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PATENT SPECIFICATION

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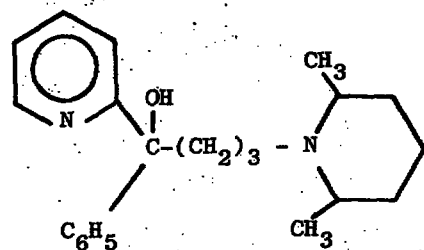
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(54) α -PHENYL-2-PYRIDINEMETHANOL
 COMPOUNDS AND METHOD FOR THEIR
 PRODUCTION

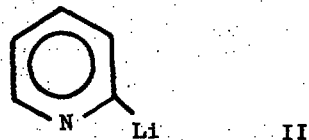
(71) We, PARKE, DAVIS & COMPANY, a corporation organized under the laws of the State of Michigan, one of the United States of America, of Joseph Campau at the River, Detroit, Michigan 48207, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, 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 new 1 - piperidine - butanol compounds and methods for their preparation. More particularly, the invention relates to (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol which has the formula

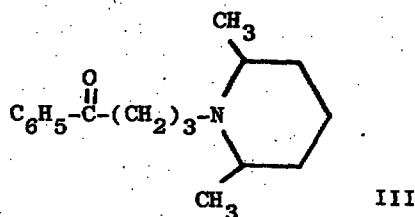


to acid-addition salts thereof, methods for the production of the foregoing compounds, pharmaceutical compositions containing said compounds and methods for treating cardiac arrhythmia using said compounds.

In accordance with the invention, the foregoing compounds can be produced by reacting a compound of the formula



with a compound of the formula



having a *cis* configuration.

This reaction is generally carried out in a solvent such as an ether (e.g. diethyl ether, tetrahydrofuran, or diethylene glycol dimethylether), as hydrocarbon (e.g. benzene, toluene, hexane or heptane), or mixtures thereof for periods of from one to twelve hours at from -80° to $+10^{\circ}\text{C}$., preferably one to two hours at -60°C . to -80°C . followed by one to three hours at from -5°C . to $+5^{\circ}\text{C}$. The preferred solvent system employs tetrahydrofuran, optionally mixed with heptane.

While at least one mole of pyridyllithium (II) should be used for each mole of piperidine compound (III), an excess of the lithium compound is preferred.

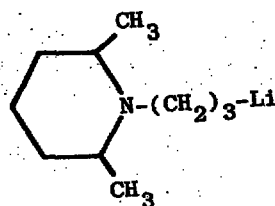
The intermediate metallic derivative of a compound of formula I is hydrolyzed under acidic (e.g. dilute aqueous hydrochloric acid, aqueous ammonium chloride, or dilute aqueous sulphuric acid), neutral or basic (e.g. dilute aqueous sodium hydroxide, or dilute aqueous potassium hydroxide) conditions, preferably neutral conditions.

The product may be isolated as the free base or an acid-addition salt thereof by suitable adjustment of the pH.

The *cis* - γ - (2,6 - dimethylpiperidino)butyrophenone is prepared by reacting an excess of *cis* - 2,6 - dimethylpiperidine with γ - chlorobutyrophenone, ethylene acetal in the presence of sodium iodide at reflux for about forty-eight hours, followed by hydrolysis of the resulting amino acetal with aqueous hydrochloric acid and then basification with aqueous sodium hydroxide.

The γ - chlorobutyrophenone, ethylene acetal is prepared by reacting γ - chlorobutyrophenone with ethylene glycol using *p* - toluenesulphonic acid as a catalyst. The reaction is carried out utilizing benzene as a solvent and a water trap coupled into the reaction system. The reaction mixture is refluxed until the desired amount of water is collected, followed by neutralization of the acid and removal of the solvent.

Also, in accordance with the invention, the compounds of the invention can be prepared by reacting a compound of the formula



having a *cis* configuration with 2 - benzoylpyridine in a suitable solvent such as an ether (e.g. diethyl ether, tetrahydrofuran, diethylene glycol dimethyl ether) for from four hours to twenty-four hours at 0°C . to 60°C . The preferred reaction conditions employ tetrahydrofuran as the solvent and a reaction time of from twelve hours to eighteen hours at a temperature range of from 20°C . to 35°C .

It is preferred to use approximately equivalent amounts of the lithium derivative of structure IV and 2-benzoylpyridine.

