PATENT SPECIFICATION

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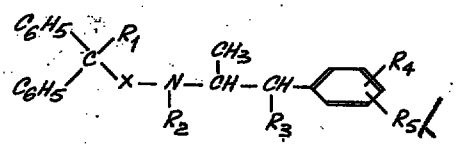
International Classification:—C07c.

COMPLETE SPECIFICATION

Basically Substituted Diphenyl-Methane Compounds and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German Law, of Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

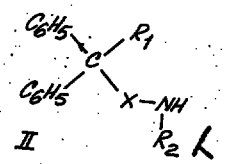
The present invention is based on the observation that compounds of the general formula



(I)

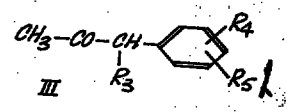
in which X represents a straight-chained or branched aliphatic hydrocarbon radical containing at most 3 carbon atoms, R_1 represents a hydrogen atom or an alkyl group (C_{1-4}), and R_2 represents a hydrogen atom or a methyl group, R_3 represents a hydrogen atom or an hydroxyl group, R_4 and R_5 each represent a hydrogen atom, an hydroxyl group or a methoxy group, possess a good action on the heart and the circulation, and can be used as physiologically tolerable acid addition salts or quaternary ammonium salts in the form of pharmaceutical preparations.

The compounds of the present invention can be made by reducing in the presence of an amine of the general formula



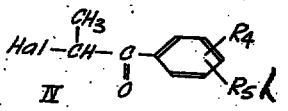
II

in which R_1, R_2 and X have the meanings given above, a ketone of the general formula



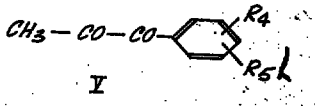
III

in which R_3, R_4 and R_5 have the meanings given above, or when R_3 = OH by reacting an amine of the above general formula, preferably in the presence of an agent capable of splitting off hydrogen halide, with a halogen-substituted ketone of the general formula



IV

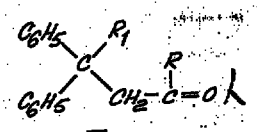
in which R_4 and R_5 have the meanings given above and Hal is a halogen atom, and by reducing the keto-group in the condensation product thus obtained, in the usual manner, to an hydroxyl group. Alternatively, when R_3 = OH, a diketone of the formula



V

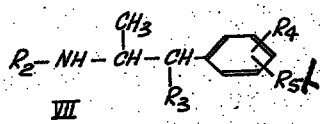
may be reduced, if desired, in a step-wise manner, in the presence of an amine of the above general formula in which R_4 and R_5 have the meanings given above. Another alternative process for the preparation of the desired diphenyl-methane derivative in which X = $-CH_2-CH_2-$ or $-CH_2-\underset{CH_3}{CH}-$ is to

reduce an aldehyde or ketone of the general formula



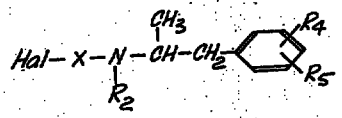
VI

in which R represents a hydrogen atom or a methyl group and R_1 has the meaning given above, in the presence of an amine of the general formula



VII

in which R_2, R_3, R_4 and R_5 have the meanings given above. Furthermore, in the case of compounds of formula I when $R_3 = H$, diphenyl - methane or diphenyl - acetonitrile may be reacted, preferably in the presence of an agent capable of splitting off hydrogen halide, with a halogen-substituted amine of the general formula



VIII

in which R_2, R_4, R_5 and X have the meanings given above; when diphenyl-acetonitrile is used, the nitrile group in the reaction products is replaced by hydrogen in the usual manner.

Diphenyl-methane derivatives of the general formula (I), which are substituted at the nitrogen atom by a methyl group, can be obtained from the corresponding compounds in which R_2 is a hydrogen atom by methylation in the usual manner, especially by reaction with aqueous formaldehyde in the presence of formic acid. The compounds of the general formula (I) in which R_4 and/or R_5 represent hydroxyl groups, can be obtained by demethylating the corresponding compounds in which R_4 and R_5 each represent a methoxy group, preferably by heating with hydrogen bromide, aluminium chloride or pyridine hydrochloride. The compounds of the general formula (I), in which R_4 and/or R_5 represent methoxy groups, are obtained from the corresponding hydroxy-compounds in which R_4 and/or R_5 are hydroxyl groups, by alkylation in the usual manner.

