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N-PHENETHYL-2-PHENYLCYCLOPROPYLAMINE DERIVATIVES

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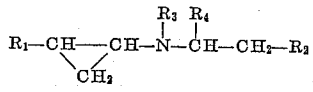
This invention relates to novel N-phenethyl-2-phenylcyclopropylamine derivatives having valuable pharmacodynamic activity.

More specifically the compounds of this invention have utility as anorexigenic agents and have a minimum of side effects such as excess motor stimulation, increased tension or jitteriness. In addition these compounds are antidepressants, ataractics and monoamine oxidase inhibitors as indicated by tryptamine potentiation.

The novel compounds of this invention are represented by the following structural formula:

FORMULA I



when:

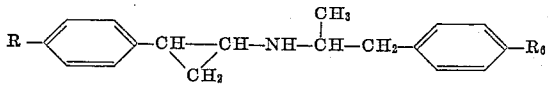
R_1 and R_2 represent phenyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, lower alkoxyphenyl, lower alkylphenyl, dichlorophenyl, di-lower alkoxyphenyl, di-lower alkylphenyl or methylenedioxyphenyl;

R_3 represents hydrogen, lower alkyl or hydroxyethyl; and

R_4 represents lower alkyl.

Advantageous compounds of this invention are represented by the following formula:

FORMULA II



when:

R_5 and R_6 represent hydrogen, chloro, trifluoromethyl, methoxy or methyl.

A particularly advantageous and preferred compound is N-(β-methylphenethyl)-2-phenylcyclopropylamine.

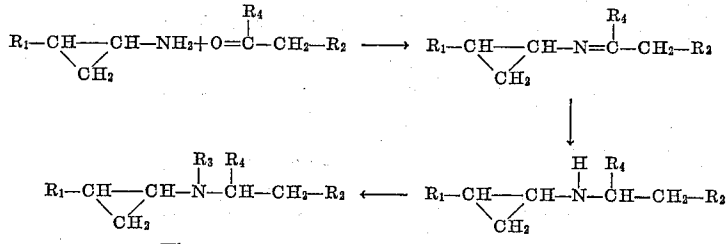
By the terms "lower alkyl" and "lower alkoxy" where used herein alone or in combination with other terms, groups having from 1 to 4, preferably 1–2, carbon atoms are indicated.

The compounds of this invention may be present as cis or trans isomers as well as *d* or *l* optical isomers. It is intended to include in this invention all of these isomers, the separated cis and trans isomers and the resolved *d*, *l*, *d'* and *l'* isomers as well as the mixtures of cis-trans, *dl* and *d'l'* isomers. At present the trans and

d isomers appear to possess particularly advantageous anorexigenic activity and are therefore preferred.

This invention also includes pharmaceutically acceptable salts of the above defined bases formed with nontoxic organic and inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and thiophylline acetic acids as well as with the 8-halotheophyllines, for example, 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts which is well-known to the art.

The compounds of this invention are prepared according to the following synthetic procedure:



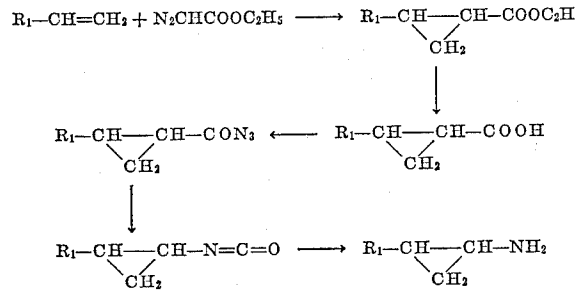
The terms R_{1-4} are as previously defined.

The phenylcyclopropylamine starting material is condensed with at least an equimolar amount, preferably an excess of the benzyl alkyl ketone. The reaction is preferably carried out in an organic solvent in which the reactants are substantially soluble and with which the reactants are substantially unreactive such as an aromatic hydrocarbon, for example benzene, toluene or xylene or a lower alkyl alcohol such as ethanol or isopropanol at elevated temperature such as from about 70–150° C. for about 1–4 hours. Removal of the solvent gives the intermediate Schiff base. Reduction of this intermediate by hydrogenation in the presence of a hydrogenation catalyst such as Raney nickel, palladium-on-charcoal or platinum oxide at about 40–60 p.s.i. for about 2–4 hours gives the N-phenethyl - 2 - phenylcyclopropylamines of Formula I when R_3 is hydrogen.

