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MONOAMINE OXIDASE INHIBITION

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This invention relates to antidepressant and hypotensive compositions of trans 2-phenylcyclopropylamine, or the methyl or dimethylamino analogues and the method of treating depressed and hypertensive human beings with these compositions.

Prior to the present invention the important advances in the treatment of the mentally disturbed have been largely in the excited group of patients through the use of central nervous system depressant compounds commonly referred to as transquilizers. These transquilizers provide relief in many cases for tense, anxious and overstimulated people. A large portion of the population of mental hospitals, however, consists of depressed and regressed psychotics the opposite side of human tensions. There are also many ambulatory nonpsychotic depressed and regressed patients. These patients are either not responsive to transquilizers or are aggravated by the use of these drugs. The usual therapy for these patients is a stimulant or shock treatment, depending upon the degree of depression. The need of a safe, effective composition with a minimum of side effects for use in this area has been great.

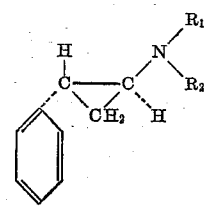
The compositions of this invention exhibit potent monoamine oxidase inhibitory properties. This inhibitory property of monoamine oxidase is associated with antidepressant compounds, as for example, the iproniazid like compounds. Results of the tryptamine potentiation test in rats, which is a reflection of amine oxidase inhibitory activity shows the trans isomer of 2-phenylcyclopropylamine to be significantly more potent than the cis isomer. Combination studies in rabbits with trans 2-phenylcyclopropylamine and reserpine in which signs of central excitement and pyrexia are observed indicate that this combination is dramatically more powerful than the iproniazid like compounds and reserpine combinations. This particular test procedure is an indication of the activity of monoamine oxidase inhibition. In vitro tests measuring the rate of disappearance of serotonin when incubated with whole rat brain homogenate again indicate that trans 2-phenylcyclopropylamine is considerably more potent than iproniazid like compounds as a monoamine oxidase inhibitor.

The composition in accordance with this invention is very useful as a psychic energizer, i.e., useful in treating depressed and regressed psychotics as well as ambulatory nonpsychotic depressed patients. In the treatment of this group of psychotics it induces antidepressant activity without any substantial amount of severe side effects such as jitteriness, excessive stimulation or increased tension observed from closely related compounds such as amphetamine. Also, unlike the related sympathominetic amines such amphetamine, ephedrine and epinephrine which all cause a rise in blood pressure in humans, the novel compositions of this invention unexpectedly brings about a lowering of blood pressure and demonstate hypotensive characteristics.

More specifically the compositions of this invention

contain a phenylcyclopropylamine free base or a nontoxic acid addition salt thereof, the free base having the formula:

FORMULA I



in which R_1 and R_2 represent hydrogen or methyl groups.

In their most advantageous forms, the compositions in accordance with this invention will also contain a nontoxic pharmaceutical carrier in addition to the medicinal agent.

The phenylcyclopropylamine of Formula I or a nontoxic acid addition salt there of will be present in an amount to produce antidepression and antihypertensive activity. Preferably the composition will contain the trans 2-phenylcyclopropylamine ingredient in an amount of from about 5 mg. to about 150 mg., advantageously from about 10 mg. to about 100 mg. per dosage unit.

The pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil, and water. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preperation can be tabletted, placed on a hard gelatin capsule or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 gm. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, placed in an ampule or in a liquid suspension.

The method in accordance with this invention comprises administering internally a compound of Formula I or a nontoxic addition salt thereof admixed with a pharmaceutical carrier, for example, any of the above compositions. The 2-phenylcyclopropylamine ingredient preferably will be, per unit, in an amount of from about 5 mg. to about 150 mg. and advantageously from about 10 mg. to about 100 mg. The administration may be parenterally or orally, the latter being the preferable route of administration. Advantageously equal doses will be administered one to four times daily. Preferably the daily dosage will be from about 5 mg. to about 600 mg. and most advantageously from about 10 mg. to about 200 mg. of active medicament in pharmaceutical forms. When the administration described above is carried out, both antidepression and antihypertension results are obtained.

