phenyl ring needs some explanation. This distance is solely dependent upon the torsion angle τ_1, whose range is severely restricted by the methyl group on the alpha-carbon atom. A rotation of τ_1 by 10° in the appropriate direction, however, brings the distance between the N atom and the plane in the range of 1·2 — 1·4 Å and that between the O atom and the plane in the range of 0·8 — 1·1 Å. It is noted that the O and N atoms are on opposite sides of the phenyl ring. The 0·83 Å distance between the O atom and the plane closely approximates the distance (0·66 — 0·67 Å) between the alcoholic O atom and the plane in the folded conformation of noradrenaline and norephedrine.

It may be concluded that the conformation of phenmetrazine as observed in the solid state is in excellent agreement with the pharmacophore derived from quantum calculations.

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REFERENCES

CARLSTROM, D. & HACKSELL, I. (1974). *Acta Cryst.*, B30, 2477–2480.
COUBEILS, J. L., COURRIÈRE, PH. & PULLMAN, B. (1972). *J. medl Chem.*, **15**, 453–455.
KIER, L. B. (1969). *J. Pharm. Pharmac.*, **21**, 93–96.
PULLMAN, B., COUBEILS, J. L., COURRIÈRE, PH. & GERVOIS, J.-P. (1972). *J. medl Chem.*, **15**, 17–23.

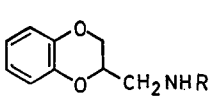
The α-adrenoceptor blocking effects of a new benzodioxane

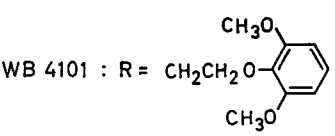
Since the first report on the pharmacological activity of the benzodioxanes (Fourneau & Bovet, 1933), members of this series have been shown to inhibit the excitatory responses of many smooth muscle structures to adrenergic stimuli. These effects are mediated through blockade of α-adrenoceptors.

Preliminary studies on a series of benzodioxanes have been described (Fenton, Green & others, 1965; Green, Shapero & Wilson, 1969), and in the present study WB 4101, WB 4109 and WB 4371, members of this series, have been evaluated for their α-adrenoceptor blocking effects on rat isolated vas deferens.

Vasa deferentia from male Charles River rats (250–300 g) were set up in organ baths and bathed in Tyrode solution, maintained at 37° and aerated with a mixture of 5% carbon dioxide in oxygen.

Isometric contractions were recorded using Devices transducers and two-channel recorders. Log dose-response relations for noradrenaline were recorded before and during exposure to varying concentrations of WB 4101, WB 4109, WB 4371, phentolamine, yohimbine and thymoxamine. Graded doses of noradrenaline were





WB 4101 : R = CH_2CH_2O (3,4-dimethoxyphenyl) HCl

WB 4109 : R = $CH_2CH_2OCH_2CH_2OCH_3$ HCl

WB 4371 : R = $CH_2CH_2CH_2SO_2C(Et_2)CH_3$ HCl

given at 5 min intervals, the bathing solution being changed twice between doses. The α-adrenoceptor blocking agents were left in contact with the tissue for 2 min before noradrenaline log dose-response relations were recorded. Control vasa showed that the log dose-response relations for noradrenaline did not vary significantly during the time period of each experiment.

Results showed that all the blockers used exhibited a competitive type of blockade in that the antagonists all caused a parallel shift of the dose response curve for noradrenaline to the right, the blockade produced was reversible and could be overcome by excess agonist. The comparative potency of these blockers was established by measuring their pA_2 (Schild, 1947) values: pA_2 value mean $\pm$ s.e. (n), phentolamine 6·7 $\pm$ 0·03 (4), thymoxamine 6·4 $\pm$ 0·07 (4), yohimbine 6·1 $\pm$ 0·06 (4), WB 4371 5·1 $\pm$ 0·05 (4), WB 4109 5·3 $\pm$ 0·07 (4), WB 4101 9·8 $\pm$ 0·04 (6).

The benzodioxanes, WB 4371 and WB 4109 have a less potent effect than the standard α-adrenoceptor blocking agents phentolamine, thymoxamine and yohimbine. However, the benzodioxane WB 4101 was a more potent antagonist of noradrenaline, having a pA_2 value of 9·8.

The reasons for the marked potency of WB 4101 on the rat vas deferens may be explained by studying the structure-activity relations of compounds which bind to the α-receptor. It has been suggested (Ariens, 1960; Ariens & Simonis, 1969; Tuttle & Moran, 1969) that antagonists of the α-receptor, which exhibit widely differing chemical structure, may bind to the central, nucleophilic group within the receptor, as do agonists, but that the rest of the molecule may bind over a wide area around this group. Evidence that α-receptor antagonists interact with protein in smooth muscle has been presented by Graham & Mottram (1971). An α-receptor site, based on protein, has been proposed by Mottram (1970), in which the structure of the receptor is based on a tripeptide.

Sympathomimetic amines, and their antagonists, have a common primary site of attachment in this proposed receptor, the nucleophilic site, but otherwise their molecules occupy different areas about this site. It is envisaged however, that the molecular structure of the benzodioxane, renders this antagonist capable of binding centrally to the nucleophilic site, but that the rest of the molecule extends across both the area receptive to the catecholamine agonists and also the area receptive to their antagonists. This would result in a very close fit between the drug and the receptor, as suggested by the very high pA_2 value for WB 4101.

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REFERENCES

ARIENS, E. J. (1960). *Ciba Foundation Symposium on Adrenergic Mechanisms*, 253–263.
ARIENS, E. J. & SIMONIS, A. M. (1969). *Acta Physiol. Pharmac.*, **15**, 78.
FENTON, H., GREEN, P. N., SHAPERO, M. & WILSON, C. (1965). *Nature*, 206, 725.
FOURNEAU, E. & BOVET, D. (1933). *Archs int. Pharmacodyn. Thér.*, **46**, 178–191.
GRAHAM, J. D. P. & MOTTRAM, D. R. (1971). *Br. J. Pharmac.*, **42**, 428–436.
GREEN, P. N., SHAPERO, M. & WILSON, C. (1969). *J. medl. Chem.*, **12**, 326.
MOTTRAM, D. R. (1970). Ph.D. Thesis, 160–170.
SCHILD, H. O. (1947). *Br. J. Pharmac. Chemother*, **2**, 189–206.
TUTTLE, R. R. & MORAN, N. C.(1969). *J. Pharmac., exp. Ther.*, **169**, 255–263.