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PATENT SPECIFICATION

949,732

NO DRAWINGS

949,732

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International Classification:—C 07 d.

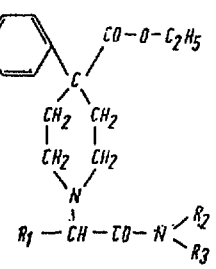
COMPLETE SPECIFICATION

New Piperidine Derivatives and process for their production

We, J. R. GEIGY 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 processes for the production of new piperidine derivatives having valuable pharmacological properties as well as the new compounds obtained by these processes.

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



I

wherein R_1 represents hydrogen or an alkyl radical having at most 3 carbon atoms,

R_2 represents hydrogen, a cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, heterocyclic or heterocyclic-alkyl radical, in which radicals alkyl or alkoxy groups having at most 4 carbon atoms or dialkylamino groups the alkyl portions of which each contain at most 4 carbon atoms can be present as substituents and in rings of aromatic character, halogen atoms, carbethoxy, nitro or acetylamino groups can be present as substituents,

R_3 represents hydrogen or an alkyl or alkenyl radical having at most 4 carbon atoms whereby an alkyl radical R_3 can also be bound to an alkyl radical R_2 direct or by way of an oxygen atom, or an imino group or an alkylimino group having at most 4 carbon atoms, as well as their salts with acids, have valuable pharmacological properties, in particular central depressing, anti-tussive, analgesic and spasmolytic activity and, at the same time, relatively slight toxicity. Furthermore, they potentiate the action of other medicaments, in particular anaesthetics.

They can be administered perorally as such or in the form of their salts and, in the form of aqueous solutions of their salts, also parenterally.

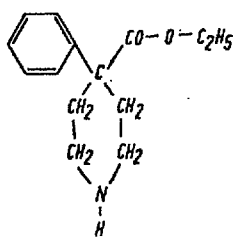
In the compounds of the general formula I, R_1 can be hydrogen, the methyl, ethyl, n-propyl or isopropyl radical. R_2 is, for example, hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cycloheptyl or cyclooctyl radical, or a phenyl, benzyl, α-phenylethyl, β-phenylethyl, α-methyl-β-phenylethyl or γ-phenylpropyl radical, the benzene ring of which can be substituted, e.g. by one or more low alkyl radicals, fluorine, chlorine or bromine atoms and/or by a dimethylamino, diethylamino, di-n-butylamino, acetamido, methoxy, ethoxy, propoxy or nitro group. In addition, R_2 is, for example, a tetrahydrofurfuryl, piperidinoethyl, pyrrolidinyl-(1)-ethyl, α-pyridyl, β-pyridyl, γ-pyridyl, β-[4 - methyl - piperazinyl - (1)] - ethyl, pyrimidinyl - (2), 4,6 - dimethyl - pyrimidinyl - (2), 2,6 - dimethyl - pyrimidinyl - (4), 2,6 - dimethoxy - pyrimidinyl - (4), morpholinoethyl, thiazolyl-(2), 4-methyl-thiazolyl-(2), benzthiazolyl-(2), or 4,6-dimethoxy-s-triazinyl-(2) radical and R_3 is, for example, hydrogen or a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, allyl, methallyl or crotyl radical. In addition, R_2 and R_3 together with the adjacent nitrogen atom can be, for

[*Price 4s. 6d.*]

example, the ethyleneimine, 3,3-dimethyl-azetidine, pyrrolidine, piperidine, hexamethyl-eneimine, heptamethyleneimine, morpholine, piperazine or 1-methyl-piperazine radical.

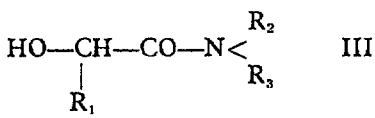
The radicals given above as examples of R_1—R_3 are only examples to illustrate the invention which is in no way limited to the production of compounds which only contain the radicals mentioned.

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



II

is reacted with reactive esters of hydroxy-alkane carboxylic acid amides of the general formula

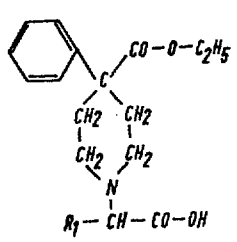


III

wherein R_1, R_2 and R_3 have the meanings given above, in particular with the halides thereof.

