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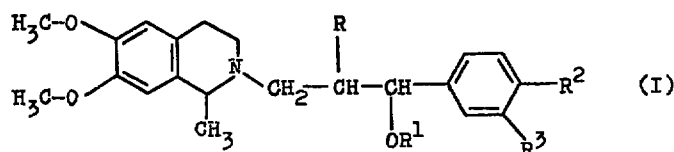


(54) TETRAHYDRO-ISOQUINOLINE DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, ROCHE PRODUCTS LIMITED, a British Company of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with tetrahydro-isoquinoline derivatives and a process for the manufacture thereof.

The tetrahydro-isoquinoline derivatives provided by the invention are compounds of the general formula



wherein R represents a lower-alkyl or lower-cycloalkyl group, R¹ represents a hydrogen atom or a lower-alkanoyl group and R² and R³ each represent a lower-alkyl group or R² and R³ together represent a trimethylene, tetramethylene or butadien-(1,3)-ylene-(1,4) group, and acid addition salts thereof.

The tetrahydro-isoquinoline derivatives aforesaid have an analgesic and/or antitussive activity and also reduce intestinal motility.

It will be appreciated that the term "lower alkyl" is used in this description and in the accompanying claims to mean both straight-chain and branched-chain alkyl groups containing from 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl). The preferred lower-alkyl values for R are ethyl, isobutyl and hexyl and the preferred lower-alkyl value for R² and R³ is methyl. The term "lower cycloalkyl" is used to mean cycloalkyl groups containing from 3 to 6 carbon atoms, namely cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cyclohexyl group is the preferred lower-cycloalkyl group. The term "lower alkanoyl" is used to mean alkanoyl groups containing up to 6 carbon atoms such as acetyl, propionyl and butyryl. The acetyl group is the preferred lower-alkanoyl group.

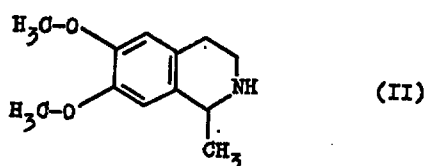
A preferred class of tetrahydro-isoquinoline derivatives provided by the invention comprises those compounds of formula I in which R² and R³ each represent a lower-alkyl group and their acid addition salts. Especially preferred tetrahydro-isoquinoline derivatives provided by the invention are:

6,7 - dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - 4 - methyl-pentyl] - 1 - methyl - 1,2,3,4 - tetrahydro - isoquinoline,
 6,7 - dimethoxy - 2 - [2 - (α - acetoxy - 3,4 - dimethyl - benzyl) - 4 - methyl-pentyl] - 1 - methyl - 1,2,3,4 - tetrahydro - isoquinoline,

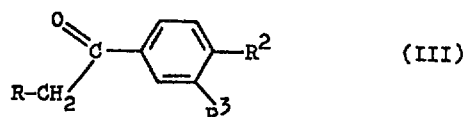
- 6,7 - dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - octyl] - 1-methyl - 1,2,3,4 - tetrahydro - *isoquinoline*,
 2 - [2 - (α - acetoxy - 3,4 - dimethyl - benzyl) - octyl] - 6,7 - dimethoxy - 1-methyl - 1,2,3,4 - tetrahydro - *isoquinoline*,
 5 2 - [2 - *cyclohexyl* - 3 - (3,4 - dimethyl - phenyl) - 3 - hydroxy - propyl] - 6,7-dimethoxy - 1 - methyl - 1,2,3,4 - tetrahydro - *isoquinoline*,
 2 - [3 - acetoxy - 2 - *cyclohexyl* - 3 - (3,4 - dimethyl - phenyl) - propyl] - 6,7-dimethoxy - 1 - methyl - 1,2,3,4 - tetrahydro - *isoquinoline*,
 10 2 - [2 - ethyl - 3 - [5,6,7,8 - tetrahydro - naphthyl - (2)] - 3 - hydroxy - propyl] - 6,7 - dimethoxy - 1 - methyl - 1,2,3,4 - tetrahydro - *isoquinoline*

and their acid addition salts, particularly the hydrochlorides.

