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1-(PYRIDYL-LOWER ALKYL)-1,2,3,4-TETRAHYDRO-ISOQUINOLINES

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The present invention concerns polyhydro-isoquinoline compounds. It relates more especially to 1-(pyridyl-lower alkyl) - 2 - R - 1,2,3,4 - tetrahydro-isoquinolines, in which lower alkyl separates the pyridyl group from the 1-position of the isoquinoline nucleus by at least two carbon atoms, and R represents a hydrocarbon radical, salts, N-oxides or quaternary ammonium compounds thereof, as well as procedure for the manufacture of such compounds.

The pyridyl group in the above compounds is represented primarily by 3-pyridyl or 4-pyridyl, as well as 2-pyridyl; these pyridyl radicals are preferably unsubstituted, but may also be substituted by lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy and the like, phenyl, or any other suitable substituent.

Lower alkyl separating the pyridyl group from the 1-position of the isoquinoline nucleus has from two to four, preferably from two to three carbon atoms; it may be represented by lower alkylene having from two to four, preferably from two to three carbon atoms and separating the pyridyl group from the 1-position of the isoquinoline nucleus by at least two carbon atoms, e.g. 1,2-ethylene, 1-methyl-1,2-ethylene, 2-methyl-1,2-ethylene, 1,3-propylene, 1-methyl-1,3-propylene, 1,4-butylene and the like.

The radical R attached to the nitrogen atom of the isoquinoline nucleus stands primarily for an aliphatic radical, especially lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl and the like, as well as lower alkenyl, e.g. allyl, 2-methyl-allyl and the like. It may also stand for a cycloaliphatic radical, such as cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, a cycloaliphatic-aliphatic radical, such as cycloalkyl-lower alkyl, e.g. cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclohexylethyl and the like, a carbocyclic aryl-aliphatic radical, such as phenyl-lower alkyl, e.g. benzyl, 1-phenylethyl, 2-phenylethyl and the like.

The 1,2,3,4-tetrahydro-isoquinoline nucleus may contain other substituents. For example, the 2-position, or more especially the 3-position may be substituted by lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like. The hexacyclic carbocyclic aromatic portion of the 1,2,3,4-tetrahydro-isoquinoline represents a 1,2-phenylene radical, which may be substituted by one or more than one of them or of different substituents, such as lower alkyl, e.g. methyl, ethyl, isopropyl, n-butyl and the like, hydroxyl, etherified hydroxyl, such as lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, phenyl-lower alkoxy, e.g. benzyloxy and the like, or lower alkylenedioxy, e.g. methylenedioxy and the like, esterified hydroxyl, such as halogeno, e.g. fluoro, chloro, bromo and the like, lower alkanoyloxy, e.g. acetyloxy, propionyloxy and the like, trifluoromethyl, nitro, amino, such as N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino and the like, or any other suitable substituent. A substituted 1,2-phenylene radical may therefore be represented, for example, by lower alkyl-1,2-phenylene, e.g. methyl-1,2-phenylene (such as 4-methyl-1,2-phenylene, 4,5-dimethyl-1,2-phenylene and the like), ethyl-1,2-phenylene (such as 4-ethyl-1,2-phenylene and the like), n-propyl-1,2-phenylene (such as 4-propyl-1,2-phenylene and the like), isopropyl-1,2-phenylene (such as 3-isopropyl-1,2-phenylene and the like), or any other analogous lower alkyl-1,2-phenylene radicals, hydroxy-1,2-phenylene (such as 3-hydroxy-1,2-phenylene, 4,5-dihydroxy-1,2-phenylene and the like), lower alkoxy-1,2-phenylene, e.g. methoxy-1,2-phenylene (such as 4-methoxy-1,2-phenylene, 5-methoxy-1,2-phenylene, 4,5-dimethoxy-1,2-phenylene and the like), ethoxy-1,2-phenylene (such as 4-ethoxy-1,2-phenylene, 5-ethoxy-1,2-phenylene, 4,5-diethoxy-1,2-phenylene and the like), n-propyloxy-1,2-phenylene (such as 4-n-propyloxy-1,2-phenylene and the like), isopropyloxy-1,2-phenylene (such as 4-isopropyloxy-1,2-phenylene and the like), n-butyloxy-1,2-phenylene (such as 5-n-butyloxy-1,2-phenylene and the like), or any other analogous lower alkoxy-1,2-phenylene radical, lower alkylenedioxy - 1,2 - phenylene, e.g. methylenedioxy-1,2-phenylene (such as 4,5-methylenedioxy - 1,2 - phenylene and the like) or any other analogous lower alkylenedioxy-1,2-phenylene radical, halogeno-1,2-phenylene, e.g. fluoro-1,2-phenylene (such as 4-fluoro-1,2-phenylene and the like), chloro-1,2-phenylene (such as 4-chloro-1,2-phenylene, 4,5-dichloro-1,2-phenylene, and the like), bromo-1,2-phenylene (such as 4-bromo-1,2-phenylene, 6-bromo-1,2-phenylene and the like) or any other analogous halogeno-1,2-phenylene radical, trifluoromethyl-1,2-ethylene (such 4-trifluoromethyl-1,2-phenylene and the like), nitro-1,2-phenylene (such as 4-nitro-1,2-phenylene and the like), N,N-di-lower alkyl-1,2-phenylene, e.g. N,N - dimethylamino-1,2-phenylene (such as 4-N,N-dimethylamino-1,2-phenylene and the like), N-ethyl-N-methyl-amino-1,2-phenylene (such as 5-N-ethyl-N-methylamino-1,2-phenylene and the like), N,N-diethylamino-1,2-phenylene (such as 4-N,N-diethylamino-1,2-phenylene and the like), or any other suitably substituted 1,2-phenylene radical.

