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(19)

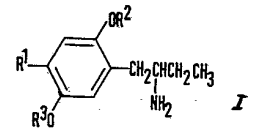
(54) SUBSTITUTED PHENYLBUTYLAMINES

(71) I, ALEXANDER THEODOR SHULGIN, a citizen of the United States of America, of 1483 Shulgin Road, Lafayette, State of California 94549, United States of America, do hereby declare this invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel substituted phenylbutylamines which are useful for enhancing the learning capacity of mammals, to a method of preparing the novel compounds and to a method of enhancing the learning capacity of mammals. The invention also relates to compositions useful in the method of enhancing the learning capacity of mammals.

Numerous compounds structurally related to amphetamine (methylphenethylamine) have been prepared and reported in the literature and are the subject matter of various patents. Of particular interest with respect to the compounds disclosed herein are U.S. Patent No. 3,547,999: Chemistry and Structure-Activity Relationships of the Psychotomimetics which appeared in the book, Psychotomimetic Drugs, Ed. D. H. Effron, Raven Press 1970 and Shulgin, A. T., Sargen, T. and Naranjo, C.: and Structure-Activity Relationships of One-Ring Psychotomimetics, Nature, 221—537 (1969). These prior art references disclose compounds closely related to the compounds of the present invention. However, none of the compounds is disclosed as having the activity of the compounds of the present invention. The Shulgin article in Psychotomimetic Drugs at pages 35—36 indicates that a "four-chain compound" had been synthesized; however, the particular compound synthesized is not named, the structure is not disclosed, the method of preparation is not disclosed and no utility is disclosed in the article.

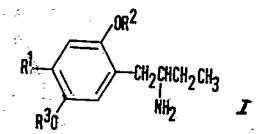
Accordingly the present invention provides a compound of the general formula



I

wherein R^1 is a (lower)alkyl, cyclopropyl, or cyclopropylmethyl group and R^2 and R^3 each represent a (lower)alkyl group.

The present invention also provides a pharmaceutical composition useful for enhancing the learning capacity of mammals which comprises an effective amount of a compound selected from the group consisting of a racemic compound of the formula



I

wherein R^1 is a (lower)alkyl, cyclopropyl or cyclopropyl-methyl group and R^2 and R^3 each represent a (lower)alkyl group, an optically active dextrorotatory or levorotatory isomer or a pharmaceutically acceptable nontoxic salt thereof and a pharmaceutically acceptable carrier.

In another aspect the present invention provides a method of enhancing the learning capacity of mammals which comprise administering to said mammal an effective amount of a compound of formula I or the dextrorotatory or levorotatory isomer or pharmaceutically acceptable nontoxic salt thereof.

The compounds of formula I contain an asymmetric carbon atom and thus normally occur as a racemic mixture of the dextro- and levoratatory optical isomers. Both the dextro- and levoratatory isomers of these compounds, as well as the racemic mixtures may be used in the composition and method described above and are considered to be an integral part of the invention.

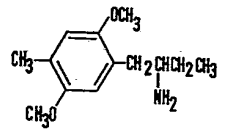
The present invention includes within its

scope the dextro- and levorotatory isomers of the compounds of formula I; and the pharmaceutically acceptable nontoxic salts thereof.

The pharmaceutically acceptable nontoxic salts include the organic and inorganic acid addition salts, e.g. the hydrochloric, sulfuric, *p*-toluene sulfonic, methane sulfonic, tartaric, fumaric, hydrobromic, hydriodic, glycolic, citric, maleic, phosphoric, succinic and acetic acid salts. Such salts may be prepared by conventional methods by reacting the free base with the desired acid on about an equivalent basis.

By the term "(lower)alkyl" as used herein is meant both straight chain and branched chain alkyl groups containing from 1 to 4 carbon atoms, i.e. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl and t-butyl.

The preferred embodiment of the present invention consists of the dextro- and levorotatory isomers of the compound of the formula



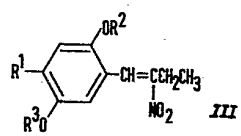
II

and the pharmaceutically acceptable nontoxic salts thereof. The most preferred embodiment is the levorotatory isomer of formula II.

Another preferred embodiment is the compound of formula I wherein R^1 is ethyl and R^2 and R^3 are each methyl, or a pharmaceutically acceptable nontoxic salt thereof.