The trans isomer of 2-phenylcyclopropylamine is prepared by reacting styrene with ethyl diazoacetate and forming the ester, ethyl 2-phenylcyclopropanecarboxylate. The resulting ester is hydrolyzed to the 2-phenylcyclopropanecarboxylic acid. At this stage there are 3 to 4 parts of the trans isomer to 1 part of the cis isomer. A complete separation is accomplished by recrystallizing the acid from hot water. The pure trans isomer comes

out as crystalline material while the cis isomer stays in solution. The trans 2-phenylcyclopropanecarboxylic acid is then reacted with thionyl chloride to form the acid chloride which is then successively treated with sodium azide and subjected to the curtius degradation. The isocyanate formed by this procedure is hydrolyzed readily to the 2-phenylcyclopropylamine or reduced to the secondary monomethylamine. The dimethylamino derivatives are obtained by methylation of the primary amine with a mixture of aqueous formaldehyde and formic acid.

Preferably the hydrochloride salt of the trans 2-phenylcyclopropylamine is used, however, either the base itself or a nontoxic, pharmaceutically acceptable acid addition salt of the base may be used, such as the salt derived from sulfuric, nitric, phosphoric, citric, acetic, lactic, mandelic, salicylic, tartaric, ethanedisulfonic, sulfamic, acetylsalicylic, succinic, fumaric, maleic, hydrobromic, benzoic and like nontoxic acids. The salts are best prepared by reacting the free base with a stoichiometric amount of the desired organic or inorganic acid in a suitable solvent such as ethyl acetate-ether solution, ethanol, acetone, water or various combinations of solvents.

The invention will be further clarified by the following specific examples of preparations in accordance with this invention.

Example 1

A solution containing 167 g. of stabilized styrene and 183 g. of ethyl diazoacetate is cooled to 0° C. and dropped into 83.5 g. of styrene with stirring, in a dry nitrogen atmosphere, at 125°–135° C. This produced the ester ethyl 2-phenylcyclopropanecarboxylate.

A solution of the above ester (207.8 g.) and 64.5 g. of sodium hydroxide in 80 cc. of water and 600 cc. of ethanol is refluxed for 9 hours. The carboxylic acid of 2-phenylcyclopropane is liberated with 200 cc. of concentrated hydrochloric acid. The 2-phenylcyclopropanecarboxylic acid contains 3 to 4 parts of the trans isomer to 1 part of the cis isomer. The acid is recrystallized from hot water. The pure trans isomer comes out as crystalline material (solid) while the cis isomer stays in solution.

A solution of 4.62 g. of 2-phenylcyclopropanecarboxylic acid in 15 cc. of dry benzene is refluxed with 4 cc. of thionyl chloride for five hours, the volatile liquids are removed and the residue once more distilled with benzene. Fractionation of the residue yields the carbonyl chloride of 2-phenylcyclopropane.

A mixture of 15 g. of technical sodium azide and 50 cc. of dry toluene is stirred and warmed and a solution of 10 g. of 2-phenylcyclopropanecarbonyl chloride in 50 cc. of dry toluene is added slowly. Inorganic salts are filtered and washed well with dry benzene and the solvents are removed under reduced pressure. The residual isocyanate is a clear red oil of characteristic odor. It is cooled to 10° C. and treated cautiously with 100 cc. of 55% hydrochloric acid. After most of the evolution of carbon dioxide has subsided the mixture is refluxed for 13 hours the cooled solution is diluted with 75 cc. of water and extracted with three 50 cc. portions of ether. The acid solution is evaporated under reduced pressure with occasional additions of toluene to reduce foaming.

The almost dry residue is cooled to 0° C. and made strongly alkaline with a 50% potassium hydroxide solution. The amine is extracted into several portions of ether, dried over potassium hydroxide, the solvent removed, and the base fractionated.