To prepare the N-alkylated compounds of Formula I, the N-unsubstituted compounds prepared above are reacted with at least one mole of an alkyl halide such as a chloride or bromide in the presence of an acid-binding agent such as an alkali metal amide or carbonate, for example sodium amide or potassium carbonate. The reaction is carried out in a solvent in which at least one of the reactants is soluble such as an aromatic hydrocarbon, for example benzene, toluene or xylene, conveniently at reflux temperature of the solvent.

The N-hydroxyethyl compounds of this invention (Formula I in which R_3 is hydroxyethyl) are prepared by reacting the N-unsubstituted compounds with ethylene oxide in methanol, preferably at reflux temperature.

The 2-phenylcyclopropylamine starting materials are either known to the art or are prepared from the appropriately substituted styrene as follows:



The styrene is condensed with ethyl diazoacetate to give an ethyl 2-phenylcyclopropanecarboxylate which can be fractionally distilled to separate the cis and trans isomeric carboxylates. The carboxylates are saponified by refluxing with an aqueous alcohol solution of an alkali metal hydroxide such as potassium or sodium hydroxide to give the corresponding carboxylic acids. Alternatively, the isomeric mixture of carboxylates can be saponified as above to give a mixture of carboxylic acids which can be then separated into the cis and trans isomers by fractional crystallization.

The 2-phenylcyclopropanecarboxylic acids are converted to the acid chlorides by means of thionyl chloride or phosphorus pentachloride. The acid chloride is converted to the azide which is converted to the isocyanate. Hydrolysis of the isocyanate gives the 2-phenylcyclopropylamine starting materials. The separated cis and trans amines are prepared when the corresponding cis or trans carboxylic acid or ester intermediates obtained as described above are used.

The benzyl alkyl ketone starting materials are either known to the art or are prepared by reacting a properly substituted phenyl acetic acid with an excess of an acid anhydride, for example, acetic, propionic, butyric or valeric anhydride in the presence of a basic catalyst such as an alkali metal salt of a carboxylic acid, for example, sodium acetate; potassium propionate; pyridine; isoquinoline; tri-n-butylamine or β-picoline preferably at reflux temperature for about 6–24 hours. The ketones are isolated by fractional distillation.

The separated trans and vis isomers of the compounds of this invention are prepared by using the appropriate trans or cis phenylcyclopropylamine starting material prepared as described above. To prepare the separated *d* and *l* isomers of compounds of this invention, the appropriate *d* or *l* phenylcyclopropylamine starting material is used. The resulting *d'l'* mixture is resolved by fractional crystallization of salts of the products such as the maleate or citrate salts. For example when *d*-trans-N-(β-methylphenethyl)-2-cyclopropylamine is condensed with benzyl methyl ketone and the resulting Schiff base is hydrogenated the product is the *d'l'* mixture of *d*-trans-N-(β-methylphenethyl)-2-cyclopropylamine. Converting this base to the maleate salt and fractionally crystallizing gives the separated *d, d'*-trans and *d,l'*-trans isomers.

The following examples are not limiting but are illustrative of compounds of this invention and the procedures for their preparation.

Example 1

A mixture of 11.2 g. of trans-2-phenylcyclopropylamine, 13.0 g. of benzyl methyl ketone and 200 ml. of dry benzene is refluxed azeotropically for 2.5 hours. The solvent is removed and the resulting Schiff base is dissolved in 100 ml. of ethanol. Platinum oxide (0.3 g.) is added and the alcoholic solution is hydrogenated at 50 p.s.i. for three hours. Filtration and concentration in vacuo gives crude trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine.

This base is dissolved in 50 ml. of ethyl acetate and

treated with 10 g. of maleic acid in 125 ml. of warm ethyl acetate. The precipitate is filtered and recrystallized from isopropanol-ether to give trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine maleate, M.P. 112–113° C.

Example 2

A mixture of 11.2 g. of cis-2-phenylcyclopropylamine, 13.0 g. of benzyl methyl ketone and 200 ml. of benzene is refluxed azeotropically for three hours and worked up as in Example 1 and hydrogenated using platinum oxide as catalyst to give cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine.

An ethanolic solution of the free base is treated with excess ethereal hydrogen chloride to give the hydrochloride salt.

Example 3

4-trifluoromethylstyrene (30.0 g.) and 35.0 g. of ethyl diazoacetate are mixed at 0° C. and the mixture gradually heated to 150° C. The reaction is maintained at this temperature for three hours and then the mixture is distilled under reduced pressure. The main fraction is collected which consists of ethyl 2-(4-trifluoromethylphenyl) cyclopropanecarboxylate.

