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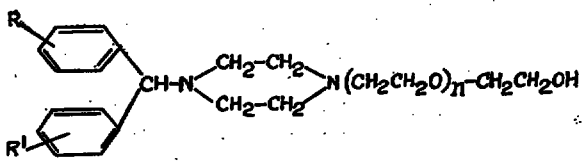
International Classification:—**C07d.**

COMPLETE SPECIFICATION

New Derivatives of N-Mono-Benzhydryl-Piperazine and process for the preparation thereof

I, HENRI MORREN, of 171, Avenue Jupiter, 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 new derivatives of piperazine of the general formula:



(I)

in which R and R^1 each represent an atom of hydrogen or of halogen, an alkyl group or an alkoxy group; R and R^1 can be in an ortho, meta or para position and *n* represents the number 1 or 2.

The invention also relates to various methods of preparing these products, their mineral or organic acid addition salts and their mono-quaternary ammonium derivatives.

It has been found that products of this formula have considerable biological activity. In some cases they produce an antihistaminic action, while in other cases they have a strong sedative action. When substitution is effected in the para position, the therapeutic activity is often very great but this is not a general rule.

According to the present invention, these products are prepared by reacting a 1-R,R^1-benzhydryl-piperazine with a halogenated derivative having the formula

$$Hal—(CH_2CH_2O)_n—CH_2CH_2OH$$

in which Hal represents an atom of halogen, in the presence of an acid acceptor; or by converting a 1-(R,R^1 - benzhydryl) - 4 - (2^1-hydroxyethyl)-piperazine by means of thionyl chloride into 1-(R,R^1-benzhydryl) - 4 - (2^1-chloroethyl)-piperazine and reacting the latter with a metallic derivative having the form $OH—(CH_2CH_2O)_nM$ in which M represents an atom of an alkali metal; or by reacting a 1-(R,R^1-benzhydryl) - 4 - (2^1 - hydroxyethyl)-piperazine, or its derivative from an alkaline metal, with a halogenated derivative having the formula $Hal—(CH_2CH_2O)_nH$; or by reacting an R,R^1-benzhydryl halide with a piperazine derivative having the formula

$$HN—(C_4H_8)—N—(CH_2\ CH_2O)_n—CH_2CH_2OH;$$

or by reacting a 1-R,R^1-benzhydryl-piperazine with ethylene oxide.

In the particular case of compounds which correspond to the general formula (I) and in which *n* represents the number 2, these substances can also be prepared by converting a 1-(R,R^1 - benzhydryl) - 4 - [2^1-(2^{11}-hydroxy-ethoxy)-ethyl]-piperazine by means of thionyl chloride into 1-(R,R^1-benzhydryl) - 4 - [2^1-(2^{11}-chlorethoxy)-ethyl]-piperazine and reacting the latter with a monometallic derivative of glycol; or by reacting a 1-(R,R^1-benzhydryl) - 4 - [2^1 - (2^{11} - hydroxy - ethoxy)-ethyl]-piperazine with a monohalohydrin of glycol.

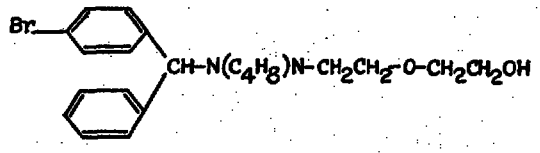
The invention will now be described with reference to the following Examples.

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EXAMPLE 1.

Preparation of 1-*p*-bromobenzhydryl-4-[2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine



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1-*p*-bromobenzhydryl-piperazine is first prepared by the action of *p*-bromobenzhydryl chloride on piperazine (boiling point: 147° C/0.01 mm Hg.).

A mixture of 0.1 mol of 1-*p*-bromobenzhydryl-piperazine, 0.2 mol of 2-(2¹-chlorethoxy)-ethanol, 0.1 mol of triethylamine and 50 cm³ of xylene is heated at 130 to 140° C for 6 hours.

After cooling, the substance is dissolved in dilute hydrochloric acid, whereafter an extraction is effected with benzene to remove the excess 2-(2¹-chlorethoxy)-ethanol. The acid solution is saturated with potassium carbonate and extracted with benzene, whereafter the benzene solution is washed and distilled.

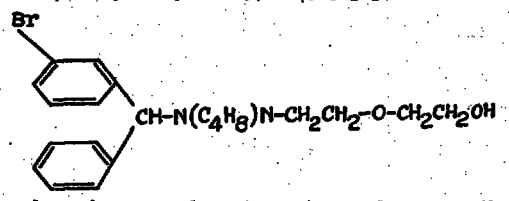
An 80% yield is obtained of 1-*p*-bromobenzhydryl - 4 - [2¹ - (2¹¹ - hydroxyethoxy)-ethyl]-piperazine which has a boiling point of 224° C/0.01 mm Hg.

