

PATENT SPECIFICATION

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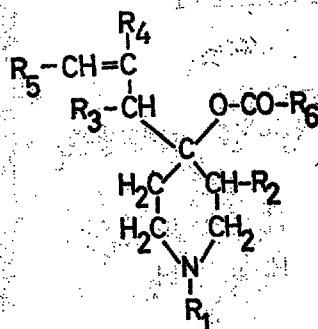
COMPLETE SPECIFICATION

Piperidine Derivatives and Processes for their Production

We J. R. GRIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, 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 concerns new piperidine derivatives which have valuable pharmacological properties and also processes for the production of these new compounds.

It has surprisingly been found that piperidine derivatives of the general formula



(I)

wherein

R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the cyclohexyl radical or a phenylalkyl radical having at most 9 carbon atoms,

R_2 , R_3 , R_4 and R_5 each independently represent hydrogen or methyl radicals, and R_6-CO- represents the acyl radical of acetic or propionic acid,

and their salts with inorganic and organic acids, have valuable pharmacological properties. On oral and also parenteral and rectal administration, they have, in particular, anti-

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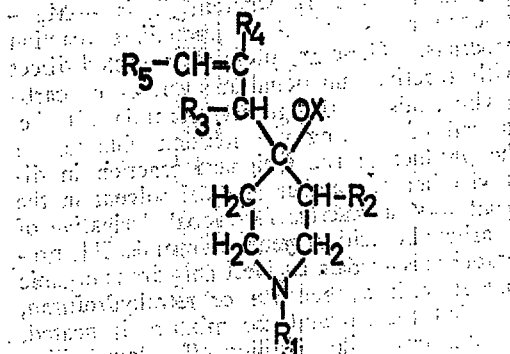
tussive and also analgetic activity and, at the same time, have relatively low toxicity. They are thus suitable for reducing tussive irritation and also for the relief or removal of pain of various origin.

Accordingly the invention also provides a composition comprising, as active ingredient, at least one compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof with an organic or inorganic acid, together with at least one pharmaceutically acceptable carrier.

In the compounds of general formula I and the starting materials therefor which are given below, R_1 represents an alkyl radical such as the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec. butyl, n-amyl, isoamyl, n-hexyl or n-octyl radical; alkenyl radicals such as the allyl, crotyl or methallyl radical; the cyclohexyl radical, a phenyl alkyl radical such as the benzyl, 2-phenylethyl or 3-phenylpropyl radical.

The radical R_6-CO- is the acyl radical of acetic acid or propionic acid.

To produce the compounds of general formula I, a compound of the general formula



(II)

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wherein

X represents hydrogen, a monovalent cation or the normal equivalent of a polyvalent cation, particularly a metal ion, and

5 R_1, R_2, R_3, R_4 and R_5 have the meanings given above,

is reacted with a reactive functional derivative of a carboxylic acid of the general formula III

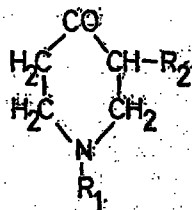


or, if X is a hydrogen atom, with the free acid or with a corresponding ketene. For example, a hydroxy compound or metal compound thereof embraced by general formula II is

15 treated with a halide, cyanide, anhydride or mixed anhydride of a carboxylic acid of the general formula III.

Starting materials of the general formula II are obtained by reacting 4-piperidones of

20 the general formula IV



(IV)

wherein R_1 and R_2 have the meanings given above and of which some representatives are known and others can be produced analogously, with metal-organic compounds which

25 contain alkenyl radical of general formula V



wherein R_3, R_4 and R_5 have the meanings given above, in particular with corresponding alkenyl magnesium halides in ethereal solvents according to Grignard. Compounds of the

30 general formula II wherein X is $-Mg-$ halogen are obtained as immediate reaction products. These are preferably reacted direct with reactive functional derivatives of carboxylic acids of the general formula III, i.e.