A solution of 11.5 g. of potassium hydroxide in 12 ml. of water and 50 ml. of 95% ethanol is added to 17.6 g. of ethyl 2-(4-trifluoromethylphenyl)cyclopropanecarboxylate. The solution is refluxed for eight hours, then concentrated, acidified with hydrochloric acid and filtered to give after fractional recrystallization the separate isomeric cis- and trans-2-(4-trifluoromethylphenyl)cyclopropanecarboxylic acids.

Trans-2-(4-trifluoromethylphenyl)cyclopropanecarboxylic acid is esterified with an ethereal solution of diazomethane; the methyl ester converted to the acid hydrazide with 100% hydrazine hydrate in ethanol; the hydrazide diazotized and decomposed by heating in a toluene-methanol solution to the methyl urethan; and the urethan hydrolyzed with a saturated methanolic solution of barium hydroxide octahydrate to yield trans-2-(4-trifluoromethylphenyl)cyclopropylamine.

A mixture of 13.3 g. of trans-2-(4-trifluoromethylphenyl)cyclopropylamine, 14.7 g. of benzyl methyl ketone and 225 ml. of dry benzene is refluxed azeotropically for 2.5 hours. Removal of the solvent and hydrogenation of the resulting Schiff base using a platinum oxide catalyst (0.35 g.) gives, after filtering and concentrating, trans-N-(β-methylphenethyl)-2-(4-trifluoromethylphenyl)cyclopropylamine.

An ethyl acetate solution of the free base is treated with excess maleic acid to give the maleate salt.

Example 4

Under a nitrogen atmosphere, a stirred solution consisting of 9.9 g. of magnesium shavings, one ml. of ethyl bromide, a crystal of iodine and 10 ml. of dry ether is slowly treated with 83.5 g. of 4-bromobenzotrifluoride in 300 ml. of dry ether. The mixture is refluxed for two hours. A solution of 66 g. of triethyl orthoformate in 90 ml. of dry ether is added and the mixture is then refluxed for 18 hours. The ether is removed in vacuo. A mixture of 150 g. of crushed ice and 375 ml. of cold 6 N hydrochloric acid is added to the residue. The mixture is refluxed under nitrogen for two hours and the resulting oil steam distilled. Extracting the distillate with ether, drying, concentrating and distilling the extract gives 4-trifluoromethylbenzaldehyde.

A mixture of 87 g. of the above prepared benzaldehyde is refluxed with 12 g. of lithium aluminum hydride in ether for 12 hours. Ether is added, followed by water. Filtration, concentration and distillation gives 4-trifluoromethylbenzyl alcohol, B.P. 65–67° C. (0.4 mm.).

A mixture of 63 g. of 4-trifluoromethylbenzyl alcohol and 210 g. of 48% hydrobromic acid is refluxed for three hours. Dilution with water, extraction with ether and distillation of the extracts gives 4-trifluoromethyl-

benzyl bromide, B.P. 73–75° C. (0.4 mm.). This bromomethylbenzene (80 g.) is refluxed for 1.5 hours with 21.2 g. of sodium cyanide, 19.1 g. of water and 82.4 g. of ethanol. The solvents are removed and the residue is diluted with water and extracted with benzene. The extract is distilled to give 4-trifluoromethylbenzyl cyanide.

The above prepared cyano compound is refluxed for 16 hours in dioxane containing 50 ml. of concentrated hydrochloric acid. Removal of the solvent leaves 4-trifluoromethylphenylacetic acid.

A mixture of 50 g. of 4-trifluoromethylphenylacetic acid, 100 ml. of acetic anhydride and 25 g. of anhydrous sodium acetate is refluxed for 24 hours. Water is added to the cooled mixture which is then heated to 90° C., cooled and extracted with benzene. The extract is washed with water, with aqueous sodium carbonate and again with water. The benzene is evaporated and the residue distilled to give 4-trifluoromethylbenzyl methyl ketone.

2-phenylcyclopropylamine (11.2 g.), 4-trifluoromethylbenzyl methyl ketone (20.0 g.) and benzene (200 ml.) are refluxed azeotropically for 2.5 hours. The benzene is removed in vacuo. The residue is dissolved in 100 ml. of ethanol, then hydrogenated with 0.3 g. of platinum oxide for three hours at 50 p.s.i. Filtration and concentration leaves crude N-(β-methyl-4-trifluoromethylphenethyl)-2-phenylcyclopropylamine.

The free base in ethanol solution is treated with ethereal hydrogen chloride to give the hydrochloride salt.

