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PATENT SPECIFICATION

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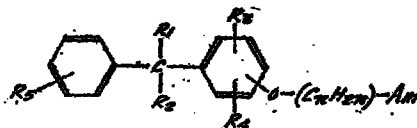
Int. Cl.:—C 07 c, d

COMPLETE SPECIFICATION

New Diphenylalkanes and process for preparing same

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides compounds having the formula



in which each of the groups R_1 and R_2 is an alkyl group, Am is tertiary amino, the group of the formula $-(C_nH_{2n})-$ is lower alkylene separating the group Am from the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, each of R_3 and R_4 is hydrogen, lower alkyl, lower alkoxy, halogeno, trifluoromethyl, or the group of the formula $-O-(C_nH_{2n})-Am$, in which Am and the group of the formula $-(C_nH_{2n})-$ have the previously-given meanings, and R_5 represents hydrogen, lower alkyl, lower alkoxy, halogeno and/or trifluoromethyl, an unsubstituted phenyl radical or a phenyl radical substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl and wherein at least one of R_3 , R_4 or R_5 is other than hydrogen, acid addition salts, N-oxides, acid addition salts of N-oxides or quaternary ammonium compounds thereof as well as a process for the preparation of such compounds. The term "lower" modifies the expressions associated with it to have at most seven carbon atoms.

In the formula given above, the symbol R_5 stands for one or more than one of the same or of different substituents mentioned above which may be attached to any of the positions available for substitution. Throughout the specification and claims, unless otherwise stated, lower alkyl radicals are those containing from one to seven carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or tertiary butyl; lower alkoxy groups are those having from one to seven carbon atoms, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy or secondary butyloxy, halogen atoms are chloro, bromo or iodo.

The radicals R_1 and R_2 are especially lower alkyl, having preferably from one to four carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

The tertiary amino group Am is preferably an N, N-di-lower alkylamino group, in which lower alkyl has from one to four carbon atoms, especially N,N-diethylamino, as well as N,N-dimethylamino, N-methyl-N-ethylamino, N,N-di-n-propylamino or N,N-di-isopropylamino or an N-cycloalkyl-N-lower alkyl-amino, in which cycloalkyl has from three to eight, preferably from five to seven, ring carbon atoms, and lower alkyl has from one to four carbon atoms, e.g. N-cyclopentyl-N-methyl-amino, N-cyclohexyl-N-methyl-amino or N-cyclohexyl-N-ethyl-amino.

Furthermore, the tertiary amino group Am may also represent 1-N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms, 1-N,N-aza-alkylene-imino, in which alkylene has from four to six carbon atoms, or 1-N,N-oxa-alkylene-

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imino or 1-N,N-thia-alkylene-imino, in which alkylene has preferably four carbon atoms. Together with the nitrogen atom, such alkylene, aza-alkylene, oxa-alkylene or thia-alkylene radicals represent for example pyrrolidino groups, e.g. pyrrolidino or 2-methyl-pyrrolidino, piperidino groups, e.g. piperidino, 2-methyl-piperidino or 4-methyl-piperidino, or 1 - N,N - (1,6 - hexylene) - imino, 1 - N,N - (1,7 - heptylene)-imino, 1 - N,N - (aza - alkylene) - imino groups, particularly 1 - N,N - (N - lower alkyl - aza - alkylene) - imino groups, in which alkylene has from four to six carbon atoms, such as piperazino or particularly 4-lower alkyl-piperazino, e.g. 4 - methyl - 1-piperazino, 4 - ethyl - 1 - piperazino or 4 - hydroxyethyl - 1 - piperazino, 1 - N,N - (3 - aza - 1,6 - hexylene) - imino, particularly 1 - N,N - (3 - aza - 3 - lower alkyl - 1,6 - hexylene) - imino, e.g. 1 - N,N - (3 - aza - 3 - methyl - 1,6 - hexylene) - imino, or 1 - N,N - (4 - aza - 1,7 - heptylene) - imino, particularly 1 - N,N - (4 - aza - 4 - lower alkyl - 1,7 - heptylene) - imino, e.g. 1 - N,N - (4 - aza - 4 - methyl - 1,7 - heptylene) - imino, morpholino groups, e.g. morpholino or 3-methyl-morpholino, or thiamorpholino groups, e.g. thiamorpholino, or any other equivalent tertiary amino group.

In the lower alkylene radical $-(C_nH_{2n})-$ separating the tertiary amino group Am from the oxygen atom by at least two carbon atoms the letter n stands for an integer from two to seven, above all two or three carbon atoms. The alkylene radical is therefore represented for example by 1,2-ethylene, 1 - methyl - 1,2 - ethylene, 2 - methyl-1,2 - ethylene, 1,3-propylene, but may also be 1,3-butylene, 2,3-butylene, 3,4-butylene, 1,4-butylene, 1,4-pentylene, 1,5-pentylene, 1,5-hexylene, 1,6-hexylene and 1,7-heptylene.

The lower alkyl radicals R_2 and R_4 may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl or tertiary butyl; lower alkoxy radicals R_2 and R_4 have preferably from one to four carbon atoms, e.g. they are methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy or secondary butyloxy; halogeno substituents R_2 and R_4 are fluoro, chloro, bromo or iodo; a substituent R_2 or R_4 of the formula $-O-(C_nH_{2n})-Am$, is preferably one in which Am and n have the meanings given above.

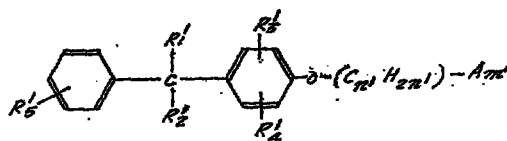
Quaternary ammonium compounds of the compounds of this invention are those formed with reactive esters from alcohols, particularly lower alkanols, e.g. methanol, ethanol, n-propanol, isopropanol, or phenyl-lower alkanols, e.g. benzyl alcohol and 1-phenyl- or 2-phenyl-ethanol. As reactive esters there come into consideration those with strong inorganic or organic acids, e.g. hydrohalic acids, sulfuric acids and sulfonic acids such as hydrochloric, hydrobromic or hydriodic acid, sulfuric acid, lower alkane sulfonic acids, e.g. methane or ethane sulfonic acid, hydroxy-lower-alkane sulfonic acids, e.g. 2-hydroxy-ethane sulfonic acid, or benzene sulfonic acids, e.g. *p*-toluene sulfonic acid. Also included as quaternary ammonium compounds are the corresponding quaternary ammonium hydroxides, and other quaternary ammonium compounds having as anions those of other acids, particularly those of the organic carboxylic acids mentioned hereinafter.

The compounds of this invention have antifungal properties and can be used accordingly. For example, they show antidermatophyte effects against fungi, causing superficial dermatophytoses, such as *Trychophyton mentagrophytes*, *Trychophyton gallinae*, *Trychophyton interdigitale*, *Microsporum audouini*, *Microsporum canis*, and *Microsporum gypseum*, and can be used in the treatment of infections caused by such micro-organisms, particularly of fungal infections of the skin, such as dermatophytosis (athlete's foot). They have also antifungal effects against fungi causing chronic infections of the skin and subcutaneous tissue, such as *Sporotrichium schenkii*, or fungi causing deep seated systemic mycoses, such as *Candida albicans*, *Cryptococcus neoformans* and *Histoplasma capsulatum*, and can be used in the treatment of infections caused by such microorganisms.

Furthermore, the compounds of this invention are active against actinomycetes, such as *Nocardia asteroides*, against bacteria, such as gram-positive bacteria, for example *Diplococcus pneumoniae* and *Staphylococcus aureus*, or gram negative bacteria, for example, *Escherichia coli* and *Pseudomonas aeruginosa*, and against protozoa, such as *Trichomonas vaginalis*, and can, therefore, be used in the treatment of infections caused by such actinomycetes, bacteria and protozoa.

