

PATENT SPECIFICATION

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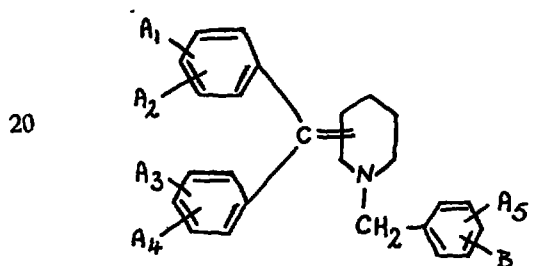


(54) NEW DERIVATIVES OF PIPERIDINE

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

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



(I)

wherein

A_1 , A_2 , A_3 , A_4 , A_5 and B, which may be
 the same or different, are hydrogen or
 halogen atoms or halomethyl, alkyl,
 alkoxy, nitro, cyano or amino radicals
 or

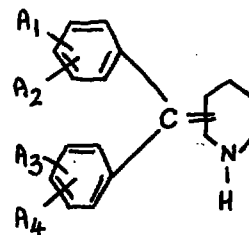
A_5 and B can together represent a bivalent
 alkylene, alkenylene or alkadienylene
 radical containing 3 to 5 carbon atoms
 or an alkylendioxy radical containing
 up to 3 carbon atoms, said bivalent
 radical being connected to two adjacent
 carbon atoms of the benzene nucleus,
 with the proviso that when A_1 , A_2 , A_3 , A_4 ,
 A_5 and B are all hydrogen atoms, the
 diphenyl-methylene radical is in the ortho-
 or meta-position with regard to the nitrogen
 atom in the piperidine nucleus;

and the addition salts thereof with pharma-
 ceutically acceptable inorganic or organic
 acids.

When A_5 and B together represent an
 alkylene radical, this can be, for example, a
 butylene radical, when they represent an
 alkenylene radical, this can be, for example, a
 butenylene radical, when they represent an
 alkadienylene radical, this can be, for example,
 a butadienylene radical, and when they repre-
 sent an alkylendioxy radical, this can be, for
 example, a methylenedioxy radical.

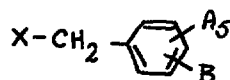
The new compounds of general formula (I)
 may be prepared in the following manner:—

1. Condensation of an appropriately substi-
 tuted diphenylmethylenepiperidine of the
 general formula:—



(II)

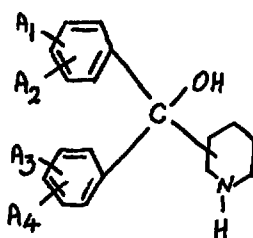
wherein A_1 , A_2 , A_3 and A_4 have the same meanings as above, with a benzyl compound of the general formula:—



(III)

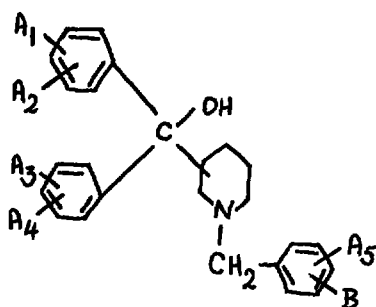
- 5 wherein A_5 and B have the same meanings as above and X is a halogen atom or an equivalent reactive group, in an inert solvent in the presence of an acid acceptor;

- 10 2. Condensation of an α,α -diphenyl-piperidine-carbinol of the general formula:—



(IV)

- 15 in which A_1 , A_2 , A_3 and A_4 have the same meanings as above, with a benzyl compound of general formula (III) in an inert solvent and in the presence of an acid acceptor to give a compound of the general formula:—



(V)

- 20 wherein A_1 , A_2 , A_3 , A_4 , A_5 and B have the same meanings as above, whereafter this compound (V) is reacted with a dehydration agent

in order to remove the elements of water to give the desired product (I).

The new compounds according to the present invention, be they in the form of the free bases or be they in the form of salts with pharmaceutically acceptable inorganic or organic acids, are strong pharmacological agents having anti-histaminic and anti-allergic properties. They also have a favourable action on the cerebral, peripheral and coronary circulations, as well as on the rhythm of contraction of the heart. They are also active against motion sickness.

There is already known a compound which is closely related to the new compounds according to the present invention which is the para homologue of the ortho and meta compounds of general formula (I) in which A_1 , A_2 , A_3 , A_4 , A_5 and B are all hydrogen atoms. However, this compound was synthesised by C. M. Lee, A. H. Beckett and J. K. Sugden (Tetrahedron, 22, 2721/1966) only for the elucidation of the structure, in correlation with the NMR spectrum, of certain 4-cyanomethylene-piperidines which were N-substituted, the pharmacological properties thereof not having been studied by these authors. Consequently, it could not have been foreseen that the new compounds according to the present invention possess a strong pharmacological activity.