35 instead of reacting the solution obtained of the product of the Grignard reaction in diethyl ether or another ethereal solvent in the usual way, a reactive functional derivative of

40 a carboxylic acid of general formula III, preferably dissolved in an inert anhydrous organic solvent such as benzene or tetrahydrofuran, is added thereto and the mixture is heated,

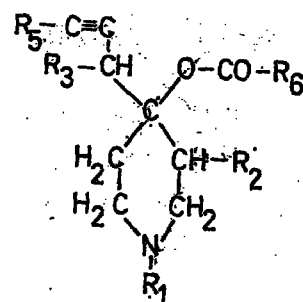
45 if necessary while distilling off a low boiling solvent of the Grignard reaction, until the reaction is complete.

In addition, free hydroxy compounds of the general formula II can also be produced

by partial hydrogenation of the triple bond of the hydroxy compounds of general formula VII mentioned below. This is done analogously to the second process mentioned below for the production of end products of general formula: In this way, for example, by hydrogenation of 1-substituted 4-(2'-butenyl)-4-piperidinols, also the correspondingly substituted 4-(2'-butenyl)-4-piperidinols are obtained, whilst on reacting 2-butenylmagnesium halides with piperidones of the general formula IV, due to allyl rearrangement, 1-substituted 4-(1'-methylallyl)-4-piperidinols are obtained.

In the acylation of free hydroxy compounds of the general formula II, anhydrides and halides of lower alkanolic acids in excess can serve at the same time as reaction medium; other acylating agents are used in inert organic solvents such as diethyl ether, tetrahydrofuran or benzene. If desired, an acid binding agent, e.g. a tertiary organic base such as pyridine or triethylamine, can be added but it is not necessary for a complete reaction. Compounds of general formula II wherein X is hydrogen are acylated at temperatures from 0° to about 100° as the corresponding starting materials of general formula II, which are tertiary hydroxy compounds, very easily split off water on reaction with acylating agents at higher temperatures.

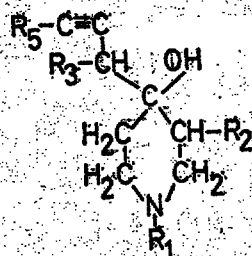
Compounds of the general formula I wherein R_4 is hydrogen and R_3 and R_5 are hydrogen or methyl radicals are produced by a second process by treating compounds of the general formula VI



(VI)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings given above, with hydrogen until the equimolar amount has been taken up, the treatment being performed in the presence of a catalyst suitable for the partial hydrogenation of triple bonds. As catalyst, e.g. palladium $CaCO_3$ -lead-acetate in ethanol, partially deactivated *in situ* by the addition of quinoline, is used (Lindlar catalyst cf. *Helv. Chim. Acta* 30, 1923 (1947)).

The starting materials of general formula VI are obtained, e.g., by acylating hydroxy compounds of the general formula VII



(VII)

wherein R_1 , R_2 , R_3 , and R_5 have the meanings given above; the acylation can be performed completely analogously to that of free hydroxy compounds or metal compounds of the general formula II. Some representative starting materials of the general formula II containing hydrogen as R_2 , R_3 , and R_5 can be produced in the manner described in British Patent Specification No. 923170. Representative starting materials of general formula VII containing hydrogen as R_1 , R_2 , and R_3 may be produced by reacting propargyl bromide with activated magnesium, zinc or aluminium in a mixture of tetrahydrofuran and toluene and condensing the metal-organic compound formed with a 4-piperidone of the general formula IV. Instead of propargyl bromide, analogous compounds can also be used which produce compounds of the general formula VII containing a methyl group as radical R_2 and/or R_3 . The process is advantageously modified by using coarse aluminium turnings which are first amalgamated by means of metallic mercury and then treated with mercury chloride instead of such turnings simply activated with mercury chloride.

As mentioned above, the new piperidine derivatives are administered orally, rectally or parenterally. The daily dosages of the free bases or of non-toxic salts thereof vary between 1 and 800 mg. for adult patients. Suitable dosage units such as dragées (sugar coated tablets), tablets, suppositories or ampoules preferably contain 1—200 mg. of a piperidine derivative which can be produced according to the invention or of a non-toxic salt thereof as active substance.