According to the process provided by the invention, the tetrahydro-*isoquinoline* derivatives aforesaid are manufactured by reacting a compound of the formula



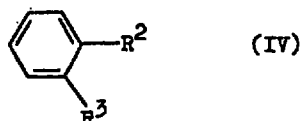
- 15 or an acid addition salt thereof, with formaldehyde and a ketone of the general formula 15



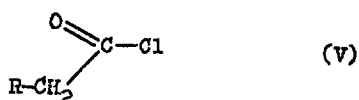
- 20 wherein R, R² and R³ have the significance given above, by a MANNICH reaction (the reaction being carried out in the presence of an acid when a compound of formula II is used), reducing the reaction product either catalytically or by treatment with an alkali-metal aluminium hydride or alkali-metal borohydride and, if desired, lower-alkanoylating the reduction product and, also if desired, converting the reduction or lower-alkanoylation product into the free base or into an acid addition salt. 20

- 25 The compounds of formula II hereinbefore and their acid addition salts are known and can be obtained, for example, by reducing 1-methyl-6,7-dimethoxy-3,4-dihydro-*isoquinoline* and, where required, converting the product into an acid addition salt. 25

The ketone starting materials of formula III hereinbefore are also known and can be prepared, for example, by reacting a compound of the general formula



- 30 wherein R² and R³ have the significance given earlier, with a compound of the general formula 30

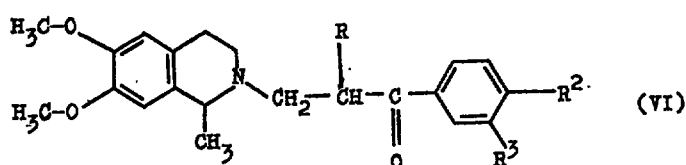


- 35 wherein R has the significance given earlier, under the conditions of a FRIEDEL-CRAFT reaction. A preferred class of ketone starting materials of formula III comprises those in which R² and R³ each represent a lower-alkyl group. 35

- 40 It will be appreciated that the MANNICH reaction can be carried out using either an acid addition salt of a compound of formula II, formaldehyde and a ketone of formula II or a compound of formula II, formaldehyde and a ketone of formula III in the presence of an acid. Suitable acids include the hydrohalic acids (especially hydrochloric acid), sulphuric acid and strong organic acids such as trichloro-acetic acid. It is advantageous to use more than one mol of acid per mol of a compound of 40

formula II. The MANNICH reaction can conveniently be carried out by heating the reactants together in an inert organic solvent (e.g. an alkanol containing from 1 to 4 carbon atoms such as methanol or ethanol) for a period of up to *ca* 72 hours. In certain circumstances it may be advantageous to add further quantities of formaldehyde to the reaction mixture during the course of the reaction (e.g. at 24 hours and 48 hours when the reaction is carried out for a period of 72 hours). The formaldehyde is suitably provided in the form of a polymer thereof such as paraformaldehyde. In a preferred embodiment, this reaction is carried out using an acid addition salt (especially a hydrohalide salt such as the hydrochloride) of a compound of formula II and, in this case, it may be advisable to include in the reaction mixture a small amount of the acid corresponding to the acid addition salt used.

The MANNICH reaction described earlier yields an acid addition salt of a compound of the general formula



wherein R, R² and R³ have the significance given earlier, which is then reduced. The catalytic reduction can suitably be carried out in an alkanol containing from 1 to 4 carbon atoms (e.g. methanol or ethanol) using hydrogen in the presence of a platinum or palladium catalyst (e.g. palladium-on-carbon or platinum oxide). This catalytic reduction can conveniently be carried out at room temperature and at atmospheric pressure. The reduction using an alkali-metal aluminium hydride or alkali-metal borohydride can suitably be carried out at room temperature or at a temperature below room temperature in an inert organic solvent. Where an alkali-metal aluminium hydride is used suitable solvents include anhydrous ethers such as diethyl ether and tetrahydrofuran and where an alkali-metal borohydride is used suitable solvents include alkanols containing from 1 to 4 carbon atoms such as methanol and ethanol or dioxan or an aqueous solution thereof. Lithium aluminium hydride is the preferred alkali-metal aluminium hydride and sodium borohydride is the preferred alkali-metal borohydride.

The foregoing reduction yields a compound of formula I in which R¹ represents a hydrogen atom or an acid addition salt thereof depending upon the reduction system employed. The reduction product can, if desired, be lower-alkanoylated to yield a compound of formula I in which R¹ represents a lower-alkanoyl group, or an acid addition salt thereof. The lower-alkanoylation can be carried out in accordance with methods known *per se*; for example using a lower-alkanoyl halide such as acetyl chloride or propionyl bromide or an anhydride or an alkanolic acid containing up to 6 carbon atoms such as acetic anhydride. According to a preferred embodiment, the lower-alkanoylation is carried out using an anhydride of an alkanolic acid containing up to 6 carbon atoms in the presence of a catalytic amount of a strong acid such as perchloric acid as a lower-alkanoylation catalyst.

Preferred embodiments of the foregoing process comprise reacting 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride with 1,2-dimethyl-4-*isocaproyl*-benzene, 1,2-dimethyl-4-octanoyl-benzene, 4-(2-cyclohexyl-acetyl)-1,2-dimethyl-benzene or 2-butyryl-5,6,7,8-tetrahydro-naphthalene and reducing the reaction product and, if desired, in the case of the first three embodiments acetylating the reduction product.

