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1-(4-PIPERIDYL)-BUTANONES

Hans Herbert Kühnis, Basel, and Ulrich Renner, Riehen, near Basel, Switzerland, assignors to Geigy Chemical Corporation, Ardsley, N.Y.

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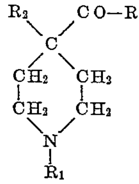
ABSTRACT OF THE DISCLOSURE

4-alkanoylpiperidine derivatives being further substituted in 4-position by allyl, propinyl or alkyl having from 2 to 4 carbon atoms and in 1-position by alkyl having at most 10 carbon atoms, cinnamyl or phenyl-loweralkyl, wherein the phenyl moiety is unsubstituted or substituted by halogen, loweralkyl or loweralkoxy, whereby the substituted or unsubstituted phenyl-loweralkyl contains at most 12 carbon atoms, and wherein the phenyl group is bound directly to the loweralkyl group or by way of various other moieties, such as hydroxymethylene, imino or alkenylimino, and the pharmaceutically acceptable acid addition salts thereof, have analgesic and antitussive activities; pharmaceutical compositions and methods of alleviating pain and producing an antitussive effect with these compounds are provided; an illustrative embodiment is 1-[1 - (3-phenylpropyl)-4-allyl-4-piperidyl]-butanone fumarate.

DETAILED DESCRIPTION

The present invention relates to novel piperidine derivatives with valuable pharmacological properties, to pharmaceutical compositions, and to methods of alleviating pain and producing an antitussive effect comprising administering these compounds.

More in particular, the present invention relates to compounds of the formula



(I)

wherein

R_1 is alkyl having at most 10 carbon atoms, cinnamyl or phenyl-loweralkyl wherein the phenyl moiety is unsubstituted or substituted by halogen up to the atomic number 35, loweralkyl or loweralkoxy, whereby the substituted or unsubstituted phenyl-loweralkyl contains at most 12 carbon atoms, and wherein the phenyl moiety is bound directly to the loweralkyl group or by way of oxygen, a carbonyl, a hydroxymethylene, an imino, a loweralkanoyloxymethylene, a loweralkylimino, a loweralkenylimino, or a loweralkanoylimino group,

R_2 is allyl or propinyl or alkyl containing from 2 to 4 carbon atoms, and

R_3 is alkyl containing from 2 to 4 carbon atoms, and the pharmaceutically acceptable acid addition salts thereof, which compounds have been found to have in particular analgesic and antitussive activity. Some of them also possess a tranquilizing action on the central nervous system. These activities are combined with a favorable therapeutic index.

By the term "lower alkyl" and derivations thereof utilizing the root "alk," such as "loweralkoxy," "loweralkanoyloxy" and the like, is intended a group comprising a branched or straight hydrocarbon chain containing from one to four carbon atoms.

Halogen up to the atomic number 35 can be fluoro, chloro or bromo.

In the compounds of the Formula I and in the relevant starting materials mentioned below, R_1 denotes, e.g. alkyl groups, such as the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec. butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl or n-decyl groups; alkenyl groups such as the allyl, crotyl, 1-methylallyl or 2-methylallyl group; the benzyl group, the p-fluorobenzyl, o-, m- or p-chlorobenzyl, p-bromobenzyl, 3,4-dichlorobenzyl, p-methylbenzyl, p-isopropylbenzyl, p-methoxybenzyl, p-ethoxybenzyl, p-isopropoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl group, or the 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 4-phenylbutyl, 2-phenoxyethyl, 3-phenoxypropyl, 4-phenoxybutyl, phenacyl, 2-benzolethyl, 3-benzoylpropyl, 2-hydroxy-2-phenylethyl, 2-methoxy-2-phenylethyl, 2-ethoxy-2-phenylethyl, 3-hydroxy-3-phenylpropyl, 3-methoxy-3-phenylpropyl, 3-ethoxy-3-phenylpropyl, 4-hydroxy-4-phenylbutyl, 4-methoxy-4-phenylbutyl, 4-ethoxy-4-phenylbutyl, 2-acetoxy-2-phenylethyl, 2-propionoxy-2-phenylethyl, 3-acetoxy-3-phenylpropyl, 3-propionoxy-3-phenylpropyl or 4-acetoxy-4-phenylbutyl group which are unsubstituted in the benzene nucleus, or the corresponding groups substituted in the benzene nucleus analogously to the aforementioned benzyl groups; methyl, ethyl, and n-propyl groups which are substituted in their ω-position by the anilino, o-toluidino, m-toluidino, p-toluidino, 3,4-xylidino, 2,6-xylidino, p-ethyl-anilino, m-fluoroanilino, p-fluoroanilino, o-chloroanilino, n-chloroanilino, p-chloroanilino, p-bromoanilino, o-anisidino, m-anisidino, p-anisidino, o-phenethidino, m-phenetidino, p-phenetidino, N-methylanilino, N-ethyl-anilino, N-n-propyl-anilino, N-allyl-anilino, N-phenyl-acetamido, (N-o-tolyl-acetamido), (N-m-tolyl-acetamido), (N-p-tolyl-acetamido), (N-3,4-xylyl-acetamido), (N-2,6-xylyl-acetamido), (N-mesityl-acetamido), (N-p-ethylphenyl-acetamido), (N-n-isopropylphenyl-acetamido), (N-m-fluorophenyl - acetamido), (N-p-fluorophenyl-acetamido), (N-o-chlorophenyl-acetamido), (N-m-chlorophenyl-acetamido), (N-p-chlorophenyl-acetamido), (N-3,4-dichlorophenyl-acetamido), (N-p-bromophenyl-acetamido), (N-m-methoxyphenyl-acetamido), (N-p-methoxyphenyl-acetamido), (N-p-ethoxyphenyl-acetamido) or (N-propoxyphenyl-acetamido) group; the cinnamyl group.

A preferred subclass of compounds are, on account of their pharmacological activity, the compounds of Formula I, wherein

R_1 is lower alkyl, cinnamyl or phenyl-loweralkyl, wherein the phenyl moiety is bound directly to the loweralkyl group or by way of a hydroxymethylene, a loweralkanoyloxymethylene, and imino, a loweralkenylimino or a lower alkanoylimino group, and wherein the phenyl moiety is unsubstituted or substituted by halogen up to the atomic number 35,

R_2 is allyl, propinyl or propyl, and

R_3 is propyl,

and the pharmaceutically acceptable acid addition salts thereof.

Preferred members of this subclass are, on account of their strong analgesic activity, the following compounds:

1-[1-(3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone,

1-[1-(3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone,

1-[1-(3-phenylpropyl)-4-propyl-4-piperidyl]-1-1-butanone,

1-[1-(3-hydroxy-3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone,

1-[1-(3-hydroxy-3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone,
1-[1-(3-propionoxy-3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone, and
1-[1-(2-anilinoethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone.

On account of their mild to moderate analgesic activity are preferred:

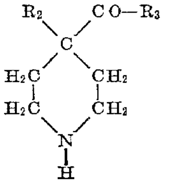
1-[1-(2-phenylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone,
1-[1-(2-phenylpropyl)-4-(allyl)-4-piperidyl]-1-butanone,
1-{1-[2-(N-phenylpropionamido)-ethyl)]-4-(2-propinyl)-4-piperidyl}-1-butanone,
1-[1-cinnamyl-4-(2-propinyl)-4-piperidyl]-1-butanone, and
1-{1-[2-(N-allylanilino)-ethyl]-4-(2-propinyl)-4-piperidyl}-1-butanone.