An especially advantageous method of preparing a compound of the present invention is to reduce a ketone of the formula III, in the presence of an amine of the formula II. As examples of these amines there may be used 1:1 - diphenyl - propylamine - (3), 1:1 - diphenyl - ethylamine - (2), 2:2 - diphenyl - butylamine - (1), 2:2 - diphenyl-propylamine - (1), 2:2 - diphenyl - amylamine - (1), 2:2 - diphenyl - hexylamine-(1), 1:1 - diphenyl - 3 - methyl - propylamine - (3), N - methyl - 1:1 - diphenyl-propylamine - (3), N - methyl - 1:1 - diphenyl - ethylamine - (2), N - methyl - 2:2 - diphenyl - butylamine - (1), N-methyl-2:2 - diphenyl - propylamine-(1), N-methyl-2:2 - diphenyl - amylamine - (1), N-methyl-2:2 - diphenyl - hexylamine - (1) and N-methyl - 1:1 - diphenyl - 3 - methyl-propylamine-(3). As examples of suitable ketones there may be used phenyl - acetone, (3:4-dihydroxy or dimethoxy - phenyl) - acetone, (2 - hydroxy or methoxy - phenyl) - acetone, (3 - hydroxy or methoxy - phenyl) - acetone, (4 - hydroxy or methoxy - phenyl)-acetone, α - phenyl - α - hydroxy - acetone, α - (3:4-dihydroxy or dimethoxy-phenyl)-α-hydroxy-acetone, α - (2 - hydroxy or methoxy-phenyl) - α - hydroxy - acetone, α - (3-hydroxy or methoxy - phenyl) - α - hydroxy-acetone and α - (4 - hydroxy or methoxy-phenyl) - α - hydroxy - acetone. The reduction in the presence of the amine is preferably carried out by catalytic hydrogenation, for example by using a metal of the eighth Group of the Periodic Table as the hydrocarbon catalyst, preferably nickel in the presence of a suitable solvent for example an aqueous alcohol, an alcohol or water. A noble metal or a Raney-catalyst may also be used. The reduction may also be carried out by means of nascent hydrogen obtained, for example, from aluminium amalgam and alcohol, sodium amalgam, lithium - aluminium-hydride or sodium boron-hydride, or it may be carried out electrolytically.

The amines corresponding to formula II may be reacted with a halogen substituted ketone of the formula IV. As examples of suitable halogenated ketones there may be mentioned α - bromethyl - phenyl - ketone, α - chlorethyl - phenyl - ketone, α - bromethyl - (3 - methoxy - phenyl) - ketone, α-bromethyl - (4 - methoxy - phenyl) - ketone, α - chlorethyl - (3:4 - dimethoxy - phenyl)-ketone, α - bromethyl - (3:4 - dimethoxy-phenyl)-ketone. If desired, the reaction may be carried out in a suitable inert organic solvent, such as ether, chloroform or an aromatic hydrocarbon with prolonged heating. Advantageously, the hydrogen halide liberated during the reaction, is bound by an excess of one molecular proportion of the amine used as starting material. The hydrogen halide may also be bound by means of one of the usual acid-binding agents, such as an alkali metal carbonate, an alkali metal hydroxide, an alkaline earth metal carbonate or an alkaline earth metal hydroxide, or by

means of an organic base, such as pyridine or quinoline which may also be used as the reaction medium. The reaction mixtures obtained are worked up in the usual manner by separating the hydrohalic acid salt of the base used, for example, by precipitation with ether or shaking with water.

The products of the process may be purified by distillation. The amino-ketones thus obtained are then reduced in the usual manner to give the corresponding amino alcohols. For example, catalytically by means of a metal of the eighth Group of the Periodic Table and preferably a nickel catalyst, in the presence of one of the usual solvents, for example, an aqueous alcohol, an alcohol or water. A noble metal or a Raney-catalyst may also be used. Alternatively, the reduction may be carried out by means of nascent hydrogen obtained, for example, from aluminium amalgam and alcohol, sodium amalgam, lithium- or aluminium-hydride or sodium boron-hydride. The reduction may also be carried out electrolytically.

The desired compounds may also be obtained by reducing in the presence of an amine of formula II a diketone of the formula V. As examples of suitable di-ketones, there may be mentioned (1:2 - dioxo - propyl)-benzene, 4 - (1:2 - dioxo - propyl) - anisol, 3 - (1:2 - dioxo - propyl) - anisol, 4 - (1:2-dioxo - propyl) - phenol, 3 - (1:2 - dioxo-propyl) - phenol, 1 - (1:2 - dioxo - propyl)-phenol, 3 - (1:2 - dioxo - propyl) - phenol, 1 - (1:2 - dioxo - propyl) - 3:4 - dimethoxy-benzene and 1 - (1:2 - dioxo - propyl)-3:4-dihydroxy - benzene. In this reaction, the amine reacts preferentially with the keto group adjacent to the methyl group. The other keto group may be reduced simultaneously or subsequently in the manner already described.