The compounds of formula I can be converted into acid addition salts by treatment with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid and phosphoric acid and with organic acids such as acetic acid, tartaric acid, maleic acid, citric acid and toluenesulphonic acid. The pharmaceutically acceptable acid addition salts are preferred. Where an acid addition salt of a compound of formula I is obtained according to the process of this invention, such salt can be converted into the free base by treatment with alkali.

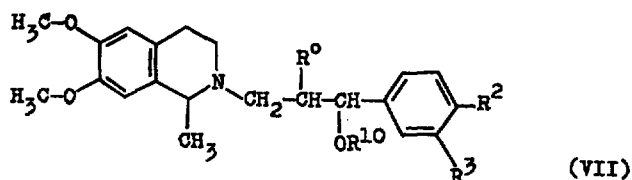
It will be appreciated that the *isoquinoline* derivatives provided by the invention can occur in racemic and optically active form and that the invention includes within its scope both the racemic and the optically active forms. A racemate can, if desired, be separated into its optical isomers in accordance with methods known *per se*; for example, by fractional crystallisation of its salts formed with optically active acids. The optical isomers can, however, also be obtained by using an optionally active

starting material of formula II or by resolving an appropriate intermediate obtained during the process.

As mentioned earlier, the tetrahydro-*isoquinoline* derivatives provided by the invention possess analgesic and/or antitussive activity. They have an analgesic and/or antitussive activity comparable with that of codeine and dihydrocodeine, two well-known and widely used analgesics, and also with that of corresponding tetrahydro-*isoquinoline* derivatives in which R and R¹ each represent a hydrogen atom. Accordingly, the compounds of formula I and their pharmaceutically acceptable acid addition salts may be used as analgesic and/or antitussive agents.

In addition to the aforementioned activities, it has surprisingly been found that the tetrahydro-*isoquinoline* derivatives provided by the invention substantially reduce gut motility when compared with the corresponding tetrahydro-*isoquinoline* derivatives in which R and R¹ each represent a hydrogen atom. Accordingly, the compounds of formula I and their pharmaceutically acceptable acid addition salts may be used as agents for alleviating diarrhoea.

The aforementioned analgesic and intestinal motility activities of the tetrahydro-*isoquinoline* derivatives provided by this invention is shown in the following Table which also includes activities for codeine, dihydrocodeine and two corresponding tetrahydro-*isoquinoline* derivatives in which R and R¹ each represents a hydrogen atom. For the sake of convenience, reference will be made in the Table to the following general formula:



TABLE

Compound				LD ₅₀ (mg/kg per os in mice)	Analgesia: PD ₅₀ (mg/ kg per os in mice)	Intestinal Motility: Standard Effective Dose (mg/ kg per os in mice)
R ^o	R ¹⁰	R ²	R ³			
—CH ₂ —CH(CH ₃) ₂	H	—CH ₃	—CH ₃	355	4.5	0.8
—CH ₂ —CH(CH ₃) ₂	—COCH ₃	—CH ₃	—CH ₃	325	12.5	3.3
—(CH ₂) ₅ CH ₃	H	—CH ₃	—CH ₃	500	1.5	1.1
—(CH ₂) ₅ CH ₃	—COCH ₃	—CH ₃	—CH ₃	1600	6.0	0.45
—CH ₂ —CH ₃	H	—(CH ₂) ₄ —	—(CH ₂) ₄ —	400	4.5	2.5
	H	—CH ₃	—CH ₃	600	9.0	1.9
	—COCH ₃	—CH ₃	—CH ₃	400	6.0	0.85
H	H	—CH ₃	—CH ₃	155	8.0	43
H	H	— (CH ₂) ₄ —	— (CH ₂) ₄ —	320	18.0	30
codeine				370	6.0	8.5
dihydrocodeine				870	—	6.1

The compounds of formula I hereinbefore and their pharmaceutically acceptable acid addition salts can be used as medicaments in the form of pharmaceutical compositions which contain them in association with a compatible pharmaceutical carrier. The carrier material may be an organic or inorganic inert carrier material which is suitable for enteral (e.g. oral) or parenteral administration. Examples of such carrier materials are water, gelatin, starch, talc, magnesium stearate, lactose and polyalkylene glycols.

The pharmaceutical compositions can be made up in solid form (e.g. tablets, dragées and capsules) or in liquid form (e.g. solutions, suspensions and emulsions).