The compounds of this invention also have antiparasite, particularly taeniocidal (anti-tapeworm), properties and also stimulating and endocrine effects.

Particularly useful are the compounds of the formula



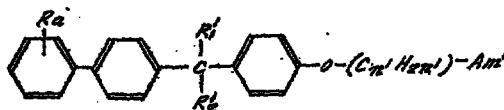
in which each of the groups R_1^1 and R_2^1 is lower alkyl, having preferably from one to four carbon atoms, especially methyl, Am^1 is N,N-di-lower alkylamino, in which lower alkyl has preferably from one to four carbon atoms, the group $-(C_nH_{2n1})-$ is alkyl-

5 ene having two or three, particularly two, carbon atoms and separates the group Am^1 from the oxygen atom by two or three carbon atoms, and each of R_3^1 and R_4^1 is hydrogen, lower alkyl, particularly methyl, halogeno, especially chloro, or the group of the formula $-O-(C_nH_{2n1})-Am^1$, in which Am^1 and the group of the formula

$-(C_nH_{2n1})-$ have the above-given meanings, R_5^1 is hydrogen, lower alkyl, particu-

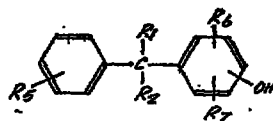
10 larly methyl, halogeno, particularly chloro, phenyl, (lower alkyl)-phenyl, particularly (methyl)-phenyl, (halogeno)-phenyl, particularly (chloro)-phenyl, wherein one or more than one halogeno, particularly chloro, atom may be attached to the phenyl groups, and wherein at least one of the radicals R_3^1 , R_4^1 or R_5^1 is other than hydrogen, and the acid addition, particularly the pharmaceutically acceptable, non-toxic acid addition, salts thereof.

Also those compounds having the formula



in which R_a is hydrogen, lower alkyl, lower alkoxy or halogeno, each of the symbols R_1^1 and R_2^1 stands for lower alkyl having from one to four carbon atoms, Am^1 is N,N-di-lower alkyl-amino, the letter n^1 stands for 2 or 3, and the group of the formula $-(C_nH_{2n1})-$ separates Am^1 from the oxygen atom by two or three carbon atoms may be particularly mentioned. Especially valuable as an antifungal compound is 2 - (4-chloro - phenyl) - 2 - [4 - (2 - N,N - diethylamino - ethoxy) - phenyl] - propane and its therapeutically acceptable salts.

25 The compounds of the present invention may be prepared according to methods known per se, for example by converting in a compound of the formula



in which R_1 , R_2 and R_5 have the previously-given meanings, and each of the symbols R_6 and R_7 stands for hydrogen, lower alkyl, lower alkoxy, halogeno, trifluoromethyl or hydroxyl, or a salt thereof, any hydroxyl group attached to the phenyl moiety into the group of the formula $-O-(C_nH_{2n1})-Am$, in which Am and the group of the formula $-(C_nH_{2n1})-$ have the previously-given meanings.

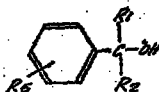
The conversion of a hydroxyl group into the group of the formula $-O-(C_nH_{2n1})-Am$ is carried out according to known procedures. For example, the starting material may be converted into a salt thereof, such as a metal, particularly on alkali metal, e.g. lithium, sodium or potassium, compound thereof. Formation of the salt may be achieved, for example, by reacting the starting material with a metal compound-forming reagent, such as an alkali metal, e.g. sodium or potassium, an alkali metal hydride or amide, e.g. lithium hydride, sodium hydride, sodium amide or potassium amide or any other suitable reagent, such as an alkali metal lower alkanolate, e.g. lithium, sodium or potassium methanolate, ethanolate or tertiary butanolate, or an alkali metal compound of a hydrocarbon, e.g. butyl lithium, phenyl lithium or phenyl sodium. The preparation of the metal compounds is carried out in the presence of an inert solvent, e.g. liquid ammonia, hexane, benzene, toluene, xylene, diethyl ether, p-dioxane, tetrahydrofuran, diethyleneglycol dimethylether or N,N-dimethylformamide,

or any other suitable solvent, such as a lower alkanol, e.g. methanol or ethanol; the choice of the solvent depends primarily on the type of reagent used and/or on the solubility properties of the starting material.

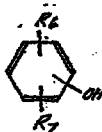
The starting material, particularly the metal compound thereof, is then reacted with a compound of the formula $X-(C_nH_{2n})-Am$, in which Am and the group of the formula $-(C_nH_{2n})-$, separating the group Am from the atom X by at least two carbon atoms, have the previously-given meanings, and X stands for a halogen atom, particularly chlorine, bromine or iodine.

The reaction of the starting material, particularly a metal compound thereof, with the reagent of the formula $X-(C_nH_{2n})-Am$, in which Am, X and the group of the formula $-(C_nH_{2n})-$ have the previously-given meanings, is carried out in the presence of a suitable diluent, for example, the solvent used for the preparation of a metal compound, which, if desired, may be replaced or diluted with another solvent.

The starting materials used in the above reaction are known or may be prepared according to known methods, for example, by reacting a compound of the formula



in which R_1 , R_2 and R_6 have the previously-given meanings, with a phenolic compound of the formula



in which R_6 and R_7 have the previously-given meanings, in the presence of a Lewis acid, particularly a Friedel-Crafts reagent, e.g. aluminum chloride.

Depending upon the method of working, the new compounds are obtained in the free base form or in the form of acid-addition salts.

The acid addition salts of the compounds of this invention are, for example, pharmaceutically acceptable, non-toxic acid addition salts, such as those with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric and phosphoric acids, or organic acids, such as organic carboxylic acids, e.g. formic, acetic, propionic, pivalic, glycolic, lactic, malonic, succinic, maleic, hydroxymaleic, malic, tartaric, citric, benzoic, salicylic, 4-amino-salicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, nicotinic and isonicotinic acid or organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, ethane 1,2-disulfonic, 2-hydroxyethane sulfonic, *p*-toluene sulfonic and naphthalene 2-sulfonic acid, or any other suitable acid. Other acid addition salts may be used as intermediates, for example for the manufacture of other, such as pharmaceutically acceptable, non-toxic, acid addition salts, or in the purification of the free compound, as well as for characterization and identification purposes. Salts which may be prepared primarily for identification purposes are, for example, those with acidic organic nitro compounds, e.g. picric, picrolonic and flavianic acid, or metal complex acids, e.g. phosphotungstic, phosphomolybdic, chloroplatinic and Reinecke acid.

A resulting acid addition salt may be converted into the free base, for example by treating it with an alkaline reagent, such as a metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide, a metal carbonate, e.g. sodium, potassium or calcium carbonate or hydrogen carbonate, ammonia, or with a hydroxyl ion exchange preparation, or any other suitable reagent.

A resulting acid addition salt, particularly an acid addition salt with an inorganic acid, may be converted into another acid addition salt, for example by reacting it with a metal, e.g. sodium, barium or silver, salt of an acid, preferably in a suitable diluent, in which a resulting inorganic salt is insoluble and is removed from the reaction, or by treating it with an anion exchange preparation. A free base may be converted into an acid addition salt thereof by reacting it or a solution thereof in a suitable solvent or solvent mixture with an acid or a solution thereof, or with a suitable anion exchange preparation, and isolating the desired salts. A salt may be obtained in the form of a hydrate thereof or may contain solvent of crystallization.

An N-oxide of the compounds of this invention may be prepared, for example, by treating the free base with an N-oxidizing-reagent, such as hydrogen peroxide, ozone or a peracid, e.g. peracetic, perbenzoic, monoperphthalic and, persulfuric acid, in a suitable inert solvent. An N-oxide may be converted into an acid addition salt thereof according to the above method.