In an alternative form of the process of the present invention, an aldehyde or ketone of the formula VI is reduced in the presence of an amine of the formula VII. As examples of suitable aldehydes or ketones there may be used, 1:1 - diphenyl - propionaldehyde-(3), 2:2 - diphenyl - butyraldehyde - (4), 1:1 - diphenyl - ethyl - (2) - methyl-ketone. This reduction may also be carried out in the manner described above.

In another advantageous method of preparing the desired compounds, diphenyl-acetonitrile or diphenyl-methane is reacted with a halogen-substituted amine of the formula VIII. As examples of suitable halogen-substituted amines there may be mentioned 1 - phenyl - 2 - (chlorethyl-methylamino) - propane, 1 - phenyl - 2 - (chlorethyl - benzylamino) - propane, 1 - (3:4 - di-methoxy - phenyl) - 2 - (chlorethyl-methylamino) - propane, 1 - (3:4 - dimethoxy - phenyl) - 2 - (chlorethyl-benzylamino)-propane, 1 - phenyl - 2 - (chlormethyl-ethyl-amino) - propane, 1 - phenyl - 2 - (chlormethyl - benzylamino) - propane, 1 - (4 - methoxy - phenyl) - 2 - chlorethyl - benzyl-amino) - propane, 1 - (2 - methoxy-phenyl)-2 - (chlorethyl - benzylamino) - propane, 1 - (3 - methoxy - phenyl) - 2 - (chlorethyl - methylamino) - propane. This reaction may, in principle, be carried out in an analogous manner to that described in Liebigs "Annalen der Chemie 561, page 52 (1948). Advantageously, the reaction is conducted in an inert organic solvent such as benzene, toluene, or xylene. As examples of agents capable of splitting off hydrogen halide, there may be mentioned sodamide, sodium phenyl, lithium phenyl and metallic sodium. Two out of three necessary reaction components, i.e., diphenyl-acetonitrile, an agent capable of splitting off hydrogen halide and a halogen substituted amine, are advantageously dissolved or suspended in the solvent, and the third component is then added in several portions. After the whole of the third component has been added, the mixture is advantageously boiled for some time under reflux, and then, after the addition of water, the reaction mixture is worked up in the usual manner, for example by extracting the basic components from the organic solvent by means of a dilute acid. When diphenyl-methane is used as starting material, phenyl-sodium is advantageously used as the agent capable of splitting of hydrogen halide. When diphenyl-acetonitrile is used as starting material the nitrile group still present in the products obtained by the process can be replaced by a hydrogen atom in known manner, for example, by the method described in Liebigs "Annalen der Chemie" 561, page 52 (1948), by prolonged heating with sodamide, in benzene or toluene. The nitrile group may also be hydrolyzed by means of a strong acid, for example, sulphuric acid of 70% strength to give a carboxyl group which can then be removed by heating. If a benzyl group is attached to the nitrogen atom, this group may be split off in the usual manner, for example, by catalytic hydrogenation in the presence of a noble metal catalyst.

When R_2 in Formula (I) represents a hydrogen atom, the NH-group can be methylated in the usual manner, for example by means of aqueous formaldehyde and using palladium as catalyst in a solvent which is suitable for hydrogenations. The methylation may also be carried out in known manner by means of aqueous formaldehyde in the presence of formic acid, by heating the reaction mixture for some time on a steam bath.

The compounds of the general formula (I) in which R_4 and/or R_5 each represent a hydroxyl group, may be obtained by demethylation in known manner of an appropriate compound in which R_4 and/or R_5

each represent a methoxy group.

This demethylation may be carried out by heating the methoxy-substituted compound in the presence of hydrogen bromide, aluminium chloride or pyridine-hydrochloride.

The compounds of the general formula (I), in which R_4 and/or R_5 each represent a methoxy group, may be prepared by alkylation of an appropriate compound in which R_4 and/or R_5 each represent a hydroxyl-group. The hydroxy compound may, for example, be reacted with dimethyl-sulphate, diethyl-sulphate, methyl-iodide, ethyl-iodide or with another alkylating agent, if necessary in the presence of a base such as an alkali metal hydroxide or an alkaline earth metal hydroxide. The reaction with a dialkyl-sulphate generally commences at room temperature. Alkylation by means of an alkyl-halide may be achieved by heating, if necessary, in an autoclave.