The following Examples illustrate the process provided by the invention:

Example 1

A) The preparation of the starting material:

134.5 g of isocaproyl chloride were added dropwise at room temperature to a vigorously stirred suspension of 133.5 g of aluminium chloride in 1200 ml of dry dichloromethane. The resulting mixture was stirred at room temperature for a further 2 hours, then cooled in ice-water, treated dropwise over 0.5 hour with 106 g of *ortho*-xylene, stirred at room temperature for 3 hours, allowed to stand at room temperature overnight, and poured on to ice-cold hydrochloric acid. The lower organic layer was separated off, washed successively with water, dilute aqueous sodium hydroxide solution, water and brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The oily residue was distilled to give 119.7 g of 1,2-dimethyl-4-isocaproyl-benzene as a pale-yellow oil of boiling point 160°—166° C/15 mm.

B) The process

A mixture of 61.2 g of 1,2-dimethyl-4-isocaproyl-benzene, 73.2 g of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride, 13.5 g of paraformaldehyde, 0.5 ml of concentrated hydrochloric acid and 150 ml of methylated spirits was heated under reflux for 72 hours, further quantities of paraformaldehyde (13.5 g on each occasion) being added after 24 hours and 48 hours. After cooling, the resulting mixture was concentrated under reduced pressure. The residual gum was triturated with diethyl ether to give a pale-yellow semi-crystalline solid which was filtered off, washed well with water to remove unchanged starting materials, dried and crystallised from isopropanol to yield 47.0 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride as a white solid of melting point 168°—169° C.

A suspension of 38.33 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and 2 g of 5% palladium-on-carbon in 500 ml of methanol was hydrogenated at room temperature and atmospheric pressure until the theoretical amount of hydrogen (0.084 mol) had been absorbed. The catalyst was then filtered off and the filtrate evaporated under reduced pressure. The residue was crystallised from methanol/(ethyl acetate) to yield 32.4 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxybenzyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride as a white crystalline solid of melting point 231°—232° C.

10.0 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and a mixture of 0.5 ml of 70% perchloric acid and 100 ml of acetic anhydride were warmed on a water-bath for 0.5 hour. The resulting solution was allowed to stand at room temperature for 4 days, then poured on to ice, made basic with aqueous sodium hydroxide solution while cooling with ice and extracted three times with dichloro-methane. The combined dichloro-methane extracts were washed with water, dried over anhydrous sodium sulphate, filtered and the filtrate evaporated under reduced pressure. The oily residue was dissolved in ethanol, treated with ethanolic hydrogen chloride and evaporated under reduced pressure. The viscous residue was crystallised from ethyl acetate to yield 8.0 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-4-methyl-pentyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the form of white crystals of melting point 182°—184° C.

Example 2

Reaction of the free base of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline with propionyl chloride in the presence of triethylamine gave 2-[2-(α -propionoxy-3,4-dimethyl-benzyl)-4-methyl-pentyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline, which was isolated in the form of its hydrochloride of melting point 171°—173° C (from ethyl acetate).

Example 3

A) The preparation of the starting material:

1,2-Dimethyl-4-octanoyl-benzene was prepared from octanoyl chloride, aluminium chloride and *ortho*-xylene in dichloro-methane by a procedure analogous to that described in part A of Example 1.

B) The process:

A mixture of 23.2 g of 1,2-dimethyl-4-octanoyl-benzene, 24.4 g of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride, 4.5 g of paraformaldehyde, 0.2 ml of concentrated hydrochloric acid and 50 ml of methylated spirits was heated under reflux for 72 hours, further quantities of paraformaldehyde (4.5 g on each occasion) being added after 24 hours and 48 hours. After cooling, the resulting mixture was worked up to yield 11.4 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-octyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 170°—172° C (from ethyl acetate).

A suspension of 4.9 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-octyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride and 1 g of 5% palladium-on-carbon in 100 ml of methanol was hydrogenated in the manner described in the second paragraph of part B of Example 1 and the resulting mixture was worked up to yield 3.8 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-octyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 201°—203° C (from *isopropanol*).

1.96 g of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-octyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride were heated with a mixture of 0.2 ml of 70% perchloric acid and 25 ml of acetic anhydride in a manner analogous to that described in the final paragraph of part B of Example 1 and the resulting mixture was worked up to yield 1.25 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-octyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 174°—176° C (from *isopropanol*).

Example 4

A) The preparation of the starting material:

4-(2-Cyclohexyl-acetyl)-1,2-dimethyl-benzene was prepared from 107 g of 2-cyclohexyl-acetyl chloride, 94 g of aluminium chloride and 70 g of *ortho*-xylene in dichloro-methane by a procedure analogous to that described in part A of Example 1.