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

EXAMPLE 1

4 - diphenyl - methylene - 1 - (4 - *tert.*-butyl - benzyl) - piperidine.

A mixture of 15 g. 4-diphenyl-methylene-piperidine, 15.5 g. *p-tert.*-butyl-benzyl bromide and 9.5 g. anhydrous sodium carbonate in 40 ml. xylene is heated to 120°C. for 8 hours. After cooling the reaction mixture, the sodium bromide formed is filtered off and the filtrate is extracted with dilute hydrochloric acid (10 ml. concentrated hydrochloric acid and 35 ml. water). The hydrochloride formed is only slightly soluble and separates out from the filtrate by crystallisation. The precipitated hydrochloride is filtered off, washed with isopropanol and dried. There is thus obtained 4-diphenyl-methylene-1-(4-*tert.*-butyl-benzyl)-piperidine which, after recrystallisation from isopropanol, has a melting point of 286—287°C.

- 75 Calculated for $C_{29}H_{33}N.HCl$ 8.20% Cl^- 3.24% N
found 8.46% 3.27%

- 80 The following compounds are prepared in an analogous manner. The melting point given is that of the hydrochloride except for compounds 33, 34, 35, 39, 47 and 49, which were isolated as free bases. Compound 26

was isolated both as free base and as hydrochloride. The solvent used for recrystallisation is indicated in brackets after the melting point.

(11)

1. 4 - (4 - chlorodiphenyl - methylene) - 1- (4 - *tert.* - butyl - benzyl) - piperidine; m.p. 283.5—285.5°C. (isopropanol).

$C_{29}H_{32}ClN.HCl$ calc. : 3.0% N 7.59% Cl^- 15.20% total Cl
 found: 3.04% 7.57% 15.15%

2. 4 - (3 - chlorodiphenyl - methylene) - 1- (4 - *tert.* - butyl - benzyl) - piperidine; m.p. 273—275°C. (isopropanol).

$C_{29}H_{32}ClN.HCl$ calc. : 3.00% N 7.59% Cl^- 15.20% total Cl
 found: 3.07% 7.54% 15.06%

3. 4 - (2 - chlorodiphenyl - methylene) - 1- (4 - *tert.* - butyl - benzyl) - piperidine; m.p. 281—282°C. (isopropanol).

$C_{29}H_{32}ClN.HCl$ calc. : 3.00% N 7.59% Cl^- 15.20% total Cl
 found: 2.99% 7.58% 15.02%

4. 4 - (4 - fluorodiphenyl - methylene) - 1- (4 - *tert.* - butyl - benzyl) - piperidine; m.p. 276—278°C. (isopropanol).

$C_{29}H_{32}FN.HCl$ calc. : 3.11% N 7.85% Cl^- 4.22% F
 found: 3.04% 7.93% 3.98%

5. 4 - (4 - trifluoromethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl-benzyl) - piperidine; m.p. 264—265°C. (isopropanol).

$C_{30}H_{32}F_3N.HCl$ calc. : 2.80% N 7.09% Cl^- 11.39% F
 found: 2.90% 7.04% 11.24%

6. 4 - (3 - trifluoromethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl-benzyl) - piperidine; m.p. 252—253°C. (isopropanol).

$C_{30}H_{32}F_3N.HCl$ calc. : 2.80% N 7.09% Cl^- 11.39% F
 found: 2.80% 7.25% 11.32%

7. 4 - (4 - chloro - 4' - fluorodiphenyl-methylene) - 1 - (4 - *tert.* - butyl-benzyl) - piperidine; m.p. 278—279°C. (isopropanol).

$C_{29}H_{31}ClFN.HCl$ calc. : 2.89% N 7.31% Cl^- 14.62% total Cl
 found: 2.83% 7.12% 14.23%
 calc. : 3.92% F
 found: 4.20%

8. 4 - (3,4 - dimethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl-benzyl)-piperidine; m.p. 270—271°C. (isopropanol).

$C_{31}H_{37}N.HCl$ calc. : 3.04% N 7.70% Cl^-
 found: 3.04% 7.62%

9. 4 - diphenyl - methylene - 1 - *o* - xylyl- piperidine; m.p. 257—258°C. (isopropanol).

$C_{26}H_{27}N.HCl$ calc. : 3.59% N 9.09% Cl^-
 found: 3.42% 8.87%

10. 4 - diphenyl - methylene - 1 - *m* - xylyl- piperidine; m.p. 256—257°C. (isopropanol).

$C_{26}H_{27}N.HCl$ calc. : 3.59% N 9.09% Cl^-
 found: 3.62% 9.15%

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11. 4 - (4 - chlorodiphenyl - methylene) - 1-*p*-xylyl-piperidine; m.p. 257—258°C. (methanol).