The corresponding dihydrochloride is prepared by dissolving this base in absolute alcohol and reacting with an excess of gaseous hydrochloric acid.

The product crystallises if a suitable quantity of anhydrous ether is added. Melting point of the dihydrochloride: 190—191° C.

EXAMPLE 2.

Preparation of 1-*m*-bromobenzhydryl-4-[2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine



A mixture of 1.5 mol of N-mono-(2-hydroxyethyl)-piperazine and 1 mol of *m*-bromobenzhydryl chloride is carefully heated, with agitation, and maintained at about 150° C for 15 minutes.

The substance is dissolved in water and extracted with benzene after basification. If the evaporation residue of the benzene extract is purified *in vacuo*, a 75% yield is obtained of 1-*m*-bromobenzhydryl-4-(2¹-hydroxyethyl)-piperazine. Boiling point: 206° C/0.02 mm Hg.

73 g of 1 - *m* - bromobenzhydryl - 4 - (2¹-hydroxyethyl)-piperazine is dissolved in 300 cm³ of dry benzene. This solution is treated cold, and with agitation, with 36 g of thionyl chloride dissolved in 100 cm³ of dry benzene. Reflux heating is then carried out until sulphur dioxide ceases to be evolved.

The solvent is evaporated *in vacuo*, the residue is dissolved in anhydrous acetone and the hydrochloride of 1 - *m* - bromobenzhydryl-4-(2¹ - chloroethyl) - piperazine produced is filtered.

The corresponding base is liberated by treating the aqueous solution of this hydrochloride with an excess of potassium carbonate. The base is extracted in benzene and the benzene solution dried on potassium carbonate.

This benzene solution is then added to an equimolecular solution of the monosodium derivative of ethyleneglycol in a considerable excess of ethyleneglycol. The benzene is removed by distillation and the residue heated, with continuous agitation, in a boiling water-bath for 3 hours.

Excess glycol is removed by distillation *in vacuo* and the residue dissolved in water and benzene. The benzene extract is washed in water several times, concentrated *in vacuo* and the residue distilled in a high vacuum.

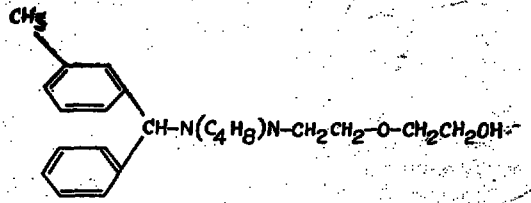
The 1-*m*-bromobenzhydryl - 4 - [2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine obtained distils at 225° C/0.02 mm Hg.

The corresponding dihydrochloride is prepared by adding a slight excess of an alcohol solution of hydrochloric acid to an alcohol solution of the base. Melting point: 208—210° C.

A monoquaternary derivative with a melting point of 181° C can be produced by treating the base with methyl iodide. Monoquaternisation of the base by dimethyl sulphate gives a salt having an amorphous form.

EXAMPLE 3.

Preparation of 1-*m*-methylbenzhydryl-4-[2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine



The 1 - *m* - methylbenzhydryl - 4 - (2¹-hydroxyethyl)-piperazine is produced by the process described in Example 2 for the preparation of the corresponding *m*-brominated derivative, that is, by the action of the *m*-methylbenzhydryl chloride on the N-mono-(2-hydroxyethyl)-piperazine. The 1-*m*-methylbenzhydryl - 4 - (2¹ - hydroxyethyl)-piperazine

distils at 176° C/0.05 mm Hg.

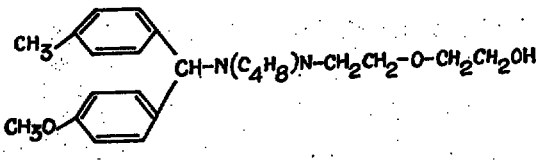
A mixture of 0.2 mol of 1-*m*-methylbenzhydryl - 4 - (2^1-hydroxyethyl)-piperazine, 300 cm^3 of xylene, 15 g of anhydrous sodium carbonate and 30 g of glycol bromohydrin is heated under reflux for 48 hours.

After cooling, extraction is effected with dilute hydrochloric acid. The acid solution is treated with an excess of potassium carbonate and extracted with benzene. After evaporation of the solvent, distillation is effected in a high vacuum. The condensation product boils at 210° C/0.1 mm Hg. Melting point of the corresponding dihydrochloride is 197—199° C.