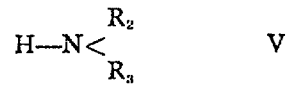
The reaction is performed preferably in the presence of inorganic or organic acid binding agents such as, e.g. sodium or potassium carbonate or tertiary organic bases such as triethylamine, tributylamine, dimethyl-aniline or pyridine. It is performed in an inert organic solvent such as, e.g. anhydrous methanol, ethanol, butanol or isopropanol, dimethyl-formamide, benzene, toluene or decaline, in the warm, e.g. at the boiling temperature of the solvents mentioned. Various starting materials of the general formulae II and III are known and others can be produced in an analogous manner.

A second process for the production of compounds of the general formula I consists in reacting a carboxylic acid of the general formula



IV

wherein R_1 has the meaning given above, or a reactive functional derivative thereof, particularly a halide, with a compound of the general formula



V

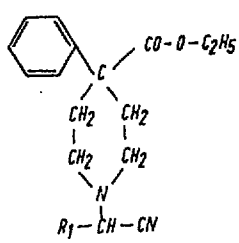
wherein R_2 and R_3 have the meanings given above.

As reactive functional derivatives of carboxylic acids of the general formula IV, in particular their halides, low alkyl esters as well as, e.g. mixed anhydrides with acetic acid or carbonic acid half esters, can be employed.

For example, halides, in particular chlorides, of acids of the general formula IV or their hydrochlorides are reacted with amines of the general formula V in the presence of acid binding agents, in particular in the presence of excess amine in the presence or absence of an inert organic solvent such as, e.g. toluene, benzene, methylene chloride or trichloro-ethylene.

By reacting compounds of the general formula II with low halogen carboxylic acids, e.g. in alcohol at room temperature, the carboxylic acids of the general formula IV are obtained which serve as starting materials for the above process either direct or after they have been converted into reactive functional derivatives, in particular into the hydrohalides of their halides, by treatment with inorganic acid halides.

A third process for the production of compounds of the general formula I in which R_1 has the meaning given above and R_2 and R_3 represent hydrogen, consists in partially saponifying a compound of the general formula



VI

wherein R_1 has the meaning given above, preferably in an acid medium, e.g. with the aid of polyphosphoric acid.

If desired, the compounds of the general formula I are converted in the known manner into their salts with inorganic or organic acids. Acids suitable for salt formation are e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, lactic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and mandelic acid.

The following examples further illustrate the production of the new compounds according to the invention. Parts are given therein as parts by weight; their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

EXAMPLE 1

5.3 Parts of 4-phenyl-4-carbethoxy-piperidine carbonate (4-phenyl-isonipecotinic acid ethyl ester carbonate produced according to Thorp & Walton, J. Chem. Soc. *1948*, 559), 3.4 parts of chloroacetanilide (produced according to Jacobs & Heidelberg, J. Am. Chem. Soc. *39*, 1441 (1917)) and 8.5 parts of anhydrous sodium carbonate in 50 parts by volume of anhydrous butanol are refluxed for 14 hours. After cooling, precipitated inorganic salts are filtered off and the butanol is distilled off in vacuo. On spraying the oily residue with ether, the product crystallises out. After recrystallising once from acetone/hexane, 1 - phenylcarbamoylmethyl - 4-phenyl - 4 - carbethoxy - piperidine is obtained in the form of colourless crystals which melt at 97—98°.

To convert it into the hydrochloride, anhydrous hydrogen chloride is passed through the ethereal solution of the base. After recrystallising once from methanol/ether, the hydrochloride is obtained in the form of white crystals which melt at 170—171° (on decomposition).

EXAMPLE 2

2.64 Parts of 4-phenyl-4-carbethoxy-piperidine carbonate dissolved in 25 parts by volume of anhydrous butanol are boiled with 4.25 parts of anhydrous sodium carbonate and a solution of 1.70 parts of 2-chloroacetamido-pyridine (produced according to Tschitschibabin, Berichte der Deutschen Chemischen Gesellschaft *57*, 2092 (1924)) in 50 parts by volume of anhydrous butanol is slowly added dropwise. On completion of the addition, the reaction mixture is refluxed for 10 hours. After cooling, the inorganic salts are filtered off and the filtrate is evaporated to dryness in vacuo. The residue is taken up in 50 parts by volume of ether, decoloured with a spoonful of animal charcoal and recrystallised from acetone/hexane. The 1 - [N - (2^1 - pyridyl)-carbamoylmethyl] - 4 - phenyl - 4 - carbethoxy - piperidine is obtained in the form of colourless crystals which melt at 109—110°.

