists prosympal (**2**), piperoxan (**3**), and dibozane (**4**) were prepared by methods establishing the absolute configuration of each. (2*S*)-3-(2′-Hydroxyphenoxy)-1,2-propanediol ditosylate (**10**) was prepared from (2*R*)-3-tosyloxy-1,2-propanediol acetonide (**6**). Intramolecular displacement afforded (2*S*)-tosyloxymethylbenzodioxan [(2*R*)-**11**]. Reaction of (2*R*)-**11** with the appropriate amine (diethylamine, piperidine, or piperazine) afforded the 2*S* isomers of **2**, **3**, and **12**, respectively. Reaction of (2*S*)-**12** with (2*R*)-**11** afforded the *SS* isomer of **4**. Reaction of (2*S*)-3-benzyloxy-1,2-propanediol ditosylate (**14**) with catechol (NaOMe) afforded (2*R*)-benzyloxymethylbenzodioxan (**15**). Subjecting **15** to hydrogenolysis, tosylation, and displacement with the appropriate amine afforded 2*R* isomers of **2**, **3**, and **12**. Reaction of (2*R*)-**12** with (2*S*)-**11** afforded (*RR*)-**4**. Reaction of (2*R*)-**12** with (2*R*)-**11** afforded *meso*-**4**. The *S* isomers were more effective antagonists to the α-adrenergic response of methoxamine-induced contraction of rabbit aortic strips by twofold in **2** and 18–19-fold in **3** and **4**. *meso*-**4** was as effective as the *SS* isomer of **4**. The results are interpreted in terms of a similar conformational distribution of aminoalkyl, oxygen, and aromatic functional groups of the (*S*)-benzodioxans and (*R*)-epinephrine.

The search for compounds which alter responses to the adrenergic neurotransmitters has long been a focal point in the search for useful therapeutic agents. Among the groups of compounds which are effective agents in reversing the pressor response to epinephrine (**1**) are the 2-alkylaminobenzodioxans.[3,4] Some of the compounds were used clinically as antihypertensive agents because of their α-adrenergic blocking properties but since have been discarded because of the usual adverse affects associated with blockade of α-adrenergic receptors.[3,5] However, some of the compounds, e.g., prosympal (**2**),[4,6a] piperoxan (**3**),[4,6] and dibozane (**4**),[4,6c,d] remain as very important pharmacological tools because their α-adrenergic receptor antagonism is a competitive blockade. Additionally, the alkylaminomethylbenzodioxan system remains as a focal point for the study of other amines, some of which have similar activity, e.g., guanoxan,[7] acetoxatrine,[8] and spiroxamide.[9]

Although the α-adrenergic receptor antagonist properties of the compounds have been widely studied, only a single report appears in the literature relative to the effect of absolute stereochemistry on these properties. (−)-Prosympal (**2**) was five to six times more potent than the (+) isomer in reversing the pressor response to epinephrine in cats and was also a more potent miotic by a factor of four- to eightfold.[10]



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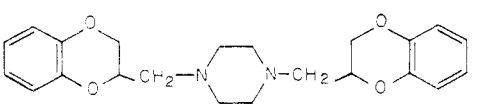
2, X = NEt_2
3, X = c-NC_5H_{10}



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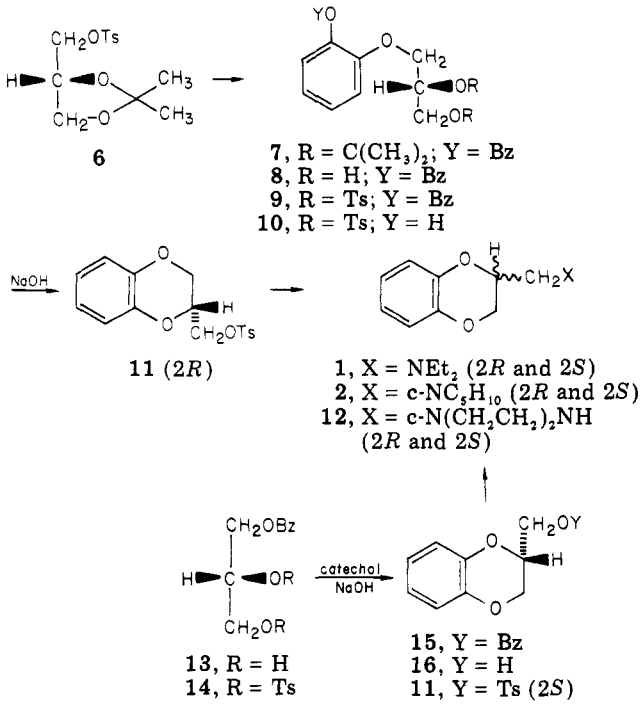
Our investigation of this system is related to our continuing interest in glycerol derivatives which can be readily synthesized as either *R* or *S* enantiomers and as such can be used in determination of absolute configuration of

Scheme I



drugs. These benzodioxans can be regarded as disguised glycerol derivatives. In this communication we report synthesis of the enantiomers of these three benzodioxans by methods which establish the absolute configuration of each and the results of testing of the compounds for α-adrenergic blocking effects.

Synthesis. Chiral compounds derived from (2*R*)-glyceraldehyde-2,3-acetonide (**5**), available from (2*R*,3*R*,4*R*,5*R*)-mannitol,[11] were used for starting materials in *both* enantiomers of the dioxans (Scheme I). (2*R*)-Tosyloxy-1,2-propanediol acetonide (**6**)[12] was converted to **7** (79% yield) by displacement of the tosylate using sodium 2-benzyloxyphenolate. The acetonide was hydrolyzed in the presence of 1 N HCl affording diol (2*R*)-**8** (96% yield). Tosylation, using 2 equiv of tosyl chloride, proceeded smoothly to produce ditosylate **9** (2*S* stereochemistry).[13] The benzyl ether was removed by hydrogenolysis producing 2*S*-ditosylate **10**. Intramolecular ring closure afforded the (2*R*)-tosyloxymethylbenzodioxan **11** in excellent yield.