Conversion to the hydrochloride proceeds best in ethyl acetate-ether solution. The crude salt is recrystallized by dissolving it in the least amount of cold methanol and precipitation with absolute ethyl acetate and ether. The colorless needles thus obtained have a melting point of 151–154° C.

Example 2

A solution of 5 g. of trans 2-phenylcyclopropylamine (as prepared in Example 1) and 4.3 g. of benzaldehyde in 10 cc. of absolute ethanol is refluxed for three hours. The solvent is removed in vacuo and the benzal derivative distilled.

A mixture of 6 g. of trans 2-phenylcyclopropylbenzalamine and 7.7 g. of methyl iodide is heated in a sealed tube at 95° C. for seven hours. The reaction product is boiled with 75 ml. of 95% ethanol for four hours, the solvent removed in vacuo, the base liberated with 40% potassium hydroxide solution and extracted with ether. The dried ether extract is evaporated and the residue distilled to give trans 2-phenylcyclopropylmethylamine.

An ethereal solution of the free base treated with anhydrous hydrogen chloride gas yields the hydrochloride salt.

Example 3

Trans 2-phenylcyclopropylamine (as prepared in Example 1) is methylated by adding 10.2 g. of 40% aqueous formaldehyde to a cooled solution of 5 g. of 2-phenylcylcopropylamine in 13.2 g. of 90% formic acid and the mixture is refluxed for 14 hours. The cooled reaction mixture is treated with 5.5 cc. of concentrated hydrochloric acid, the solution is evaporated in vacuo. The residue is made alkaline with 50% potassium hydroxide solution and the solution extracted with ether. The dried ether extracts are evaporated to give the residual trans 2-phenylcyclopropyldimethylamine.

The free base dissolved in ethyl acetate is added to a solution of mandelic acid in ethanol. Concentration of the resulting solution and cooling yields the crystalline trans 2-phenylcyclopropyldimethylamine mandelate.

Example 4

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropylamine hydrochloride	75.00
Magnesium stearate	2.00
Lactose	130.00

The above powders are thoroughly mixed and filled into a #2 hard gelatin capsule.

Example 5

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropylmethylamine hydrochloride	25.00
Magnesium stearate	2.00
Lactose	265.00

The ingredients are mixed and filled into a #2 hard gelatin capsule.

Example 6

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropylamine	50.00
Calcium sulfate, dihydrate (terra alba)	125.00
Sucrose	25.00
Starch	15.00
Talc	5.00
Stearic acid	3.00

The sucrose, calcium sulfate and trans 2-phenylcyclopropylamine hydrochloride are thoroughly mixed, granulated with hot 10% gelatin solution. The wetted mass is passed through a #6 mesh screen directly onto drying trays. The granules are dried at 120° F. and passed through a #20 mesh screen. These granules are then mixed with the starch, talc and stearic acid, passed through a #60 mesh screen and then compressed into tablets.

Example 7

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropyldimethylamine sulfate	5.00
Lactose	250.00
Starch	13.00
Talc	5.00
Magnesium stearate	2.50

The lactose and trans 2-phenylcyclopropylamine sulfate are mixed and granulated with hot 10% gelatin. The magnesium stearate, talc and starch are admixed according to procedure of Example 4 and compressed into a tablet.

Example 8

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropylamine acetate	150.00
Magnesium stearate	2.00
Lactose	125.00

The ingredients are mixed and filled into a #2 hard gelatin capsule.

Example 9

Ingredients:	Amounts, mg.
Trans 2-phenylcyclopropylamine maleate	50.00
Peanut oil	225.00

The ingredients are mixed to a thick slurry and filled into a soft gelatin capsule.

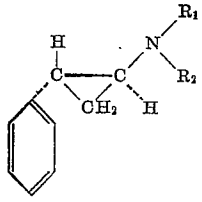
Example 10

Ingredients:	Amounts, gms.
Trans 2-phenylcyclopropylamine hydrochloride	2.0
Sodium chloride	0.375
Water for injection, q.s., 100.00 ml.	