The dihydrochloride is obtained by passing anhydrous hydrogen chloride through the methanolic solution of the base and precipitating with ether. After recrystallisation from methanol/ether, white crystals which melt at 195—200° (on decomposition) are obtained.

EXAMPLE 3

Starting from 5.3 parts of 4-phenyl-4-carbethoxy-piperidine carbonate and 3.5 parts of 2 - chloroacetamido - thiazole, 1 - [N-(2^1 - thiazolyl) - carbamoylmethyl] - 4-phenyl - 4 - carbethoxy - piperidine is obtained analogously to example 2, M.P. 115—116°.

Dihydrochloride, M.P. 175—180° (on decomposition).

EXAMPLE 4

2.64 Parts of 4-phenyl-4-carbethoxy-piperidine carbonate are dissolved in 7.5 parts by volume of acetic acid and the solution is heated for 5 minutes at 100°. The solution is then cooled to 15° and first 0.32 parts of paraformaldehyde and then 0.825 parts of potassium cyanide, dissolved in 1.5 parts by volume of water, are added. The reaction mixture is stirred for 12 hours at 40° and then evaporated to dryness in vacuo. The evaporation residue is dissolved in ether and is repeatedly extracted with 2 N-sodium carbonate and then with water. After drying with sodium sulphate and distilling off the solvent, the remaining 1 - cyanomethyl - 4 - phenyl-4 - carbethoxy - piperidine can be recrystallised from isopropanol/water. M.P. 69—70°.

2.72 Parts of 1 - cyanomethyl - 4 - phenyl-4 - carbethoxy - piperidine and 25 parts of polyphosphoric acid are heated together while stirring for 30 minutes at 110—120°. After cooling, the reaction mixture is poured onto ice water and the solution is extracted with ether to remove non-reacted starting material. The reaction is made alkaline with concentrated sodium hydroxide solution while cooling with ice and the alkaline solution is repeatedly extracted with ether. The ethereal solution is washed with water, dried with sodium sulphate and then evaporated to dryness. The remaining 1 - carbamoylmethyl - 4-phenyl - 4 - carbethoxy - piperidine melts, after recrystallisation from benzene/petroleum ether, at 92—94°.

EXAMPLE 5

2.91 Parts of 1 - carboxymethyl - 4-phenyl - 4 - carbethoxy - piperidine (produced from 4 - phenyl - 4 - carbethoxy-piperidine carbonate and chloroacetic acid by allowing to stand for several days in methanol) and 0.79 parts of pyridine are dissolved in 60 parts by volume of methylene chloride and a solution of 1.19 parts of thionyl chloride in 10 parts by volume of methylene chloride is added while stirring at 0—5°. The mixture is stirred for 2 hours at 0—5°. A solution of 0.93 parts of aniline and 0.79 parts of pyridine in 10 parts by volume of methylene chloride is then added dropwise at 0—5° and the reaction mixture is then stirred for 8 hours at room temperature. The solvent is then distilled off in vacuo, 2 N-sodium carbonate solution is added to the residue which is then repeatedly extracted with ether. The ethereal solution is washed several times with 2 N-sodium carbonate solution and then with water and finally is repeatedly extracted with 2 N-hydrochloric acid. The 1-phenylcarbamoylmethyl - 4 - phenyl - 4 - carbethoxy-

piperidine can be obtained direct in crystalline form from the hydrochloric acid solution by the careful addition of concentrated sodium hydroxide solution at 0—5°. M.P. 97—98°. The hydrochloride melts at 170—171°. The preparation is identical with the compound described in example 1.

The following 4 - phenyl - 4 - carbethoxy-piperidines, which correspond to the general formula 1, can be produced by the processes described in the above examples. In the following Table, only the substituent in the 1-position is given.