The bases obtained as end-products of the process of this invention may be converted into acid addition salts by means of inorganic or organic acids. As examples of inorganic acids there may be considered hydrohalic acids, such as hydrochloric acid and hydrobromic acid, sulphuric acid, phosphoric acid and amidosulphonic acid. As examples of organic acids there may be mentioned formic acid, acetic acid, propionic acid, lactic acid, maleic acid, succinic acid, tartaric acid, benzoic acid, salicylic acid, citric acid, aceturic acid, hydroxyethane-sulphonic acid and ethylene-diamine-tetracetic acid. When the basic residue of the product of the present process contains a tertiary nitrogen atom, the compound may also be converted into a quaternary ammonium salt by means of an alkyl-halide.

The compounds of the present invention have an extremely beneficial influence on cardiac and general blood vascular circulation. For example, by infusing 2-(1:1-diphenyl - propyl - (3) - amino) - 3 - phenyl-propane into rabbit's hearts, by the method of Langendorff, at the rate of 20 micrograms per minute, a strong dilation of the coronary vessels was obtained. This dilation reached a maximum with an administration of 30 micrograms per minute. After the infusion was discontinued, the increased blood flow was still maintained for a considerable time. Furthermore, the rate of heart-beat was reduced, and this had an influence on the whole body of the animal. The administration of small doses of this compound also causes distinct dilation of the blood vessels in a rabbit's ear which has been isolated and perfused by the Kraskow-Pissemski method. 5 Micrograms cause slight dilation and 150 micrograms a very considerable dilation of these vessels.

The compounds of the present invention cause the dilation of the coronary and peripheral blood vessels even when administered in such small doses that the toxicity (for example of 2 - (1:1 - diphenyl - propyl-(3) - amino) - 3 - phenyl - propane, of which the lethal dose is 15—20 milligrams per kilogram) is practically negligible.

Similarly, when 2 - (1:1 - diphenyl-propyl-(3) - amino) - 3 - phenyl - propane is used for clinical examinations, it causes dilation of the coronary vessels. It also results in an increased peripheral blood circulation. The dilation of the coronary vessels occurs very rapidly and, compared with the known nitro compounds, for example, the tetra-nitric acid ester of erythritol, this dilation is maintained for some time (several hours). As single doses, 5—10 mg of the compound are administered.

The compounds of the invention may be administered in unit dosage form as indicated above as such or as acid addition or quaternary ammonium salts thereof, or in admixture or in conjunction with pharmaceutically suitable carriers, either parenterally or orally. For oral administration, the compounds may be in the form of tablets or dragees which also contain the usual carriers such as lactose, starch, tragacanth or magnesium stearate, as well as the said compound as active ingredient.

The following Examples illustrate the invention:

EXAMPLE 1.

15 grams of α - phenyl - α - hydroxyacetone were hydrogenated by means of palladium in the presence of 21.1 grams of 1:1-diphenyl - propylamine-(3) in 200 cc of isopropanol. The calculated amount of hydrogen was taken up at room temperature. The separated oily base was dissolved in alcohol by heating. After filtration of the solution, water was added thereto until it became turbid. 24.5 grams of 2 - (1:1 - diphenyl-propyl - (3) - amino) - 3 - hydroxy-3-phenyl-propane were obtained, which melted at 108° C. By adding an equivalent proportion of aminosulphonic acid in water, filtration and concentration of the filtrate, 28 grams of the aminosulphonic acid salt of the propane derivative were obtained.

EXAMPLE 2.

By hydrogenating 6.7 grams of phenyl-acetone in the presence of 10.6 grams of 1:1 - diphenyl - propylamine - (3) in methanol, by means of palladium at 50° C., and otherwise conducting the experiment in an analogous manner to that of Example 1, 14 grams of 2 - (1:1 - diphenyl - propyl - (3) - amino) - 3 - phenyl - propane boiling at 195—198° C. under a pressure of 0.5 mm of mercury were obtained. This product crystallised out after prolonged standing and had a melting point of about 38—40° C. The hydrochloride of this compound, prepared in the usual manner, melted at 188—190° C.

The glycollic acid salt of the compound melted at 140—142° C.

EXAMPLE 3.

