

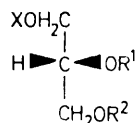
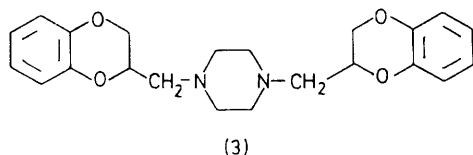
Absolute Configuration of 2-Alkylaminomethylbenzodioxans, Competitive α -Adrenergic Antagonists

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Summary The optical isomers of several *NN*-dialkylamino-methylbenzodioxans, 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),^{2,4,6} and dibozane (3)^{2,4} are very important pharmacological tools because of their competitive antagonist properties at α -adrenergic receptors.



(4), X = Ts, R¹ R² = CMe₂

(5), X = C₆H₄OCH₂Ph-2, R¹ R² = CMe₂

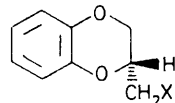
(6), X = C₆H₄OCH₂Ph-2, R¹ = R² = H

(7), X = C₆H₄OCH₂Ph-2, R¹ = R² = Ts

(8), X = C₆H₄OH-2, R¹ = R² = Ts

(11), X = CH₂Ph, R¹ = R² = H

(12), X = CH₂Ph, R¹ = R₂ = Ts



(1), X = NEt₂

(2), X = N (piperazine ring)

(9), X = OTs

(10), X = N (piperidine ring)

(13), X = OCH₂Ph (enantiomer)

(14), X = OH (enantiomer)

Ts = *p*-MeC₆H₄SO₂

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.

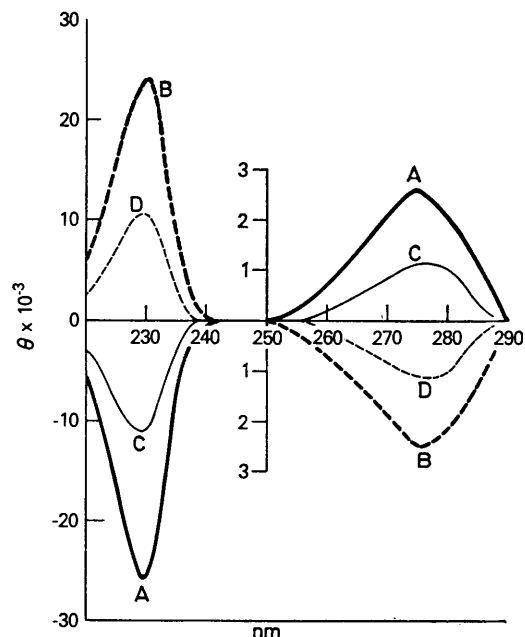


FIGURE. C.d. spectra of enantiomers of (2) and (3) (HCl salts in MeOH): (A), (*RR*)-(3); (B), (*SS*)-(3); (C), (*2R*)-(2); and (D) (*2S*)-(2). C.d. measurements (in deg cm² mol⁻¹) were recorded on a Cary 60 instrument with c.d. attachment.

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

used as starting materials for both enantiomers.⁵ Compound (4)⁷ was converted into (5) (79% yield) using 2-benzyloxyphenol⁸ (NaOMe, 1 equiv., EtOH, 24 h, reflux). Hydrolysis of the acetonide (1N HCl in 1:1 acetone-H₂O, reflux, 2 h) afforded the (2*R*)-diol (6) (96% yield), m.p. 92–93 °C (CCl₄). Tosylation (Ts = *p*-MeC₆H₄SO₂) (2 equiv.), pyridine, 0 °C, 24 h) proceeded smoothly producing (7) [(2*S*)-stereochemistry]† in 55% yield, m.p. 80–82 °C (Et₂O). 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 °C⁹ (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.

† 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).

¹ For a review of antihypertensive adrenergic blocking agents, see: L. H. Werner and W. E. Barrett, in 'Antihypertensive Agents,' ed. E. Schlittler, Academic Press, New York, 1967, Ch. X, pp. 331–392.

² E. Fourneau, D. Bovet, and P. Maderni, *J. Pharm. Chim.*, 1933, **18**, 185; E. Fourneau and D. Bovet, *Compt. rend. Soc. Biol.*, 1933, **113**, 388.

³ M. Nickerson, *Pharmacol. Rev.*, 1957, **9**, 246; A. B. Demson, Jr., S. Bardhanabaedyna, and H. D. Green, *Circulation Res.*, 1954, **2**, 537; W. Rosenblatt, T. M. Haymond, S. Bellet, and G. Koelle, *Amer. J. Sci.*, 1954, **227**, 179.

⁴ E. Fourneau and D. Bovet, *Arch. Intern. Pharmacodyn.*, 1933, **46**, 178; D. Bovet and A. Simon, *ibid.*, 1937, **55**, 15; C. E. Rapela and H. O. Green, *J. Pharmacol. Exptl. Therap.*, 1961, **132**, 29.

⁵ E. Baer, *Biochem. Preparations*, 1952, **2**, 31.

⁶ D. Bovet and A. Simon, *Bull. Sci. Pharmacol.*, 1935, **42**, 466 (*Chem. Abs.*, 1936, **30**, 769).

⁷ E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, 1939, **123**, 463; J. C. Sowden and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1942, **64**, 1291.

⁸ O. Schmidt and W. Blank, *Chem. Ber.*, 1956, **89**, 283.

⁹ E. Fourneau, P. Maderni, and Y. de Lestrangé, *J. Pharm. Chim.*, 1933, **18**, 185.

¹⁰ J. Trepouel and Y. Dunant, *Bull. Sci. Pharm.*, 1935, **42**, 259.

¹¹ E. Fourneau, U.S.P. 2,056,046 (*Chem. Abs.*), 1936, **30**, 8530.

¹² B. Belleau and J. Puranen, *J. Medicin. Chem.*, 1963, **6**, 325; D. Triggle and B. Belleau, *Canad. J. Chem.*, 1962, **40**, 1201.

¹³ A. Griin, U.S.P. 2,366,102 (1944) (*Chem. Abs.*), 1946, **40**, 2271; J. Trepouel and Y. Dunant, *Bull. Sci. Pharm.*, 1935, **42**, 459.

¹⁴ A. P. Swain, U.S.P. 2,695,294 (1954) (*Chem. Abs.*), 1955, **49**, 14,039.

Hydrogenolysis (2 atm, Pd-C catalyst) gave (14) [(2*R*)-stereochemistry], m.p. 71–73 °C (EtOH-H₂O) 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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