B) The process:

A mixture of 23.0 g of 4-(2-cyclohexyl-acetyl)-1,2-dimethyl-benzene, 24.4 g of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride, 4.5 g of paraformaldehyde, 0.2 ml of concentrated hydrochloric acid and 50 ml of methylated spirits was heated under reflux for 72 hours, further quantities of paraformaldehyde (4.5 g on each occasion) being added after 24 and 48 hours. After cooling, the resulting mixture was worked up to yield 11.2 g of 2-[2-cyclohexyl-3-(3,4-dimethyl-phenyl)-3-oxo-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 200°—201° C (from ethanol).

A suspension 4.86 g of 2-[2-cyclohexyl-3-(3,4-dimethyl-phenyl)-3-oxo-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride and 1 g of 5% palladium-on-carbon in 200 ml of methanol was hydrogenated in the manner described in the second paragraph of part B of Example 1 and the resulting mixture was worked up to yield 2.6 g of 2-[2-cyclohexyl-3-(3,4-dimethyl-phenyl)-3-hydroxy-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 225°—226° C [from methanol/(ethyl acetate)].

2 g of 2-[2-cyclohexyl-3-(3,4-dimethyl-phenyl)-3-hydroxy-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride were treated with a mixture of 25 ml of acetic anhydride and 0.1 ml of 70% perchloric acid in a manner analogous to that described in the final paragraph of part B of Example 1 and the resulting mixture was worked up to yield 1.1 g of 2-[3-acetoxy-2-cyclohexyl-3-(3,4-dimethyl-phenyl)-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride of melting point 190°—191° C (from *isopropanol*/ether).

Example 5

A) The preparation of the starting material:

2-Butyryl-5,6,7,8-tetrahydro-naphthalene (boiling point 115°—123° C/0.7 mm) was prepared by procedure analogous to that described in part A of Example 1 from 26 g of butyryl chloride, 37.2 g of aluminium chloride and 39.5 g of tetralin in 200 ml of dichloro-methane.

B) The process:

5 A mixture of 20.2 g of 2-butyryl-5,6,7,8-tetrahydro-naphthalene, 24.4 g of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and 4.5 g of paraformaldehyde was heated at reflux for 72 hours in 50 ml of ethanol containing 0.2 ml of concentrated hydrochloric acid. Further quantities of paraformaldehyde (4.5 g each time) were added to the mixture after 24 hours and 48 hours. The mixture was worked up in the manner described in the first paragraph of part B of Example 1 to yield 20.1 g of 2-[2-ethyl-3-[5,6,7,8-tetrahydro-naphthyl-(2)]-3-oxo-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride as a white solid of melting point 197°—198° C.

10 1 g of sodium borohydride was added to a solution of 2.3 g of 2-[2-ethyl-3-[5,6,7,8 - tetrahydro - naphthyl - (2)] - 3 - oxo - propyl] - 6,7 - dimethoxy - 1-methyl - 1,2,3,4-tetrahydro-isoquinoline hydrochloride in 50 ml of ethanol and 5 ml of 2-N sodium hydroxide. The mixture was stirred for 6 hours, evaporated under reduced pressure to remove the ethanol and the residue was partitioned between dichloromethane and water. The organic phase was separated, washed with water and dried over anhydrous sodium sulphate. The sodium sulphate was removed by filtration, the filtrate evaporated to dryness and the residue dissolved in ethanol. The ethanolic solution was then treated with ethanolic hydrogen chloride and the resulting solution was evaporated under reduced pressure to give a white solid which was recrystallised from ethyl acetate to yield 2-[2-ethyl-3-[5,6,7,8-tetrahydro-naphthyl-(2)]-3-hydroxy-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride of melting point 178°—182° C.

Example 6

25 A) The preparation of the starting material:

3',4'-Dimethyl-propiophenone (boiling point=135°—140° C/15 mm) was prepared from propionyl chloride, aluminium chloride and *ortho*-xylene in dichloromethane by a procedure analogous to that described in part A of Example 1.

B) The process:

30 Reaction of 3',4'-dimethyl-propiophenone with 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and paraformaldehyde in a manner analogous to that described in the first paragraph of part B of Example 1 gave 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-propyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride of melting point 183° C (from isopropanol).

35 Hydrogenation of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-propyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the presence of platinum oxide in a manner analogous to that described in the second paragraph of part B of Example 1 gave 6,7-dimethoxy-2-[2-methyl-3-(3,4-dimethyl-phenyl)-3-hydroxy-propyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline, which was isolated in the form of its hydrochloride of melting point 210°—212° C (from methanol).

40 Acetylation of 6,7-dimethoxy-2-[2-methyl-3-(3,4-dimethyl-phenyl)-3-hydroxy-propyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride with acetic anhydride in a manner analogous to that described in the final paragraph of part B of Example 1 gave 2-[3-acetoxy-2-methyl-3-(3,4-dimethyl-phenyl)-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride and crystallized from ethyl acetate to give a white crystalline solid of melting point 157°—160° C.