Conversion of the (2*R*)-benzodioxan tosylate to the corresponding α-adrenergic antagonist was readily accomplished using an excess of the appropriate amine at reflux for 24 h. Reaction of (2*R*)-**11** with excess piperazine afforded (2*S*)-**12**[13] isolated as a dihydrochloride salt, an intermediate suitable for preparation of the dibozane enantiomers **4**.

The conversion of (2*R*)-glyceraldehyde-2,3-acetonide (**5**) into (2*S*)-3-tosyloxy-1,2-propanediol acetonide (enantiomer of **6**) has also been reported.[1,12] Protection of the hydroxyl group at C-1 [of the (2*S*)-glycerol-2,3-acetonide formed by reduction of **5**] as a benzyl ether is required. Subsequent steps performed were hydrolysis of the acetonide function, formation of the monotosylate at C-3, and removal of the benzyl ether followed by formation of the acetonide. However, since this process involved an additional five steps, we hoped to find a more direct route to the *R* enantiomer of **2** and **3**.

(2*R*)-3-Benzyloxypropanediol (**13**), the first intermediate in the above-discussed sequence, was converted to ditosylate (2*S*)-**14** by tosylation of both hydroxyl groups. The tosylate groups were then displaced using catechol (2 equiv of NaOH). Hydrogenolysis of (2*R*)-**15** gave (2*R*)-**16**. Steps to the *R* isomers then involved tosylation to afford (2*S*)-**11** followed by displacement with the necessary amine.

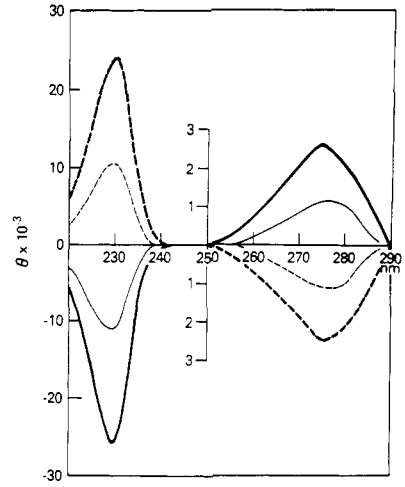


Figure 1. CD spectra of enantiomers of **3** and **4** (HCl salts in MeOH): heavy solid line, (*RR*)-**4**; heavy dashed line, (*SS*)-**4**; light solid line, (2*R*)-**3**; light dashed line, (2*S*)-**3**.

The dibozane enantiomers (*RR*)-**4** and (*SS*)-**4** were prepared from (2*R*)-**12** and (2*S*)-**12** by allowing these amines to react with tosylates (2*S*)-**11** and (2*R*)-**11**, respectively, in ethanol at reflux for 24 h. Similarly, we have prepared the meso isomer of **4** by allowing (2*R*)-**12** to react with (2*R*)-**11** under the same conditions.

The results of circular dichroism spectral determinations appear in Figure 1 (**3** and **4** only). Consistently, in the CD spectra of these enantiomers and those of **2** and **12** (not shown, data in the Experimental Section), the *S* isomers show a negative ^1L_B transition with the maximum near 275 nm and a much stronger positive ^1L_A transition with the maximum near 230 nm. The expected magnitude of these transitions in the dibozane enantiomers is about twice as large as observed in the other benzodioxans because of the presence of two chromophores.

Optical Purity. The nearly equal intensities of the CD bands of enantiomers suggest that no significant differences in the degree of racemization occur in the synthetic sequences after separation of routes, with the possible exception that in similar processes in each of the schemes racemization could occur to similar extents. The additional possibility of racemization in the early steps, e.g., formation and reduction of (2*R*)-glyceraldehyde-2,3-acetonide, also remained. These potential problems suggested the need for an investigation of the optical purity of the benzodioxans.

The NMR spectra of the racemate and the *R* and *S* isomers of prosympal (**2**) in the presence of a chiral shift reagent were very informative (Figure 2). In the presence of various molar ratios of tris(heptafluropropylhydroxymethylenecamphorato)europium (THFC-Eu), beginning at MR = 0.11 (THFC-Eu-**2**) the spectrum of racemate begins to show two different *C*-methyl groups. At molar ratios greater than 0.70 complete separation of two triplets occurs. The synthesized individual *R* and *S* enantiomers showed no peaks assignable to methyl groups of the "wrong enantiomer". Spectra of an admixture of the synthesized enantiomers in a *R*/*S* ratio of 90:10 in the presence of THFC-Eu produced the expected two different methyl groups, integrating in the ratio 9:1 indicating the method is sufficiently sensitive to detect an enantiomeric impurity of less than 10% and probably less than 5% of the "wrong isomer". We interpret these results to indicate the dioxans are of at least 90% ee and perhaps better.

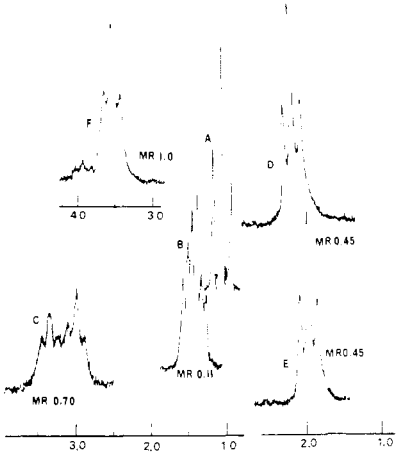


Figure 2. 60-MHz NMR spectra of the terminal methyl group of prosympal (2), recorded in $CDCl_3$ in the presence of various amounts of THFC-Eu: A, B, and C, racemate of 2 with various molar ratios (MR) of THFC-Eu; D, (2*R*)-2, MR = 0.45; E, (2*S*)-2, MR = 0.45; F, 90:10 mixture of (2*R*)-2 and (2*S*)-2, MR = 1.0.

