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PATENT SPECIFICATION

942,152



NO DRAWINGS

942,152

Date of Application and filing Complete Specification: Dec. 14, 1960.
No. 43068/60.
Application made in Switzerland (No. 537) on Jan. 19, 1960.
Application made in Switzerland (No. 8807) on Aug. 3, 1960.
Application made in Switzerland (No. 10897) on Sept. 27, 1960.
Complete Specification Published: Nov. 20, 1963.
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Index at acceptance:—Class C2, C(1E4K4, 1E4K6, 1Q4, 1Q6C, 1Q8A, 1Q9F1, 1Q11D, 1Q11G, 3A13C4C, 3A13C6B, 3A13C10D, 3A13C10F).

International Classification:—C 07 d.

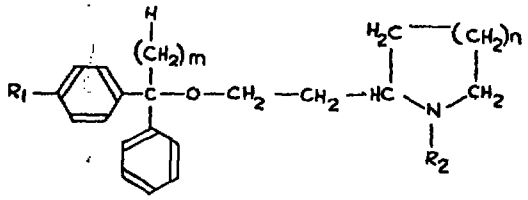
COMPLETE SPECIFICATION

Improvements in or relating to Benzhydryl Ethers

We, SANDOZ LTD., of Lichtstrasse, Basle 35, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new piperidine and pyrrolidine derivatives and their production.

The present invention provides compounds of the formula I,



I

in which

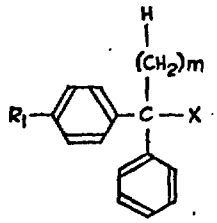
R_1 represents a hydrogen, fluorine, chlorine or bromine atom, an alkyl group containing from one to three carbon atoms inclusive, or an alkoxy group containing from one to three carbon atoms inclusive,

R_2 represents an alkyl group containing from one to four carbon atoms inclusive, with the proviso that R_1 and R_2 need not be dissimilar,

m represents 0, 1, 2 or 3, and

n represents 1 or 2, with the proviso that $m + n$ must be at least 2.

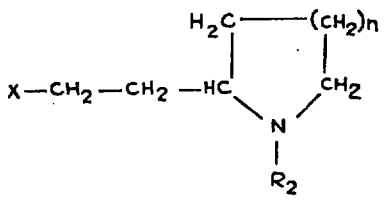
The present invention also provides a process for the production of the compounds having the general formula I above, characterised in that a diphenyl-methyl compound of the general formula II



II

[Price 4s. 6d.]

wherein R_1 and m have the above significance, is reacted with a compound of the general formula III,



III

wherein R_2 and n have the above significance, and one of the two symbols X in the formulae II and III represents the hydroxy group, and the other symbol X represents a chlorine or bromine atom; the resulting compounds may be converted to their acid addition salts.

One method of carrying out the process of the present invention may be effected as follows: 1-methyl-piperidyl-(2)-ethanol is condensed with *p*-chlorophenyl-phenyl-chloromethane in the presence of a hydrogen halide binding agent, for example anhydrous sodium carbonate, at an elevated temperature for several hours. Subsequently the reaction mixture is mixed with an inert organic solvent, for example benzene, inorganic salts are removed by filtration and the filtrate evaporated in a vacuum. Compounds of the formula I may likewise be obtained by reacting a compound of the general formula II wherein X represents a hydroxy group, with a compound of the general formula III, wherein X represents a bromine or chlorine atom, in an inert solvent, for example benzene, in the presence of sodamide. In order to complete the reaction, heating to the boil is effected for several hours and, subsequently, evaporation in a vacuum of the filtrate resulting from filtering off the inorganic salts. The end product of the general formula I is isolated from the residue by fractional distillation in a high vacuum.

The present invention also includes the acid addition salts of the compounds I. Examples of suitable acids for conversion of the compounds I into their acid addition salts are as follows:—hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic and fumaric.

