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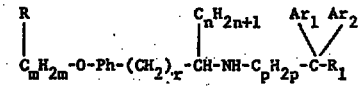
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(54) NEW 1-(AZACYCLIC ARALKOXYPHENYL)-2- OR 3-(BIS-ARYLALKYLAMINO)-ALKANES, PROCESS FOR THEIR MANUFACTURE AND PHARMACEUTICAL PREPARATIONS CONTAINING THEM

(71) We, CIBA-GEIGY AG, a Swiss body corporate, 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 concerns the manufacture of new 1-(azacyclic aralkoxyphenyl)-2 or 3-(bis-arylalkylamino)-alkanes of the general Formula I



(I)

wherein R is an unsubstituted mono- or bicyclic nitrogen-containing aromatic radical in which the nitrogen-containing ring has 5 or 6 members, or such radical substituted by one or more than one member of lower alkyl, hydroxy, lower alkoxy, halogeno, trifluoromethyl or amino; Ph is unsubstituted phenylene, or phenylene substituted by one member listed for R; each of Ar_1 and Ar_2 is unsubstituted phenyl, or phenyl substituted by one member listed for R; each of m and p is an integer from 1 to 4; n is such from 0 to 4; r is 1 or 2 and R_1 is hydrogen or hydroxy; or salts thereof.

Said azacyclic radicals R contain preferably one nitrogen atom and are advantageously monocyclic, such as 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl; but may also have two aromatic rings, such as 2-, 3- or 4-indolyl or -quinolyl, 1-, 3- or 4-isoindolyl or -isoquinolyl. They are preferably unsubstituted, but may also be substituted, advantageously by one or two members of the group consisting of lower alkyl, e.g. methyl, ethyl, n- or i-propyl or -butyl; hydroxy; lower alkoxy, e.g. methoxy, ethoxy, n- or i-propoxy or -butoxy; halogeno, e.g. fluoro, chloro or bromo; trifluoromethyl; or amino.

The term "lower", referred to above or hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, advantageously such with one or two carbon atoms.

The phenylene radical Ph and phenyl radicals Ar_1 and Ar_2 are preferably unsubstituted 1,4-phenylene, but also 1,2- or 1,3-phenylene or phenyl respectively, but also phenyl or phenylene substituted by one member of lower alkyl, lower alkoxy, halogeno or trifluoromethyl, e.g. those listed for R. The substituent R_1 is preferably hydrogen, but also hydroxy.

The lower alkyl group C_nH_{2n+1} preferably represents methyl, but also any other member mentioned above. The lower alkylene group C_mH_{2m} preferably stands for $(CH_2)_m$, especially methylene, but also for 1,1- or 1,2-ethylene, 1,1-, 2,2-, 1,2- or 1,3-propylene or -butylene; and C_pH_{2p} preferably represents $(CH_2)_p$ especially 1,2-ethylene, but also any other of said alkylene groups.

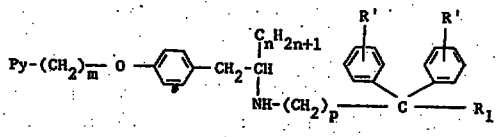
Salts of the compounds of Formula I are preferably therapeutically acceptable acid addition salts, e.g. those derived from the acids listed below.

The compounds of the invention exhibit valuable pharmacological properties, primarily hypotensive, antihypertensive and bradycardic activity. This is demonstrable

in animal tests, using advantageously mammals, e.g. rats, cats, dogs or monkeys, as test objects. The animals may either be normotensive or hypertensive, e.g. genetically or adrenal regeneration hyptertensive rats. Said compounds can be applied to them enterally or parenterally, advantageously orally, or subcutaneously, intravenously, intraperitoneally or intraduodenally, for example within gelatin capsules or in the form of starchy suspensions or aqueous solutions respectively. The applied dosage may range between about 0.1 and 100 mg/kg/day, preferably between about 1 and 50 mg/kg/day, advantageously between about 5 and 25 mg/kg/day. The lowering effect on the blood pressure is recorded either directly by means of a catheter, for example placed in the dog's femoral or the rat's caudel artery, or indirectly by sphygmomanometry at the rat's tail, and a transducer, expressing the blood pressure prior and after dosing in mm Hg. Thus, for example, the d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane, a representative member of the compounds of the invention, advantageously in the form of its maleate, fumarate or oxalate, or preferably as the levorotatory antipode thereof, are very effective in said hypertensive rats at p.o. doses as low or lower than 5 mg/kg/day and maximally about 24 hours after dosing. Antihypertensive doses cause only minor impairment of sympathetic nerve function, unlike antihypertensive agents which act by adrenergic neuron blockade, as assessed by pressor responses to electrical stimulation of the spinal cord of pithed rats. Said member also differs from certain centrally acting antihypertensive agents which cause sedation. Furthermore, they do not produce sedation in monkeys at hypotensive doses, as does α-methyldopa. Accordingly, the compounds of the invention are useful antihypertensive and bradycardic agents, for example in the treatment or management of primary or secondary hypertension, or angina pectoris respectively. They are also useful intermediates in the preparation of other valuable products, especially of pharmacologically active compositions.