Instead of sodium carbonate, an alkaline oxide or the reaction product itself can be used as acceptor of hydrohalic acid.

EXAMPLE 4.

Preparation of 1-(*p*-methyl-p^1-methoxy)-benzhydryl-4-[2^1-(2^{11} - hydroxyethoxy) - ethyl]-piperazine



A mixture of 0.2 mol of N-mono-[2^1-(2^{11}-hydroxyethoxy) - ethyl] - piperazine with a xylene solution of 0.2 mol of (*p*-methyl-p^1-methoxy)-benzhydryl chloride is heated at about 140° C for 3 hours.

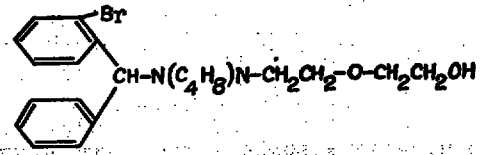
The substance is dissolved in dilute hydrochloric acid and the unconverted benzhydryl chloride is extracted with benzene.

The acid solution is basified with an excess of potassium carbonate and then extracted with benzene. After evaporation of the solvent, the residue is distilled in a high vacuum.

The 1 - (*p* - methyl - p^1 - methoxy) - benzhydryl - 4 - [2^1-(2^{11}-hydroxyethoxy)-ethyl]-piperazine has a boiling point of 225—230° C/0.01 mm Hg.

EXAMPLE 5.

Preparation of 1-*o*-bromobenzhydryl-4-[2^1-(2^{11}-hydroxyethoxy)-ethyl]-piperazine



A toluene solution of 2 equivalents of ethylene oxide is added to a toluene solution of N-mono - *o* - bromobenzhydryl-piperazine. The reaction is produced by heating in an autoclave at about 170° C for one hour.

After cooling, distillation is effected *in vacuo* and the following products yielded *seriatim*: toluene, *o*-bromobenzhydryl-piperazine which has not reacted (boiling point: 160° C/0.02 mm Hg), 1-*o*-bromobenzhydryl-4-(2^1-hydroxyethyl)piperazine (boiling point: 198° C/0.02 mm Hg) and 1-*o*-bromobenzhydryl-4-[2^1-(2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point: 215—220° C/0.01 mm Hg.).

EXAMPLE 6.

Preparation of various derivatives

The products for which the formulae are given hereinafter were prepared by the processes described in Examples 1 to 5, using the appropriate benzhydrylated derivative.

1 - *o* - chlorobenzhydryl - 4 - [2^1 - (2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point of the base: 215° C/0.015 mm Hg).

The dihydrochloride does not crystallise and is precipitated in the amorphous state by ether. The salt produced contains one molecule of ether; it has a partial melting point at about 90° C and a total melting point at 165° C.

The monoquaternary derivative with a melting point of 168° C is produced by treating the base with methyl iodide.

1 - *m* - chlorobenzhydryl - 4 - [2^1 - (2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point of the base: 215° C/0.5 mm Hg, melting point of the dihydrochloride: 213° C).

1 - (*p* - chloro - p^1 - chloro) - benzhydryl-4-[2^1 - (2^{11} - hydroxyethoxy) - ethyl]-piperazine (boiling point of the base: 245° C/0.1 mm Hg, melting point of the dihydrochloride: 205—207° C).

1 - *o* - methylbenzhydryl - 4 - [2^1 - (2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point of the base: 194° C/0.1 mm Hg).

1 - *m* - methoxybenzhydryl - 4 - [2^1-(2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point of the base: 225° C/0.07 mm Hg, melting point of the dihydrochloride: 190—191° C).

1 - *o* - amyloxybenzhydryl - 4 - [2^1 - (2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point of the base: 252° C/0.1 mm Hg).

As starting materials there may be used, if desired:

1-*o*-chlorobenzhydryl - piperazine (boiling point: 154° C/0.01 mm Hg),

1-*m*-chlorobenzhydryl - piperazine (boiling point: 162° C/0.1 mm Hg),

1-*o*-bromobenzhydryl - piperazine (boiling point: 160° C/0.02 mm Hg),

1-*m*-bromobenzhydryl - piperazine (boiling point: 185° C/1 mm Hg),

1 - *p*, p^1 - dichlorobenzhydryl - piperazine (melting point: 106° C, crystallised from petroleum ether),

1-*o*-methylbenzhydryl - piperazine (boiling point: 148° C/0.01 mm Hg),

1-*m*-methylbenzhydryl - piperazine (boiling

point: 150° C/0.05 mm Hg),

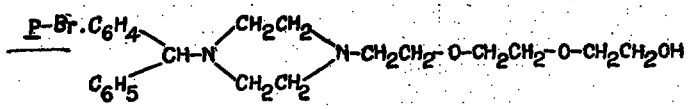
1-*m*-methoxybenzhydryl - piperazine (boiling point: 160° C/0.02 mm Hg),

1-*o*-amyloxybenzhydryl - piperazine (boiling point: 192—195° C/0.2 mm Hg),

1-(*p* - methyl - p^1 - methoxy) - benzhydryl-piperazine (boiling point: 180—185° C/0.2 mm Hg).