Example 7

50 A) The preparation of the starting material:

1,2-Dimethyl-4-hexanoyl-benzene (boiling point=167°—168° C/9 mm) was prepared from caproyl chloride, aluminium chloride and *ortho*-xylene in dichloromethane by a procedure analogous to that described in part A of Example 1.

B) The process:

55 Reaction of 1,2-dimethyl-4-hexanoyl-benzene with 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and paraformaldehyde in a manner analogous to that described in the first paragraph of part B of Example 1 gave 6,7-dimethoxy - 2 - [2 - (3,4 - dimethyl - benzoyl) - hexyl] - 1 - methyl - 1,2,3,4 - tetrahydro-isoquinoline which was isolated in the form of its hydrochloride melting at 184°—186° C after recrystallization from methanol/(ethyl acetate).

60 Hydrogenation of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-hexyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the presence of palladium-on-carbon in a manner analogous to that described in the second paragraph of part B of Example

1 give 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-hexyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline in the form of its hydrochloride melting at 247°—248° C after recrystallization from methanol/(ethyl acetate).

- 5 Acetylation of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-hexyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in a manner analogous to that described in the final paragraph of part B of Example 1 gave 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-hexyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride and crystallized from methanol/(ethyl acetate) to give a crystalline solid of melting point 158°—160° C.

10 Example 8 10

A) The preparation of the starting material:

1,2-Dimethyl-4-isovaleryl-benzene (boiling point=150°—160° C/15 mm) was prepared from isovaleryl chloride, aluminium chloride and *ortho*-xylene in dichloromethane by a procedure analogous to that described in part A of Example 1.

15 B) The process: 15

Reaction of 1,2-dimethyl-4-isovaleryl-benzene with 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and paraformaldehyde in a manner analogous to that described in the first paragraph of part B of Example 1 gave 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-3-methyl-butyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride melting at 213°—215° C after recrystallization from methanol/(ethyl acetate).

20 Hydrogenation of 6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-3-methyl-butyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the presence of palladium-on-carbon in a manner analogous to that described in the second paragraph of part B of Example 1 gave 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-3-methyl-butyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline in the form of its hydrochloride melting at 240°—241° C after recrystallization from methanol/(ethyl acetate).

25 Acetylation of 6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-3-methyl-butyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in a manner analogous to that described in the final paragraph part B of Example 1 gave 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-3-methyl-butyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride of melting point 219°—220° C (from methanol).

35 Example 9 35

A) The preparation of the starting material:

5-Isocaproyl-indane (boiling point=137°—140° C/0.1 mm) was prepared from iso-caproyl chloride, aluminium chloride and indane in dichloro-methane by a procedure analogous to that described in part A of Example 1.

40 B) The process: 40

Reaction of 5-isocaproyl-indane with 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and paraformaldehyde in a manner analogous to that described in the first paragraph of part B of Example 1 gave 6,7-dimethoxy-2-[2-(5-indanecarbonyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride of melting point 163°—164° C (from isopropanol).

45 Hydrogenation of 6,7-dimethoxy-2-[2-(5-indane-carbonyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the presence of palladium-on-carbon gave 6,7-dimethoxy-2-[3-hydroxy-3-(5-indanyl)-2-isobutyl-propyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline in the form of its hydrochloride melting at 239°—240° C after recrystallization from methanol/(ethyl acetate).

50 Example 10 50

Reaction of 1,2-dimethyl-4-isocaproyl-benzene with (—)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride and paraformaldehyde in a manner analogous to that described in the first paragraph of part B of Example 1 gave (+)-6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline which was isolated in the form of its hydrochloride; melting point=128°—129° C, $[\alpha]_{436}^{20} = +20.2^\circ$ (c=0.5 in methanol).

Hydrogenation of (+)-6,7-dimethoxy-2-[2-(3,4-dimethyl-benzoyl)-4-methyl-

pentyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride in the presence of palladium-on-carbon in a manner analogous to that described in the second paragraph of part B of Example 1 gave (+)-6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* as its hydrochloride of melting point 230°—231° C; $[\alpha]_{D}^{20} = +135^{\circ}$ (c=0.5 in methanol).