Still another preferred embodiment is the compound of formula I wherein R^1 is methyl and R^1 and R^3 are each ethyl, or a pharmaceutically acceptable nontoxic salt thereof.

The compounds of formula I are prepared as exemplified below by reducing a 2-nitro-1-(2,5 - (lower)alkoxy - 4 - (lower)alkylphenyl)-butene-1 of the formula



III

wherein R^1, R^2 and R^3 are as described above, with, for example, lithium aluminum hydride in the presence of a nonreactive solvent medium. Suitable solvents include diethyl ether, tetrahydrofuran, diethylene glycol, dimethyl ether and the like. The reaction proceeds at temperatures from about 0°C. to 150°C. Preferably the reaction is carried out at the boiling temperature of the reaction mixture and under reflux and about 2 moles of lithium aluminum hydride per mole of butene are used. The preferred solvent is ether.

The general procedures for the preparation of the compounds of this invention and the starting materials are described in U.S. Patent No. 3,547,999.

The racemic compounds of formula I may be resolved by forming a mixture of the two diastereoisomeric salts of said compounds with a dextrorotatory ring-substituted tartranilic acid, e.g., nitro, chloro or bromo substituted, separating said diastereoisomeric salts by fractional crystallization and converting the separated diastereoisomeric salts to the respective optical isomers of the compound, preferably by treatment with a strong base, e.g. sodium carbonate, potassium carbonate and the like. (+) - 2' - Nitrotartranilic acid and (+)-2'-chlorotartranilic acid are particularly useful in the resolution of the racemic compounds of Formula I. The general resolution procedure using tartranilic acids is described in U.S. 3,452,086 and by T. A. Montzka et al. J. Org. Chem. *33*, 3993 (1968).

The compounds of formula I in the form of racemic mixtures or their dextrorotatory or levorotatory isomers possess learning enhancement activity making them useful for enhancing the learning capacity of mammals. The compounds while structurally related to amphetamine do not produce amphetamine-like central nervous system stimulant activity in mammals.

The learning enhancement activity of the compounds of this invention was determined by the shuttle box acute acquisition, pole climb acute acquisition and pole climb chronic avoidance acquisition tests.

Shuttle Box—Acute Acquisition

Male hooded rats (500—700 gm.) were used as experimental subjects. The compounds are administered either subcutaneously or orally 30 minutes prior to shuttle box test. (shuttle box—manufactured by Lehigh Valley Electronics Co.). Each trial is 60 seconds long consisting of a 5 second avoidance period, during which the animal is required to move to the other side of shuttle box to avoid shock, and a 5 second shock period, if the animal fails to move during the avoidance period. During these 10 seconds the cue light is lit on the other side of the test box but turned off if the animal moves to the other side of the box. The rat is given a maximum of 100 trials or until it acquires the ability to avoid 8 shocks out of 10 consecutive trials. Its score is the number of the trial which is the last trial prior to avoiding 8 shocks out of 10.

Pole Climb—Acute Acquisition—

Male hooded rats (200—300 gms.) were used as experimental subjects. The compounds are administered subcutaneously 30 minutes prior to placement of the animal into the pole climb chamber (Cook, L., and Weidley, E. (1957), Ann. N.Y. Sci., 66, p. 740). Each

trial is 60 seconds long consisting of a 5 second avoidance period, during which a sound is sounded and the animal has to jump up onto the pole and a 5 second shock period if the animal fails to jump. During the avoidance and shock periods the tone and electric shock are turned off if the animal jumps onto the pole. The animal is given a maximum of 100 trials or until it acquires the ability to avoid 8 shocks out of 10 consecutive trials. Its score is the number of the trial which is the last trial prior to attaining avoidance of 8 to 10 consecutive trials.

Pole Climb—Chronic Avoidance Acquisition—

A similar procedure was used as in the pole climb-acute acquisition procedure described above but each animal was given 20 trials every day and the number of avoidances was determined. With each day there was an improvement in the performance; the number of avoidance responses increased.

When (±) - 2 - amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane hydrochloride and the dextrorotatory and levorotatory isomers were tested according to the foregoing procedures the following results were obtained.

