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A comparison between the solid state conformation of phenmetrazine and the α-sympathomimetic pharmacophore pattern

Some time ago one of us proposed phenmetrazine as a structure obeying the α-adrenergic pattern proposed by Pullman, Coubeils & others, (1972) and Coubeils, Courrière & Pullman (1972). This feature pattern derived from PCILO calculations on a number of phenethylamines is in agreement with that suggested by Kier (1969). The recent X-ray structural analysis of Carlstrom & Hacksell (1974) prompted us to compare in detail the crystal conformation of phenmetrazine with the predicted conformation.

Using a computer program (ROTRAN) developed in this laboratory we translated and rotated the molecule in such a way that the resulting orientation facilitates the inspection of the atomic coordinates with respect to a given molecular plane.

In Fig. 1 phenmetrazine is oriented so that the phenyl ring lies in the xy-plane and the N atom in the xz-plane. The torsion angles τ_1 and τ_2 as observed in the crystal are −105° and −175° respectively. This conformation is typical for many phenethylamines and is in agreement with one of the energy minima found in amphetamine by the PCILO calculations ($\tau_1 = -90°$ and $\tau_2 = 180°$). In fact, inspection of Fig. 1 shows a striking resemblance with the pharmacophore derived from the PCILO calculations. The distances between the O atom, the centre of the phenyl ring and the N atom are virtually identical to those of the suggested pharmacophore.

The slight departure of the distance from the N atom to the plane through the

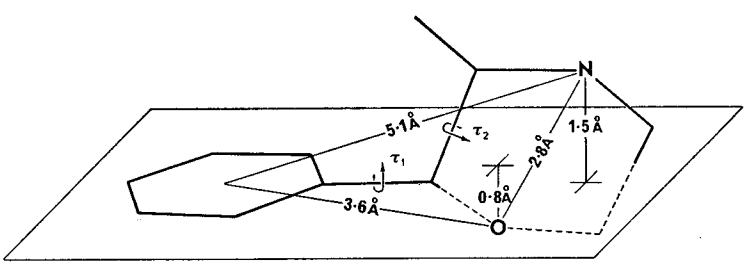

FIG. 1. Phenmetrazine as seen with the phenyl ring in the xy-plane and the N atom in the xz-plane.

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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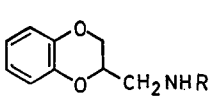
The α-adrenoceptor blocking effects of a new benzodioxane

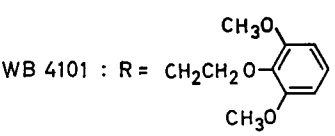
Since the first report on the pharmacological activity of the benzodioxanes (Fourneau & Bovet, 1933), members of this series have been shown to inhibit the excitatory responses of many smooth muscle structures to adrenergic stimuli. These effects are mediated through blockade of α-adrenoceptors.

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