Quaternary ammonium derivatives of the compounds of this invention may be obtained, for example, by reacting the base with a reactive ester of an alcohol, such as one of those mentioned at the beginning e.g. with a lower alkyl halide, di-lower alkyl-sulfate, lower alkyl sulfonate, or a phenyl-lower alkyl halide. A resulting quaternary ammonium compound may be converted into another quaternary ammonium compound, such as a quaternary ammonium hydroxide, for example by reacting a quaternary ammonium halide with silver oxide, or a quaternary ammonium sulfate with barium hydroxide, by treating a quaternary ammonium salt with a hydroxyl ion exchange preparation, by electrodialysis or any other suitable method. A quaternary ammonium hydroxide may be converted into a quaternary ammonium salt by reacting the former with a suitable acid. A quaternary ammonium salt may also be converted directly into another quaternary ammonium compound; thus, a quaternary ammonium iodide may be reacted with freshly prepared silver chloride or with hydrochloric acid in anhydrous methanol to yield the desired quaternary ammonium chloride, or a quaternary ammonium salt may be treated with a suitable anion exchange resin and thus be converted into another quaternary ammonium salt. A quaternary ammonium compound may be obtained in the form of its hydrate or may contain solvent of crystallization.

A mixture of resulting isomeric compounds may be separated into the single isomers. For example, a mixture of diastereoisomers may be separated into the individual racemic compounds on the basis of physico-chemical differences, such as solubility, for example, by fractional crystallization. Racemates may be resolved into the optically active d- and l-forms according to known resolution procedures, for example, by forming a salt of the free racemic base with one of the optically active forms of an acid containing an asymmetric carbon atom. Especially useful as optically active forms of salt-forming acids having an asymmetric carbon atom are D-tartaric acid and L-tartaric acid, as well as the optically active forms of malic, mandelic, 10-camphor sulfonic acid, quinic acid. From a resulting salt, the free and optically active base may be obtained according to the method described above, and a free and optically active base may be converted into its acid addition salts, N-oxide, acid addition salts of an N-oxide or quaternary ammonium compounds according to the methods described above.

In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

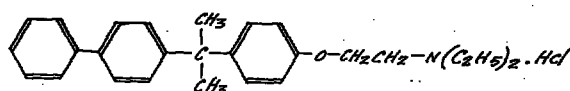
The new diphenylalkanes of this invention, and their N-oxides, quaternary ammonium derivatives and physiologically tolerable acid addition salts may be used in the form of pharmaceutical preparations, suitable for enteral or primarily topical application, which contain these compounds in admixture with a pharmaceutical organic or inorganic solid or liquid carrier. For making up the preparations there can be employed carriers which do not react with the new compounds, such as water, vaseline, gelatine, lactose, starches, stearic acid, magnesium stearate, sodium lauryl sulphate, acacia, tragacanth, talc, vegetable oils, ethyl alcohol, benzyl alcohol, cetylalcohol, petrolatum, gums, propylene, glycol, polyalkylene glycols or any other carrier used for pharmaceutical preparations. The latter may be in solid form, for example, as capsules, tablets and dragees, or in liquid form, for example, as solutions or suspensions, or as emulsions, such as creams and salves. If necessary, these preparations may contain auxiliary substances, such as preserving, stabilizing, wetting and emulsifying agents, salts for varying the osmotic pressure and buffers. They may also contain, in combination, other useful substances.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade.

EXAMPLE 1

To a mixture of 3.8 g of 2 - (p - biphenyl) - 2 - (4 - hydroxyphenyl) - propane in 8 ml of N,N-dimethylformamide is added 0.63 g of a mineral oil suspension of sodium hydride (of 53 per cent strength). To the resulting slurry is added 1.78 g of 2-N,N-diethylaminoethyl chloride in 8 ml of toluene while stirring. The reaction mixture is warmed to approximately 50°C. to form a clear brown solution; stirring is continued for two hours at room temperature, and the mixture is allowed to stand for

fifteen hours. The inorganic precipitate is filtered off, the filtrate is concentrated under reduced pressure and the oily residue is diluted with water. The aqueous phase is extracted several times with diethyl ether, the combined organic extracts are shaken with 2N aqueous hydrochloric acid, whereupon a colorless crystalline material precipitates which is collected and air-dried to yield the 2 - (p - biphenyl) - 2 - [4 - (2 - N,N-diethylaminoethoxy) - phenyl] - propane hydrochloride of the formula



The salt is recrystallized from 95 per cent ethanol, m.p. 120—123°C.

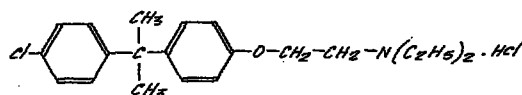
The starting material used in the above example is prepared as follows: While stirring and heating it on a steam bath, a mixture of 8.05 g of molten phenol and 1.77 g of aluminum chloride is treated portionwise with a molten mixture of 5.7 g of α,α - dimethyl - 4 - phenyl - benzylalcohol and 3.0 g of phenol. Stirring and heating is maintained for an additional hour, and the reaction mixture is then decomposed with ice and concentrated hydrochloric acid. The resulting mixture is extracted three times with ethyl acetate, and the combined organic extracts are washed with a concentrated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The remaining oil is distilled; the fraction collected at 185—205°C./0.08 mm Hg crystallizes spontaneously to yield the desired 2 - (p - biphenyl) - 2 - [4 - (2 - N,N-diethylaminoethoxy) - phenyl] - propane, m.p. 119—120°C., after trituration with pentane.

EXAMPLE 2

A suspension of 3.5 g 2 - (p - biphenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane hydrochloride in a 2N-aqueous solution of sodium carbonate is shaken with ethyl acetate. The organic extract is washed with an aqueous sodium chloride solution, dried over sodium sulfate and evaporated to dryness. The residual oil is distilled to yield the 2 - (p - biphenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane as a colorless viscous oil, b.p. 217—220°C./0.1 mm Hg.

EXAMPLE 3

To a solution of 12.33 g of 2 - (4 - chlorophenyl) - 2 - [4 - (hydroxy - phenyl) - propane in a mixture of 75 ml of N,N-dimethylformamide and 40 ml of toluene is added in portions 2.4 g of a 53 per cent suspension of sodium hydride in mineral oil while stirring and cooling. After the hydrogen evolution ceases, a solution of 7.0 g of 2-N,N-diethylamino ethyl chloride in 35 ml of toluene is added dropwise while stirring and cooling. Stirring is continued for an additional three hours at room temperature, and the reaction mixture is then allowed to stand at that temperature for fifteen hours. The inorganic precipitate is filtered off, the filtrate is concentrated to a volume of about 50 to 80 ml, diluted with water and extracted with 300 ml of diethyl ether. The ether extract is separated and washed with 100 ml of 2N aqueous hydrochloric acid; the acid solution is separated, and after a few minutes, the 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane hydrochloride of the formula



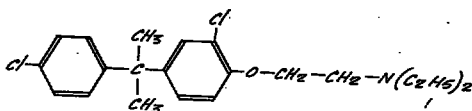
precipitates, is collected and recrystallized from a mixture of ethanol and diethyl ether, m.p. 185—186°C.

The starting material used in the above example is prepared as follows: To the ice-cooled Grignard reagent prepared from 284.0 g of methyl iodide and 48.6 g of magnesium turnings in 550 ml of diethyl ether is added dropwise a solution of 154.6 g of 4-chloro-acetophenone in 200 ml of diethyl ether while stirring. The reaction mixture is allowed to stand at room temperature and is then heated to reflux for two hours. The Grignard complex is decomposed by slowly adding 300 ml of a saturated aqueous solution of ammonium chloride and 300 ml of water while stirring and cooling in an ice bath; 300 ml of diethyl ether is added, and the organic layer is separated, washed and dried over sodium sulfate. The solvent is removed, and the 2 - (4 - chlorophenyl) - 2-propanol is obtained by distilling the residue, b.p. 92—96°C./3 mm Hg.

