United States Patent Office

3,414,578

Patented Dec. 3, 1968

3,414,578

1 - (3',4' - DI - LOWER-ALKYLPHENYL)-2-[PHENYL-PYRIDYL - (2') - PROPYLAMINO]-PROPANOL-(1) AND DERIVATIVES THEREOF

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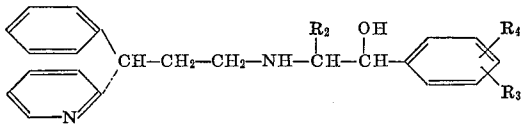
Claims priority, application Germany, Nov. 5, 1965, F 47,601
2 Claims. (Cl. 260—296)

The present invention relates to basically substituted phenyl-propane derivatives corresponding to the general Formula I

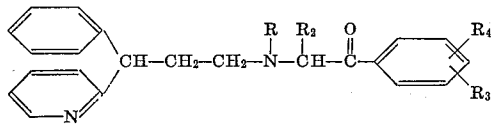


(I)

in which R_2 represents hydrogen or the methyl group, R_3 and R_4 are alkyl groups containing at most 4 carbon atoms and salts of said compounds.

The present invention also provides a process for the manufacture of the aforesaid compounds which show a favorable action on cardiac and blood vascular circulation. The process comprises:

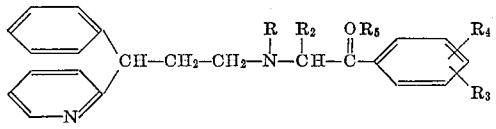
(a) reducing compounds of the general Formula II



(II)

in which R represents hydrogen or the benzyl group and R_2–R_4 have the meanings given above,

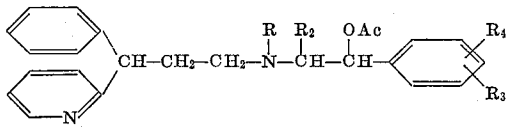
(b) treating compounds of the general Formula III



(III)

in which R–R_4 have the meanings given above and R_5 represents an alkyl or the benzyl group, with ether separating agents or by catalytic hydrogenation,

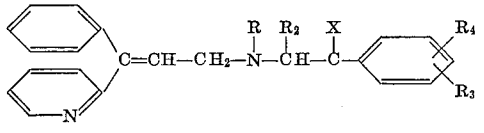
(c) hydrolizing in an alkaline or acid medium compounds of the general Formula IV



(IV)

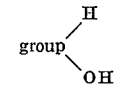
in which R–R_4 have the meanings given above and Ac represents an acyl group,

(d) catalytically hydrogenating compounds of the general Formula V

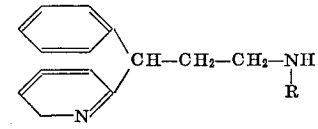


(V)

in which R–R_4 have the meanings given above and X represents an oxygen atom or the

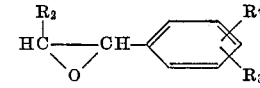


(e) reacting compounds corresponding to the general Formula VI



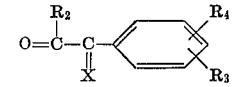
(VI)

in which R has the meaning given above, either with ethyleneoxides corresponding to the general Formula VII



(VII)

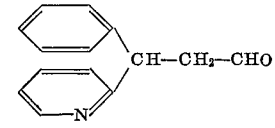
in which R_2–R_4 have the meanings given above or condensing compounds corresponding to the Formula VI with compounds corresponding to the general Formula VIII



(VIII)

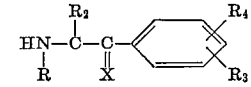
in which R_2–R_4 have the meanings given above and reducing the condensation product simultaneously or subsequently,

(f) condensing phenyl-propionaldehydes corresponding to the general Formula IX



(IX)

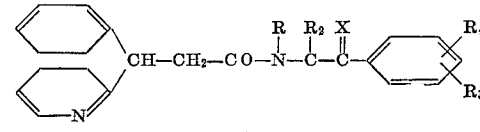
with compounds corresponding to the general Formula X



(X)

in which X, R and R_2–R_4 have the meanings given above and reducing the condensation product simultaneously or subsequently,

(g) reducing compounds of the general Formula XI



(XI)

in which X and R–R_4 have the meanings given above with complex metal hydrides,

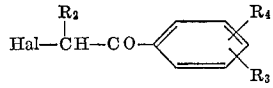
during all the above-mentioned methods the subsequent cleavage of an N-benzyl group which may be present, and converting the basic compounds obtained into their physiologically tolerated salts, if desired, by treatment with inorganic or organic acids.