Example 5

4-chlorostyrene (48.5 g.) and 70.0 g. of ethyl diazoacetate are mixed carefully at 0° C. The mixture is gradually heated to 160° C. and the exothermic reaction is maintained at this temperature by alternate heating and cooling as required. After the initial exothermic reaction is completed, the mixture is held at 160° C. for four hours. The mixture is distilled under reduced pressure and the fraction, B.P. 126–165° C. at 1–2 mm., is collected. The above fraction is redistilled through a 12" Vigreux column to give two fractions B.P. 121–6° C. at 0.8 mm., which is predominately cis-ethyl 2-(4-chlorophenyl)cyclopropanecarboxylate, and B.P. 136–140° C. at 0.8 mm., which is predominately trans-ethyl 2-(4-chlorophenyl)cyclopropanecarboxylate.

To 7.6 g. of trans-ethyl 2-(4-chlorophenyl)cyclopropanecarboxylate is added a solution of 5.7 g. of potassium hydroxide in 5.7 ml. of water and 25 ml. of 95% ethanol. The resulting solution is refluxed for four hours and then concentrated in vacuo. The residue is dissolved in 40 ml. of water and the solution adjusted to pH 1 with 10% hydrochloric acid solution. The crystalline precipitate is recrystallized from boiling water to give colorless needles, M.P. 114–116° C., of trans-2-(4-chlorophenyl)cyclopropanecarboxylic acid.

A mixture of 54.0 g. of trans-2-(4-chlorophenyl)cyclopropanecarboxylic acid and 75 ml. of thionyl chloride is allowed to stand at room temperature for 20 hours. Excess thionyl chloride is removed in vacuo, the last traces being stripped with benzene. The residue is distilled under reduced pressure to give a colorless oil, B.P. 131–133° C. at 1.4 mm., trans-2-(4-chlorophenyl)cyclopropanecarbonyl chloride.

Technical sodium azide (22.5 g.) is covered with 75 ml. of dry toluene and the mixture is heated gradually while a solution of 18.0 g. of trans-2-(4-chlorophenyl)-cyclopropanecarbonyl chloride in 75 ml. of dry toluene is added slowly over a period of 15 minutes. The mixture is refluxed for three hours, cooled, and the precipitated salts are filtered. The filtrate is evaporated in vacuo to leave the isocyanate as a red oil. The oily isocyanate is cooled and 150 ml. of concentrated hydrochloric acid is added. The mixture is stirred and refluxed for 20 hours. The resulting solution is concentrated in vacuo to give a crystalline residue of the hydrochloride salt. Recrystallization from ethanol-ether affords colorless crystals, M.P. 192–195° C. of trans-2-(4-chlorophenyl)cyclopropylamine hydrochloride.

The free base is liberated from the above hydrochloride salt by neutralizing an aqueous solution of the salt with dilute alkali, extracting with benzene and evaporating the benzene extract to give the residual trans-2-(4-chlorophenyl)cyclopropylamine.

A mixture of 14.0 g. of trans-2-(4-chlorophenyl)cyclopropylamine, 13.0 g. of benzyl methyl ketone and 200 ml. of benzene is refluxed azeotropically for three hours. Concentration in vacuo, addition of 100 ml. of ethanol and 0.3 g. of platinum oxide, hydrogenation for three hours at 50 p.s.i., filtration and concentration gives trans-N-(β-methylphenethyl)-2-(4-chlorophenyl)-cyclopropylamine.

A sample of the free base is treated with excess citric acid in acetone. Concentrating, cooling and filtering gives the citrate salt.

By saponifying the cis-ethyl 2-(4-chlorophenyl)-cyclopropane carboxylate prepared above, esterifying the resulting cis acid with diazomethane in ether, refluxing the resulting methyl ester with hydrazine hydrate in ethanol and diazoting the hydrazide with hydrochloric acid and sodium nitrite, the cis azide is formed. Rearrangement of the azide by refluxing in methanol for five hours gives the methyl urethan which is hydrolyzed by refluxing with a saturated methanolic solution of barium hydroxide octahydrate for 36 hours. Filtering and concentrating to dryness gives, as the residue, cis-2-(4-chlorophenyl)-cyclopropylamine.

Substituting cis-2-(4-chlorophenyl)cyclopropylamine for the trans isomer in the above described reaction gives cis-N-(β-methylphenethyl)-2-(4-chlorophenyl)cyclopropylamine.

Example 6

A mixture of 2.5 g. of trans-N-(β-methylphenethyl)-2-(4-chlorophenyl)cyclopropylamine, prepared as in Example 5, 1.6 g. of methyl iodide, 0.4 g. of sodium amide and 100 ml. of dry benzene is refluxed for six hours. Water is added to the cooled mixture. The organic layer is extracted with dilute hydrochloric acid. The aqueous extracts are made basic with sodium bicarbonate and extracted with benzene. Evaporation of the solvent from the benzene extracts leaves trans-N-methyl-N-(β-methylphenethyl)-2-(4-chlorophenyl)cyclopropylamine.