The present invention also includes pharmaceutical compositions containing, in addition to an inert carrier, a compound having the general formula I and/or an acid addition salt thereof.

The compounds of the formula I above have highly interesting pharmacodynamic properties which properties are useful in the field of pharmaceuticals. The compounds illustrated hereinafter in the examples have a relatively low toxicity, a pronounced histamine inhibiting effect and a weak acetylcholine inhibiting (atropine like) effect. These properties are those required of antihistamines. An especially useful antihistaminic is N-methyl-2-[2¹-(α-methyl-*p*-chlorobenzhydryloxy)-ethyl]-pyrrolidine. The compounds of the present invention are therefore useful either as pharmaceutical compounds themselves or may be used as intermediate products for the manufacture of pharmaceuticals.

The following examples illustrate the invention without, however, limiting it; the temperatures are all stated in degrees Centigrade, and the melting and boiling points are uncorrected.

EXAMPLE 1:

N-Methyl-2-[2¹-(*p*-chloro-benzhydryloxy)-ethyl]-piperidine.

11.9 g of *p*-chlorophenyl-phenyl-chloromethane, 7.2 g of 1-methyl-piperidyl-(2)-ethanol and 5.5 g of anhydrous sodium carbonate are heated while stirring to 125° for 8 hours. Subsequently some benzene is added to the reaction mixture which has been cooled somewhat, the inorganic salts are filtered off and the filtrate is evaporated in a vacuum. The residue is distilled in a vacuum, whereby a mixture of the two isomeric N-methyl-2-(2¹-*p*-chloro-benzhydryloxy-ethyl)-piperidines distils over at 0.02 mm of Hg and at a bath temperature of 180—200° in the form of a pale yellow oil.

EXAMPLE 2:

N-methyl-2-[2¹-(benzhydryloxy)-ethyl]-piperidine.

24.7 g of benzhydryl bromide, 14.3 g of N-methyl-piperidyl-(2)-ethanol and 10.6 g of anhydrous sodium carbonate are heated to 125° for 8 hours while stirring. Subsequently about 100 cc of benzene are added to the slightly cooled reaction mixture, the resulting inorganic salts are filtered off and then the filtrate is evaporated in a vacuum. The residue is fractionally distilled in a high vacuum, whereby N-methyl-2-(2¹-benzhydryloxy-ethyl)-piperidine distils over at 162°/0.02 mm Hg. $n_D^{21.5} = 1.5538$.

The neutral naphthalene-1,5-disulphonate has a melting point of 211 to 213° after recrystallisation from methanol.

In manner analogous to that described above the following compounds are obtained from N-methyl-piperidyl-(2)-ethanol and a diphenyl-methyl halide of the formula II:

Example No.	Substance	B.p./mm of Hg refractive index	Starting Material (Formula II)
3	N-Methyl-2-[2¹-(*p*-bromobenzhydryloxy)-ethyl]-piperidine	181—183°/0.08 $n_D^{24} = 1.5733$	*p*-Bromophenyl-phenyl-chloromethane
4	N-Methyl-2-[2¹-(*p*-fluorobenzhydryloxy)-ethyl]-piperidine	149—151°/0.01 $n_D^{23} = 1.5426$	*p*-Fluorophenyl-phenyl-chloromethane
5	N-Methyl-2-[2¹-(*p*-methylbenzhydryloxy)-ethyl]-piperidine	175°/0.08 $n_D^{22.5} = 1.5506$	*p*-Methylphenyl-phenyl-bromomethane
6	N-Methyl-2-[2¹-(*p*-methoxybenzhydryl-oxy)-ethyl]-piperidine	180—181°/0.04 $n_D^{24} = 1.5548$	*p*-Methoxyphenyl-phenyl-chloromethane

EXAMPLE 7:

N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-piperidine.

