

PATENT SPECIFICATION

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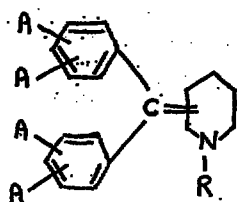


(54) PIPERIDINE DERIVATIVES

(71) We, UCB (UNION CHIMIQUE-
 CHEMISCHE BEDRIJVEN) SOCIÉTÉ ANONYME,
 of 4, Chaussée de Charleroi, Saint-Gilles-les-
 Bruxelles, Belgium, a Body Corporate
 organised under the laws of Belgium, do here-
 by 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 is concerned with new
 piperidine derivatives and with the preparation
 thereof. It is also concerned with compositions
 containing the new piperidine derivatives and
 with the therapeutic use thereof.

The new piperidine derivatives according to
 the present invention are diphenyl-methylene-
 piperidines of the general formula:—



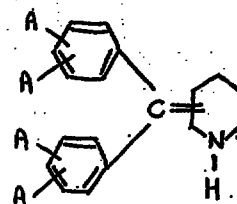
(I)

wherein A is a hydrogen or halogen atom or
 a cyano group or a halomethyl, alkyl or alkoxy
 radical and R is a hydroxyalkyl, hydroxy-
 alkoxyalkyl or hydroxyalkoxyalkoxyalkyl radi-
 cal, the alkyl and alkoxy groups of which are
 straight or branched chained and contain up
 to 4 carbon atoms; and the addition salts
 thereof with pharmaceutically acceptable acids.

The new compounds according to the pre-
 sent invention can be prepared by one of the
 following methods:

a) condensation of a diphenyl-methylene-
 piperidine of the general formula:

[Price 25p]



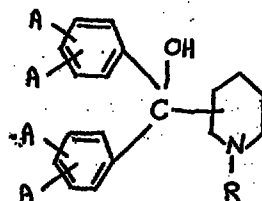
(II)

in which A has the same meaning as
 above, with a compound of the general
 formula:



in which R has the same meaning as above
 and Z is a reactive atom or group which is
 capable of reacting with the hydrogen atom
 on the nitrogen atom of the piperidine,
 Z preferably being a halogen atom;

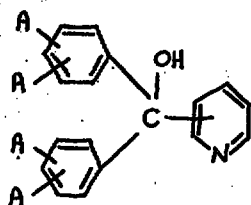
b) submitting an α,α -diphenyl-N-R-piperidine
 methanol of the general formula:



(IV)

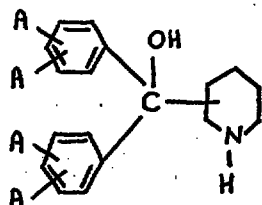
in which A and R have the same meanings
 as above, to the action of a dehydration
 agent, such as anhydrous hydrogen chloride
 in alcoholic solution.

The intermediates of general formula (II) can be prepared by the reduction of an α, α -diphenyl-pyridine-methanol of the general formula:



(V)

in which A has the same meaning as above, to give the corresponding α, α -diphenyl-piperidine-methanol of the general formula:



(VI)

in which A has the same meaning as above, followed by dehydration to give the desired intermediate of general formula (II).

The intermediates of general formula (IV) can be obtained by the condensation of an α, α -diphenyl-piperidine-methanol of the above-given general formula (VI) with a compound of the above-given general formula (III).

The new compounds (I) according to the present invention, either in the form of the free bases or in the form of addition salts with pharmaceutically acceptable inorganic and organic acids, are very strong pharmacological agents which act upon the cardiovascular,

Analysis:

70	$C_{22}H_{26}ClNO_2.HCl$			
	calc.:	total Cl	17.36%	Cl ⁻ 8.68% N 3.43%
	found:		17.38%	8.64% 3.38%

This compound is prepared from 4 - (*p*-chlorodiphenyl - methylene) - piperidine (m.p. 72—73°C.) which, in turn, is prepared by the dehydration of 4 - (α - *p* - chlorophenyl - α - phenyl) - piperidine - methanol, which is a known substance.

Analysis:

85	$C_{22}H_{26}ClNO_2.HCl$			
	calc.:	total Cl	17.36%	Cl ⁻ 8.68% N 3.43%
	found:		17.77%	8.88% 3.48%

pulmonary and central nervous system and can also be used as anti-histaminics and as anti-serotoninics.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1.

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine.

A mixture of 28 g. 4 - (diphenyl - methylene) - piperidine and 25 g. 2 - (2 - chloroethoxy) - ethanol in 60 ml. xylene is heated for 8 hours at 120°C. in the presence of 17.5 g. anhydrous sodium carbonate.

After cooling, the reaction mixture is filtered and the filtrate is subsequently extracted with dilute hydrochloric acid (20 ml. concentrated hydrochloric acid and 70 ml. water). The acidic solution is separated, rendered alkaline with a concentrated solution of sodium hydroxide (about 35 ml. of 40% solution) and the base thus liberated is extracted with benzene. The benzene extract is washed with water and then dried over anhydrous sodium sulphate. The solution is then evaporated to dryness under reduced pressure.

The residue is dissolved in isopropanol and then converted into the hydrochloride. There is thus obtained 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine, which melts at 221—222°C., with decomposition.