By non-toxic salts of the bases usable according to the invention are meant salts with those acids the anions of which are pharmacologically acceptable in the usual dosages, i.e. they have no toxic effects. It is also of advantage if the salts to be used crystallise well and are not or are only slightly hygroscopic. Examples of non-toxic salts are the salts with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, β -hydroxyethanesulphonic acid, acetic acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric

acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

Dosage units for oral administration preferably contain between 1% and 90% of a piperidine derivative of the general formula I or a non-toxic salt thereof as active substance. They are produced by working up the active substance into tablets or dragée cores 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 gelatines, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols (Carbowaxes) ("Carbowax" is a registered Trade Mark) of suitable molecular weights. The dragée cores 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.

In addition, for the treatment of coughs in particular, also, for example, lozenges as well as liquid forms for oral administration such as cough syrups prepared with the usual auxiliaries, and drops can be considered.

Dosage units for rectal administration are, e.g. suppositories which consists 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 rectal capsules which contain a combination of the active substance or a suitable salt thereof with polyethylene glycols (Carbowaxes) of suitable molecular weight.

Ampoules for parenteral, particularly intramuscular, administration preferably contain a water soluble salt of a piperidine derivative of general formula I in a concentration of, preferably, 0.5—5%, optionally together with suitable stabilising agents and buffer substances, in aqueous solution.

The following prescriptions further illustrate the production of tablets and dragées:

a) 250 g. of 1-methyl-4-allyl-4-acetoxy-piperidine hydrochloride are mixed with 175.80 g. of lactose and 169.70 g. of potato starch, the mixture is moistened with an alcoholic solution of 10 g. of stearic acid and granulated through a sieve. After drying, 160 g. of potato starch, 200 g. of talcum, 2.50 g. of magnesium stearate and 32 g. of colloidal silicon dioxide are mixed in and the mixture is pressed into 10,000 tablets each weighing 100 mg. and containing 25 mg. of active substance. The tablets can be grooved if desired for better adaptation of the dosage.

b) A granulate is produced from 250 g. of 1-methyl-4-allyl-4-acetoxy-piperidine hydrochloride, 175.90 g. of lactose and the

alcoholic solution of 10 g of stearic acid. After drying, the granulate is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate and the whole is pressed into 10,000 dragée cores. These are then coated with a concentrated syrup made of 522.28 g of crystalline saccharose, 6 g of Shellack, 10 g of gum arabic, 215 g of talcum, 15 g of colloidal silicon dioxide, 0.22 g of dyestuff and 1.5 g of titanium dioxide and dried. The dragées obtained each weigh 145 mg and contain 25 mg of active substance.

c) To produce a cough syrup, 20 g of 1-methyl-4-allyl-4-acetoxy-piperidine hydrochloride, 42 g of *p*-hydroxybenzoic acid methyl ester, 18 g of *p*-hydroxybenzoic acid propyl ester and 5,000 g of crystallised sugar and also any flavouring desired are dissolved in distilled water up to 10 litres.

d) To produce drops for the treatment of coughs, 500 g of 1-methyl-4-allyl-4-acetoxy-piperidine hydrochloride, 10 g of ascorbic acid, sweetener, e.g. 5 g of sodium cyclamate, flavouring as desired and 2,500 g of sorbitol (70%) are dissolved in distilled water up to 10 litres.

The following examples further illustrate the performance of the processes according to the invention but are by no means the sole methods of performing same. The temperatures are given in degrees Centigrade.

EXAMPLE 1

10.2 g of magnesium filings in 30 ml of abs. ether are placed in a 750 ml four-necked flask and a little allyl bromide is added dropwise while stirring. As soon as the reaction has begun, 100 ml of abs. ether are added and 50.8 g of allyl bromide are added dropwise in such a way that the ether remains boiling under reflux and then the whole is stirred for another 10 minutes. 28.2 g of 1-propyl-4-piperidone in 50 ml of abs. ether are then added dropwise, the whole is refluxed for 15 minutes, heating is interrupted and 109.2 g of propionic anhydride in 70 ml of abs. benzene are added dropwise. The yellowish suspension is then refluxed for 6 hours, poured onto ice, made acid with concentrated hydrochloric acid and the ethereal phase is extracted three times with 6N hydrochloric acid. The combined acid extracts are made alkaline with concentrated ammonia, extracted four times with chloroform, dried, concentrated and distilled. The 1-propyl-4-allyl-4-propionyloxy-piperidine boils at 88°/0.04 Torr. The hydrochloride is produced therefrom with ethereal hydrochloric acid in abs. ether. It melts at 225–226° (recrystallised from isopropanol/ether).