Salts of the new compounds of this invention are particularly non-toxic, pharmacologically and therapeutically acceptable, acid addition salts, for example, those with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, those with organic carboxylic acids, e.g. formic, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, ascorbic, hydroxymaleic, dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, cinnamic, mandelic, salicyclic, 4-aminosalicyclic, 2-phenoxybenzoic, 2-acetoxy-benzoic acid and the like, or those with organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, ethane 1,2-disulfonic acid, benzene sulfonic, p-toluene sulfonic acid and the like. Salts which may be prepared primarily for identification purposes, are, for example, those with acidic organic nitro compounds, e.g. picric, picrolonic, flavianic acid and the like, or metal complex acids, e.g. phosphotungstic, phosphomolybdic, chloroplatinic, Reinecke acid and the like. Mono- or poly-salts may be formed depending on the conditions used for the salt formation.

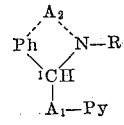
Also included within the scope of the present invention are the N-oxides of the afore-mentioned compounds, as well as the acid addition salts of such N-oxides.

Quaternary ammonium compounds of the compounds of this invention may be mono-or di-quaternary ammonium compounds depending on the conditions for the quaternization reaction. Quaternary ammonium compounds are particularly the lower alkyl, e.g. methyl, ethyl, N-propyl, isopropyl and the like, or phenyl lower alkyl, e.g. benzyl, 1-phenylethyl, 2-phenylethyl and the like, quaternary ammonium halides, e.g. chloride, bromide, iodide and the like, lower alkyl sulfates, e.g. methyl sulfate and the like, or sulfonates, e.g. methane sulfonate, ethane sulfonate, 2-hydroxy-ethane sulfonate, p-toluene sulfonate and the like. Also included as quaternary ammonium compounds are the corresponding quaternary ammonium hydroxides, and the salts of such hydroxides with acids, particularly with the organic carboxylic acids mentioned herein above.

Depending on the number of asymmetric carbon atoms the chromane compounds of this invention may be ob-

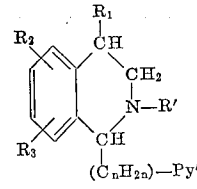
tained as mixtures of racemates, racemates or antipodes, the separation and resolution of which will be discussed and illustrated herein below.

The compounds of this invention may, therefore, be represented by the formula:



in which Py represents a pyridyl radical having the above given meaning, A_1 stands for an alkylene radical having from two to four, preferably from two to three carbon atoms separating the pyridyl radical from the 1-position of the isoquinoline nucleus by at least two carbon atoms, R stands for a hydrocarbon radical, A_2 represents a 1,2-ethylene radical, which may contain lower alkyl groups as substituents, and Ph stands for a 1,2-phenylene radical, which may be substituted as shown hereinbefore, salts, N-oxides or quaternary ammonium derivatives thereof.