Table I. Competitive Antagonist Effects of Chiral Benzodioxans on Methoxamine-Induced Contraction of Rabbit Aortic Strips

Compound	pA_2[a]	S/R ratio	$-\text{Log } K_D$[b]
(*S*)-Prosympal [(2*S*)-2]	5.60 ± 0.12	2.2	6.21
(*R*)-Prosympal [(2*R*)-2]	5.26 ± 0.12		
(*S*)-Piperoxan [(2*S*)-3]	7.12 ± 0.17	18.2	6.51
(*R*)-Piperoxan [(2*R*)-3]	5.86 ± 0.14		5.99
(*SS*)-Dibozane [(*SS*)-4]	7.66 ± 0.08	19.1	6.85
(*RR*)-Dibozane [(*RR*)-4]	6.38 ± 0.11		6.25
meso-Dibozane (*meso*-4)	7.53 ± 0.18		

[a] ±SEM (n = 5). [b] Affinity for [^{3}H]dihydroazepetine binding site of α-adrenoreceptor related protein from rat vas deferens. Data from ref 14.

Pharmacological Testing. The compounds were tested for competitive α-adrenergic blocking effects in rabbit aortic strips, using methoxamine as the agonist. The results appear in Table I. In all cases, the *S* enantiomer was more potent than the *R* enantiomer by twofold in prosympal (2) and 18–19-fold in piperoxan (3) and dibozane (4). The meso isomer of dibozane (4) is equiactive with the more potent *SS* isomer suggesting that a single *S*-chiral center is sufficient for activity in the dibozane system.

The greater potency of *S* enantiomers in this assay is similar to that observed in the ability to displace the radiolabeled antagonist [^{3}H]dihydroazepetine from α-adrenoreceptor related protein from rat vas deferens, although a greater *S*/*R* ratio is observed. Only three- to fourfold differences were noted in the latter assay.

Discussion

Interpretation of greater potency of *S* enantiomers of the benzodioxans by comparison of their stereochemistry with that of (*R*)-(−)-epinephrine is ambiguous. For such stereochemical comparisons the alkylamine side chains are considered to be equivalent. Considering stereochemical analogies between the (*S*)-benzodioxan isomers and (*R*)-epinephrine, the oxygen substituents (hydroxyl and OAr) would be equivalent, leaving the aromatic ring of epinephrine to be considered analagous to the alkyl substituent of the benzodioxan ring.

When the (*R*)-benzodioxan enantiomer is compared to epinephrine, the OAr substituent would be stereochemically equivalent to the aromatic ring of epinephrine (seemingly a reasonable analogy) but that leaves the alkyloxy chain of the dioxan being similar to the hydroxyl substituent of epinephrine. Both analogies suffer from weaknesses, and neither seems clearly more plausible than the other.

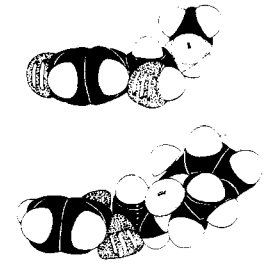
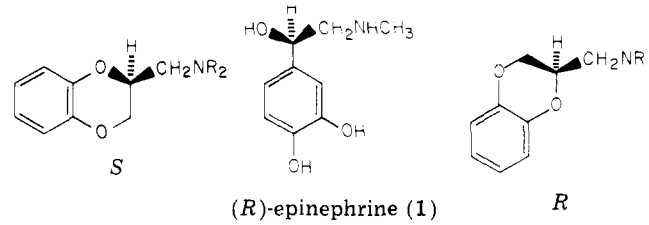
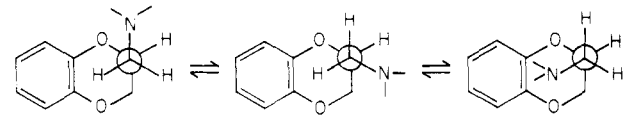


Figure 3. Drawings of CPK models of (2*S*)-3 (piperoxan) and (*R*)-epinephrine (1).



A comparison of Newman projections about the C-2 methine-α-methylene carbon suggested that major contributors to the conformational equilibrium would be conformer A and B. Conformer A would be expected to



be slightly more favorable than B, based on the smaller interaction of the amine nitrogen and ether oxygen than amine nitrogen and methylene group, if other factors did not complicate the comparison.

A study of space-filling models supports conformer A. In CPK models the (*S*)-benzodioxan enantiomer can be made to approximate a reasonable conformation of (*R*)-epinephrine, whereas the (*R*)-benzodioxan enantiomer cannot. The conformation of epinephrine chosen for comparison is one which has a great deal of conformational freedom and which is also attractive because of potential intramolecular interaction of OH and NH_2. It is similar to suggested preferred solution conformations of ephedrines, etc., of gauche disposition of the OH and NH_2 groups in the free base (or OH and $^+NH_3$ in salts).[15-17] Such conformations have been speculated upon in terms of adrenergic receptor agents.[17,18] However, NMR evidence has suggested no preferred conformation of epinephrine salts, since an average coupling constant for the protons α to the amino function was observed.[19] Conformational freedom in the models and the results with the related ephedrines, however, suggested a possible comparison.

