950,897

PATENT SPECIFICATION

NO DRAWINGS

950,897

Date of Application and filing Complete Specification: Nov. 21, 1961.

No. 41519/61.

Application made in Switzerland (No. 13251) on Nov. 25, 1960.

Complete Specification Published: Feb. 26, 1964.

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A595/G

Index at acceptance:—C2 C(3A10E1, 3A10E4A4, 3A10E5A, 3A10E5E, 3A10E5F1A, 3A10E5F1C, 3A10E5F1E, 3A10E5F2A, 3A10E5F3D, 3A10E5J)

International Classification:—C 07 d

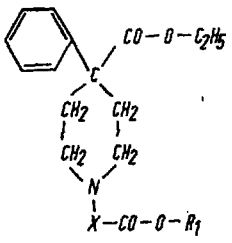
COMPLETE SPECIFICATION

New Piperidine Derivatives and processes for their manufacture

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 which have 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

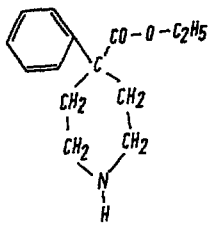
wherein R_1 represents hydrogen, an alkyl, aromatic, araliphatic or heterocyclic radical, and is preferably hydrogen, an alkyl radical having at most 8 carbon atoms, the phenyl, benzyl or furfuryl radical, and X represents a straight or branched chain alkylene radical having 2—4 carbon atoms, at least 2 carbon atoms of which form the direct chain between N and CO and preferably represents the ethylene, the 1,2 - propylene or the trimethylene radical, as well as their salts with acids have useful pharmacological properties, in particular central depressing, anti-tussive, analgetic 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 orally as such or in the form of their salts and, in the form of aqueous solutions of their salts, they can also be administered parenterally.

In addition, they are suitable as intermediate products for the production of other analgetically active substances. In the compounds of the general formula I R_1 is, for example, hydrogen, a methyl, ethyl, n-propyl, isopropyl, n - butyl, n - hexyl, n - octyl, n - dodecyl or a phenyl, benzyl, α - phenylethyl, β - phenylethyl, α - methyl - β - phenylethyl, γ-phenylpropyl, α - pyridyl, β - pyridyl, γ - pyridyl, tetrahydrofurfuryl or a furfuryl radical.

X is, for example, the ethylene, 1,2 - propylene, trimethylene, 1,2 - butylene 2,3-butylene, 1,3 - butylene, 1,3 - isobutylene or tetramethylene radical.

The radicals R_1 given above are only examples to illustrate the invention which is by no means limited to the production of compounds which contain only the radicals mentioned.

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



I

[*Price 4s. 6d.*]

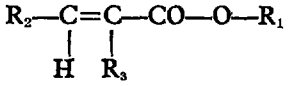
is reacted with halogen alkanoic acids or the esters thereof of the general formula

$$Hal—X—CO—O—R_1 \qquad III$$

wherein Hal represents a halogen atom, in particular chlorine or bromine and R_1 and X have the meanings given above.

The reaction is performed, if desired, in the presence of inorganic or organic acid binding agents, e.g. sodium or potassium carbonate, or tertiary organic bases such as triethylamine, tributylamine, dimethyl - aniline or pyridine, in the presence or absence of an inert organic solvent, e.g. methanol, ethanol, benzene, toluene, xylene, decalin or dimethyl formamide, and it is performed in the warm, for example, at the boiling temperature of the solvents mentioned. The starting material of the general formula II and numerous starting materials of the general formula III are known and others can be produced in an analogous manner.

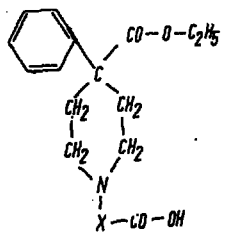
Compounds of the general formula I in which X is the ethylene, 1,2 - propylene or 2,3 - butylene radical are obtained by another process by adding compounds of the general formula II above to compounds of the general formula



IV

wherein R_2 and R_3 are hydrogen or methyl radicals and R_1 has the meaning given above. The addition can be made, for example, by warming the reaction components in organic solvents such as ethanol or another low alkanol used as alcohol component in the compound of formula IV, in dioxan, benzene or toluene. Numerous starting materials of the general formula IV, in particular acrylic acid ester, α-methacrylic acid ester and crotonic acid ester, are known and others can be produced in an analogous manner.