The compounds of this invention exert analgesic properties, and can be used as analgetic agents to raise the threshold of pain and alleviate symptoms connected with acute pain, for example, in connection with surgery and the like, or chronic pain. Compounds with particularly outstanding analgesic properties are those of the formula:



in which Py' represents pyridyl, e.g. 3-pyridyl, 4-pyridyl and the like, the letter *n* stands for one of the whole members 2 and 3, the group of the formula—(C_nH_{2n})— separates the pyridyl group Py' from the 1-position of the isoquinoline nucleus by at least two carbon atoms, R' stands for lower alkyl, R_1 represents hydrogen or lower alkyl, particularly methyl, and each of the groups R_2 and R_3 stands for hydrogen, hydroxyl, lower alkoxy, e.g. methoxy, ethoxy and the like, phenyl-lower alkoxy, e.g. benzyloxy and the like, halogeno, e.g. fluoro, chloro, bromo and the like, or, when taken together, for lower alkylenedioxy, e.g. methylenedioxy and the like, or the pharmacologically acceptable, non-toxic acid addition salts of such compounds. These compounds are represented by the 6,7-dimethoxy-2-lower alkyl-1-(2-pyridylethyl)-1,2,3,4-tetrahydro-isoquinolines, in which lower alkyl stands for methyl, ethyl, n-propyl, isopropyl and the like, and pyridyl represents primarily 3-pyridyl or 4-pyridyl, or pharmacologically acceptable, non-toxic acid addition salts thereof.

The new compounds of this invention may be used as medicaments in the form of pharmaceutical preparations, which contain the new 1,2,3,4-tetrahydro-isoquinoline compounds in admixture with a pharmaceutical organic or inorganic, solid or liquid vehicle suitable for enteral, e.g. oral, or parenteral administration. For making up the preparations there may be used substances, which do not react with the new compounds, such as water, gelatine, lactose, starches, lactic acid, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalklene glycols, or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as capsules, tablets or dragees, or in liquid form, for example as solutions, suspensions or emulsions. If desired, they may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying agents and the like, salts for varying the osmotic pressure, buffers, etc. They may also contain, in combination, other therapeutically useful substances.

The compounds of the present invention may be prepared according to methods known per se, for example, by introducing into a 1-(pyridyl-lower alkyl)-1,2,3,4-tetrahydro-isoquinoline or a salt thereof, the group R having the previously given meaning, and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting a free compound into a salt, an N-oxide, a salt of an N-oxide or a quaternary ammonium compound thereof, and/or, if desired, separating a mixture of isomers into the single isomers.

The introduction of the group R may be carried out according to known methods, for example, by treating the starting material with a one molar equivalent of a reactive ester of an alcohol of the formula R—OH, in which R has the previously given meaning. A reactive ester of such alcohol is particularly one formed with a strong inorganic acid, e.g. hydrochloric, hydrobromic, hydrodic, sulfuric acid and the like, or a strong organic sulfonic acid, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, p-toluene sulfonic acid and the like; reactive esters are therefore, for example, the lower alkyl halides, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl chloride, bromide or iodide and the like, phenyl-lower alkyl halides, e.g. benzyl, 1-phenylethyl, 2-phenylethyl chloride or bromide and the like, di-lower alkyl sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, lower alkyl lower alkane sulfonates, e.g. methyl or ethyl methane sulfonate or ethane sulfonate and the like, lower alkyl p-toluene sulfonates, e.g. methyl p-toluene sulfonate and the like, cycloalkyl p-toluene sulfonates, e.g. cyclopentyl p-toluene sulfonate, cyclohexyl p-toluene sulfonate and the like, or any other suitable reactive ester. The reactive ester is preferably reacted with the starting material in the form of a metal compound, particularly of an alkali metal, e.g. lithium, sodium and the like compound; the latter is prepared by treatment with a suitable reagent capable of forming such compound, for example, with an alkali metal hydride, e.g. sodium hydride and the like, or any other equivalent reagent. The formation of the metal compound, as well as the treatment of the latter with the reactive ester is preferably carried out in the presence of a suitable inert solvent, if necessary, while cooling or at an elevated temperature and/or in a closed vessel and/or in the atmosphere of an inert gas, e.g. nitrogen.