10 grams of the base obtained in Example 2 were shaken with 3 grams of aqueous formaldehyde of 40% strength and 150 cc of methanol in the presence of palladium and hydrogen. After the calculated amount of hydrogen had been taken up, the reaction mixture was filtered and concentrated. The oily residue, consisting of 2-[1:1-diphenyl-propyl - (3) - methylamino] - 3 - phenyl-propane, was heated with 2.5 grams of glycollic acid and 50 cc of water. The solution thus obtained was filtered and concentrated. The oily residue crystallised after some time and 8 grams of 2 - (1:1-diphenyl-propyl-(3) - methylamino) - 3 - phenyl - propane-glycollate which melted at 84—86° C., were obtained.

EXAMPLE 4.

9.7 Grams of 3:4 - dimethoxy - phenyl-acetone were hydrogenated at 50° C. in the presence of 10.6 grams of 1:1 - diphenyl-propylamine-(3) in an analogous manner to that described in Example 1. The oily hydrogenation product consisting of 2-[1:1-diphenyl - propyl - (3) - amino] - 3 - (3:4-dimethoxyphenyl)-propane was heated with 3.8 grams of glycollic acid and 50 cc of water. After filtration and cooling, 14.4 grams of 2 - (1:1 - diphenyl - propyl - (3) - amino)-3 - (3:4 - dimethoxy - phenyl) - propane-glycollate which melted at 146—147° C. were obtained.

EXAMPLE 5.

8.3 Grams of α - (3 - hydroxy - phenyl)-α-hydroxyacetone were hydrogenated at 70° C. in an analogous manner to that described in Example 1, in the presence of 10.55 grams of 1:1 - diphenyl - propyl - amine - (3). The oily hydrogenation product consisting of 2 - [1:1 - diphenyl - propyl - (3) - amino]-3 - hydroxy - 3 - (*m* - hydroxy - phenyl)-propane was diluted with normal hydrochloric acid. The oily hydrochloride thus obtained solidified and prolonged standing. After recrystallisation from alcohol/ether, 14.5 grams of 2 - (1:1 - diphenyl - propyl-(3)-amino)-3 - hydroxy - 3 - (meta - hydroxy - phenyl)-propane - hydrochloride which melted at 206—208° C. were obtained.

EXAMPLE 6.

8.2 Grams of para-methoxy-phenylacetone were hydrogenated at 65—70° C. in an analogous manner to that described in Example 1, in the presence of 10.6 grams of 1:1 - diphenyl - propylamine - (3). The hydrochloride of the hydrogenation product 2 - [1:1 - diphenyl - propyl - (3) - amino]-3 - (*p* - methoxy - phenyl) - propane was obtained as in Example 5, and was boiled for two hours under reflux with 60 cc of aqueous hydrobromic acid of 48% strength. The red oily layer which separated out solidified on cooling. After shaking the solid product with sodium hydroxide solution and ether, it was filtered. Carbon dioxide was then introduced into the aqueous-alkaline solution until a pH-value of 8 was obtained. The oily base which soon solidified was recrystallised from ethyl acetate, to give 8 grams of 2 - [1:1 - diphenyl - propyl-(3)-amino] - 3 - (para-hydroxy-phenyl)-propane, which melted at 144—145° C.

EXAMPLE 7.

By hydrogenating 6.7 grams of phenyl-acetone in an analogous manner to that described in Example 1 in the presence of 11.25 grams of 2:2 - diphenyl - butyl - (1) - amine, 16.7 grams of oily 2 - [2:2 - diphenyl-butyl - (1) - amino] - 3 - phenyl - propane, were obtained. The maleate of this base melted at 135—137° C., and the phosphate thereof melted at 187—188° C.

EXAMPLE 8.

21.2 grams of 1:1 - diphenyl - propyl-amine - (3) and 13.4 grams of phenyl-acetone were dissolved in 200 cc of alcohol. 230 cc of water were added to the reaction mixture which was then boiled for 6 hours under reflux in the presence of 15 grams of amalgamated aluminium. The mixture was filtered and the filtrate was then concentrated under reduced pressure. The residue was then distilled, and 22 grams of 2 - (1:1 - diphenyl-propyl - (3) - amino) - 3 - phenyl - propane, boiling at 180—190° C. under a pressure of 0.3 mm of mercury, were obtained. The glycollic acid salt of this base melted at 141—142° C.

EXAMPLE 9.

10.6 grams of 1:1 - diphenyl - propyl-amine-(3), 6.7 grams of phenyl-acetone and 50 cc of benzene was heated for 30 minutes on a steam bath. After evaporation of the solvent under reduced pressure, 50 cc of methanol and 3 cc of water was added to the residue. Several portions of sodium boron hydride, each portion weighing 1.2 grams, were introduced into the reaction mixture, whereby the temperature rose to about 40° C. After standing for some time, the mixture was acidified with dilute hydrochloric acid, and then the methanol was removed by distillation under reduced pressure. 15.3 grams of crystalline 2 - [1:1 - diphenyl - propyl-(3) - amino] - 3 - phenyl - propane - hydrochloride melting at 190—192° C. were obtained.