The following Examples illustrate pharmaceutical compositions containing the tetrahydro-*isoquinoline* derivatives provided by the invention:

Example A

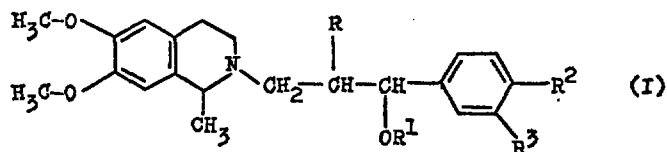
15 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-octyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride, 102 g of corn starch, 30 g of hydrated silica and 3 g of magnesium silicate were thoroughly mixed and the mass obtained was pressed into tablets each weighing 150 mg.

Example B

3 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-octyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* hydrochloride, 44 g of lactose, 48 g of corn starch and 5 g of talc were thoroughly mixed and the mass obtained was pressed into tablets each weighing 100 mg.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein R represents a lower-alkyl or lower-*cyclo*alkyl group, R¹ represents a hydrogen atom or a lower-alkanoyl group and R² and R³ each represent a lower-alkyl group or R² and R³ together represent a trimethylene, tetramethylene or butadien-(1,3)-ylene-(1,4) group, and acid addition salts thereof.

2) Compounds of formula I in claim 1, wherein R² and R³ each represent a lower-alkyl group, and acid addition salts thereof.

3) 6,7 - Dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - 4 - methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

4) 6,7 - Dimethoxy - 2 - [2 - (α - acetoxy - 3,4 - dimethyl - benzyl) - 4 - methyl-pentyl] - 1 - methyl - 1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

5) 6,7 - Dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - octyl] - 1-methyl-1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

6) 2 - [2 - (α - Acetoxy - 2,4 - dimethyl - benzyl) - octyl] - 6,7 - dimethoxy - 1-methyl - 1,2,3,4 - tetrahydro - *isoquinoline* and acid addition salts thereof.

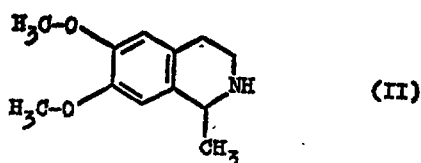
7) 2 - [2 - *Cyclohexyl* - 3 - (3,4 - dimethyl - phenyl) - 3 - hydroxy - propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

8) 2 - [3 - Acetoxy - 2 - *cyclohexyl* - 3 - (3,4 - dimethyl-phenyl) - propyl] - 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

9) 2 - [2 - Ethyl - 3 - [5,6,7,8 - tetrahydro - naphthyl - (2)] - 3 - hydroxy-propyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-*isoquinoline* and acid addition salts thereof.

10) A pharmaceutical composition comprising a compound as set forth in any one of claims 1 to 9 inclusive or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

11) A process for the manufacture of the tetrahydro-*isoquinoline* derivatives claimed in claim 1, which process comprises reacting a compound of the formula



or an acid addition salt thereof, with formaldehyde and a ketone of the general formula



pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride in the presence of palladium-on-carbon in a manner analogous to that described in the second paragraph of part B of Example 1 gave (+)-6,7-dimethoxy-2-[2-(3,4-dimethyl- α -hydroxy-benzyl)-4-methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline as its hydrochloride of melting point 230°—231° C; $[\alpha]_{D}^{20} = +135^{\circ}$ ($c=0.5$ in methanol).

The following Examples illustrate pharmaceutical compositions containing the tetrahydro-isoquinoline derivatives provided by the invention:

Example A

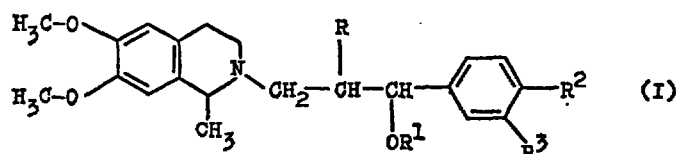
15 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-octyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride, 102 g of corn starch, 30 g of hydrated silica and 3 g of magnesium silicate were thoroughly mixed and the mass obtained was pressed into tablets each weighing 150 mg.

Example B

3 g of 2-[2-(α -acetoxy-3,4-dimethyl-benzyl)-octyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride, 44 g of lactose, 48 g of corn starch and 5 g of talc were thoroughly mixed and the mass obtained was pressed into tablets each weighing 100 mg.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein R represents a lower-alkyl or lower-cycloalkyl group, R¹ represents a hydrogen atom or a lower-alkanoyl group and R² and R³ each represent a lower-alkyl group or R² and R³ together represent a trimethylene, tetramethylene or butadien-(1,3)-ylene-(1,4) group, and acid addition salts thereof.

2) Compounds of formula I in claim 1, wherein R² and R³ each represent a lower-alkyl group, and acid addition salts thereof.