On account of their antitussive activity are preferred:

1-(1-methyl-4-allyl-4-piperidyl)-butanone,
1-[1-bromobenzyl)-4-allyl-4-piperidyl]-1-butanone, and
1-{1-[2-(N-phenylacetamido)-ethyl]-4-allyl-4-piperidyl}-1-butanone.

Above preferred compounds are also used in the form of their pharmaceutically acceptable acid addition salts, particularly in the form of the addition salt with fumaric acid.

To produce the new piperidine derivatives of the Formula I and their acid addition salts, a compound of the Formula II



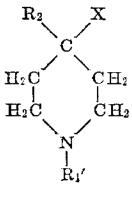
(II)

wherein R_2 and R_3 have the meaning given under Formula I is reacted with a reactive ester of a compound of the Formula III

$$(R_1—OH \qquad (III)$$

wherein R_1 has the meaning given under Formula I, and optionally the obtained compound of Formula I is converted into an additional salt with an inorganic or organic acid. The reaction is carried out at room temperature or at a moderately increased temperature in a suitable organic solvent, such as, e.g. ethanol, acetone, diethyl ketone or dimethyl formamide. Optionally, the reaction is accelerated by the addition of acid binding agents, such as, e.g. potassium carbonate, and/or catalysts, such as, e.g. potassium iodide. Suitable reactive esters of compounds of the Formula III are, in particular, hydrohalic acid esters, such as bromides, chlorides and iodides, also arene sulphonic acid esters, e.g. p-toluene sulphonic acid esters. The starting materials of the Formula II are, for their part, new compounds, the production of which is explained below.

According to a second process, compounds of the Formula I, with the exception of compounds, which contain an alkanoyloxy group as R_1, and the corresponding acid addition salts are produced by reacting a compound of Formula IV



(IV)

wherein

R_1' is a group corresponding to the definition for R_1 given under Formula I, whereby groups containing a carbonyl or alkanoyloxy moiety are excepted, and if X represents the —COCl group also the imino or hydroxyl containing groups R_1' are excepted, and

X represents —CN, —COCl or a lower alkoxy carbonyl group and R_2 has the meaning given under Formula I,

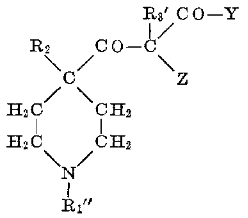
with a magnesium organic compound of the Formula V

$$Hal—Mg—R_3 \qquad (V)$$

wherein Hal represents chlorine, bromine or iodine and R_3 has the meaning given under Formula I, or, in the case where X denotes —COCl, also with a corresponding zinc or cadmium organic compound, and the liberating from the direct reaction product the compound of the Formula I and, optionally, converting it into an addition salt with an inorganic or organic acid. The reactions are performed under the usual conditions of the Grignard reaction, at room temperature or at moderately raised temperatures. Reactions of acid chlorides with magnesium organic compounds, are however carried out at appreciably lower temperatures of ca. −70° to −30°. Suitable as reaction media are the normal appropriate organic solvents containing ether oxygen, which can be used for producing magnesium organic compounds, such as diethyl ether, dibutyl ether or tetrahydrofuran, on their own or in admixture with inert organic solvents, such as benzene or toluene. Optionally, the reaction temperature is raised towards the end of the reaction by distilling off the ether from its mixture with an inert organic solvent having a higher boiling point. The decomposition of the direct reaction products is carried out in the normal manner, e.g. using water and dilute hydrochloric acid. Optionally, by means of a gradual temperature increase, a ketal grouping contained in R_1' can be split and the corresponding carbonyl group liberated. Where R_1' contains an imino or hydroxyl group, i.e. a reactive hydrogen atom, the, at least, double molecular amount of metal-organic compound is used in place of the, at least, molecular amount for the compound of the Formula II.

The production of the starting materials of the Formula IV is explained in more detail below.

According o a third process, the compounds of the Formula I and their acid addition salts are produced by reacting a compound of the Formula VI



(VI)

wherein

R_1'' is a group according to the definition of R_1 with exception of the groups containing an imino, hydroxyl, alkanoyloxymethylene or alkanoylimino group,

R_2 has the meaning given under Formula I,

R_3 is methyl, ethyl or propyl,

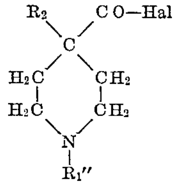
Y is lower alkyl, and

Z is the —COOY group or the cyano group

with an acid and if desired, liberating from the obtained acid addition salt of a compound of the Formula I this compound and converting the latter, or the initially obtained salt into another addition salt with an inorganic or organic acid.

For example a compound of Formula VI is reacted with a concentrated mineral acid, e.g. concentrated hydrochloric acid, hydrobromic acid or sulphuric acid at a temperature range of 60°–150°, whereby the necessary reaction temperature and duration can be easily determined by means of the evolution of carbon dioxide.

For the production of the starting materials of Formula VI, for example, an acid halide of Formula VII



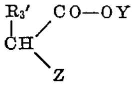
(VII)

wherein

Hal is chlorine or bromine and

R_1'' is a group corresponding to the definition for R, with the exception of groups containing an amino, imino or hydroxy group, and

R_2 has the meaning given under Formula I, is reacted with an alkali metal compound or an alkoxymagnesium compound of a malonic acid diester or cyanoacetic acid ester of the Formula VIII



$$R_3'-CH(CO-OY)-Z$$

(VIII)

wherein R_3', X and Y have the meanings given under Formula VI.

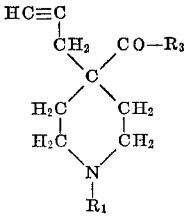
As solvents are used, for example, ether, methanol, ethanol or benzene.

The starting materials for the Formula II and IV, for the first and second process and the acid halides of the Formula VII used as starting materials in the third process can, for example, be produced as follows: By reacting isonipecotamide with a reactive ester of a compound of the Formula III, selected according to the definition for R_1', analogously to the first mentioned process for the production of compounds of the Formula I, and then by splitting off of water, e.g., by boiling with thionyl chloride in benzene or in chloroform, or by heating with phosphorus pentoxide, isonipecotonitriles, substituted in 1-position by the group R_1', are obtained. Analogously, correspondingly substituted lower isonipecotic acid alkyl esters can be obtained by the reaction of lower isonipecotic acid alkyl esters with reactive esters of compounds of the Formula III, which are selected according to the definition of R_1''. A further production process is the quaternisation of lower isonicotinic acid alkyl esters with reactive esters of compounds of the Formula III, selected according to the definition for R_1'', and subsequent catalytic hydrogenation, e.g. in the presence of rhodium/aluminium oxide/catalysts. The 1-substituted nitriles and esters of isonipecotic acid are coverted into their alkali metal derivatives and the latter reacted with allyl halides or (2-propinyl)-halides, e.g. with the bromides or iodides, to give nitriles or esters of the Formula IV. Suitable as reaction medium for these condensations is, for example, a mixture of absolute diethyl ether or tetrahydrofuran with 1,2 - dimethoxyethane (ethylene glycol dimethylether). The required alkali metal compounds of 1-substituted isonipecotonitriles and isonipecotic acid alkyl esters are produced in situ from other suitable alkali metal compounds. Triphenylmethyl lithium, which as such a compound is particularly suitable, is preferably formed likewise in situ from another organic lithium compound, such as phenyl lithium, by adding, for example, a solution of triphenyl methane in 1,2-dimethoxyethane to the phenyl lithium produced in the known manner, which is present in diethyl ether. Since the triphenylmethyl lithium produces intensively coloured solutions, its formation and also its consumption by the subsequently added 1-substituted isonipecotinic acid ester can be easily followed. In place of triphenylmethyl lithium, it is also possible to use, for example, triphenylmethyl sodium or -potassium. The aforementioned stages of the process are for the most part slightly exothermic and can be carried out at room temperature or at slightly elevated temperature. It must also be possible, depending on the starting materials and amounts thereof used, for the reaction mixture, if necessary, to be cooled.