EXAMPLE 10.

22.4 grams of 1:1 - diphenyl - ethyl-(2)-methyl-ketone were heated with 13.5 grams of 1 - phenyl - 2 - amino - propane to a temperature within the range of 50—60° C. 200 cc of isopropyl-alcohol were then added to the reaction mixture, and this mixture was then hydrogenated in the presence of palladium at 120° C. under a pressure of 100 atmospheres gauge. After filtration and con-

centration under reduced pressure, 2-[1:1-diphenyl - butyl - (3) - amino] - 3 - phenyl-propane boiling at 180—185° C. under a pressure of 0.3 mm of mercury was obtained in the form of a colourless oil. This oil was dissolved in double its volume of absolute alcohol and the equivalent proportion of aminosulphonic acid was added and this mixture was heated until a solution was obtained. After cooling the solution and adding ether, the aminosulphonic acid salt of the above base having a melting point (after recrystallisation from water) of 147—148° C. was obtained.

EXAMPLE 11.

A mixture comprising 23.5 grams of chlorobenzene and 33.6 grams of diphenyl-methane was added dropwise, while stirring, at 35° C., to 10.1 grams of finely divided sodium metal in 50 cc of benzene. As the temperature stopped rising 42.3 grams of 2 - (N - chlorethyl - N - methyl) - amino-3 - phenyl - propane were added dropwise at 30—40° C. The reaction mixture was boiled for 1 hour under reflux, then cooled and the water was added cautiously. The benzene layer was dried over sodium sulphate, and the residue after evaporation of the solvent was fractionally distilled under reduced pressure. 2 - [1:1 - diphenyl - propyl - (3) - methylamino] - 3 - phenyl - propane boiling at 170—175° C. under a pressure of 0.08 mm of mercury was obtained. The glycollic acid salt of this base melted at 84—85° C.

EXAMPLE 12.

33 grams of 2 - [1:1 - diphenyl-1-cyano-propyl - (3) - methyl - amino] - 3 - phenyl-propane were dissolved in 150 cc of benzene, and the solution was then boiled for 2 hours under reflux with 33 grams of sodamide. After sucking off the excess sodamide, the benzene was distilled under reduced pressure. The residue (28 grams) was then distilled. 20 grams of 2 - [1:1 - diphenyl - propyl-(3) - methylamino] - 3 - phenyl - propane were obtained, as a colourless oil which boiled at 170—175° C. under a pressure of 0.08 mm of mercury.

EXAMPLE 13.

10.6 grams of 1:1 - diphenyl - propyl-amine - (3) and 7.4 grams of (1:2 - dioxo-propyl)-benzene in 100 cc of isopropanol and in the presence of palladium black were shaken with hydrogen. One tenth of a molecular proportion of hydrogen was taken up. The product of hydrogenation was isolated in a manner analogous to that described in Example 1. 2 - [1:1 - diphenyl - propyl-(3) - amino] - 3 - hydroxy - 3 - phenyl-propane which melted at 109° C., was obtained.

EXAMPLE 14.

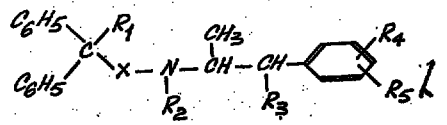
5 cc of bromine were added dropwise to 13.4 grams of propionphenone. When the evolution of hydrogen bromide had ceased, 100 cc of methylene chloride were added to the bromo-propiophenone thus obtained, and the mixture together with 42 grams of 1:1-diphenyl - propylamine - (3) was boiled for 1 hour under reflux. A white crystalline magma was obtained. After filtering this magma under suction, the filtrate was concentrated under reduced pressure. The oily residue (40 grams) was dissolved in alcohol, converted into the oxalate thereof by addition of the calculated quantity of oxalic acid (20 grams). The oxalate, which melted at about 200° C., was decomposed by means of sodium carbonate solution, and the free base thus obtained was taken up in ether. After drying the ether solution and distilling the ether, 20.8 grams of the amino-ketone in the form of an oil, were obtained. This oil was dissolved in 200 cc of alcohol and shaken at 60° C. with hydrogen in the presence of palladium black. After the hydrogenation mixture had taken up the calculated quantity of hydrogen, the catalyst was removed by filtration. 19 grams of 2 - [1:1 - diphenyl-propyl - (3) - amino] - 3 - hydroxy - 3 - phenyl-propane melting at 109—110° C. were obtained.