EXAMPLE 7.

1 - *p* - bromobenzhydryl - 4 - {2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



A mixture of 0.1 mol of 1-*p*-bromobenzhydryl-piperazine, 0.2 mol of monochlorohydrin of triethyleneglycol, 0.2 mol of triethylamine and 30 cm³ of xylene is heated at 140° C for 6 hours.

After cooling, the substance is dissolved in dilute hydrochloric acid, whereafter a benzene extraction is performed to remove the excess of chlorinated compound.

The acid solution is saturated with potassium carbonate and extracted with benzene. The benzene solution is then washed with water and distilled.

An 80% yield is obtained of 1-*p*-bromobenzhydryl - 4 - {2^1 - [2^{11} - (2^{111} - hydroxyethoxy)-ethoxy]-ethyl}-piperazine which has a boiling point of 243—250° C/0.02 mm Hg.

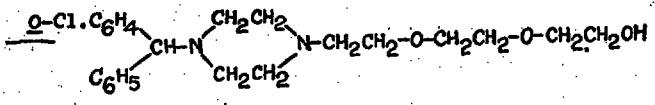
The base thus produced can be converted into dihydrochloride by dissolution in anhydrous ether, filtering on animal charcoal and treatment with an excess of a solution of hydrochloric acid in ether. The salt produced is amorphous and has no definite melting point.

This base can also be quaternised if it is treated in acetone with a considerable excess of methyl bromide or methyl iodide. The quaternary derivatives produced have no definite melting point but analysis shows the fixation of a molecule of alkyl halide, probably on the nitrogen connected to the ether-oxide chain.

The corresponding *p*-chlorinated derivative can be produced in the same way by using 1-*p*-chlorobenzhydryl-piperazine instead of 1-*p*-bromobenzhydryl-piperazine. The base produced has a boiling point of 250° C/0.01 mm Hg. The dihydrochloride and the corresponding quaternary derivatives can be produced as above.

EXAMPLE 8.

1-*o*-chlorobenzhydryl-4-{2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



A mixture of 1.5 mol of 1-(2^1-hydroxyethyl)-piperazine and 1 mol of *o*-chlorobenzhydryl chloride is heated at 150° C for 15 minutes. The substance is dissolved in water, basified by caustic soda and extracted with benzene.

By purifying the benzene extract *in vacuo*, a 75% yield is obtained of 1-*o*-chlorobenzhydryl - 4 - (2^1 - hydroxyethyl) - piperazine which has a boiling point of 205° C/0.02 mm Hg.

0.2 mol of 1-*o*-chlorobenzhydryl-4-(2^1-hydroxyethyl)-piperazine is dissolved in 300 cm³ of dry benzene and a solution of 36 g of thionyl chloride in 100 cm³ of dry benzene is added cold with agitation. Reflux heating is then carried out until sulphur dioxide has ceased to be evolved.

The solvent is evaporated *in vacuo*, the residue is dissolved in anhydrous acetone and the hydrochloride formed is filtered. The corresponding base is liberated by treating the aqueous solution of this hydrochloride with an excess of potassium carbonate. A benzene extraction is effected and the benzene solution of the base is dried over potassium carbonate.

This benzene solution is then added to an equimolecular solution of the monosodium derivative of diethyleneglycol in a considerable excess of diethyleneglycol. The benzene is removed by distillation and the residue is heated in a boiling water-bath with agitation for 3 hours.

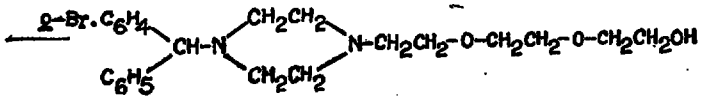
The excess diethyleneglycol is removed *in vacuo* and the residue dissolved in water and then in benzene. The benzene extract is washed several times in water, then purified *in vacuo*.

The 1-*o*-chlorobenzhydryl-4-{2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine obtained distills at 240—245° C/0.01 mm Hg.

The process described in the preceding example can be used to convert this base into the dihydrochloride or the quaternary derivative.