Finally, if desired, it is possible to convert compounds of the general formula I into other compounds also embraced by this formula. For example, if desired, compounds embraced by the general formula I of the general formula



V

wherein X has the meaning given above are esterified by condensing them, possibly after conversion into reactive functional derivatives such as halides or anhydrides, in particular mixed anhydrides with acetic acid, with hydroxy compounds of the general formula

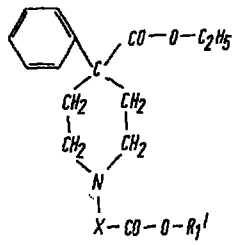
$$R_1^1—OH \qquad VI$$

in which R_1^1 has the meaning given above for R_1 with the exception of hydrogen, the condensation being performed in the presence of acid binding agents, or the compounds of the general formula V can be reacted with a diazo-alkane preferably having at most 8 carbon atoms whereupon the esters embraced by the general formula I are obtained. Such esters are also obtained by reacting salts, in particular metal salts, of compounds of the general formula

$$R_1^{11}—OH \qquad VII$$

wherein R_1^{11} has the meaning given for R_1 in general formula I with the exception of hydrogen and aromatic radicals.

On the other hand, if desired, diesters which are also embraced by the general formula I, i.e. compounds of the general formula



VIII

wherein R_1^1 and X have the meanings given above but R_1^1 is preferably an alkyl radical having at most 8 carbon atoms, can be partially hydrolysed to the corresponding compounds of the general formula I while retaining the carbethoxy group in 4-position, in which latter compounds R_1 is hydrogen. This is done, for example, by heating the diesters in the equimolar amount of an alcoholic/aqueous soda or caustic potash lye.

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

50 Parts by volume of benzene are added to 5.3 parts of 4 - phenyl - 4 - carbethoxypiperidine carbonate (4 - phenyl - iso - nipecotinic acid ethyl ester carbonate, produced according to Thorp & Walton, J. Chem. Soc. *1948*, ~~599~~) and the mixture is refluxed until all the substance has dissolved with development of carbon dioxide. A solution of 1.70 parts of β - chloropropionic acid phenyl ester in 20 parts by volume of benzene is then added dropwise at 20° whereupon the reaction mixture is refluxed for 15 minutes. After cooling, the 4 - phenyl - 4 - carbethoxy - piperidine hydrochloride which has precipitated is filtered off, the filtrate is evaporated to dryness in vacuo, the residue is taken up in 500 parts by volume of ether and the ethereal solution is repeatedly extracted with 2 N-sodium hydroxide solution. The ethereal solution is washed with water until the washings are neutral and then an excess of dry ice is added and the 4-phenyl - 4 - carbethoxy - piperidine carbonate precipitated in this way is filtered off. The ethereal filtrate is concentrated whereupon 1-(β - carbophenoxyethyl) - 4 - phenyl - 4 - carbethoxy - piperidine remains. Its hydrochloride from methanol/ether melts at 152—154°.

The following compounds are obtained in an analogous manner:

1 - (α - carbethoxy - propyl) - 4 - phenyl-4 - carbethoxy - piperidine, $B.P._{0.0001}$ 158—161°, M.P. of the hydrochloride from methanol/ether: 111—113°;

1 - (β - carbo - tert. butoxy - ethyl) - 4 - phenyl - 4 - carbethoxy - piperidine hydrochloride.

EXAMPLE 2

2.9 Parts of 4 - phenyl - 4 - carbethoxy - piperidine carbonate are dissolved in 50 parts by volume of anhydrous alcohol and the solution is refluxed until the development of carbon dioxide is completed. Then a solution of 1 part of acrylic acid ethyl ester in 10 parts by volume of anhydrous alcohol is added dropwise to the boiling solution and the reaction mixture is refluxed for another 2 hours. After distilling off the solvent, the 1 - (β - carbethoxyethyl) - 4 - phenyl - 4 - carbethoxy - piperidine which remains is purified by distillation and it then boils at 140—141° under 0.01 mm Hg pressure. To produce the hydrochloride, the base is dissolved in the calculated amount of 1 N - hydrochloric acid and evaporated to dryness in vacuo. The hydrochloride so obtained melts, after recrystallisation from methanol/ether, at 140—141°.