The intermediate metallic derivative of a compound of formula I is hydrolyzed under acidic (e.g. dilute aqueous hydrochloric acid, aqueous ammonium chloride, or dilute aqueous sulphuric acid), neutral or basic (e.g. dilute aqueous sodium hydroxide, or dilute aqueous potassium hydroxide) conditions, preferably neutral conditions.

The product may be isolated as the free base or an acid-addition salt thereof by suitable adjustment of the pH.

The *cis* - 1 - (3 - lithiopropyl) - 2,6 - dimethylpiperidine is prepared by reacting one equivalent of *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine with two equivalents of lithium over a six-hour period in tetrahydrofuran. After filtration, the remaining solution is reacted directly with benzophenone.

The *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine is prepared by reacting thionyl chloride with *cis* - 2,6 - dimethyl - 1 - piperidinepropanol in benzene at a temperature of from 0°C . to 5°C . for thirty minutes followed by two hours at reflux. The chlorinated product is isolated as the hydrochloride by filtration.

The *cis* - 2,6 - dimethyl - 1 - piperidinepropanol is prepared by reacting 3 - bromopropanol with an excess of *cis* - 2,6 - dimethyl - piperidine in refluxing xylene for a period of about two hours. The *cis* - 2,6 - dimethyl - 1 - piperidinepropanol is separated by distillation.

The free base of formula I forms acid-addition salts, which are also part of this invention, with any of variety of inorganic and organic acids. Typical acid-addition salts are formed with such acids as hydrochloric, hydrobromic, sulphuric, sulphamic, nitric, phosphoric, acetic, citric, tartaric, succinic, oxalic, benzoic, maleic, malic, lactic, gluconic, naphthalene - 1,5 - disulphonic, methanesulphonic, *p* - toluenesulphonic, and pamoic acids. The free bases and their salt forms are interconvertible by adjustment of the pH. They differ in solubility properties but are otherwise equivalent for the purposes of the invention.

The compounds of the invention can exist in anhydrous form as well as in solvated, including hydrated, forms. In general, the hydrated forms and the solvated forms with pharmaceutically-acceptable solvents are equivalent to the anhydrous or unsolvated form for the purposes of the invention. The compounds of the inventions may also be obtained as R and S isomers by standard resolution techniques.

The compounds of the invention are new chemical compounds of value as pharmacological agents. More specifically, these compounds are antiarrhythmic agents. The activity of these compounds is shown by way of the following antiarrhythmic screen.

Dogs were operated on according to the procedure reported in Circulation 1, 1318 (1950). (+, -) - *cis* - α - [3 - (2,6 - Dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridine - methanol, lidocaine and quinidine were tested intravenously nineteen to twenty-four hours after coronary artery ligation. The degree of effectiveness of the compound was determined by the degree of conversion of ventricular ectopic beats to sinus beats. The table shown below gives the results of the screen performed on (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol and the known antiarrhythmic agents, lidocaine and quinidine.

TABLE

Compound	Dose*	Time Post Dose	% Conversion
Lidocaine	10 mg/kg i.v.	5 min. 20 min. 55 min.	92 0 0
Quinidine	20 mg/kg i.v.	5 min. 20 min. 55 min.	66 35 41
(+, -) <i>cis</i> - α -[3-(2,6-dimethyl-1-piperidinyl)propyl]- α -phenyl-2-pyridinemethanol	5 mg/kg i.v.	2 min. 20 min. 55 min.	91 76 66

*Dose calculated as free base, tested as salts.

In addition the present invention relates to pharmaceutical compositions and methods employing (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridine - methanol and pharmaceutically acceptable acid-addition salts thereof. Some typical examples of pharmaceutically acceptable acid-addition salt forms are the hydrochloride, sulphate, phosphate, citrate, pamoate, acetate and maleate salts.

The present invention also provides a pharmaceutical composition in dosage unit form comprising a pharmaceutical carrier and a compound in accordance with the present invention in which the acid-addition salts are pharmaceutically acceptable acid-addition salts. Preferably such a composition has between 1 and 200 mg. of active ingredient per dosage unit.

More particularly, (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol and pharmaceutically acceptable acid-addition salts thereof are highly useful in controlling cardiac arrhythmias in mammals, such as cats, dogs, horses and human beings, when administered in amounts ranging from 0.1 mg. to 10 mg. per kg. of body weight per

day, and such dosage units are employed that a total of from 7 mg. to 700 mg. of active ingredient for a subject of about 70 kg. body weight are administered in a 24 hour period, preferably in divided doses. A preferred dosage regimen employs a range of from 1 mg. to 5 mg. of active ingredient per kg. of body weight per day and wherein the total daily dosage is divided into four units and each taken after an appropriate time interval.