3) 6,7 - Dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - 4 - methyl-pentyl]-1-methyl-1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

4) 6,7 - Dimethoxy - 2 - [2 - (α - acetoxy - 3,4 - dimethyl - benzyl) - 4 - methyl-pentyl] - 1 - methyl - 1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

5) 6,7 - Dimethoxy - 2 - [2 - (3,4 - dimethyl - α - hydroxy - benzyl) - octyl] - 1-methyl-1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

6) 2 - [2 - (α - Acetoxy - 2,4 - dimethyl - benzyl) - octyl] - 6,7 - dimethoxy - 1-methyl - 1,2,3,4 - tetrahydro - isoquinoline and acid addition salts thereof.

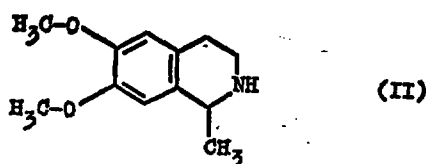
7) 2 - [2 - Cyclohexyl - 3 - (3,4 - dimethyl - phenyl) - 3 - hydroxy - propyl] - 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

8) 2 - [3 - Acetoxy - 2 - cyclohexyl - 3 - (3,4 - dimethyl-phenyl) - propyl] - 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

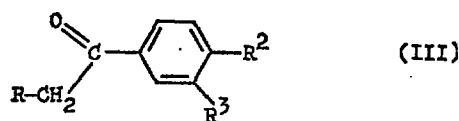
9) 2 - [2 - Ethyl - 3 - [5,6,7,8 - tetrahydro - naphthyl - (2)] - 3 - hydroxy-propyl] - 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline and acid addition salts thereof.

10) A pharmaceutical composition comprising a compound as set forth in any one of claims 1 to 9 inclusive or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

11) A process for the manufacture of the tetrahydroisoquinone derivatives claimed in claim 1, which process comprises reacting a compound of the formula



or an acid addition salt thereof, with formaldehyde and a ketone of the general formula



wherein R, R² and R³ have the significance given in claim 1, by a MANNICH reaction (the reaction being carried out in the presence of an acid when a compound of formula II is used), reducing the reaction product either catalytically or by treatment with an alkali-metal aluminium hydride or alkali-metal borohydride and, if desired, lower-alkanoylating the reduction product and, also if desired, converting the reduction or lower-alkanoylation product into the free base or into an acid addition salt.

12) A process according to claim 11, wherein the formaldehyde is provided in the form of a polymer thereof.

13) A process according to claim 12, wherein said polymer is paraformaldehyde.

14) A process according to claim 11, claim 12 or claim 13, wherein the MANNICH reaction is carried out using an acid addition salt of a compound of formula II.

15) A process according to claim 14, wherein said acid addition salt is a hydrohalide salt.

16) A process according to claim 15, wherein said hydrohalide salt is the hydrochloride.

17) A process according to any one of claims 11 to 16 inclusive, wherein the catalytic reduction of the reaction product is carried out using a platinum or palladium catalyst.

18) A process according to claim 17, wherein an alkanol containing from 1 to 4 carbon atoms is used as a solvent for the catalytic reduction.

19) A process according to any one of claims 11 to 16 inclusive, wherein lithium aluminium hydride is used as the alkali-metal aluminium hydride.

20) A process according to any one of claims 11 to 16 inclusive, wherein sodium borohydride is used as the alkali-metal borohydride.

21) A process according to any one of claims 11 to 20 inclusive, wherein the lower-alkanoylation is carried out using a lower-alkanoyl halide or an anhydride of an alkanic acid containing up to 6 carbon atoms.

22) A process according to claim 21, wherein the lower-alkanoylation is carried out using an anhydride of an alkanic acid containing up to 6 carbon atoms in the presence of a catalytic amount of a strong acid as a lower alkanoylation catalyst.

23) A process according to claim 22, wherein said strong acid is perchloric acid.

24) A process according to claim 11, wherein a ketone of formula III in which R² and R³ each represent a lower-alkyl group is used as the starting material.

25) A process according to claim 11, wherein 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride is reacted with 1,2-dimethyl-4-isocaproyl-benzene, the reaction product is reduced and, if desired, the reduction product is acetylated.

26) A process according to claim 11, wherein 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride is reacted with 1,2-dimethyl-4-octanoyl-benzene, the reaction product is reduced and, if desired, the reduction product is acetylated.

27) A process according to claim 11, wherein 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride is reacted with 4-(2-cyclohexyl-acetyl)-1,2-dimethyl-benzene, the reaction product is reduced and, if desired, the reduction product is acetylated.

28) A process according to claim 11, wherein 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride is reacted with 2-butyryl-5,6,7,8-tetrahydronaphthalene and the reaction product is reduced.

29) A process for the manufacture of the tetrahydro-isoquinoline derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 10.

30) Tetrahydro-isoquinoline derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 11 to 29 inclusive.



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