PATENT SPECIFICATION

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COMPLETE SPECIFICATION

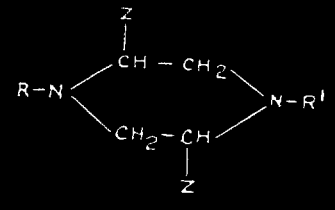
1.4-Aralkyl Piperazines and process for the preparation thereof

I, HENRI MORREN, of 171, Rue du Hêtre, Forest-Bruxelles, Belgium, of Belgian nationality, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 1.4- arlkyl piperazines and a process for the preparation thereof.

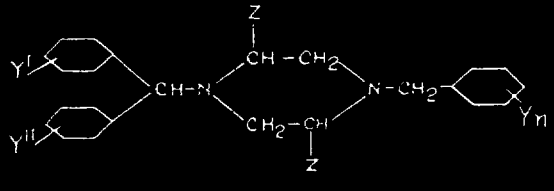
It is known that certain derivatives of piperazine substituted on the nitrogen atoms, i.e. in positions 1 and 4 have remarkable therapeutic properties. For this reason, asymmetrically substituted derivatives have been prepared which correspond to the type $R—N(C_4H_8)N—R^1$, where R and R^1 designate different substituents, respectively containing cyclic groups and aliphatic groups.

The present invention relates broadly to new 1.4-aralkyl piperazines of the general formula:—



wherein R and R^1 represent aralkyl groups of different kinds, and Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms.

The invention further relates to piperazine derivatives of the general formula:—

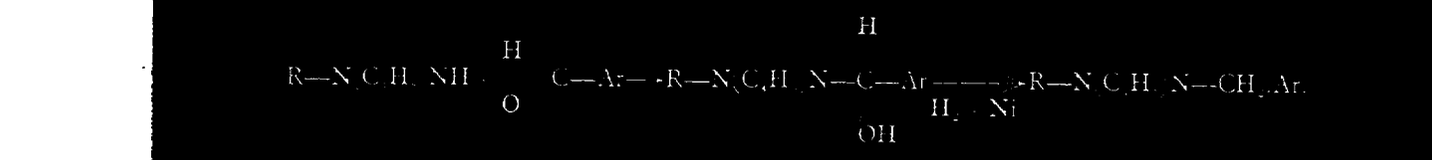


wherein each of Y, Y^1 and Y^{11} represent a member selected from the group consisting of a hydrogen atom, a halogen atom, an alkyl radical with 1 to 4 carbon atoms and an alkoxy radical with 1 to 4 carbon atoms, Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, and *n* stands for the figure 1 and Y is a halogen, and either the figure 1 or the figure 2 when Y is an alkyl or an alkoxy radical.

The present invention also relates to the preparation of derivatives of piperazine as set forth in either of the foregoing general formulæ.

This process is based, on the one hand, on the principle of reacting a 1-aralkyl piperazine with a halide of another aralkyl, that is, to cause a halide of R^1 to react on a $R—N(C_4N_8)NH$ compound or inversely to cause a halide of R to react on a $HN(C_4H_8)N—R^1$ compound. It comprises moreover the formation of an intermediate compound which is obtained by reaction between an R-piperazine and an R^1 having an aldehydic function, and the reduction of this intermediate compound by means of hydrogen under pressure in the presence of a catalyst in accordance with the following

equation, in which R is represented by —CH_2—Ar (Ar = aryl):



The experienced chemist will be able to find still other methods of preparation of 1.4-aralkyl piperazines.

The present invention comprises furthermore the selection of the substituted or unsubstituted benzhydryl group and of the likewise substituted or unsubstituted benzyl group as aralkyl groups designated above by R and R^1.

The following examples give further details about the nature of the invention, of the process of preparation and of the exact composition of the substituted benzhydryl and benzyl groups.

EXAMPLE 1.

1-BENZHYDRYL-4-BENZYL-PIPERAZINE.



A mixture of 0.1 mol. monobenzylpiperazine, 0.1 mol. benzhydryl chloride and 0.11 mol. triethylamine in 125 cm^3 of toluene or xylene is heated in an autoclave vessel, for 4 hours at 150—160° C.

After cooling, the triethylamine hydrochloride is filtered and the filtrate is distilled. The resulting product is 1-benzhydryl-4-benzyl-piperazine of B.P. (boiling point) 200°C/1 mm. Hg. crystallizing easily in alcohol: M.P. (melting point) 120° C.