For preparing the amino alcohols of the general Formula I according to the method described sub (a) the amino ketones of the general Formula II are reduced.

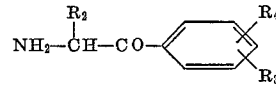
The reduction of the keto group can be carried out for instance by catalytic hydogenation with the aid of metals of the 8th group of the Periodic System, preferably by

means of nickel catalysts, in the presence of appropriate solvents such, for instance, as aqueous alcohols, alcohols or water. The compounds may likewise be reduced by means of nascent hydrogen, for instance, aluminium amalgam and alcohol, sodium amalgam, lithium-aluminium hydride, sodium boron hydride or likewise electrolytically.

The starting ketones of the general Formula II can be prepared, for instance, by reaction of 1-phenyl-1-pyridyl-(2')-propyl(3)-amine with halogenated ketones of the general formula

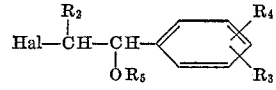


This reaction is advantageously carried out in the presence of agents splitting off hydrogen halides. The starting substances corresponding to the general Formula II may likewise be prepared by reacting 1-phenyl-1-pyridyl-(2')-3-halogen-propanes with the corresponding amino-ketones of the general formula

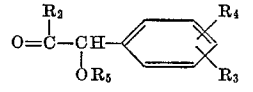


The products corresponding to the general Formula I can likewise be prepared by dealkylating in the usual manner according to the method described sub (b) corresponding compounds which as R_5 contain an alkyl group, or by splitting off a benzyl group from compounds containing the latter as R_5. The dealkylation can be carried out, for instance, by heating the compounds with hydrogen bromide or with aluminium chloride or with pyridine-hydro-chloride. The benzyl radical is advantageously separated catalytically while using noble metal catalysts, such for instance as palladium black, or by boiling with hydrobromic acid.

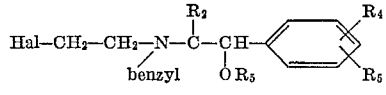
The starting substances corresponding to the general Formula III used according to the operation method described sub (b) are prepared in an analogous manner to that applied for the compounds of the general Formula II. 1-phenyl-1-pyridyl(2)-propyl(3)-amine can be reacted, for instance, with halogenated ethers corresponding to the formula



or with oxo-compounds of the general formula



The reaction with the oxo-compounds must take place with simultaneous or subsequent reduction. Finally, the starting substances according to the general Formula III can likewise be prepared from 2-benzyl-pyridine, by reaction with halogenated ethers of the general formula

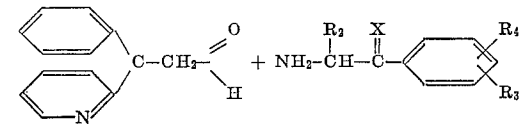


an eventually present CN-group being split off by a method known per se. The N-benzyl group can be separated prior to or after the cleavage of ether, preferably by catalytic hydrogenation. If R_5 likewise represents a benzyl group, the two O- and N-benzyl groups can be separated off in one operation by catalytic hydrogenation.

The starting materials of the general Formula IV used for the operation method mentioned sub (c) can be prepared correspondingly as described for compounds II and III. As starting substances there are mentioned, for instance, compounds of the general Formula IV, in which Ac represents the acetyl, propionyl or benzoyl radical. The hydrolysis is carried out in the usual manner in an aqueous-alkaline medium or with alcoholic or aqueous-alcoholic solution. It can likewise be realized by means of dilute acids such as hydrochloric acid or sulfuric acid.

