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Note

1-Methyl-2-phenylcyclopropylamine

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Zeller *et al.*[1] have recently presented data from which they concluded that the most suitable inhibitors of monoamine oxidase (MAO) contain a two-atom chain connected to an aromatic ring, with a hydrogen α to an amino group. They suggested that this α-hydrogen is necessary to bind these agents to the active site of the enzyme.

We have now found that the substitution of the α-hydrogen in 2-phenylcyclopropylamine (tranylcypromine) by a methyl group produces an MAO inhibitor, 1-methyl-2-phenylcyclopropylamine, with a potency, both *in vivo* and *in vitro*, approximately equal to that of 2-phenylcyclopropylamine. Since 1-methyl-2-phenylcyclopropylamine has no α-hydrogen, this observation is incompatible with Zeller's postulate and indicates that the high affinity of the 2-phenylcyclopropylamines for MAO must be attributed entirely to other chemical and/or physical properties of their molecules.

The high potency of the cyclopropane derivatives relative to that of phenylalkylamines,[1] e.g. 2-amino-1-phenylpropane, may be due to the peculiar steric or polar characteristics of the cyclopropane system. Perhaps the rigid cyclopropane ring fixes the 2-phenylcyclopropylamine molecule in a configuration optimal for attachment to the enzyme. However, the nearly equal potency of the *cis* and *trans* isomers of this amine[1,2] is difficult to explain on this basis. The unsaturated character of the cyclopropane

ring is well known. This property, in the case of 2-phenylcyclopropylamine derivatives, is reflected in the ease with which these amines undergo ring-opening reactions.[3] Possibly the high electron density of the cyclopropane ring provides a focus for bonding of the amine to the enzyme.

It may be pertinent to note, in this regard, that in the hydrazine derivatives which are potent MAO inhibitors,[1] e.g. benzylhydrazine, the atom (nitrogen) α to the terminal amino group possesses an unshared pair of electrons. Finally, although the ability of 2-phenylcyclopropylamines to undergo ring opening[3] under physiological conditions has not been studied, one cannot rule out the possibility, until more knowledge of the mechanism of their biological action is obtained, that this process is in some way involved in their MAO-inhibiting action.

Experimental

Chemistry

1-Methyl-2-phenylcyclopropanecarboxylic acid. A solution of freshly distilled methyl methacrylate (212 g) in dry ether (100 ml) was added to a solution of phenyldiazomethane (*ca.* 34 g) in 1·5 l. of dry ether and hydroquinone (4 g) over a period of 1·5 h at 0–5°. After standing overnight, the ether and excess methyl methacrylate were distilled off at 15 mm, and the residual oil was heated at 120–135°/15 mm for 1·5 h until no more nitrogen was evolved. The tan oil distilled at 88–94°/1·3 mm; the yield was 38·5 g (68 per cent).

This ester (32 g) was dissolved in 95 per cent ethanol (200 ml) and water (50 ml) containing potassium hydroxide (40 g). The mixture was refluxed for 12–15 h, diluted with water (200 ml), extracted with ether, and acidified with dilute hydrochloric acid. The product was extracted with ether, and the extracts were dried and concentrated. The residue crystallized from low-boiling petroleum ether, m.p. 80–82°. Literature m.p.,[4] 79–80°. The yield was 24 g (80 per cent).

1-Methyl-2-phenylcyclopropylamine. To a stirred solution of 1-methyl-2-phenylcyclopropanecarboxylic acid (6·16 g, 0·035 mole) in acetone (15 ml) and water (7·5 ml) was added at −5° a solution of triethylamine (4·05 g, 0·04 mole) in acetone (30 ml)

followed by a solution of ethyl chlorocarbonate (4·35 g, 0·04 mole) in acetone (10 ml).[5] After stirring the mixture at −5 to 0° for 30 min, a solution of sodium azide (3·25 g, 0·05 mole) in water (20 ml) was added, and stirring was continued for an additional 2 h. The reaction mixture was poured into an ice-cold saturated salt solution and extracted with three 100-ml portions of ether. The combined ethereal solutions were dried over sodium and calcium sulphate and evaporated at 30°/15 mm. A solution of the residual azide in 50 ml of dry toluene was refluxed for 2 h until nitrogen evolution ceased, and the solvent was then removed under vacuum. To the oily residue was added 18 per cent hydrochloric acid (35 ml) and the mixture was refluxed for 18–20 h. After cooling, the acidic mixture was extracted with ether, made alkaline with 10 per cent sodium hydroxide solution and extracted with ether. The ethereal solution was dried and concentrated. The product distilled at 60–61°/1·5 mm, yield, 2·3 g (44 per cent). The *sulphate* salt melted at 183–184°.

Anal. Calcd. for $C_{10}H_{13}N \cdot \frac{1}{2}H_2SO_4 \cdot H_2O$: C, 56·05; H, 7·52. Found: C, 55·90; H, 7·59.

Determination of MAO Inhibition

1-Methyl-2-phenylcyclopropylamine sulphate was tested orally for its ability to potentiate tryptamine convulsions in rats, a sensitive *in vivo* procedure for measuring monoamine oxidase inhibition.[6,7] The oral ED_{50} was found to be 0·53 (0·35–0·81) mg/kg (0·36 mg/kg, calculated as the base) which indicates that the compound is approximately one-half to one-third as potent as *trans*-2-phenylcyclopropylamine.

In vitro determination of monoamine oxidase activity was performed according to the procedure of Bogdanski *et al.*[8] using homogenates of whole rat brain prepared in 2 volumes of water. Serotonin was used as a substrate and was extracted from the incubation mixture and assayed according to the nitrosonaphthol method of Udenfriend *et al.*[9] Using this procedure it was found that 1-methyl-2-phenylcyclopropylamine sulphate was 2–4 times more potent as an inhibitor of the enzyme activity than was *trans*-2-phenylcyclopropylamine.[10] The concentrations of the two drugs, calculated as the free base, that inhibited the enzyme activity by 50 per cent were: *trans*-2-phenylcyclopropylamine,

$9 \cdot 7 \times 10^{-7}$M, 1-methyl-2-phenylcyclopropylamine, $2 \cdot 5$–$5 \cdot 0 \times 10^{-7}$M.

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