EXAMPLE 2

The following compounds may be produced in an analogous manner to Example 1.

- 1-propyl-4-allyl-4-acetoxy-piperidine, B.P. 75°/0.03 Torr, hydrochloride M.P. 227°; 65
- 1-methyl-4-allyl-4-propionyloxy-piperidine, B.P. 70–75°/0.06 Torr, hydrochloride M.P. 157–158°; 70
- 1-methyl-4-allyl-4-acetoxy-piperidine, B.P. 59–65°/0.05 Torr, hydrochloride M.P. 167–168°; 75
- 1-(2'-phenylethyl)-4-allyl-4-acetoxy-piperidine, B.P. 136–140°/0.02 Torr, hydrochloride M.P. 246°; 75
- 1-(2'-phenylethyl)-4-allyl-4-propionyloxy-piperidine, B.P. 152°/0.05 Torr, hydrochloride M.P. 228–230°; 80
- 1-(3'-phenylpropyl)-4-allyl-4-acetoxy-piperidine, B.P. 149–154°/0.05 Torr, hydrochloride M.P. 182–183°; 80
- 1-(3'-phenylpropyl)-4-allyl-4-propionyloxy-piperidine, B.P. 155–160°/0.01 Torr, hydrochloride M.P. 148–149°; 85
- 1-ethyl-4-allyl-4-propionyloxy-piperidine, B.P. 72–72°/0.01 Torr, hydrochloride M.P. 176–177°, citrate M.P. 173–174°; 90
- 1-ethyl-4-allyl-4-acetoxy-piperidine, B.P. 70°/0.01 Torr, hydrochloride M.P. 183°, citrate M.P. 158°; 90
- 1,4-diallyl-4-acetoxy-piperidine, B.P. 65–66°/0.015 Torr, hydrochloride M.P. 173–174°; 95
- 1,4-diallyl-4-propionyloxy-piperidine, B.P. 87–90°/0.05 Torr, hydrochloride M.P. 205–207°.

EXAMPLE 3

The following compounds may be produced in an analogous manner to Example 1.

- 1-benzyl-4-allyl-4-acetoxy-piperidine, hydrochloride, M.P. 197–198°; 100
- 1-n-butyl-4-allyl-4-acetoxy-piperidine, hydrochloride, M.P. 238°; 105
- 1-n-butyl-4-allyl-4-propionyloxy-piperidine, hydrochloride, M.P. 222°; 105
- 1-cyclohexyl-4-allyl-4-acetoxy-piperidine, hydrochloride, M.P. 250°; 110
- 1-cyclohexyl-4-allyl-4-propionyloxy-piperidine, hydrochloride, M.P. 234°; 110
- 1-n-octyl-4-allyl-4-acetoxy-piperidine, hydrochloride, M.P. 221–222°; 115
- 1-n-octyl-4-allyl-4-propionyloxy-piperidine, hydrochloride, M.P. 196–197°; 115
- 1-isopropyl-4-allyl-4-acetoxy-piperidine, hydrochloride, M.P. 220°; 120
- 1-isopropyl-4-allyl-4-propionyloxy-piperidine, hydrochloride, M.P. 198–199°; 120
- 1-(2'-phenyl-ethyl)-3-methyl-4-allyl-4-acetoxy-piperidine, maleate, M.P. 130–131°; 125
- 1-(2'-phenyl-ethyl)-3-methyl-4-propionyloxy-piperidine, maleate, M.P. 117–118°, and

1 - methyl - 4 - (2' - butenyl) - 4 - acetoxy - piperidine, citrate, M.P. 192—193°.

EXAMPLE 4

14.58 g of magnesium filings in 25 ml of abs. ether are placed in a 1500 ml four-necked flask and a little crotyl bromide (1-bromo-2-butene) is added dropwise. When the reaction has started, 215 ml of abs. ether are added and the remainder of 27 g of crotyl bromide is slowly added over 4—5 hours while stirring. The reaction mixture is then stirred for another 30 minutes, 11.3 g of 1-methyl-4-piperidone in 100 ml of abs. ether are added in 10 minutes, the mixture is refluxed for 30 minutes, 50 ml of acetic anhydride are added and the yellow suspension is refluxed for another two hours. The mixture is then poured onto ice, acidified with concentrated hydrochloric acid, and the ethereal phase is extracted three times with 6N hydrochloric acid. The combined acid extracts are made alkaline with concentrated ammonia, extracted four times with chloroform, the chloroform solution is dried and concentrated and the residue is distilled. The 1 - methyl - 4 - (1' - methylallyl) - 4 - acetoxy-piperidine boils at 59—65°/0.05 Torr.