Particularly useful are compound of the general Formula I, in which is unsubstituted 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-indolyl or -quinolyl, 1-, 3- or 4-isoindolyl or -isoquinolyl, or such radicals substituted by up to two members of lower alkyl, lower alkoxy or halogen, Ph is 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or 1,4-phenylene, (lower alkoxy)-1,3- or 1,4-phenylene, (halogeno)-1,3- or 1,4-phenylene or (trifluoromethyl)-1,3- or 1,4-phenylene, each of Ar_1 and Ar_2 is phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or (trifluoromethyl)-phenyl, each of m, n and p is an integer from 1 to 4, r is the integer 1 or 2 and R_1 is hydrogen or hydroxy, or a therapeutically useful acid addition salt thereof.

Outstanding compounds are those of the general Formula II



(II)

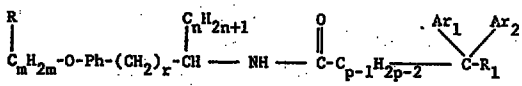
wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one or two members of alkyl, alkoxy, fluoro or chloro, R' is hydrogen, alkyl, alkoxy, fluoro, chloro or trifluoromethyl, wherein alkyl or alkoxy has 1—4 carbon atoms, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy, or therapeutically useful acid addition salts thereof.

Preferred are those compounds of the general Formula II, wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one member of methyl, methoxy or chloro, R' is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy, or therapeutically useful acid addition salts thereof.

More preferred are those compounds of the general Formula II, wherein Py is 2- or 4-pyridyl, each of m and n is one, p is two and each of R_1 and R' is hydrogen, or therapeutically useful acid addition salts thereof.

The compounds of the invention are prepared according to methods known per se, advantageously by:

1) reducing carbonyl compounds of the general Formula III



(III)

The reduction of the amides III is performed according to known methods,

advantageously with boranes or with simple or complex light metal hydrides, such as aluminium hydride, preferably alkali metal aluminium hydrides, e.g. lithium aluminium hydride, sodium aluminium hydride or lithium or sodium tri-lower alkoxy- or bis-alkoxyalkoxyaluminium hydrides, such as lithium tri-t. butoxy- or sodium sodium bis-(2-methoxy-ethoxy)-aluminium hydride.

The starting material can be prepared according to methods known per se, e.g. those illustrated by the examples herein. Thus, for example, the starting materials of the Formula III are obtained from the corresponding phenolates, such as alkali metal, e.g. sodium or potassium salts, of the phenols

$$HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})—NH—CO—C_{p-1}H_{2p-2}—CH(Ar_1, Ar_2)$$

and reactive esters of the alcohols $R—C_mH_{2m}—OH$, e.g. such derived from a strong inorganic or organic acid, preferably a hydrohalic, e.g. hydrochloric, -bromic or -iodic acid, or an alkane or benzene sulfonic acid, e.g. methane, p-toluene or m-bromobenzene sulfonic acid. Also amines

$$R—C_mH_{2m}—O—Ph—(CH_2)_rCH—(C_nH_{2n+1})—NH_2$$

can be reacted with reactive, function derivatives of the acids

$$HOOC—C_{p-1}H_{2p-2}C—R_1(Ar_1, Ar_2),$$

e.g. halides or anhydrides thereof. The former amines or phenols are either known or can be obtained by condensing compounds of Formula

$$HO—Ph—(CH_2)_r—CHNH_2—C_nH_{2n+1},$$

with said alcohol or acid derivatives respectively, in subsequent steps.

Another method for preparing the compounds of the general Formula I consists in

2) condensing a compound of the general Formula IV

$$R—C_mH_{2m}—T \qquad (IV)$$

wherein T is a reactive esterified hydroxy group, with a compound of the general Formula V

$$HO—Ph—(CH_2)_r—\underset{\displaystyle C_nH_{2n+1}}{\underset{|}{CH}}—NH—C_pH_{2p}—CR_1Ar_1Ar_2 \qquad (V)$$

or a reactive salt thereof.

A reactive esterified hydroxy group is for example derived from a strong inorganic or organic acid, preferably a hydrohalic, e.g. hydrochloric, -bromo or -iodic acid, or an alkane or benzene sulfonic acid, e.g. methane, p-toluene or m-bromobenzene sulfonic acid. The condensation of the starting materials IV and V is preferably carried out with the use of reactive salts of the phenols, such as alkali metal, e.g. sodium or potassium salts, or in the presence of condensing agents, neutralizing the eliminated acid, such as inorganic or organic (nitrogen) bases, e.g. alkali or alkaline earth metal carbonates or hydrogencarbonates; tri-lower alkylamines or pyridines.

The starting materials IV and V are similarly prepared as the above starting material, e.g. from $HO—Ph—(CH_2)_r—CH(C_nH_{2n+1})NH_2$ by condensation with $U—C_pH_{2p}—CH(Ar_1Ar_2)$, wherein U is a reactive esterified OH.

The corresponding starting material of Formulae III, IV and V, wherein $R—C_mH_{2m}$ is unsubstituted or substituted benzyl, e.g. $Ar_1—CH_2$, is described in applicant's South African Patent No. 75/5018, issued November 3, 1976. It can be hydrogenolyzed as shown in Examples 8 or 10 of the present application, in order to yield starting materials suitable for the preparation of compounds of Formulae I or II.