The same product is transformed into dihydrochloride which after recrystallization in alcohol, melts at 225° C.

In lieu of triethylamine as acceptor of hydro-halogenic acid, it is possible to use sodium carbonate or bicarbonate, other inorganic bases, or organic bases such as quinoline, or it is possible previously to transform the benzylpiperazine into its sodium derivative by means of sodium amide. It is not necessary to heat in an autoclave vessel, nevertheless, it must be heated under reflux during some days and the final yield is lower.

EXAMPLE 2.

1-BENZHYDRYL-4-BENZYL-PIPERAZINE.

0.1 mol. of monobenzhydrylpiperazine is dissolved in 100 cm^3 of toluene and 0.1 mol. of finely ground $NaNH_2$ is added. The mixture is heated under reflux for 1 hour, the mass is cooled and 0.1 mol. of benzyl chloride is then added. The whole is then heated under reflux for 2 hours.

The solvent is evaporated and the residue is dissolved in chloroform. This solution is washed with a saturated solution of K_2CO_3 and dried on K_2CO_3. The solvent is evaporated and the residue is distilled under high vacuum. The product of the condensation distils near 200° C./1 mm. Hg. and, after recrystallization in alcohol, it melts at 120° C. The product is transformed into dihydrochloride of M.P. 225° C., identical with the compound obtained in the preceding example.

In lieu of preparing the sodium derivative of the benzhydryl-piperazine which is subsequently treated with benzyl chloride, it is possible to perform the reaction on the benzhydryl-piperazine itself, by using an acceptor of hydrohalogenic acid such as sodium bicarbonate or other inorganic bases, organic bases such as triethylamine.

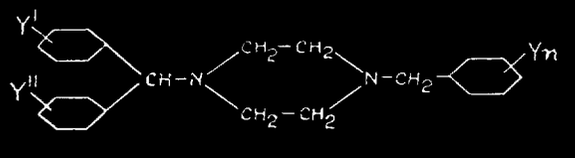
EXAMPLE 3.

1-BENZHYDRYL-4-BENZYL-PIPERAZINE.

A mixture of 0.1 mol. of monobenzhydrylpiperazine, 45 gr. of benzaldehyde, 100 cm^3 of absolute alcohol and 5 gr. of Raney nickel is heated at about 50° C. for several hours under a pressure of 50 kgr. of hydrogen. Afterwards, the catalyst is separated, the solvent is evaporated and the residue is fractionated under high vacuum.

The 1-benzhydryl-4-benzyl-piperazine boils near 205° C./1.5 mm. Hg. and is transformed into dihydrochloride identical with the compound obtained in Example 1.

According to any of the Examples 1, 2 or 3, it is possible to prepare substituted 1.4-aralkyl-piperazines corresponding to the general formula



where Y, Y^1 and Y^{11} may be identical or different, and represent a hydrogen or a halogen atom, an alkyl radical (CH_3 or C_2H_5) or an alkoxy radical (OCH_3 or OC_2H_5). In these cases, suitably substituted benzhydrylic and benzylic derivatives are used.

As regards the benzhydryl-piperazines substituted in para position which are necessary in Examples 2 and 3, these can be obtained, for instance, by condensation of the halogenides of the corresponding benzhydryls with carbethoxypiperazine in the presence of a slight excess of triethylamine in a

toluenic medium, at about 150° C. in a closed vessel. The triethylamine hydrohalogenide is discarded, the solvent is evaporated and the residue is immediately treated with an alcoholic solution of KOH at boiling point during 48 hours. After evaporation of the alcohol, the residue is treated with benzene and washed with water. The residue of the evaporation and the benzenic solution form the raw substituted benzhydryl-piperazine which is then reacted as described in Examples 2 or 3.

The substituted benzhydryl-piperazines may also be obtained by catalytic debenzylation of compounds such as 1-*p*-halo, or 1-*p*-methyl-benzhydryl-4-benzyl-piperazine as hereafter described in Example 4.

EXAMPLE 4.

1-*p*-CHLORBENZHYDRYL-4-*p*-METHOXYBENZYL-PIPERAZINE.

32.3 gr. of 1-*p*-chlorobenzhydryl-4-benzyl-piperazine, dissolved in 300 cm³ of alcohol are heated in an autoclave vessel, in the presence of Raney nickel, under a pressure of 100 kgr. H_2, at about 150° C. for 6 hours.