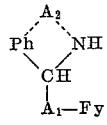
The introduction of the substituent R may also be performed by acylating the starting material, for example, by treating it with a reactive functional derivative of an organic carboxylic acid, for example, a lower alkyl, e.g. methyl, ethyl and the like, ester or a halide, e.g. chloride and the like, of such carboxylic acid, or with the carboxylic acid itself in the presence of a suitable reagent, e.g. dicyclohexyl carbodiimide and the like, and converting the carbonyl portion of the resulting amide into a methylene group by reduction with a hydride, for example, with a light metalhydride, particularly an aluminum hydride, e.g. lithium aluminum hydride and the like, or with catalytically activated hydrogen, for example, hydrogen in the presence of a copper chromate catalyst, or with an electrolytic hydrogenation procedure. The above reactions are carried out according to known methods.

A methyl group represented by R may also be introduced according to other methods, for example, by treating the 1-(pyridyl-lower alkyl)-1,2,3,4-tetrahydro-isoquinoline starting material with formaldehyde in the presence of a reducing reagent, e.g. formic acid, hydrogen in the presence of a hydrogenation catalyst, e.g. palladium and the like, or any other suitable reducing reagent; this methylation reaction is carried out according to known methods.

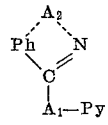
The starting material used in the above reaction may be prepared, for example, by removing in a 1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinoline compound the double bond extending from the 1-position, and, if desired, carrying out the optional steps. The removal of the double bond may be carried out according to known reduc-

tion methods, for example, by treatment with a metal borohydride, e.g. sodium borohydride and the like, if necessary, in the presence of an activator, e.g. aluminum chloride and the like, or with catalytically activated hydrogen, for example, hydrogen in the presence of a noble metal catalyst, such as a palladium catalyst, a platinum catalyst and the like, or any other suitable reagent.

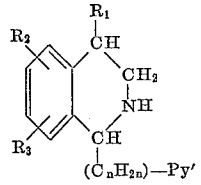
The 1-(pyridyl-lower alkyl)-1,2,3,4-tetrahydro-isoquinoline compounds, which compounds are used as the starting materials in the process for the preparation of the N-substituted isoquinolines, and the 1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinoline compounds, which are used in the preparation of the former, and in which compounds lower alkyl separates the pyridyl radical from the 1-position of the isoquinoline nucleus by at least two carbon atoms, and the salts of these compounds are new and intended to be included within the scope of this invention. They may be represented by the formulae:



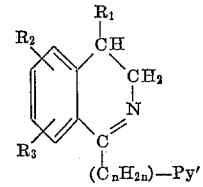
and



in which Py, A_1, A_2 and Ph have the previously given meaning, or the salts, N-oxides and quaternary ammonium compounds thereof. A preferred group of 1-(pyridyl-lower alkyl)-1,2,3,4-tetrahydro-isoquinolines is represented by the formula:

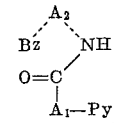


in which Py', n, R_1, R_2 and R_3 have the previously given meaning, and the group $-(C_nH_{2n})-$ separates the pyridyl group Py' from the 1-position of the isoquinoline nucleus by at least two carbon atoms, and salts thereof, and is illustrated by the 6,7-dimethoxy-1-(2-pyridylethyl)-1,2,3,4-tetrahydro-isoquinolines and the acid addition salts thereof. A preferred group of 1-pyridyl-lower alkyl-3,4-dihydro-isoquinoline intermediates are those of the formula:



in which Py', n, R_1, R_2 and R_3 have the previously given meaning, and the group $-(C_nH_{2n})-$ separates the pyridyl group Py' from the 1-position of the isoquinoline nucleus by at least two carbon atoms, and the acid addition salts thereof; these compounds are illustrated by the 6,7-dimethoxy-1-(pyridyl - lower alkyl)-3,4-dihydro-isoquinolines and the acid addition salts thereof. Whereas the 1-(pyridyl-lower alkyl)-1,2,3,4-tetrahydro-isoquinolines, in which the nitrogen atom of the isoquinoline nucleus is unsubstituted have no appreciable pharmacological activity and are used as intermediates only, the 1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinolines, particularly those having the previously shown formulae, and particularly the 6,7-dimethoxy-1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinolines, and the pharmacologically and therapeutically acceptable, non-toxic acid addition salts thereof, show analgesic properties and can be used as analgetic agents, for example, as shown hereinbefore.