To a mixture of 28.2 g of phenol and 6.7 g of aluminum chloride (prepared by adding the latter in portions to the phenol while stirring) is given in portions a mixture of 17.1 g of 2 - (4 - chloro - phenyl) - 2 - propanol and 9.4 g of phenol while stirring and cooling with water. The reaction mixture is stirred at room temperature for two hours, allowed to stand for fifteen hours and is then heated for one hour at 40—50°C. while stirring. It is added to 100 ml of 6N aqueous hydrochloric acid while stirring; the organic layer is separated and the excess phenol is removed by distillation at temperatures up to 130°C./13 mm Hg. The oily residue is distilled to yield the 2-(4-chloro-phenyl)-2-(4-hydroxy-phenyl)-propane, which crystallizes from hexane, m.p. 72—74°C.

EXAMPLE 4

A solution salt, prepared by reacting 5.6 g of 2 - (4 - chloro - phenyl) - 2 - (3-chloro - 4 - hydroxy - phenyl) - propane in 25 ml of N,N-dimethylformamide and 25 ml of toluene, with 1.0 g of a 53 per cent suspension of sodium amide in mineral oil, is treated with a solution of 3.0 g of N,N-diethylaminoethyl chloride in toluene; the reaction mixture is worked up as described in Example 3 to yield the 2 - (4-chloro - phenyl) - 2 - [3 - chloro - 4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane of the formula



which is purified by distillation, b.p. 170°C./0.05 mm Hg;

The starting material used in the above example is prepared as follows: A mixture of 7.41 g of 2 - (4 - chloro - phenyl) - 2 - (4 - hydroxy - phenyl) - propane and 10.0 g of sulfuryl chloride is refluxed on the steam bath for three hours. The excess of sulfuryl chloride is evaporated and the residue is taken up into diethyl ether; the organic solution is washed with an aqueous solution of sodium hydrogen carbonate and a saturated solution of sodium chloride, dried over sodium sulfate and evaporated. The straw-colored residue is distilled to yield the desired 2 - (4 - chloro - phenyl) - 2 - (3-chloro - 4 - hydroxy - phenyl) - propane, b.p. 165—170°C./0.15 mm Hg.

Other compounds, which may be prepared according to the above procedure, are, for example, 2 - (4 - chloro - phenyl) - 2 - [3 - chloro - 4 - (2 - N,N - diethylaminoethoxy) - 5 - methyl - phenyl] - propane, which is converted into its hydrochloride, m.p. 146—148°C.; the 2 - (4 - chloro - phenyl) - 2 - (3 - chloro - 4 - hydroxy - 5-methyl - phenyl) - propane starting material, b.p. 125—126°C./0.05 mm Hg, is prepared by reacting 2 - (4 - chloro - phenyl) - 2 - propanol with 2 - chloro - 6 - methyl-phenol in the presence of aluminum chloride and purified by converting the compound into its benzoate and reconverting it, m.p. 129—130°C.; 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - 3,5 - dimethyl - phenyl] - propane, b.p. 171—173°C./0.05 mm Hg, which is converted into its hydrochloride, m.p. 173—174°C.; the 2 - (4 - chloro - phenyl) - 2 - (3,5 - dimethyl - 4 - hydroxyphenyl) - propane starting material, m.p. 47—48°C., is prepared by adding 17.1 g of 2 - (4 - chloro - phenyl) - 2 - propanol and then 12.2 g of 2,6-xylenol to a mixture of 36.6 g of 2,6-xylenol and 6.7 g of aluminum chloride; 2 - (p - biphenyl) - 2 - [3 - chloro - 4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane, b.p. 207—210°C./0.08 mm Hg; the 2 - (p-biphenyl) - 2 - (3 - chloro - 4 - hydroxy - phenyl) - propane starting material, b.p. 180—185°C./0.05 mm Hg, is prepared by reacting 2.72 g of 2 - (p - biphenyl) - 2 - (4 - hydroxy - phenyl) - propane with 1.8 g of sulfuryl chloride in the presence of 10 ml of benzene; 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - 2 - (4 - methyl-phenyl) - propane, which is converted into its hydrochloride, m.p. 188—189°C., after recrystallization from acetone; the 2 - (4 - hydroxy - phenyl) - 2 - (4 - methyl-phenyl) - propane starting material, m.p. 69—70°C. (after crystallization from pentane) is prepared by adding 15.0 g of 2 - (4 - methyl - phenyl) - 2 - propanol to a mixture of 6.7 g of aluminum chloride and 19.0 g of phenol;

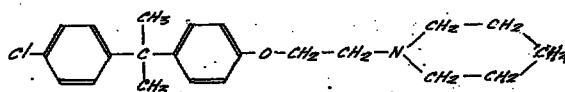
EXAMPLE 5

To a solution of 2.3 g of 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane in 50 ml of 95 per cent ethanol is added 3 ml of ethyl bromide; the reaction mixture is placed into a stainless steel bomb and is heated on a steam bath for fifteen hours. The solvent is removed under reduced pressure, and the residue is crystallized by adding diethyl ether. The desired 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] - propane ethobromide is recrystal-

lized from a mixture of acetone and diethyl ether and dried under reduced pressure, m.p. 132—146°C.

EXAMPLE 6

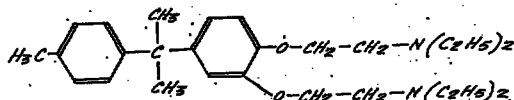
To a solution of 5.0 g of 2 - (4 - chloro - phenyl) - 2 - (4 - hydroxy - phenyl) - propane in 100 ml of a 1:1-mixture of N,N-dimethylformamide and toluene is added 3.8 g of freshly recrystallized 2-piperidino-ethyl chloride hydrochloride; the resulting mixture is cooled to 5°, and treated, in small portions, with a total of 1.95 g of a 53 per cent suspension of sodium hydride in mineral oil. After completing the addition of the sodium hydride the reaction mixture is stirred at room temperature for 5 hours and then allowed to stand for 15 hours. The inorganic precipitate is filtered off, the filtrate is concentrated to a volume of about 15 ml and is diluted with water. The basic material is extracted with 1N hydrochloric acid, the acidic extract is made basic with solid sodium carbonate hydrate and is extracted with diethyl ether. The organic solution yields the 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane of the formula



as a colorless viscous oil, which is converted into its hydrochloride by treatment with a solution of hydrogen chloride in diethyl ether; the salt melts at 183—185°C. after recrystallization from a 5:1:5-mixture of acetone, ethanol and diethyl ether.

EXAMPLE 7

To a solution of 4.0 g of 2 - (3,4 - dihydroxy - phenyl) - 2 - (4 - methyl - phenyl) - propane in N,N-dimethylformamide is added 1.72 g of a 53 per cent suspension of sodium hydride in mineral oil and then 4.0 g of 2-N,N-diethylaminoethyl chloride in 80 ml of a 1:1-mixture of N,N-dimethylformamide and toluene; the reaction is carried out as described in Example 1 and yields the 2 - [3,4 - bis - (2 - N,N - diethylaminoethoxy) - phenyl] - 2 - (4 - methyl - phenyl) - propane of the formula



which is collected at 175—180°C./0.05 mm Hg and purified by redistillation, b.p. 178—180°C./0.05 mm Hg.

The starting material used in the above example is prepared as follows: To a mixture of 13.4 g of aluminum chloride and 22.0 g of catechol is added in portions 22.0 g of 2 - (4 - methyl - phenyl) - 2 - propanol while stirring. The resulting suspension is diluted with 150 ml of hexane; the reaction mixture is heated to 80°C., then decomposed with 100 ml 2N hydrochloric acid and heated on the steam bath for fifteen minutes while stirring. The aqueous layer is separated and discarded; the organic phase is washed with 100 ml of warm water, diluted with 100 ml of diethyl ether and extracted with 100 ml of a 2 per cent aqueous solution of sodium hydroxide. The aqueous extract is acidified and yields the 2 - (3,4 - dihydroxy - phenyl) - 2 - (4 - methyl - phenyl) - propane, m.p. 84—85°C.