The catalyst is filtered, the solvent is evaporated and the residue is fractionated under a high vacuum. *p*-chloro-benzhydryl-piperazine (B.P. 180—185° C/1 mm. Hg.) is isolated with a yield of 75%.

This product is then treated with *p*-methoxybenzyl chloride according to the Example 2. 1-*p*-chloro-benzhydryl-4-*p*-methoxybenzyl-piperazine boils at 245—250° C./1.5 mm. Hg. and the corresponding dihydrochloride melts at 210° C.

The same product may also be obtained according to Examples 1 or 3.

EXAMPLE 5.

1-*p*-CHLOROBENZHYDRYL-4-BENZYL-PIPERAZINE.

$$\begin{matrix} p\text{-Cl.C}_6\text{H}_4 \\ \text{C}_6\text{H} \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_5$$

B.P. 235—240° C./0.5 mm. Hg.
Dihydrochloride: M.P. 210° C.

EXAMPLE 6.

1-*p*-BROMOBENZHYDRYL-4-BENZYL-PIPERAZINE.

$$\begin{matrix} p\text{-Br.C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_5$$

B.P. 240—245° C./1.5 mm. Hg.
Dihydrochloride: M.P. 215° C.

EXAMPLE 7.

1-*p*,*p*'-DICHLOROBENZHYDRYL-4-BENZYL-PIPERAZINE.

$$\begin{matrix} p\text{-Cl.C}_6\text{H}_4 \\ p\text{-Cl.C}_6\text{H}_4 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_5$$

B.P. 200—205° C./0.5 mm. Hg.
Dihydrochloride: M.P. 235° C.

EXAMPLE 8.

1-*p*-METHYLBENZHYDRYL-4-BENZYL-PIPERAZINE.

$$\begin{matrix} \text{p-CH}_3\text{.C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_5$$

B.P. 210—220° C./1 mm. Hg.
Dihydrochloride: M.P. 212° C.

EXAMPLE 9.

1-*p*-METHOXYBENZHYDRYL-4-BENZYL-PIPERAZINE.

$$\begin{matrix} p\text{-CH}_3\text{O.C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_5$$

B.P. 220° C./2 mm. Hg.
Dihydrochloride: M.P. 198° C.

EXAMPLE 10.

1-BENZHYDRYL-4-*p*-METHYLBENZYL-PIPERAZINE.

$$\begin{matrix} \text{C}_6\text{H}_5 \\ \text{C}_6\text{H}_5 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_4\text{.}p\text{-CH}_3$$

B.P. 215—220° C./1 mm. Hg.
Dihydrochloride: M.P. (inst.) 218° C.

EXAMPLE 11.

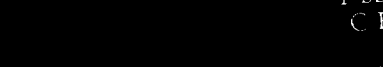
1-*p*-CHLOROBENZHYDRYL-4-*p*-METHYL-BENZYL-PIPERAZINE.

$$\begin{matrix} p\text{-Cl.C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \end{matrix} > \text{CH—N(C}_4\text{H}_8\text{)N—CH}_2\text{C}_6\text{H}_4\text{.—CH}_3$$

B.P. 225—230° C./1 mm. Hg.
Dihydrochloride: M.P. 218° C.
p-methylbenzyl-piperazine,
$\text{HN(C}_4\text{H}_8\text{)N—CH}_2\text{.C}_6\text{H}_4\text{.CH}_3$

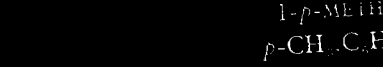
which is necessary when the products of examples 10 and 11 are prepared according to the method of Example 1, is obtained by the action of a halide of *p*-methyl benzyl on piperazine or on carbethoxy-piperazine, in this last case followed by decarboxylation. *p*-methylbenzyl-piperazine boils at 120° C./2 mm. Hg.

EXAMPLE 12.
1-BENZHYDRYL-4-*p*-METHOXYBENZYL-PIPERAZINE.



B.P. 225—230° C./1 mm. Hg. M.P. 114° C. (recryst. alcohol).
Dihydrochloride: M.P. 222° C.

EXAMPLE 13.
1-*p*-METHYLBENZHYDRYL-4-*p*-METHOXY-BENZYL-PIPERAZINE.



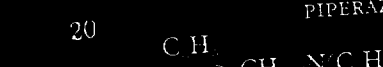
B.P. 240—250° C./1 mm. Hg.
Dihydrochloride: M.P. (inst.) 218° C.

EXAMPLE 14.
1-BENZHYDRYL-4-*m*-METHYLBENZYL-PIPERAZINE.