The 1-substituted 4-allyl- and 4-(2-propinyl)-isonipecotinoyl chlorides respectively, which are likewise embraced by the general Formula V, are obtained from the corresponding esters in the normal manner, e.g. by hydrolysis and treatment of the formed acids or their hydrochlorides with oxalyl chloride. The other acid halides, which are comprised by the Formula VII, are obtained in an analogous manner.

In order to obtain starting materials of the Formula II, lower isonipecotic acid alkyl esters or isonipecotamide are, for example, firstly reacted with chloroformic acid benzyl ester instead of with reactive esters of compounds of the Formula III. The thus obtained 1-benzyloxycarbonyl isonipecotinic acid ester or the 1-carbobenzyloxy isonipecotonitrile obtained from the amide after subsequent splitting off of water, are converted, analogously to the above stated reaction sequence, into their alkali metal derivatives and the latter condensed with allyl or (2 - propinyl)-halides. The obtained 4 - allyl or 4-(2-propinyl)-1-benzyloxycarbonyl isonipecotic acid esters or -isonipeconitriles are reacted either directly with magnesium organic compounds of the Formula V, analogously to the second mentioned process for production of compounds of the Formula I, and the 1-carbobenzyloxy group in the reaction products is split off by a treatment with hydrogen bromide in glacial acetic acid, or the carbobenzyloxy group is firstly split off in the same manner and then during the subsequent Grignard reaction, the double molecular amount of magnesium organic compound of the Formula V is used. The starting materials of the Formula II are also obtained by reacting a compound of the Formula I, obtained according to the second or third mentioned process, wherein R_1 denotes the methyl or benzyl group, with chloroformic acid benzyl ester and splitting the obtained 1-benzyloxycarbonyl compound, e.g. again in the aforestated manner by means of hydrogen bromide in glacial acetic acid.

In addition, compounds are produced, according to a fourth process, of the Formula I, wherein R_2 represents the allyl group, and their addition salts with inorganic and organic acids by reacting a compound of the more restricted Formula IX



(IX)

which is already comprised by the Formula I and wherein R_1 and R_3 have the meaning given under Formula I, in the presence of a catalyst suitable for the partial hydrogenation of triple bonds, with hydrogen until the equimolecular amount has been taken up. As the catalyst, use is made, for example, of palladium on $CaCO_3$, partially deactivated with lead acetate, in ethanol as the solvent, and further deactivated in situ by the addition of quinoline, (Lindlar catayst, see, Helv. Chim. Acta 35,450 (1952)). Optionally, the obtained compound of the Formula I is converted into an addition salt with an inorganic or organic acid.

Optionally, the piperidine derivatives of the general Formula I obtained using the process according to the invention are subsequently converted in the normal manner into their addition salts with inorganic and organic acids.

For example, a solution of a piperidine derivative of the Formula I in an organic solvent, such as diethyl ether, methanol or ethanol, is mixed with the acid, desired as the salt component or a solution thereof, and the salt which precipitates direct, or after the addition of a second organic liquid, such as, e.g. diethyl ether to methanol, is isolated.

For use as active substances for medicaments, pharmaceutically acceptable acid addition salts can be used instead of free bases, i.e. salts with those acids the anions of which, in the case of the dosages in question, have either no pharmacological action or which, in themselves, have a desired pharmacological action. Furthermore, it is of advantage if the salts to be used as active substances, crystallise well and are not, or only slightly, hygroscopic. Hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, β-hydroxyethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic, aid, succinic acid, fumaric, acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, embonic acid, cyclohexylamine sulphonic acid or 1,5-naphthalene disulphonic acid, for example, can be used.

The analgesic activity of the compounds of the invention is illustratively demonstrated in mice according to the method of Gross, Helv. Physiol. Acta. 5, C. 31 (1947) whereby the apparatus of H. Friebel and C. Reichle, Arch. exp. Path. and Pharmakol. 226, 551 (1955), is used.

The apparatus comprises an electrically heated lamp which is placed in the focus of a semi-elliptical metal concave mirror. Under the mirror, on a turn-table, there are located 10 small plexiglass cages, each holding a white mouse in such a position that the mouse-tail rests stretched out in a small groove on a plexiglass plate. The turn-table can be turned so that the mouse-tails, one after the other, come to be placed into the second focus of the elliptical mirror. Pain is induced by the convergent heat radiation from the mirror and the time is measured from the moment when the heat reaches the mouse-tail till the moment at which the mouse twitches its tail.

Two series of 10 mice each are tested prior to the administration of the test compound and the normal reaction time for each mouse is recorded. Then the test compound is administered intraperitioneally or orally and the reaction times after the injection are recorded, thus enabling determination of the intensity and the duration of the analgesic effect of the test compound administered.

Thus it is determined that the fumarate of 1-[1-(3-phenylpropyl)-4-allyl-4-piperidyl]-1 - butanone exhibits an analgesic effect if administered intrapeitoneally in amounts of about 1.7 mg./kg. and orally of about 19 mg./kg. Similar results are obtained with other preferred members of the strong analgesic group.

1-[1-(2-phenylethyl)-4-(2-propinyl)-4 - piperidyl] - 1-butanone, as an example of the moderate analgesic group, exhibits in form of its fumarate and analgesic effect in amounts of about 12 mg./kg. on intraperitoneal and of about 26 mg./kg. on oral administration. Similar results are obtained with the other preferred members of the mild to moderate analgesic group.

It is to be noted that the favorable relation between the intraperitioneal and the peroral activities is of particular advantage, as it shows that the compounds of the invention are very well absorbed and that they are, therefore, suitable for oral application.

The antitussive activity of the compound of the present invention is demonstrated according to the method of R. Domenjoz, Arch. exp. Path. and Pharmakol. 215, 19–24 (1952).

Healthy cats of normal weight are narcotized by intraperitoneal injection of 30–65 mg./kg. of aprobarbital so that a relatively superficial narcosis is obtained. About 45 minutes after the injection of the narcotic, the preparation of the Nervus laryngeus superior is started by fitting on an irritation-electrode. An apparatus manufactured by "Grass Medical Instruments," Type SD 5, allowing irritation of the aforesaid nerve with rectangular current-impulses of any desired frequency and intensity is connected to the electrode. The irritation-frequency applied is 5 cycles at an irritation-intensity between 0.5 and 3 volts.

The irritation-duration is about 8 seconds and the interval between two irritations is about 120 seconds. For the registrations of the cough reflexes, a Marey capsule is used. A respiration-cannula is introduced through the oral cavity down to the glottic chink. The test compound is injected intravenously in form of an 0.5% aqueous solution just before the irritation starts. Cough reflexes are inhibited with about 1–3 mg./kg. of 1-(1-methyl-4-allyl-4-piperidyl)-1-butanone fumarate.