The resulting compounds of the invention can be converted into each other according to known methods.

The compounds of the invention are obtained in the free form or in the form of their acid addition salts, depending on the conditions under which the process is carried out. Salts that are obtained can be converted into the free bases in known manner, for example, with ammonia, alkalies or ion exchanges. Free bases that are obtained can be converted into salts with acids, especially those that are suitable for

the formation of therapeutically useful acid addition salts. Such acids are inorganic acids, for example, mineral acids, such as a hydrohalic, e.g. hydrochloric or hydrobromic acid; sulfuric, phosphoric, nitric or perchloric acid; or organic acids, such as aliphatic or aromatic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycollic, lactic, malic, tartatic, citric, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; methionine, tryptophane, lysine or arginine, or ascorbic acid. These or other salts, for example, the picrates, can also be used in the purification of the free compounds.

In view of the close relationship between the salts and the free compounds, whenever such is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

Resulting mixtures of isomers can be separated into the single isomers by methods in themselves known, e.g. by fractional distillation, crystallization and/or chromatography. Racemic products can likewise be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g. by the fractional crystallization of d- or l-tartrates.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

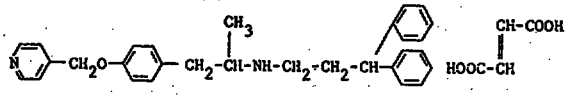
The invention further includes any variant of the present process in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75%, preferably about 1 to 50% of the active ingredient.

The following examples illustrating the invention are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade, and all parts parts wherever given are parts by weight. If not specified, all evaporations are carried out under reduced pressure.

Example 1.

The mixture of 10 g of 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane (prepared as described by Ehrhart et al, U.S. Patent 3,152,173), 50 ml of dimethylsulfoxide, 5 ml of water and 2.4 g of sodium hydroxide is stirred at 60° for one hour. To this are added 4.9 g of 4-pyridylmethyl chloride hydrochloride and the whole is stirred under nitrogen at ambient temperature over night. The mixture is poured into 300 ml of water and extracted with methylene chloride. The extract is treated with charcoal, dried and evaporated. The residue is taken up in diethyl ether, the solution washed with 3N aqueous sodium hydroxide, dried and evaporated. The residue is dissolved in the minimum amount of methanol-ethyl acetate, the solution neutralized with methanolic fumaric acid and refrigerated, whereupon the d,l - 1-[4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane fumarate of the formula



separates, melting at 142—144°.

Example 2.

The mixture of 18.8 g of l - 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrochloride, 150 ml of dimethylsulfoxide and 15 ml of 10N aqueous sodium hydroxide is stirred for 75 minutes at room temperature under nitrogen, whereupon 8.2 g of 4-pyridylmethyl chloride hydrochloride are added and the whole is stirred 20 hours at room temperature. The mixture is poured into 1500 ml of water, extracted with methylene chloride, the extract dried and evaporated. The residue is dissolved in 500 ml of diethyl ether, the solution washed with 2N aqueous sodium hydroxide and saturated aqueous sodium chloride, dried and evaporated. 20.6 g of the residue are dissolved in the minimum amount of isopropanol and the solution combined with that of 5.48 g of fumaric acid in isopropanol, the mixture diluted with ethyl acetate and filtered. The residue is taken up in 2N aqueous sodium hydroxide, the mixture extracted with ethyl acetate, the extract dried and evaporated. The residue is taken up in isopropanol and the solution neutralized with isopropanolic oxalic acid, to yield the l - 1 - [4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3-diphenylpropylamino) - propane hemioxalate melting at 19—200°, $[M]_D = -35.4°$ (5% in methanol). Analogously the acetate hemihydrate is prepared, m.p. 85—88°, $[M]_D = -48.2°$ (c=1 in methanol) and the diacetone-2-keto-L-glutonate, m.p. 211—212°, $[M]_D = -89.6°$ (c=0.5 in dimethylacetamide).

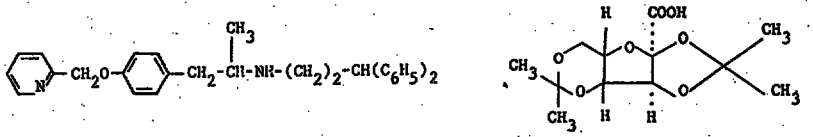
The starting material is prepared as follows: The mixture of 23 g of l - (1 - (4-hydroxyphenyl) - 2 - aminopropane, 31.2 g of 3,3 - diphenylacrolein, 150 ml of anhydrous ethanol and 4 g of 10% palladium on charcoal is hydrogenated at 3.3 atm. for 6 hours. It is filtered, the filtrate evaporated, the residue dissolved in 400 ml of isopropanol and the solution combined with 12.5 ml of concentrated hydrochloric acid. After standing overnight the precipitate is collected and washed with isopropanol and diethyl ether, to yield the l - 1 - (4 - hydroxyphenyl) - 2 (3,3 - diphenylpropylamino) - propane hydrochloride melting at 244—247°; $[M]_D = -35.1°$ (5% in methanol).

Example 3.