$C_{26}H_{26}ClN.HCl$	calc. :	3.30% N	8.35% Cl^-	16.70% total Cl
	found:	3.18%	8.21%	16.35%

12. 4 - (4 - chlorodiphenyl - methylene) - 1-*m*-xylyl-piperidine; m.p. 233—234°C. (isopropanol).

$C_{26}H_{26}ClN.HCl$	calc. :	3.30% N	8.35% Cl^-	16.70% total Cl
	found:	3.25%	8.28%	16.42%

13. 4 - diphenyl - methylene - 1 - (4-methoxy - benzyl) - piperidine; m.p. 271—272°C. (ethanol).

$C_{26}H_{27}NO.HCl$	calc. :	3.45% N	8.73% Cl^-
	found:	3.46%	8.95%

14. 4 - diphenyl - methylene - 1 - (3-methoxy - benzyl) - piperidine; m.p. 216—217°C. (isopropanol).

$C_{26}H_{27}NO.HCl$	calc. :	3.45% N	8.73% Cl^-
	found:	3.49%	8.87%

15. 4 - (2 - chlorodiphenyl - methylene) - 1- (4 - methoxy - benzyl) - piperidine; m.p. 272—273°C. (ethanol).

$C_{26}H_{26}ClNO.HCl$	calc. :	3.18% N	8.05% Cl^-	16.10% total Cl
	found:	3.18%	8.14%	16.3%

16. 4 - (3 - chlorodiphenyl - methylene) - 1- (4 - methoxy - benzyl) - piperidine; m.p. 253—254°C. (methanol).

$C_{26}H_{26}ClNO.HCl$	calc. :	3.18% N	8.05% Cl^-	16.10% total Cl
	found:	3.24%	8.10%	16.32%

17. 4 - (4 - chlorodiphenyl - methylene) - 1- (4 - methoxy - benzyl) - piperidine; m.p. 256—257°C. (isopropanol).

$C_{26}H_{26}ClNO.HCl$	calc. :	3.18% N	8.05% Cl^-	16.10% total Cl
	found:	3.08%	7.97%	15.81%

18. 4 - (4 - chlorodiphenyl - methylene) - 1- (3 - methoxy - benzyl) - piperidine; m.p. 236—237°C. (methanol).

$C_{26}H_{26}ClNO.HCl$	calc. :	3.18% N	8.05% Cl^-	16.10% total Cl
	found:	3.26%	7.84%	15.63%

19. 4 - (4 - trifluoromethyl - diphenyl-methylene) - 1 - (4 - methoxybenzyl)-piperidine; m.p. 257—258°C. (isopropanol).

$C_{27}H_{26}F_3NO.HCl$	calc. :	2.97% N	7.47% Cl^-	12.02% F
	found:	2.94%	7.46%	11.75%

20. 4 - diphenyl - methylene - 1 - (4 - chloro - benzyl)-piperidine; m.p. 264—265°C. (isopropanol).

$C_{25}H_{24}ClN.HCl$	calc. :	3.41% N	8.63% Cl^-	17.26% total Cl
	found:	3.40%	8.74%	17.2%

- | | | | |
|---------------------|---------|---------|----------|
| $C_{28}H_{31}N.HCl$ | calc. : | 3.35% N | 8.48% Cl |
| | found: | 3.31% | 8.43% |

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31. 4 - diphenyl - methylene - 1 - (4 - *n*-butyl - benzyl) - piperidine; m.p. 240—241°C. (isopropanol).

$C_{29}H_{33}N.HCl$	calc. :	3.24% N	8.24% Cl^-
	found:	3.22%	8.14%

32. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - isopropyl - benzyl) - piperidine; m.p. 249—250°C. (isopropanol).

$C_{28}H_{30}ClN.HCl$	calc. :	3.09% N	7.83% Cl^-	15.67% total Cl
	found:	3.11%	7.68%	15.34%

33. 4 - (4 - fluorodiphenyl - methylene) - 1 - (4 - *n* - butyl - benzyl) - piperidine; m.p. of the base 76—77°C. (petroleum ether b.p. 40—60°C.).

$C_{29}H_{32}FN$	calc. :	3.38% N	4.59% F
	found:	3.43%	4.59%

34. 4 - diphenyl - methylene - 1 - (4 - tri-fluoromethyl - benzyl) - piperidine; m.p. of the base 100—101°C. (petroleum ether b.p. 40—60°C.).

$C_{26}H_{24}F_3N$	calc. :	3.43% N	13.98% F
	found:	3.22%	13.84%

35. 3 - diphenyl - methylene - 1 - (4 - iso-propyl - benzyl) - piperidine; m.p. of the base 106—107°C. (petroleum ether b.p. 40—60°C.).

