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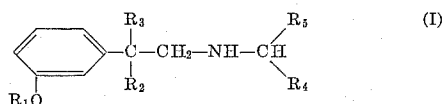
N-SUBSTITUTED PHENYLALKYLAMINES

Walter Krohs, Bad Soden, Taunus, and Leopold Ther and Gerhard Vogel, Frankfurt am Main, Germany, assignors to Farbwerke Hoechst Aktiengesellschaft vormals Meister Lucius & Brüning, Frankfurt am Main, Germany, a corporation of Germany
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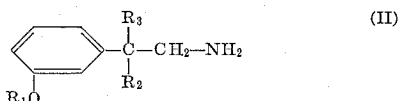
The present invention relates to new phenylalkylamines which are distinguished by analgesic properties and to their method of manufacture. The present invention further provides pharmaceutical preparations having analgesic properties and containing said substances as active ingredients.

We have found that phenylalkylamines of the general Formula I



in which R₁ represents hydrogen, an alkyl group having from 1 to 4 carbon atoms or the benzyl group, R₂ represents an alkyl group having from 2 to 4 carbon atoms, R₃ represents a pentyl group or a cyclopentyl group and R₄ and R₅ represent an alkyl group having from 1 to 4 carbon atoms or, together with the combining carbon atom, members of a saturated carbocycle having from 5 to 6 carbon atoms, possess valuable therapeutical properties, particularly analgesic action and that said compounds may be obtained by

(a) The reaction of an amine of the general Formula II



wherein R₁—R₃ have the meanings given above, with a ketone of the general Formula III



in which R₆ represents an alkyl group having 1 to 4 carbon atoms and R₇ represents a saturated or unsaturated hydrocarbon radical having up to 4 carbon atoms, or in which R₆ and R₇ together with the combining carbon atom, are members of a saturated carbocycle having 5 to 6 carbon atoms, in the presence of activated hydrogen;

(b) The reaction of an amine of the general Formula II given above with an ester of the general Formula IV



in which R₄ and R₅ have the meanings given above and X represents an inorganic or organic acid residue, if desired, by means of an agent splitting off the acid residue;

(c) Heating an amine of the general Formula II given above with an alcohol of the general Formula V



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wherein R₄ and R₅ have the meanings given above, and, if desired, splitting off the alkyl group in the products in which the substituent R₁ represents an alkyl group according to known methods and, if desired, alkylating the products in which R₁ represents hydrogen by means of an alkylating agent and, if desired reducing catalytically the products in which R₁ represents a benzyl group in order to split off the benzyl group; and, if desired, converting the basic compounds obtained into the corresponding addition salts by means of inorganic or organic physiologically tolerable acids.

The most advantageous method of preparation of the products according to the invention is to react amines of the general Formula II with ketones of the Formula III.

The alkyl radicals R₂, R₄ and R₅ may be the same or different and may be straight chained or branched. There may be mentioned, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and sec. butyl radicals.

As amines there may be used, for example:

- 2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-butylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-pentylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-3-methyl-butylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-3-methyl-pentylamine-(1),
- 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1),
- 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-pentylamine-(1),
- 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-3-methyl-butylamine-(1),
- 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-3-methyl-pentylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-pentyl-(3'')-butylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-pentyl-(3'')-pentylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-pentyl-(3'')-3-methyl-butylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-pentyl-(3'')-3-methyl-pentylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-cyclopentyl-pentylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-cyclopentyl-3-methyl-butylamine-(1),
- 2-(3'-hydroxy-phenyl)-2-cyclopentyl-3-methyl-pentylamine-(1),
- 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1),
- 2-(3'-methoxy-phenyl)-2-cyclopentyl-pentylamine-(1),
- 2-(3'-methoxy-phenyl)-2-cyclopentyl-3-methyl-butylamine-(1),
- 2-(3'-methoxy-phenyl)-2-cyclopentyl-3-methyl-pentylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-cyclopentyl-butylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-cyclopentyl-pentylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-cyclopentyl-3-methyl-butylamine-(1),
- 2-(3'-ethoxy-phenyl)-2-cyclopentyl-3-methyl-pentylamine-(1),
- 2-(3'-benzyloxy-phenyl)-2-cyclopentyl-butylamine-(1),
- 2-(3'-benzyloxy-phenyl)-2-cyclopentyl-pentylamine-(1),
- 2-(3'-benzyloxy-phenyl)-2-cyclopentyl-3-methyl-butylamine-(1),
- 2-(3'-benzyloxy-phenyl)-2-cyclopentyl-3-methyl-pentylamine.