TABLE 1

Acute Avoidance Acquisition by Breeder Rats in the Shuttle Box

Compound	Dose (mg/kg)	No. of Animals	No. Trials required to reach 80% Avoidance
(+)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride	1 sc	8	57
	5 sc	10	58
	10 sc	10	47
	10 po	9	58
(−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride	1 sc	9	65
	5 sc	10	43
	10 sc	9	39
	10 po	7	66
(±)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride	1 sc	6	67
	10 sc	8	37
Saline	—	20	85

TABLE 2

Acute Avoidance Acquisition by Adult Rat in the Pole Climb

Compound	Dose (mg/kg sc)	No. of Animals	No. Trials required to reach 80% Avoidance
(+)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride	10	10	85
(−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride	10	10	65
Saline	—	10	100

TABLE 3

Chronic Avoidance Acquisition by Adult Rats in the Pole Climb

(12 Rats Used) No. Avoidances/240 Trials

Treatment Day	(+)-2-amino-1-(2,5-dimethoxy-4-methyl-phenyl)-butane hydrochloride 5 mg/kg sc	(−)-2-amino-1-(2,5-dimethoxy-4-methyl-phenyl)-butane hydrochloride 5 mg/kg sc	Saline
−1	17/240	18/240	20/240
1	56/240	63/240	51/240
2	76/240	85/240	63/240
3	91/240	108/240	77/240
4	103/240	101/240	94/240

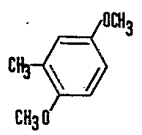
The above test results disclose that the racemic mixture (±) - 2 - amino - 1 - (2,5-dimethoxy - 4 - methylphenyl)butane hydrochloride, and the dextrorotatory and levorotatory isomers exhibit learning enhancing activity, the levorotatory isomer appeared to exhibit greater activity than the dextrorotatory isomer. No increase in locomotion activity was observed after administration of the racemic mixture or either of the isomers.

The compounds of formula I may be administer as the free bases or in the form of their nontoxic addition salts. They may be compounded and formulated into pharmaceutical preparations in unit dosage form for oral or parenteral administration with organic or inorganic solid materials or liquids which are pharmaceutically acceptable carriers. Some examples of the carriers which can be used are gelatin capsules, sugars, cellulose derivatives such as carboxymethylcellulose, gelatin, talc, magnesium stearate, vegetable oil such as peanut oil, etc., liquid petroleum, glycerin, sorbitol, ethanol, agar, elixirs, syrups and water including sterile water. The composition may take the form of tablets, powders, granules, capsules, suspensions, solutions and the like.

The compounds of formula I when administered orally or parenterally in an effective amount produce learning enhancement in mammals. An oral dosage range of about 0.1 to about 0.5 milligrams per kilogram of body weight is a convenient dosage for producing learning enhancement in mammals. However, in general, the particular dosage most suitable for a particular application, as might be expected, will vary with the age, weight and general health of the mammal under treatment and the degree of learning enhancement required. After taking into consideration these factors and any other factors to be considered, one skilled in the art of treating diseases of mammals can readily determine the appropriate dosage.

The following examples are intended to illustrate the invention described herein without unduly restricting it. Examples 1 to 3 relate to the preparation of intermediate derivatives.

Example 1.
Preparation of 2,5-Dimethoxytoluene

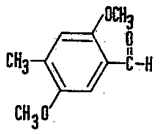


To a solution of 50 g. potassium hydroxide in methanol is added to 50 g. of toluhydroquinone. The resulting solution is heated on a steam bath, and an excess of methyl iodide (75 ml.) is added through an effective reflux condenser. The addition is continued over several hours, and the resulting combination heated at reflux for several additional hours. At this time, the reaction mixture is brought to room temperature, acidified with hydrochloric acid, and exhaustively extracted with methylene chloride.

The organic phase of the above extraction is washed with 5% sodium hydroxide solution (to remove all phenolic byproducts), then with water. The solvent remaining is concentrated by evaporation, yielding a residual neutral oil (36.9 g.). This upon distillation yielded 2,5-dimethoxytoluene as a pale amber liquid (b.p. 105—111°C @ 20 mm/Hg). The base washes yield, after acidification and extraction, 14.1 g. of a mixture of the two possible

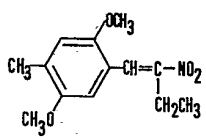
monomethylated derivatives which can be recycled in a subsequent repetition of the methylation step.

Example 2.