$C_{28}H_{31}N$	calc. :	3.67% N
	found:	3.51%

36. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - *n* - butyl - benzyl) - piperidine; m.p. 212—213°C. (isopropanol).

$C_{29}H_{32}ClN.HCl$	calc. :	3.0% N	7.60% Cl^-
	found:	2.88%	7.42%

37. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - trifluoromethyl - benzyl) - piperidine; m.p. 246—247°C. (isopropanol).

$C_{26}H_{23}ClF_3N.HCl$	calc. :	2.92% N	7.42% Cl^-	14.84% total Cl
	found:	2.91%	7.44%	15.04%

38. 4 - (4 - fluoro - 4' - trifluoromethyl-diphenyl - methylene) - 1 - (4 - isopropyl - benzyl) - piperidine; m.p. 243—244°C. (isopropanol).

$C_{29}H_{29}F_4N.HCl$	calc. :	2.77% N	7.03% Cl^-	15.07% F
	found:	2.71%	6.92%	14.85%

39. 4 - (4 - methoxy - diphenyl - methylene)- 1 - (4 - *tert.* - butyl - benzyl) - piperidine; m.p. of the base 102—103°C. (isopropanol).

$C_{30}H_{33}NO$	calc. :	3.29% N
	found:	3.26%

40. 4 - (3 - methyl - diphenyl - methylene)- 1-benzyl-piperidine; m.p. 255—256°C. (isopropanol).

$C_{28}H_{27}N.HCl$	calc. :	3.59% N	9.09% Cl^-
	found:	3.39%	9.08%

41. 4 - (4 - fluorodiphenyl - methylene) - 1-benzyl - piperidine; m.p. 251—252°C. (isopropanol).

$C_{25}H_{24}FN.HCl$	calc. :	3.56% N	4.82% F	9.0% Cl^-
	found:	3.54%	4.90%	8.81%

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42. 4 - (2 - methoxy - diphenyl - methylene)- 1 - (4 - *tert.* - butyl - benzyl) - piperidine; m.p. 251—252°C. (isopropanol).

$C_{30}H_{35}NO.HCl$	calc. :	3.03% N	7.67% Cl^-
	found:	2.98%	7.62%

43. 4 - (4 - methoxy - diphenyl - methylene)- 1 - (4 - *n* - butyl - benzyl) - piperidine; m.p. 202—203°C. (isopropanol).

$C_{30}H_{35}NO.HCl$	calc. :	3.03% N	7.67% Cl^-
	found:	3.02%	7.68%

44. 4 - diphenyl - methylene - 1 - (5 - tetralyl - methyl) - piperidine; m.p. 269—270°C. (ethanol).

$C_{29}H_{31}N.HCl$	calc. :	3.25% N	8.24% Cl^-
	found:	3.20%	8.23%

45. 4 - diphenyl - methylene - 1 - (6 - tetralyl-methyl)-piperidine; m.p. 265—266°C. (ethanol).

$C_{29}H_{31}N.HCl$	calc. :	3.25% N	8.24% Cl^-
	found:	3.23%	8.09%

46. 4 - (4 - chlorodiphenyl - methylene) - 1-(6 - tetralyl - methyl) - piperidine; m.p. 268—269°C. (isopropanol).

$C_{29}H_{30}ClN.HCl$	calc. :	3.01% N	7.71% Cl^-	15.42% total Cl
	found:	3.03%	7.68%	15.37%

47. 3 - diphenyl - methylene - 1 - (4 - fluoro- benzyl)-piperidine; m.p. of the base 103—104°C. (isopropanol).

$C_{23}H_{24}FN$	calc. :	3.91% N	5.31% F
	found:	3.83%	5.23%

48. 4 - (4 - chlorodiphenyl - methylene) - 1-(4 - cyanobenzyl) - piperidine; m.p. 246—247°C. (isopropanol).

$C_{26}H_{23}ClN_2.HCl$	calc. :	6.41% N	8.14% Cl^-	16.28% total Cl
	found:	6.41%	8.15%	16.29%

49. 4 - (3 - methyl - diphenyl - methylene)- 1 - (4 - *tert.* - butyl - benzyl) - piperidine; m.p. of the base 112—113°C. (isopropanol).

$C_{30}H_{35}N$	calc. :	3.41% N
	found:	3.40%

50. 4 - (4 - fluoro - 4' - trifluoromethyl- diphenyl - methylene) - 1 - benzyl- piperidine; m.p. 234—235°C. (isopropanol).