2 - (p - Biphenyl) - 2 - [3,4 - bis - (2 - N,N - diethylaminoethoxy) - phenyl] - propane, b.p. 219—223°C./0.05 mm Hg, is prepared by reacting the sodium salt of 2 - (p - biphenyl) - 2 - (3,4 - dihydroxy - phenyl) - propane (manufactured by treating 11.0 g of catechol and 7.0 g of aluminum chloride with 10.6 g of 2 - (p - biphenyl) - 2 - propanol in 150 ml of hexane, and reacting 3.0 g of the resulting 2 - (p - biphenyl) - 2 - (3,4 - dihydroxy - phenyl) - propane, m.p. 101—102°C., after recrystallization from a benzene-pentane mixture, with 1.04 g of a 53 per cent suspension of sodium hydride in mineral oil) with 2.4 g of 2-N,N-diethylaminoethyl chloride in 60 ml of a 1:1-mixture of N,N-dimethylformamide and toluene; the desired product is collected at 219—223°C./0.05 mm Hg.

EXAMPLE 8

A solution of 2.7 g of 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane hydrochloride in 25 ml of water is made basic with sodium car-

5 bonate; the free base is extracted several times with diethyl ether, the combined
 extracts are washed with a saturated aqueous solution of sodium chloride, dried over
 sodium sulfate and evaporated to dryness. The resulting oily residue is dissolved in
 15 ml of methanol and 2 ml of a 30 per cent aqueous solution of hydrogen peroxide is
 10 added. The solution is allowed to stand at room temperature for ninety hours. The
 excess of hydrogen peroxide is decomposed by adding 0.05 g of a palladium catalyst
 (10 per cent palladium on charcoal); the catalyst is filtered off and the colorless filtrate
 is evaporated to dryness to yield the colorless, oily 2 - (4 - chloro - phenyl) - 2 - [4 - (2 -
 piperidino - ethoxy) - phenyl] - propane N-oxide. An ethanol solution of the latter,
 15 when treated with 2.0 g of picric acid yields the 2 - (4 - chloro - phenyl) - 2 - [4 - (2 -
 piperidino - ethoxy) - phenyl] - propane - N - oxide picrate, m.p. 118—120°C.

EXAMPLE 9

2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethyl) - oxy - phenyl] -
 15 propane hydrochloride may be incorporated in a pharmaceutical preparation of the fol-
 lowing composition:

	<i>Ingredients (for 100.0 g)</i>	
	2-(4-chlorophenyl)-2-[4-(2-N,N- diethylaminoethoxy)-phenyl]- propane hydrochloride	1.0 g
20	Liquid petrolatum	5.0 g
	White petrolatum	94.0 g

The 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] -
 propane hydrochloride is mixed with the liquid petrolatum by using a mortar until an
 adequate reduction in particle size is accomplished. The white petrolatum is then
 25 slowly blended with this mixture; the ointment is passed through a three roller mill,
 until total uniformity is obtained and filled into epoxy lined tubes (5.0 g).

A cream, containing 1 per cent of 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N -
 diethylaminoethoxy) - phenyl] - propane hydrochloride as the active ingredient is
 prepared as follows:

30	<i>Ingredients (for 100.0 g)</i>	
	2-(4-chloro-phenyl)-2-[4-(2-N,N- diethylaminoethoxy)-phenyl]- propane hydrochloride	1.0 g
	Propylene glycol	15.0 g
35	Sodium lauryl sulfate	2.0 g
	Cetyl alcohol	15.0 g
	Phenyl mercuric acetate	0.002 g
	Purified water g.s.	100.0 g

40 The phenylmercuric acetate is dissolved in 65 ml of water at 90°C.; subsequently the
 sodium lauryl sulfate is added and the temperature is reduced to 70°C. The cetyl
 alcohol is melted at 70°C. and added to the aqueous solution while vigorously agitating.
 Stirring is continued while cooling the mixture to 45°C.

The 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N - diethylaminoethoxy) - phenyl] -
 45 propane hydrochloride is dispersed in the propylene glycol at 45°C. and added to the
 above emulsion while agitating. Sufficient water is added to bring the weight to 100 g,
 and mixing is continued while the product cools to room temperature. The cream is
 passed through a three roller mill until total uniformity is accomplished and is filled
 into epoxy lined tubes (5 g).

50 A cream containing 2 per cent of 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N,N -
 diethylaminoethoxy) - phenyl] - propane hydrochloride as the active ingredient is pre-
 pared as follows (for 3000.0 g):

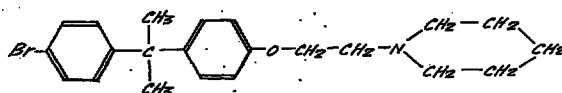
Ingredients (for 3000.0 g)

	2-(4-chloro-phenyl)-2-[4-(2-N,N-diethylaminoethoxy)-phenyl]-propane hydrochloride	60.0 g
	Glyceryl monostearate	225.0 g
5	Lanolin, anhydrous	30.0 g
	Isopropyl myristate	90.0 g
	Polyethylene glycol 4000 monostearate	300.0 g
	Stearic acid	390.0 g
	Sorbitan sesquileate	15.0 g
10	Spermaceti	180.0 g
	Propylene glycol	150.0 g
	Polysorbate 60	45.0 g
	Purified water	1515.0 g

The glyceryl monostearate, the lanolin, the isopropyl myristate, the polyethylene glycol 4000 monostearate, the stearic acid, the sorbitan sesquileate, and the spermaceti are melted together at 80°C. on the water bath. The water containing the polysorbate 60 is added while stirring at 80°C.; stirring is continued until the temperature drops below 40°C. The solution of the 2-(4-chloro-phenyl)-2-[4-(2-N,N-diethylaminoethoxy)-phenyl]-propane hydrochloride in propylene glycol is added; stirring is continued and water is added to bring the weight to 3000.0 g. The cream is passed through a homogenizer and filled into tubes.

EXAMPLE 10

To a solution of 11.5 g of 2-(4-bromo-phenyl)-2-(4-hydroxy-phenyl)-propane in 100 ml of a 1:1-mixture of N,N-dimethyl-formamide and toluene is added 7.2 g of 1-(2-chloro-ethyl)-piperidine hydrochloride. The resulting suspension is stirred, cooled in an ice-bath and treated with 3.6 g of a 53 per cent suspension of sodium hydride in mineral oil, which is added in portions. After the hydrogen evolution has ceased and stirring at room temperature has been continued for six hours, the reaction mixture is allowed to stand at room temperature for fifteen hours and is then evaporated under reduced pressure. The residue is treated with water, and the organic material is extracted with two portions of diethyl ether; the combined organic solutions are washed with 2N-hydrochloric acid and the acidic layer is made basic with a 50 per cent aqueous solution of sodium hydroxide and sodium carbonate until the pH is about 8, while cooling in an ice-bath. The resulting gummy precipitate is taken up into diethyl ether, the organic solution is dried over sodium sulfate and evaporated to dryness to yield 13.5 g of the desired 2-(4-bromo-phenyl)-2-[4-(2-piperidinoethoxy)-phenyl]-propane of the formula



which melts at 77—78°C. after recrystallization from ethanol.

By substituting in the above procedure 2-N,N-diethylaminoethyl chloride hydrochloride for the 1-(2-chloro-ethyl)-piperidine hydrochloride, the 2-(4-bromo-phenyl)-2-[4-(2-N,N-diethylaminoethoxy)-phenyl]-propane is formed.

The starting material used in the above procedure is prepared as follows: To a Grignard reagent prepared from 15.4 g of magnesium and 91 g of methyl iodide in 350 ml of diethyl ether is added dropwise while stirring and cooling in an ice-bath, 105.7 g of 4-bromo-acetophenone in 200 ml of diethyl ether. The reaction mixture is refluxed for two hours, allowed to stand at room temperature for 18 hours and again refluxed for two hours, and is then decomposed with an aqueous solution of ammonium chloride. The organic material is extracted with diethyl ether, which yields 98.0 g of the oily 2-(4-bromo-phenyl)-2-propanol, which crystallizes from pentane while cooling, m.p. 37—43°C.