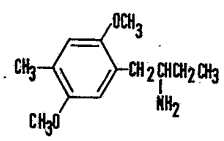
A solution of 40 ml. phosphorus oxychloride ($POCl_3$) and 45 ml. of N-methylformanilide is allowed to stand at ambient temperature for 50 minutes. There is then added 15.2 g. of 2,5-dimethoxytoluene and the resulting solution is heated on the steam bath for 140 minutes. The extremely dark viscous reaction mixture is added to 2 liters of water, and allowed to stir for several hours to complete the hydrolysis of the reaction intermediates. The solid product is removed by filtration, and after washing with water and air-drying yields of 16.6 g. of reddish crumbly crystals. This solid product is extracted with 2 × 125 ml. of boiling hexane, which on cooling deposits 12.1 g. of pale cream-coloured crystals. Recrystallization from boiling hexane, yields a brilliant white product, 2,5-dimethoxy-4-methylbenzaldehyde.

Example 3.
Preparation of 2-Nitro-1-(2,5-Dimethoxy-4-Methylphenyl)-Butene-1



A mixture of 31.6 g. of 2,5-dimethoxy-4-methylbenzaldehyde, 20.2 ml. of nitropropane, 6 ml. cyclohexylamine, and 50 ml. benzene is kept at reflux in a Dean Stark apparatus for 24 hours. Cooling results in the spontaneous crystallization of an orange product, which on filtration and drying weighs 14.9 g. Recrystallization from methanol yields the product 2 - nitro - (2,5 - dimethoxy - 4-methylphenyl)-butene-1 as an orange crystalline material, mp. 115°C.

Example 4.
Preparation of (±)-2-Amino-1-(2,5-Dimethoxy-4-Methylphenyl) Butane



A suspension of 16 g. lithium aluminum hydride in 750 ml. anhydrous ether is brought to reflux, and through a Soxhlet thimble, 19.2 g. of 2 - nitro - 1 - (2,5 - dimethoxy - 4-methylphenyl)-butene-1 is added. The reflux is maintained for 24 hours, then the reaction mixture is cooled externally with ice, and 500 ml. of a 20% solution of sulfuric acid is added cautiously. The two phase result is separated, and the aqueous fraction washed with ether. To this fraction is added 400 g. potassium sodium tartrate and the pH adjusted with aqueous sodium hydroxide until greater than 9. The product is extracted with methylene chloride, which when removed leaves a clear, colorless oil, (±) - 2 - amino - 1 - (2,5-dimethoxy - 4 - methylphenyl) butane. This is dissolved in ether, and saturated with anhydrous hydrogen chloride. The crystalline hydrochloride of (±) - 2 - amino - 1 - (2,5-dimethoxy-4-methylphenyl) butane thus obtained, after filtration and washing with additional anhydrous ether, weighed 12.0 g.

Example 5.

When in the procedure of Example 4, 2-nitro - 1 - (2,5 - dimethoxy - 4 - methylphenyl)-butene-1 is replaced by an equal molar amount of

2 - nitro - 1 - (2,5 - dimethoxy - 4 - ethylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - dimethoxy - 4 - propylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - dimethoxy - 4 - isopropylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - dimethoxy - 4 - butylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - diethoxy - 4 - methylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - dipropoxy - 4 - methylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - diisopropoxy - 4 - methylphenyl)-butene-1,
2 - nitro - 1 -(2,5 - dibutoxy - 4 - methylphenyl)-butene-1,
2 - nitro - 1 - (2 - methoxy - 5 - ethoxy - 4-methylphenyl)-butene-1,
2 - nitro - 1 - (2 - ethoxy - 5 - methoxy - 4-methylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - diethoxy - 4 - ethylphenyl)-butene-1, and
2 - nitro - 1 - (2,5 - diethoxy - 4 - propylphenyl)-butene-1,
2 - nitro - 1 - (2,5 - dimethoxy - 4 - cyclopropylmethylphenyl)-butene-1, and
2 - nitro - 1 - (2,5 - dimethoxy - 4 - cyclopropylphenyl)-butene-1

there are obtained

(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-ethylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-propylphenyl)-butane,

(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-isopropylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-butylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - diethoxy - 4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - dipropoxy - 4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - diisopropoxy-4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - dibutoxy - 4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2 - methoxy - 5-ethoxy-4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2 - ethoxy - 5-methoxy-4-methylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - diethoxy - 4-ethylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - diethoxy - 4-propylphenyl)-butane
(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-cyclopropylmethylphenyl)-butane,
(±) - 2 - amino - 1 - (2,5 - dimethoxy - 4-cyclopropylphenyl)-butane respectively .