Example 7

Ethylene oxide (4.4 g.) and trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine, prepared as in Example 1, in 100 ml. of methanol are heated at reflux for two hours. The solvent is removed in vacuo to give trans-N-hydroxethyl-N-(β-methylphenethyl)-2-phenylcyclopropylamine.

Example 8

A mixture of 16.0 g. of 2-(2,5-dichlorophenyl)-cyclopropylamine (prepared as in Example 3 using 2,5-dichlorostyrene as the starting material), 13.0 g. of benzyl methyl ketone and 200 ml. of dry toluene are refluxed azeotropically for three hours. The solvent is removed and the residue is treated with 0.3 g. of platinum oxide in 100 ml. of ethanol and hydrogenated for four hours at 50 p.s.i. The catalyst is filtered and the solvent removed to give N-(β-methylphenethyl)-2-(2,5-dichlorophenyl)cyclopropylamine.

Example 9

Benzyl methyl ketone (6.5 g.) and 8.0 g. of 2-(3,4-dimethoxyphenyl)cyclopropylamine are refluxed in 100 ml. of toluene for two hours. Removal of the solvent and hydrogenation of the residue in ethanol using platinum oxide catalyst gives N-(β-methylphenethyl)-2-(3,4-dimethoxyphenyl)cyclopropylamine.

Example 10

A mixture of 17.7 g. of 2-(3,4-methylenedioxyphenyl)-cyclopropylamine, 16.3 g. of benzyl ethyl ketone and 250 ml. of xylene is refluxed azeotropically for two hours. The xylene is evaporated in vacuo. To the residue is added 125 ml. of ethanol and 0.4 g. of palladium on charcoal. The mixture is hydrogenated for 3.5 hours at 50 p.s.i. to give, after filtering and evaporating the solvent, N-(β-ethylphenethyl)-2-(3,4-methylenedioxyphenyl)cyclopropylamine.

Example 11

p-Methoxybenzyl methyl ketone (9.0 g.), 2-phenylcyclopropylamine (6.6 g.) and benzene (100 ml.) are mixed together and refluxed azeotropically for three hours. Removing the solvent and hydrogenating the residual Schiff base in ethanol with 0.3 g. of platinum oxide gives, after filtering off the catalyst and removing the solvent in vacuo, N-(β-methyl-4-methoxyphenethyl)-2-phenylcyclopropylamine.

A solution of the free base (1.0 g.) in ether (50 ml.) is treated with excess ethereal hydrogen bromide to separate the hydrobromide salt.

Example 12

A mixture of 10.2 g. of 3,4-dichlorophenylacetic acid, 37 ml. of acetic anhydride and 37 ml. of pyridine is heated at reflux for 24 hours. Concentrating, adding benzene to the residue, washing the benzene solution with 10% aqueous sodium carbonate and with water, concentrating and distilling the residue gives 3,4-dichlorobenzyl methyl ketone.

The above prepared ketone (10.0 g.) and 2-phenylcyclopropylamine (5.6 g.) are refluxed azeotropically in dry benzene for three hours. The solvent is evaporated in vacuo and the residue is hydrogenated with 2.0 g. of Raney nickel in ethanol. Filtering and concentrating gives N-(β-methyl-3,4-dichlorophenethyl)-2-phenylcyclopropylamine.

A sample of the free base in ethanol is treated with excess tartaric acid to give, after dilution with ether, the tartrate salt.

Example 13

A mixture of 3.2 g. of N-(β-methyl-3,4-dichlorophenethyl)-2-phenylcyclopropylamine, prepared as in Example 12, 1.5 g. of ethyl bromide and 2.0 g. of sodium carbonate in 100 ml. of xylene is refluxed for five hours. After the addition of water to the reaction mixture, the separated xylene layer is extracted with dilute hydrochloric acid. The acid extracts are neutralized and extracted with benzene. Removing the benzene by distillation in vacuo yields the product, N-ethyl-N-(β-methyl-3,4-dichlorophenethyl)-2-phenylcyclopropylamine.

The free base is converted to the hydrochloride salt by treatment with ethanolic hydrogen chloride.

Example 14

Acetic anhydride (100 ml.), sodium acetate (25 g.) and 30 g. of 4-ethylphenylacetic acid are refluxed for 16 hours. Working up as in Example 12 gives 4-ethylbenzyl methyl ketone.