Analysis:

$C_{22}H_{27}NO_2.HCl$			
calc.:	Cl ⁻	9.48%	N 3.74%
found:		9.58%	3.72%

The following piperidine derivatives are prepared in an analogous manner:

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - chlorodiphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 209—210°C.

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - chlorodiphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, has a melting point of 219—220°C.

- This compound is prepared from 4 - (*m* - chlorodiphenyl - methylene) - piperidine (m.p. 82—83°C.), which, in turn, is prepared from 4 - (α - *m* - chlorophenyl - α - phenyl) - piperidine - methanol (m.p. 132—133°C.), this being obtained by the reduction of 4 - (α - *m* - chlorophenyl - α - phenyl) - pyridine - methanol (m.p. 180—181°C.).
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*o* - chlorodiphenyl - methylene) - piperidine. 10
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 243—244°C.

15 *Analysis:*

$C_{22}H_{26}ClNO_2 \cdot HCl$				
calc.:	total Cl	17.36%	Cl ⁻ 8.68%	N 3.43%
found:		17.60%	8.87%	3.57%

- This compound is prepared from 4 - (*o* - chlorodiphenyl - methylene) - piperidine (b.p. 132—134°C./0.001 mm.Hg.) which, in turn, is prepared by the dehydration of 4 - (α - *o* - chlorophenyl - α - phenyl) - piperidine - methanol (m.p. 147—149°C.), obtained by the reduction of 4 - (α - *o* - chlorophenyl - α - phenyl) - pyridine - methanol (m.p. 202—203°C.).
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - trifluoromethyl - diphenyl - methylene) - piperidine. 30
- The corresponding hydrochloride, after recrystallisation from isopropanol, has a melting point of 200—201°C.

35 *Analysis:*

$C_{23}H_{28}F_3NO_2 \cdot HCl$				
calc.:	Cl ⁻ 8.02%	F 12.89%	N 3.16%	
found:	8.55%	12.80%	3.18%	

- This compound is prepared from 4 - (*m* - trifluoromethyl - diphenyl - methylene) - piperidine (b.p. 113—115°C./0.001 mm.Hg.; m.p. of the hydrochloride 191—192°C.) which is synthesised by the dehydration of 4 - (α - (*m* - trifluoromethyl - phenyl - α - phenyl) - piperidine - methanol (m.p. of the hydrochloride 244—245°C.), this, in turn, being obtained by the reduction of 4 - (α - *m* - tri-
- fluoromethyl - phenyl - α - phenyl) - pyridine - methanol (m.p. 152—153°C.).
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - fluorodiphenyl - methylene) - piperidine. 50
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 192—193°C.

55 *Analysis:*

$C_{22}H_{26}FNO_2 \cdot HCl$				
calc.:	Cl ⁻ 9.04%	F 4.84%	N 3.57%	
found:	9.02%	4.82%	3.66%	

- This compound is prepared from 4 - (*p* - fluorodiphenyl - methylene) - piperidine (m.p. 84—85°C.) which, in turn, is prepared by the dehydration of 4 - (α - *p* - fluorophenyl - α - phenyl) - piperidine - methanol (m.p. 145—146°C.), obtained by the reduction of 4 - (α - fluorophenyl - α - phenyl) - pyridine - methanol (m.p. 195—196°C.), which is either prepared from 4 - benzoyl - pyridine and *p* - fluorophenyl magnesium bromide or from 4 - (*p* - fluorobenzoyl) - pyridine (m.p. 84—85°C.; b.p. 170—172°C./12 mm.Hg.) and phenyl magnesium bromide.
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - methyl - diphenyl - methylene) - piperidine. 75
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 213—214°C.
- Analysis:*

$C_{23}H_{29}NO_2 \cdot HCl$				
calc.:	Cl ⁻ 9.14%	N 3.61%		
found:	9.26%	3.56%		

This compound is prepared from 4 - (*p* - methyl - diphenyl - methylene) - piperidine (m.p. 64—65°C.) which, in turn, is prepared