One of the conformations of the (*S*)-benzodioxans with few intramolecular interactions (Figure 3) resembles (*R*)-ephinephrine with respect to similar spatial relationships among the amine, oxygen, and aromatic ring. Although this similarity may be only fortuitous, no similar analogy could be made between the (*R*)-benzodioxan enantiomer and (*R*)-epinephrine. Although such an analogy should not be necessarily extrapolated to represent receptor-site events, it certainly is consistent with such an occurrence and thus is attractive to explain the observed pharmacological results. Work on these and other gly-

cerol-related systems is in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as internal standard. Notations used in the descriptions are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR and NMR data are provided for only one enantiomer from each set of two. Circular dichroism spectra were recorded on a Cary Model 60 ORD instrument with a 6001-CD attachment. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

2-Benzyloxyphenol. Benzyl chloride, 38.0 g (0.30 mol), was added to a solution of 33 g (0.30 mol) of catechol and 16.8 g (0.30 mol) of powdered KOH in 100 mL of DMF. The resulting solution was heated at 80–90 °C for 5 h, cooled, diluted with $CHCl_3$ (300 mL), washed with H_2O (5 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and vacuum distillation yielded 45.0 g (75%) of 2-benzyloxyphenol: bp 125–130 °C (0.5 mm) [lit.[20] bp 157 °C (6 mm)].

(2*R*)-3-(2′-Benzyloxyphenoxy)-1,2-propanediol Acetonide (7). 2-Benzyloxyphenol, 15.0 g (0.075 mol), was mixed with 4.05 g (0.075 mol) of $NaOCH_3$ in 25 mL of aqueous EtOH and refluxed 24 h with 15.9 g (0.055 mol) of (2*R*)-3-tosyloxy-1,2-propanediol acetonide (**6**).[11,12] The solvent was evaporated and the residue was dissolved in ether (4 × 100 mL). The ether was washed with H_2O (100 mL), 5% NaOH (100 mL), and H_2O (5 × 50 mL), dried ($MgSO_4$), and evaporated to yield an oil. Vacuum distillation afforded 13.7 g (79%) of **7**: bp 120–160 °C (0.5 mm), used without further purification; α_D +13° (*c* 0.5, absolute EtOH).

(2*R*)-3-(2′-Benzyloxyphenoxy)-1,2-propanediol (8). (2*R*)-3-(2′-Benzyloxyphenoxy)-1,2-propanediol acetonide (**7**), 12.7 g (0.040 mol), was refluxed 1.5 h in 50 mL of a 1:1 mixture of acetone and aqueous 2 N HCl. Upon cooling a white solid formed which was collected by filtration, dried, and recrystallized from CCl_4 to yield 9.2 g (85%) of **8**: mp 92–93 °C; NMR ($CDCl_3$) δ 7.38 (s, 5, PhH), 6.93 (s, 4, ArH), 5.10 (s, 2, CH_2Ar), 3.90 (m, 7, H_1, H_2, H_3, and OH). Anal. ($C_{16}H_{18}O_4$) C, H.

(2*R*)-3-(2′-Benzyloxyphenoxy)-1,2-propanediol Ditosylate (9). Tosyl chloride, 9.7 g (0.05 mol), was added to an ice-cold solution of 6.85 g (0.025 mol) of diol **8** in 15 mL of anhydrous pyridine and the resulting mixture was stirred 24 h at room temperature. The solution was diluted with ethyl acetate (400 mL), washed with 1 N HCl (3 × 100 mL) and H_2O (3 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil. Crystallization from ether yielded 8.1 g (55%) of **9** as a white solid: mp 80–82 °C; NMR ($CDCl_3$) δ 7.70 (m, 4, H_2 and H_6 of Ts ring), 7.26 (m, 9, PhH and H_3 and H_5 of Ts ring), 6.88 (m, 4, ArH), 4.95 (m, 3, H_2 and CH_2Ar), 4.28 (d, 2, H_1, *J* = 6 Hz), 4.13 (d, 2, H_3, *J* = 6 Hz), 2.40 (s, 6, $ArCH_3$). Anal. ($C_{30}H_{30}S_2O_8$) C, H.

(2*R*)-3-(2′-Hydroxyphenoxy)-1,2-propanediol Ditosylate (10). A solution of 10.25 g (0.017 mol) of ditosylate **9** in 100 mL of a mixture of 1:1 ethyl acetate and methanol and 5.0 g of 10% Pd/C was hydrogenated in a low-pressure Parr apparatus, initial pressure 40 psig. The catalyst was removed by filtration and the solvent was evaporated to yield an oil. Crystallization from methanol yielded 6.6 g (79%) of **10** as white crystals: mp 119–120 °C; NMR ($CDCl_3$) δ 7.76 and 7.33 (4 d, 8, TsArH, *J* = 8 Hz), 6.85 (m, 4, ArH), 5.86 (s, 1, OH), 5.03 (m, 1, H_2, *J* = 5 Hz), 4.26 (d, 2, H_1, *J* = 5 Hz), 4.16 (d, 2, H_3, *J* = 5 Hz), 2.50 (s, 6, $ArCH_3$). Anal. ($C_{23}H_{24}S_2O_8$) C, H.

(2*R*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*R*)-11]. A solution of 4.91 g (0.010 mol) of ditosylate **10** and 0.54 g (0.010 mol) of $NaOCH_3$ in 200 mL of ethanol was refluxed for 3 h. The solvent was removed and the residue dissolved in ether (400 mL). The ether was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield 3.0 g (93%) of (2*R*)-**11** as a yellow oil: IR (neat) 3.46, 6.26, 6.70, 7.31, 7.90, 8.40, 8.50, 9.14, 9.58, 12.05, 12.28, 13.30, and 15.09 μ; NMR ($CDCl_3$) δ 7.86 and 7.36 (2 d, 4, TsArH, *J* = 8 Hz), 6.95 (s, 4, ArH), 4.33 (m, 5, H_2, H_3, and CH_2), 2.50 (s, 3, $ArCH_3$); CD (*c* 0.120, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −530, $[\theta]_{280}$ −670, $[\theta]_{275}$ −720, $[\theta]_{270}$ −480, $[\theta]_{260}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ +3050, $[\theta]_{230}$ +9070, $[\theta]_{225}$ ±8530.