19.8 g of α-methylbenzhydrol are added to a suspension of 4.7 g of powdered sodamide in 60 cc of benzene, whereby the sodium salt is formed at once with slight heating. Subsequently 16.2 g of N-methyl-piperidyl-(2)-ethyl chloride are added. The resulting solution is heated to the boil at reflux for 18 hours. Inorganic salts are filtered off and the filtrate is evaporated in a vacuum. The residue is fractionally distilled in a high vacuum, whereby N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-piperidine distils over at 143°/0.01 mm Hg; $n_D^{21} = 1.5526$.

The neutral naphthalene-1,5-disulphonate has a melting point of 167—169° after recrystallisation from ethanol.

In manner analogous to that described above the following compounds are obtained from N-methyl-piperidyl-(2)-ethyl chloride and an α-methylbenzhydrol of the formula II:

Example No.	Substance	B.p./mm of Hg refractive index	Starting Material (Formula II)
8	N-Methyl-2-[2¹-(α-methyl-*p*-chloro-benzhydryl-oxy)-ethyl]-piperidine	173°/0.03 $n_D^{20} = 1.5995$	Methyl-*p*-chloro-phenyl-phenyl-carbinol
9	N-Methyl-2-[2¹-(α-methyl-*p*-bromo-benzhydryloxy)-ethyl]-piperidine	166°/0.01 $n_D^{23} = 1.5689$	Methyl-*p*-bromo-phenyl-phenyl-carbinol
10	N-Methyl-2-[2¹-(α-methyl-*p*-methyl-benzhy-dryloxy)-ethyl]-piperidine	150—152°/0.01 $n_D^{22} = 1.5490$	Methyl-*p*-tolyl-phenyl-carbinol

EXAMPLE 11:

N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-pyrrolidine.

9.9 g of α-methylbenzhydrol are added to a suspension of 2.3 g of powdered sodamide in 30 cc of benzene. Subsequently 7.4 g of N-methyl-pyrrolidyl-(2)-ethyl chloride are added and the solution is heated to the boil at reflux for 20 hours. Then shaking is first effected with water and then four times each time with 25 cc of 2N hydrochloric acid. The acid extracts are made alkaline with potassium hydroxide solution while cooling strongly, and the precipitated oil is extracted with ether. After drying of the ethereal solution over potassium carbonate, the solvent is evaporated and the residue is fractionally distilled in a high vacuum, whereby N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-pyrrolidine distils over at 143°/0.02 mm Hg. $n_D^{22} = 1.5510$.

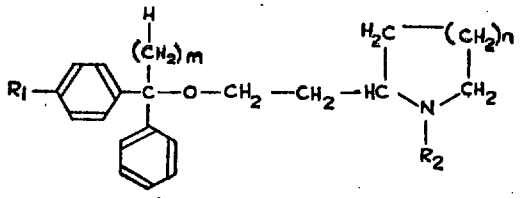
The neutral naphthalene-1,5-disulphonate melts at 175 to 176° (decomposition) after crystallisation from ethanol.

In manner analogous to that described above the following compounds are obtained from N-methyl-pyrrolidyl-(2)-ethyl chloride and a diphenyl carbinol of the general formula II:

Example No.	Substance	B.p./mm of Hg refractive index	Starting Material (Formula II)
12	N-Methyl-2-[2¹-(α-methyl-*p*-chloro-benzhydryloxy)-ethyl]-pyrrolidine	154°/0.02 $n_D^{22} = 1.5582$	Methyl-*p*-chloro-phenyl-phenyl-carbinol
13	N-Methyl-2-[2¹-(α-methyl-*p*-bromo-benzhydryloxy)-ethyl]-pyrrolidine	162°/0.02 $n_D^{22} = 1.5698$	Methyl-*p*-bromo-phenyl-phenyl-carbinol
14	N-Methyl-2-[2¹-(α-methyl-*p*-methyl-benzhydryloxy)-ethyl]-pyrrolidine	152°/0.02 $n_D^{22} = 1.5480$	Methyl-*p*-tolyl phenylcarbinol