Similar results are obtained with other compounds of the preferred members of the antitussive group.

A further method of showing the antitussive activity is to determine the manner in which tussive irritation in guinea pigs caused by sulphur dioxide is stopped as a result of subcutaneous or oral administration of the test substances: In a preliminary experiment for selecting animals for testing, male guinea pigs are exposed in a plexiglass chamber to a SO_2-CO_2-air mixture, flowing through at atmospheric pressure, and with a constant mixture ratio of 20 ml.:1.5 liters:10.5 liters per minutes, until commencement of coughing or for a maximum of 120 secs. The assessment of the commencement of coughing is made by inspection. The guinea pigs reacting by coughing (ca. ⅔ of all animals) are formed into groups, each containing 6 animals. Ca. 24 hours after the preliminary test, these groups of experimental animals receive the test substance, administered subcutaneously or perorally, in various dosages suitable for ascertaining the ED_{50} in mg./kg. Exposure to the irritant gas occurs in the same manner as in the preliminary test after 30 and after 90 minutes following application of the test substances. Assessment of the commencement of coughing is again made by inspection. From the percentage figures, obtained in the case of various dosages, of animals no longer reacting to SO_2, the dosage ($=ED_{50}$) preventing the occurence of coughing in the case of 50% of the animals is determined by graphical interpolation using the Schleicher and Schüll 298½ probability graph.

The toxicity of the compounds of the invention as demonstrated in rats intravenously and perorally is of favorable low order.

The new piperidine derivatives of the Formula I and their pharmaceutically acceptable acid addition salts are suitable as active substances for pharmaceutical preparations for the amelioration and the elimination of pains of varying origin and of tussive irritation. They can be administered orally, rectally or parenterally.

The daily dosages of free bases or of pharmaceutically acceptable salts thereof vary between 0.1 to 10 mg./kg. for mammals. Suitable dosage units, such as dragées, capsules, tablets, suppositories or ampoules, preferably contain 1–100 mg. of a piperidine derivative of the Formula I, or of a pharmaceutically acceptable salt thereof.

Dosage units for oral administration preferably contain as active substance between 1% and 90% of a piperidine derivative of the Formula I, or of a pharmaceutically acceptable salt thereof. They are produced by combining the active substance with, e.g. solid, pulverulent carriers, such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The latter are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance. Other suitable dosage units for oral administration are hard gelatine capsules and also soft, closed capsules made of gelatine and a softener such as glycerin. The former preferably contain the active substance as a granulate in admixture with lubricants such as talcum or magnesium stearate, and optionally stabilisers such as sodium meta-bisulphite or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols to which stabilisers can also be added.

Also particularly for the treatment of coughs, e.g. lozengers as well as forms not made up into single dosages can be used for oral administration, e.g. cough syrups or drops prepared with the usual auxiliaries.

Suitable dosage units for rectal administration are, e.g. suppositories which consist of a combination of a piperidine derivative of the general Formula I or a suitable salt thereof with a neutral fatty foundation, or also gelatine rectals capsules containing a combination of the active substance with polyethlene glycols.

Ampoules for parenteral, particularly intramuscular, also intravenous, administration preferably contain a water soluble salt of a piperidine derivative of the Formula I as active substance in a concentration of, preferably, 0.5–5%, optionally together with suitable stabilisers, in aqueous solution.

The following prescriptions further illustrate the production of forms for administration according to the invention:

(a) 5 g. of active substance, e.g. 1-[1-(3-hydroxy-3-phenyl-propyl)-4-allyl-4-piperidyl]-1-butanone fumarate, 30 g. of lactose and 5 g. of highly dispersed silicic acid are mixed. The mixture is moistened with a solution of 5 g. of gelatine and 7.5 g. of glycerin in distilled water and is then granulated through a sieve. The granulate is dried, sieved and carefully mixed with 3.5 g. of potato starch, 3.5 g. of talcum and 0.5 g. of magnesium stearate. The mixture is used to press out 1000 tablets each weighing 60 mg. and each containing 5 mg. of active substance.

(b) 5 g. of active substance, e.g. 1-[1-(3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, 15. g. of lactose and 20 g. of starch are mixed. The mixture is moistened with a solution of 5 g. of gelatine and 7.5 g. of glycerin in distilled water and is then granulated through a sieve. The granulate is dried, sieved and carefully mixed with 3.5 g. of talcum and 0.5 g. of magnesium stearate. The mixture is used to press out 1000 dragée cores. These are subsequently coated with a concentrated syrup made from 26.66 g. of crystallised saccharose, 17.5 g. of talcum, 1 g. of shellac, 3.75 g. of gum arabic, 1 g. of highly dispersed silicic acid and 0.090 g. of dyestuff, and dried. The obtained dragées each weigh 110 mg. and each contain 5 mg. of active substance.

(c) To produce 1000 capsules each containing 10 mg. of active substance, 10 g. of 1-[1-(2-phenylethyl) - 4 - (2-propinyl) - 4 - piperidyl] - 1 - propanone hydrochloride are mixed with 263 g. of lactose. The mixture is evenly moistened with an aqueous solution of 2 g. of gelatine and is granulated through a suitable sieve (i.e. sieve III, Ph. Helv. V). The granulate is mixed with 10 g. of dried maize starch and 15 g. of talcum and is then evenly filled into 1000 hard gelatin capsules, size 1.

(d) A suppository mixture is prepared from 2.0 g. of 1-[1-(3-phenylpropyl)-4-allyl - 4 - piperidyl]-1-pentanone fumarate and 168.0 g. of adeps solidus and the mixture used to fill 1000 suppositories each containing 20 mg. of active substance.

(e) 500 mg. of 1-[1-(3 - hydroxy - 3 - phenylpropyl)-4-(allyl) - 4 - piperidyl] - 1 - butanone fumarate and 2.2 g. of glycerin are dissolved in distilled water made up on 100 ml. The solution is used to fill 100 ampoules each of 1 ml. and each containing 5 mg. of active substance.

The following examples illustrate the production of the new compounds of the Formula I but in no way limit the scope of the invention. The temperatures are given in degrees centigrade.

EXAMPLE 1

The solution of the Grignard compound is produced in the usual manner in a 250 ml. four-necked flask, from 2.21 g. of magnesium and 10.82 g. of propyl bromide in 35 ml. of abs, ether. 4.14 g. of 4-allyl isonipecotic acid ethyl ester in 25 ml. of absolute ether are then added dropwise. 45 ml. of absolute toluene are added, the ether distilled off and the reaction mixture then refluxed for 15 hours. It is then decomposed with water and 2 N hydrochloric acid. The organic phase, after the addition of ether, is separated, shaken thoroughly with concentrated ammonia and brine, dried and concentrated.

The residue of 1.3 g. of crude 1-(4-allyl-4-piperidyl)-1-butanone is immediately refluxed for 12 hours with 1.3 g. of 2-phenylethyl bromide, 2 g. of sodium carbonate and a little sodium iodide in 18 ml. of acetone. The reaction mixture is then filtered by suction, the filtrate washed with acetone, concentrated by evaporation and the residue taken up in methylene chloride. The methylene chloride solution is likewise filtered, concentrated and the residue distilled. The 1-[1-(2-phenylethyl)-4-allyl-4-piperidyl]-1-butanone boils at 130–140°/0.02 torr. From this is produced the fumarate by dissolving in ether and mixing with 95% of the theoretical amount of fumaric acid.

