Absolute Configuration of 2-Alkylaminomethylbenzodioxans, Competitive α-Adrenergic Antagonists

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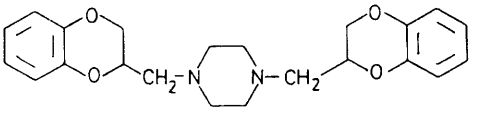
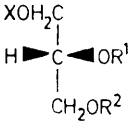
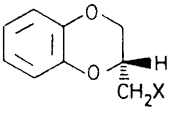
Summary The optical isomers of several *NN*-dialkylaminomethylbenzodioxans, prosympal, piperoxan, and dibozane, important competitive α-adrenergic receptor antagonists, were prepared by synthetic methods establishing the absolute configuration of each.

BLOCKING of α-adrenergic responses has long been a focal point in the search for compounds with useful antihypertensive properties.[1] Among the groups of compounds first studied were the 2-alkylaminomethylbenzodioxans,[1] of which many are very potent agents in reversing the pressor response to epinephrine and have sedative properties.[1,2] Although none of the compounds remain today as clinically useful antihypertensive agents because of adverse effects,[1,3] several compounds, *e.g.* prosympal (**1**),[2,4] piperoxan (**2**),[2,4,5] and dibozane (**3**)[2,4] are very important pharmacological tools because of their competitive antagonist properties at α-adrenergic receptors.



(3)





(4), X = Ts, R^1R^2 = CMe_2
(5), X = $C_6H_4OCH_2Ph$-2, R^1R^2 = CMe_2
(6), X = $C_6H_4OCH_2Ph$-2, R^1 = R^2 = H
(7), X = $C_6H_4OCH_2Ph$-2, R^1 = R^2 = Ts
(8), X = C_6H_4OH-2, R^1 = R^2 = Ts
(11), X = CH_2Ph, R^1 = R^2 = H
(12), X = CH_2Ph, R^1 = R^2 = Ts

(1), X = NEt_2
(2), X = N
(9), X = OTs
(10), X = N NH
(13), X = OCH_2Ph (enantiomer)
(14), X = OH (enantiomer)

Ts = *p*-$MeC_6H_4SO_2$

Only one report related to the effects of absolute stereochemistry on the pharmacological properties of these α-adrenergic antagonists has appeared, which indicated that the (−)-isomer of prosympal (**1**) was 5—6 times more potent than the (+)-isomer in reversing the pressor response of epinephrine (in cats), and it was also a more potent miotic (4—8 times).[6] In this communication we report the synthesis of the enantiomers of these three benzodioxans, establishing the absolute configuration of each by synthetic methods that allow easy preparation of a large number of other chiral 2-substituted benzodioxans of known absolute configuration.

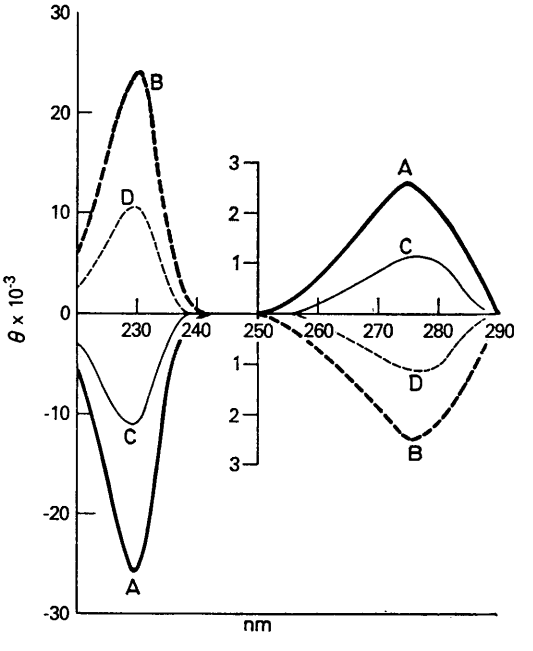


FIGURE. C.d. spectra of enantiomers of (**2**) and (**3**) (HCl salts in MeOH): (A), (*RR*)-(**3**); (B), (*SS*)-(**3**); (C), (2*R*)-(**2**); and (D) (2*S*)-(**2**). C.d. measurements (in deg cm^2 mol^{-1}) were recorded on a Cary 60 instrument with c.d. attachment.