The compounds of the present invention may be administered by any convenient route such as orally, intraperitoneally, subcutaneously, intramuscularly or intravenously.

Compositions according to the present invention having the desired clarity, stability, and adaptability for parenteral use are obtained by dissolving from 0.10% to 10.0% by weight of active compound in a vehicle such as water, a polyhydric aliphatic alcohol or mixtures thereof. In addition to water, especially satisfactory are glycerin, propylene glycol, and the polyethylene glycols. The polyethylene glycols consist of a mixture of non-volatile, normally liquid, polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from 200 to 1500. Although the amount of active compound dissolved in the above vehicle may vary from 0.10% to 20.0% by weight, it is preferred that the amount of active compound employed be from 1.0% to 10.0% by weight. Although various mixtures of the aforementioned non-volatile polyethylene glycols may be employed, it is preferred to use a mixture having an average molecular weight of from 200 to 400.

In addition to the active compounds, the parenteral solutions of the present invention may also contain various preservatives which may be used to prevent bacterial and fungal contamination. The preservatives which may be used for such purpose are, for example, benzyl alcohol, myristyl - gamma - picolinium chloride, phenyl mercuric nitrate, benzalkonium chloride, phenethyl alcohol, *p* - chlorophenyl - α - glycerol ether, methyl and propyl parabens, and thimerosal. As a practical matter it is also convenient to employ antioxidants. Suitable antioxidants include, for example, sodium bisulphite, sodium metabisulphite, and sodium formaldehyde sulfoxylate. Generally, from 0.05% to 0.2% concentrations of antioxidant are employed.

The preferred concentration of active compound is 1 to 50 mg./ml. of the finished compositions when intramuscular injection is the purpose for which the compositions are intended. They are equally adapted to intravenous administration when diluted with water or diluents employed in intravenous therapy such as isotonic glucose in appropriate quantities. For this use, initial concentrations down to 0.5 to 25 mg./ml. of active compound are satisfactory. They are also adapted to oral administration when diluted with drinking water.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers and chewing gum. Such compositions and preparations should contain at least 0.1% of active compound. The percentage in the compositions and preparations may, of course, be varied and may conveniently be between 5% to 75% or more of the weight of the unit. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 1 and 200 milligrams of active compounds.

The tablets, troches, pills and capsules may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit, for instance, tablets, pills or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry

or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially nontoxic in the amounts employed.

The invention is illustrated by the following Examples:

Example 1:

At -78°C . 180 ml. of a 1.6M solution of butyl lithium in heptane is added with stirring to 200 ml. of tetrahydrofuran. The mixture is stirred under nitrogen while a solution of 43 g. of 2 - bromopyridine in 50 ml. of tetrahydrofuran is added slowly while maintaining the temperature below -65°C . After stirring for one hour, the mixture is treated with a solution of 65 g. of *cis* - γ - (2,6 - dimethylpiperidino)butyrophenone in 70 ml. of tetrahydrofuran over a period of 10 minutes and stirred at -65 to -75°C . for one additional hour. The mixture is stirred and allowed to warm to 0°C . over a period of 2 hours, then treated with 30 ml. of water. The supernatant organic layer is decanted from the precipitated solid and evaporated at reduced pressure to about one-third its previous volume. The residue is poured into 2.5 l. of cold dilute aqueous sodium hydroxide. The resulting precipitate of (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidiny)propyl] - α - phenyl - 2 - pyridinemethanol is removed by filtration, washed with water and dried; m.p. $70-71^{\circ}\text{C}$. after crystallization from petroleum ether.

If the product is recrystallized from aqueous methanol, a monohydrate results; m.p. $101-102^{\circ}\text{C}$.

The monohydrochloride salt is prepared by dissolving the anhydrous free base in 2 - propanol and adding an equivalent amount of a 10% solution of dry hydrogen chloride in 2 - propanol, followed by dilution with ether and filtration of the precipitated salt; m.p. $171-172^{\circ}\text{C}$.