A mixture of 16.0 g. of 4-ethylbenzyl methyl ketone, 11.2 g. of 2-phenylcyclopropylamine and 200 ml. of dry benzene are refluxed azeotropically for 2.5 hours. Removing the solvent and hydrogenating the residue with 0.3 g. of platinum oxide in 100 ml. of ethanol at 50 p.s.i. for three hours gives N-(β-methyl-4-ethyl-phenethyl)-2-phenylcyclopropylamine.

An ethyl acetate solution of the free base is treated with excess maleic acid. Filtration of the precipitate and recrystallization from isopropanol-ether gives the maleate salt.

Example 15

A mixture of 12.7 g. of 2-(4-fluorophenyl)-cyclopropylamine (prepared by substituting 4-fluorostyrene for the 4-chlorostyrene in the process described in Example 5), 14.3 g. of 4-methylbenzyl methyl ketone (prepared by reacting 4-methylphenylacetic acid with acetic anhydride and sodium acetate as in Example 14) and 100 ml. of dry benzene is refluxed azeotropically for 2.5 hours. The solvent is removed and the residue is hydrogenated in ethanol with 0.3 g. of platinum oxide as catalyst. The catalyst is filtered off and the solvent is evaporated in vacuo to give N-(β-methyl-4-methylphenethyl)-2-(4-fluorophenyl)cyclopropylamine.

Example 16

Two grams of 3,4-methylenedioxybenzyl methyl ketone, 1.3 g. of trans-2-phenylcyclopropylamine and 25 ml. of benzene are refluxed azeotropically for 2.5 hours. The solvent is removed in vacuo. The residue is dissolved in ethanol and hydrogenated for three hours at 50 p.s.i. using a platinum oxide catalyst. Filtering and concentrating gives trans-N-(β-methyl-3,4-methylenedioxyphenethyl)-2-phenylcyclopropylamine.

Example 17

A mixture of 1.6 g. of 2-(2-ethylphenyl)cyclopropylamine (prepared by the process of Example 5 starting with 2-ethylstyrene), 1.8 g. of 4-chlorobenzyl methyl ketone and 50 ml. of toluene is refluxed azeotropically for 2.5 hours. The toluene is evaporated in vacuo. Ethanol (50 ml.) and platinum oxide (0.1 g.) are added to the residue. The mixture is hydrogenated at 50 p.s.i. for three hours. The catalyst is filtered off and the solvent removed to give N-(β-methyl-4-chlorophenethyl)-2-(2-ethylphenyl)cyclopropylamine.

A sample of the free base is treated with excess fumaric acid in ethanol. Concentrating, diluting with ether and filtering gives the fumarate salt.

Example 18

A mixture of 1.5 g. of 2-(3-methylphenyl)-cyclopropylamine (prepared as in Example 5 from 3-methylstyrene) and 2.2 g. of 4-butoxybenzyl methyl ketone is refluxed azeotropically in benzene for three hours. The solvent is evaporated and the residue is hydrogenated in ethanol with 0.1 g. of platinum oxide. Working up as in Example 17 gives N-(β-methyl-4-butoxyphenethyl)-2-(3-methylphenyl)cyclopropylamine.

An ethanol solution of the base is treated with excess hydrogen chloride to give, after concentrating and cooling, the hydrochloride salt.

Example 19

A mixture of 13.5 g. of 2-(2,4-dimethylphenyl)-cyclopropylamine (prepared as in Example 5 from 2,4-dimethylstyrene), 13.0 g. of benzyl methyl ketone and 200 ml. of benezene is refluxed for four hours. Removing the solvent, adding ethanol and platinum oxide to the residue, hydrogenating for three hours at 50 p.s.i. and working up as in Example 17 gives N-(β-methylphenethyl)-2-(2,4-dimethylphenyl)cyclopropylamine.

Example 20

A mixture of 11.2 g. of trans-2-phenylcyclopropylamine, 21.5 g. of 3,4-diethoxybenzyl methyl ketone and 200 ml. of benzene is refluxed azeotropically for two hours. The benzene is removed in vacuo. The residue is hydrogenated in ethanol with a platinum oxide catalyst to give trans-N-(β-methyl-3,4-diethoxyphenethyl)-2-phenylcyclopropylamine.

Example 21

Valeric anhydride (40 ml.), pyridine (40 ml.) and 4-fluorophenylacetic acid (8.0 g.) are refluxed for six hours. Working up as in Example 12 gives 4-fluorobenzyl butyl ketone.