(2*S*)-2-Piperidinomethyl-1,4-benzodioxan Hydrochloride [(2*S*)-Piperoxan Hydrochloride] [(2*S*)-3 HCl]. (2*R*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*R*)-**11**], 1.30 g (0.004 mol), was refluxed 24 h with 10 g (0.12 mol) of piperidine. The solvent was removed and the residue was suspended in 50 mL of 2.5% NaOH and extracted with $CHCl_3$ (3 × 80 mL). The $CHCl_3$ was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in ether and the HCl salt was precipitated by addition of gaseous HCl–saturated ether. The precipitated oil was crystallized from absolute ethanol–ether to yield 0.58 g (54%) of (2*S*)-**3** HCl: mp 182–185 °C (lit.[22] racemic mp 232–234 °C); IR (KBr) 2.83, 3.40, 3.80, 3.96, 6.29, 6.71, 7.92, and 13.25 μ; NMR ($CDCl_3$) δ 6.95 (s, 4, ArH), 5.26 (br s, 1, NH), 4.60–1.70 (m, 15, H_1, H_2, and CH_2); λ_{max}^{MeOH} 217 nm (log ε 3.84), 276 (3.39); CD (*c* 0.016, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −480, $[\theta]_{275}$ −1120, $[\theta]_{265}$ −400, $[\theta]_{255}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ +3050, $[\theta]_{230}$ +11 170, $[\theta]_{225}$ +5480, $[\theta]_{220}$ +2070. Anal. ($C_{14}H_{20}NO_2Cl$) C, H.

(2*S*)-2-Diethylaminomethyl-1,4-benzodioxan Hydrochloride [(2*S*)-Prosympal Hydrochloride] [(2*S*)-2 HCl]. (2*R*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*R*)-**11**], 0.98 g (0.003 mol), was refluxed 24 h with 24 g (0.33 mol) of diethylamine. The solvent was removed and the residue suspended in 100 mL of 2.5% NaOH and extracted with $CHCl_3$ (3 × 80 mL). The $CHCl_3$ was washed with H_2O (3 × 80 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in ether and the HCl salt was precipitated by the addition of gaseous HCl–saturated ether. Crystallization of the oil from isopropyl alcohol–ether yielded 0.26 g (34%) of (2*S*)-**2** HCl as flakes: mp 129–130 °C (lit.[21] mp 129–130 °C, racemic mp 125–127 °C); IR (KBr) 2.80, 3.38, 3.65, 3.74, 4.00, 6.26, 6.70, 6.82, 7.90, 9.17, 9.54, 9.78, 10.89, 13.10, and 13.30 μ; NMR ($CDCl_3$) δ 6.95 (s, 4, ArH), 5.20 (br s, 1, NH), 4.26 (m, 3, H_2 and H_3), 3.33 (br m, 6, CH_2), 1.43 (t, 6, CH_3, *J* = 8 Hz); λ_{max}^{MeOH} 217 nm (log ε 3.84), 2.76 (3.40); CD (*c* 0.10, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −370, $[\theta]_{275}$ −1180, $[\theta]_{265}$ −520, $[\theta]_{255}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ +1820, $[\theta]_{230}$ +10 590, $[\theta]_{255}$ +5780. Anal. ($C_{13}H_{19}NO_2Cl$) C, H, N.

2-(1-Piperazinylmethyl)-1,4-benzodioxan Dihydrochloride [(2*S*)-12 2HCl]. (2*R*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*R*)-**11**], 3.2 g (0.01 mol), was refluxed 36 h with 17 g (0.2 mol) of piperazine in 50 mL of ethanol. The solvent was removed and the residue was suspended in 100 mL of 2.5% NaOH and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in ethanol and the 2HCl salt precipitated by addition of excess gaseous HCl–saturated ether to yield 2.16 g (86%) of (2*S*)-**12** 2HCl: mp 217–220 °C (EtOAc–MeOH); IR (KBr) 2.79, 3.18, 3.40, 3.60, 3.78, 3.95, 4.05, 7.94, 9.12, 10.40, 10.88, 11.63, 11.95, 13.30, and 14.35 μ; NMR (D_2O) δ 6.91 (s, 4, ArH), 5.10–4.60 (m, 3, HOD), 4.50–4.20 (m, 3, H_2 and H_3), 4.00–3.60 (m, 10, CH_2); CD (*c* 0.108, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −600, $[\theta]_{275}$ −1040, $[\theta]_{265}$ −490, $[\theta]_{250}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ +4040, $[\theta]_{230}$ +11 320, $[\theta]_{225}$ +7670, $[\theta]_{220}$ 0. Anal. ($C_{13}H_{20}N_2O_2Cl_2 \cdot 0.5H_2O$) C, H; N: calcd, 8.85; found, 8.39.

(*SS*)-1,4-Bis[2-(1,4-Benzodioxanyl)methyl]piperazine Dihydrochloride [(*SS*)-Dibozane Dihydrochloride] [(*SS*)-4 2HCl]. Sodium methoxide, 0.324 g (0.006 mol), was added to 0.918 g (0.003 mol) of (2*S*)-2-(1-piperazinylmethyl)-1,4-benzodioxan dihydrochloride [(2*S*)-**12** 2HCl] in 10 mL of ethanol and the mixture was refluxed 24 h with 0.96 g (0.003 mol) of (2*R*)-tosyloxymethyl-1,4-benzodioxan [(2*R*)-**11**]. The reaction mixture was diluted with 30 mL of 5% NaOH and extracted with $CHCl_3$ (4 × 50 mL). The $CHCl_3$ was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil. Crystallization from absolute ethanol yielded 0.40 g (35%) of **4**: mp 150–151 °C (lit.[6c] racemic mp 162–167 °C); IR (KBr) 3.40, 3.51, 6.29, 6.71, 7.91, 9.60, 9.90, 10.75, 11.65, 12.20, and 13.29 μ; NMR ($CDCl_3$) δ 6.95 (s, 8, ArH), 4.30 (m, 6, H_2 and H_3), 2.66 (m, 12, CH_2).