In an analogous manner, are produced:

1-[1-(2-benzoylethyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 133–135°;

1-[1-(4-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 173–175°;

1-[1-(3-phenoxypropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 180–182°;

1-[1-(2-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 201–203°;

1-(1,4-diallyl-4-piperidyl)-1-butanone hydrochloride, M.P. 140–142°;

1-[1-(2-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 173–175°;

1-[1-[2-(N-phenyl-acetamido)-ethyl]-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 143–145°;

1-[1-(3-hydroxy-3-phenylpropyl -4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 131–133°;

1-[1-(2-p-methoxy-2-phenylethyl)-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 132–133°;

1-[1-[2-(N-allyl-anilino)-ethyl]-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 135–137°;

1-[1-(3-p-fluorobenzoyl-propyl)-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 150–152°;

1-[1-(2-phenylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone hydrochloride, M.P. 210–212°;

1-[-(2-anilinoethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone hydrochloride, M.P. 210–212°;

1-[1-(2-anilinoethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 151–152°;

1-[1-[2-(N-phenyl-propionamido)-ethyl]-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 123–125°;

1-[1-(2-benzoylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 157–158°;

1-[1-cinnamyl-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 177°;

1-[1-(3-hydroxy-3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 150–151°;

1-[1-(2-phenoxyethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 163–164°;

1-[1-(3-propionoxy-3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 162°;

1-[1-(3-p-fluorobenzoyl-propyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 146–148°;

1-[1-[2-(N-allyl-anilino)-ethyl]-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 156–158°;

1-[1-(3-p-methoxyphenyl-propyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 156°;,

1-[1-(2-phenethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 176°;

1-[1-(3-phenyl-propyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 172–173°;
1-[1-(2-anilino-ethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 146–148°;
1-[1-cinnamyl-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 178–179°;
1-[1-(2-phenoxy-ethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 159–160°;
1-[1-(3-hydroxy-3-phenylpropyl)-4-propyl-4-piperidyl]-butanone fumarate, M.P. 146–7°.

The 4-allyl isonipecotic acid ethyl ester required in the above example is produced as follows:

(a) 2.03 g. of lithium wire cut into small pieces are added under nitrogen to 22.8 g. of bromobenzene in 180 ml. of ether while stirring in a 750 ml. four-necked flask, whereby the ether commences to boil. After the reaction has subsided, the mixture is refluxed for a further 2½ hours. 35.4 g. of triphenyl methane in 150 ml. of abs. 1.2-dimethoxyethane are added all at once to the obtained solution of phenyl lithium, whereby the solution becomes dark red in colour, due to the formation of triphenylmethyl lithium, and gently boils. After stirring at room temperature for 20 minutes, 42.3 g. of 1-benzyloxycarbonyl isonipecotic acid ethyl ester (produced by reaction of isonipecotic acid ethyl ester in the presence of 1 N sodium bicarbonate solution) in 50 ml. of absolute ether are added at 28°. The dark red solution loses its colour, accompanied by a slight increase in temperature. The solution is stirred for 10 minutes at room temperature and then mixed all at once with 18.0 g. of allyl bromide in 40 ml. of abs. ether. The mixture is stirred for 2½ hours at room temperature, whereby it assumes a yellowish colour and lithium bromide precipitates. The reaction mixture is then decomposed with 40 ml. of water and evaporated almost to dryness in the rotary evaporator. The residue is taken up to 50 ml. of ether and the obtained ether solution extracted three times with 2 N hydrochloric acid. The ether solution is then dried and concentrated and the residue left standing over night, whereby the triphenyl methane crystallises out. The whole mixture is suspended in cold methanol, the triphenyl methane filtered off by suction and the filtrate concentrated. The residue is distilled in high vacuum, whereby the 1-benzyloxycarbonyl - 4 - allyl isonipecotic acid ethyl ester converts at 170–192°/0.07 torr.

(b) 8.0 g. of 1-benzyloxycarbonyl-4-allyl isonipecotic acid ethyl ester are stirred with 40 ml. of a saturated solution of hydrogen bromide in glacial acetic acid and 9 ml. of abs. ether in a 100 ml. round flask for 2 hours by means of a magnetic stirrer. The initially intense evolution of carbon dioxide gradually subsides. The solution is then concentrated in the rotary evaporator and the residue taken up in 6 N hydrochloric acid. The acidified solution is washed with ether, made alkaline, while cooling well, with concentrated ammonia solution and extracted with chloroform. The chloroform solution is dried, concentrated and the 4-allyl isonipecotic acid ethyl ester, which remains behind, is further reacted as quickly as possible.

EXAMPLE 2

1.3 g. of crude 1-(4-allyl-4-piperidyl)-1-butanone (see Example 1, first paragraph) are refluxed for 6 hours with 1.4 g. of 3-phenylpropyl bromide, 2 g. of sodium carbonate and 50 mg. of sodium iodide in 20 ml. of acetone. The reaction mixture is then filtered by suction and the filtrate washed with hot acetone. The filtrate is concentrated in vacuo, the residue dissolved in methylene chloride, the solution dried and concentrated and the residue distilled in a bulb tube. The 1-[1-(3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone boils in the air-bath at 160–180°/0.01 torr. The hydrobromide, M.P. 169–170°, is produced from this in the usual manner.

EXAMPLE 3

3.23 g. of magnesium chips in 20 ml. of abs. ether are placed into a 300 ml. four-necked flask. 2 ml. of undiluted propyl bromide are then added and the reaction started by the addition of iodine. When the reaction is under way, 14.35 g. of propyl bromide in 25 ml. of abs. ether are added dropwise in such a manner that the ether boils. At the end of the reaction, stirring is continued for a further 10 minutes and then 16.2 g. of 1-(3-phenylpropyl)-4-allyl isonipecotonitrile in 45 ml. of absolute ether are added dropwise. The reaction is thereby slightly exothermic. The reaction mixture is then refluxed for 2 hours. While cooling with ice, it is then decomposed with water and 2 N hydrochloric acid and the ether phase separated off. The ether solution is dried and concentrated and the residue distilled. The obtained 1-[1-(3-phenylpropyl) - 4-allyl - 4-piperidyl] - 1-butanone boils at 137–145°/0.03 torr. The hydrobromide is produced from this in the usual manner, M.P. 169–170°, using ethereal hydrogen bromide solution.