- by the dehydration of 4 - (α - *p* - methylphenyl - α - phenyl) - piperidine - methanol (m.p. 140—141°C.), obtained by the reduction of 4 - (α - *p* - methylphenyl - α - phenyl) - pyridine - methanol (m.p. 195—196°C.).
- 5 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - methyl - diphenyl - methylene) - piperidine.
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 217—219°C.
- 10 *Analysis:*
 $C_{23}H_{29}NO_2.HCl$
 calc.: Cl 9.14% N 3.61%
 found: 9.16% 3.62%
- This compound is prepared from 4 - (*m* - methyl - diphenyl - methylene) - piperidine (m.p. 77—78°C.) which is, in turn, obtained by the dehydration of 4 - (α - *m* - methylphenyl - α - phenyl) - piperidine - methanol (m.p. 117—118°C.), prepared by the reduction of 4 - (α - *m* - methylphenyl - α - phenyl) - pyridine - methanol (m.p. 178—179°C.).
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - (diphenyl - methylene) - piperidine. 25
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 180—181°C.
- Analysis:*
 $C_{22}H_{27}NO_2.HCl$
 calc.: Cl⁻ 9.48% N 3.74%
 found: 9.65% 3.73%
- This compound is prepared from 3 - (diphenyl - methylene) - piperidine (m.p. 87—88°C.) which, in turn, is prepared from 3 - α,α - diphenyl - piperidine - methanol.
- 30
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (4 - chloro - 4' - fluorodiphenyl - methylene) - piperidine.
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 204—205°C.
- 40
- Analysis:*
 $C_{22}H_{25}ClFNO_2.HCl$
 calc.: total Cl 16.62% Cl⁻ 8.31% F 4.45% N 3.28%
 found: 16.70% 8.38% 4.60% 3.31%
- This compound is prepared from 4 - (4 - chloro - 4' - fluorodiphenyl - methylene) - piperidine (m.p. 103—104°C.) which, in turn, is obtained by the dehydration of 4 - (α - 4 - chlorophenyl - α - 4' - fluorophenyl) - piperidine - methanol (m.p. 144—145°C.), prepared by the reduction of 4 - (α - 4 - chlorophenyl - α - 4' - fluorophenyl) - pyridine - methanol (m.p. 182—183°C.).
- 55
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - trifluoromethyl - diphenyl - methylene) - piperidine.
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 202—203°C.
- 60
- Analysis:*
 $C_{23}H_{26}F_3NO_2.HCl$
 calc.: Cl⁻ 8.02% F 12.89% N 3.13%
 found: 8.16% 12.90% 3.19%
- This compound is prepared from 4 - (*p* - trifluoromethyl - diphenyl - methylene) - piperidine (b.p. 107—109°C./0.001 mm.Hg.) which, in turn is prepared by the dehydration of 4 - α - *p* - trifluoromethyl - phenyl - α - phenyl - piperidine - methanol (m.p. 167—169°C. after recrystallisation from isopropanol), obtained by the reduction of 4 - α - *p* - trifluoromethyl - phenyl - α - phenyl - pyridine - methanol (m.p. 157—158°C. after recrystallisation from isopropanol).
- 70
- 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - *t* - butyl - diphenyl - methylene) - piperidine.
- The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 203—204°C.
- 80
- Intermediate compounds:*
 4 - *p* - *t* - butyl - diphenyl - methylene - piperidine (m.p. 95—97°C., after recrystallisation from petroleum ether (b.p. 40—60°C.))
 4 - α - *p* - *t* - butyl - phenyl - α - phenyl - piperidine - methanol (m.p. 90—92°C., after recrystallisation from petroleum ether (b.p. 40—60°C.))
 4 - α - *p* - *t* - butyl - phenyl - α - phenyl - pyridine - methanol (m.p. 188—189°C., after recrystallisation from benzene).
- 90
- 95

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 -
(3,4 - dimethyl - diphenyl - methylene) -
piperidine.

The corresponding hydrochloride, after re-
crystallisation from isopropanol, melts at
219—220°C.

Analysis:

$C_{24}H_{31}NO_2 \cdot HCl$
calc.: Cl⁻ 8.82% N 3.48%
found: 8.90% 3.36%

Intermediate products:

4 - (3,4 - dimethyl - diphenyl - methylene) -
piperidine (m.p. 96—98°C., after re-
crystallisation from petroleum ether (b.p.
40—60°C.))

4 - α - (3,4 - dimethylphenyl) - α - phenyl -
piperidine - methanol (m.p. of the corres-
ponding hydrochloride, after recrystallisa-
tion from isopropanol, 223—224°C.)

4 - α - (3,4 - dimethyl - phenyl) - α - phenyl -
pyridine - methanol (m.p. 161—162°C.,
after recrystallisation from ethanol)

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 -
(*p* - methoxy - diphenyl - methylene) - piperi-
dine.

The corresponding hydrochloride, after re-
crystallisation from isopropanol, melts at
207—208°C.

Analysis:

$C_{23}H_{29}NO_3 \cdot HCl$
calc.: Cl⁻ 8.77% N 3.46%
found: 8.87% 3.48%

Intermediate products:

4 - *p* - methoxy - diphenyl - methylene -
piperidine (m.p. 89—90°C., after recrystal-
lisation from petroleum ether (b.p. 40—
60°C.))

4 - α - *p* - methoxyphenyl - α - phenyl -
piperidine - methanol (which is a known
compound).

Analysis:

$C_{24}H_{30}FNO_3 \cdot HCl$
calc.: Cl⁻ 8.13%
found: 8.07%

1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] -
ethyl } - 4 - (*p* - trifluoromethyl - diphenyl -
methylene) - piperidine.

Analysis:

$C_{25}H_{30}F_3NO_3 \cdot HCl$
calc.: Cl⁻ 7.29%
found: 7.33%

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 -
(*o* - methoxy - diphenyl - methylene) - piperi-
dine.

The corresponding hydrochloride, after re-
crystallisation from isopropanol, melts at
205—206°C.

Analysis:

$C_{23}H_{29}NO_3 \cdot HCl$
calc.: Cl⁻ 8.77% N 3.46%
found: 8.80% 3.60%

Intermediate products:

4 - *o* - methoxy - diphenyl - methylene -
piperidine (b.p. 128—130°C./0.001 mm.
Hg.)