Resolution of 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane.

Example 6.

A. (+) - 2 - Amino - 1 - (2,5 - dimethoxy-4-methylphenyl)butane hydrochloride.

(±) - 2 - Amino - 1 - (2,5 - dimethoxy-4-methylphenyl)butane (17.9 g., 80.2 mmoles) and 10.82 g. (40.1 mmoles) of (±)-2'-nitrotartranilic acid were dissolved in 85 ml. of hot 95% ethanol. The solution was cooled, seeded with salt previously obtained on a test tube scale, and allowed to stand undisturbed at room temperature (20—25°C.) until crystallization was complete (at least 18 hours). The solid was filtered, sucked as free of mother liquor as possible, and washed with 10 ml. of cold (−15°C.) 95% ethanol in two portions. The mother liquor and washings were reserved for recovery of the (−)-isomer. The product was air-dried to give 12.32 g. (62.5%) of fluffy, yellowish crystals. Two recrystallizations in a like manner from 10 ml./g. of 95% ethanol gave 8.64 g. of the pure (+)-2'-nitrotartranilic acid salt of (+)-2-amino-1-(2,5-dimethoxy - 4 - methylphenyl)butane, mp. 155.5—157°C.

Anal. Calcd. for $C_{23}H_{31}N_3O_9$:
C, 55.97; H, 6.33; N, 8.52.
Found:
C, 55.63; H, 6.19; N, 8.43.

This salt was dissolved in 100 ml. of hot ethanol. The solution was cooled and poured into excess dilute potassium carbonate solution. The mixture was extracted with two portions of ether; the combined ether extracts were washed with dilute potassium carbonate solution, dilute sodium bicarbonate solution, and three portions of water. Drying and evaporation of the solvent gave 3.8 g. of pure (+)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane as a light yellow oil which crystallized upon standing, $[\alpha]_{365}^{26}+155.3°$ (*c* 1.273, 95% ethanol). The salt was formed with HCl gas in anhydrous ether. The solid was filtered, washed with ether and air-dried to give 4.34 g. of slightly yellowish powder. Recrystallization from 105 ml. of 2-propanol provided 3.70 g. of pure (+)-2-amino-1-(2,5-dimethoxy - 4 - methylphenyl)butane hydrochloride as colorless, fluffy needles, mp. 245—246°C., $[\alpha]_{365}^{23}+49.8°$ (*c* 1.000, 95% EtOH). The overall yield was 35% of available (+)-isomer.

Anal. Calcd. for $C_{13}H_{21}NO_2.HCl$:
C, 60.10; H, 8.54; N, 5.39;
Cl, 13.65.
Found:
C, 59.79; H, 8.57; N, 5.18;
Cl, 13.57.

B. (−) - 2 - Amino - 1 - (2,5 - dimethoxy-4-methylphenyl)butane hydrochloride.

The mother liquor from isolation of the (+)-isomer was evaporated and the residue was converted to the free base as described above. The oil thus obtained and 9.37 g. (36.1 mmoles, 0.9 molar equiv.) of (+)-2'-chlorotartranilic acid were dissolved in 85 ml. of hot 95% ethanol. The solution was cooled, seeded with salt previously obtained on a test tube scale, and allowed to stand undisturbed at room temperature until crystallization was complete (at least 18 hours). The solid was filtered, washed with 10 ml. of cold (−15°) 95% ethanol, and air-dried; 13.22 g. of light yellowish, fluffy crystals was obtained (76%). Two recrystallizations in a like manner from 10 ml./g. of 95% ethanol gave 7.99 g. (60% recovery) of pure, colorless (+)-2'-chlorotartranilic acid salt of (−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane, mp. 182.5—184°C.

Anal. Calcd. for $C_{23}H_{31}ClN_2O_7$:
C, 57.19; H, 6.47; N, 5.80;
Cl, 7.34.
Found:
C, 56.91; H, 6.56; N, 5.90;
Cl, 7.16.

This salt was converted to the free base as described for the (+)-isomer. Pure (−)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane (3.6 g.) was recovered as an almost colorless oil which crystallized upon standing, $[\alpha]_{365}^{23.5}-156.3°$ (*c* 1.274, 95% ethanol). The salt was formed with anhydrous HCl and the colorless powder (4.18 g.) thus obtained was recrystallized from 110 ml. of 2-propanol to give 3.64 g of pure (−)-2-amino-1 - (2,5 - dimethoxy - 4 - methylphenyl)-butane hydrochloride as colorless, fluffy needles, mp. 245—246°C., $[\alpha]_{365}^{24}-49.9°$ (*c*

1.000, 95% ethanol). The overall yield was 35% of available (−)-isomer.