Compounds derived from (2*R*)-glyceraldehyde 2,3-acetonide, available from (2*R*,3*R*,4*R*,5*R*)-mannitol, were

used as starting materials for both enantiomers.[5] Compound (**4**)[7] was converted into (**5**) (79% yield) using 2-benzyloxyphenol[8] (NaOMe, 1 equiv., EtOH, 24 h, reflux). Hydrolysis of the acetonide (1N HCl in 1:1 acetone–H_2O, reflux, 2 h) afforded the (2*R*)-diol (**6**) (96% yield), m.p. 92—93 °C (CCl_4). Tosylation (Ts = *p*-$MeC_6H_4SO_2$) (2 equiv.), pyridine, 0 °C, 24 h) proceeded smoothly producing (**7**) [(2*S*)-stereochemistry]† in 55% yield, m.p. 80—82 °C (Et_2O). Hydrogenolysis (2 atm, Pd-C catalyst, in 1:1 EtOAc–MeOH) afforded the (2*S*)-ditosylate (**8**) (79% yield), m.p. 119—120 °C (MeOH). Ring closure [NaOMe (1 equiv.), EtOH, reflux] afforded (2*R*)-tosyloxymethylbenzodioxan (**9**) (92% yield) as an oil. Compound (**9**) [(2*R*)-stereochemistry] was converted into the corresponding α-adrenergic antagonist (**1**), m.p. [(2*S*)-(**1**)·HCl] 129—130 °C[9] (racemic: 125—127 °C,[10] λ_{max} (MeOH) 217 (log ε 3·84) and 276 (3·40) nm, and (**2**), m.p. [(2*S*-(**2**)·HCl] 182—185 °C (racemic: 232—236 °C),[11] λ_{max} (MeOH) 217 (log ε 3·84) and 276 3·39) nm [(2*S*)-stereochemistry]† using 20 molar excesses of diethylamine and piperidine (24 h, reflux), respectively. Reaction of (2*R*)-(**9**) with an excess of piperazine (EtOH, reflux, 36 h) afforded (2*S*)-(**10**)† isolated as the dihydrochloride, m.p. 217—220 °C.

The (*R*)-enantiomers of (**1**) and (**2**) were prepared starting from (2*R*)-3-benzyloxypropanediol (**11**),[12] also available from (2*R*)-glyceraldehyde 2,3-acetonide. Compound (**11**) was converted in 77% yield into (**12**) [(2*S*)-stereochemistry]† by tosylation (TsCl, pyridine, 0 °C, 24 h). Displacement with catechol [NaOMe (2 equiv.), EtOH, 24 h, reflux] afforded (**13**) [(2*R*)-stereochemistry]† (88% yield), as an oil. Hydrogenolysis (2 atm, Pd–C catalyst) gave (**14**) [(2*R*)-stereochemistry], m.p. 71—73 °C (EtOH–H_2O) in 55% yield.[13] Tosylation (TsCl, pyridine, 0 °C, 24 h) afforded (2*S*)-(**9**),† which was converted into the (2*R*)-enantiomers of (**1**), m.p. [(2*R*)-(**1**)·HCl] 129—130 °C,[9,10] (**2**), m.p. [(2*R*)-(**2**)·HCl] 181—184 °C, and (**10**), m.p. (2*S*)-**11**, 217—220 °C, as described for the (2*S*)-enantiomers.

The dibozane enantiomers (*RR*)-(**3**), m.p. 149—151 °C, and (*SS*)-(**3**), m.p. 150—151 °C (*meso*: 162—167 °C),[14] λ_{max} (MeOH) [(**3**)·2HCl] 217 (log ε 4·14) and 276 (3·72) n.m, were prepared from (2*R*)-(**10**) and (2*S*)-(**10**) by allowing these amines to react with (2*S*)-(**9**) and (2*R*)-(**9**) respectively (EtOH, reflux, 24 h).† Similarly, the *meso*-isomer of (**3**), m.p. 165—167 °C, was prepared by allowing (2*S*)-(**10**) to react with (2*S*)-(**9**) under the same conditions.

The c.d. spectra for the enantiomers of piperoxan (**2**) and dibozane (**3**) appear in the Figure. Consistently, in the c.d. spectra of these enantiomers, and in those of prosympal (**1**) and (**10**) (not shown), the (*S*)-isomers show a negative ^1L_B transition, maximum near 275 nm and a much stronger positive ^1L_A transition, maximum near 230 nm. As expected, the magnitude of these transitions in the enantiomers of dibozane (**3**) is *ca.* twice as large as those observed for the other benzodioxans.

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† The absolute stereochemistry as designated by the Cahn–Ingold–Prelog system (R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81; *Angew. Chem. Internat. Edn.*, 1966, **5**, 385) changes with different substituents in the conversion of (**6**) into (**7**), (**9**) into (**10**) [or (**1**), (**2**), (**3**)], and (**14**) into (**9**), although no stereochemical change at the asymmetric carbon has occurred. In the synthetic steps, a single inversion occurs in each sequence, (**8**) → (**9**), and (**12**) → (**13**).

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