As ketone of the Formula III there may be used, for example, the following compounds: acetone, methylethyl-ketone, methylpropyl-ketone, methylbutyl-ketone, methylisopropyl-ketone, methylisobutyl-ketone, diethyl-ketone, dipropyl-ketone, methylvinyl-ketone, isopropylidene-acetone (mesityloxide), cyclopentanone or cyclo-hexanone.

The amines of the Formula II to be used as starting sub-

stances are advantageously prepared by hydrogenation of the correspondingly substituted cyanides in the presence of catalysts of the 8th group of the Mendeléeff Periodic System. The cyanides may be prepared by reacting the correspondingly substituted benzyl-cyanides with sodium amide and alkyl or cyclopentyl halides in a solvent immiscible with water.

The reduction of an amine of the general Formula II in the presence of a ketone of the general Formula III may, for example, be effected catalytically with the use of metals of the 8th group of the Mendeléeff Periodic System, preferably with palladium catalysts. The reaction may be varied in wide limits and may be adapted to special conditions. It can, for example, be carried out in the presence of an excess amount of ketone simultaneously serving as solvent. The reaction is preferably effected at a temperature up to 50° C. and under a pressure of hydrogen of 50 atmospheres. When operating according to this method, the excess ketone is not hydrogenated to yield the corresponding carbinol and may be recovered. It is, however, also possible to operate without the use of the excess ketone and to use another appropriate solvent, for example, methanol. Instead of palladium, nickel catalysts (Raney nickel) may also be used. It is likewise possible to carry out the reduction with the use of nascent hydrogen, for example, by using aluminum amalgam and alcohol, sodium amalgam, lithium-aluminum hydride or sodium boron hydride. The reduction, may furthermore, be carried out by electrolysis.

According to another advantageous method of preparing the compounds of the invention, the amines of the Formula II may be reacted with the esters of inorganic or organic acids of the Formula IV. There may be used for example, isopropyl iodide, sec. butyl-bromide, 3-bromopentane, 2-bromo-3-methylbutane, 2-bromo-4-methylpentane, cyclopentyl-bromide, cyclohexyl-bromide, p-toluene-sulfonic acid isopropyl-ester, or di-isopropyl-sulfate.

The reaction is preferably performed by heating the reactants in an appropriate solvent, for example, ethanol, isopropanol, benzene, toluene or xylene, at temperatures between 80 and 130° C. The heating period depends on the temperature and the reactivity of the ester component and usually amounts to 1 to 20 hours. In order to bind the acids that have formed during the reaction the amine of the Formula II may be used in an excess of one to several times the molar quantity, and a solvent immiscible with water, in which the amine salt formed during the reaction is insoluble, may be used. For binding the acids formed there may also be used instead of the excess amine other basic compounds, for example, sodium bicarbonate, anhydrous sodium carbonate or tertiary amines, such as triethylamine or diethylaniline. The reaction may also be carried out without using solvents by heating both reaction components to temperatures between 80 and 130° C., the use of the amine in a bimolar excess being advantageous.

Another method of preparing the compounds of the invention consists in heating amines of the Formula II with alcohols of the Formula V in the presence of Raney nickel for a prolonged period of time at temperatures between 100° C. and 120° C. The heating period depends on the structure of the starting substances used and is generally between 5 and 15 hours.

