PATENT SPECIFICATION

NO DRAWINGS

837,986

Date of Application and filing Complete Specification: July 8, 1957.
No. 21624/57.
Application made in Belgium on July 10, 1956.
Application made in Belgium on Sept. 14, 1956.
Complete Specification Published: June 22, 1960.

Index at acceptance:—Class 2(3) B4A1, C1E4K(3:4), C1E7K4, C3A12(A4A:B3:C1:C4:C6), C3A13A1(A4:K), C3A13A3(A4:B1:L), C3A13C(4C:6C:9:10C:10D:10F:10H).

International Classification:—C07d.

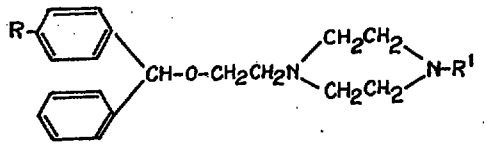
COMPLETE SPECIFICATION

New Piperazine Derivatives 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 piperazine derivatives and process for the preparation thereof.

It is known that compounds of the formula



Formula A

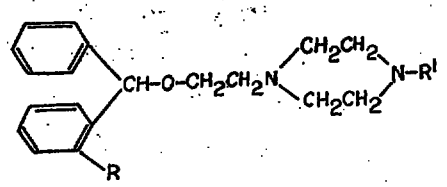
in which R represents a hydrogen or halogen atom or an alkyl or alkoxy group in the para position, and R^1 a hydrogen or halogen atom, or an alkyl, cycloalkyl or aralkyl, substituted or unsubstituted, group, have a considerable antihistaminic activity.

An exhaustive pharmacodynamic examination of these substances has shown that they also have a noticeable antiulcerous activity.

It has now been found that this antiulcerous activity is considerably enhanced by the displacement of the R substituent in the benzhydryl radical from the para to the ortho position.

By using Shay's pharmacological test (H. Shay, S. A. Komarov, S. Fels, D. Meranze, M. Gruenstein, H. Siplet, Gastroenterology, 5, (1945), 43—61), it is found that substances having the general formula A have an antiulcerous activity when administered subcutaneously or "*per os*" in a 100 to 20 mgr./kg. dose.

On the other hand, products of the general formula

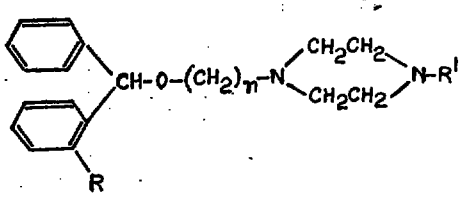


Formula B

in which R and R^1 have the same meaning as in Formula A above, have a marked antiulcerous activity in Shay's test when administered subcutaneously or "*per os*" in a 0.1 to 1 mgr./kgr. dose.

The pharmacological action of these substances, from the viewpoint of their antiulcerous activity, is not known. In fact, these compounds have neither an anticholinergic action nor a parasympathetic ganglioplegic action. These actions are generally regarded as essential in the treatment of gastric ulcers. The substances of the present invention have not these properties. They offer therefor the appreciable advantage of not producing unpleasant secondary effects (for example dryness of the mouth and mydriasis), as do the pharmaceuticals hitherto used as antiulcerous agents.

The present invention relates to new piperazine derivatives having the following general structure



Formula C

wherein R represents a halogen atom or an alkyl radical in the ortho position,
R^1 represents an alkyl, hydroxyalkyl,

hydroxyalkoxyalkyl, aralkoxyalkyl, cycloalkyl or aralkyl radical, any carbocylic ring of which may be substituted by an alkyl or alkoxy radical or a halogen atom,

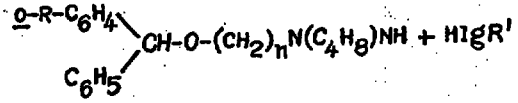
or R^1 is an alkanoyl radical or an aroyl radical which may be halogen substituted, and n is an integer of from 2 to 6.

The present invention also concerns various methods of preparing these products and their mineral and organic acid addition salts.

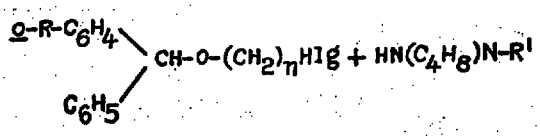
The substances of the present invention have only a low anti-histaminic activity but possess a valuable antiulcerous activity.

In accordance with the present invention, the preparation of these products is carried out

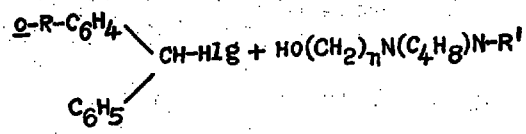
— either by reacting a 1-mono[omega-(*o*-R - benzhydryloxy) - alkyl] - piperazine with an R^1 halide, optionally in the presence of a hydrohalic acid acceptor:



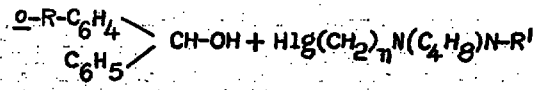
— or by reacting an omega-(*o*-R-benzhydryloxy)-alkyl halide with a 1-mono-R^1-piperazine, optionally in the presence of a hydrohalic acid acceptor:



— or by reacting an *o*-R-benzhydryl halide and a 1-(omega-hydroxyalkyl)-4-R^1-piperazine, optionally in the presence of a hydrohalic acid acceptor:

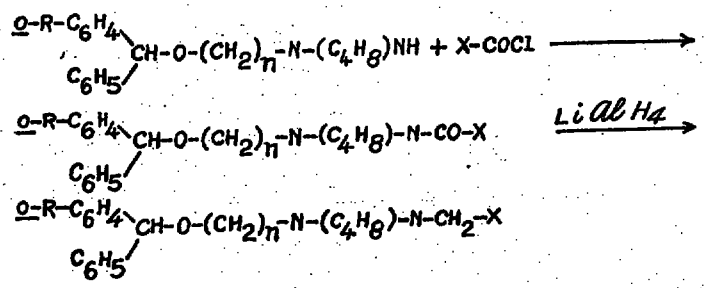


— or by reacting a 1-(omega-halogen-alkyl)-4-R^1-piperazine with an *o*-R-benzhydrol, optionally in the presence of a hydrohalic acid acceptor:



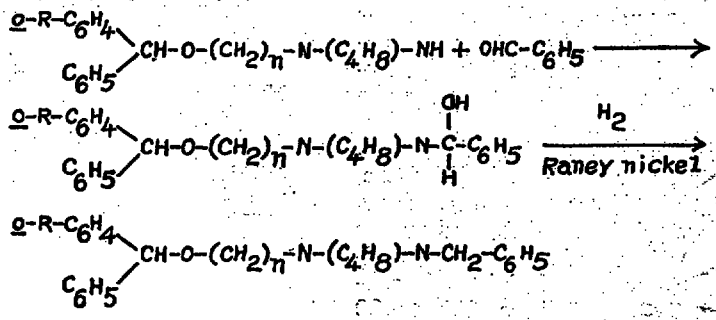
(The hydrohalic acid acceptors referred to above are organic bases, especially tertiary amines, triethylamine being particularly preferred.)

— or by reacting a 1-mono-[omega-(*o*-R-benzhydryloxy)-alkyl]-piperazine with an acid chloride and, if desired, reducing the amide formed by means of lithium-aluminium hydride:



(in this case —CH_2—X is equal to R^1)

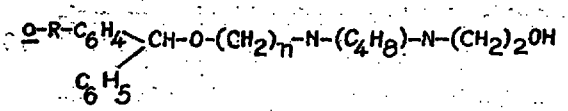
— or by reacting an aldehyde with a 1-[mono-(omega-*o* - R - benzhydryloxy)-alkyl]-piperazine and reducing the product obtained by hydrogen in the presence of Raney nickel:



Instead of the above reactions, the R^1 chain may be linked to the piperazine in several steps. Thus, for example, when R^1 is

——(CH_2)—O—$(CH_2)_2OH$,

the following compound can first be prepared:



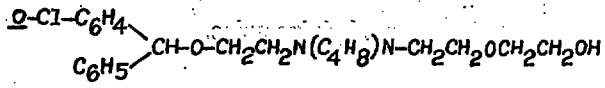
whereafter this product may be condensed with ethylene chlorhydrin or ethylene oxide.

Such particular syntheses are obviously included in the present invention.

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

EXAMPLE 1.

1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4 - [2 - (2 - hydroxyethoxy) - ethyl] - piperazine.



A mixture of 0.1 mole of 1-mono-[2-(*o*-chlorobenzhydryloxy)-ethyl]-piperazine, 0.11 mole of triethylamine and 0.1 mole of 2-(2-chloroethoxy)-ethanol in 100 cc. of toluene is heated for 15 hours at 100°C. with stirring.

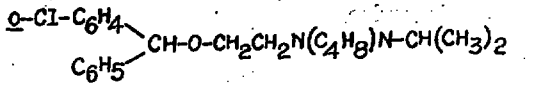
After the reaction, the triethylamine hydrochloride is filtered off and the toluene solution is washed with water. The solvent is evaporated and the residue is rectified *in vacuo*.

The desired condensation product having a boiling point of 230°C./0.1 mm. Hg. is obtained in a yield of 80%.

The corresponding dihydrochloride is prepared by treating an alcoholic solution of the base with dry hydrochloric acid and adding an excess of anhydrous ether. Melting point of the dihydrochloride: 150°C.

EXAMPLE 2.

1 - [2 - *o*-chlorobenzhydryloxy) - ethyl] - 4-isopropyl-piperazine.



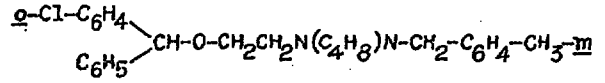
A mixture of 1 mole of 1-mono-isopropyl-piperazine, 1.1 mole of triethylamine and 1 mole of 2-(*o*-chlorobenzhydryloxy)-ethyl chloride in 600 cc. of xylene is heated under reflux for 18 hours.

The triethylamine hydrochloride is filtered off and the xylene solution is washed with an aqueous sodium hydroxide solution and then with water. The solvent is driven off and the residue is rectified *in vacuo*. The condensation product distilling at 184—186°C./0.4 mm. Hg. is obtained in a yield of 88%.

The corresponding dihydrochloride is prepared in an alcoholic medium. Melting point: 203°C.

EXAMPLE 3.

1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4-*m*-methylbenzyl-piperazine.



A mixture of 0.1 mole of 1-*m*-methylbenzyl-4-(2-hydroxyethyl)-piperazine and 0.1 mole of *o*-chlorobenzhydryl chloride is heated for 3 hours at 160°C. in a nitrogen atmosphere.