The hydrochloride is produced by adding ethereal hydrochloric acid to the solution of the base in abs. ether. It melts at 198° (recrystallised from acetone).

1 - Methyl - 4 - (1' - methylallyl) - 4 - propionoxy-piperidine is produced in the same way. Its hydrochloride melts at 207° (recrystallised from acetone/isopropanol).

EXAMPLE 5

a) 5.1 g of magnesium filings in 15 ml of ether are placed in a 350 ml flask and a little allyl bromide is added dropwise. When the reaction has started, 60 ml of abs. ether are added and the remainder of 25.4 g of allyl bromide is added while stirring so that the ether remains boiling under reflux. The whole is then stirred for another 10 minutes whereupon 11.3 g of 1-methyl-4-piperidone in 30 ml of abs. ether are slowly added. After refluxing for 30 minutes, ice is added to the mixture which is then acidified with concentrated hydrochloric acid and the ethereal phase is extracted three times with 6N hydrochloric acid. The combined acid extracts are made alkaline with concentrated ammonia and extracted with chloroform, the chloroform solution is dried and concentrated and the residue is distilled. The 1 - methyl - 4 - allyl - 4 - piperidinol boils at 60—64°/0.01 Torr; the citrate melts at 95—97° (recrystallised from methanol/ether). 1 - Propyl - 4 - allyl - 4 piperidinol, B.P. 69—76°/0.02 Torr, is obtained in the same way.

b) 7.6 g of the product of a), are refluxed for 3 hours with 40 ml of acetic anhydride.

The reaction solution is then evaporated in a rotary evaporator, ice is added to the residue which is then made strongly alkaline and extracted five times with chloroform. The chloroform solution is dried and concentrated and the residue is distilled. The 1 - methyl - 4 - allyl - 4 - acetoxy - piperidine boils at 112—115°/12 Torr; the hydrochloride melts at 167—168° (recrystallised from isopropanol/ether).

1 - Methyl - 4 - allyl - 4 - propionoxy - piperidine is produced in the same way. The hydrochloride melts at 157—158° (recrystallised from isopropanol/ether).

EXAMPLE 6

3.5 g of 1 - methyl - 4 - allyl - 4 - piperidinol hydrochloride and 250 mg of *p*-toluene sulphonic acid are dissolved in 150 ml of chloroform. Ketene freshly prepared from acetone is passed through this solution (Quedbeck apparatus, Angew. Chemie 68, 369 (1956)). The progress of the reaction is followed by thin layer chromatography (silica gel with 0.5% sodium hydroxide solution, eluant: methanol). No starting material can be detected after 15 minutes. The solution turns yellow during the reaction and the temperature rises about 40°. The solution is concentrated to half its volume and extracted twice with 100 ml of 2N hydrochloric acid each time. The acid solution is made alkaline with sodium carbonate, the product which precipitates is extracted three times with 10 ml of ether each time, dried with anhydrous sodium sulphate and concentrated. The oily 1 - methyl - 4 - allyl - 4 - acetoxy - piperidine is converted into the citrate. M.P. of citrate 181°.

EXAMPLE 7

2 g of 1 - methyl - 4 - (2' - propinyl) - 4 - acetoxy - piperidine are hydrogenated at room temperature under normal pressure with 500 mg of palladium/CaCO₃-lead-acetate in ethanol and 200 mg of quinoline. After the calculated amount of hydrogen has been taken up (about 23 minutes), the catalyst is filtered off, the filtrate is evaporated and the residue is distilled. The hydrochloride of 1 - methyl - 4 - allyl - 4 - acetoxy - piperidine produced from the distillate melts at 167—168° and is identical with the product produced in Example 2.