The above 1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinoline compounds, salts, N-oxides and quaternary ammonium compounds thereof, may be prepared for example, by treating an N-(pyridyl-lower alkyl-carbonyl)-2-phenylethyl-amine, particularly a compound of the formula:

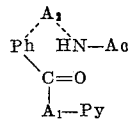


in which Py, A_1 and A_2 have the previously given meaning, and Bz stands for a phenyl radical, in which at least one of the o-positions is unsubstituted, or a salt of such compound, with a ring closing reagent, and, if desired, carrying out the optional steps.

The above ring closure is performed according to known methods; preferred reagents used in the above procedure are acidic ring closing reagents containing phosphorous, for example, phosphorous oxychloride, phosphorus pentachloride, phosphorus trichloride, phosphorus pentoxide and the like. Ring closure is effected in the absence or presence of a suitable inert solvent, preferably at an elevated temperature, and, if necessary, in a closed vessel and/or in the atmosphere of an inert gas, e.g. nitrogen and the like.

The starting materials used in the above preparation of the intermediates may be prepared according to known methods, for example, by acylating a 2-phenylethylamine with pyridyl-lower alkane carboxylic acid (for example in the presence of a reagent, such as dicyclohexylcarbodiimide and the like), or with a reactive functional derivative, such as lower alkyl, e.g. methyl, ethyl and the like, ester or a halide, e.g. chloride and the like, of such acid; the acylation reaction is performed according to known methods.

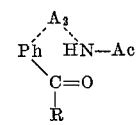
The 1-(pyridyl-lower alkyl)-3,4-dihydro-isoquinolines used as the intermediates in the preparation of the starting materials may also be obtained, for example, by treating an N-acyl-2-[o-(pyridyl-lower alkyl-carbonyl)-phenyl]-ethylamine, particularly a compound of the formula:



in which Py, A_1, A_2 and Ph have the previously given meaning, and Ac stands for the acyl radical of an organic carboxylic acid, or salt thereof, with a strong acid, and if desired, carrying out the optional steps.

The acyl group, particularly the group Ac in the above formula representing the intermediates, is preferably the radical of an aliphatic carboxylic acid, such as a lower alkanoic acid, e.g. acetic, propionic acid and the like, a carbocyclic aryl carboxylic acid, such as a monocyclic carbocyclic aryl carboxylic acid, e.g. benzoic acid and the like, or any other suitable carboxylic acid. Ring closure is achieved by treatment with a strong acid, especially a strong mineral acid, e.g. hydrochloric, sulfuric acid and the like, if necessary, at an elevated temperature, and/or in the presence of an additional inert diluent.

The starting materials used in the above preparation of the intermediates may be manufactured according to known methods, for example, by reacting an N-acyl-2-(O-lower alkanoyl-phenyl)-ethylamine, particularly a compound of the formula:



in which Ph, A_2 and Ac have the previously given meaning, and R stands for lower alkyl, particularly methyl, with a pyridyl carboxaldehyde or a pyridyl-lower alkane carboxaldehyde, if necessary, in the presence of a Claisen condensation reagent, such as an alkali metal lower alkanolate, e.g. sodium methanolate and the like, and removing in a resulting N-acyl-2-[o-(pyridyl-lower alkenyl-carbonyl)-phenyl]-ethyl-amine compound the carbon-carbon double bond, for example by treatment with hydrogen in the presence of a suitable catalyst, e.g. a palladium catalyst and the like, to form the desired starting material.

The 1-(pyridyl-lower alkyl)-2-R-1,2,3,4-tetrahydroisoquinolines, in which R represents a hydrocarbon radical, and the salts, N-oxides or quaternary ammonium compounds thereof, may also be prepared by removing in a 1-(pyridyl-lower alkyl)-2-R-1,2-dihydro-isoquinoline or a salt thereof the double bond extending from the 3-position, and, if desired, carrying out the optional steps.

The removal of the double bond may be carried out according to known reduction methods, for example, by treatment with catalytically activated hydrogen, e.g. hydrogen in the presence of a metal, e.g. platinum, palladium and the like, catalyst, preferably in solution with an inert diluent.