Anal. Calcd. for $C_{13}H_{21}NO_2.HCl$:
C, 60.10; H. 8.54; N, 5.39;
Cl, 13.65.
Found:
C, 59.93; H, 8.70; N, 5.44;
Cl, 13.73.

Example 7.

When in the procedure of Example 6 (+)-2 - amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane is replaced by an equal molar amount of each of the racemic compounds produced in Example 5 there are obtained the individual dextrorotatory and levorotatory isomers of each compound.

Example 8.

Tablets are prepared from the following formulations.

Formulation A

	Per tablet, mg.
2 - amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane hydrochloride	10
Cornstarch	100
Methylcellulose 400	175
Magnesium stearate	3
Total	288

Each tablet contains 10 mg. of active ingredient.

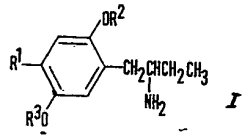
Formulation B

	Per tablet, mg.
2 - amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane hydrochloride	10
Monocalcium phosphate	70
Dicalcium phosphate	70
Lactose	70
Magnesium stearate	3
Total	223

A mixture of monocalcium phosphate, dicalcium phosphate and lactose is prepared to which is added magnesium stearate and 2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)-butane hydrochloride and then tabletted by conventional means. Each tablet contains 10 mg. of active ingredient.

WHAT I CLAIM IS:—

1. A compound of the general formula



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wherein R^1 is a (lower)alkyl, cyclopropyl, or cyclopropylmethyl group and R^2 and R^3 each represent a (lower)alkyl group.

2. The dextrorotatory or levoratatory isomer of the compound claimed in claim 1.

3. A compound as claimed in claim 1 or claim 2 wherein R^1, R^2 and R^3 are each a methyl group.

4. A compound as claimed in claim 1 or claim 2 wherein R^1 is an ethyl group and R^2 and R^3 are each a methyl group.

5. A compound as claimed in claim 1 or claim 2 wherein R^1 is a methyl group and R^2 and R^3 are each an ethyl group.

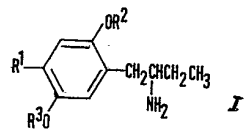
6. The levorotatory isomer of a compound as claimed in any one of claims 3 to 5.

7. The dextrorotatory isomer of a compound as claimed in claim 3.

8. A pharmaceutically acceptable nontoxic salt of a compound as claimed in any one of the preceding claims.

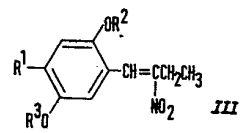
9. The hydrochloride salt of a compound as claimed in any one of claims 3 to 7.

10. A process for the preparation of a compound of the general formula



I

wherein R^1, R^2 and R^3 are as defined in claim 1 and the dextrorotatory and levorotatory isomers and pharmaceutically acceptable nontoxic salts thereof; which process comprises reducing a compound of the formula



III

wherein R^1, R^2 and R^3 are as defined above at a temperature of from about 0°C. to 150°C. and, if desired, further performing either or both of the operations of (a) resolving the so-produced racemic product of formula I into its optical isomers by the steps of forming a mixture of the two diastereoisomeric salts of said

racemic product with a dextrorotatory ring-substituted tartranilic acid, separating said diastereoisomeric salts by fractional crystallization and converting the separated diastereoisomeric salts to the respective optical isomers or (b) converting by methods known *per se* the racemic compound of formula I or an optical isomer thereof to a pharmaceutically acceptable nontoxic salt thereof.

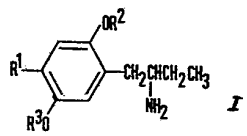
11. A process as claimed in claim 10 wherein the reduction step is performed using lithium aluminum hydride in the presence of a non-reactive solvent medium.

12. A process as claimed in claim 11 wherein the nonreactive solvent is diethyl ether, tetrahydrofuran or diethylene glycol dimethyl ether, the reduction is carried out at the boiling temperature of the reaction mixture and under reflux, and about two moles of lithium aluminium hydride are employed per mole of compound III.