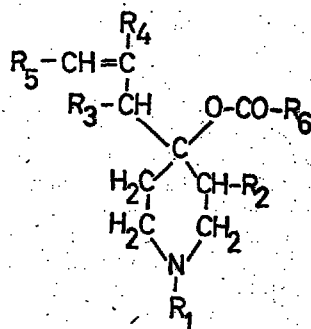
EXAMPLE 8

5.64 g of magnesium in 15 ml of abs. ether are placed in a Grignard apparatus and 31.3 g of methallyl bromide are added by first entering 2—3 ml thereof, and, as soon as the reaction has started, 60 ml of ether and then the remainder of the methallyl bromide, the latter being added dropwise within 30 minutes. The whole is then refluxed for 10 minutes and the N - methyl

- piperidone is added to 40 ml of ether. After the reaction has subsided, the solution is refluxed for 30 minutes. 50 ml of propionic anhydride in 50 ml of abs. benzene are then added and the whole is refluxed for 6 hours. Ice and concentrated hydrochloride are then added, the acid phase is removed and the organic phase is extracted twice with 2N hydrochloric acid. The aqueous extracts are combined, made alkaline with concentrated ammonia, extracted four times with chloroform, dried, evaporated and distilled. The 1-methyl-4-methallyl-4-propionyloxy-piperidine boils under 0.04 Torr at 60—65°.
- The citrate is produced therefrom in the usual way and is recrystallised from methanol when it then melts at 177—178°.

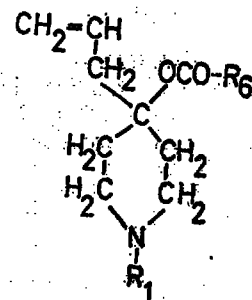
WHAT WE CLAIM IS:—

1. Piperidine derivatives of the general formula I



wherein

- R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the cyclohexyl radical or a phenylalkyl radical having at most 9 carbon atoms,
- R_2 , R_3 , R_4 and R_5 each independently represent hydrogen or methyl radicals, and R_6 -CO— represents the acyl radical of acetic or propionic acid, and their salts with inorganic and organic acids.
2. Piperidine derivatives of the general formula I given in claim 1, wherein R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the benzyl, 2-phenylethyl or 3-phenylpropyl radical, and R_2 , R_3 , R_4 , R_5 and R_6 -CO— have the means given in claim 1, and their salts with inorganic and organic acids.
3. Piperidine derivatives of the general formula Ia



wherein R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the cyclohexyl radical or a phenylalkyl radical having at most 9 carbon atoms and R_6 -CO— has the meaning given in claim 1 and their acid addition salts thereof.

4. Piperidine derivatives of the general formula Ia given in claim 3, wherein R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the benzyl, 2-phenylethyl or 3-phenylpropyl radical, and R_6 -CO— has the meaning given in claim 1, and their salts with inorganic and organic acids.

5. 1 - (2'-phenylethyl) - 4 - allyl - 4 - acetoxy-piperidine.

6. 1 - methyl - 4 - allyl - 4 - acetoxy - piperidine.

7. 1 - propyl - 4 - allyl - 4 - acetoxy - piperidine.

8. 1 - ethyl - 4 - allyl - 4 - propionyloxy - piperidine.

9. 1 - methyl - 4 - (1'-methylallyl) - 4 - acetoxy-piperidine.

10. 1 - methyl - 4 - allyl - 4 - propionyloxy - piperidine.

11. 1,4 - diallyl - 4 - propionyloxy - piperidine.

12. 1 - (2'-phenylethyl) - 3 - methyl - 4 - allyl-4-propionyloxy-piperidine.

13. 1 - benzyl - 4 - allyl - 4 - acetoxy - piperidine.

14. 1 - n - butyl - 4 - allyl - 4 - propionyloxy-piperidine.

15. 1 - n - octyl - 4 - allyl - 4 - propionyloxy-piperidine.

16. 1 - propyl - 4 - allyl - 4 - propionyloxy-piperidine.

17. 1 - (2'-phenylethyl) - 4 - allyl - 4 - propionyloxy-piperidine.

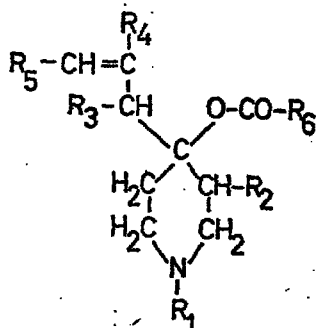
18. 1 - (3'-phenylpropyl) - 4 - allyl - 4 - propionyloxy-piperidine.