EXAMPLE 3

0.66 Parts of 1 - (β - carbethoxyethyl) - 4-phenyl - 4 - carbethoxy - piperidine are dissolved in 20 parts by volume of methanol. 2.2 Parts by volume of 1 N - sodium hydroxide solution are added and the whole is refluxed for 1 hour. After the methanol has been completely distilled off in vacuo, 50 parts of water are added to the residue and the alkaline solution is extracted twice with ether. The aqueous/alkaline solution is filtered through a column of 20 parts of "Amberlite" IRC 50 (H^+ form) ("Amberlite" is a Registered Trade Mark), washed with 500 parts of water and the combined filtrates are evaporated to dryness in vacuo. The crude 1 - (β - carboxy - ethyl) - 4 - phenyl - 4 - carbethoxy - piperidine so obtained is recrystallised from acetone/hexane when it then melts at 142—143°.

EXAMPLE 4

5.3 Parts of 4 - phenyl - 4 - carbethoxy - piperidine carbonate and 4.4 parts of methacrylic acid methyl ester are refluxed for 3 hours. After cooling, the reaction mixture is dissolved in 300 parts by volume of ether and non-reacted 4 - phenyl - 4 - carbethoxy - piperidine, in the form of the carbonate, is removed. After distillation, 1 - (β - carbo - methoxypropyl) - 4 - phenyl - 4 - carbethoxy-piperidine remains which boils at 157—159° under 0.001 mm Hg pressure.

The hydrochloride, produced as described in example 2 melts, after recrystallisation from acetone/petroleum ether, at 115—117°.

1 - (B - carbethoxy - isopropyl) - 4 - phenyl - 4 - carbethoxy - piperidine $B.P._{0.0001}$ 170—175°, M.P. of the hydrochloride (from methanol/ether) 145—147°, is obtained in an analogous manner.

EXAMPLE 5

2.1 Parts of 4 - phenyl - 4 - carbethoxy - piperidine carbonate and 1 part of acrylic acid methyl ester are refluxed at 80° for 2 hours. After cooling, the reaction mixture is taken up in 500 parts by volume of ether and an excess of solid carbon dioxide is added to this solution. The excess 4 - phenyl - 4 - carbethoxy - piperidine carbonate which precipitates is removed by filtration and the ethereal solution is concentrated. The oily product is taken up in benzene and is purified through a column of 10 parts of aluminium oxide activity I ("Woelm"). The 1 - (β - carbomethoxyethyl) - 4 - phenyl - 4 - carbethoxy - piperidine is recrystallised from benzene. M.P. 45—47°.

The following compounds are produced in the same way:

1 - (β - carbobenzyloxyethyl) - 4 - phenyl-4 - carbethoxy - piperidine, M.P. 180—190° under 0.01 mm

1 - (β - carbofurfuryloxyethyl) - 4 - phenyl-4 - carbethoxy - piperidine, hydrochloride M.P. 118—120°.

EXAMPLE 6

1 Part of 1-(β-carbethoxy-ethyl)-4-phenyl-4 - carbethoxy - piperidine in 20 parts by

volume of methylene chloride and 0.26 parts of pyridine are cooled to 0°. Then 0.39 parts of thionyl chloride in 5 parts by volume of methylene chloride are added dropwise at 0—5°. On completion of the addition, the whole is stirred for two hours with ice cooling. A solution of 0.35 parts of benzyl alcohol and 0.26 parts of pyridine in 5 parts by volume of methylene chloride is then added at 0° and the whole is stirred overnight at room temperature. After evaporating off the solvent, the residue is taken up in 300 parts by volume of ether and the ethereal solution is extracted three times with 2 N-sodium carbonate solution. The ether solution is washed neutral with water, dried with sodium sulphate and concentrated. The 1 - (β - carbobenzyloxy - ethyl)-4 - phenyl - 4 - carbethoxy - piperidine obtained distills at 180—190° under 0.01 mm.