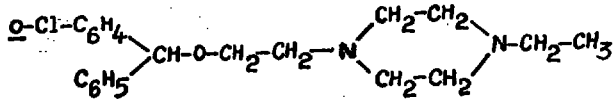
After cooling, the mass is taken up in benzene and in a 20% aqueous sodium hydroxide solution. The benzene solution is decanted, washed with water and concentrated. The condensation product is rectified under a high vacuum. Boiling point: 240°C./0.1 mm. Hg. Yield: 50%.

The corresponding dihydrochloride is prepared in an alcoholic medium. Melting point: 224—226°C.

The preparation of the 1-*m*-methylbenzyl-4-(2-hydroxyethyl)-piperazine is described by H. Morren and al. /Ind. chim. Belge, *19*, (1954), 1176—96/.

EXAMPLE 4.

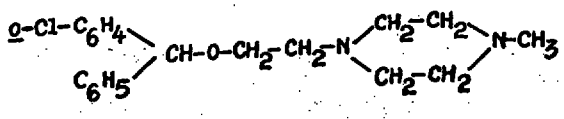
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl]-4-ethylpiperazine.



0.1 mole of 1[2-(*o*-chlorobenzhydryloxy)-ethyl]-4-acetylpiperazine, prepared by the process described in Example 7, is added to a suspension in ether of 0.15 mole of lithium-aluminium hydride and the mixture is heated under reflux for 18 hours under a current of nitrogen. The complex formed is then decomposed by the careful addition of a saturated solution of Seignette salt with vigorous cooling. The reaction product is extracted with ether, dried and distilled under a high vacuum. 1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4-ethyl-piperazine, b.p. 178—180°C./0.03 mm. Hg., is obtained in a yield of 88%. Melting point of the dihydrochloride is 186—188°C.

EXAMPLE 5.

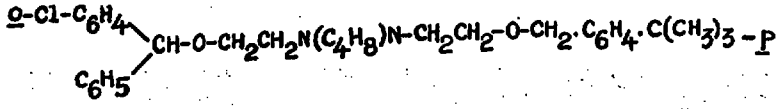
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4 - methylpiperazine.



0.1 mole of 1-mono-[2-(*o*-chlorobenzhydryloxy)-ethyl]-piperazine is treated with 24 cc. of a 40% aqueous formaldehyde solution in 100 cc of ethanol and the whole is hydrogenated in an autoclave in the presence of Raney nickel under a pressure of 50 kg. of hydrogen for 3 hours at 60°C. The alcohol is evaporated off and the residue extracted with benzene. On distillation, the methyl derivative is obtained in a yield of 95%. Boiling point 185—190°C./0.1 mm. Hg. Melting point of the dihydrochloride is 200°C.

EXAMPLE 6.

1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4-[2 - (*p* - t. - butyl - benzyloxy) - ethyl]-piperazine.

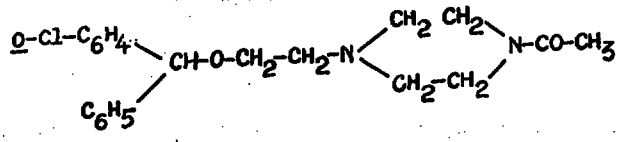


0.1 mole of *o*-chlorobenzhydrol is reacted with 0.1 mole of 1-[2-(*p*-t.-butylbenzyloxy)-ethyl]-4-(2-chloroethyl)-piperazine (preparation described in Ind. chim. Belge, *19*, (1954), 1176—96) by heating for 3 hours at 160°C. in a nitrogen atmosphere. The condensation product is obtained in a yield of 50%. Boiling point: 275°C./0.1 mm. Hg.

The corresponding dihydrochloride was prepared in a mixture of alcohol and ether.

EXAMPLE 7.

1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4-acetylpiperazine.

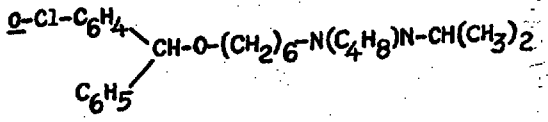


This compound is prepared in accordance with the process of Example 1 from 1-mono-[2 - (*o*-chlorobenzhydryloxy) - ethyl] - piperazine and acetyl chloride in the presence of triethylamine and in a toluene solution. The heating time is 1 hour. The product is obtained in a yield of 94%. Boiling point: 220°C./0.02 mm. Hg.

Similarly, 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl] - 4 - (*o*-chlorobenzoyl) - piperazine, b.p. 255° C./0.1 mm. Hg., is prepared from 1 - mono-[-2-(*o*-chlorobenzhydryloxy)-ethyl]-piperazine and *o*-chlorobenzoyl chloride. Melting point of the dihydrochloride: 210—212°C.

EXAMPLE 8.

1 - [6 - (*o*-chlorobenzhydryloxy)- hexyl] - 4-isopropylpiperazine.



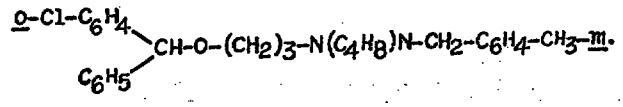
A mixture of 0.1 mole of 1-isopropyl-piperazine, 0.11 mole of triethylamine and 0.1 mole of 6-(*o*-chlorobenzhydryloxy)-hexyl-chloride in 100 cc. of toluene is heated under reflux for 15 hours.