To a solution of 37.6 g of phenol and 13.3 g of aluminum chloride is added dropwise a mixture of 43.0 g of 2-(4-bromo-phenyl)-2-propanol and 18.8 g of phenol while stirring and cooling in an ice-bath. The reaction mixture is stirred for an additional five hours, then allowed to stand at room temperature for fifteen hours, and decomposed with ice and concentrated hydrochloric acid. The organic material is extracted with three portions of diethyl ether; the organic solutions are combined, washed with



water and a saturated aqueous solution of sodium chloride, dried over sodium sulfate and evaporated to yield 67.0 g of an oily material, which is purified by distillation. The desired 2 - (4 - bromo - phenyl) - 2 - (4 - hydroxy - phenyl) - propane is collected at 155—185°/0.02 mm Hg, crystallizes from hexane and melts at 89—90° after recrystallization from hexane.

The 2 - (4 - iodo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane is prepared by reacting a solution of about equivalent amounts of 2 - (4 - iodo - phenyl) - 2 - (4 - hydroxyphenyl) - propane and 1 - (2 - chloroethyl) - piperidine hydrochloride in a mixture of N,N-dimethylformamide and toluene in the presence of an excess of a 53 per cent suspension of sodium hydride and carrying out the reaction as previously described. The starting material is obtained by treating a methyl magnesium iodide Grignard reagent with 4-iodoacetophenone and treating the resulting 2 - (4 - iodo - phenyl) - 2 - propanol with phenol in the presence of aluminum chloride as described in the above Example.

EXAMPLE 11

A mixture of 0.25 g of 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane and 5 ml of 2N aqueous hydrochloric acid is heated on a water bath to complete solution. On cooling, the 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane hydrochloride precipitates as an oil and crystallizes on standing. It is filtered off, and recrystallized from acetone, m.p. 200—201°C.

EXAMPLE 12

To a solution of 7.0 g of 2 - (4 - bromo - phenyl) - 2 - (4 - hydroxy - phenyl) - propane in a mixture of 25 ml of N,N-dimethylformamide and 15 ml of toluene is added in portions 2.4 g of a 53 per cent suspension of sodium mineral oil. After the hydrogen evolution ceases, 2.1 g of ethylene chlorohydrin in 20 ml of toluene is slowly added while stirring. The reaction mixture is allowed to stand at room temperature for twenty hours and then filtered; the filtrate is concentrated under reduced pressure to a volume of about 25 ml and diluted with water. The organic material is extracted with benzene, the organic solution is washed with a saturated aqueous solution of sodium chloride, and a small amount of benzene is distilled off azeotropically to remove traces of water.

The resulting benzene solution of 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - hydroxy - ethoxy) - phenyl] - propane is cooled in an ice-bath and treated dropwise with a solution of 5 ml of thionyl chloride in 25 ml of benzene. The reaction mixture is allowed to warm to room temperature and is then heated to about 50°C. until the evolution of hydrogen chloride and sulfur dioxide ceases. The resulting reaction mixture is concentrated under reduced pressure to a volume of about 20 ml, diluted with 50 ml of benzene and again concentrated to about 30 ml to remove traces of thionyl chloride.

The resulting benzene solution of 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - chloro - ethoxy) - phenyl] - propane is treated with 15 ml of piperidine; the reaction mixture is diluted with 50 ml of benzene and is then heated under reflux for two hours. Upon working up the reaction mixture according to the procedure described in Example 10, the 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane is obtained, m.p. 77—78°C. after recrystallization from ethanol.

EXAMPLE 13

The compounds of this invention, being useful, for example, in the treatment of superficial dermatophytoses, may be applied in the form of pharmaceutical compositions for topical use, (i.e. emulsions, such as creams, ointments, lotions and the like), containing from about 0.1 per cent to about 10 per cent, especially from about 0.5 per cent to about 5 per cent, of the active ingredient, i.e. a 2 - (4 - halogeno - phenyl) - 2 - [4 - (2 - R - ethyl) - oxy - phenyl] - propane, in which halogeno has an atomic weight greater than 77, and R is N,N-di-lower alkyl-amino or 1-piperidino, or an acid addition, particularly a pharmaceutically acceptable acid addition salt, thereof.

The above compositions are prepared according to known methods used in the art of manufacturing pharmaceutical compositions.

For example, an ointment containing 1 per cent of 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane as the active ingredient is prepared as follows (for 100.0 g):



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Ingredients

2-(4-bromo-phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane	1.0 g
Liquid petrolatum	5.0 g
White petrolatum	94.0 g.

The 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane is mixed with the liquid petrolatum by using a mortar until an adequate reduction in particle size is accomplished. The white petrolatum is then slowly blended with this mixture; the ointment is passed through a three roller mill, until total uniformity is obtained and filled into epoxy lined tubes (5.0 g).

A cream, containing 1 per cent of 2 - (4 - bromophenyl) - 2 - [4 - (2 - piperidino-ethoxy) - phenyl] - propane as the active ingredient is prepared as follows (for 100.0 g):

Ingredients

2-(4-bromo-phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane	1.0 g
Propylene glycol	15.0 g
Sodium lauryl sulfate	2.0 g
Cetyl alcohol	15.0 g
Phenyl mercuric acetate	0.002 g
Purified water q.s.	100.0 g

The phenylmercuric acetate is dissolved in 65 ml of water at 90°C.; subsequently the sodium lauryl sulfate is added and the temperature is reduced to 70°C. The cetyl alcohol is melted at 70°C. and added to the aqueous solution while vigorously agitating. Stirring is continued while cooling the mixture to 45°C.

The 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl]-propane is dispersed in the propylene glycol at 45°C. and added to the above emulsion while agitating. Sufficient water is added to bring the weight to 100 g, and mixing is continued while the product cools to room temperature. The cream is passed through a three roller mill until total uniformity is accomplished and is filled into epoxy lined tubes (5 g).

A cream containing 2 per cent of 2 - (4 - bromophenyl) - 2 - [4 - (2 - piperidino-ethoxy) - phenyl] - propane as the active ingredient is prepared as follows (for 3000.0 g):

Ingredients

2-(4-bromo-phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane	60.0 g
Glyceryl monostearate	225.0 g
Lanolin, anhydrous	30.0 g
Isopropyl myristate	90.0 g
Polyethylene glycol 4000 monostearate	300.0 g
Stearic acid	390. g
Sorbitan sesquioleate	15.0 g
Spermaceti	180.0 g
Propylene glycol	150.0 g
Polysorbate 60	45.0 g
Purified water	1515.0 g.

The glyceryl monostearate, the lanolin, the isopropyl myristate, the polyethylene glycol 4000 monostearate, the stearic acid, the sorbitan sesquioleate, and the spermaceti are melted together at 80°C. on the water bath. The water containing the polysorbate 60 is added while stirring at 80°C. stirring is continued until the temperature drops below 40°C. The solution of the 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane in propylene glycol is added; stirring is continued and water is added to bring the weight to 3000.0 g. The cream is passed through a homogenizer and filled into tubes.