In an analogous manner, are produced:

1-[1-(4-methylbenzyl)-4-allyl - 4-piperidyl] - 1-butanone hydrochloride, M.P. 173–175°;
1-[1-(3-phenoxypropyl)-4-allyl-4-piperidyl] - 1-butanone hydrochloride, M.P. 180–182°;
1-[1-(2-phenylpropyl) - 4-allyl-4-piperidyl] - 1-butanone hydrochloride, M.P. 201–203°;
1-(1,4-diallyl - 4-piperidyl) - 1-butanone hydrochloride, M.P. 140–142°;
1-[1-(2-methylbenzyl) - 4-allyl - 4-piperidyl] - 1-butanone hydrochloride, M.P. 173–175°;
1-[1-(3-hydroxy-3-phenylpropyl) - 4-allyl - 4-piperidyl-1-butanone hydrochloride, M.P. 131–133°;
1-[1-(2-p-methoxy-2-phenylethyl) - 4-allyl - 4-piperidyl]-1-butanone fumarate, M.P. 132–133°;
1-[1-[2-(N-allyl-anilino) - ethyl]-4-allyl - 4-piperidyl]-1-butanone fumarate, M.P. 135–137°;
1-[1-(2-phenylethyl) - 4-(2-propinyl) - 4-piperidyl] - 1-butanone hydrochloride, M.P. 210–212°;
1-[1-(2-anilinoethyl) - 4-(2-propinyl) - 4-piperidyl] - 1-butanone fumarate, M.P. 151–152°;
1-[1-cinnamyl - 4-(2-propinyl) - 4-piperidyl] - 1-butanone fumarate, M.P. 177°;
1-[1-(3-hydroxy - 3-phenylpropyl) - 4 - (2-propinyl) - 4-piperidyl]-1-butanone fumarate, M.P. 150–151°;
1-[1-(2-phenoxyethyl) - 4-(2-propinyl) - 4-piperidyl]-1-butanone fumarate, M.P. 163–164°;
1-[1-[2-(N-allyl-anilino) - ethyl] - 4-(2-propinyl) - 4-piperidyl]-1-butanone fumarate, M.P. 156–158°;
1-[1-(3-p-methoxyphenyl-propyl) - 4-(2-propinyl) - 4-piperidyl]-1-butanone fumarate, M.P. 156°;
1-[1-(2-phenethyl) - 4-propyl - 4-piperidyl]-1-butanone fumarate, M.P. 176°;
1-[1-(3-phenyl-propyl) - 4-propyl - 4-piperidyl]-1-butanone fumarate, M.P. 172–173°;
1-[1-(2-anilino-ethyl) - 4-propyl-4-piperidyl]-1-butannoe fumarate, M.P. 146–148°;
1-[1-cinnamyl-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 178–179°;
1-[1-(2-phenoxy-ethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 159–160°;
1-[1-(3-hydroxy-3-phenylpropyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 146–7°.

The nitrile required as starting material is produced as follows:

(a) 0.40 g. of lithium wire cut into small pieces are added, while stirring, to 4.5 g. of bromobenzene in 60 ml. of absolute ether in a 200 ml. four-necked flask under nitrogen, whereby the ether commences to boil. After the reaction has subsided, the mixture is refluxed for another 2½ hours. 6.35 g. of triphenyl methane in 25 ml. of absolute 1.2-dimethoxyethane are added all at once to the obtained solution of phenyl lithium, whereby, due to the formation of triphenylmethyl lithium, the solution becomes dark red in colour and gently boils. After 20 minutes stirring at room temperature, 5.8 g. of 1-(3-phenylpropyl) isonipecotonitrile (produced by reacting isonipecotamide with 3-phenylpropyl bromide in the presence of sodium carbonate and sodium iodide in boiling acetone, and boiling the 1-(3-phenylpropyl) isonipecotamide with thionyl chloride in chloroform) in 5 ml. of absolute ether are added at 28°. The dark red solution loses its colour, accompanied by a slight increase in temperature. The solution is stirred for 10 minutes at room temperature and then mixed all at once with 3.4 g. of allyl bromide in 20 ml. of absolute ether. The mixture is stirred for 2½ hours at room temperature, whereby it assumes a yellowish colour and lithium bromide precipitates. The reaction mixture is then decomposed with 20 ml. of water and concentrated in the rotary evaporator. Ether is added to the residue and the obtained ether solution extracted four times with dilute hydrochloric acid. The acid extracts are rendered alkaline and exhaustively extracted with chloroform, the chloroform extracts then being dried and concentrated. The residue is taken up in ether, the ether solution dried and concentrated and the residue distilled. The 1-(3-phenylpropyl)-4-allyl isonipecotonitrile boils at 140–150°/0.01 torr (air bath). The hydrochloride prepared with hydrogen chloride in ether, melts after recrystallization from acetone methanol at 219–220°.

EXAMPLE 4

The Grignard compound is produced in the usual manner from 1.46 g. of magnesium and 6.55 g. of ethyl bromide in 30 ml. of absolute ether in a 100 ml. four-necked flask. 6 g. of 1-(3-phenylpropyl)-4-allyl isonipecotic acid ethyl ester in 18 ml. of absolute ether are then added. The reaction is only slightly exothermic. 50 ml. of absolute toluene are then added and the ether is distilled off. The starting material is then refluxed for 12 hours and decomposed, while cooling with ice, with water and 2 N hydrochloric acid. The organic phase is, if necessary, separated with the addition of ether, thoroughly shaken with concentrated ammonia and brine, dried, evaporated and distilled. The 1-[(3-phenylpropyl)-4-allyl-4-piperidyl]-propanone boils in the air bath at 160–180°/0.02 torr. The fumarate is produced from this in the usual manner, M.P. 150–152°.

The ester required as starting material is obtained as follows:

(a) 20 g. of isonicotinic acid ethyl ester are refluxed with 75.5 g. of 3-phenylpropyl bromide in 100 ml. of ethanol for 5 hours. The ethanol is then evaporated off in vacuo, the residue dissolved in water and the aqueous solution extracted three times with ether. With concentration of the aqueous solution in vacuo and finally high vacuum, the ethyl ester of the 4-carboxyl-1-(3-phenylpropyl) pyridinium bromide remains behind.

(b) 24.1 g. of the above quaternary salt are hydrogenated in the presence of rhodium/aluminum oxide/catalyst (5% Rh) in 200 ml. of ethanol at room temperature and 3–4 atm. pressure. The catalyst is then filtered off and the filtrate concentrated. The residue is covered with chloroform and made alkaline with concentrated sodium hydroxide solution. The chloroform is separated and the aqueous phase exhaustively extracted with chloroform. The combined chloroform solutions are washed with saturated sodium chloride solution, dried and concentrated and the residue is distilled under high vacuum. The 1-(3-phenylpropyl)-isonipecotic acid ethyl ester boils at 130–132°/0.08 torr.

(c) 0.98 g. of lithium wire cut into small pieces and washed with petroleum ether are added while stirring to 11.0 g. of bromobenzene in 100 ml. of absolute ether under nitrogen, whereby the ether commences to boil. After the reaction has subsided, the mixture is refluxed for a further 2½ hours. 17.1 g. of triphenyl methane in 80 ml. of absolute 1,2-dimethoxyethane are added all at once to the obtained solution of phenyl lithium, whereby, due to the formation of triphenylmethyl lithium, the solution becomes dark red in colour and gently boils. After 20 minutes stirring at room temperature, 18.3 g. of 1-(3-phenylpropyl) isonipecotic acid ethyl ester in 20 ml. of absolute ether are added at 28°. The dark red solution loses its colour accompanied by a slight increase in temperature. The solution is stirred for 10 minutes at room temperature and subsequently mixed with 8.45 g. of allyl bromide in 20 ml. of absolute ether all at once. The mixture is stirred for 2½ hours at room temperature, whereby it assumes a yellowish colour and lithium bromide precipitates. The reaction mixture is then decomposed with 10 ml. of water and concentrated in the rotary evaporator. Ether is added to the residue and the obtained ether solution extracted four times with dilute hydrochloric acid. The acid extracts are made alkaline and exhaustively extracted with chloroform, the chloroform extracts then being dried and concentrated. The residue is taken up in ether, the ether solution dried and concentrated and the residue distilled. The 1-(3-phenylpropyl)-4-allyl isonipecotic acid ethyl ester boils at 178°/0.01 torr. fumarate M.P. 138° (from isopropanol).