WHAT WE CLAIM IS:—

1. A process for the production of compounds of the formula I and their acid addition salts,



I

in which

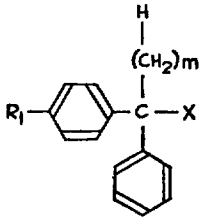
R_1 represents a hydrogen, fluorine, chlorine or bromine atom, an alkyl group containing from one to three carbon atoms inclusive, or an alkoxy group containing from one to three carbon atoms inclusive,

R_2 represents an alkyl group containing from one to four carbon atoms inclusive, with the proviso that R_1 and R_2 need not be dissimilar,

m represents 0, 1, 2 or 3, and

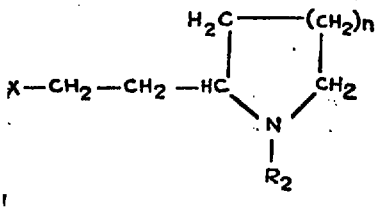
n represents 1 or 2, with the proviso that $m + n$ must be at least 2,

characterized in that a diphenyl-methyl compound of the general formula II,



II

wherein R_1 and m have the above significance, is reacted with a compound of the general formula III,



III

wherein R_2 and n have the above significance, and one of the two symbols X in the formula II and III represents the hydroxy group, and the other symbol X represents a chlorine or bromine atom, the resulting product being salified with an organic or inorganic acid when it is desired to produce an acid addition salt.

2. A process for the production of the compounds having the general formula I stated in claim 1 and their acid addition salts substantially as herein described with reference to any one of the Examples.

3. Compounds having the general formula I stated in claim 1 and their acid addition salts whenever produced by the process claimed in either one of the two preceding claims.

4. The compounds having the general formula I stated in claim 1 and their acid addition salts.

5. N-methyl-2-[2¹-(*p*-chloro-benzhydryloxy)-ethyl]-piperidine.

6. N-methyl-2-[2¹-(benzyhydryloxy)-ethyl]-piperidine.

7. N-methyl-2-[2¹-(*p*-bromo-benzhydryloxy)-ethyl]-piperidine.

8. N-methyl-2-[2¹-(*p*-fluoro-benzhydryloxy)-ethyl]-piperidine.

9. N-methyl-2-[2¹-(*p*-methyl-benzhydryloxy)-ethyl]-piperidine.

10. N-methyl-2-[2¹-(*p*-methoxy-benzhydryloxy)-ethyl]-piperidine.

* C L M S *

11. N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-piperidine.
12. N-methyl-2-[2¹-(α-methyl-*p*-chloro-benzhydryloxy)-ethyl]-piperidine.
13. N-methyl-2-[2¹-(α-methyl-*p*-bromo-benzhydryloxy)-ethyl]-piperidine.
14. N-methyl-2-[2¹-(α-methyl-*p*-methyl-benzhydryloxy)-ethyl]-piperidine.
15. N-methyl-2-[2¹-(α-methyl-benzhydryloxy)-ethyl]-pyrrolidine.
16. N-methyl-2-[2¹-(α-methyl-*p*-chloro-benzhydryloxy)-ethyl]-pyrrolidine.
17. N-methyl-2-[2¹-(α-methyl-*p*-bromo-benzhydryloxy)-ethyl]-pyrrolidine.
18. N-methyl-2-[2¹-(α-methyl-*p*-methyl-benzhydryloxy)-ethyl]-pyrrolidine.
19. The acid addition salts of the compounds claimed in any one of claims 5 to 18.
20. Pharmaceutical compositions containing in addition to an inert carrier, a compound claimed in any one of claims 3 to 19.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1963. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

SPECIFICATION NO. 942,152

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British Company.

THE PATENT OFFICE D 84345/1(5)/R.109 200 12/63 PL