The mixture of 5.7 g of 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrobromide, 3.2 g of said propane hydrochloride, 50 ml of dimethylsulfoxide and 6.7 ml of 10N-aqueous sodium hydroxide is stirred at 60° for one hour. It is cooled with ice, combined with 3.6 g of 3-pyridylmethyl chloride hydrochloride, the mixture stirred until all solids are dissolved, heated to 60° for one hour and stirred for 18 hours at room temperature. It is poured into ice-water, extracted with ethyl acetate, the extract washed with saturated aqueous sodium chloride, dried and evaporated. The residue is taken up in ethanol, the solution acidified with 2.45 g of maleic acid in ethanol, and diluted with diethyl ether, to yield the d,l - 1 - [4 - (3-pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate melting at 135—137°.

Example 4.

To the solution of 10.36 g of d,l - 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane in 75 ml of dimethylsulfoxide and 6 ml of 10N aqueous sodium hydroxide, stirred for 45 minutes under nitrogen, 4.92 g of 2-pyridylmethyl chloride hydrochloride in 50 ml of dimethylsulfoxide are added dropwise and the mixture is stirred for 18 hours at room temperature. It is poured into 500 ml of water, extracted with methylene chloride, the extract dried and evaporated. The residue is dissolved in the minimum amount of ethanol and the solution neutralized with ethanolic diacetone-2-keto-L-gulonic acid hydrate and the mixture diluted with water to incipient turbidity. The precipitate formed on cooling is collected and recrystallized from aqueous ethanol, to yield the d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2-(3,3 - diphenylpropylamino) - propane diacetone-2-keto-L-gulonate of the formula



melting at 147—150°, $[M]_D = -48.3°$ (c=1 in methanol)

Analogously its levorotatory isomer is obtained as hemihydrate (from the starting material of Example 2), melting at 180—182°, $[M]_D = -81.3°$, or the corresponding maleate melting at 164—165°, $[M]_D = -52.5°$ (for both: c=1 in methanol).

Reacting said d,l- starting material with an equivalent amount of α-quinolylmethyl chloride hydrochloride, the d,l - 1 - [4 - (2 - quinolylmethoxy) - phenyl] - 2 - (3,3-diphenylpropylamino) - propane is obtained, the maleate of which melts at 177—179°.

Example 5.

To the solution of 7.8 g of 1 - (3 - methyl - 4 - hydroxyphenyl) - 2- (3,3-diphenylpropylamino) - propane in 18.5 ml of dimethylsulphoxide is added 1 ml of 10N aqueous sodium hydroxide and the whole is stirred 40 minutes at 60°. To this is added 0.82 g of 2-pyridylmethyl chloride hydrochloride and the whole stirred overnight at ambient temperature. The mixture is poured into 100 ml of water, the solution made strongly basic with 5 ml of 10N aqueous sodium hydroxide and extracted with diethyl ether. The extract is washed with saturated aqueous sodium chloride, dried and evaporated. The residual oil is taken up in the minimum amount of isopropanol, the solution treated with 0.58 g of maleic acid and heated on the steam bath to achieve homogeneity. After cooling, the precipitate is collected, washed with diethyl ether and dried, to afford the d,l - 1 - [3 - methyl - 4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, melting at 177—178°.

Example 6.

The mixture of 5 g of 1 - (4 - hydroxyphenyl) - 3 - (3,3 - diphenylpropylamino)-butane (U.S. Patent 3,262,977), 1.2 g of sodium hydroxide, 10 ml of water and 100 ml of dimethylsulphoxide is heated to 60° for 30 minutes. Thereupon 2.3 g of 2-pyridylmethyl chloride hydrochloride are added and the mixture is stirred at ambient temperature overnight and then diluted with water. It is extracted with ethyl acetate, the extract washed with saturated aqueous sodium chloride, dried and evaporated. The residual oil is redissolved in 200 ml of dry ethyl acetate, the solution treated with 3.2 g of maleic acid and stirred for 5 hours. The precipitate is collected and recrystallized from isopropanol, to afford the pure d,l - 1 - [4 - (2 - pyridylmethoxy - phenyl]-3 - (3,3 - diphenylpropylamino) - butane maleate melting at 155—156°.

Example 7.

The mixture of 4.3 g of 1 - (3 - fluoro - 4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane hydrobromide, 1.4 g of sodium hydroxide in 5 ml of water and 50 ml of dimethylsulphoxide is heated to 60° and 1.7 g of 2-pyridylmethyl chloride hydrochloride are added. The whole is stirred overnight at ambient temperature, diluted with water and extracted with ethyl acetate. The extract is washed with saturated aqueous sodium chloride, dried and evaporated. The residual oil is taken up in warm methanol, the solution filtered, the filtrate treated with 1 g of maleic acid and then refrigerated. The precipitate is collected, washed with ethyl acetate and dried, to afford the d,l - 1 - [3 - fluoro - 4 - (2 - pyridylmethoxy) - phenyl] - 2-(3,3 - diphenylpropylamino) - propane maleate, melting at 146—150°.

Example 8.