Intermediates

a) *cis* - γ - (2,6 - Dimethylpiperidino)butyrophenone

A mixture of 619 g. of γ - chlorobutyrophenone, ethylene acetal, 700 g. of *cis* - 2,6 - dimethylpiperidine and 16 g. of sodium iodide is stirred and heated at reflux for 48 hours. The mixture is cooled, diluted with 1 l. of anhydrous ether and filtered to remove *cis* - 2,6 - dimethylpiperidine hydrochloride. The filter cake is washed with 1 l. of ether and the filtrate and washings combined. The resulting ether solution is washed five times with 500 ml. portions of water, then extracted with a solution of 300 ml. of concentrated hydrochloric acid in 3 l. of water. The acid extract is washed with 500 ml. of ether, then heated to $70-80^{\circ}$ and allowed to cool to room temperature over a period of 16 hours. The resulting solution is basified with 50% aqueous sodium hydroxide and the organic layer is separated. The aqueous layer is extracted with 500 ml. of ether and the extract is combined with the organic layer. The combined extract is washed several times with water, dried and evaporated. The oily residue is distilled at reduced pressure to give *cis* - γ - (2,6 - dimethylpiperidino)butyrophenone; b.p. $138-141^{\circ}\text{C}/0.1$ mm.

b) γ - Chlorobutyrophenone, Ethylene Acetal

A mixture of 500 g. of γ - chlorobutyrophenone, 225 g. of ethylene glycol, 10 g. of *p* - toluenesulphonic acid and 1.5 l. of benzene is heated at reflux under a water separator until water collection ceases. The resulting solution is cooled, neutralized with 10 ml. of triethylamine and evaporated at reduced pressure to give γ - chlorobutyrophenone, ethylene acetal, suitable for use without further purification. (The pure material boils at $100-118^{\circ}\text{C}/0.1-0.8$ mm. and melts at $57-59^{\circ}\text{C}$.).

Example 2:

A solution of 18.9 g. of *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine in 50 ml. of tetrahydrofuran is added dropwise under a nitrogen atmosphere to a stirred mixture of 1.4 g. of lithium wire and 50 ml. of tetrahydrofuran over a period of 2 hours. After the addition is complete, the mixture is stirred another 4 hours under nitrogen, the excess lithium metal removed manually and a solution of 18.3 g. of 2 - benzoylpyridine in 100 ml. of tetrahydrofuran is added dropwise with stirring over a period of 2 hours. The mixture is stirred for 16 hours, then treated with 5 ml. of water. The organic phase is decanted from the precipitated solid and evaporated at reduced pressure to about one-fourth its previous volume. This solution is poured into 400 ml. of water, the solution is acidified with acetic acid and washed

with ether. The aqueous acid solution is basified with aqueous sodium hydroxide and extracted with ether. The ether extract is washed with water, dried and evaporated to give (+, -) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol; m.p. (monohydrate) 100—102°C. after crystallization from aqueous methanol.

Intermediates

a) *cis* - 1 - (3 - Chloropropyl) - 2,6 - dimethylpiperidine

A stirred solution of 171 g. of *cis* - 2,6 - dimethyl - 1 - piperidinepropanol in 400 ml. of benzene is cooled to 0—5° and 143 g. of thionyl chloride is added dropwise over a period of 30 minutes. The mixture is then heated at reflux for 2 hours, cooled and diluted with 1 l. of ether. The resulting precipitate of *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine hydrochloride is collected by filtration; m.p. 173—174°C. after crystallization from 2 - propanol - ether. The free base is prepared as needed by dissolving the hydrochloride in a minimum amount of water, cooling and adding a slight excess of 50% aqueous sodium hydroxide. The liberated base is immediately extracted with several portions of benzene. The extracts are combined, dried and evaporated to give the free base, *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine.

b) *cis* - 2,6 - Dimethyl - 1 - piperidinepropanol

A stirred solution of 460 g. of *cis* - 2,6 - dimethylpiperidine in 300 ml. of xylene is treated with 278 g. of 3 - bromopropanol over a period of 15 minutes. The mixture is stirred and heated at reflux for 2 hours, then allowed to cool while stirring for 16 hours. The mixture is filtered and the filtrate evaporated at reduced pressure. The residue is distilled at reduced pressure to give *cis* - 2,6 - dimethyl - 1 - piperidinepropanol; b.p. 147—149°C./25 mm.

Example 3:

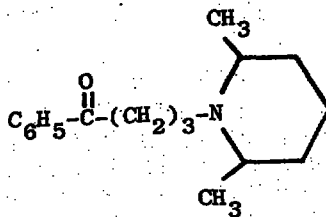
Preparation of Capsule Formulation

30	Ingredient (+, -) - <i>cis</i> - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol hydrochloride Starch Magnesium stearate	Milligrams per Capsule 200 80 5	30
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35 The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a full weight of 285 milligrams per capsule.