1 - (β - carbofurfuryloxy - ethyl) - 4 - phenyl - 4 - carbethoxy - piperidine is obtained in the same way. The hydrochloride melts at 118—120°.

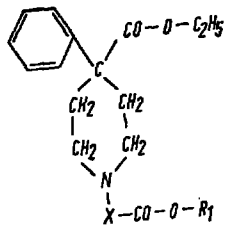
EXAMPLE 7

A mixture of 5.28 parts of 4 - phenyl - 4 - carbethoxy - piperidine carbonate in 100 parts by volume of anhydrous decalin is boiled for 15 minutes whereupon a solution is obtained. Then 15.6 parts of γ-bromobutyric acid ethyl ester, 2.5 parts of anhydrous potassium carbonate and 0.1 parts of potassium iodide are added and the whole is refluxed for 2 hours while excluding moisture. After cooling, the reaction mixture is diluted with 200 parts by volume of ether and then extracted several times with ice cold dilute hydrochloric acid. The oily base which is obtained from the hydrochloric acid solution by the addition of concentrated NaOH at 0—5° is extracted with ether, the ether phase is washed first with sodium carbonate solution and then with water and, after drying with sodium sulphate, is concentrated. The 1 - (γ - carbethoxy - propyl) - 4 - phenyl - 4 - carbethoxy - piperidine which remains boils at 195—200° under 10^{-4} mm pressure. The maleic acid salt melts, after recrystallisation from methanol - ether, at 111.5—113.5°.

The 1 - (γ - carbomethoxy - propyl) - 4 - phenyl - 4 - carbethoxy - piperidine obtained in an analogous manner boils at 169—171° under 10^{-4} mm pressure. Its maleate melts at 117—118.5° (from methanol-ether).

WHAT WE CLAIM IS:—

1. Compounds of the general formula

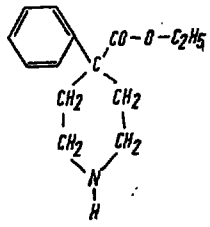


I

wherein R_1 represents hydrogen, an alkyl, aromatic, araliphatic or heterocyclic radical, and X represents a straight or branched chain alkylene radical having 2—4 carbon atoms, at least 2 carbon atoms of which form the direct chain between N and CO as well as of their acid addition salts.

2. Compounds of the general formula I, as defined in claim 1, in which R_1 represents hydrogen, an alkyl radical having at most 8 carbon atoms, the phenyl, benzyl or furfuryl radical and X represents the ethylene, the 1,2-propylene or the trimethylene radical.

3. A process for the production of compounds of the general formula I as defined in claim 1, and their acid addition salts, which comprises reacting a compound of the general formula



II

with a halogen alkane carboxylic acid or the ester thereof of the general formula

$$Hal—X—CO—O—R_1 \qquad III$$

wherein Hal represents a halogen atom and R_1 and X have the meanings given in claim 1.

volume of methylene chloride and 0.26 parts of pyridine are cooled to 0°. Then 0.39 parts of thionyl chloride in 5 parts by volume of methylene chloride are added dropwise at 0—5°. On completion of the addition, the whole is stirred for two hours with ice cooling. A solution of 0.35 parts of benzyl alcohol and 0.26 parts of pyridine in 5 parts by volume of methylene chloride is then added at 0° and the whole is stirred overnight at room temperature. After evaporating off the solvent, the residue is taken up in 300 parts by volume of ether and the ethereal solution is extracted three times with 2 N-sodium carbonate solution. The ether solution is washed neutral with water, dried with sodium sulphate and concentrated. The 1 - (β - carbobenzyloxy - ethyl)-4 - phenyl - 4 - carbethoxy - piperidine obtained distills at 180—190° under 0.01 mm.

1 - (β - carbofurfuryloxy - ethyl) - 4 - phenyl - 4 - carbethoxy - piperidine is obtained in the same way. The hydrochloride melts at 118—120°.

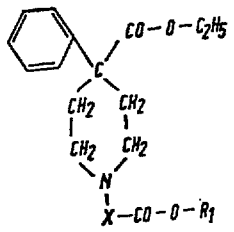
EXAMPLE 7

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The 1 - (γ - carbomethoxy - propyl) - 4 - phenyl - 4 - carbethoxy - piperidine obtained in an analogous manner boils at 169—171° under 10^{-4} mm pressure. Its maleate melts at 117—118.5° (from methanol-ether).