A mixture of 5.6 g. of 2-phenylcyclopropylamine, 9.4 g. of p-fluorobenzyl butyl ketone and 100 ml. of benzene is refluxed azeotropically for 2.5 hours. The benzene is removed in vacuo and the residue is hydrogenated in ethanol for three hours using platinum oxide as catalyst. Filtering and concentrating gives, as the residue, N-(β-butyl-4-fluorophenethyl)-2-phenylcyclopropylamine.

The free base in ethyl acetate is treated with excess maleic acid. Cooling and filtering yields the maleate salt.

Example 22

A mixture of 11.2 g. of 2-phenylcyclopropylamine, 15.7 g. of benzyl propyl ketone and 200 ml. of toluene is refluxed azeotropically for three hours. The solvent is removed and the residue is hydrogenated in ethanol using 0.3 g. of platinum oxide. Filtering and concentrating gives N-(β-propylphenethyl)-2-phenylcyclopropylamine.

The above prepared amine (2.8 g.), butyl bromide (1.6 g.), 1.0 g. of sodium amide and 50 ml. of toluene are mixed together and heated at reflux for six hours. Working up as in Example 13 gives N-butyl-N-(β-propylphenethyl)-2-phenylcyclopropylamine.

Treating the base in ethanol with excess ethereal hydrogen chloride, diluting with ether and filtering furnishes the hydrochloride salt.

Example 23

A mixture of 6.6 g. of 2-phenylcyclopropylamine, 10.0 g. of 3-methoxybenzyl methyl ketone and 100 ml. of dry benzene are refluxed azeotropically for three hours. Removing the solvent and hydrogenating the resulting Schiff base in ethanol at 50 p.s.i. for three hours using platinum oxide as catalyst gives N-(β-methyl-3-methoxyphenethyl)-2-phenylcyclopropylamine.

Methyl iodide (1.6 g.), 0.4 g. of sodium amide and 75 ml. of benzene are mixed with 3.0 g. of the above prepared amine. Refluxing the mixture for six hours and working up as in Example 6 gives N-methyl-N-(β-methyl-3-methoxyphenethyl-2-phenylcyclopropylamine.

Example 24

A mixture of 1.9 g. of 2-(4-butylphenyl)-cyclopropylamine (prepared as in Example 5 from 4-butylstyrene), 2.0 g. of 3,5-dimethylbenzyl methyl ketone (prepared by reacting 3,5-xylylacetic acid with acetic anhydride and pyridine as in Example 12) and 50 ml. of benzene is refluxed azeotropically for 2.5 hours, then concentrated in vacuo. The residue is treated with 40 ml. of ethanol and 0.1 g. of platinum oxide and hydrogenated for three hours at 50 p.s.i. Filtering and evaporating the solvent gives N-(β-methyl-3,5-dimethylphenethyl)-2-(4-butylphenyl)cyclopropylamine.

Example 25

Substituting 3,4-dichlorostyrene in the process of Example 5, trans-2-(3-,4-dichlorophenyl)cyclopropylamine is obtained. This amine (15.0 g.) is refluxed azeotropically with 13.0 g. of benzyl methyl ketone in benzene for three hours. Removing the solvent and hydrogenating the resulting Schiff base in ethanol with 0.3 g. of platinum oxide gives, after filtering and removing the solvent in vacuo, trans-N-(β-methylphenethyl)-2-(3,4-dichlorophenyl)cyclopropylamine. The base is dissolved in ethyl acetate and treated with 10 g. of maleic acid in warm ethyl acetate. Cooling, filtering and recrystallizing from isopropanol-ether gives trans-N-(β-methylphenethyl)-2-(3,4-dichlorophenyl)cyclopropylamine hydrochloride.

Example 26

A solution of 70 g. of *dl*-trans-2-phenylcyclopropylamine in 50 ml. of ethanol and 59 ml. of ether is added to a solution of 79 g. of *d*-tartaric acid in 400 ml. of ethanol. The mixture is cooled to 0° C. and filtered. The product is recrystallized five times from ispropanol to give the *d*-tartrate salt of *l*-trans-2-phenylcyclopropylamine, M.P. 188–190° C.; $[\alpha]_D^{25}=-30.5$ (1% in water). This tartrate salt is suspended in water and treated with excess 40% sodium hydroxide solution. Extraction with ether and removal of the solvent from the extracts gives *l*-trans-2-phenylcyclopropylamine.

The isopropanolic mother liquors from the five recrystallizations described above are concentrated. The residue is dissolved in warm water, cooled and made strongly alkaline with 40% sodium hydroxide. The mixture is extracted with ether and the extracts are concentrated and distilled to give an oil, B.P. 50° C. (0.4 mm.). Treatment of this product with *l*-tartaric acid in ethanol and recrystallization of the resulting *l*-tartrate salt from ethanol gives the *l*-tartrate salt of *d*-trans-2-phenylcyclopropylamine, M.P. 189–191° C.; $[\alpha]_D^{25}=+31.0$ (1% in water). The tartrate salt is dissolved in warm water and treated with excess sodium hydroxide solution. Extraction with ether and concentration of the extracts gives *d*-trans-2-phenylcyclopropylamine.