(*SS*)-Dibozane dihydrochloride [(*SS*)-**4** HCl] was prepared by the addition of excess gaseous HCl–saturated ether to a solution of 0.128 g (0.0003 mol) of (*SS*)-**4** in absolute ethanol. The precipitate was collected to yield 0.140 g (94%) of (*SS*)-**4** 2HCl: mp >250 °C (lit.[6c] mp >250 °C); IR (KBr) 2.85, 3.40, 3.58, 3.65, 3.78, 3.91, 4.07, 6.11, 6.25, 6.70, 7.92, 9.58, 10.37, 10.87, 11.62, 11.95, 13.25, and 14.35 μ; NMR (Me_2SO-d_6) δ 6.95 (s, 8, ArH), 5.02 (br s, 2, NH), 4.70–3.40 (m, 18, CH and CH_2); λ_{max}^{MeOH} 217 nm (log ε 4.14), 276 (2.72); CD (*c* 0.108, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −1430, $[\theta]_{275}$ −2490, $[\theta]_{265}$ −1180, $[\theta]_{250}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ +6590, $[\theta]_{230}$ +22 800,

$[\theta]_{225}$ +15 970. Anal. ($C_{22}H_{28}N_2O_4Cl_2$) C, H, N.

***meso*-1,4-Bis[2-(1,4-Benzodioxanyl)methyl]piperazine Dihydrochloride (*meso*-Dibozane Dihydrochloride) (*meso*-4 2HCl).** Sodium methoxide, 0.302 g (0.0056 mol), was added to 0.857 g (0.0028 mol) of (2*S*)-2-(1-piperazinylmethyl)-1,4-benzodioxan dihydrochloride [(2*S*)-**12** 2HCl] in 15 mL of aqueous ethanol and the mixture refluxed 48 h with 0.89 g (0.0027 mol) of (2*S*)-2-tosyloxymethyl-1,4-benzodioxan [(2*S*)-**11**]. The reaction mixture was diluted with 50 mL of 5% NaOH and extracted with $CHCl_3$ (3 × 80 mL). The $CHCl_3$ was washed with H_2O (3 × 100 mL), dried (Na_2SO_4), and evaporated affording an oil. Crystallization from absolute ethanol yielded 0.270 g (27%) of *meso*-**4** as a white solid: mp 165–167 °C (lit.[6c] racemic mp 162–167 °C); IR (KBr) 3.40, 3.51, 6.29, 6.71, 7.91, 9.60, 9.90, 10.75, 11.65, 12.20, and 13.29 μ; NMR ($CDCl_3$) δ 6.95 (s, 8, ArH), 4.30 (m, 6, H_2 and H_3), 2.66 (m, 12, CH_2). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

A solution of 0.90 g (0.005 mol) of *meso*-dibozane (*meso*-**4**) in absolute ethanol was converted to the 2HCl salt by the addition of excess gaseous HCl–saturated ether to yield 0.41 g (90%) of *meso*-**4** 2HCl: mp >250 °C (lit.[6c] mp >250 °C). Anal. ($C_{22}H_{28}N_2O_4Cl_2$) C, H, N.

(2*S*)-3-Benzyloxy-1,2-propanediol Ditosylate (14). To a cold (0 °C) solution of 9.1 g (0.05 mol) of **13**[23] in 20 mL of anhydrous pyridine was added 19.0 g (0.10 mol) of *p*-TsCl. After stirring 24 h at room temperature, 400 mL of ether was added and the solution was washed with 2 N HCl (3 × 100 mL) and H_2O (5 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil which solidified. Crystallization from ether yielded 19.6 g (80%) of **14** as a white solid: mp 62–64 °C; NMR ($CDCl_3$) δ 7.76 (2 d, 4, H_2 and H_6 of Ts ring, J = 8 Hz), 7.33 (m, 7, ArH and H_3 and H_5 of Ts ring), 4.76 (m, 1, H_2, J = 6 Hz), 4.43 (s, 2, CH_2Ar), 4.23 (d, 2, H_1, J = 6 Hz), 3.66 (d, 2, H_3, J = 6 Hz), 2.48 (s, 6, $ArCH_3$). Anal. ($C_{24}H_{26}S_2O_7$) C, H.

(2*R*)-2-Benzyloxymethyl-1,4-benzodioxan (15). Sodium methoxide, 4.32 g (0.080 mol), was added to an ethanolic solution of 4.40 g (0.04 mol) of catechol and the mixture was refluxed 24 h with 9.80 g (0.02 mol) of ditosylate **14**. The ethanol was removed and the residue was partitioned between 300 mL of ether and 100 mL of 2.5% NaOH. The ether was washed with H_2O (5 × 50 mL), dried ($MgSO_4$), and evaporated to yield 4.5 g (88%) of an oil. Vacuum distillation afforded 3.5 g (70%) of **13**: bp 140 °C (1 mm); α_D +10° (*c* 0.5, EtOH); IR (neat) 3.22, 3.36, 3.42, 6.24, 6.67, 7.83, 9.01, 9.54, 11.80, 13.32, and 14.30 μ; NMR ($CDCl_3$) δ 7.36 (s, 5, PhH), 6.90 (s, 4, ArH), 4.63 (s, 2, CH_2Ar), 4.40 (m, 3, H_2 and H_3), 3.75 (d, 2, CH_2, J = 5 Hz); CD (*c* 0.152, MeOH) $[\theta]_{300}$ 0, $[\theta]_{280}$ +570, $[\theta]_{275}$ +640, $[\theta]_{270}$ +300, $[\theta]_{260}$ +120, $[\theta]_{250}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −4720, $[\theta]_{230}$ −8620, $[\theta]_{225}$ −5050, $[\theta]_{220}$ 0.