EXAMPLE 5

23.7 g. of 1-(3-phenylpropyl)-4-allyl isonipecotic acid ethyl ester (produced according to Examples (4a), (b) and (c)) are refluxed with 100 ml. of 20% potassium hydroxide solution and 160 ml. of absolute ethanol for 15 hours. The solution is then made neutral with concentrated hydrochloric acid and concentrated in the rotary evaporator. The dry residue of crude 1-(3-phenylpropyl)-4-allyl isonipecotic acid hydrochloride is dissolved in 200 ml. of methylene chloride and a mixture of 120 ml. of oxalyl chloride in 80 ml. of methylene chloride is added dropwise. The reaction mixture is then evaporated to dryness in vacuo at 30° and the acid chloride dissolved in 150 ml. of absolute benzene. This solution is added dropwise at 30° to a cadmium Grignard solution produced in the usual manner from 7.32 g. of magnesium, 37 g. of propyl bromide and 33 g. of cadmium chloride in 240 ml. of absolute ether and 150 ml. of absolute benzene. The reaction mixture heats up during this process. After the addition is completed, the mixture is refluxed for a further 30 minutes. While cooling with ice, the mixture is decomposed with water and 2 N hydrochloric acid. The organic phase is separated, thoroughly shaken with conc. aqueous ammonia solution and saturated sodium chloride solution dried and concentrated. The residue remaining behind is distilled in high vacuum, whereby the 1-[1(3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone converts at 137–145°/0.03 torr. The hydrobromide prepared from this is in the usual way using ethereal hydrogen bromide solution melts at 169–170°.

In an analogous manner are obtained:

1-[1-(2-benzoylethyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 133–135°;

1-[1-(4-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 173–175°;

1-[1-(3-phenoxypropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 180–182°;

1-[1-(2-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 201–203°;

1-(1,4-diallyl-4-piperidyl)-1-butanone hydrochloride, M.P. 140–142°;

1-[1-(2-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride, M.P. 173–175°;

1-[1-(2-p-methoxy-2-phenylethyl)-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 132–133°;

1-[1-(3-p-fluorobenzoyl-propyl)-4-allyl-4-piperidyl]-1-butanone fumarate, M.P. 150–152°;

1-[1-(2-phenylethyl)-4-(2-propionyl)-4-piperidyl]-1-butanone hydrochloride, M.P. 210–212°;

1-[1-(2-benzoylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 157–158°;

1-[1-cinnamyl-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 177°;
1-[1-(2-phenoxyethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 163–164°;
1-[1-(3-propionoxy-3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 162°;
1-[1-(3-p-fluorobenzoyl-propyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 146–148°;
1-[1-(3-p-methoxyphenyl-propyl)-4-(2-propinyl)-4-piperidyl]-1-butanone fumarate, M.P. 156°;
1-[1-(2-phenethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 176°;
1-[1-(3-phenyl-propyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 172–173°;
1-[1-cinnamyl-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 178–179°;
1-[1-(2-phenoxy-ethyl)-4-propyl-4-piperidyl]-1-butanone fumarate, M.P. 159–160°.

EXAMPLE 6

The Grignard compound is produced in the usual manner in a 250 ml. four-necked flask using 3.48 g. of magnesium and 17.6 g. of propyl bromide in 50 ml. of ether. 13.6 g. of 1-(3-phenylpropyl)-4-(2-propinyl) isonipecotic acid ethyl ester in 50 ml. of ether are then added. The reaction is only slightly exothermic. 125 ml. of toluene are then added, and the ether distilled off. The mixture is then refluxed for 15 hours and subsequently decomposed, while cooling with ice, with water and 2 N hydrochloride acid. The organic phase is separated, shaken thoroughly with conc. aqueous ammonia solution and saturated sodium chloride solution, dried and concentrated and the residue distilled in high vacuum. The 1-[1-(3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone boils at 180–187°/0.02 torr. The fumarate, M.P. 170–171°, is produced from this using ethereal fumaric acid solution.

The 1 - (3-phenylpropyl)-4-(2-propinyl) isonipecotic acid ethyl ester, B.P. 170–172°/0.05 torr., fumarate M.P. 153° (from isopropanol), which is required as starting material, is produced completely analogously to Examples (4a), (b) and (c) using the same amount of propargyl bromide (3-bromopropine) in place of allyl bromide in the case of (c).

Analogously to the above example, using corresponding amounts of ethyl bromide, and n-butyl bromide respectfully, the following are obtained.

1-[1-(3-phenylpropyl) - 4 - (2 - propinyl)4-piperidyl]-1-propanone and its fumarate and
1 - [1 - (3 - phenylpropyl)-4-(2-propinyl)4-piperidyl]-1-pentanone and its fumarate respectively.

The 1 - [1 - (2 - phenylethyl)4-(2-propinyl)-4-piperidyl]-1-butanone and its fumarate are also produced analogously from the corresponding starting materials.

EXAMPLE 7

Analogously to example 4, but using 7.5 g. of methyl iodide, 8.2 g. of n-butyl bromide and 9.1 g. of n-pentyl bromide and 7.3 g. of allyl bromide respectively, the following are obtained:

1 - [1 - (3 - phenylpropyl)-4-allyl-4-piperidyl]-1-ethanone, fumarate, M.P. 174–177°;
1 - [1 - (3 - phenylpropyl) - 4 - allyl-4-piperidyl]-1-pentanone, fumarate M.P. 164–165°;
1 - [1 - (3 - phenylpropyl)-4-allyl-4-piperidyl]-1-hexanone, fumarate M.P. 156–158°, and
1 - [1 - (3 - phenylpropyl)-4-allyl-4-piperidyl[-but-3-en-1-on and also its fumarate.

EXAMPLE 8

Analogously to Example 4, but using 7.4 g. of n-propyl bromide in place of ethyl bromide, the corresponding ketones and their fumarates and hydrochlorides respectively are obtained from the below stated 1-substituted 4-allyl isonipecotic acid ethyl esters produced analogously to Examples (4a), (b) and (c). From 1 - methyl - 4 - allyl isonipectotic acid ethyl ester, B.P. 108–110°/17 torr, the 1 - (1 - methyl - 4 - allyl-4-piperidyl)-1-butanone, fumarate M.P. 127–129°;

from 1 - n - propyl-4-allyl isonipecotic acid ethyl ester, B.P. 74–80°/0.01 torr, the 1 - (1 - n - propyl-4-allyl-4-piperidyl)-1-butanone, fumarate M.P. 140–141°;
from 1-n-octyl-4-allyl isonipecotic ethyl ester, B.P. 130–140°/0.01 torr, fumarate M.P. 147–148°, the 1-(1-n-octyl - 4 - allyl-4-piperidyl)-1-butanone, hydrochloride M.P. 184–185°;
from 1-benzyl-4-allyl isonipecotic acid ethyl ester, B.P. 135–143°/0.4 torr, hydrochloride M.P. 148°, the 1-(1-benzyl - 4 - allyl-44-piperidyl)-1-butanone, hydrochloride M.P. 154–155°;
from 1-(p-bromobenzyl)-4-allyl isonipecotic acid ethyl ester, the 1 - [1 - (p-bromobenzyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 176–177°;
from 1-(4-phenylbutyl)-4-allyl isonipecotic acid ethyl ester, B.P. 136–147°/0.01 torr, fumarate M.P. 101–102°, the 1 - [1 - (4-phenylbutyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 149–151°;
from 1-cinnamyl-4-allyl isonipecotic acid ethyl ester, B.P. 143–152°/0.01 torr, fumarate M.P. 133–134°, the 1-(1 - cinnamyl - 4 - allyl-4-piperidyl)-1-butanone, hydrochloride M.P. 161–162°;
from 1-(2-phenoxyethyl)-4-allyl isonipecotic acid ethyl ester B.P. 186–193°/1.0 torr, fumarate M.P. 107–108°, the 1 - [1 - (2 - phenoxyethyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 161–163°;
from 1-(2-anilinoethyl)-4-allyl isonipecotic acid ethyl ester, B.P. 150–180°/0.01 torr (air bath), using 12.3 g. of n-propyl bromide and 24.3 g. of magnesium, the 1-[1 - (2 - anilinoethyl) - 4 - allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 173–174°.