4 - α - *o* - methoxyphenyl - α - phenyl -
piperidine - methanol (m.p. 104—105°C.,
after recrystallisation from petroleum ether
(b.p. 40—60°C.))

4 - α - *o* - methoxyphenyl - α - phenyl -
pyridine - methanol (m.p. 132—133°C.,
after recrystallisation from isopropanol.

1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] -
ethyl } - 4 - (diphenyl - methylene) - piperi-
dine.

The corresponding hydrochloride, after re-
crystallisation from isopropanol, melts at
144—145°C.

Analysis:

$C_{24}H_{31}NO_3 \cdot HCl$
calc.: Cl⁻ 8.48% N 3.35%
found: 8.49% 3.33%

1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] -
ethyl } - 4 - (*p* - fluorodiphenyl - methylene) -
piperidine.

The corresponding hydrochloride, after re-
crystallisation from ethyl-acetate, melts at
130—132°C.

The corresponding hydrochloride, after re-
crystallisation from isopropanol, melts at
120—121°C.

$C_{25}H_{30}F_3NO_3 \cdot HCl$
calc.: Cl⁻ 7.29%
found: 7.33%

1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl } - 4 - (m - trifluoromethyl - diphenyl - methylene) - piperidine.

5 The corresponding fumarate, after recrystallisation from isopropanol, melts at 135—136°C.

Analysis:

$C_{28}H_{20}F_3NO_8 \cdot C_4H_4O_4$
calc.: F 10.07% N 2.47%
found: 10.14% 2.49%

10

1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl } - 4 - (p - chlorodiphenyl - methylene) - piperidine.

15 The corresponding fumarate, after recrystallisation from isopropanol, melts at 102—103°C.

Analysis:

$C_{24}H_{20}ClNO_8 \cdot C_4H_4O_4$
calc.: Cl 6.66% N 2.63%
found: 6.30% 2.59%

20

1 - (2,3 - dihydroxypropyl) - 4 - (diphenyl - methylene) - piperidine.

Analysis:

45

$C_{20}H_{22}ClNO \cdot HCl$
calc.: Cl⁻ 9.73% total Cl 19.46% N 3.84%
found: 9.92% 19.83% 3.85%

1 - (2 - hydroxyethyl) - 4 - (p - fluorodiphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 211—212°C.

Analysis:

$C_{21}H_{25}NO_2 \cdot HCl$
calc.: Cl⁻ 9.85% N 3.89%
found: 9.74% 3.86%

1 - (2 - hydroxyethyl) - 4 - (diphenyl - methylene) - piperidine. 30

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 229—230°C.

Analysis:

calc.: Cl⁻ 10.74% N 4.24%
found: 10.26% 4.26%

35

1 - (2 - hydroxyethyl) - 4 - (p - chlorodiphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 185—186°C.

40

Analysis:

55

$C_{20}H_{22}FNO \cdot HCl$
calc.: Cl⁻ 10.19% F 5.46% N 4.27%
found: 10.48% 5.42% 3.99%

1 - (2 - hydroxyethyl) - 4 - (p - methoxy - diphenyl - methylene) - piperidine.

60 The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 190—191°C.

Analysis:

$C_{21}H_{25}NO_2 \cdot HCl$
calc.: Cl⁻ 9.85% N 3.89%
found: 10.20% 3.80%

1 - (3 - hydroxypropyl) - 4 - (diphenyl - methylene) - piperidine. 75

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 190—191°C.

Analysis:

$C_{21}H_{27}NO \cdot HCl$
calc.: Cl⁻ 10.31% N 4.07%
found: 10.48% 4.01%

80

65 1 - (2 - hydroxyethyl) - 4 - (m - methyl - diphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 201—202°C.

70

Analysis:

$C_{21}H_{25}NO \cdot HCl$
calc.: Cl⁻ 10.31% N 4.07%
found: 10.34% 4.02%

1 - (4 - hydroxybutyl) - 4 - (diphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 185—186°C.

85

Analysis:

$C_{22}H_{27}NO \cdot HCl$
calc.: Cl⁻ 9.90% N 3.91%
found: 9.86% 3.91%

90

1 - (2 - hydroxyethyl) - 3 - (diphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 164—165°C.

Analysis:



calc.: Cl⁻ 10.74% N 4.24%
found: 11.1% 4.22%

10 1 - (3 - hydroxypropyl) - 3 - (diphenyl - methylene) - piperidine.

The corresponding hydrochloride, after recrystallisation from isopropanol, melts at 176—177°C.

Analysis:



calc.: Cl⁻ 10.31% N 4.07%
found: 10.26% 4.02%

20 1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl } - 4 - (4 - chlorodiphenyl - methylene) - piperidine.

The corresponding fumarate, after recrystallisation from isopropanol, melts at 102—103°C.

Analysis:



calc.: Cl 6.66% N 2.63%
found: 5.52% 2.59%

30 1 - { 2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl } - 4 - (3 - trifluoromethyl - diphenyl - methylene) - piperidine.

The corresponding fumarate, after recrystallisation from isopropanol, melts at 135—136°C.

Analysis:



calc.: F 10.07% N 2.47%
found: 10.14% 2.47%

EXAMPLE 2.