(2*R*)-2-Hydroxymethyl-1,4-benzodioxan (16). A solution of 1.28 g (0.005 mol) of benzyl ether **15** in 100 mL of methanol with 1.0 g of 10% Pd/C was shaken overnight in a low-pressure Parr apparatus, initial pressure 40 psig. The catalyst was filtered and the solvent was removed to yield an oil. Crystallization from EtOH–H_2O yielded 0.46 g (55%) of **16** as white needles: mp 71–73 °C (lit. mp 81 °C,[24] racemic mp 86 °C);[25] $[\alpha]_D$ +34.0° (*c* 0.10, absolute EtOH); IR (KBr) 2.80, 3.40, 3.46, 6.28, 6.70, 7.90, 9.08, 9.58, and 13.35 μ; NMR ($CDCl_3$) δ 6.88 (s, 4, ArH), 4.91 (br s, 1, OH), 4.20 (m, 3, H_2 and H_3), 3.86 (d, 2, CH_2, J = 4 Hz); CD (*c* 0.106, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ +1530, $[\theta]_{280}$ +1740, $[\theta]_{275}$ +1660, $[\theta]_{270}$ +1220, $[\theta]_{260}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −6010, $[\theta]_{230}$ −11 000, $[\theta]_{225}$ −9400, $[\theta]_{220}$ −6900. Anal. ($C_9H_{10}O_3$) C, H.

(2*S*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*S*)-11]. To a solution of 0.52 g (0.003 mol) of alcohol **16** in 4 mL of anhydrous pyridine at 0 °C was added 0.59 g (0.003 mol) of *p*-TsCl and the mixture was stirred 18 h at room temperature. The solution was diluted with 100 mL of ether and washed with 1 N HCl (3 × 100 mL) and H_2O (5 × 100 mL), dried ($MgSO_4$), and evaporated to yield 0.74 g (77%) of (2*S*)-**11** as a yellow oil: CD (*c* 0.132, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ +530, $[\theta]_{280}$ +730, $[\theta]_{275}$ +870, $[\theta]_{270}$ +490, $[\theta]_{260}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −4270, $[\theta]_{230}$ −9460, $[\theta]_{225}$ −9210.

(2*R*)-2-Diethylaminomethyl-1,4-benzodioxan Hydrochloride [(2*R*)-Prosympal Hydrochloride] [(2*R*)-2 HCl]. (2*S*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*S*)-**11**], 2.2 g (0.006 mol), was refluxed 36 h with 22.0 g (0.30 mol) of diethylamine. The diethylamine was removed by rotary evaporation and the residue was partitioned between 100 mL of 2.5% NaOH and 300 mL of ether. The ether was washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in absolute ether and the HCl salt was precipitated by the addition of gaseous HCl–saturated ether. Crystallization from isopropyl alcohol–ether yielded 0.73 g (49%) of (2*R*)-**2** HCl as flaky crystals: mp 129–130 °C (lit.[21] mp 129–130 °C, racemic mp 125–127 °C); CD (*c* 0.106, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ +340, $[\theta]_{275}$ +1170, $[\theta]_{265}$ +530, $[\theta]_{255}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −1990, $[\theta]_{230}$ −10 870, $[\theta]_{225}$ −6500. Anal. ($C_{13}H_{19}NO_2Cl$) C, H, N.

(2*R*)-2-Piperidinomethyl-1,4-benzodioxan Hydrochloride [(2*R*)-Piperoxan Hydrochloride] [(2*R*)-3 HCl]. (2*S*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*S*)-**11**], 1.43 g (0.004 mol), was refluxed 18 h in 17 g (0.20 mol) of piperidine. The piperidine was removed and the residue was suspended in 100 mL of 2.5% NaOH and extracted with $CHCl_3$ (3 × 80 mL). The $CHCl_3$ was washed with H_2O (2 × (100 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in absolute ether and the HCl salt was precipitated by addition of gaseous HCl–saturated ether. Crystallization from absolute ethanol–ether yielded 0.56 g (56%) of (2*R*)-**3** HCl as white crystals: mp 182–185 °C (lit.[22] racemic mp 232–234 °C); CD (*c* 0.104, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ +300, $[\theta]_{275}$ +1110, $[\theta]_{265}$ +590, $[\theta]_{255}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −2240, $[\theta]_{230}$ −11 320, $[\theta]_{225}$ −7870, $[\theta]_{220}$ −3700. Anal. ($C_{14}H_{20}NO_2Cl$) C, H, N.

(2*R*)-2-(1-Piperazinylmethyl)-1,4-benzodioxan Dihydrochloride [(2*R*)-12 2HCl]. (2*S*)-2-Tosyloxymethyl-1,4-benzodioxan [(2*S*)-**10**], 3.2 g (0.01 mol), was refluxed 36 h with 17.0 g (0.20 mol) of piperazine in 25 mL of ethanol. The solvent was removed and the residue was suspended in 50 mL of 2.5% NaOH and extracted with $CHCl_3$ (4 × 80 mL). The $CHCl_3$ was washed with H_2O (3 × 150 mL), dried ($MgSO_4$), and evaporated to yield an oil. The oil was dissolved in EtOH and the 2HCl salt obtained by addition of gaseous HCl–saturated ether to yield 2.25 g (73%) of (2*R*)-**17** 2HCl: mp 217–220 °C (EtOAc–MeOH); CD (*c* 0.108, MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ +510, $[\theta]_{275}$ +1020, $[\theta]_{265}$ +540, $[\theta]_{250}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −4080, $[\theta]_{230}$ −11 630, $[\theta]_{225}$ −7840, $[\theta]_{220}$ 0.