Another method of operation of the process according to (d) consists in hydrogenating the C—C-double linkage in compounds of the Formula V. The reduction is advantageously carried out by catalytic hydrogenation by using metals of the 8th group of the Periodic System, preferably with precious metals. As solvents there are used the solvents usually applied for the hydrogenation, for instance, alcohols, water or aqueous alcohols.

The starting compounds of the general Formula V are prepared, for instance, by condensation of compounds of the general Formula XII with amines of the general Formula XIII



(XII) (XIII)

and partial hydrogenation according to Bull. Soc. Chim. France, 1952, p. 1046.

A further advantageous possibility for preparing the desired compounds comprises (e) reacting amines of the general Formula VI with ethylene-oxides of the general Formula VII, the reaction advantageously being performed in the presence of a solvent such as, for example, ethanol, and at an elevated temperature.

As ethylene-oxides there are mentioned, for instance:

1-(3,4-dimethylphenyl)-ethylene-oxide,
1-(3,4-dimethylphenyl)-2-methyl-ethylene-oxide,
1-(3,4-diethyl-phenyl)-ethylene-oxide,
1-(3,4-diethylphenyl)-2-methyl-ethylene-oxide.

A further possibility of preparing the compounds claimed, by starting from amines of the general Formula VI consists in subjecting to reduction ketones or aldehydes of the general Formula VIII in the presence of said amines. As ketones or aldehydes of said type the following compounds may be used:

1-(3,4-dimethylphenyl)-1,2-dioxo-propane,
1-(3,4-diethylphenyl)-1,2-dioxo-propane,
1-(3,4-dimethylphenyl)-1,2-dioxo-ethane,
1-(3,4-diethylphenyl)-1,2-dioxo-ethane,
1-(3,4-dimethylphenyl)-glycol-(2)-aldehyde,
1-(3,4-dimethylphenyl)-1-hydroxy-2-oxo-propane,
1-(3,4-diethylphenyl)-glycol(2)-aldehyde,
1-(3,4-diethyl-phenyl)-1-hydroxy-2-oxo-propane.

The reduction favorably proceeds by catalytic hydrogenation of equimolar amounts of the two compounds in the presence of an inert solvent. As catalysts, metals of the 8th group of the Periodic System are used, preferably precious metals.

The most suitable solvents are those generally used for hydrogenation, for instance, alcohols, aqueous alcohols or water. Nickel catalysts may likewise be used. It is likewise possible first to condense the oxo compounds of the Formula VIII with the amines of the Formula VI and then to reduce the condensation product with nascent hydrogen, for instance with aluminium amalgam and alcohol, sodium amalgam, lithium-aluminium-hydride or sodium boron-hydride. The reduction may likewise be carried out electrolytically. The condensation is characterized by the fact that preferably the keto-group adjacent to the methyl group or the aldehyde group reacts with the amine; the other oxo group may be reduced simultaneously or subsequently to the hydroxyl group in the manner mentioned sub (a).

An appropriate amine which may be used as starting

substance for the reaction according to (e), is for example 3-phenyl-3-pyridyl(2)-propyl-amine.

According to the same method there can likewise be used α-hydroxy-ketones or aldehydes of the Formula VIII in which the hydroxy-group is protected by an alkyl, benzyl or acyl group which may subsequently be separated according to (b) or (c).

A further possibility of preparing the products according to the invention consists in condensing phenyl-pyridyl(2)-propionaldehyde of the Formula IX with amino-alcohols or amino-ketones of the Formula X according to the method described sub (f). The reaction of the aldehydes with the amino alcohols with simultaneous or subsequent reduction is, in principle, carried out according to the method described sub (e) for the preparation of the products of the invention, by starting from 1-phenyl-3-amino-propanes of the Formula VI and oxo-compounds of the general Formula VIII.