EXAMPLE 9.

1-*o*-bromobenzhydryl-4-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy]-ethyl}-piperazine



The 1-*o*-bromobenzhydryl-4-(2¹-hydroxyethyl)-piperazine is prepared, by the process described in Example 8 for preparing the corresponding *o*-chlorinated derivative, by the action of *o*-bromobenzhydryl chloride on 1-(2¹-hydroxyethyl)-piperazine. The 1-*o*-bromobenzhydryl - 4 - (2¹ - hydroxyethyl) - piperazine distils at 206° C/0.02 mm Hg.

A mixture of 0.2 mol of 1-*o*-bromobenzhydryl - 4 - (2¹ - hydroxyethyl) - piperazine, 15 g of anhydrous sodium carbonate, 40 g of monobromhydrin of diethyleneglycol and 300 cm³ of xylene is heated under reflux for 48 hours.

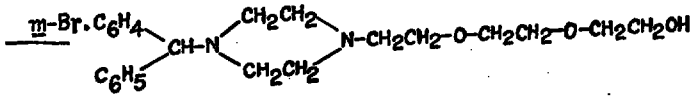
After cooling, the substance is extracted with dilute hydrochloric acid. An excess of potassium carbonate is added to the acid solution and a benzene extraction effected. After evaporation of the solvent, distillation is effected in a high vacuum. The condensation product distils at 240—246° C/0.005 mm Hg.

Instead of sodium carbonate, an alkaline hydroxide, an alkaline-earth oxide or the reaction product itself can be used as acceptor of hydrobromic acid.

The dihydrochloride and the corresponding quaternary derivatives can be produced by the process described in Example 7.

EXAMPLE 10.

1-*m*-bromobenzhydryl-4-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



0.2 mol of 1 - *m* - bromobenzhydryl - 4-[2¹ - (2¹¹ - hydroxyethoxy) - ethyl]-piperazine is dissolved in 250 cm³ of dry benzene. 36 g of thionyl chloride is added cold and with mechanical agitation, whereafter the mixture is heated until sulphur dioxide has ceased to evolve. Cooling and filtering is performed and the hydrochloride produced is washed with anhydrous acetone.

The corresponding base is liberated by treating the aqueous solution of this hydrochloride with an excess of potassium carbonate; the base is extracted with benzene and the benzene solution dried on potassium carbonate.

This solution is then added to an equimolecular solution of the monosodium derivative of ethyleneglycol in a considerable excess of glycol. The benzene is removed by distillation and the residue heated, with agitation, in a boiling water-bath for 3 hours.

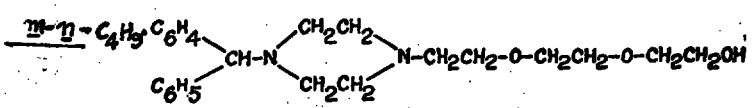
Excess glycol is removed by distillation *in vacuo*. The residue is dissolved in water and then in benzene. The benzene extract is washed several times in water, concentrated *in vacuo* and distilled.

The condensation product distils at 240—245° C/0.01 mm Hg.

The dihydrochloride and corresponding quaternary derivatives can be prepared using the process described in Example 7.

EXAMPLE 11.

1-*m*-*n*-butyl-benzhydryl-4-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



The 1-*m*-*n* - butyl - benzhydryl-4-[2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine with a boiling point of 210—215° C/0.01 mm Hg is prepared using one of the processes described in Examples 1 to 6 and more particularly by the action of 2-(2¹-chlorethoxy)-ethanol on 1-*m*-*n*-butyl-benzhydryl-piperazine. This latter product, which has a boiling point of 160—162° C/0.01 mm Hg, is produced by the action of *m*-*n*-butyl-benzhydryl chloride (boiling point: 148—150° C/0.1 mm Hg) on piperazine.

The chloride is prepared in known manner from *m*-*n*-butyl-benzhydrol which is produced by the action of benzaldehyde on the magnesium derivative of *m*-bromobutyl-benzene, followed by decomposition of the resultant complex by water.

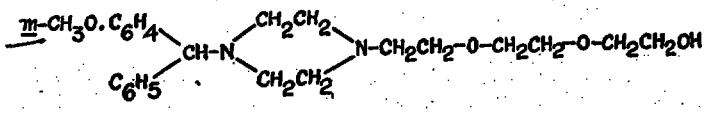
A mixture of 0.2 mol of 1-*m*-*n*-butyl-benzhydryl - 4 - [2¹ - 2¹¹ - hydroxyethoxy)-ethyl]-

piperazine, 15 g of anhydrous sodium carbonate and 30 g of monobromhydrin of glycol is reflux heated for 48 hours.