The salts are dissolved in part of the water and then the volume is brought up to 100 ml. The solution is then filtered through a selas filter, filled into ampuls and autoclaved.

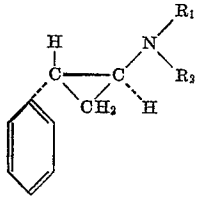
What is claimed is:

1. The method of producing monoamine oxidase inhibition which comprises interally administering a dosage unit of from about 5 mg. to about 150 mg. of a compound selected from the group consisting of the free base and its nontoxic, pharmaceutically acceptable, acid addition salts, said free base having the formula:



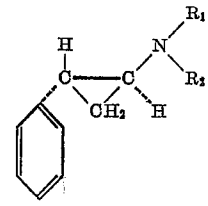
in which R_1 and R_2 are members selected from the group consisting of hydrogen and methyl.

2. The method of producing monoamine oxidase inhibition which comprises internally administering a daily dosage regimen of from about 5 mg. to about 600 mg. of a compound selected from the group consisting of the free base and its nontoxic, pharmaceutically acceptable, acid addition salts, said free base having the formula:



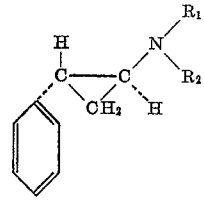
in which R_1 and R_2 are members selected from the group consisting of hydrogen and methyl.

3. The method of producing monoamine oxidase inhibition which comprises orally administering from one to four times daily a dosage unit of from about 10 mg. to about 100 mg. of a compound selected from the group consisting of the free base and its nontoxic, pharmaceutically acceptable, acid addition salts, said free base having the formula:



in which R_1 and R_2 are members selected from the group consisting of hydrogen and methyl.

4. The method of producing monoamine oxidase inhibition which comprises orally administering a daily dosage regimen of from about 10 mg. to about 200 mg. of a compound selected from the group consisting of the free base and its nontoxic, pharmaceutically acceptable, acid addition salts, said free base having the formula:



in which R_1 and R_2 are members selected from the group consisting of hydrogen and methyl.

5. The method of producing monoamine oxidase inhibition which comprises orally administering a daily dosage regimen of from about 10 mg. to about 200 mg. of a member selected from the group consisting of trans-2-phenylcyclopropylamine and its nontoxic, pharmaceutically acceptable, acid addition salts.

6. The method in accordance with claim 5 characterized in that said member is essentially free from its cis isomer.

7. The method of producing monoamine oxidase inhibition which comprises orally administering a daily dosage regimen of from about 10 mg. to about 200 mg. of trans-2-phenylcyclopropylamine sulfate.

8. The method of producing monoamine oxidase inhibition which comprises orally administering a daily dosage regimen of from about 10 mg. to about 200 mg. of a member selected from the group consisting of trans-2-phenylcyclopropyldimethylamine and its nontoxic, pharmaceutically acceptable, acid addition salts.

9. The method in accordance with claim 8 characterized in that said member is trans-2-phenylcyclopropyldimethylamine sulfate.

10. The method of producing monoamine oxidase inhibition which comprises orally administering to depressed patients from one to four times daily a dosage unit of from about 5 mg. to about 150 mg. of a compound selected from the group consisting of trans-2-phenylcyclopropylamine and its nontoxic, pharmaceutically acceptable, acid addition salts.

References Cited in the file of this patent

UNITED STATES PATENTS

2,520,516 Zoeren ---------- Aug. 29, 1950

OTHER REFERENCES

Laurence: B.M.J., No. 5072, March 22, 1958, pp. 700–702.

Krantz: Pharmacologic Principles of Medical Practice, 3rd ed., 1954, pp. 616–617.

Biel et al., Annal of N.Y. Acad. of Science, vol. 80, Art. 3, Sept. 17, 1959, pp. 568–582. (Result of conference Nov. 20–22, 1958.)