WHAT WE CLAIM IS:—

- 40 1. (+, -) - *cis* - α - [3 - (2,6 - Dimethyl - 1 - piperidinyl) - propyl] - α - phenyl - 2 - pyridinemethanol and acid-addition salts thereof.
2. (+, -) - *cis* - α - [3 - (2,6 - Dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol hydrochloride.
3. A process for the production of a compound of Claim 1 which comprises reacting 2 - pyridyllithium with a compound of the formula



45 having a *cis* configuration, hydrolyzing the formed intermediate and isolating the product as the free base or as an acid-addition salt.

4. A process for the production of a compound of Claim 1 which comprises reacting a compound of the formula

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with ether. The aqueous acid solution is basified with aqueous sodium hydroxide and extracted with ether. The ether extract is washed with water, dried and evaporated to give (+,-) - *cis* - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol; m.p. (monohydrate) 100—102°C. after crystallization from aqueous methanol.

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Intermediates

a) *cis* - 1 - (3 - Chloropropyl) - 2,6 - dimethylpiperidine

A stirred solution of 171 g. of *cis* - 2,6 - dimethyl - 1 - piperidinepropanol in 400 ml. of benzene is cooled to 0—5° and 143 g. of thionyl chloride is added dropwise over a period of 30 minutes. The mixture is then heated at reflux for 2 hours, cooled and diluted with 1 l. of ether. The resulting precipitate of *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine hydrochloride is collected by filtration; m.p. 173—174°C. after crystallization from 2 - propanol - ether. The free base is prepared as needed by dissolving the hydrochloride in a minimum amount of water, cooling and adding a slight excess of 50% aqueous sodium hydroxide. The liberated base is immediately extracted with several portions of benzene. The extracts are combined, dried and evaporated to give the free base, *cis* - 1 - (3 - chloropropyl) - 2,6 - dimethylpiperidine.

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b) *cis* - 2,6 - Dimethyl - 1 - piperidinepropanol

A stirred solution of 460 g. of *cis* - 2,6 - dimethylpiperidine in 300 ml. of xylene is treated with 278 g. of 3 - bromopropanol over a period of 15 minutes. The mixture is stirred and heated at reflux for 2 hours, then allowed to cool while stirring for 16 hours. The mixture is filtered and the filtrate evaporated at reduced pressure. The residue is distilled at reduced pressure to give *cis* - 2,6 - dimethyl - 1 - piperidinepropanol; b.p. 147—149°C./25 mm.

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Example 3:

Preparation of Capsule Formulation

30	Ingredient (+,-) - <i>cis</i> - α - [3 - (2,6 - dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol hydrochloride	Milligrams per Capsule	30
	Starch	200	
	Magnesium stearate	80 5	

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The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a full weight of 285 milligrams per capsule.

WHAT WE CLAIM IS:—

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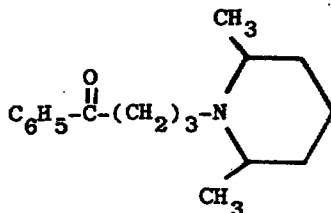
1. (+,-) - *cis* - α - [3 - (2,6 - Dimethyl - 1 - piperidinyl) - propyl] - α - phenyl - 2 - pyridinemethanol and acid-addition salts thereof.

2. (+,-) - *cis* - α - [3 - (2,6 - Dimethyl - 1 - piperidinyl)propyl] - α - phenyl - 2 - pyridinemethanol hydrochloride.

3. A process for the production of a compound of Claim 1 which comprises reacting 2 - pyridyllithium with a compound of the formula

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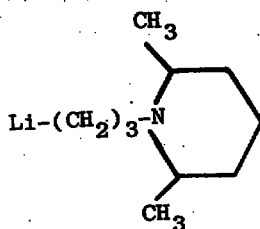
having a *cis* configuration, hydrolyzing the formed intermediate and isolating the product as the free base or as an acid-addition salt.

4. A process for the production of a compound of Claim 1 which comprises reacting a compound of the formula



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having a *cis* configuration with 2 - benzoylpyridine, hydrolyzing the formed intermediate and isolating the product as the free base or as an acid-addition salt.

5. A pharmaceutical composition in dosage unit form, comprising a pharmaceutical carrier and a compound of Claim 1 wherein said acid-addition salts are pharmaceutically acceptable acid-addition salts.

6. The pharmaceutical composition of Claim 6 having between 1 and 200 mg. of active ingredient per dosage unit.

7. A process for producing a compound as claimed in claim 1, substantially as described in either Example 1 or 2.

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