For the preparation of the products of the invention in which the substituent R₁ represents a hydrogen atom, it is advantageous to prepare first the corresponding alkoxy or benzyloxy compound according to one of the indicated methods. The alkoxy compounds may then be converted in the usual manner, for example by heating with hydrogen chloride, hydrogen bromide, aluminum chloride or pyridinehydrochloride into the corresponding hydroxy compounds. If benzyloxy compounds are used as starting substances, for example 2-(3'-benzyloxy-phenyl)-2-cyclopentyl-butylamine-(1), the reaction can be carried out

in one or two stages of operation. When introducing for example the radical



into a compound of the Formula I by hydrogenating an amine of the Formula II together with a ketone of the Formula III in the presence of palladium as catalyst, the benzyl group is split off in this step of operation. If, however, the radical



is introduced according to other methods, for example, by reacting an amine of the Formula II with an ester of the Formula IV, the benzyloxy group is not affected and—if desired—can be split off in a further step of this reaction, for example, by means of noble metals of the 8th group of the Mendeléeff Periodic System as catalysts.

On the other hand, if according to one of the above-described methods there are obtained products in the formulae of which R₁ represents a hydrogen atom, the hydroxy group can be converted into the methoxy or ethoxy group by ethylation in the usual manner, for example with dimethylsulfate or diethylsulfate in an alkaline solution.

The products of the present invention can be converted into the corresponding acid addition salts by treatment with inorganic or organic acids. For the salt formation the following physiologically tolerable acids may be used: inorganic acids, for example a hydrohalic acid, particularly hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, amido-sulfo acid, and organic acids such as acetic acid, propionic acid, oxalic acid, malic acid, succinic acid, lactic acid, maleic acid, fumaric acid, sorbic acid, citric acid, acetic acid, aspartic acid, p-amino-benzoic acid, salicylic acid and ethylenediamine-tetracetic acid.

The analgesic activity of the new products of the invention was demonstrated in mice according to the method of Wolff, Hardy, Goodell, J. Clin. Inv. 19, 659 (1940). When applying this method, the preparation was administered subcutaneously or orally to a number of mice and the period of time in which the animals reacted to the thermal irritation was examined prior to and after administration of the products. This method was modified in such a way that by a process of "all or nothing" certain criteria were used in order to ascertain the percentage of animals showing positive response in the test. Thus, relatively exact relations of the effective doses could be found. Upon subcutaneous administration the lowest effective dose (dosis effectiva minima 50) of 0.85 milligram/kilogram was ascertained for the N-sec. butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1)-hydrochloride according to this method. In comparison with the known 2-dimethylamino-4,4-diphenylheptanone (5)-hydrochloride the lowest effective dose of the latter substance amounts to 1.5 milligrams/kilogram on subcutaneous administration. Upon subcutaneous administration the present preparation thus proved to be twice as potent as the known 2-dimethylamino-4,4-diphenylheptanone (5)-hydrochloride. When given to mice which are in a state of excitement caused by subcutaneous injection of 1-phenyl-2-methylamino-propane hydrochloride according to the method by Ther (Deutsche Apotheker-Zeitung 1953, p. 292), the above-mentioned compound showed a distinctly sedative action. Examination methods in the goldhamster (*Mesocricetus auratus*) according to Ther, Vogel and Werner, Arzneimittelforschung 9, 351 (1959), and examination methods in the cotton rat according to Vogel and Ther, Arzneimittelforschung 10, 806 (1960), have demonstrated sedative neuroleptic action.

Toxicity tests have revealed that the products of the present invention are to be considered harmless.

For example, in mice the lethal dose 50 for N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1)-hydrochloride is 30 milligrams/kilogram in the case of intravenous injection, 250 milligrams/kilogram in the case of subcutaneous injection and 900 milligrams/kilogram in the case of oral administration. Long-term toxicity tests showed that the compound when administered orally to dogs for 28 days in a dose of 10 milligrams/kilogram was tolerated without causing pathologic symptoms in the clinical picture and in post mortem examinations.

In clinical trials N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1)-hydrochloride revealed a marked analgesic action when administered in a dose of 2 to 4 milligrams. The products of the present invention can be applied either in form of the free amines or in the form of their addition salts with physiologically tolerable acids as analgesic medicaments, if desired, in admixture with suitable solid or liquid pharmaceutical carriers such as water, vegetable oils, starch, lactose or talcum, if desired, with auxiliary agents such as stabilizing, preserving and emulsifying agents. The compounds are preferably administered in the form of solutions or suspensions for injections, and of tablets, dragees, capsules and suppositories.