$C_{26}H_{23}F_4N.HCl$	calc. :	3.03% N	7.67% Cl^-
	found:	2.89%	7.54%

51. 4 - (4 - trifluoromethyl - diphenyl-methylene) - 1 - (5 - tetralyl - methyl)- piperidine; m.p. 235—236°C. (methanol).

$C_{30}H_{30}F_3N.HCl$	calc. :	2.81% N	7.11% Cl^-	11.43% F
	found:	2.80%	7.12%	11.26%

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EXAMPLE 2

4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

This compound already described in Example 1 (compound 1) can also be prepared in the following manner:

A mixture of 18.11 g. α -(4-chlorophenyl)- α -phenyl-4-piperidine-methanol, 14.7 g. *p*-*tert.*-butyl-benzyl bromide and 9.5 g. anhydrous sodium carbonate in 45 ml. xylene is heated to 120°C. for 8 hours. After filtration of the reaction mixture to remove the precipitated sodium bromide formed, the fil-

trate is evaporated in a vacuum and the residue is dissolved in 1 litre ethanol. The solution is then saturated with gaseous hydrogen chloride, while cooling. After leaving the reaction mixture to stand overnight, it is boiled under reflux for 1—2 hours. Excess solvent is then evaporated off and the residue is recrystallised from isopropanol. There is thus obtained the hydrochloride of 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine, which has a melting point of 283.5—285.5°C.

Calculated for $C_{29}H_{32}ClN.HCl$

	3.00% N	7.59% Cl	15.20% total Cl
found:	3.03%	7.60%	15.2%

The following compounds are prepared in an analogous manner:

1. 2 - diphenyl - methylene - 1 - (4 - *tert.* - butyl - benzyl) - piperidine; after recrystallisation from benzene, the base has a melting point of 191—193°C.

$C_{29}H_{33}N$
calc. : 3.54% N
found: 3.50%

2. 3 - diphenyl - methylene - 1 - (4 - *tert.* - butyl - benzyl) - piperidine; m.p. of the base 135—136°C.

$C_{29}H_{33}N$
calc. : 3.54% N
found: 3.58%

3. 2 - (4 - fluorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine; after recrystallisation from petroleum ether (b.p. 40—60°C.), it has a melting point of 198—200°C.

$C_{29}H_{32}FN$
calc. : 3.38% N 4.59% F
found: 3.28% 4.42%

4. 2 - diphenyl - methylene - 1 - (4 - trifluoromethyl - benzyl) - piperidine; dehydration agent used: 50% sulphuric acid; m.p. of the base 116—117°C. (isopropanol).

$C_{26}H_{24}F_3N$
calc. : 3.43% N 13.90% F
found: 3.32% 13.70%

5. 3 - diphenyl - methylene - 1 - (4 - *n*-butyl - benzyl) - piperidine; dehydration agent used: 50% sulphuric acid; m.p. 191—192°C. (isopropanol).

$C_{29}H_{33}N.HCl$
calc. : 3.24% N 8.20% Cl
found: 3.26% 8.03%

For the pharmacological tests, the following compound according to the present invention were used:

A. 4 - diphenyl - methylene - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

B. 4 - diphenyl - methylene - 1 - (4 - methoxy - benzyl) - piperidine.

C. 4 - diphenyl - methylene - 1 - piperonyl-piperidine.

D. 4 - (4 - fluorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

E. 4 - (2 - chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

F. 4 - (3 - chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

G. 4 - (2 - chloro - diphenyl - methylene) - 1 - (4 - methoxy - benzyl) - piperidine.

H. 4 - (4 - trifluoromethyl - diphenyl-methylene) - 1 - (4 - methoxy - benzyl)-piperidine.

I. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - methoxy - benzyl) - piperidine.

J. 4 - (4 - *tert.* - butyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine.

K. 4 - diphenyl - methylene - 1 - (4 - *n*-butyl - benzyl) - piperidine.

L. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - isopropyl - benzyl) - piperidine.

- M. 4 - (4 - fluorodiphenyl - methylene) - 1 - (4 - *n* - butyl - benzyl) - piperidine.
 N. 4 - (4 - fluoro - 4' - trifluoromethyl - diphenyl - methylene) - 1 - (4 - isopropyl - benzyl) - piperidine.
 5 O. 4 - (2 - methoxy - diphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.
 P. 4 - diphenyl - methylene - 1 - (4 - isopropyl - benzyl) - piperidine.
 10 Q. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - *n* - butyl - benzyl) - piperidine.
 R. 4 - (4 - chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.
 15 S. 4 - (4 - chloro - 4' - fluorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.
 T. 4 - (4 - trifluoromethyl - diphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

I. Activity on blood circulation.

The haemodynamic effects were studied in anaesthetised dogs subjected to artificial respiration under the experimental conditions described by D. Wellens and E. Wauters (Arch. int. Pharmacodyn. 171, 246—250/1968).