After the reaction, the triethylamine hydrochloride is filtered off, and the filtrate is first washed with an aqueous sodium hydroxide solution (20%) and then with water.

The toluene solution is concentrated and then distilled *in vacuo*. The condensation product is obtained in a yield of 71%. Boiling point: 230—233°C/0.2 mm. Hg. The corresponding dihydrochloride is prepared in an alcoholic medium. Melting point: 230°C.

EXAMPLE 9.

1 - [3 - (*o*-chlorobenzhydryloxy) - propyl]-4-(*m*-methylbenzyl)-piperazine.



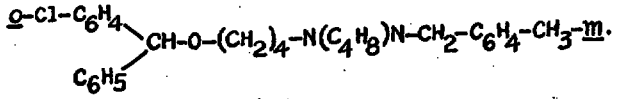
A mixture of 0.1 mole of 1-[3-(*o*-chlorobenzhydryloxy)-propyl]-piperazine, 0.11 mole triethylamine and 0.1 mole of *m*-methylbenzyl bromide in 100 cc. of toluene is heated for 15 hours at 100°C. with stirring.

The reaction is completed as in Example 8 and the condensation product is obtained in a yield of 85%. Boiling point: 250°C./0.5 mm. Hg.

Melting point of the hydrochloride: 233—234°C.

EXAMPLE 10.

1 - [4 - (*o*-chlorobenzhydryloxy) - butyl]-4-(*m*-methylbenzyl)-piperazine.



A mixture of 0.1 mole of 1-(4-hydroxy-butyl)-4-*m*-methylbenzyl-piperazine and 0.1 mole of *o*-chlorobenzhydryl-chloride is heated at 160°C. in a nitrogen atmosphere for 3 hours.

After cooling, the mass is taken up in benzene and in a 20% aqueous sodium hydroxide solution. The benzene solution is decanted, washed with water and then concentrated.

The condensation product is rectified *in vacuo*. Yield: 50% Boiling Point; 245—250° C./0.1 mm. Hg.

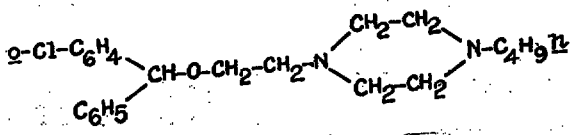
Melting point of the dihydrochloride: 225°C.

EXAMPLE 11.

Preparation of various derivatives.

The products, the formulae of which are given in the following, were prepared by the processes described in Examples 1 to 10:

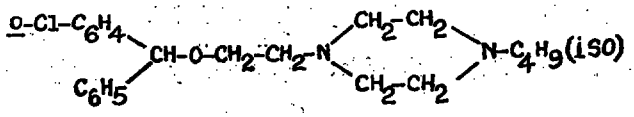
1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl] - 4 - *n*-butyl-piperazine.



Boiling point of the base: 210°C./0.1 mm. Hg.

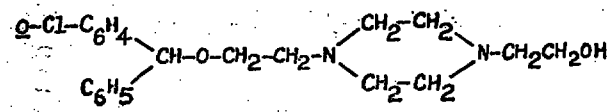
Melting point of the dihydrochloride: 200—203°C.

1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4-isobutyl-piperazine

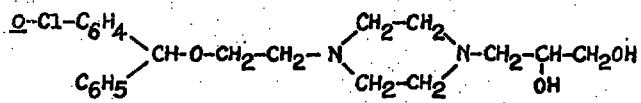


Boiling point of the base: 188—190°C./0.02 mm. Hg.

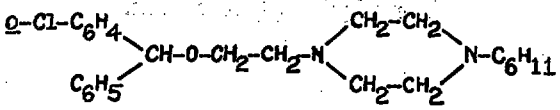
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl]-4 - (2 - hydroxyethyl) - piperazine



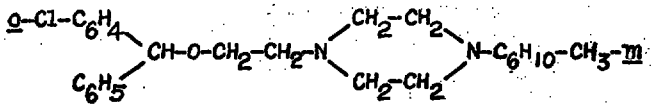
Boiling point of the base: 230°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 150°C.
1 [2 - (*o*-chlorobenzhydryloxy) - ethyl]-4-(2,3-dihydroxypropyl)-piperazine



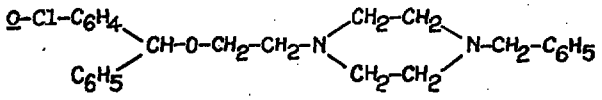
Boiling point of the base: the product decomposes.
Melting point of the dihydrochloride: 147—150°C.
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl]-4-cyclohexyl-piperazine



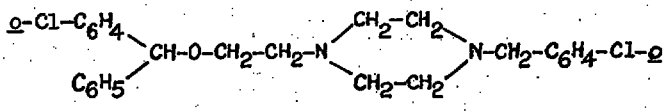
Boiling point of the base: 235—240°C./0.05 mm. Hg.
Melting point of the dihydrochloride: 230—233°C.
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl]-4-(3-methylcyclohexyl)-piperazine



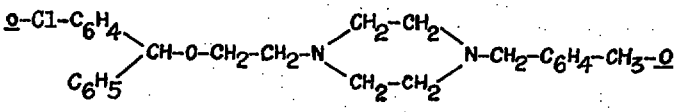
Boiling point of the base: 230—232°C./0.01 mm. Hg.
Melting point of the dihydrochloride: 214—215°C.
1 - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4 - benzyl-piperazine