As starting substances for said reaction the following amines may be used:

1-(3,4-dimethylphenyl)-1-hydroxy-2-amino-ethane,
1-(3,4-dimethylphenyl)-1-hydroxy-2-amino-propane,
1-(3,4-diethylphenyl)-1-hydroxy-2-amino-ethane,
1-(3,4-diethylphenyl)-1-hydroxy-2-amino-propane

as well as the 1-oxo-2-amino-ethanes corresponding to the above-mentioned 1-hydroxy-compounds.

According to the same method, amino alcohols of the Formula X may likewise be used in which the hydroxy group is protected by an alkyl, benzyl or acyl radical which may subsequently be separated according to (b) or (c).

According to a further method of operation according to (g) it is likewise possible to reduce carboxylic acid amides of the Formula XI, most favorably by means of lithium-aluminium-hydride. The reduction is advantageously carried out in the presence of inert organic solvents such as ether, dioxane or tetrahydrofurane. It is suitable to added the amide to the lithium-aluminium-hydride suspension in one of the above-mentioned solvents, to boil the reaction mixture for some time under reflux, to decompose it cautiously by means of water and to work it up in the usual manner by separating the organic from the inorganic constituents. The reduction of the carboxylic acid amides in order to obtain the amines is likewise possible by electrolysis. The amides of the Formula XI can be prepared in the usual manner from the corresponding pyridyl-propionic acid chlorides by reaction with amines of the Formula X.

The products of the invention, constituting basic compounds, can be converted into the corresponding salts by means of inorganic or organic acids. As inorganic acids there may be used: hydrohalic acid such as hydrochloric acid and hydrobromic acid, sulfur acid, phosphoric acid and amidosulfonic acid. As organic acids the following are mentioned, for example: acetic acid, propionic acid, lactic acid, glycolic acid, gluconic acid, maleic acid, succinic acid, tartaric acid, benzoic acid, salicylic acid, citric acid, aceturic acid, hydroxy-ethane-sulfonic acid and ethylene-diamine-tetracetic acid.

The products of the invention are valuable medicaments having a very favorable action on cardiac and blood vascular circulation. For example, a single injection of 5γ of 1-(3',4'-dimethylphenyl)-2-(m-methoxy-diphenyl-propylamino)-propanol-(1) in the test on the isolated heart of guinea pigs according to Langendorff causes an increase of the perfusion of the coronary vessels within the same range as that caused by administering 5γ of the known compounds 1-phenyl-2-[3',3'-diphenyl-propyl-(1')-amino]-propane.

The advantage of the new products consists, however, above all, in that in addition to their dilating action on the coronary vessels they show an excellent β-sympathicolytic action. β-sympathicolytically active substances inhibit the effect of adrenalin and isopropyl-noradrenalin which consists in increasing the heart rate and the contracting power of the heart. Adrenalin and isopropyl-noradrenalin likewise activate cardiac metabolism indirectly and by the above-mentioned actions also directly. An activation of the sympathetic nervous system starting at an unsuitable moment for which the two substances constitute a particular example, may cause anoxemia of the heart, particularly if the coronary vessels show constrictions (due to calcareous degeneration). A β-sympathicolytic action protects the heart against a high increase in metabolism.

In addition to their favorable action on cardiac and blood vascular circulation, the products of the present invention show a favorable hypotensive effect.

For example, the 1-(3',4'-dimethylphenyl)-2-[phenyl-pyridyl-(2'')-propylamino]-propanol - (1) - hydrochloride lowers the blood pressure considerably and for a prolonged period in rats suffering from renal high pressure.

In 11 rats suffering from renal high pressure, the blood pressure amounted, on an average, to 192 mm. Hg. Two hours after subcutaneous administration of 40 milligrams/kilogram of the product of the invention the blood pressure diminished to 136 mm. Hg and 24 hours after injection it amounted to 168 mm. Hg, i.e. it had not yet attained again the initial value.

The same product moreover shows a strong β-sympathicolytic action. In the tracheal chain according to Castillo it provokes with only 2.5γ per 50 cc. of Tyrode's solution a reduction by about 50% of the action of 5γ of isopropyl-noradrenalin.