TABLE

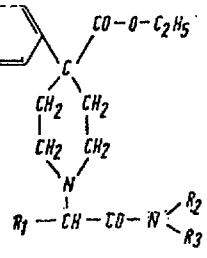
Compound No.	Substituent in 1-position	B.P. or M.P. of the base	M.P. of a salt of the base
1	1-(α-phenylcarbamoyl)-ethyl-	$B.P._{0.05}$ 192—197°	hydrobromide 195—196°
2	1-(N-methyl-N-phenyl-carbamoyl)-methyl-	$B.P._{0.04}$ 183—~~198°~~ 189°	hydrobromide 197—198°
3	1-(N-ethyl-N-phenyl-carbamoyl)-methyl-	$B.P._{0.005}$ 172—~~197°~~ 177°	diphosphate 116—119°
4	1-[α-(N-phenyl-N-methyl-carbamoyl)-ethyl]-	M.P. 81—82°	hydrobromide 138—140°
5	1-[α-(3^1-methyl-phenyl-carbamoyl)-ethyl]-	$B.P._{0.03}$ 196—200°	hydrochloride 184—185°
6	1-(4^1-methyl-phenyl-carbamoyl)-methyl-	M.P. 91—92°	hydrochloride 225—230°
7	1-(3^1-methyl-phenyl-carbamoyl)-methyl-	M.P. 73—73.5°	hydrochloride 182—187°
8	1-(2^1-methyl-phenyl-carbamoyl)-methyl-	M.P. 109—110°	hydrochloride 95—98°
9	1-(2^1,5^1-dimethyl-phenyl-carbamoyl)-methyl-	M.P. 101—102°	hydrochloride 154—157°
10	1-(2^1,3^1-dimethyl-phenyl-carbamoyl)-methyl-	M.P. 104—105°	hydrochloride 115—119°
11	1-(2^1,6^1-dimethyl-phenyl-carbamoyl)-methyl-	M.P. 112—113°	hydrochloride 110—113°
12	1-(2^1,4^1,6^1-trimethyl-phenyl-carbamoyl)-methyl-	M.P. 133—134°	hydrochloride 129—134°
13	1-(3^1-methoxy-phenyl-carbamoyl)-methyl-	M.P. 68—71°	hydrochloride 165—168°
14	1-(2^1-methoxy-phenyl-carbamoyl)-methyl-	M.P. 108—109°	malcate 118—119°
15	1-(4^1-methoxy-phenyl-carbamoyl)-methyl-	M.P. 77—78°	hydrochloride 200—205°
16	1-(2^1-chloro-phenyl-carbamoyl)-methyl-	M.P. 100—101°	malcate 157—158°

TABLE—cont.

Compound No.	Substituent in 1-position	B.P. or M.P. of the base	M.P. of a salt of the base
17	1-(4¹-chloro-phenyl-carbamoyl)-methyl-	M.P. 78—79°	hydrochloride 200—206°
18	1-(4¹-nitro-phenyl-carbamoyl)-methyl-	M.P. 128—129°	hydrochloride 236—240°
19	1-(4¹-acetylamino-phenyl-carbamoyl)-methyl-	M.P. 136—137°	hydrochloride 191—192°
20	1-(4¹-dimethylamino-phenyl-carbamoyl)-methyl-	M.P. 109—110°	dihydrochloride 142—145°
21	1-(4¹-carbethoxy-phenyl-carbamoyl)-methyl-	M.P. 112—113°	hydrochloride 115—118°
22	1-(α-benzyl-carbamoyl)-ethyl-	$B.P._{0.01}$ 175—180°	hydrochloride 184—185°
23	1-benzyl-carbamoyl-methyl-	M.P. 68.5—69.5°	hydrochloride 156—157°
24	1-(β-phenyl-ethyl-carbamoyl)-methyl-	M.P. 58—59°	phosphate 148—149°
25	1-cyclohexyl-carbamoyl-methyl-	M.P. 98—99°	hydrochloride 133—134°
26	1-[N-(2¹-methylpyridyl-(6¹))-carbamoylmethyl]-	M.P. 129—130°	dihydrochloride 203—204°
27	1-[N-(4¹-methylpyridyl-(6¹))-carbamoylmethyl]-	M.P. 123.4—124.5°	~~dihydrochloric~~ 210—213°
28	1-[N-benzthiazolyl-(2¹)-carbamoylmethyl]-	M.P. 149—151°	~~hydrochlorid~~ 234—235°
29	1-[N-furfuryl-(2¹)-carbamoyl-methyl]-	M.P. 83—84°	maleate 155—156°
30	1-pyrrolidinyl-(1¹)-carbonyl-methyl-	M.P. 79—80°	hydrobromide 159—160°
31	1-piperidino-carbonyl-methyl	M.P. 112—114°	hydrochloride 141—142°
32	1-morpholino-carbonyl-methyl-	M.P. 96—97°	hydrobromide 190—191°
33	1-(4¹-methyl-piperazinyl)-(1¹)-carbonyl-methyl-	M.P. 75—76°	hydrobromide 274—275°