A mixture of 16.5 g. of *d*-trans-2-phenylcyclopropylamine and 16.7 g. of benzyl methyl ketone is refluxed azeotropically for two hours. Hydrogenation of the resulting Schiff base as in Example 1 gives *dl', d'l'*-trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine. This amine is added slowly to a hot solution of 14.4 g. of maleic acid and 125 ml. of ethyl acetate to give, on cooling, the maleate salt. Fractional crystallization of this salt from isopropanol gives *d,d'*-trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine maleate and and *d,l'*-trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine maleate. The free bases are obtained by dissolving the salt in warm water, neutralizing with sodium hydroxide, extracting with ether and evaporating the ether from the extracts.

Substituting *l*-trans-2-phenylcyclopropylamine for the corresponding *d* isomer in the above reaction gives *l,l'*-trans-N-(β-methylphenethyl)-2-phenylcyclopropylamine and the corresponding *l,d' isomer.*

Example 27

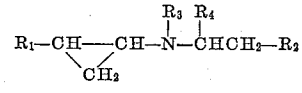
d,l-Cis-2-phenylcyclopropylamine is separated by means of recrystallization of its tartrate salts into *d*-cis-2-phenylcyclopropylamine and *l*-cis-2-phenylcyclopropylamine as in Example 26.

Condensation of *d*-cis-2-phenylcyclopropylamine with benzyl methyl ketone and hydrogenation of the resulting Schiff base gives *d,d'l'*-cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine. This product (8.8 g.) is taken into 60 ml. of ethyl acetate and 100 ml. of ethanol. Maleic acid (8.8 g.) in 120 ml. of ethyl acetate is added to give the maleate salt. Fractional crystallization of the salts give *d,d'*-cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine maleate and *d,l'*-cis-N-(β-methylphenethyl-2-phenylcyclopropylamine maleate. Neutralizing an aqueous solution of the maleate salt with sodium hydroxide, extracting with ether and concentrating the extracts give the *d,d'*-cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine and the corresponding *d,l'* isomer.

If in the preceding process *l*-cis-2-phenylcyclopropylamine is substituted for the *d* isomer, *l,d'*-cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine and *l,l'*-cis-N-(β-methylphenethyl)-2-phenylcyclopropylamine are obtained.

What is claimed is:

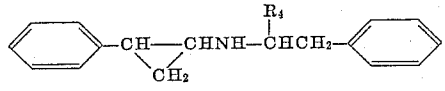
1. A chemical compound of the class consisting of a free base and the salts with nontoxic, pharmaceutically acceptable acids, the free base having the structural formula:



in which R_1 and R_2 are members selected from the group consisting of phenyl, chlorophenyl, fluorophenyl, trifluoromethylphenyl, lower alkoxyphenyl, lower alkylphenyl, dichlorophenyl, di-lower alkylphenyl, di-lower

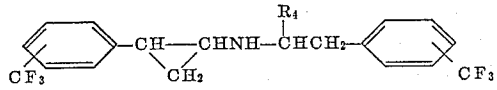
alkoxyphenyl and methylenedioxyphenyl; R_3 is a member selected from the group consisting of hydrogen, lower alkyl and hydroxyethyl; and R_4 is lower alkyl.

2. A chemical compound having the structural formula:



in which R_4 is lower alkyl.

3. A chemical compound having the structural formula:



in which R_4 is lower alkyl.

4. Cis-N-(β-methylphenethyl) - 2 - phenylcyclopropylamine.

5. Cis-N-(β - methylphenyl) - 2 - phenylcyclopropylamine hydrochloride.

6. Trans - N - (β - methylphenethyl)-2-phenylcyclopropylamine.

7. Trans-N-(β-methylphenethyl) - 2 - phenylcyclopropylamine maleate.

8. Cis-N-(β-methylphenethyl) - 2 - (4-chlorophenyl)-cyclopropylamine.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,106,578 October 8, 1963

Carl Kaiser et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 12, line 3, for "-(β-methylphenyl)-" read -- -(β-methylphenethyl)- --.

Signed and sealed this 21st day of April 1964.

(SEAL)
Attest:
ERNEST W. SWIDER

Attesting Officer

EDWARD J. BRENNER

Commissioner of Patents