For parenteral administration a dose of 1 to 20 mg. may be taken into consideration and for oral administration a dose of 5 to 50 milligrams.

The following examples serve to illustrate the invention, but they are not intended to limit it thereto:

EXAMPLE 1

N-sec.butyl-2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1)

30 grams of 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1) and 150 grams of methylethylketone were hydrogenated at 50° C. in the presence of palladium as catalyst until the hydrogen ceased to be absorbed. After separation from the catalyst and elimination of the excess methylethylketone by distillation N-sec.butyl-2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1) was obtained in a quantitative yield. The corresponding fumarate melted at 107° C.

The 2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1), boiling point₅=148-152° C. serving as starting substance was obtained by hydrogenation of (3-methoxy-phenyl)-ethylpentyl-(3'')-acetonitrile (boiling point₆=148-150° C.) prepared by reacting (3-methoxy-phenyl)-ethyl-acetonitrile with sodium amide and 3-bromopentane.

EXAMPLE 2

N-sec.butyl-2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-butylamine-(1)

By heating under reflux the N-sec.butyl-2-(3'-methoxy-phenyl)-2-pentyl-(3'')-butylamine-(1) with hydrobromic acid of 48% strength for 8 hours, the methyl group was split off. The N-sec.butyl-2-(3'-hydroxy-phenyl)-2-pentyl-(3'')-butylamine-(1) was obtained in a quantitative yield and formed a fumarate which melted at 167° C.

EXAMPLE 3

N-isopropyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1)

(a) 20 grams of 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) were hydrogenated in 100 grams of acetone according to the prescriptions given in Example 1. The N-isopropyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) was obtained in a quantitative yield. Its hydrochloride melted at 145° C.

(b) The same compound was obtained by heating for

15 hours at 100° C. 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) with excess isopropanol and a large quantity of Raney nickel.

(c) The same compound was obtained by heating for 3 hours at 100° C. 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) with one mol of diisopropyl sulfate.

EXAMPLE 4

N-sec.butyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1)

(a) 300 grams of 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) were hydrogenated in 750 grams of methylethylketone according to the prescriptions given in Example 1. The N-sec.butyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) was obtained in a quantitative yield. Its hydrochloride melted at 185° C.

(b) The same compound was obtained by hydrogenating 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) with methylvinylketone and palladium as catalyst at 50° C. until the hydrogen ceased to be absorbed.

The 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1), boiling point₅=174-176° C., serving as starting substance was obtained by hydrogenation of (3-methoxy-phenyl)-ethyl-cyclopentyl-acetonitrile (melting point₃=154-156° C.) prepared by reacting (3-methyl-phenyl)-ethylacetonitrile with sodium amide and cyclopentylbromide.

EXAMPLES 5-9

From 2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1) there were obtained the following compounds according to the process described in Example 1 by the hydrogenation with ketones:

(5) With methylisopropylketone there was obtained the N-[3''-methyl-butyl-(2'')]-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1). Melting point of the hydrochloride: 131° C.

(6) With methylpropylketone there was obtained the N-pentyl-(2'')-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1). Melting point of the hydrochloride 200° C.

(7) With diethylketone there was obtained the N-pentyl-(3'')-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1). Melting point of the hydrochloride 155° C.

(8) With cyclopentanone there was obtained the N-cyclopentyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1). Melting point of the hydrochloride 230° C.

(9) With cyclohexanone there was obtained the N-cyclohexyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-butylamine-(1). Melting point of the hydrochloride 195° C.

EXAMPLES 10-17

By heating the 3-methoxy compounds described in the Examples 3 to 9 for 8 hours under reflux with hydrobromic acid of 48% strength the methyl group was split off, while the corresponding hydroxyphenyl derivatives were formed. The following products were prepared in this manner.

(10) N-isopropyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1); melting point of the hydrochloride: 206° C.

(11a) N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1); melting point of the hydrochloride: 178° C.

(11b) The same compound was obtained by hydrogenating at 50° C. the 2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1), which had been obtained by demethylation of the corresponding methoxy compound with hydrobromic acid of 48% strength and which formed a fumarate melting at 150° C., with methylethylketone and palladium as catalyst.