After cooling, extraction is effected with dilute hydrochloric acid. The acid solution is treated with an excess of potassium carbonate and extracted with benzene. After evaporation of the solvent, distillation is effected in a high vacuum. The condensation product boils at 250—255° C/0.001 mm Hg.

EXAMPLE 12.

1-*m*-methoxybenzhydryl-4-{2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



1-{2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine is prepared by the action of one mol of monochlorhydrin of triethyleneglycol on 3 mols of piperazine hexahydrate at 120° C. Thereafter heating is carried out at 150° C for 2½ hours.

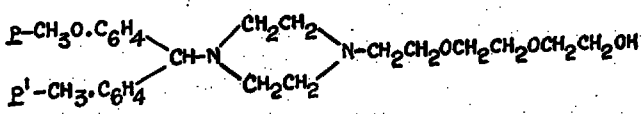
After cooling, one mol of an 8 N solution of caustic soda is added. The water is distilled at a pressure of a few centimetres of mercury. The substance is dissolved in boiling alcohol and the insoluble sodium chloride produced is filtered. The alcohol is then removed and, by distillation, a 65% yield is obtained of 1-{2^1-[2^{11}-(2^{111}-hydroxyethoxy)-ethoxy]-ethyl}-piperazine which has a boiling point of 155° C/1 mm Hg.

An equimolecular mixture of the above product and *m*-methoxybenzhydryl chloride is heated in a xylene solution at about 140° C for 3 hours.

The substance is dissolved in dilute hydrochloric acid and the unconverted *m*-methoxybenzhydryl chloride is extracted with benzene. The acid solution is basified with an excess of potassium carbonate and then extracted with benzene. After evaporation of the solvent, the residue is purified *in vacuo* and the 1-*m*-methoxybenzhydryl - 4 - {2^1 - [2^{11} - (2^{111}-hydroxyethoxy) - ethoxy] - ethyl}-piperazine, which distils at 245—250° C/0.01 mm Hg, is separated out.

EXAMPLE 13.

1-(*p*-methoxy - p^1 - methyl) - benzhydryl-4-{2^1-[2^{11}-(2^{111} - hydroxyethoxy) - ethoxy]-ethyl}-piperazine



A toluene solution of 3 equivalents of ethylene oxide is added to a toluene solution of 1 - (*p* - methoxy - p^1 - methyl) - benzhydryl-piperazine. The reaction is performed by heating in an autoclave at about 170° C for 1 hour.

After cooling, purification is carried out *in vacuo* and the following are yielded *seriatim*: toluene, 1-(*p*-methoxy-p^1-methyl)-benzhydryl-piperazine (boiling point: 180—185° C/0.2 mm Hg), 1 - (*p* - methoxy - p^1 - methyl)-benzhydryl-4-(2^1-hydroxyethyl)-piperazine (boiling point: 208° C/0.02 mm Hg), 1-(*p*-methoxy-p^1 - methyl) - benzhydryl - 4 - [2^1 - (2^{11}-hydroxyethoxy) - ethyl] - piperazine (boiling point: 225—230° C/0.01 mm Hg) and 1-(*p*-methoxy - p^1 - methyl) - benzhydryl - 4-{2^1 - [2^{11} - (2^{111} - hydroxyethoxy) - ethoxy]-ethyl}-piperazine (boiling point: 245—250° C/0.01 mm Hg).

EXAMPLE 14.

Using one or other of the methods described in Examples 7 to 13, it is possible to prepare:

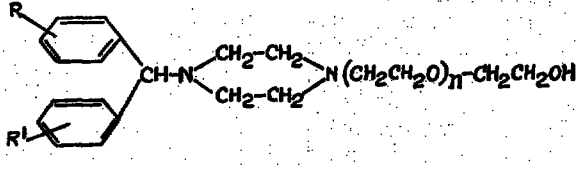
1 - benzhydryl - 4 - {2^1-[2^{11}-(2^{111}-hydroxyethoxy) - ethoxy] - ethyl}-piperazine (boiling point: 220—225° C/0.02 mm Hg);

1-*p*-chlorobenzhydryl - 4 - {2^1-[2^{11}-(2^{111}-hydroxyethoxy) - ethoxy] - ethyl} - piperazine (boiling point: 250° C/0.01 mm Hg);

1-*m*-methylbenzhydryl - 4 - {2^1-[2^{11}-(2^{111}-hydroxyethoxy) - ethoxy] - ethyl} - piperazine (boiling point: 230—235° C/0.01 mm Hg);

WHAT I CLAIM IS:—

1. New derivatives of piperazine having the general formula:



in which R and R^1 each represent an atom of hydrogen or of halogen, an alkyl group or an alkoxy group; R and R^1 can be in ortho, meta or para position and *n* represents the number 1 or 2.