The mixture of 3.4 g of 1 - (4 - hydroxyphenyl) - 2 - (2,2 - diphenylethylamino) - propane, 1 g of sodium hydroxide in 5 ml of water, and 50 ml of dimethylsulphoxide is warmed to 60°, and 1.7 g of 2-pyridylmethyl chloride hydrochloride are added. The mixture is stirred overnight at ambient temperature, then diluted with water and extracted with ethyl acetate. The extract is washed with saturated aqueous sodium chloride, dried, evaporated and the residue dissolved in 30 ml of warm methanol. The solution is treated with 1.1 g of maleic acid, cooled and then treated with 30 ml of diethyl ether. The precipitate formed is washed with ethyl acetate and dried, to afford the d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (2,2 - diphenylethylamino) - propane maleate, melting at 167—169°.

The starting material is prepared as follows: The mixture of 4.6 g of d,l - 1-(4 - benzyloxyphenyl) - 2 - (2,2 - diphenylethylamino) - propane hydrochloride, 0.4 g of sodium hydroxide, 50 ml of ethanol and 0.5 g of 10% palladium on carbon is shaken under hydrogen at 3 atmospheres for 72 hours. The mixture is filtered and the filtrate evaporated, to afford the 1 - (4 - hydroxyphenyl) - 2 - (2,2 - diphenylethylamino) - propane, which is used without further purification.

Similarly the d,l - 1 - (4 - benzyloxyphenyl) - 2 - (3,3 - diphenylpropylamino)-butane hydrochloride is hydrogenated and converted into the d,l - 1 - [4 - (2-pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - butane maleate, melting

at 122.5 to 124.5°. Analogously, the d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - [4,4 - di - (4 - fluorophenyl) - butylamino] - propane maleate is prepared, m.p. 169—171°.

Example 9.

The mixture of 21.76 g of d,l - 1 - (4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropylamino) - propane, 6.3 ml of 10N aqueous sodium hydroxide and 100 ml of dimethylsulphoxide is stirred at 60° for 2 hours, whereupon 8.91 g of 5-methyl-2-pyridylmethyl chloride are added. The whole is stirred at ambient temperature for 24 hours, diluted with 400 ml of water and extracted with methylene chloride. The extract is dried, evaporated, the residual oil taken up in isopropanol and the solution acidified with maleic acid in isopropanol until the pH of 5 is reached, to yield the d,l - 1 - [4 - (5 - methyl - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate, melting at 155—157°.

Analogously, the d,l - 1 - [4 - (6 - methyl - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane maleate is prepared, melting at 131—133°.

Example 10.

The mixture of 1.9 g of N - [2 - (4 - hydroxyphenyl) - ethyl] - 3,3 - diphenylpropylamine, 0.6 ml of 10 N aqueous sodium hydroxide and 40 ml of dimethylsulphoxide is heated at 60° for 1/2 hour and then treated with a mixture of 0.94 g of 2-pyridylmethyl chloride hydrochloride and 0.6 ml of 10 N aqueous sodium hydroxide. It is stirred under nitrogen at ambient temperature for 20 hours, diluted with 50 ml of water and 7 ml more 10 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract is washed with saturated aqueous sodium chloride, dried, evaporated and the resulting oil taken up in chloroform. The solution is diluted with dry diethyl ether and the solid formed discarded. The residual solution is washed with 2 N aqueous sodium hydroxide, dried, evaporated and the residue taken up in the minimum amount of isopropanol. The solution is acidified with maleic acid, whereupon the *r* - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - ethane - maleate is obtained, melting at 181—182°.

The starting material is prepared as follows: The mixture of 7.5 g of N - [2 - (4 - benzyloxyphenyl) - ethyl] - 3,3 - diphenylpropylamine, 125 ml of ethanol and 0.25 g of 10% palladium on charcoal is shaken under 3 atmospheres of hydrogen for 20 hours. 4.5 g of fresh catalyst are added and hydrogenolysis continued at 3 atmospheres for 70 hours. The mixture is filtered and evaporated, to afford the N-[2 - (4 - hydroxyphenyl) - ethyl] - 3,3 - diphenylpropylamine of sufficient purity.

Example 11.

To the mixture of 15 g of d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropionamido) - propane in 150 ml of tetrahydrofuran is added dropwise at 0° and under nitrogen 200 ml of 1 molar borane in tetrahydrofuran. The mixture is then stirred and refluxed under nitrogen overnight, cooled to 0°, treated gradually with 200 ml of methanol, warmed to 50° and evaporated. The residue is again taken up in 200 ml of methanol, warmed to 50° and evaporated. The residue is then salified as described in Example 4, to yield the identical d,l - 1 - [4 - (2-pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane diacetone-2 - keto - L - gulonate, melting at 147—150°.

The starting material is prepared as follows: The mixture of 6 g of d,l - 4 - (2-pyridylmethoxy) - amphetamine, 10.9 g of 3,3 - diphenylpropionic anhydride, 80 ml of benzene and 2 drops of concentrated sulphuric acid is heated at reflux for 18 hours. The cooled mixture is washed with aqueous sodium bicarbonate and water, dried and evaporated, to yield the d,l - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3-diphenylpropionamido) - propane.