The cardiac, musculo-cutaneous and cerebral outputs were measured by means of periarterial probes placed, respectively, around the femoral (A), carotid (B) and coronary (C) arteries, the aorta (D) and the vertebral arteries (E).

The maximum score per animal "2" was assigned to a compound which brought about an increase of circulation of at least 20% for at least 20 minutes. The maximum score per experiment carried out on two dogs was 4, with the possibility of the intermediates of from 0 to 4. For the purpose of comparison, the corresponding values for two known compounds, papaverine and theophylline, are also given.

Compounds	Doses mg./kg,	Output scores				
		(A)	(B)	(C)	(D)	(E)
X	2	1.5	2	2	2	1.5
Y	20	0	1.5	1	2	4
A	2	1	2	4	0	2.5
B	2	3	3	—	1	1.5
C	2	3	1	0	1	2
D	2	1	3	4	1	2
E	2	4	4	—	4	4
F	2	1	2	0	1	1
	5	4	3	1	3	4
G	2	2	4	4	1	4
H	1	1	—	3	3.5	4
I	2	2	2	3	1.5	2.5
J	2	4	0	—	0	0
K	2	3	2	—	2	4
L	2	3	2	—	1	4
M	2	4	2	—	2	4
N	2	2	2	—	3	2
O	2	3	3	—	3	3

X = papaverine
 Y = theophylline

II. Anti-arrhythmic effects.

Dogs were anaesthetised by means of intraperitoneal injection of pentobarbital. The electrocardiogram and the systemic arterial pressure was recorded. Ouabain was intravenously injected until persistent arrhythmia was produced, manifested by ventricular tachycardia or, more often, by manifold ventricular extra-systoles. After definitive production of the arrhythmia (control period of 30 minutes), the compounds to be tested were intravenously injected. Return to aricular rhythm within 10 minutes was considered to be an indication of anti-arrhythmic activity.

Under these experimental conditions, the anti-arrhythmic effect of the compounds according to the present invention was confirmed at an intravenous dose of 5 mg./kg.:

compound S: two positive experiments
compound F: two positive experiments
dihydroquinidine (reference compound): 3 positive experiments.

Consequently, these compounds prove to have an anti-arrhythmic effect in dogs.

III. Anti-histaminic activity.

The anti-histaminic activity of the compounds according to the present invention was studied in guinea-pigs, using the method of D. Bovet and A. M. Staub (C.R. Soc. Biol. 124, 547/1937) as slightly modified by S. Levis & al. (Arch. Intern. Pharmacol. 109, 128/1954). This test consists in determining the number of intravenously injected toxic doses of histamine which are neutralised by the previous administration of an anti-histaminic agent. The amplitude and duration of the activity were evaluated.

The test compounds were administered intravenously (2.5 mg./kg.) or orally (2.5 mg./kg. by means of a catheter).

The minimum intravenous dose of histamine which kills 100% of control guinea-pigs (300 to 400 g. body weight) varied between 0.4 and 0.5 mg./kg.

In the following Table, the toxic doses of histamine are given which were neutralised by the intravenous administration of the mentioned compounds after 1, 4, 24 and 48 hours, respectively:

Compound	1 hour	4 hours	24 hours	48 hours
A	1500	800	800	800
D	1000	—	1400	1600
E	800	—	1400	—
F	1000	—	1000	—
K	1400	—	1400	—
L	1000	—	1400	—
M	1400	—	1200	—
O	1400	—	800	—
P	1400	—	1400	800
Q	600	—	1400	—
R	1200	1800	2000	1800
S	100	1400	1000	1000
T	10	1400	1800	2000

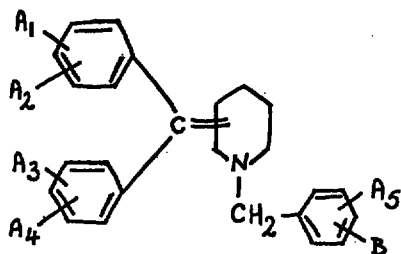
The compounds according to the invention may be used as free bases or as addition salts with inorganic or organic pharmaceutically acceptable acids. They may be administered orally, rectally or parenterally in association

with the usual pharmaceutical liquid or solid excipients, for example, in unit doses of 10 to 50 mg., depending upon the mode of administration.