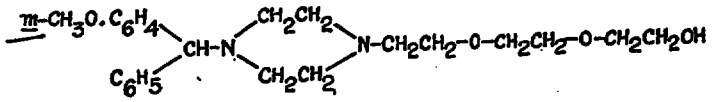
2. Acid addition salts of mineral or organic

piperazine, 15 g of anhydrous sodium carbonate and 30 g of monobromhydrin of glycol is reflux heated for 48 hours.

After cooling, extraction is effected with dilute hydrochloric acid. The acid solution is treated with an excess of potassium carbonate and extracted with benzene. After evaporation of the solvent, distillation is effected in a high vacuum. The condensation product boils at 250—255° C/0.001 mm Hg.

EXAMPLE 12.

1-*m*-methoxybenzhydryl-4-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine



1-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine is prepared by the action of one mol of monochlorhydrin of triethyleneglycol on 3 mols of piperazine hexahydrate at 120° C. Thereafter heating is carried out at 150° C for 2½ hours.

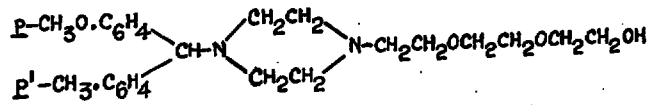
After cooling, one mol of an 8 N solution of caustic soda is added. The water is distilled at a pressure of a few centimetres of mercury. The substance is dissolved in boiling alcohol and the insoluble sodium chloride produced is filtered. The alcohol is then removed and, by distillation, a 65% yield is obtained of 1-{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine which has a boiling point of 155° C/1 mm Hg.

An equimolecular mixture of the above product and *m*-methoxybenzhydryl chloride is heated in a xylene solution at about 140° C for 3 hours.

The substance is dissolved in dilute hydrochloric acid and the unconverted *m*-methoxybenzhydryl chloride is extracted with benzene. The acid solution is basified with an excess of potassium carbonate and then extracted with benzene. After evaporation of the solvent, the residue is purified *in vacuo* and the 1-*m*-methoxybenzhydryl - 4 - {2¹ - [2¹¹ - (2¹¹¹-hydroxyethoxy) - ethoxy] - ethyl}-piperazine, which distils at 245—250° C/0.01 mm Hg, is separated out.

EXAMPLE 13.

1-(*p*-methoxy - *p*¹ - methyl) - benzhydryl-4-{2¹-[2¹¹-(2¹¹¹ - hydroxyethoxy) - ethoxy]-ethyl}-piperazine



A toluene solution of 3 equivalents of ethylene oxide is added to a toluene solution of 1 - (*p* - methoxy - *p*¹ - methyl) - benzhydryl-piperazine. The reaction is performed by heating in an autoclave at about 170° C for 1 hour.

After cooling, purification is carried out *in vacuo* and the following are yielded *seriatim*: toluene, 1-(*p*-methoxy-*p*¹-methyl)-benzhydryl-piperazine (boiling point: 180—185° C/0.2 mm Hg), 1 - (*p* - methoxy - *p*¹ - methyl)-benzhydryl-4-(2¹-hydroxyethyl)-piperazine (boiling point: 208° C/0.02 mm Hg), 1-(*p*-methoxy-*p*¹ - methyl) - benzhydryl - 4 - [2¹ - (2¹¹-hydroxyethoxy) - ethyl] - piperazine (boiling point: 225—230° C/0.01 mm Hg) and 1-(*p*-methoxy - *p*¹ - methyl) - benzhydryl - 4-{2¹ - [2¹¹ - (2¹¹¹ - hydroxyethoxy) - ethoxy]-ethyl}-piperazine (boiling point: 245—250° C/0.01 mm Hg).

EXAMPLE 14.

Using one or other of the methods described in Examples 7 to 13, it is possible to prepare:

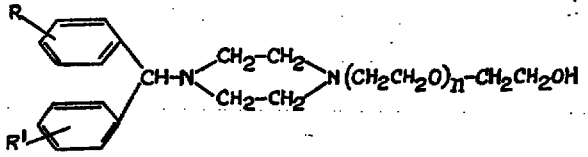
1 - benzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy) - ethoxy] - ethyl}-piperazine (boiling point: 220—225° C/0.02 mm Hg);

1-*p*-chlorobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy) - ethoxy] - ethyl} - piperazine (boiling point: 250° C/0.01 mm Hg);

1-*m*-methylbenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy) - ethoxy] - ethyl} - piperazine (boiling point: 230—235° C/0.01 mm Hg);

WHAT I CLAIM IS:—

1. New derivatives of piperazine having the general formula:



in which R and R¹ each represent an atom of hydrogen or of halogen, an alkyl group or an alkoxy group; R and R¹ can be in ortho, meta or para position and *n* represents the number 1 or 2.