EXAMPLE 15.

17 grams of 2 - [1:1 - diphenyl - propyl-(3) - amino] - 3 - (para - hydroxyphenyl)-propane were shaken with 50 cc of dilute sodium hydroxide solution and 6.3 grams of dimethyl-sulphate. After completion of the reaction, the precipitated oil was separated and converted into the hydrochloride of 2-[1:1 - diphenyl - propyl - (3) - amino] - 3 - (para-methoxy-phenyl)-propane by means of dilute hydrochloric acid.

WHAT WE CLAIM IS:—

1. Diphenyl-methane compounds of the general formula



in which X represents a straight-chain or branched aliphatic hydrocarbon radical containing at most 3 carbon atoms, R_1 represents a hydrogen atom or an alkyl group (C_{1-4}), R_2 represents a hydrogen atom or a methyl group, R_3 represents a hydrogen atom or a hydroxyl group, R_4 and R_5 each represent a hydrogen atom, a hydroxyl group or a methoxy group.

2. Physiologically tolerable acid addition salts and quaternary ammonium salts of the compounds claimed in claim 1.

3. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - hydroxy - 3 - phenyl - propane.

4. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - phenyl - propane.

5. 2 - (1:1 - Diphenyl - propyl - (3) - methylamino) - 3 - phenyl - propane.

centration under reduced pressure, 2-[1:1-diphenyl - butyl - (3) - amino] - 3 - phenyl-propane boiling at 180—185° C. under a pressure of 0.3 mm of mercury was obtained in the form of a colourless oil. This oil was dissolved in double its volume of absolute alcohol and the equivalent proportion of aminosulphonic acid was added and this mixture was heated until a solution was obtained. After cooling the solution and adding ether, the aminosulphonic acid salt of the above base having a melting point (after recrystallisation from water) of 147—148° C. was obtained.

EXAMPLE 11.

A mixture comprising 23.5 grams of chlorobenzene and 33.6 grams of diphenylmethane was added dropwise, while stirring, at 35° C., to 10.1 grams of finely cut sodium metal in 50 cc of benzene. As soon as the temperature stopped rising 42.3 grams of 2 - (N - chlorethyl - N - methyl) - amino-3 - phenyl - propane were added dropwise at 30—40° C. The reaction mixture was boiled for 1 hour under reflux, then cooled and the water was added cautiously. The benzene layer was dried over sodium sulphate, and the residue after evaporation of the solvent was fractionally distilled under reduced pressure. 2 - [1:1 - diphenyl - propyl - (3) - methylamino] - 3 - phenyl - propane boiling at 170—175° C. under a pressure of 0.08 mm of mercury was obtained. The glycollic acid salt of this base melted at 84—85° C.

EXAMPLE 12.

33 grams of 2 - [1:1 - diphenyl-1-cyano-propyl - (3) - methyl - amino] - 3 - phenyl-propane were dissolved in 150 cc of benzene, and the solution was then boiled for 2 hours under reflux with 33 grams of sodamide. After sucking off the excess sodamide, the benzene was distilled under reduced pressure. The residue (28 grams) was then distilled. 20 grams of 2 - [1:1 - diphenyl - propyl-(3) - methylamino] - 3 - phenyl - propane were obtained, as a colourless oil which boiled at 170—175° C. under a pressure of 0.08 mm of mercury.

EXAMPLE 13.

10.6 grams of 1:1 - diphenyl - propylamine - (3) and 7.4 grams of (1:2 - dioxopropyl)-benzene in 100 cc of isopropanol and in the presence of palladium black were shaken with hydrogen. One tenth of a molecular proportion of hydrogen was taken up. The product of hydrogenation was isolated in a manner analogous to that described in Example 1. 2 - [1:1 - diphenyl - propyl-(3) - amino] - 3 - hydroxy - 3 - phenyl-propane which melted at 109° C., was obtained.

EXAMPLE 14.