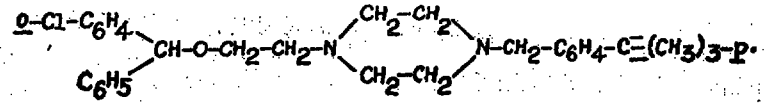
Boiling point of the base: 230—235°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 210°C.
1 - [2 - (*o* - chlorobenzhydryloxy) - ethyl]-4-(*o*-chlorobenzyl)-piperazine



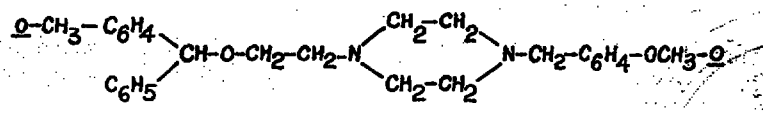
Boiling point of the base: 240—241°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 208—209°C.
1- [2 - (*o*-chlorobenzhydryloxy - ethyl] - 4 - (*o*-methylbenzyl)-piperazine



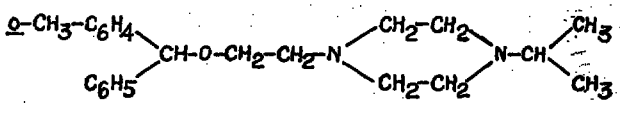
Boiling point of the base: 235°C./0.005 mm. Hg.
1 [2 - (*o*-chlorobenzhydryloxy) - ethyl] - 4 - (*p*-t. butylbenzyl)-piperazine



Boiling point of the base: 245—250°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 212—214°C.
1 - [2 - (*o*-methylbenzhydryloxy) - ethyl]-4-(*o*-methoxybenzyl)-piperazine

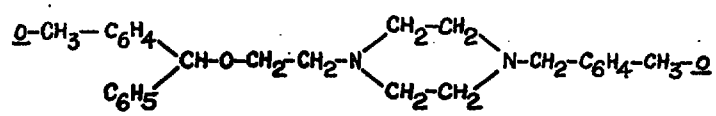


Boiling point of the base 234—236°C./0.01 mm. Hg.
1 - [2 - (*o*-methylbenzhydryloxy) - ethyl]-4-isopyropyl)-piperazine



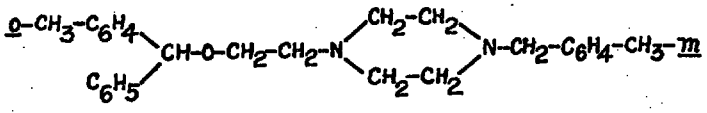
Boiling point of the base 175°C./0.002 mm. Hg.

1 - [2 - (*o*-methylbenzhydryloxy) - ethyl] - 4-(*o*-methylbenzyl)-piperazine



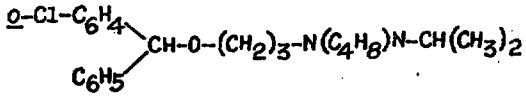
Boiling point of the base: 218—220°C./0.01 mm. Hg.

1 [2 - (*o*-methylbenzhydryloxy) - ethyl]-4-(*m*-methylbenzyl)-piperazine



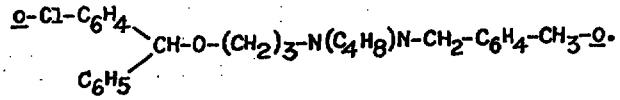
Boiling point of the base: 224°C./0.015 mm. Hg.

1 - [3 - (*o*-chlorobenzhydryloxy) - propyl] - 4 - isopropyl - piperazine



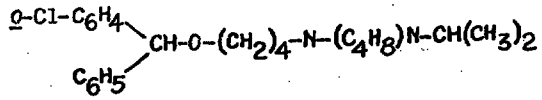
Boiling point of the base: 215°C./0.7 mm. Hg.
Melting point of the dihydrochloride: 230—232°C.

1 - [3 - (*o*-chlorobenzhydryloxy) - propyl]- 4-(*o*-methylbenzyl)-piperazine



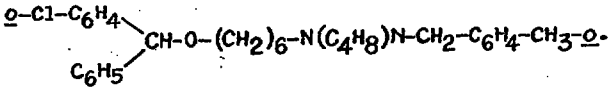
Boiling point of the base: 265°C./0.5 mm. Hg.
Melting point of the dihydrochloride: 215°C.

1 - [4 - (*o*-chlorobenzhydryloxy) - butyl] - 4 - isopropyl - piperazine



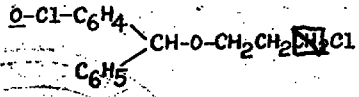
Boiling point of the base 210°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 220°C.

1 - [6 - (*o*-chlorobenzhydryloxy) - hexyl]- 4-(*o*-methylbenzyl)-piperazine



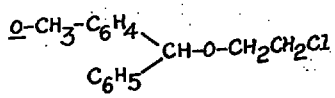
Boiling point of the base: 265—270°C./0.1 mm. Hg.
Melting point of the dihydrochloride: 218°C.