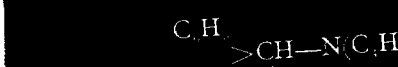
B.P. 226—227° C./2 mm. Hg. M.P. (recrystl. alcohol) 100° C.
Dihydrochloride: M.P. 222° C.

EXAMPLE 15.
1-BENZHYDRYL-4-*p*-CHLOROBENZYL-PIPERAZINE.



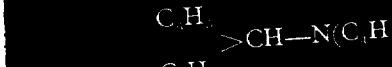
B.P. 230—232° C./1 mm. Hg.
Dihydrochloride: M.P. 232° C.

EXAMPLE 16.
1-BENZHYDRYL-4-*p*-ETHYLBENZYL-PIPERAZINE.



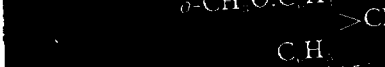
B.P. 205—210° C./1.5 mm. Hg.
Dihydrochloride: M.P. 230° C.

EXAMPLE 17.
1-BENZHYDRYL-4-*p*-ETHOXYBENZYL-PIPERAZINE.



B.P. 248—250° C./2 mm. Hg.
Dihydrochloride: M.P. 212° C.

EXAMPLE 18.
1-*o*-METHOXYBENZHYDRYL-4-BENZYL-PIPERAZINE.



B.P. 210—215° C./2 mm. Hg.
Maleate: M.P. 172° C.

EXAMPLE 19.
1-*m*-CHLOROBENZHYDRYL-4-BENZYL-PIPERAZINE.

B.P. 225—230° C./1.5 mm. Hg.
Dihydrochloride: M.P. 228° C.

EXAMPLE 20.
1-BENZHYDRYL-4-*o*-METHYLBENZYL-PIPERAZINE.

B.P. 200—205/1 mm. Hg.
Dihydrochloride: M.P. 218° C.

EXAMPLE 21.
1-BENZHYDRYL-4-*o*-METHOXYBENZYL-PIPERAZINE.

B.P. 225—230° C./1 mm. Hg.
Dihydrochloride: M.P. 182° C.
Fumarate: M.P. 215° C.

EXAMPLE 22.
1-BENZHYDRYL-4-*m*-ETHOXYBENZYL-PIPERAZINE.

B.P. 215° C./1 mm. Hg. M.P. (recryst. 65 alcohol) 82° C.
Dihydrochloride: M.P. 218° C.

EXAMPLE 23.
1-BENZHYDRYL-4-*m*-CHLOROBENZYL-PIPERAZINE.

B.P. 205—210° C./2 mm. Hg. M.P. (recryst. alcohol) 96° C.
Dihydrochloride: M.P. 238° C.

EXAMPLE 24.
1-BENZHYDRYL-4-(3',5'-DIMETHYLBENZYL)-PIPERAZINE.

C_6H_5
$>CH—N(C_4H_8)N—CH_2C_6H_3(CH_3)_2$
C_6H_5

B.P. 233° C./2 mm. Hg. M.P. (recryst. alcohol) 128° C.
Dihydrochloride: 222° C.

EXAMPLE 25.
1-*p*-CHLOROBENZYHYDRYL-4-*m*-METHYLBENZYL-PIPERAZINE.

p-Cl.C_6H_4
$>CH—N(C_4H_8)N—CH_2C_6H_4$.*m*-$CH_3$
C_6H_5

B.P. 230° C./2 mm. Hg.
Dihydrochloride: M.P. 215° C.

EXAMPLE 26.
1-*o*-METHYLBENZHYDRYL-4-BENZYL-PIPERAZINE.

o-$CH_3.C_6H_4$
$>CH—N(C_4H_8)N—CH_2C_6H_5$
C_6H_5

B.P. 195—200° C./2 mm. Hg.
Dihydrochloride: M.P. 210° C.

EXAMPLE 27.
1-*o*-BROMOBENZHYDRYL-4-BENZYL-PIPERAZINE.

o-Br.C_6H_4
$>CH—N(C_4H_8)N—CH_2C_6H_5$
C_6H_5

B.P. 210° C./0.5 mm. Hg.
Dihydrochloride: M.P. 232° C.

EXAMPLE 28.
1-*m*-ETHOXYBENZHYDRYL-4-BENZYL-PIPERAZINE.

m-$C_2H_5O.C_6H_4$
$>CH—N(C_4H_8)N—CH_2C_6H_5$
C_6H_5

B.P. 215—220° C./2 mm. Hg.
Dihydrochloride: M.P. 198° C.