Example 12

Preparation of 10,000 tablets each containing 50.0 mg of the active ingredient:

Formula:	
l-1-[4-(2-pyridylmethoxy)-phenyl]-2-(3,3-diphenyl-propylamino) - propane maleate	500 g
Lactose	1,706 g
Corn starch	90 g
Polyethylene glycol 6,000	90 g
Talcum powder	90 g
Magnesium stearate	24 g
Purified water	q.s.

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 45 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 180 ml of water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets using concave punches with 7.1 mm diameter, uppers bisected.

Preparation of 10,000 capsules each containing 100 mg of the active ingredient:

Formula:	
d,l-1-[4-(4-pyridylmethoxy)-phenyl]-2-(3,3-diphenyl-propylamino)-propane fumarate	1,000 g
Lactose	2,800 g
Talcum powder	200 g

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance is placed in a suitable mixer and mixed first with the talcum, then with the lactose until homogeneous. No. 1 capsules are filled with 400 mg each, using a filling machine.

Analogously tablets and capsules are prepared from the remaining compounds illustrated by the previous examples.

Example 13.

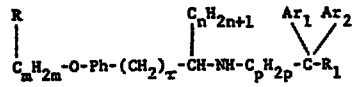
To the solution of 8000 ml of 1 molar borane in tetrahydrofuran, diluted with 10,000 ml of tetrahydrofuran, 710 g of l - 1 - [4 - (2 - pyridylmethoxy - phenyl] - 2-(3,3 - diphenylpropionamido) - propane are added portionwise over a period of 30 minutes while stirring under nitrogen at −5°. After addition, the mixture is allowed to warm to room temperature over 1 hour and the clear colorless solution is gently warmed to reflux. After refluxing for 5 hours, the mixture is allowed to stir overnight at room temperature. It is cooled again to −5° and 3000 ml of 37% hydrochloric acid are added in a gentle stream over a period of 45 minutes. The reaction vessel is set for distillation and the tertahydrofuran is removed at a pressure of 5 mm Hg and at 50°. The residual turbid solution is treated with 8000 ml of water and the aqueous solution is washed with 4000 ml of diethyl ether. The aqueous solution is then stirred and cooled to 5° and basified with 1800 ml of 50% aqueous sodium hydroxide to pH= 13 and extracted with diethyl ether. The extract is dried, filtered and evaporated at 40°, leaving the l-1-[4-(2-pyridylmethoxy)-phenyl]-2-(3,3-diphenylpropylamino)-propane. 685 g thereof are dissolved in 5000 ml of ethyl acetate and the solution is filtered into a 12000 ml flask, fitted with a stirrer, thermometer and an addition funnel. The clear solution is stirred while the solution of 182.6 g of maleic acid in 250 ml of methanol is added in a gentle stream. The resulting suspension is stirred for 4 hours, cooled to 5° and filtered. The white crystals obtained are washed with 1000 ml of cold ethyl acetate and dried *in vacuo* at 60° to yield the corresponding maleate. 800 g thereof are dissolved in 4000 ml of absolute ethanol/water (1:1) at 80° and the clear solution is allowed to come to room temperautre and stand overnight, when crystallization is completed. The crystals are filtered off, washed with 200 ml of absolute ethanol/water (1:1) and dried *in vacuo* at 60°. Said recrystallization is repeated once more to yield said l-maleate, melting at 165—166°. 665 g thereof are dissolved in 3000 ml of boiling absolute ethanol and the solution treated with 20 g of decolorizing charcoal. The mixture is filtered and the almost colorless filtrate is allowed to come to room temperature when crystallization is complete. The crystals are filtered off, washed with 250 ml of absolute ethanol and dried *in vacuo* at 60° to give said l-maleate having $[M]_D = -46.97°$ (c=1 in methanol).

The starting material is prepared as follows: To the solution of 609.1 g of l - 1-(4 - hydroxyphenyl) - 2 - (3,3 - diphenylpropionamido) - propane in 2000 ml of dimethylsulfoxide, 450 ml of 10 N aqueous sodium hydroxide are added in a gentle stream. The yellow solution is stirred at room temperature for 2 hours, whereupon the solution of 375 g of 2-pyridylmethyl chloride hydrochloride in 1700 ml of dimethylsulfoxide is added in a gentle stream over 1 hour. The resulting suspension is stirred overnight at room temperature and 6000 ml of water are added in a gentle stream. After addition is complete, the suspension is stirred for 1.5 hours at room temperature,

filtered and the residue washed with 4000 ml of water. It is dried *in vacuo* at 60° to yield the 1 - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropionamido) - propane, melting at 156—158°; $[M]_D = +38.75°$ (c=2 in dimethylsulfoxide).

WHAT WE CLAIM IS:—

1. A compound of the general Formula I

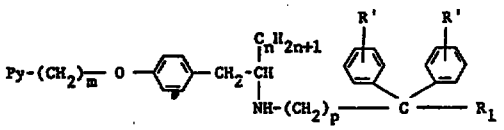


(I)

wherein R is an unsubstituted mono- or bicyclic nitrogen-containing aromatic radical in which the nitrogen-containing ring has 5 or 6 members, or such radical substituted by one or more than one member of lower alkyl, hydroxy, lower alkoxy, halogeno, trifluoromethyl or amino; Ph is unsubstituted phenylene or phenylene substituted by one member listed for R; each of Ar_1 and Ar_2 is unsubstituted phenyl, or phenyl substituted by one member listed for R; each of m and p is an integer from 1 to 4; n is such from 0 to 4; r is 1 or 2 and R_1 is hydrogen or hydroxy.