As initial products, there may be used: 2-(*o*-chlorobenzhydryloxy)-alkyl chloride



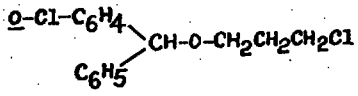
This compound is obtained in a yield of 90% by reacting 2-chloroethanol with *o*-chlorobenzhydrol in the presence of concentrated sulphuric acid and in presence of benzene by the method described for the analogous derivative of benzhydrol in Organic Synthesis, *33*, (1953), p. 11—12. Boiling point: 143°C./0.1 mm. Hg.

2 - (*o*-methylbenzhydryloxy)-ethyl chloride



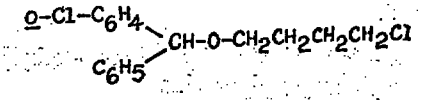
Same process as above, but starting with *o*-methylbenzhydrol. Boiling point: 137°C./0.04 mm. Hg.

3 - (*o*-chlorobenzhydryloxy)-propyl chloride



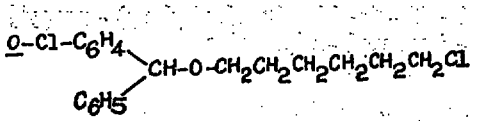
Same process as above but starting with 3-chloropropanol. Boiling point: 155°C./0.3 mm. Hg.

4 - (*o*-chlorobenzhydryloxy) - butyl chloride



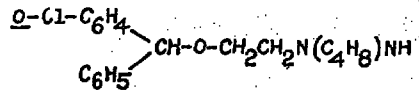
Same process as above, starting with 4-chlorobutanol. Yield: 90%. Boiling point: 165—168°C./0.05 mm. Hg.

6 - (*o*-chlorobenzhydryloxy) - hexyl chloride



Same process as above, starting with 6-chlorohexanol. Yield: 75%. Boiling point: 180—182°C./0.01 mm. Hg.

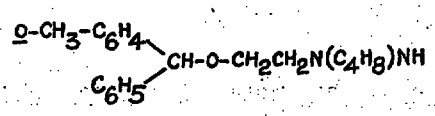
1 - mono - [2 - (*o*-chlorobenzhydryloxy) - ethyl] - piperazine



A mixture of 3.5 moles of anhydrous piperazine, 1 mole of 2-(*o*-chlorobenzhydryloxy) - ethyl chloride in 100 cc. of xylene is heated under reflux for 4 hours. The desired mono-substituted piperazine derivative is obtained in a yield of 85%. Boiling point 185°C./0.007 mm. Hg.

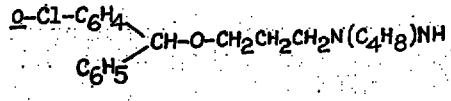
Melting point of the dihydrochloride, prepared in alcohol: 105—107°C.

1 - mono - [2 - (*o* - methylbenzhydryloxy)-ethyl] - piperazine



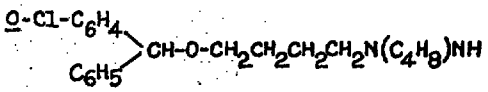
Prepared by the method described for the corresponding chlorinated derivative. B.P.: 168—170°C./0.005 mm. Hg.

1 - [3 - (*o*-chlorobenzhydryloxy) - propyl]-piperazine



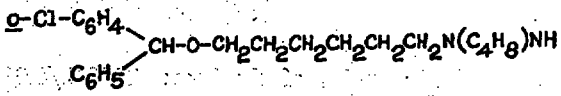
A mixture of 3.5 moles of anhydrous piperazine and 1 mole of 3-(*o*-chlorobenzhydryloxy)-propyl chloride in 100 cc. of xylene is heated under reflux for 4 hours. The desired mono-substituted piperazine derivative is obtained in a yield of 70%. Boiling point: 190°C./0.01 mm. Hg.

1 - [4 - (*o*-chlorobenzhydryloxy) - butyl]-piperazine



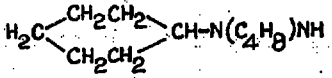
Boiling point: 195°C./0.001 mm. Hg.

1 - [6 - (*o*-chlorobenzhydryloxy) - hexyl]-piperazine



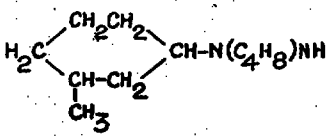
Boiling point: 210°C./0.001 mm. Hg.

1 - mono - cyclohexyl - piperazine



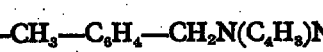
A solution of cyclohexyl bromide in xylene is heated under reflux for several hours with an excess of anhydrous piperazine. Boiling point: 129—131°C./12 mm. Hg. Yield: 30%.

1 - mono - (3 - methylcyclohexyl) - piperazine



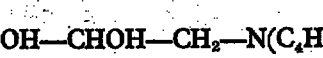
As in the foregoing, but using 3-methylcyclohexyl bromide. Boiling point: 132—134° C./11 mm. Hg.

1 - mono - (*o*-methylbenzyl) - piperazine



As in the foregoing, but using *o*-methylbenzyl bromide. Boiling point: 88°C./0.1 mm. Hg.

1 - mono - (2,3 - dihydroxypropyl)-piperazine



Obtained by adding one mole of epoxypropanol to a solution of 2 moles of piperazine hexahydrate in 750 cc. of water at a temperature lower than 30°C. The mass is stirred for several hours at this temperature and then allowed to stand for 24 hours. The product is concentrated *in vacuo* and the residue is rectified. The product (Boiling point: 146°C./0.1 mm. Hg.), is obtained in a yield of 40%. Melting point: 70°C.