13. A process as claimed in any one of claims 10 to 12 wherein the resolution step is carried out by forming a mixture of the diastereoisomeric salts of the racemic compound of formula I with (+)-2'-nitrotartranilic acid or (+)-2'chlorotartranilic acid, separating the diastereoisomeric salts by fractional crystallization and converting the separated diastereoisomeric salts to the respective dextrorotatory and levorotatory optical isomers by treatment with a strong base.

14. A process as claimed in claim 10 substantially as hereinbefore described with reference to any one of Examples 4 to 7.

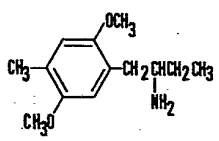
15. A pharmaceutical composition for enhancing the learning capacity of mammals which comprises an effective amount of at least one compound of the general formula



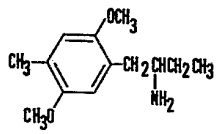
I

wherein R^1, R^2 and R^3 are as defined in claim 1 or a dextrorotatory or levorotatory isomer or pharmaceutically acceptable nontoxic salt thereof and a pharmaceutically acceptable carrier.

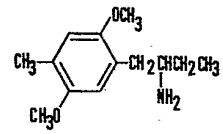
16. A composition as claimed in claim 15 wherein said compound is of the formula



17. A composition as claimed in claim 15 wherein said compound is a pharmaceutically acceptable nontoxic salt of the compound of the formula



18. A composition as claimed in claim 15 wherein said compound is the hydrochloride salt of the compound of the formula



19. A composition as claimed in claim 16 wherein said compound is (−)-2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane.

20. A composition as claimed in claim 16 wherein said compound is a pharmaceutically acceptable nontoxic salt of (−)-2-amino-1-(2,5 - dimethoxy - 4 - methylphenyl)butane.

21. A composition as claimed in claim 16 wherein said compound is (−)-2-amino-1-(2,5 - dimethoxy - 4 - methylphenyl) butane hydrochloride.

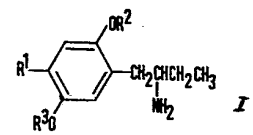
22. A composition as claimed in claim 16 wherein said compound is (+)-2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane.

23. A composition as claimed in claim 16 wherein said compound is a pharmaceutically acceptable nontoxic salt of (+)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane.

24. A composition as claimed in claim 16 wherein said compound is (+)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride.

25. A composition as claimed in any one of claims 16 to 24 in unit dosage form.

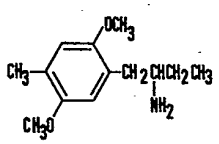
26. A method of enhancing the learning capacity of mammals which comprises administering to said mammal an effective amount of a compound of the general formula



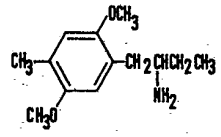
I

wherein R^1, R^2 and R^3 are as defined in claim 1 or a dextrorotatory or levorotatory isomer or a pharmaceutically acceptable nontoxic salt thereof.

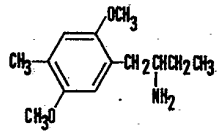
27. A method as claimed in claim 26 wherein the compound administered has the formula



28. A method as claimed in claim 26 wherein the compound administered is a pharmaceutically acceptable nontoxic salt of the compound of the formula



29. A method as claimed in claim 26 wherein the compound administered is the hydrochloride salt of the compound of the formula



30. A method as claimed in claim 26 wherein the compound administered is (−)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane.

31. A method as claimed in claim 26 wherein the compound administered is a pharmaceutically acceptable nontoxic salt of (−)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane.

32. A method as claimed in claim 26 wherein the compound administered is (−)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane hydrochloride.

33. A method as claimed in claim 26 wherein the compound administered is (+)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane.

34. A method as claimed in claim 26 wherein the compound administered is a pharmaceutically acceptable nontoxic salt of (+)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane.

35. A method as claimed in claim 26 wherein the compound administered is (+)-2-amino - 1 - (2,5 - dimethoxy - 4 - methylphenyl)butane hydrochloride.

36. A method as claimed in claim 26 which comprises administering to the mammal a dose of from about 0.1 to about 0.5 milligrams per kilogram of body weight of said compound.

37. A compound of the formula I as defined in claim 1 which has been prepared by a process as claimed in any one of claims 10 to 14.

38. A method as claimed in claim 26 substantially as specifically described herein.

39. A composition as claimed in claim 15 substantially as hereinbefore described in Example 8.

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