WHAT WE CLAIM IS:—

1. A process for the production of new piperidine derivatives of the general formula



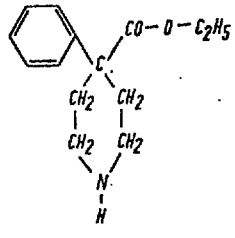
I

wherein R_1 represents hydrogen or an alkyl radical having at most 3 carbon atoms,

R_2 represents hydrogen, a cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, heterocyclic or heterocyclic-alkyl radical, in which radicals alkyl or alkoxy groups having at most 4 carbon atoms or dialkylamino groups, the alkyl portions of which each contain at most 4 carbon atoms, can be present as substituents and, in rings of aromatic character, halogen atoms, nitro or acetylamino groups can be present as substituents,

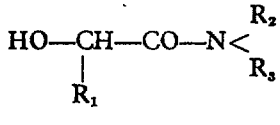
R_3 represents hydrogen or an alkyl or alkenyl radical having at most 4 carbon atoms whereby an alkyl radical R_3 can be bound to an alkyl radical R_2 direct or by way of an oxygen atom, or an imino group or an alkylimino group having at most 4 carbon atoms,

as well as their salts, which comprises reacting a compound of the formula



II

with a reactive ester of a hydroxy alkane carboxylic acid amide of the general formula

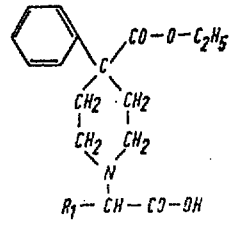


III

and, if desired, converting the compound of the general formula I into a salt with an inorganic or organic acid.

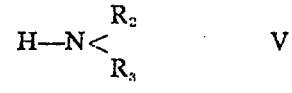
2. A modification of the process claimed in claim 1 in which R_2 in Formulae I and III is a carbethoxy-substituted aryl radical.

3. A process for producing piperidine derivatives of the general formula I defined in claim 1, characterised by reacting a carboxylic acid of the general formula



IV

wherein R_1 has the meaning given in claim 1, or a reactive functional derivative thereof, with a compound of the general formula



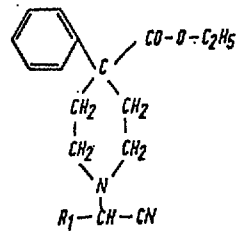
V

wherein R_2 and R_3 have the meanings given in claim 1.

4. A modification of the process claimed in claim 3 in which R_2 is a carbethoxy-substituted aryl radical.

5. A process as claimed in claim 3 or 4 in which the reactive functional derivative is a halide.

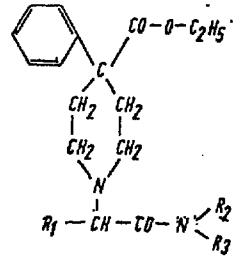
6. A process for the production of compounds of the general formula I defined in claim 1 wherein R_1 has the meaning given in claim 1 and R_2 and R_3 represent only hydrogen, which comprises partially saponifying a compound of the formula



VI

wherein R_1 has the meaning given in claim 1.

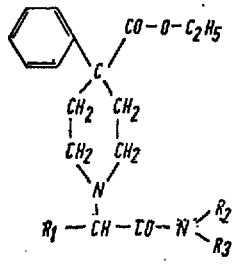
7. A piperidine derivative of the general formula



I

wherein R_1, R_2 and R_3 have the meanings given in claim 1, and the salts thereof with inorganic or organic acids.

8. A piperidine derivative of the general formula



I

wherein R_1 and R_3 have the meanings defined in claim 1 and R_2 is a carbethoxy-substituted aryl radical.

9. A process for the production of piperidine derivatives claimed in claim 7 substantially as hereinbefore described in Example 1, 2 or 3.

10. A process for the production of piperidine derivatives claimed in claim 7 substantially as hereinbefore described in Example 4 or 5.

11. Piperidine derivatives claimed in claim 7 as described in any one of the Examples and the Table.

12. Piperidine derivatives as claimed in claim 8 as described in the Table.

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ERRATA

SPECIFICATION No. 949,732

Page 4, Compound 2, *for* "183—198°" *read* "183—189°"

Page 4, Compound 3, *for* "172—197°" *read* "172—177°"

Page 5, Compound 27, *for* "dihydrochlorid" *read* "dihydrochloride"

Page 5, Compound 28, *for* "hydrochlorid" *read* "hydrochloride"

THE PATENT OFFICE
22nd May 1964

* C L M S *