40 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine.

The preparation of this compound has already been described in Example 1. It can also be prepared by the dehydration of 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (α,α - diphenyl) - piperidine - methanol in the following manner:

A solution of 5 g. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (α,α - diphenyl) - piperidine - methanol hydrochloride in 500 ml. ethanol is saturated in the cold with gaseous hydrogen chloride. After leaving to stand overnight, the reaction mixture is boiled under reflux for 20 minutes.

55 The reaction mixture is then evaporated to dryness and the residue recrystallised from isopropanol. The product obtained has a melting point of 221—222°C.

Analysis:



calc.: Cl⁻ 9.48% N 3.74%
found: 9.48% 3.78%

The 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (α,α - diphenyl) - piperidine - methanol, which is here used as starting material, is prepared from 4 - (α,α - diphenyl) - piperidine - methanol and 2 - (2 - chloroethoxy) - ethanol in the manner described in Example 1 for the condensation of the same chlorohydrin with 4 - (diphenyl - methylene) - piperidine. After recrystallisation from isopropanol, the corresponding hydrochloride has a melting point of 229—230°C.

The following compounds have been prepared by the same method:

1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - (diphenyl - methylene) - piperidine.

(The preparation of this compound by the first method has already been described in Example 1).

4 g. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - α,α - diphenyl - piperidine - methanol hydrochloride are dissolved in 100 ml. ethanol. The solution is saturated in the cold with gaseous hydrogen chloride and then boiled under reflux for about 4 hours. The residue obtained after evaporation under vacuum on a water-bath, is crystallised from isopropanol.

The corresponding hydrochloride of the product obtained melts at 180—181°C. (no depression of m.p. when this compound is mixed with the one obtained by the first method).

Analysis:



calc.: Cl⁻ 9.48% N 3.74%
found: 10.09% 3.77%

The 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - α,α - diphenyl - piperidine - methanol used as starting material was prepared from 3 - α,α - diphenyl - piperidine - methanol and 2 - (2 - chloroethoxy) - ethanol in the manner described in Example 1 for the condensation of the same chlorohydrin with 4 - diphenyl - methylene - piperidine.

After recrystallisation from isopropanol, the corresponding hydrochloride of the product obtained melts at 147—148°C.

Analysis:



calc.: Cl⁻ 9.04% N 3.57%
found: 9.11% 3.49%

1 - (2 - hydroxyethyl) - 2 - (diphenyl - methylene) - piperidine.

A solution of 10 g. 1 - (2 - hydroxyethyl) - 2 - α,α - diphenyl - piperidine - methanol hydrobromide in 100 ml. concentrated hydrobromic acid is heated for 4 hours at 100°C.

The reaction mixture is cooled in an ice-salt mixture and the supernatant solution is decanted off. The residue is twice evaporated to dryness under vacuum on a water-bath, while adding each time 50 ml. isopropanol. The residue is finally crystallised from acetone. The corresponding hydrobromide of the product obtained melts at 283—284°C.

Analysis:

10	$C_{20}H_{23}NO.HBr$
	calc.: Br ⁻ 21.34% N 3.74%
	found: 21.92% 3.70%

The 1 - (2 - hydroxyethyl) - 2 - α,α - diphenyl - piperidine - methanol used as starting material is prepared as follows:

A mixture of 20 g. 2 - α,α - diphenyl - piperidine - methanol, 30 g. ethylene bromohydrin and 12 g. anhydrous sodium carbonate is heated for 6 hours at 90—95°C. After cooling, 40 ml. benzene are added and the suspension is filtered off and washed with benzene and then with water and is thereafter dried. The corresponding hydrobromide of the product obtained melts at 224—225°C.

Analysis:

25	$C_{20}H_{25}NO_2.HBr$
	calc.: Br ⁻ 20.37% N 3.57%
	found: 19.76% 3.56%

EXAMPLE 3.

30 *Pharmacologic Tests.*

In these tests, use was made of the following compounds according to the present invention:

- 35 compound I: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine.
 compound II: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - chlorodiphenyl - methylene) - piperidine.
 40 compound III: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - chlorodiphenyl - methylene) - piperidine.
 compound IV: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*o* - chlorodiphenyl - methylene) - piperidine.
 45 compound V: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - fluorodiphenyl - methylene) - piperidine.
 compound VI: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - methylidiphenyl - methylene) - piperidine.
 50 compound VII: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - methylidiphenyl - methylene) - piperidine.
 55 compound VIII: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - methoxy - diphenyl - methylene) - piperidine.

compound IX: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*o* - methoxydiphenyl - methylene) - piperidine. 60

compound X: 1 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl - 4 - (diphenyl - methylene) - piperidine.

compound XI: 1 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl - 4 - (*p* - fluorodiphenyl - methylene) - piperidine. 65

compound XII: 1 - (2 - hydroxyethyl) - 4 - (diphenyl - methylene) - piperidine.

compound XIII: 1 - (2 - hydroxyethyl) - 4 - (*p* - fluorodiphenyl - methylene) - piperidine. 70

compound XIV: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*m* - trifluoromethyl - diphenyl - methylene) - piperidine.

compound XV: 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - chloro - *p'* - fluorodiphenyl - methylene) - piperidine. 75