(12) N-[3''-methyl-butyl-(2'')]-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1); melting point of the hydrochloride: 164° C.

(13) N-pentyl-(2'')-2-(3'-hydroxy-phenyl)-2-cyclo-

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pentyl-butylamine-(1); melting point of the hydrochloride: 212° C.

(14) N-pentyl-(3'')-2-(3'-hydroxy-phenyl) - 2 - cyclopentyl-butylamine-(1); melting point of the hydrochloride: 184° C.

(15) N-cyclopentyl-2-(3'-hydroxy-phenyl)-2 - cyclopentyl-butylamine-(1); melting point of the hydrochloride: 209° C.

(16) N-cyclohexyl-2-(3'-hydroxy-phenyl)-2 - cyclopentyl-butylamine-(1); melting point of the hydrochloride: 236° C.

(17) N-sec.butyl-2-(3'-ethoxy-phenyl)-2 - cyclopentyl-butylamine-(1) was obtained by causing diethylsulfate in alkaline solution to act on N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-butylamine-(1) obtained according to Example 11.

EXAMPLE 18

N-sec.butyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-pentylamine-(1)

16 grams of 2-(3'-methoxy-phenyl)-2-cyclopentyl-pentylamine-(1) were hydrogenated and worked up in 150 grams of methylethylketone according to the prescription given in Example 1. The N-sec.butyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-pentylamine-(1) was obtained in a quantitative yield. Its hydrochloride melted at 127° C. The 2-(3'-methoxy-phenyl)-2-cyclopentyl - pentylamine-(1) (boiling point₅=178-180° C.) serving as starting substance was obtained by hydrogenation of (3-methoxy-phenyl) - propyl - cyclopentyl - acetonitrile (boiling point₅=168-170° C.). The latter compound can be prepared from 3-methoxybenzylcyanide, sodium amide and propyl bromide and by subsequent reaction of the (3 - methoxy - phenyl) - propylacetonitrile (boiling point₅=134-135° C.) obtained with sodium amide and cyclopentylbromide.

EXAMPLE 19

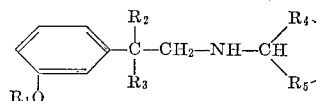
N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-pentylamine-(1)

By heating under reflux the N-sec.butyl-2-(3'-methoxy-phenyl)-2-cyclopentyl-pentylamine-(1) with hydrobromic acid of 48% strength for 8 hours, the methyl group was split off. The N-sec.butyl-2-(3'-hydroxy-phenyl)-2-cyclopentyl-pentylamine-(1) was obtained in a quantitative yield. Its hydrochloride melted at 228° C.

We claim:

1. The compounds selected from the group consisting of (1) phenylalkylamines of the general Formula I

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(I)

in which R₁ is selected from the group consisting of hydrogen, an alkyl group having from 1 to 4 carbon atoms and the benzyl group, R₂ represents an alkyl group having from 2 to 4 carbon atoms, R₃ is selected from the group consisting of a pentyl group and a cyclopentyl group, and R₄ and R₅ are selected from the group consisting of an alkyl group having from 1 to 4 carbon atoms and, together with the combining carbon atom, members of a saturated carbocycle having from 5 to 6 carbon atoms, and (2) addition salts of said compounds with physiologically compatible acids.

2. N-sec.butyl-2-(3'-hydroxy-phenyl) - 2 - pentyl-(3'')-butylamine-(1).

3. N-isopropyl-2-(3'-methoxy-phenyl) - 2 - cyclopentyl-butylamine-(1).

4. N-isopropyl-2-(3'-hydroxy-phenyl) - 2 - cyclopentyl-butylamine-(1).

5. N-sec.butyl-2-(3'-hydroxy-phenyl) - 2 - cyclopentyl-butylamine-(1).

6. N-pentyl-(3'')-2-(3'-hydroxy-phenyl) - 2 - cyclopentyl-butylamine-(1).

7. N-sec.butyl-2-(3'-hydroxy-phenyl) - 2 - cyclopentyl-butylamine-(1)-hydrochloride.

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CHARLES B. PARKER, *Primary Examiner*.

MORRIS O. WOLK, *Examiner*.