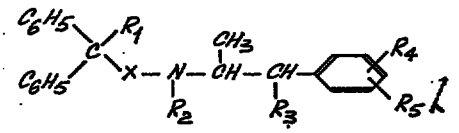
5 cc of bromine were added dropwise to 13.4 grams of propionphenone. When the evolution of hydrogen bromide had ceased, 100 cc of methylene chloride were added to the bromo-propiophenone thus obtained, and the mixture together with 42 grams of 1:1-diphenyl - propylamine - (3) was boiled for 1 hour under reflux. A white crystalline magma was obtained. After filtering this magma under suction, the filtrate was concentrated under reduced pressure. The oily residue (40 grams) was dissolved in alcohol, converted into the oxalate thereof by addition of the calculated quantity of oxalic acid (20 grams). The oxalate, which melted at about 200° C., was decomposed by means of sodium carbonate solution, and the free base thus obtained was taken up in ether. After drying the ether solution and distilling the ether, 20.8 grams of the amino-ketone in the form of an oil, were obtained. This oil was dissolved in 200 cc of alcohol and shaken at 60° C. with hydrogen in the presence of palladium black. After the hydrogenation mixture had taken up the calculated quantity of hydrogen, the catalyst was removed by filtration. 19 grams of 2 - [1:1 - diphenyl-propyl - (3) - amino] - 3 - hydroxy - 3 - phenyl-propane melting at 109—110° C. were obtained.

EXAMPLE 15.

17 grams of 2 - [1:1 - diphenyl - propyl-(3) - amino] - 3 - (para - hydroxyphenyl)-propane were shaken with 50 cc of dilute sodium hydroxide solution and 6.3 grams of dimethyl-sulphate. After completion of the reaction, the precipitated oil was separated and converted into the hydrochloride of 2-[1:1 - diphenyl - propyl - (3) - amino] - 3 - (para-methoxy-phenyl)-propane by means of dilute hydrochloric acid.

WHAT WE CLAIM IS:—

1. Diphenyl-methane compounds of the general formula



in which X represents a straight-chain or branched aliphatic hydrocarbon radical containing at most 3 carbon atoms, R_1 represents a hydrogen atom or an alkyl group (C_{1-4}), R_2 represents a hydrogen atom or a methyl group, R_3 represents a hydrogen atom or a hydroxyl group, R_4 and R_5 each represent a hydrogen atom, a hydroxyl group or a methoxy group.

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3. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - hydroxy - 3 - phenyl - propane.

4. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - phenyl - propane.

5. 2 - (1:1 - Diphenyl - propyl - (3) - methylamino) - 3 - phenyl - propane.

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6. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - (3:4 - dimethoxy - phenyl)-propane.

7. 2 - [1:1 - Diphenyl - propyl - (3) - amino] - 3 - hydroxy - 3 - (meta - hydroxy-phenyl)-propane.

8. 2 - [1:1 - Diphenyl - propyl - (3) - amino] - 3 - (para - hydroxy - phenyl) - propane.

9. 2 - [2:2 - Diphenyl - butyl-(1)-amino]-3-phenyl-propane.

10. 2 - [1:1 - Diphenyl - butyl - (3) - amino]-3-phenyl-propane.

11. 2 - [1:1 - Diphenyl - propyl - (3) - amino]-3-(para-methoxy-phenyl)-propane.

12. A physiologically tolerable acid addition salt of quaternary ammonium salt of the compound claimed in any one of claims 3—11.

13. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - hydroxy - 3 - phenyl - propane-aminosulphonate.

14. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - phenyl - propane-hydrochloride.

15. 2 - (1:1 - Diphenyl - propyl - (3) - amino)-3-phenyl-propane glycollate.

16. 2 - (1:1 - Diphenyl - propyl - (3) - methylamino)-3-phenyl-propane-glycollate.

17. 2 - (1:1 - Diphenyl - propyl - (3) - amino) - 3 - (3:4 - dimethoxy - phenyl) - propane glycollate.

18. 2 - [1:1 - Diphenyl - propyl - (3) - amino] - 3 - hydroxy - 3 - (meta - hydroxy-phenyl)-propane hydrochloride.

19. 2 - [2:2 - Diphenyl - butyl - (1) - amino]-3-phenyl-propane maleate.

20. 2 - [2:2 - Diphenyl - butyl - (1) - amino]-3-phenyl-propane phosphate.

21. 2 - [1:1 - Diphenyl - butyl - (3) - amino]-3-phenyl-propane-aminosulphonate.

22. 2 - [1:1 - Diphenyl - propyl - (3) - amino] - 3 - (para - methoxy - phenyl) - propane hydrochloride.

23. Pharmaceutical preparations which comprise a compound claimed in any one of claims 1—22 in admixture or conjunction with a pharmaceutical carrier.

24. Pharmaceutical preparations in unit dosage form, of which each unit comprises 5 to 10 milligrams of a compound claimed in any one of claims 1—22 in admixture or conjunction with a pharmaceutical carrier.

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