Bronchodilating effects

1. *In bronchitic dogs.*

Method: The dogs are rendered bronchitic by exposure to sulphur dioxide (c.f. J. Lulling, J. Prignot, P. Lievens, Arch. Pharmak. u. exp. Path. 261, 1—25/1968). In these animals, the viscous resistance (R) of the respiratory tract is particularly high. 80

Results: A very distinct decrease of the resistance (R), exceeding 50%, is obtained after administration of compound I (2 mg./kg. intravenously) or compound X (0.1 mg./kg. intravenously or 1 mg./kg. per os). 85

A less important decrease (30%) was found after administration of compounds XI and XII (0.32 mg./kg. intravenously). 90

A similar effect is obtained after intravenous administration of theophylline at a dosage of 4 mg./kg. 95

2. *In guinea-pigs.*

Method: A variant of the Konzett-Rossler method (cfr. H. Konzett and R. Rossler, Arch. exp. Path. Pharmacol. 195, 71—74/1940) is used. The anaesthetized and curarized guinea-pig is subjected to artificial respiration. The endotracheal pressure is recorded. Repeated bronchial spasms are induced by successive intravenous injections of acetylcholine, histamine or serotonin. The 50% efficacious dose (ED 50) which inhibits these spasms is calculated. 100

Results: The ED 50 towards the various induced bronchospasms are given in the following Table. 105

These compounds prove to have a moderate anti-bronchoconstricting effect towards acetylcholine and considerable antagonistic effects towards histaminic and, particularly, serotoninic bronchospasms. 110 115

Compound	ED 50 (in mg./kg.)		
	Serotonin	Acetylcholine	Histamine
I	0.0075	1.5	0.030
II	0.065	9	0.1
IV	0.048	2.1	0.17
V	0.01	8.5	0.065
VI	0.003	9	0.1
VII	0.0045	4.5	0.1
VIII	0.013	7.8	0.043
IX	0.004	2.45	0.23
X	0.007	0.65	0.07
XI	0.01	1.6	0.076
XII	0.039	3.6	0.11
XIII	0.018	5.2	0.007
XIV	0.0045	8	0.55
Theophylline	3.5	7	3.5

Antihistaminic activity

5 The antihistaminic activity of these substances has been studied in guinea-pigs by the Bovert and Staub method (C. R. Soc. Biol. 124, 547/1937) as modified by S. Levis et al. (Arch. Intern. Pharmacod. 109, 128/1957). This test consists in determining the number of toxic doses of intravenously injected histamine which are neutralised by the previous administration of an antihistaminic agent. The extent and the duration of this activity are evaluated.

The compound to be tested are administered intravenously (2.5 mg./kg.) or orally (2.5 mg./kg., per catheter).

In the control animals, the minimum dose of intravenously administered histamine hydrochloride which kills 100% of guinea-pigs of 300 to 400 g. body weight, varies between 0.4 and 0.5 mg./kg.

The results are given in the following Table:

Compound	No. of toxic doses of histamine neutralised			
	after 1 hour		after 4 hours	
	intravenously	orally	intravenously	orally
I	600			
II	600	600		
III	1200	1000		
V	1200	1000		
X	800		1000	
XI	1000			
XV	600	600	400	600

The activity of compound XV, after 24 hours, is still 400 (when administered intravenously) and 600 (when administered orally).

5 *Circulatory effects "in vivo"*

Method: In anaesthetized dogs, subjected to artificial respiration, the haemodynamic effects are studied under the experimental conditions described by Wellens and Wauters (Arch. int. Pharmacodyn. 171, 246—250/1968). The cardiac, musculo-cutaneous and cerebral outputs are measured by means of peri-arterial probes placed around the aorta and the femoral and vertebral arteries, respectively.

Results: The musculo-cutaneous peripheric output is considerably stimulated by most of the tested compounds. A significant increase (more than 20%, during more than 20 minutes) is observed after intravenous administration of 1 mg./kg. of compounds I and V and of 2 mg./kg. of compounds II, VI, X, XI, XII and XIV. In certain cases, the increase in femoral output is very significant (50 to 100%) and may last for more than 1 or 2 hours. Such effects are observed after administration of compound V (0.1 to 2 mg./kg. intravenously or 2 to 10 mg./kg. intraduodenally).

30 Because of its physiological regulation, the cerebral output cannot be subjected to variations which are as significant as those observed in the musculo-cutaneous circulation.

A moderate but significant increase in cerebral output is produced by several of the tested compounds, particularly by compound V (1 mg./kg. intravenously) and compound XII (2 mg./kg. intravenously).

The vasodilating effects on femoral and cerebral circulation are relatively specific, in the sense that they are accompanied by a much lesser or even nil stimulation of the cardiac output.

In the same experimental conditions, theophylline does not appreciably increase the femoral output; on the other hand, it produces a high increase of cerebral output but only at the intravenous dose of 20 mg./kg. This latter effect is accompanied by an important acceleration of cardiac rhythm.

Conclusion:

The tested compounds according to the present invention have a beneficial effect upon the blood supply in the musculo-cutaneous and cerebral regions.