EXAMPLE 29.
1-*p*-METHOXY-*p'*-METHYLBENZHYDRYL-4-BENZYL-PIPERAZINE.

p-$CH_3O.C_6H_4$
$>CH—N(C_4H_8)N—CH_2C_6H_5$
p-$CH_3.C_6H_4$

B.P. 245—247° C./1 mm. Hg.
Dihydrochloride: M.P. 272° C.

EXAMPLE 30.
1-*p*,*p'*-DIMETHOXYBENZHYDRYL-4-BENZYL-PIPERAZINE.

p-$CH_3O.C_6H_4$
$>CH—N(C_4H_8)N—CH_2C_6H_5$
p-$CH_3O.C_6H_4$

M.P. (recryst. alcohol) 100° C.
Dihydrochloride: M.P. 237° C.

EXAMPLE 31.
1-*o*,*o'*-DIMETHOXYBENZHYDRYL-4-BENZYL-PIPERAZINE.

o-$CH_3O.C_6H_4$
$>CH—N(C_4H_8)N—CH_2C_6H_5$
o-$CH_3O.C_6H_4$

M.P. (recryst. alcohol) 102° C.
Dihydrochloride: M.P. 185° C.

EXAMPLE 32.
1-BENZHYDRYL-4-*p*-(*n*-PROPYL)BENZYL-PIPERAZINE.

C_6H_5
$>CH—N(C_4H_8)N—CH_2C_6H_4$.*p*-$C_3H_7$
C_6H_5

M.P. 108—110° C.
Dihydrochloride: M.P. 266° C.

EXAMPLE 33.
1-BENZHYDRYL-4-*p*-(*n*-BUTYL)BENZYL-PIPERAZINE.

C_6H_5
$>CH—N(C_4H_8)N—CH_2C_6H_4$.*p*-$C_4H_9$
C_6H_5

M.P. (inst.) 93° C.
Dihydrochloride: M.P. 224° C.

EXAMPLE 34.
1-BENZHYDRYL-4-*p*-(TERTIARY BUTYL)-BENZYL-PIPERAZINE.

C_6H_5
$>CH—N(C_4H_8)N—CH_2C_6H_4$.*p*-$C(CH_3)_3$
C_6H_5

M.P. 139—141° C.
Dihydrochloride: M.P. 256° C.

EXAMPLE 35.

1-BENZHYDRYL-4-*m*-(TERTIARY BUTYL)-BENZYL-PIPERAZINE.

$$(C_6H_5)_2CH{-}N(C_4H_8)N{-}CH_2C_6H_4\text{-}m\text{-}C(CH_3)_3$$

B.P. 198—201° C./0.05 mm. Hg.
Dihydrochloride: M.P. 232° C.

EXAMPLE 36.

1-BENZHYDRYL-4-(3',4'-DIMETHOXY)-BENZYL-PIPERAZINE.

$$(C_6H_5)_2CH{-}N(C_4H_8)N{-}CH_2C_6H_3(OCH_3)_2$$

M.P. 86—87° C.
Dihydrochloride: M.P. 230° C.

EXAMPLE 37.

1-*p*-CHLORBENZHYDRYL-(3',5'-DIMETHYL-BENZYL)-PIPERAZINE.

$$(p\text{-}ClC_6H_4)(C_6H_5)CH{-}N(C_4H_8)N{-}CH_2C_6H_3(CH_3)_2$$

B.P. 218—225° C/0.001 mm. Hg.
Dihydrochloride: M.P. 231° C.

EXAMPLE 38.

1-*p*-CHLORBENZHYDRYL-4-*p*-(*n*-BUTYL)BENZYL-PIPERAZINE

$$(p\text{-}ClC_6H_4)(C_6H_5)CH{-}N(C_4H_8)N{-}CH_2C_6H_4\text{-}p\text{-}C_4H_9$$

B.P. 220—230° C./0.001 mm. Hg.
Dihydrochloride: M.P. 221° C.

EXAMPLE 39.

1-*p*-CHLORBENZHYDRYL-4-*p*-(TERTIARY BUTYL) BENZYL-PIPERAZINE.

$$(p\text{-}ClC_6H_4)(C_6H_5)CH{-}N(C_4H_8)N{-}CH_2C_6H_4\text{-}p\text{-}C(CH_3)_3$$

B.P. 230—240° C./0.001 mm. Hg.
Dihydrochloride: M.P. 265—266° C.