19. 1 - (3'-phenylpropyl - 4 - allyl - 4 - acetoxy-piperidine.

- piperidone is added to 40 ml of ether. After the reaction has subsided, the solution is refluxed for 30 minutes. 50 ml of propionic anhydride in 50 ml of abs. benzene are then added and the whole is refluxed for 6 hours. Ice and concentrated hydrochloride are then added, the acid phase is removed and the organic phase is extracted twice with 2N hydrochloric acid. The aqueous extracts are combined, made alkaline with concentrated ammonia, extracted four times with chloroform, dried, evaporated and distilled. The 1-methyl-4-methyl-4-propionyloxy-piperidine boils under 0.04 Torr at 60—65°. The citrate is produced therefrom in the usual way and is recrystallised from methanol when it then melts at 177—178°.

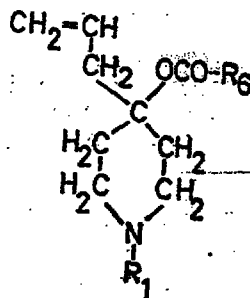
WHAT WE CLAIM IS:—

1. Piperidine derivatives of the general formula I



wherein

- R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the cyclohexyl radical or a phenylalkyl radical having at most 9 carbon atoms,
- R_2 , R_3 , R_4 and R_5 each independently represent hydrogen or methyl radicals, and
- R_6 -CO— represents the acyl radical of acetic or propionic acid, and their salts with inorganic and organic acids.
2. Piperidine derivatives of the general formula I given in claim 1, wherein
- R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the benzyl, 2-phenylethyl or 3-phenylpropyl radical, and
- R_2 , R_3 , R_4 , R_5 and R_6 -CO— have the means given in claim 1,
- and their salts with inorganic and organic acids.
3. Piperidine derivatives of the general formula Ia



wherein R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the cyclohexyl radical or a phenylalkyl radical having at most 9 carbon atoms and R_6 -CO— has the meaning given in claim 1 and their acid addition salts thereof.

4. Piperidine derivatives of the general formula Ia given in claim 3, wherein R_1 represents an alkyl or alkenyl radical having at most 8 carbon atoms, the benzyl, 2-phenylethyl or 3-phenylpropyl radical, and R_6 -CO— has the meaning given in claim 1, and their salts with inorganic and organic acids.

5. 1-(2'-phenylethyl)-4-allyl-4-acetoxypiperidine.

6. 1-methyl-4-allyl-4-acetoxypiperidine.

7. 1-propyl-4-allyl-4-acetoxypiperidine.

8. 1-ethyl-4-allyl-4-propionyloxy-piperidine.

9. 1-methyl-4-(1'-methylallyl)-4-acetoxypiperidine.

10. 1-methyl-4-allyl-4-propionyloxy-piperidine.

11. 1,4-diallyl-4-propionyloxy-piperidine.

12. 1-(2'-phenylethyl)-3-methyl-4-allyl-4-propionyloxy-piperidine.

13. 1-benzyl-4-allyl-4-acetoxypiperidine.

14. 1-n-butyl-4-allyl-4-propionyloxy-piperidine.

15. 1-n-octyl-4-allyl-4-propionyloxy-piperidine.

16. 1-propyl-4-allyl-4-propionyloxy-piperidine.

17. 1-(2'-phenylethyl)-4-allyl-4-propionyloxy-piperidine.

18. 1-(3'-phenylpropyl)-4-allyl-4-propionyloxy-piperidine.

19. 1-(3'-phenylpropyl)-4-allyl-4-acetoxypiperidine.

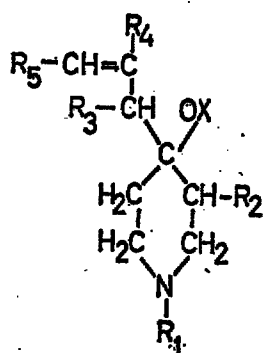
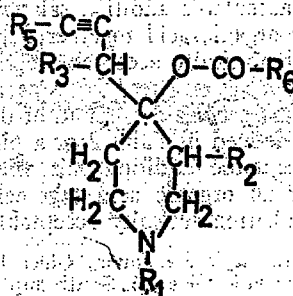


20. 1 - methyl - 4 - (1'methylallyl - 4 - propionyloxy-piperidine.