Coronary-dilating effect as measured by the Langendorff method

Method: The isolated rabbit heart is fibrillated by electric stimulation. The coronary region is perfused by cannulation of the aorta. The perfusion pressure is constant and the output of the perfusion liquid (Tyrode solution) is measured.

Results: These are given in the following Table:

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Compound	Concentration µg./ml.	Increase of output in %	Number of animals
I	1	37	12
	2	65	12
	5	134	12
	20	148	12
II	5	113	12
	20	145	12
III	5	103	12
IV	5	81	12
V	1	24	12
	2	55	12
	5	142	12
	20	116	12
VI	5	119	9
VII	5	121	9
	20	172	12
X	5	75	12
	20	153	12
Theophylline	20	31	12
	50	39	12
	100	76	12
	200	147	12

Conclusion:

In this test, the various compounds have a very significant coronary-dilating effect, which is far greater than that of theophylline.

Effects on the central nervous system

The activity of the compounds according to the present invention on the central nervous system has been determined by means of the following tests:

Potentiation of pentobarbital: P. Janssen, C. Van de Westeringh, A. Jaguenau, P. Demoen, B. Hermans, G. Van Daele, K. Schellekens,

C. van der Eycken, C. Niemegeers, J. Med. Pharm. Chem. 1, 281—297/1959.

Rotating rod: N. W. Dunham, T. S. Miya, J. Am. Pharm. Assoc. 46, 208—209/1957.

Behaviour (exciting or sedative): S. Irwin, Gordon Research Conference on Medicinal Chemistry, Aug. 1959, 3—7, Colby Junior College, New London).

Electro-encephalogram (abbreviated EEG): S. Giurgea and Moeyersoons, Med. Exp. 8, 66/1963.

The results obtained by these tests are summarised in the following Table:



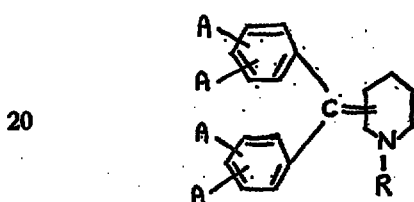
Compound	Potentiation of pentobarbital	Rotating rod	Behaviour		EEG
			exc.	sed.	
I	M O 14	R P 31	+	+	sedative
II	M O 44	R P 13.5	+		sedative
IV	M O 14	R P 33	+		
V	M O 7	R P 21	+	+	active
VIII	M O 5	R P 16	+	+	
X	M O 9		+	+	
XV	M O 16.5	R P 10.5	+	+	

Signification of the letters and numerical values: M = mouse; O = oral administration; R = rat; P = parenteral administration; the numerical values are expressed in mg./kg. animal body weight; the smaller the numerical value, the greater the activity of the tested compound.

Whether in the form of free bases or of salts of inorganic or organic pharmaceutically acceptable acids, the compounds according to the present invention may be administered orally, rectally or parenterally in unit doses of 10 to 60 mg. and, in accordance with the mode of administration, in admixture with solid or liquid pharmaceutical excipients.

WHAT WE CLAIM IS:—

1. Diphenyl-methylene-piperidines of the general formula:



wherein A is a hydrogen or halogen atom or a cyano group or a halomethyl, alkyl or alkoxy radical and

R is a hydroxyalkyl, hydroxyalkoxyalkyl or hydroxyalkoxyalkoxyalkyl radical, each alkyl and alkoxy radical containing up to 4 carbon atoms;

or the addition salts thereof with pharmaceutically acceptable acids.

30 2. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (m - chlorodiphenyl - methylene) - piperidine.

3. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (o - chlorodiphenyl - methylene) - piperidine.

4. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - fluorodiphenyl - methylene) - piperidine.

5. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (diphenyl - methylene) - piperidine.

6. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - chlorodiphenyl - methylene) - piperidine.

7. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine.

8. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (p - fluorodiphenyl - methylene) - piperidine.

9. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - methoxy - diphenyl - methylene) - piperidine.

10. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (4 - chloro - 4' - fluorodiphenyl - methylene) - piperidine.

11. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (m - trifluoromethyl - diphenyl - methylene) - piperidine.

12. 1 - (2 - hydroxyethyl) - 4 - (diphenyl - methylene) - piperidine.

13. 1 - (2 - hydroxyethyl) - 4 - (p - fluorodiphenyl - methylene) - piperidine.

14. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - methyl - diphenyl - methylene) - piperidine.

15. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (m - methyl - diphenyl - methylene) - piperidine.

16. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - (diphenyl - methylene) - piperidine.

17. 1 - [2 - (2 - hydroxyethoxy) - ethyl] -



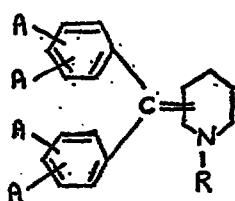
Compound	Potentiation of pentobarbital	Rotating rod	Behaviour		EEG
			exc.	sed.	
I	M O 14	R P 31	+	+	sedative
II	M O 44	R P 13.5	+		sedative
IV	M O 14	R P 33	+		
V	M O 7	R P 21	+	+	active
VIII	M O 5	R P 16	+	+	
X	M O 9		+	+	
XV	M O 16.5	R P 10.5	+	+	

Signification of the letters and numerical values: M = mouse; O = oral administration; R = rat; P = parenteral administration; the numerical values are expressed in mg./kg. animal body weight; the smaller the numerical value, the greater the activity of the tested compound.