EXAMPLE 40.

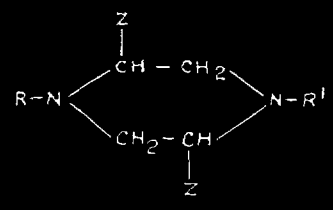
1-*p*-CHLORBENZHYDRYL-4-*m*-(TERTIARY BUTYL)-BENZYL-PIPERAZINE

$$(p\text{-}ClC_6H_4)(C_6H_5)CH{-}N(C_4H_8)N{-}CH_2C_6H_4\text{-}m\text{-}C(CH_3)_3$$

B.P. 217—220° C./0.1 mm. Hg.
Dihydrochloride: M.P. 240° C.

The compounds of Examples 5 to 40 may be obtained indifferently according to the methods of Examples 1 to 3; the compounds of Examples 10 to 17 and 20 to 25 and 32 to 40 may also be prepared according to the method of Example 4.

By selecting as starting point a piperazine having alkyl groups on two atoms of carbon, there are obtained according to the indications of Examples 1 to 4 derivatives of the formula



in which

R and R' represent aralkyl groups of different natures, and

Z represents an alkyl group.

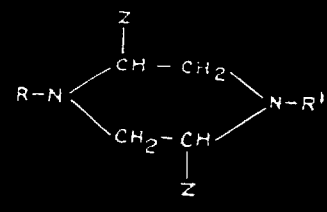
According to the initial substance used in carrying out the invention, say either piper-

azine or 2.5-dialkyl-piperazine, it will be possible to obtain either the piperazine derivatives mentioned in the above Examples or the corresponding derivatives of 2.5-dialkyl-piperazine.

Among the 2.5-dialkyl-piperazines, it has been noticed that 2.5-dimethyl-piperazine is particularly suitable. Its derivatives substituted in positions 1 and 4 have therapeutical properties analogous to those of piperazine derivatives. However, there is no reason to believe that this would not be the case with derivatives of other 2.5-dialkyl-piperazines, such for example as 2.5-diethyl-piperazines, or 2-methyl-5-ethyl piperazine or again any analogous propylic or butylic derivative. Likewise, there is no reason for thinking that the present process would not be suitable for preparing 1.4-aralkyl derivatives of piperazines substituted in positions 2 and 5 by the higher alkyl radicals mentioned above. Similar considerations are premissable as regards piperazine derivatives carrying only a single alkyl radical either in position 2 or in position 5. However of all the 2.5-dialkyl-piperazines the methylated compounds is the easiest to prepare. The compounds having alkyl radicals with a higher number of carbon atoms are technically less easily available and for this reason they seem to be at present of a smaller technical interest.

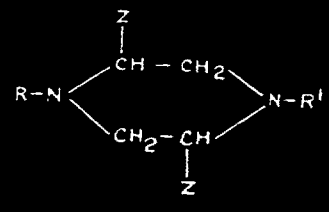
What I claim is:—

1. A 1.4-aralkylpiperazine of the formula



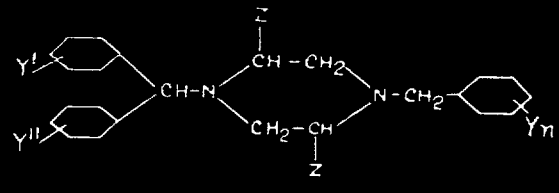
wherein R and R' represent aralkyl groups of different kinds, and Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms.

2. A 1.4-aralkylpiperazine of the formula



where R and R' represent aralkyl groups of different kinds, one of said groups being a benzhydryl group and the other a benzyl group, and Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms.

3. A 1.4 aralkylpiperazine as claimed in claim 2, of the formula



wherein each of Y, Y' and Y'' represent a member selected from the group consisting of a hydrogen atom, a halogen atom, an alkyl radical with 1 to 4 carbon atoms and an alkoxy radical with 1 to 4 carbon atoms, Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, and *n* stands for the figure 1 when Y is a halogen, and either the figure 1 or the figure 2 when Y is an alkyl or an alkoxy radical.