1 - (4 - hydroxybutyl) - 4 - (*m*-methylbenzyl) - piperazine

$HO—CH_2CH_2CH_2CH_2—N(C_4H_8)N—CH_2—C_6H_4CH_3m.$

A mixture of 0.3 mole of 1-*m*-methylbenzylpiperazine and 0.4 mole of 4-chlorobutanol in 100 cc. of butanol is heated under reflux for 10 hours. The solvent is driven off, the residue is made alkaline with a 20% sodium hydroxide solution and extracted with benzene, and the benzene solution is washed with water and concentrated. A product having a boiling point of 135°C./0.001 mm. Hg. is obtained in a yield of 80%.

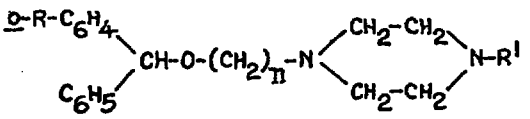
1 - (3 - hydroxypropyl) - 4 - (*o*-methylbenzyl) - piperazine

$HO—CH_2CH_2CH_2—N(C_4H_8)N—CH_2—C_6H_4—CH_3o.$

Prepared as above from 1-*o*-methylbenzylpiperazine
(Boiling point: 110°C./0.3 mm. Hg. and 3-chloropropanol
(Boiling point: 168—170°C./0.5 mm. Hg.).

WHAT I CLAIM IS:—

1. Piperazine derivatives of the general formula:



wherein R is a halogen atom or an alkyl radical, R^1 is an alkyl, hydroxyalkyl, hydroxyalkoxyalkyl, aralkoxy alkyl, cycloalkyl or aralkyl radical, any carbocyclic ring of which may be substituted by an alkyl or alkoxy radical or a halogen atom or R^1 is an alkanoyl radical or an aroyl radical which may be halogen substituted, and *n* is an integer of from 2 to 6; and acid addition salts thereof.

2. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-methyl-piperazine.

3. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-ethyl-piperazine.

4. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-isopropyl-piperazine.

5. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-*n*-butyl-piperazine.

6. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-isobutyl-piperazine.

7. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(2-hydroxyethyl)-piperazine.

8. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-[2-(2-hydroxyethoxy)-ethyl]-piperazine.

9. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-[2-(*p*-t.-butylbenzyloxy)ethyl]-piperazine.

10. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(2,3-dihydroxypropyl)-piperazine.

11. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-cyclohexyl-piperazine.

12. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(3-methyl-cyclohexyl)-piperazine.

13. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-benzyl-piperazine.

14. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-chlorobenzyl)-piperazine.

15. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-methylbenzyl)-piperazine.

16. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*m*-methyl-benzyl)-piperazine.

17. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*p*.t.-butylbenzyl)-piperazine.

18. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-methoxybenzyl)-piperazine.

19. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-acetyl-piperazine.

20. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-chlorobenzoyl)-piperazine.

21. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-isopropyl-piperazine.

22. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-(*o*-methylbenzyl)-piperazine.

23. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-(*m*-methylbenzyl)-piperazine.

24. 1 - [3 - (*o* - chlorobenzhydryloxy)-propyl]-4-isopropyl-piperazine.

25. 1 - [3 - (*o* - chlorobenzhydryloxy)-propyl]-4-(*o*-methylbenzyl)piperazine.

26. 1 - [3 - (*o* - chlorobenzhydryloxy)-propyl]-4-(*m*-methylbenzyl)-piperazine.

27. 1 - [4 - (*o* - chlorobenzhydryloxy)-butyl]-4-isopropyl-piperazine.

28. 1 - [4 - (*o* - chlorobenzhydryloxy)-butyl]-4-(*m*-methylbenzyl)-piperazine.

29. 1 - [6 - (*o* - chlorobenzhydryloxy)-hexyl]-4-isopropyl-piperazine.

30. 1 - [6 - (*o* - chlorobenzhydryloxy)-hexyl]-4-(*o*-methylbenzyl)-piperazine.

31. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-mono - [omega - (*o*-R-benzhydryloxy)-alkyl]-piperazine with an R^1-halide, optionally in the presence of a hydrohalic acid acceptor.

32. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-mono-R^1-piperazine with an omega-(*o*-R-benzhydryloxy)-alkyl halide, optionally in the presence of a hydrohalic acid acceptor.

33. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-(omega-halogenalkyl)-4-R^1-piperazine with an *o*-R-benzhydrol, optionally in the presence of a hydrohalic acid acceptor.

34. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting an *o*-R-benzhydryl halide with a 1-(omega-hydroxyalkyl)-4-R^1-piperazine, optionally in the presence of a hydrohalic acid acceptor.

35. A process for the preparation of piperazine derivatives of the general formula given

$HO—CH_2CH_2CH_2CH_2—N(C_4H_8)N—CH_2—C_6H_4CH_3m.$

A mixture of 0.3 mole of 1-*m*-methylbenzyl-piperazine and 0.4 mole of 4-chlorobutanol in 100 cc. of butanol is heated under reflux for 10 hours. The solvent is driven off, the residue is made alkaline with a 20% sodium hydroxide solution and extracted with benzene, and the benzene solution is washed with water and concentrated. A product having a boiling point of 135°C./0.001 mm. Hg. is obtained in a yield of 80%.