EXAMPLE 9

28.2 g. of ethyl malonic acid diethyl ester with 3.45 g. of finely dispersed sodium are stirred in 900 ml. of absolute ether in a four-necked flask for 15 hours. To the thick suspension of sodium-ethyl-malonic acid diethyl ester are added 17.1 g. of 1-(2-phenyl-ethyl)-4-allyl-isonipecotinoyl-chloride hydrochloride. The mixture is firstly stirred at room temperature and then refluxed for an hour. It is then decomposed with ice and 5 N hydrochloric acid and the ether phase separated. It is again extracted with ether and the aqueous phase is then made alkaline with conc. ammonia. It is extracted with ether whereby, after evaporation, the (1-phenyl-ethyl-4-allyl-4-piperidyl)-dicarbethoxy-butanone remains. 9.1 g. of the crude above mentioned produce are mixed with 20 ml. of concentrated hydrochloric acid and refluxed for 2 hours. The solution is then evaporated in vacuo, the residue is taken up in a little water, made alkaline with concentrated ammonia and extracted with ether. It is dried, evaporated and distilled in the air-bath at 130–140°/0.02 torr. It is chromatographed on silica gel in chloroform-methanol 97:3. The base is then converted into the fumarate in the usual manner. The 1-[1-(2-phenyl - ethyl) - 4 - allyl - 4 - piperidyl]-1-butanone-hydrochloride melts at 210–212°.

The following were produced in the same manner:

1 - [1 - (2 - benzoylethyl) - 4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 133–135°,
1 - [1 - (4 - methylbenzyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 173–175°,
1 - [1 - (3 - phenoxypropyl) - 4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 180–182°,
1-[1-(2-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 201–203°,
1-(1,4-diallyl-4-piperidyl)-1-butanone, hydrochloride M.P. 140–142°,
1-[1-(2-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone, hydrochloride M.P. 173–175°,
1-[1-(2-p-methoxy-2-phenylethyl)-4-allyl-4-piperidyl]-1-butanone, fumarate M.P. 132–133°,

1-[1-[2-(N-allyl-anilino)-ethyl]-4-allyl-4-piperidyl]-1-butanone, fumarate M.P. 135–137°,

1-[1-(3-p-fluorobenzoyl-propyl)-4-allyl-4-piperidyl]-1-butanone, fumarate M.P. 150–152°,

1-[1-(2-phenylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone, hydrochloride M.P. 210–212°,

1-[1-(2-benzoylethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone, fumarate M.P. 157–158°,

1-[1-cinnamyl-4-(2-propinyl)-4-piperidyl]-1-butanone, fumarate M.P. 177°,

1-[1-(2-phenoxyethyl)-4-(2-propinyl)-4-piperidyl]-1-butanone, fumarate M.P. 163–164°,

1-[1-(3-p-fluorobenzoyl-propyl)-4-(2-propinyl)-4-piperidyl]-1-butanone, fumarate M.P. 146–148°,

1-[1-[2-(N-allyl-anilino)-ethyl]-4-(2-propinyl)-4-piperidyl]-1-butanone, fumarate M.P. 156–158°,

1-[1-(3-p-methoxyphenyl-propyl)-4-(2-propinyl)-4-piperidyl)-1-butanone, fumarate M.P. 156°,

1-[1-(2-phenethyl)-4-propyl-4-piperidyl]-1-butanone, fumarate M.P. 176°,

1-[1-(2-methylbenzyl)-allyl-4-piperidyl]-1-butanone fumarate M.P. 172–173°,

1-[1-cinnamyl-4-propyl-4-piperidyl]-1-butanone, fumarate M.P. 178–179°,

1-[1-(2-phenoxyethyl)-4-propyl-4-piperidyl]-1-butanone, fumarate M.P. 159–160°,

EXAMPLE 10

3.12 g. of 1-[1-(3-phenylpropyl)-4-(2-propinyl)-4-piperidyl]-1-butanone are hydrogenated at room temperature under normal pressure in the presence of 0.5 g. of Lindlar catalyst (palladium on calcium carbonate, partially deactivated with lead acetate) and 0.2 g. of guinoline in 50 ml. of ethanol. After about 107% of the theoretically necessary amount of hydrogen has been taken up, hydrogenation is discontinued, the catalyst is filtered off and thoroughly washed with ethanol. The filtrate is evaporated in a rotary evaporator and the residue is distilled under high vacuum. The 1-[1-(3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone obtained boils at 160–180°/0.01 torr, its hydrobromide melts at 169–170°.

In an analogous manner, are obtained:

1-[1-(2-benzoylethyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 133–135°;

1-[1-(4-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 173–175°;

1-[1-(3-phenoxypropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 180–182°;

1-[1-(2-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 201–203°;

1-(1,4-diallyl-4-piperidyl)-1-butanone hydrochloride M.P. 140–142°;

1-[1-(2-methylbenzyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 173–175°;

1-[1-[2-(N-phenyl-acetamido)-ethyl]-4-allyl-4-piperidyl]-1-butanone fumarate M.P. 143–145°;

1-[1-(3-hydroxy-3-phenylpropyl)-4-allyl-4-piperidyl]-1-butanone hydrochloride M.P. 131–133°;

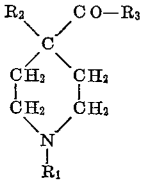
1-[1-(2-p-methoxy-2-phenylethyl)-4-allyl-4-piperidyl]-1-butanone fumarate M.P. 132–133°;

1-[1-[2-(N-allyl-anilino)-ethyl]-4-allyl-4-piperidyl]-1-butanone fumarate M.P. 135–137°;

1-[1-(3-p-fluorobenzoyl-propyl)-4-allyl-4-piperidyl]-1-butanone fumarate M.P. 150–152°.

What we claim is:

1. A compound of the formula:



wherein

R_1 is cinnamyl, 2-phenoxyethyl or 3-(p-fluorobenzoyl) propyl,

R_2 is allyl or 2-propinly, and

R_3 is n-propyl,

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 wherein R_1 is cinnamyl and R_2 is 2-propinyl.

3. A compound according to claim 1 wherein R_1 is cinnamyl and R_2 is allyl.

4. A compound according to claim 1 wherein R_1 is 2-phenoxyethyl and R_2 is 2-propinyl.

5. A compound according to claim 1 wherein R_1 is 3-(p-fluorobenzoyl)propyl and R_2 is allyl.

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HENRY R. JILES, Primary Examiner

G. T. TODD, Assistant Examiner

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