WHAT WE CLAIM IS:—

1. Compounds of the general formula

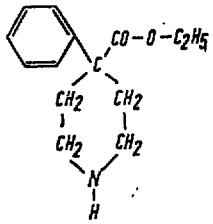


I

wherein R_1 represents hydrogen, an alkyl, aromatic, araliphatic or heterocyclic radical, and X represents a straight or branched chain alkylene radical having 2—4 carbon atoms, at least 2 carbon atoms of which form the direct chain between N and CO as well as of their acid addition salts.

2. Compounds of the general formula I, as defined in claim 1, in which R_1 represents hydrogen, an alkyl radical having at most 8 carbon atoms, the phenyl, benzyl or furfuryl radical and X represents the ethylene, the 1,2-propylene or the trimethylene radical.

3. A process for the production of compounds of the general formula I as defined in claim 1, and their acid addition salts, which comprises reacting a compound of the general formula



II

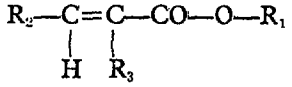
with a halogen alkane carboxylic acid or the ester thereof of the general formula

$$Hal—X—CO—O—R_1 \qquad III$$

wherein Hal represents a halogen atom and R_1 and X have the meanings given in claim 1.

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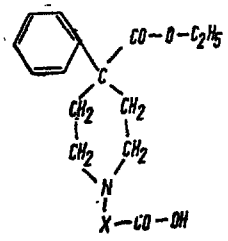
4. A process for the production of piperidine derivatives of general formula I defined in claim 1, which comprises adding a compound of the formula II given in claim 3 to a compound of the general formula



IV

wherein R_2 and R_3 represent hydrogen or methyl radicals and R_1 has the meaning given in claim 1.

5. A process for the production of piperidine derivatives of general formula I defined in claim 1, which comprises condensing a compound of the general formula



V

in which X has the meaning given in claim 1, possibly after conversion into a reactive functional derivative, with a hydroxy compound of the general formula

$$R_1^1—OH \qquad VI$$

wherein R_1^1 has the meaning given for R_1 in claim 1 with the exception of hydrogen.

6. A process for the production of compounds of the general formula 1 as defined in claim 1, which comprises reacting a compound of the general formula V as defined in claim 5, with a diazo-alkane.

7. A process as claimed in claim 6 in which said diazo-alkane has at most 5 carbon atoms.

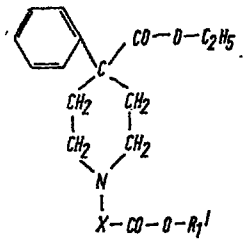
8. A process for the production of compounds of the general formula I as defined in claim 1, which comprises reacting a salt of a compound of the general formula V as defined in claim 5 with a reactive ester of a hydroxy compound of the general formula

$$R_1^{11}—OH \qquad VII$$

in which R_1^{11} has the meaning given for R_1 in claim 1 with the exception of hydrogen and aromatic radicals.

9. A process as claimed in any of claims 3, 4, 5 or 8 in which R_1 has the meaning given in claim 2 and R_1^1 has the meaning given for R_1 in claim 2 with the exception of hydrogen.

10. A process for the production of piperidine derivatives of general formula I defined in claim 1, characterised by partially hydrolysing a compound of the general formula



VIII

wherein X has the meaning given in claim 1 and R_1^1 has the meaning given in claim 5, to the corresponding compound of the general formula I in which R_1 is hydrogen.

11. A process as claimed in claim 10 in which R_1^1 has the meaning given in claim 9.

12. 1 - (β - carbethoxyethyl) - 4 - phenyl-4 - carbethoxy - piperidine.

13. Process for the production of piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in Example 1.

14. Process for the production of piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in any one of Examples 2 to 4.

15. Process for the production of piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in any one of Examples 5 to 7.

16. Piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in Example 1.

17. Piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in any one of Examples 2 to 4.

18. Piperidine derivatives of the general formula I defined in claim 1, substantially as herein described in any one of Examples 5 to 7.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool, 1.
Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

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