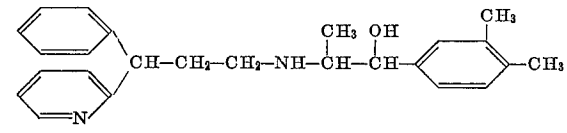
In the heart of guinea pigs isolated according to the method of Langendorff the same product by permament infusion of 0.1γ per minute caused a reduction by about one third of the increase of the heart rate provoked by 0.1γ of isopropyl-noradrenalin. 15γ of the product of the present invention distinctly activated the coronary perfusion of the heart of guinea pigs isolated according to Langendorff.

The combination of the 3 effects mentioned above imparts to the products of the present invention special advantages in comparison with the compounds hitherto known. The products of the present invention are especially suitable for the treatment of hypertonia, since in hypertonics the dilatory action on the coronary vessels is of advantage, the heart of said patients showing a considerably increased mass of muscles which must be nourished. Furthermore, the hypertonic tends to arteriosclerosis of the cardiac coronary vessels the consequences of which may be compensated by a dilatation of the small vessels free from calcification.

The following example serves to illustrate the invention but it is not intended to limit it thereto:

EXAMPLE

1-(3',4'-dimethylphenyl)-2-[phenyl-pyridyl-(2'')-propylamino]-propanol-(1)-hydrochloride

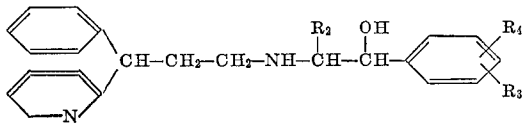


7.1 grams of β-phenyl-β-pyridyl-(2)-propionaldehyde and 6.0 grams of 1-(3',4'-dimethylphenyl)-2-aminopropanol-(1) (melting point 90° C.) (prepared by bromination of 3,4-dimethyl-propiophenone, reaction of the bromine compound with benzylamine and subsequent catalytic hydrogenation) are dissolved together in 30 cc. of benzene, whereby the solution is slightly heated. The benzene is distilled off under reduced pressure, the residue is dissolved in methanol and 1 gram of sodium-boronhydride is added in small portions, causing a vivid reaction. The product is allowed to stand for about 15 minutes, acidified by means of dilute hydrochloric acid and the methanol is distilled off under reduced pressure. The resi-

due is shaken with dilute sodium hydroxide solution and ether. The ether phase is separated, dried by means of potassium carbonate and the ether is distilled off. The residue is dissolved in a small amount of methanol and hydrochloric acid is added. After elimination of the solvent by distillation the residue is recrystallized from a mixture of acetone and ether. 9.5 grams of 1-(3',4'-dimethyl-phenyl)-2-[phenyl-pyridyl - (2'') - propylamino]-propanol-(1)-hydrochloride of a melting point of 196–197° C. are obtained.

We claim:

1. A phenylpropane of the general formula



wherein R_2 represents hydrogen or the methyl group, R_3 and R_4 represent alkyl groups containing at most 4 carbon atoms, and a pharmaceutically acceptable acid addition salt thereof.

2. 1-(3',4'-dimethylphenyl) - 2 - [phenyl-pyridyl-(2'')-propylamino]-propanol-(1).

References Cited

Barron et al.: J. Med. Chem., vol. 8 (6), pp. 836–41, 1965.

Barron et al.: Journal Pharm. and Pharmacol., vol. 17 (8), pp. 509–16, 1965.

Chem. Abstracts, vol. 63, par. 12,140, October 1965.

Chem. Abstracts, vol. 63, par. 18,021, December 1965.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,414,578 Dated December 3, 1968

Inventor(s) HANNS HANINA LEHR and MILAN MITROVIC

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 6, line 56, claim 3 "claim 2" should be:

claim 1

SIGNED AND
SEALED
MAY 19 1970

(SEAL)
Attest:

Edward M. Fletcher, Jr.
Attesting Officer

WILLIAM E. SCHUYLER, JR.
Commissioner of Patents