2. Acid addition salts of mineral or organic

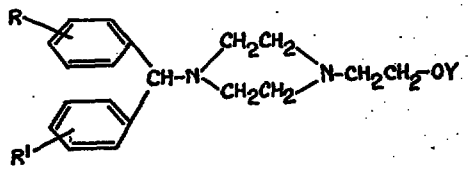
* C L M S *

acids and mono-quaternary ammonium derivatives prepared from the compounds claimed in Claim 1.

3. A process for the preparation of the compounds claimed in Claims 1 and 2, wherein a 1-R,R¹-benzhydryl-piperazine is reacted with a halogenated derivative having the formula $Hal—(CH_2CH_2O)_n—CH_2CH_2OH$ in which Hal represents an atom of halogen.

4. A process for the preparation of the compounds claimed in Claims 1 and 2, wherein a 1-R,R¹-benzhydryl) - 4 - (2¹-hydroxyethyl)-piperazine is converted by means of thionyl chloride into 1 - (R,R¹ - benzhydryl) - 4 - (2¹-chloroethyl)-piperazine and the latter is reacted with a monometallic derivative having the formula $OH—(CH_2CH_2O)_nM$ in which M represents an atom of an alkali metal.

5. A process for the preparation of the compounds claimed in Claims 1 and 2, wherein a piperazine derivative having the formula:



in which Y denotes an atom of hydrogen or an atom of an alkali metal, is reacted with a halogenated derivative having the formula $Hal—(CH_2CH_2O)_nH$ in which Hal denotes an atom of halogen.

6. A process for the preparation of the compounds claimed in Claims 1 and 2, wherein a halide of R,R¹-benzhydryl is reacted with a derivative of piperazine having the formula

$$HN—(C_4H_8)—N—(CH_2.CH_2O)_n—CH_2CH_2OH.$$

7. A process for the preparation of the compounds claimed in Claims 1 and 2, wherein a 1-R,R¹-benzhydryl-piperazine is reacted with ethylene oxide.

8. A process for the preparation of the compounds claimed in Claims 1 and 2 and in which *n* represents the number 2, wherein a 1-(R,R¹ - benzhydryl) - 4 - [2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine is converted by means of thionyl chloride into 1-(R,R¹-benzhydryl) - 4 - [2¹ - (2¹¹ - chlorethoxy)-ethyl]-piperazine and the latter is reacted with a monometallic derivative of glycol.

9. A process for the preparation of the compounds claimed in Claims 1 and 2 and in which *n* represents the number 2, wherein a 1-(R,R¹ - benzhydryl) - 4 - [2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine is reacted with a monohalohydrin of glycol.

10. As new compounds:

1-*o*-chlorobenzhydryl - 4 - [2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*m*-chlorobenzhydryl-4-[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*o*-bromobenzhydryl- 4 -[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*m*-bromobenzhydryl- 4 -[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*p*-bromobenzhydryl- 4 -[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*p*,*p*¹ - dichlorobenzhydryl - 4 - [2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine.

1-*o*-methylbenzhydryl-4-[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1-*m*-methylbenzhydryl-4-[2¹-(2¹¹-hydroxy-ethoxy)-ethyl]-piperazine.

1 - *m* - methoxybenzhydryl - 4 - [2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine.

1 - *o* - amyloxybenzhydryl - 4 - [2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine.

1 - (*p* - methyl - *p*¹ - methoxy)-benzhydryl-4-[2¹-(2¹¹-hydroxyethoxy)-ethyl]-piperazine.

1 - benzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxy-ethoxy)-ethoxy]-ethyl}-piperazine.

1-*o*-chlorobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*p*-chlorobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*o*-bnomobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*m*-bromobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*p*-bromobenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*m*-methylbenzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*m*-*n*-butyl-benzhydryl - 4 - {2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-*m*-methoxybenzhydryl- 4 -{2¹-[2¹¹-(2¹¹¹-hydroxyethoxy)-ethoxy]-ethyl}-piperazine.

1-(*p*-methoxy - *p*¹ - methyl) - benzhydryl-4-{2¹ - [2¹¹ - (2¹¹¹ - hydroxyethoxy) - ethoxy]-ethyl}-piperazine.

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