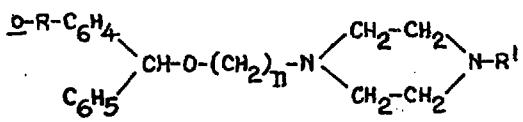
1 - (3 - hydroxypropyl) - 4 - (*o*-methylbenzyl) - piperazine

$HO—CH_2CH_2CH_2—N(C_4H_8)N—CH_2—C_6H_4—CH_3o.$

Prepared as above from 1-*o*-methylbenzyl-piperazine
(Boiling point: 110°C./0.3 mm. Hg. and 3-chloropropanol
(Boiling point: 168—170°C./0.5 mm. Hg.).

WHAT I CLAIM IS:—

1. Piperazine derivatives of the general formula:



wherein R is a halogen atom or an alkyl radical, R^1 is an alkyl, hydroxyalkyl, hydroxy-alkoxyalkyl, aralkoxy alkyl, cycloalkyl or aralkyl radical, any carbocyclic ring of which may be substituted by an alkyl or alkoxy radical or a halogen atom or R^1 is an alkanoyl radical or an aroyl radical which may be halogen substituted, and *n* is an integer of from 2 to 6; and acid addition salts thereof.

2. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-methyl-piperazine.

3. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-ethyl-piperazine.

4. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-isopropyl-piperazine.

5. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-*n*-butyl-piperazine.

6. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-isobutyl-piperazine.

7. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(2-hydroxyethyl)-piperazine.

8. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-[2-(2-hydroxyethoxy)-ethyl]-piperazine.

9. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-[2-(*p*-t.-butylbenzyloxy)ethyl]-piperazine.

10. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(2,3-dihydroxypropyl)-piperazine.

11. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-cyclohexyl-piperazine.

12. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(3-methyl-cyclohexyl)-piperazine.

13. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-benzyl-piperazine.

14. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-chlorobenzyl)-piperazine.

15. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-methylbenzyl)-piperazine.

16. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*m*-methyl-benzyl)-piperazine.

17. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*p*.t.-butylbenzyl)-piperazine.

18. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-methoxybenzyl)-piperazine.

19. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-acetyl-piperazine.

20. 1 - [2 - (*o*-chlorobenzhydryloxy)-ethyl]-4-(*o*-chlorobenzoyl)-piperazine.

21. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-isopropyl-piperazine.

22. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-(*o*-methylbenzyl)-piperazine.

23. 1 - [2 - (*o* - methylbenzhydryloxy)-ethyl]-4-(*m*-methylbenzyl)-piperazine.

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25. 1 - [3 - (*o* - chlorobenzhydryloxy)-propyl]-4-(*o*-methylbenzyl)piperazine.

26. 1 - [3 - (*o* - chlorobenzhydryloxy)-propyl]-4-(*m*-methylbenzyl)-piperazine.

27. 1 - [4 - (*o* - chlorobenzhydryloxy)-butyl]-4-isopropyl-piperazine.

28. 1 - [4 - (*o* - chlorobenzhydryloxy)-butyl]-4-(*m*-methylbenzyl)-piperazine.

29. 1 - [6 - (*o* - chlorobenzhydryloxy)-hexyl]-4-isopropyl-piperazine.

30. 1 - [6 - (*o* - chlorobenzhydryloxy)-hexyl]-4-(*o*-methylbenzyl)-piperazine.

31. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-mono - [omega - (*o*-R-benzhydryloxy)-alkyl]-piperazine with an R^1-halide, optionally in the presence of a hydrohalic acid acceptor.

32. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-mono-R^1-piperazine with an omega-(*o*-R-benzhydryloxy)-alkyl halide, optionally in the presence of a hydrohalic acid acceptor.

33. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-(omega-halogenalkyl)-4-R^1-piperazine with an *o*-R-benzhydrol, optionally in the presence of a hydrohalic acid acceptor.

34. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting an *o*-R-benzhydryl halide with a 1-(omega-hydroxy-alkyl)-4-R^1-piperazine, optionally in the presence of a hydrohalic acid acceptor.

35. A process for the preparation of piperazine derivatives of the general formula given

837,986

in claim 1, which comprises reacting a 1-mono-[omega-(*o*-benzhydryloxy)-alkyl]-piperazine with an acid chloride and, if desired, reducing the N-alkanoyl or N-aroyl-piperazine compound obtained by means of lithium-aluminium hydride to obtain the corresponding N-alkyl or N-aralkyl-piperazine.

36. A process for the preparation of piperazine derivatives of the general formula given in claim 1, which comprises reacting a 1-mono-[omega-(*o*-R-benzhydryloxy)-alkyl]-piperazine with an aldehyde and reducing the compound obtained by means of hydrogen in the presence of Raney nickel.

37. A process for the preparation of piperazine derivatives of the general formula given in claim 1, in which R^1 is a 2-(2-hydroxy-ethyl)-ethyl radical, which comprises reacting a 1-[omega-*o*-R-benzhydryloxy)-alkyl]-4-(2-hydroxy-ethyl)-piperazine with ethylene oxide or ethylene chlorhydrin.

38. A process for the preparation of piperazine derivatives of the general formula given in claim 1, substantially as hereinbefore described and with reference to any of the specific Examples.

39. Piperazine derivatives of the general formula given in claim 1, whenever prepared by the process according to any of claims 31—38.

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

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1960.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

* C L M S *