WHAT WE CLAIM IS:—

1. Diphenyl - methylene - N - benzyl-piperidines of the general formula:—



5 wherein

A₁, A₂, A₃, A₄, A₅ and B, which may be the same or different, are hydrogen or halogen atoms or halomethyl, alkyl, alkoxy, nitro, cyano or amino radicals or

A₅ and B can together represent a bivalent alkylene, alkenylene or alkadienylene radical containing 3 to 5 carbon atoms or an alkylendioxy radical containing up to 3 carbon atoms, said bivalent radical being connected to two adjacent carbon atoms of the benzene nucleus, with the proviso that when A₁, A₂, A₃, A₄, A₅ and B are all hydrogen atoms, the diphenyl-methylene radical is in the ortho or meta-position with regard to the nitrogen atom in the piperidine nucleus,

and the addition salts thereof with pharmaceutically acceptable inorganic or organic acids.

2. 4 - Diphenyl - methylene - 1 - (4 - *tert.*-butyl-benzyl)-piperidine.

3. 4 - (4 - Fluorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

4. 4 - (3 - Chlorodiphenyl - methylene) - 1 - (4 - *tert.* - butyl - benzyl) - piperidine.

5. 4 - Diphenyl - methylene - 1 - (4 - *n*-butyl - benzyl) - piperidine.

6. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - isopropyl - benzyl) - piperidine.

7. 4 - (4 - Fluorodiphenyl - methylene)-1 - (4 - *n* - butyl - benzyl) - piperidine.

8. 4 - Diphenyl - methylene - 1 - (4 - isopropyl - benzyl) - piperidine.

9. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - *tert.* - butyl - benzyl) - piperidine.

10. 4 - (4 - Chloro - 4' - fluorodiphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine.

11. 4 - (4 - Trifluoromethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine.

12. 4 - (2 - Chlorodiphenyl - methylene)-1 - (4 - *tert.* - butyl - benzene) - piperidine.

13. 4 - (3 - Trifluoromethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzene)-piperidine.

14. 4 - (3,4 - Dimethyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzene)-piperidine.

15. 4 - Diphenyl - methylene - 1 - *o*-xylyl - piperidine.

16. 4 - Diphenyl - methylene - 1 - *m*-xylyl - piperidine.

17. 4 - (4 - Chlorodiphenyl - methylene)-1 - *p* - xylyl - piperidine. 60

18. 4 - (4 - Chlorodiphenyl - methylene)-1 - *m* - xylyl - piperidine.

19. 4 - Diphenyl - methylene - 1 - (4-methoxy - benzyl) - piperidine. 65

20. 4 - Diphenyl - methylene - 1 - (3-methoxy - benzyl) - piperidine.

21. 4 - (2 - Chlorodiphenyl - methylene)-1 - (4 - methoxy - benzyl) - piperidine.

22. 4 - (3 - Chlorodiphenyl - methylene)-1 - (4 - methoxy - benzyl) - piperidine. 70

23. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - methoxy - benzyl) - piperidine.

24. 4 - (4 - Chlorodiphenyl - methylene)-1 - (3 - methoxy - benzyl) - piperidine. 75

25. 4 - (4 - Trifluoromethyl - diphenyl-methylene) - 1 - (4 - methoxy - benzyl)-piperidine.

26. 4 - Diphenyl - methylene - 1 - (4-chlorobenzyl) - piperidine. 80

27. 4 - Diphenyl - methylene - 1 - (4-nitrobenzyl) - piperidine.

28. 4 - Diphenyl - methylene - 1 - (3-nitrobenzyl) - piperidine.

29. 4 - Diphenyl - methylene - 1 - piperonyl - piperidine. 85

30. 4 - (4 - Chlorodiphenyl - methylene)-1 - piperonyl - piperidine.

31. 4 - Diphenyl - methylene - 1 - (2-naphthyl - methyl) - piperidine. 90

32. 4 - (4 - Chlorodiphenyl - methylene)-1 - benzyl - piperidine.

33. 4 - (4 - *tert.* - Butyl - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine. 95

34. 4 - (4 - *tert.* - Butyl - diphenyl-methylene) - 1 - benzyl - piperidine.

35. 4 - (4 - Methyl - diphenyl - methylene)-1 - (4 - *tert.* - butyl - benzyl) - piperidine.

36. 4 - Diphenyl - methylene - 1 - (4-trifluoromethyl - benzyl) - piperidine. 100

37. 3 - Diphenyl - methylene - 1 - (4-isopropyl - benzyl) - piperidine.

38. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - *n* - butyl - benzyl) - piperidine. 105

39. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - trifluoromethyl - benzyl) - piperidine.

40. 4 - (4 - Fluoro - 4' - trifluoromethyl-diphenyl - methylene) - 1 - (4 - isopropyl-benzyl) - piperidine. 110

41. 4 - (4 - Methoxy - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine.

42. 4 - (3 - Methyl - diphenyl - methylene)-1 - benzyl - piperidine. 115

43. 4 - (4 - Fluorodiphenyl - methylene)-1 - benzyl - piperidine.