21. 1 - (2'phenylethyl) - 3 - methyl - 4 - allyl - 4 - acetoxy - piperidine.

5 22. A pharmaceutically acceptable acid addition salts of the piperidine derivative claimed in claim 3.

23. Process for the production of a piperidine derivative of the general formula I given in claim 1, which comprises reacting a compound of the general formula II



wherein X represents hydrogen, a monovalent cation or the normal equivalent of a polyvalent cation, and

15 R_1, R_2, R_3, R_4 and R_5 have the meanings given in claim 1, with a reactive functional derivative of a carboxylic acid of the general formula III



wherein R_6 has the meaning given in claim 1, or, when X is a hydrogen atom, reacting it with the free acid or with a corresponding ketene, and if desired, converting the compound obtained of the general formula I into a salt with an inorganic or organic acid.

24. Process for the production of piperidine derivatives of the general formula I given in claim 1, which comprises reacting a compound of the general formula II given in claim 23 wherein X has the meaning given in claim 23 and R_1, R_2, R_3, R_4 and R_5 have the meanings given in claim 2, with a reactive functional derivative of a carboxylic acid of the general formula III given in claim 23, wherein R_6-CO- has the meaning given in claim 1, or, when X is a hydrogen atom, reacting it with the free acid or with a corresponding ketene, and if desired converting the compound obtained of the general formula I into a salt with an inorganic or organic acid.

25. Process for the production of a piperidine derivative of the general formula I given in claim 1 wherein R_1 represents a hydrogen atom, which comprises treating a compound of the general formula VI

(VI)
wherein R_1, R_2, R_3, R_4 and R_5-CO- have the meanings given in claim 1, with hydrogen in the presence of a catalyst suitable for the partial hydrogenation of triple bonds until the equimolar amount of hydrogen has been taken up and, if desired, converting the compound obtained of general formula I into a salt with an inorganic or organic acid.

26. Process as claimed in claim 25 wherein the catalyst used is palladium/ $CaCO_3$ -lead-acetate in ethanol, partially deactivated *in situ* by the addition of quinoline.

27. Process for the production of a piperidine derivative of the general formula I given in claim 1 wherein R_1 represents a hydrogen atom, which comprises treating a compound of the general formula VI given in claim 25, wherein R_1, R_2, R_3, R_4 and R_5-CO- have the meanings given in claim 2, with hydrogen in the presence of a catalyst suitable for the partial hydrogenation of triple bonds until the equimolar amount of hydrogen has been taken up and, if desired, converting the compound obtained of general formula I into a salt with an inorganic or organic acid.

28. Process as claimed in claim 27, wherein the catalyst used is palladium or charcoal in ethanol, partially deactivated *in situ* by the addition of quinoline.

29. Process for the production of a piperidine derivative of the general formula I given in claim 1, substantially as hereinbefore described with reference to and as illustrated in any one of Examples 1, 2, 4, 5 and 7.

30. Process for the production of a piperidine derivative of the general formula I given in claim 1 substantially as hereinbefore described with reference to and as illustrated in any one of Examples 3, 6 and 8.

31. Piperidine derivatives of the general formula I given in claim 1, substantially as hereinbefore described with reference to and as illustrated in any one of Examples 1, 2, 4, 5 and 7.

32. Piperidine derivatives of the general formula I given in claim 1, substantially as hereinbefore described with reference to and as illustrated in any one of the Examples 3, 6 and 8.

33. Medicaments comprising as active ingredients at least one compound of the general formula I defined in claim 1 or a pharma-



ceutically acceptable addition salt with an inorganic or organic acid together with at least one pharmaceutically acceptable carrier.

- 5 34. Medicaments comprising as active ingredients at least one compound of the general formula I defined in claim 2 or a pharmaceutically acceptable addition salt with an inorganic or an organic acid together with at least one pharmaceutically acceptable carrier.

35. Medicaments substantially as hereinbefore described with reference to and as illustrated in any one of the foregoing prescriptions.

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