4. Piperazine derivatives of the general formula

$$R—N(C_4H_8)N—R'$$

wherein R is selected from the group; benzhydryl, *p*-chlorobenzhydryl, *p*-bromobenzhydryl, *p*-methylbenzhydryl, *p*-methoxybenzhydryl, *m*-chlorobenzhydryl, *o*-bromobenzhydryl, *o* - methylbenzhydryl, *o* - methoxybenzhydryl, *m* - chlorobenzhydryl, *m* - ethoxybenzhydryl, *p* - methoxy - *p'* - methylbenzhydryl, *p* - *p'* - dichlorobenzhydryl, *p,p'* - dimethoxybenzydryl, *o,o'*-dimethoxybenzhydryl and R' is the group benzyl.

5. Piperazine derivates of the general formula

$$R—N(C_4H_8)N—R'$$

wherein R is selected from the group: benzhydryl *p*-chlorobenzhydryl and R' is selected from the group: *p* - methylbenzyl, *p*-methoxybenzyl, *m* - methylbenzyl, *p* - (*n*-butyl)benzyl, *p* - (tertiary butyl)benzyl, *m*-(tertiary butyl)benzyl, 3',5'-dimethylbenzyl.

6. Piperazine derivatives of the general formula

$$R—N(C_4H_8)N—R'$$

wherein R is the group benzhydryl and R' is selected from the group; *p*-chlorobenzyl, *p* - ethylbenzyl, *p* - ethoxybenzyl, *o* - methylbenzyl, *o* - methoxybenzyl, *m* - chlorobenzyl, *m* - ethoxybenzyl, *p* - (*n*-propyl(benzyl, 3',4'-dimethoxylbenzyl.

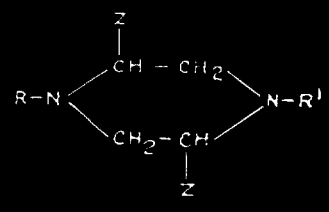
7. Piperazine derivatives of the general formula

azine or 2.5-dialkyl-piperazine, it will be possible to obtain either the piperazine derivatives mentioned in the above Examples or the corresponding derivatives of 2.5-dialkyl-piperazine.

Among the 2.5-dialkyl-piperazines, it has been noticed that 2.5-dimethyl-piperazine is particularly suitable. Its derivatives substituted in positions 1 and 4 have therapeutical properties analogous to those of piperazine derivatives. However, there is no reason to believe that this would not be the case with derivatives of other 2.5-dialkyl-piperazines, such for example as 2.5-diethyl-piperazines, or 2-methyl-5-ethyl piperazine or again any analogous propylic or butylic derivative. Likewise, there is no reason for thinking that the present process would not be suitable for preparing 1.4-aralkyl derivatives of piperazines substituted in positions 2 and 5 by the higher alkyl radicals mentioned above. Similar considerations are premissable as regards piperazine derivatives carrying only a single alkyl radical either in position 2 or in position 5. However of all the 2.5-dialkyl-piperazines the methylated compounds is the easiest to prepare. The compounds having alkyl radicals with a higher number of carbon atoms are technically less easily available and for this reason they seem to be at present of a smaller technical interest.

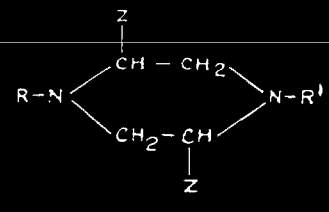
What I claim is:—

1. A 1.4-aralkylpiperazine of the formula



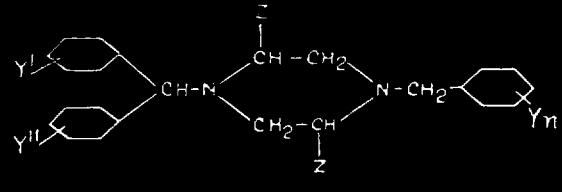
wherein R and R^1 represent aralkyl groups of different kinds, and Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms.

2. A 1.4-aralkylpiperazine of the formula



where R and R^1 represent aralkyl groups of different kinds, one of said groups being a benzhydryl group and the other a benzyl group, and Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms.

3. A 1.4 aralkylpiperazine as claimed in claim 2, of the formula



wherein each of Y, Y^1 and Y^{11} represent a member selected from the group consisting of a hydrogen atom, a halogen atom, an alkyl radical with 1 to 4 carbon atoms and an alkoxy radical with 1 to 4 carbon atoms, Z is a hydrogen atom or an alkyl radical with 1 to 4 carbon atoms, and n stands for the figure 1 when Y is a halogen, and either the figure 1 or the figure 2 when Y is an alkyl or an alkoxy radical.