44. 4 - (2 - Methoxy - diphenyl-methylene) - 1 - (4 - *tert.* - butyl - benzyl)-piperidine. 120

45. 4 - (4 - Methoxy - diphenyl-methylene) - 1 - (4 - *n* - butyl - benzyl)-piperidine.

5 46. 4 - Diphenyl - methylene - 1 - (5-tetralyl - methyl) - piperidine.

47. 4 - Diphenyl - methylene - 1 - (6-tetralyl - methyl) - piperidine.

48. 4 - (4 - Chlorodiphenyl - methylene)-1 - (6 - tetralyl - methyl) - piperidine.

10 49. 3 - Diphenyl - methylene - 1 - (4-fluorobenzyl) - piperidine.

50. 4 - (4 - Chlorodiphenyl - methylene)-1 - (4 - cyanobenzyl) - piperidine.

15 51. 4 - (3 - Methyl - diphenyl - methylene)-1 - (4 - *tert.* - butyl - benzyl) - piperidine.

52. 4 - (4 - Fluoro - 4' - trifluoromethyl-diphenyl - methylene) - 1 - benzyl-piperidine.

20 53. 4 - (4 - Trifluoromethyl - diphenyl-methylene) - 1 - (5 - tetralyl - methyl)-piperidine.

54. 2 - Diphenyl - methylene - 1 - (4-*tert.* - butyl - benzyl) - piperidine.

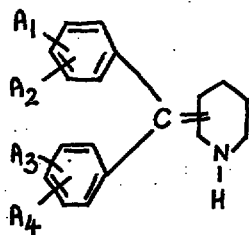
25 55. 3 - Diphenyl - methylene - 1 - (4-*tert.* - butyl - benzyl) - piperidine.

56. 2 - (4 - Fluorodiphenyl - methylene)-1 - (4 - *tert.* - butyl - benzyl) - piperidine.

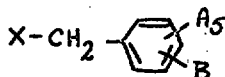
30 57. 2 - Diphenyl - methylene - 1 - (4-trifluoromethyl - benzyl) - piperidine.

58. 3 - Diphenyl - methylene - 1 - (4 - *n*-butyl - benzyl) - piperidine.

35 59. Process for the preparation of diphenyl-methylene-N-benzyl-piperidines according to claim 1, wherein a diphenyl-methylene-piperidine of the general formula:—



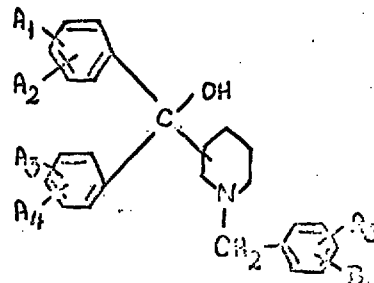
in which A₁, A₂, A₃ and A₄ have the same meanings as in claim 1, is condensed with a benzyl compound of the general formula:—



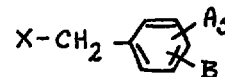
in which A₅ and B have the same meanings as in claim 1 and X is a halogen atom or an equivalent reactive group, in an inert solvent in the presence of an acid acceptor.

45 60. Process for the preparation of diphenyl - methylene - N - benzyl - piper-

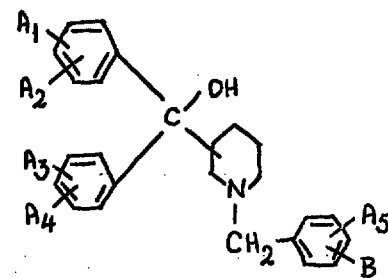
idines according to claim 1, wherein an α,α -diphenyl - piperidine - carbinol of the general formula:—



in which A₁, A₂, A₃ and A₄ have the same meanings as in claim 1, is condensed with a benzyl compound of the general formula:—



in which A₅ and B have the same meanings as in claim 1 and X is a halogen or an equivalent reactive group, in an inert solvent and in the presence of an acid acceptor to give a compound of the general formula:—



in which A₁, A₂, A₃, A₄, A₅ and B have the same meanings as in claim 1, whereafter this compound is reacted with a dehydration agent in order to remove the elements of water.

61. Process according to claim 59 or 60, wherein the product obtained is reacted with a pharmaceutically acceptable organic or inorganic acid to give the corresponding acid-addition salt.

62. Process for the preparation of diphenyl-methylene-N-benzyl-piperidines according to claim 1, substantially as hereinbefore described and exemplified.

63. Diphenyl - methylene - N - benzyl-piperidines according to claim 1, whenever prepared by the process according to any of claims 59—62.



- 5 64. Pharmaceutical compositions containing at least one diphenyl-methylene-N-benzyl-piperidine according to claim 1, in admixture with a pharmaceutical liquid or solid excipient.

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