(*RR*)-1,4-Bis[2-(1,4-Benzodioxanyl)methyl]piperazine Dihydrochloride [(*RR*)-Dibozane Dihydrochloride] [(*RR*)-4 2HCl]. Sodium methoxide, 0.324 g (0.006 mol) in 5 mL of H_2O, was added to 0.918 g of (2*S*)-**12** 2HCl (0.003 mol) in 20 mL of aqueous ethanol and the mixture was refluxed 48 h with 0.96 g (0.003 mol) of (2*R*)-**11**. The reaction mixture was diluted with 30 mL of 5% NaOH and extracted with $CHCl_3$ (3 × 75 mL). The $CHCl_3$ was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield an oil. Crystallization from absolute ethanol yielded 0.25 g (20%) of (*RR*)-**4** as white needles: mp 150–151 °C (lit.[6c] racemic mp 162–167 °C). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

Excess gaseous HCl–saturated ether was added to a solution of 0.160 g (0.00044 mol) of (*RR*)-**4** in 50 mL of absolute ethanol. The resulting precipitate was collected to yield 0.174 g (87%) of (*RR*)-**4** 2HCl: mp >250 °C (lit.[6c] mp >250 °C); CD (*c* 0.108, MeOH) $[\theta]_{285}$ +1000, $[\theta]_{275}$ +2660, $[\theta]_{265}$ +1180, $[\theta]_{250}$ 0, $[\theta]_{240}$ 0, $[\theta]_{235}$ −9420, $[\theta]_{230}$ −25 900, $[\theta]_{225}$ −17 020. Anal. ($C_{22}H_{28}N_2O_4Cl_2$) C, H, N.

Pharmacological Testing. Aortas from male New Zealand rabbits (2–4 kg) were placed in a modified Krebs–Henseleit (Krebs) solution and cut into helical strips approximately 1.5 mm wide and 2 cm long. The strips were suspended in isolated (10-mL) organ baths under 2 g of tension. The tissues were bathed in Krebs solution maintained at 37 °C and aerated by bubbling with 95% O_2–5% CO_2. The strips were allowed to equilibrate for 2 h prior to adding drugs. Muscle activity was magnified tenfold on a kymograph drum. All strips were maximally contracted by adding methoxamine in a cumulative manner. Following the maximal response the tissues were repeatedly washed until the original baseline was reached. Each strip was then incubated for 1 h with a specific concentration of the antagonist under study. Following the incubation period a second cumulative dose-effect relationship to methoxamine was obtained. The ED_{50} for methoxamine in the control period and antagonist-treated period was obtained for each strip using the appropriate dose–response curve. Three to four concentrations of antagonist were used per experiment with one concentration of antagonist per strip. All ED_{50} values were appropriately corrected for changes in sensitivity during the course of the experiment by running a "time control" tissue which received only methoxamine. The pA_2 of each antagonist was obtained according to the method of Arunlakshana and Schild.[26]

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Various 5-Substituted and 2,5-Disubstituted 1,3-Dioxanes, a New Class of Analgesic Agents

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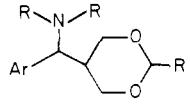
A series of 5-substituted and 2,5-disubstituted 1,3-dioxanes was prepared and evaluated for analgesic activity in mice and rats. Some of the compounds possessed significant analgesic effects; their structure–activity relationships and chemistry are discussed. These compounds represent a unique series of analgesic agents.

The compound 5-benzoyl-5-methyl-1,3-dioxane (**8**)[1] was determined to be an impurity in the Mannich reaction of propiophenone. The acid-catalyzed reaction of phenyl alkyl ketones with formaldehyde will provide compounds such as **8** and 5-benzoyl-1,3-dioxane (**6a**).[2] During the course of preparing various derivatives of **6a** and **8** for broad pharmacological screening, a new class of analgesics was found.

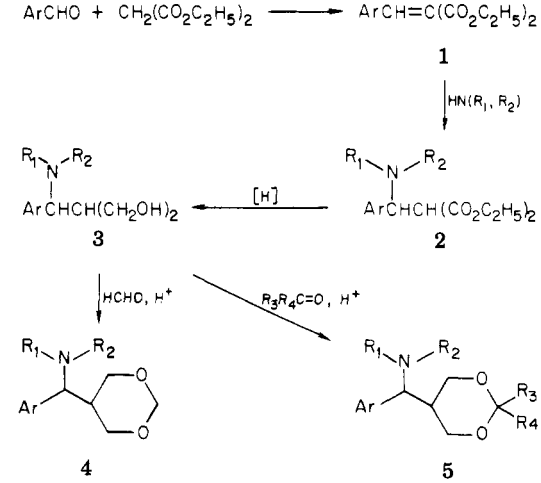
We wish to report this new class of analgesics which is represented by the following general formula



The substitutents Ar and R are illustrated in Table IV.

Chemistry. Most of the 5-substituted 1,3-dioxanes **4a–t** (Table IV) and 2,5-disubstituted 1,3-dioxanes **5a–g** (Table IV) were prepared as outlined in Scheme I. The Knoevenagel condensation[3] of arylaldehydes with diethyl malonate provided diethyl (arylmethylene)malonates **1a–p** (Table I). A Michael addition of secondary amines to

Scheme I



1a–p gave substituted diethyl malonates **2a–t** (Table II) in quantitative yields. These products **2a–t** were viscous