Whether in the form of free bases or of salts of inorganic or organic pharmaceutically acceptable acids, the compounds according to the present invention may be administered orally, rectally or parenterally in unit doses of 10 to 60 mg. and, in accordance with the mode of administration, in admixture with solid or liquid pharmaceutical excipients.

WHAT WE CLAIM IS:—

1. Diphenyl-methylene-piperidines of the general formula:



wherein A is a hydrogen or halogen atom or a cyano group or a halomethyl, alkyl or alkoxy radical and

R is a hydroxyalkyl, hydroxyalkoxyalkyl or hydroxyalkoxyalkoxyalkyl radical, each alkyl and alkoxy radical containing up to 4 carbon atoms;

or the addition salts thereof with pharmaceutically acceptable acids.

2. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (o - chlorodiphenyl - methylene) - piperidine.

3. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (o - chlorodiphenyl - methylene) - piperidine.

4. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - fluorodiphenyl - methylene) - piperidine.

5. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (diphenyl - methylene) - piperidine.

6. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - chlorodiphenyl - methylene) - piperidine.

7. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (diphenyl - methylene) - piperidine.

8. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (p - fluorodiphenyl - methylene) - piperidine.

9. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - methoxy - diphenyl - methylene) - piperidine.

10. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (4 - chloro - 4' - fluorodiphenyl - methylene) - piperidine.

11. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (m - trifluoromethyl - diphenyl - methylene) - piperidine.

12. 1 - (2 - hydroxyethyl) - 4 - (diphenyl - methylene) - piperidine.

13. 1 - (2 - hydroxyethyl) - 4 - (p - fluoro-diphenyl - methylene) - piperidine.

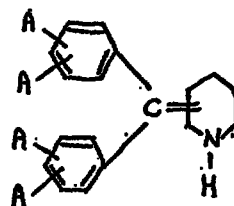
14. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (p - methyl - diphenyl - methylene) - piperidine.

15. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (m - methyl - diphenyl - methylene) - piperidine.

16. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 3 - (diphenyl - methylene) - piperidine.

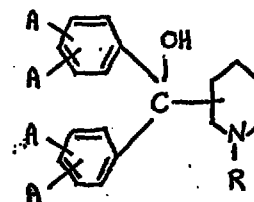
17. 1 - [2 - (2 - hydroxyethoxy) - ethyl] -

- 4 - (*p* - trifluoromethyl - diphenyl - methylene) - piperidine.
18. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*p* - *t* - butyl - diphenyl - methylene) - piperidine.
19. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (3,4 - dimethyl - diphenyl - methylene) - piperidine.
20. 1 - [2 - (2 - hydroxyethoxy) - ethyl] - 4 - (*o* - methoxy - diphenyl - methylene) - piperidine.
21. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (*p* - trifluoromethyl - diphenyl - methylene) - piperidine.
22. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (*m* - trifluoromethyl - diphenyl - methylene) - piperidine.
23. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (*p* - chlorodiphenyl - methylene) - piperidine.
24. 1 - (2,3 - dihydroxypropyl) - 4 - (diphenyl - methylene) - piperidine.
25. 1 - (2 - hydroxyethyl) - 4 - (*p* - chlorodiphenyl - methylene) - piperidine.
26. 1 - (2 - hydroxyethyl) - 4 - (*o* - methoxy - diphenyl - methylene) - piperidine.
27. 1 - (2 - hydroxyethyl) - 4 - (*m* - methyl - diphenyl - methylene) - piperidine.
28. 1 - (3 - hydroxypropyl) - 4 - (diphenyl - methylene) - piperidine.
29. 1 - (4 - hydroxybutyl) - 4 - (diphenyl - methylene) - piperidine.
30. 1 - (2 - hydroxyethyl) - 3 - (diphenyl - methylene) - piperidine.
31. 1 - (3 - hydroxypropyl) - 3 - (diphenyl - methylene) - piperidine.
32. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (4 - chlorodiphenyl - methylene) - piperidine.
33. 1 - {2 - [2 - (2 - hydroxyethoxy) - ethoxy] - ethyl} - 4 - (3 - trifluoromethyl - diphenyl - methylene) - piperidine.
34. 1 - (2 - hydroxyethyl) - 2 - (diphenyl - methylene) - piperidine.
35. Process for the preparation of compounds of the general formula given in claim 1, wherein a diphenyl-methylene-piperidine of the general formula:—



in which A has the same meaning as in claim 1, is reacted with a compound of the general formula Z—R, in which R has the same meaning as in claim 1 and Z is a reactive atom or group capable of reacting with the hydrogen atom on the nitrogen atom of the piperidine.

36. Process for the preparation of compounds of the general formula given in claim 1, wherein an α,α - diphenyl - N - R - piperidine - methanol of the general formula:—



in which A and R have the same meanings as in claim 1, is submitted to the action of a dehydration agent.

37. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

38. Compounds according to claim 1, whenever prepared by the process according to any of claims 35—37.

39. Pharmaceutical compositions, comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical excipient.

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