A cream containing 5 percent of 2 - (4 - bromo - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane as the active ingredient is prepared as follows (for 5,000.0 g):

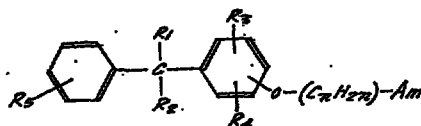
Ingredients

	2-(4-bromo-phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane	250.0 g	
	Glyceryl monostearate	375.0 g	
5	Lanolin, anhydrous	50.0 g	5
	Isopropyl myristate	150.0 g	
	Polyethylene glycol 4000 monostearate	400.0 g	
	Stearic acid	650.0 g	
	Spermaceti	300.0 g	
10	Sorbitan sesquioleate	25.0 g	10
	Polyoxyethylene sorbitan monostearate	75.0 g	
	Propylene glycol	250.0 g	
	Purified water q.s.	5000.0 g	

15 A mixture of the glyceryl monostearate, lanolin (anhydrous), isopropyl myristate, poly-
ethylene glycol 4000 monostearate, stearic acid, spermaceti and the sorbitan sesquioleate
is melted in a jacketed mixer at 70°C. Water is slowly added while stirring until the
mixture congeals; the temperature is then brought to 40°C. The polyoxyethylene
20 sorbitan monostearate is dissolved in 1600 ml of water at 75°C. and the 2-(4-bromo-
phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane is dissolved in the
solution while maintaining a temperature of about 60°C. The mixture is then diluted
with 500 ml of boiling water, and is added to the cream base while stirring. Water is
added to bring the weight up to 5000.0 g and the resulting cream is passed through a
homogenizer.

WHAT WE CLAIM IS:—

25 1. A compound of the formula

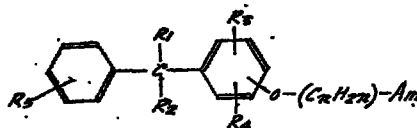


30 in which R_1 and R_2 each represents an alkyl group, Am represents a tertiary amino
group, the alkylene group of the formula $-(C_nH_{2n})-$ separates the group Am from
the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, R_3 and
 R_4 each represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy or tri-
fluoromethyl group or the group of the formula $-O-(C_nH_{2n})-$ Am as defined above,
and R_5 represents a hydrogen atom or lower alkyl, lower alkoxy or trifluoromethyl
35 group or halogen atoms or an unsubstituted phenyl radical or such a radical substituted
by lower alkyl, lower alkoxy or trifluoromethyl groups or halogen atoms, and wherein
at least one of R_3 , R_4 and R_5 is other than hydrogen, and lower alkyl and lower alkoxy
have the previously defined meanings.

40 2. An N-oxide of a compound as claimed in claim 1.
3. A quaternary ammonium derivative of a compound as claimed in claim 1.
4. An acid addition salt of a compound as claimed in either one of claims 1 and

5. A physiologically tolerable acid addition salt of a compound as claimed in
either one of claims 1 and 2.

6. A compound of the formula



45 in which R_1 and R_2 each represents an alkyl group, Am represents a tertiary amino
group, the alkylene group of the formula $-(C_nH_{2n})-$ separates the group Am from
the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, and R_3
and R_4 each represents a hydrogen or halogen atom or a lower alkoxy, lower alkyl or
trifluoromethyl group, R_5 represents hydrogen or at least one substituent selected from
lower alkyl, lower alkoxy and trifluoromethyl group and halogen atoms, and wherein
50 at least one of R_3 , R_4 and R_5 is other than hydrogen.

7. An N-oxide of a compound as claimed in claim 6.

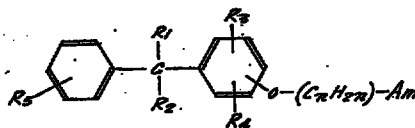
Ingredients

	2-(4-bromo-phenyl)-2-[4-(2-piperidino-ethoxy)-phenyl]-propane	250.0 g	
	Glyceryl monostearate	375.0 g	
5	Lanolin, anhydrous	50.0 g	5
	Isopropyl myristate	150.0 g	
	Polyethylene glycol 4000 monostearate	400.0 g	
	Stearic acid	650.0 g	
	Spermaceti	300.0 g	
10	Sorbitan sesquioleate	25.0 g	10
	Polyoxyethylene sorbitan monostearate	75.0 g	
	Propylene glycol	250.0 g	
	Purified water q.s.	5000.0 g	

A mixture of the glyceryl monostearate, lanolin (anhydrous), isopropyl myristate, polyethyleneglycol 4000 monostearate, stearic acid, spermaceti and the sorbitan sesquioleate is melted in a jacketed mixer at 70°C. Water is slowly added while stirring until the mixture congeals; the temperature is then brought to 40°C. The polyoxyethylene sorbitan monostearate is dissolved in 1600 ml of water at 75°C. and the 2 - (4 - bromo-phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane is dissolved in the solution while maintaining a temperature of about 60°C. The mixture is then diluted with 500 ml of boiling water, and is added to the cream base while stirring. Water is added to bring the weight up to 5000.0 g and the resulting cream is passed through a homogenizer.

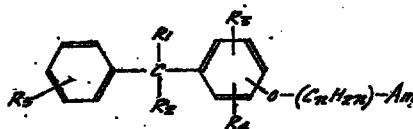
WHAT WE CLAIM IS:—

1. A compound of the formula



in which R_1 and R_2 each represents an alkyl group, Am represents a tertiary amino group, the alkylene group of the formula $-(C_nH_{2n})-$ separates the group Am from the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, R_3 and R_4 each represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy or trifluoromethyl group or the group of the formula $-O-(C_nH_{2n})-Am$ as defined above, and R_5 represents a hydrogen atom or lower alkyl, lower alkoxy or trifluoromethyl group or halogen atoms or an unsubstituted phenyl radical or such a radical substituted by lower alkyl, lower alkoxy or trifluoromethyl groups or halogen atoms, and wherein at least one of R_3 , R_4 and R_5 is other than hydrogen, and lower alkyl and lower alkoxy have the previously defined meanings.

2. An N-oxide of a compound as claimed in claim 1.
3. A quaternary ammonium derivative of a compound as claimed in claim 1.
4. An acid addition salt of a compound as claimed in either one of claims 1 and 2.
5. A physiologically tolerable acid addition salt of a compound as claimed in either one of claims 1 and 2.
6. A compound of the formula



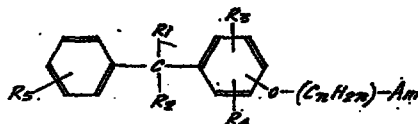
in which R_1 and R_2 each represents an alkyl group, Am represents a tertiary amino group, the alkylene group of the formula $-(C_nH_{2n})-$ separates the group Am from the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, and R_3 and R_4 each represents a hydrogen or halogen atom or a lower alkoxy, lower alkyl or trifluoromethyl group, R_5 represents hydrogen or at least one substituent selected from lower alkyl, lower alkoxy and trifluoromethyl group and halogen atoms, and wherein at least one of R_3 , R_4 and R_5 is other than hydrogen.

7. An N-oxide of a compound as claimed in claim 6.



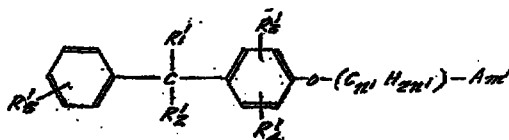
50 groups

8. A quaternary ammonium derivative of a compound as claimed in claim 6.
9. An acid addition salt of a compound as claimed in either one of claims 6 and 7.
10. A physiologically tolerable acid addition salt of a compound as claimed in either one of claims 6 and 7.
11. A compound of the formula



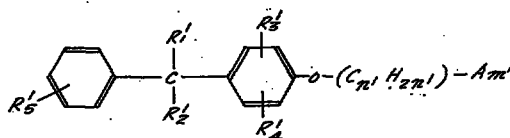
in which R_5 represents at least one lower alkyl, lower alkoxy or trifluoromethyl group or halogen atom, R_1 and R_2 each represents an alkyl group, Am represents a tertiary amino group, the alkylene group of the formula $-(C_nH_{2n})-$ separates the group Am from the oxygen atom by at least two carbon atoms, n being an integer from 2 to 7, and R_3 and R_4 each represents a hydrogen or halogen atom or a lower alkoxy, lower alkyl or trifluoromethyl group.