2. A compound of the general Formula I shown in claim 1 in which R is unsubstituted 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-indolyl or -quinolyl, 1-, 3- or 4 isoindolyl or -isoquinolyl, or such radicals substituted by up to two members of lower alkyl, lower alkoxy or halogen, Ph is 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or -1,4-phenylene, (lower alkoxy)-1,3- or -1,4-phenylene, (halogeno)-1,3- or -1,4-phenylene or (trifluoromethyl)-1,3- or -1,4-phenylene each of Ar_1 and Ar_2 is phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or (trifluoromethyl)-phenyl, each of m, n and p is an integer from 1 to 4, r is the integer 1 or 2 and R_1 is hydrogen or hydroxy.

3. A compound of the general Formula II



(II)

wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one or two members of alkyl, alkoxy, fluoro or chloro, R′ is hydrogen, alkyl, alkoxy, fluoro, chloro or trifluoromethyl, wherein alkyl or alkoxy has 1—4 carbon atoms, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy.

4. A compound of the general Formula II shown in claim 3 wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one member of methyl, methoxy or chloro, R′ is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy.

5. A compound of the general Formula II shown in claim 3 wherein Py is 2- or 4-pyridyl, each of m and n is one, p is two and each of R_1 and R′ is hydrogen.

6. 1 - [4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

7. 1 - 1 - [4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

8. 1 - [4 - (3 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

9. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

10. 1 - 1 - [4 - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

11. 1 - [4 - (2 - quinolylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

12. 1 - [3 - methyl - 4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

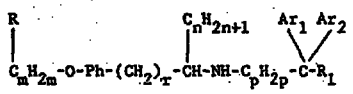
13. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 3 - (3,3 - diphenylpropylamino)-butane.

14. 1 - [3 - fluoro - 4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

filtered and the residue washed with 4000 ml of water. It is dried *in vacuo* at 60° to yield the 1 - 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropionamido) - propane, melting at 156—158°; $[M]_D = +38.75°$ (c=2 in dimethylsulfoxide).

WHAT WE CLAIM IS:—

1. A compound of the general Formula I

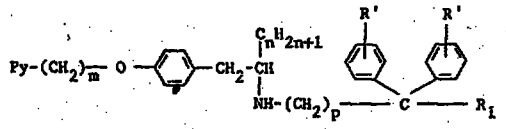


(I)

wherein R is an unsubstituted mono- or bicyclic nitrogen-containing aromatic radical in which the nitrogen-containing ring has 5 or 6 members, or such radical substituted by one or more than one member of lower alkyl, hydroxy, lower alkoxy, halogeno, trifluoromethyl or amino; Ph is unsubstituted phenylene or phenylene substituted by one member listed for R; each of Ar_1 and Ar_2 is unsubstituted phenyl, or phenyl substituted by one member listed for R; each of m and p is an integer from 1 to 4; n is such from 0 to 4; r is 1 or 2 and R_1 is hydrogen or hydroxy.

2. A compound of the general Formula I shown in claim 1 in which R is unsubstituted 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-indolyl or -quinolyl, 1-, 3- or 4 isoindolyl or -isoquinolyl, or such radicals substituted by up to two members of lower alkyl, lower alkoxy or halogen, Ph is 1,3- or 1,4-phenylene, (lower alkyl)-1,3- or -1,4-phenylene, (lower alkoxy)-1,3- or -1,4-phenylene, (halogeno)-1,3- or -1,4-phenylene or (trifluoromethyl)-1,3- or -1,4-phenylene each of Ar_1 and Ar_2 is phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or (trifluoromethyl)-phenyl, each of m, n and p is an integer from 1 to 4, r is the integer 1 or 2 and R_1 is hydrogen or hydroxy.

3. A compound of the general Formula II



(II)

wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one or two members of alkyl, alkoxy, fluoro or chloro, R′ is hydrogen, alkyl, alkoxy, fluoro, chloro or trifluoromethyl, wherein alkyl or alkoxy has 1—4 carbon atoms, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy.

4. A compound of the general Formula II shown in claim 3 wherein Py is 2-, 3- or 4-pyridyl unsubstituted or substituted by one member of methyl, methoxy or chloro, R′ is hydrogen, methyl, methoxy, fluoro, chloro or trifluoromethyl, each of m, n and p is the integer 1 or 2, and R_1 is hydrogen or hydroxy.

5. A compound of the general Formula II shown in claim 3 wherein Py is 2- or 4-pyridyl, each of m and n is one, p is two and each of R_1 and R′ is hydrogen.

6. 1 - [4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

7. 1 - 1 - [4 - (4 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

8. 1 - [4 - (3 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

9. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

10. 1 - 1 - [4 - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

11. 1 - [4 - (2 - quinolylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-propane.

12. 1 - [3 - methyl - 4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

13. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 3 - (3,3 - diphenylpropylamino)-butane.

14. 1 - [3 - fluoro - 4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino) - propane.

15. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (2,2 - diphenylethylamino)-propane.

16. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-butane.

17. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - [4,4 - di - (4 - fluorophenyl)-butylamino] - propane.

18. 1 - [4 - (5 - methyl - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenyl-propylamino) - propane.

19. 1 - [4 - (6 - methyl - 2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenyl-propylamino) - propane.

20. 1 - [4 - (2 - pyridylmethoxy) - phenyl] - 2 - (3,3 - diphenylpropylamino)-ethane.

21. The levorotatory optical antipode of a compound claimed in any one of claims 1 and 12 to 19.

22. The dextrorotatory optical antipode of a compound claimed in any one of claims 1 and 12 to 19.

23. The levorotatory optical antipode of a compound claimed in any one of claims 2 to 6, 8, 9 and 11.

24. The dextrorotatory optical antipode of a compound claimed in any one of claims 2 to 6, 8, 9 and 11.

25. A compound as claimed in any one of claims 1 and 12 to 22 in the form of a salt.

26. A compound as claimed in any one of claims 1 and 12 to 22 in the form of a therapeutically acceptable salt.

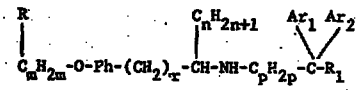
27. A compound as claimed in any one of claims 2 to 11, 23 and 24 in the form of a salt.

28. A compound as claimed in any one of claims 2 to 11, 23 and 24 in the form of a therapeutically acceptable salt.

29. A pharmaceutical preparation comprising a compound claimed in any one of claims 1, 12 to 22 and 26 in admixture or conjunction with a pharmaceutically suitable carrier.

30. A pharmaceutical preparation comprising a compound claimed in any one of claims 2 to 11, 23, 24 and 28 in admixture or conjunction with a pharmaceutically suitable carrier.

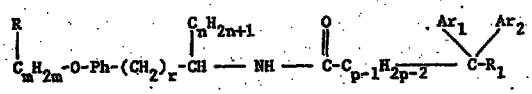
31. Process for the manufacture of new 1-(azacyclic aralkoxyphenyl)-2- or -3-(bis-arylalkylamino)-alkanes of the general Formula I



(I)

or salts thereof, which consists in

1) reducing a compound of the general Formula III



(III)

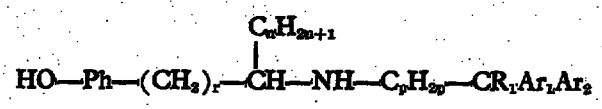
or

2) condensing of compound of the general Formula IV



(IV)

wherein T is a reactive esterified hydroxy group, with a compound of the general Formula V



or a reactive salt thereof, and if desired converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, resolving a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

32. Process as claimed in claim 31, wherein in reaction 1) the reduction of amides is preformed with a simple or complex light metal hydride.

33. Process according to claim 31, wherein in reaction 2) starting materials are used in which a reactive esterified hydroxy group T is derived from hydrochloric acid.

34. Process according to either of claims 31 and 33, wherein the reaction of starting materials of the formulae IV and V shown in claim 31 is carried out in the presence of a condensing agent.

35. Process according to any one of claims 31 to 34, wherein the levorotatory antipode of one of the compounds obtained according to the process of these claims is isolated.

36. Process according to any one of claims 31 to 34, wherein the dextrorotatory antipode of one of the compounds obtained according to the process of these claims is isolated.

37. The process claimed in claim 31 and described in any one of examples 5 to 11 and 13.

38. The compounds of the formula I shown in claim 31 and prepared according to any one of claims 31 to 37.

39. The compounds of the formula I shown in claim 31 and prepared according to any one of examples 5 to 11 and 13.

40. Process according to claim 31 for the manufacture of a compound of the general Formula I shown in claim 31 in which formula n represents an integer from 1 to 4, and the other symbols have the meanings given in claim 1, or salts thereof, which consists in

1) reducing a compound of the general Formula III given in claim 31, in which n represents an integer from 1 to 4, and the other symbols have the meanings given in claim 1 or

2) condensing a compound of the general Formula IV with a compound of the general Formula V given in claim 1, in which formula V n represents an integer from 1 to 4, and the other symbols have the meanings given in claim 31, and, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, resolving a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, if desired, resolving a racemate obtained into the optical antipodes.

41. Process as claimed in claim 40, wherein in reaction 1) the reduction is carried out according to claim 32.

42. Process as claimed in claim 40, wherein in reaction 2) a reactive esterified hydroxy group T is derived from hydrochloric acid.

43. Process as claimed in either of claims 40 and 42, wherein the reaction 2) is carried out in the presence of a condensing agent.

44. Process according to any one of claims 40 to 43, wherein the levorotatory antipode of one of the compounds obtained according to the process of these claims is isolated.

45. Process according to any one of claims 40 to 43, wherein the dextrorotatory antipode of one of the compounds obtained according to the process of these claims is isolated.

46. The process claimed in claim 40 and described in any one of examples 1 to 4.

47. The compounds of the formula I shown in claim 31 and prepared according to any one of claims 40 to 45.

48. The compounds of the formula I shown in claim 31 and prepared according to any one of examples 1 to 4.

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