4. Piperazine derivates of the general formula

$$R—N(C_4H_8)N—R^1$$

wherein R is selected from the group: benzhydryl, p-chlorobenzhydryl, p-bromobenzhydryl, p-methylbenzhydryl, p-methoxybenzhydryl, m-chlorobenzhydryl, o-bromobenzhydryl, o - methylbenzhydryl, o - methoxybenzhydryl, m - chlorobenzhydryl, m - ethoxybenzhydryl, p - methoxy - p^1 - methylbenzhydryl, p - p^1 - dichlorobenzhydryl, p,p^1 - dimethoxybenzydryl, o,o^1-dimethoxybenzhydryl and R^1 is the group benzyl.

5. Piperazine derivates of the general formula

$$R—N(C_4H_8)N—R^1$$

wherein R is selected from the group: benzhydryl p-chlorobenzhydryl and R^1 is selected from the group: p - methylbenzyl, p-methoxybenzyl, m - methylbenzyl, p - (n-butyl)benzyl, p - (tertiary butyl)benzyl, m-(tertiary butyl)benzyl, $3^1,5^1$-dimethylbenzyl.

6. Piperazine derivates of the general formula

$$R—N(C_4H_8)N—R^1$$

wherein R is the group benzhydryl and R^1 is selected from the group; p-chlorobenzyl, p - ethylbenzyl, p - ethoxybenzyl, o - methylbenzyl, o - methoxybenzyl, m - chlorobenzyl, m - ethoxybenzyl, p - (n-propyl(benzyl, $3^1,4^1$-dimethoxylbenzyl.

7. Piperazine derivates of the general formula

$$R—N\langle C_4H_8\rangle N—R$$

wherein R is the group *p*-methylbenzhydryl and R' is the group *p*-methoxybenzyl.

8. Piperazine derivatives of the general formula

$$R—N\langle C_4H_8\rangle N—R'$$

wherein R is *p*-chlor benzhydryl and R' is selected from the group 3,5-dimethylbenzyl, *p*-(*n*-butyl) benzyl, *p*-(tertiary butyl)benzyl and *m*-(tertiary butyl) benzyl.

9. Piperazine derivatives as claimed in any of claims wherein the piperazine ring is substituted in both the 2 and 5 positions by methyl.

10. A process for the preparation of derivatives of piperazine substituted in positions 1 and 4 by aralkyl groups of different natures, wherein a halide of another aralkyl is reacted on a 1-aralkylpiperazine.

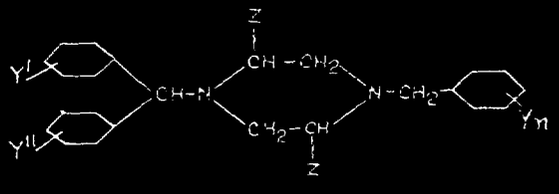
11. Process for the preparation of derivatives of piperazine substituted in positions 1 and 4 by aralkyl groups of different natures, wherein a 1-aralkyl piperazine is reacted with an aldehyde of another aralkyl, and wherein the reaction product is subjected to hydrogenation.

12. Process as claimed in Claim 10 or 11 wherein a benzhydryl group and a benzyl group are selected as the aralkyl groups of different natures.

13. Process as claimed in any of Claims 10 to 12, wherein the aralkyl groups selected are a benzhydryl group and a benzyl group, while each of these groups may be substituted on the aryl by an atom of halogen, an alkyl group, or an alkoxy group, and the benzyl group also by two alkyl or alkoxy groups.

14. Process as claimed in any of Claims 10 to 13, wherein the piperazine ring carries in positions 2 and 5 substituents formed by alkyl groups.

15. Process of preparation as described above of products corresponding to the formula:



in which Y, Y' and Y'' represent an atom of hydrogen or of

a halogen, an alkyl radical with 1 to 4 carbon atoms,

or an alkoxy radical with 1 to 4 carbon atoms;

Z represents an atom of hydrogen or an alkyl group with 1 to 4 carbon atoms;

n signifies the figure 1 where Y = halogen, and the figures 1 or 2 when Y = alkyl or alkoxy.

16. The process for the preparation of piperazine derivatives, substantially as described with reference to any one of the foregoing Examples.

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1, Great James Street, Bedford Row,
London, W.C.1.
Agent for Applicant.

ERRATA

SPECIFICATION NO. 705,979

Page 1, line 8, *for* "arlkyl" *read* "aralkyl".

Page 6, line 18, *for* "handle" *read* "halide".

THE PATENT OFFICE,
10th February, 1955

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