12. An N-oxide of a compound as claimed in claim 11.
13. A quaternary ammonium derivative of a compound as claimed in claim 11.
14. An acid addition salt of a compound as claimed in claim 11 or 12.
15. A physiologically tolerable acid addition salt of a compound as claimed in claim 11 or 12.
16. A compound of the formula



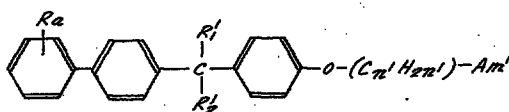
in which R_1' and R_2' each represents a lower alkyl group, Am' represents a di-lower alkyl-amino group, the alkylene group $-(C_{n'}H_{2n'})-$ contains two or three carbon atoms and separates the group Am' from the oxygen atom by two or three carbon atoms, R_3' and R_4' each represents a hydrogen or halogen atom or a lower alkyl group or the group of the formula $-O-(C_{n'}H_{2n'})-Am'$ as defined above, and R_5' stands for hydrogen, a lower alkyl group and/or a halogen atom and wherein at least one of R_3' , R_4' and R_5' is other than hydrogen.

17. A compound of the formula



in which R_1' and R_2' each represents a methyl group, Am' represents a di-alkyl-amino group in which each alkyl group contain 1 to 4 carbon atoms, the group $-(C_{n'}H_{2n'})-$ represents a 1:2 ethylene group, R_3' and R_4' each represents a hydrogen or chlorine atom or the methyl group or the group of the formula $-O-(C_{n'}H_{2n'})-Am'$ as defined above, and R_5' represents hydrogen, a methyl group and/or a chlorine atom, and wherein at least one of R_3' , R_4' and R_5' is other than hydrogen.

18. An acid addition salt of a compound as claimed in claim 16 or 17.
19. A physiologically tolerable acid addition salt of a compound as claimed in claim 16 or 17.
20. A compound of the formula



in which R_a represents a hydrogen or a halogen atom or a lower alkyl or lower alkoxy



group, R_1^1 and R_2^1 each represents an alkyl group containing one to four carbon atoms Am^1 represents an N:N-di-lower alkyl-amino group, n^1 represents 2 or 3, and the group of the formula $-(C_n^1H_{2n^1})-$ separates the group Am^1 from the oxygen atom by two or three carbon atoms.

- 5 21. A physiologically tolerable acid addition salt of a compound as claimed in claim 20. 5
22. 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N:N - diethylaminoethoxy)-phenyl] - propane.
- 10 23. 2 - (4 - chloro - phenyl) - 2 - [4 - (2 - N:N - diethylaminoethoxy) - 3:5-dimethyl - phenyl] - propane. 10
24. An acid addition salt of the compound claimed in any one of claims 22—23.
25. A physiologically tolerable acid addition salt of the compounds claimed in any one of claims 22—23.
- 15 26. The hydrochloride of the compound claimed in any one of claims 22—23. 15
27. 2 - (*p* - Bi - phenyl) - 2 - [4 - (2 - N:N - diethylaminoethoxy) - phenyl] - propane.
28. 2 - (*p* - Bi - phenyl) - 2 - [3 - chloro - 4 - (2 - N:N - diethylaminoethoxy) - phenyl] - propane.
- 20 29. An acid addition salt of the compound claimed in claim 27 or 28. 20
30. A physiologically tolerable acid addition salt of the compound claimed in claim 27 or 28.
31. 2 - (*p* - Biphenyl) - 2 - [4 - (2 - N:N - diethylaminoethoxy) - phenyl] - propane - hydrochloride.
- 25 32. 2 - (4 - Chloro - phenyl - 2 - [3 - chloro - 4 - (2 - N:N - diethylaminoethoxy) - phenyl] - propane. 25
33. 2 - (4 - Chloro - phenyl) - 2 - [3 - chloro - 4 - (2 - N:N - diethylaminoethoxy) - 5 - methyl - phenyl] - propane.
34. 2 - [4 - (2 - N:N - diethylaminoethoxy) - phenyl] - 2 - (4 - methyl-phenyl) - propane.
- 30 35. 2 - (4 - Chloro - phenyl) - 2 - [4 - (2 - N:N - diethylaminoethoxy)-phenyl] - propane ethobromide. 30
36. 2 - (4 - Chloro - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane.
- 35 37. 2 - [3:4 - Bis - (2 - N:N - diethylaminoethoxy) - phenyl] - 2 - (4 - methyl-phenyl) - propane. 35
38. 2 - (*p* - Biphenyl) - 2 - [3:4 - bis - (2 - N:N - diethylaminoethoxy)-phenyl] - propane.
39. 2 - (4 - Chloro - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane - N - oxide.
- 40 40. 2 - (4 - Chloro - phenyl) - 2 - [4 - (2 - piperidino - ethoxy) - phenyl] - propane - N - oxide picrate. 40
41. An acid addition salt of the compound claimed in any one of claims 32—34 and 36—39.
- 45 42. A physiologically tolerable acid addition salt of the compound claimed in any one of claims 32—34 and 36—39. 45
43. The hydrochloride of the compound claimed in claim 33, 34 or 36.
44. A pharmaceutical preparation which comprises a compound as claimed in claim 11 in admixture or conjunction with a pharmaceutically suitable carrier.
- 50 45. A pharmaceutical preparation which comprises an N-oxide as claimed in claim 12 in admixture or conjunction with a pharmaceutically suitable carrier. 50
46. A pharmaceutical preparation which comprises a quaternary ammonium derivative as claimed in claim 13 in admixture or conjunction with a pharmaceutically suitable carrier.
- 55 47. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 15 or 21 in admixture or conjunction with a pharmaceutically suitable carrier. 55
48. A pharmaceutical preparation which comprises the compound claimed in any one of claims 22—23 in admixture or conjunction with a pharmaceutically suitable carrier.
- 60 49. A pharmaceutical preparation which comprises a salt as claimed in claim 25 or 26 in admixture or conjunction with a pharmaceutically suitable carrier. 60
50. A pharmaceutical preparation which comprises a compound as claimed in claim 6 or 20 in admixture or conjunction with a pharmaceutically suitable carrier.



51. A pharmaceutical preparation which comprises an N-oxide as claimed in claim 7 in admixture or conjunction with a pharmaceutically suitable carrier.
52. A pharmaceutical preparation which comprises a quaternary ammonium derivative as claimed in claim 8 in admixture or conjunction with a pharmaceutically suitable carrier.
53. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 10 in admixture or conjunction with a pharmaceutically suitable carrier.
54. A pharmaceutical preparation which comprises the compound claimed in claim 27 or 28 in admixture or conjunction with a pharmaceutically suitable carrier.
55. A pharmaceutical preparation which comprises a salt as claimed in claim 30 or 31 in admixture or conjunction with a pharmaceutically suitable carrier.
56. A pharmaceutical preparation which comprises a compound as claimed in claim 1, 16 or 17 in admixture or conjunction with a pharmaceutically suitable carrier.
57. A pharmaceutical preparation which comprises an N-oxide as claimed in claim 2 in admixture or conjunction with a pharmaceutically suitable carrier.
58. A pharmaceutical preparation which comprises a quaternary ammonium derivative as claimed in claim 3 in admixture or conjunction with a pharmaceutically suitable carrier.
59. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 5 or 19 in admixture or conjunction with a pharmaceutically suitable carrier.
60. A pharmaceutical preparation which comprises the compound claimed in any one of claims 32—40 in admixture or conjunction with a pharmaceutically suitable carrier.
61. A pharmaceutical preparation which comprises a salt as claimed in claim 42 or 43 in admixture or conjunction with a pharmaceutically suitable carrier.
62. A pharmaceutical preparation having the composition substantially as described in Example 9 or 13 herein.
63. A process for the manufacture of a compound as claimed in any one of claims 1—5, 16—19 and 32—43 conducted substantially as described herein.
64. A process for the manufacture of a compound as claimed in any one of claims 6—10, 20, and 27—31 conducted substantially as described herein.
65. A process for the manufacture of a compound as claimed in any one of claims 11—15, and 21—26 conducted substantially as described herein.

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