The starting materials used in the above procedure may be prepared, for example, by reacting an 2-R-isoquinolinium compound, in which R has the previously given meaning, with a pyridyl-lower alkyl metal compound capable of introducing the desired pyridyl-lower alkyl radical into the 1-position of the isoquinolinium nucleus. Such reagent is, for example, a pyridyl-lower alkyl-Grignard reagent, such as a pyridyl-lower alkyl magnesium halide, e.g. pyridyl-lower alkyl magnesium chloride and the like; the reaction as carried out according to known methods.

The compounds of this invention may be obtained in the form of the free bases or as the salts thereof. A salt may be converted into the free base, for example, by treatment with an alkaline reagent, such as an alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, an alkali metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, ammonia, or any other suitable alkaline reagent, as well as, for example, an anion exchange resin. A free base may be converted into a pharmacologically acceptable acid addition salt by reacting the former with one of the organic acids mentioned hereinbefore. The salt-forming reaction may be carried out, for example, by treating a solution of the free base in an inert solvent or solvent mixture with the acid or a solution thereof and isolating the desired salt. The salts may also be obtained as the hemihydrates, monohydrates, sesquihydrates or polyhydrates depending on the conditions used in the formation of the salts. Mono- or bis-salts may be formed depending on the conditions used in the procedure for the preparation of the salts.

N-oxides of the compounds of the present invention may be prepared, for example, by treating a solution of the resulting compound containing a tertiary nitrogen atom or a salt thereof in an inert solvent with an N-oxidizing reagent. Such reagents are, for example, ozone, hydrogen peroxide, inorganic peracids, e.g. persulfuric acid and the like, organic persulfonic acids, e.g. p-toluene persulfonic acid and the like, or primarily organic percarboxylic acids, e.g. peracetic acid, perbenzoic acid, monoperphthalic acid and the like. The N-oxides may be obtained in the form of the free bases or the acid addition salts thereof; N-oxide free bases may be converted into their therapeutically acceptable acid addition salts or the salts may be converted into the free N-oxide bases according to the previously described procedures. Mono- or di-N-oxides may be obtained depending on the conditions used for the preparation of the N-oxides.

The quaternary ammonium compounds of the compounds of this invention may be obtained, for example, by reacting the tertiary compound and a strong inorganic or organic acid, such as a mineral acid, e.g. hydrochloric, hydrobromic, hydriodic, sulfuric acid and the like, or a strong organic acid, e.g. methane sulfonic, ethane sulfonic, 2-hydroxy-ethane sulfonic, p-toluene sulfonic acid and the like. Such esters are specifically lower alkyl halides, e.g. methyl, ethyl, n-propyl or isopropyl chloride, bromide, iodide and the like, di-lower alkyl sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, lower alkyl lower alkane sulfonates, e.g. methyl or ethyl methane sulfonate or ethane sulfonate and the like, lower alkyl hydroxy-lower alkane sulfonate, e.g. methyl or ethyl 2-hydroxy-ethane sulfonate and the like, or lower alkyl carbocyclic aryl sulfonate, e.g. methyl p-toluene sulfonate and the like, or the corresponding esters of phenyl-lower alkanols, e.g. benzyl alcohol and the like. The quaternizing reactions may be performed in the absence or presence of a solvent, under cooling, at room temperature or at an elevated temperature, at atmospheric pressure or in a closed vessel under pressure, and, if desired, in the atmosphere of an inert gas, e.g. nitrogen.

Resulting quaternary ammonium compounds may be converted into the corresponding quaternary ammonium hydroxides, for example, by reacting a quaternary ammonium halide with silver oxide or a quaternary ammonium sulfate with barium hydroxide, by treating a quaternary ammonium salt with an anion exchanger, or by electro-dialysis. From a resulting quaternary ammonium hydroxide there may be obtained quaternary ammonium salts by reacting the base with acids, for example, those used for the preparation of acid addition salts. A quaternary ammonium compound may also be converted directly into another quaternary ammonium salt without the formation of an intermediate quaternary ammonium hydroxide; for example a quaternary ammonium iodide may be reacted with freshly prepared silver chloride to yield the quaternary ammonium chloride, or a quaternary ammonium iodide may be converted into the corresponding chloride by treatment with hydrochloric acid in anhydrous methanol. Quaternary ammonium compounds may also be isolated as hydrates; depending on the conditions for their formation mono- or bis-quaternary ammonium compounds may be formed.

Resulting racemates may be resolved into the optically active forms, the levo-rotatory l-form and the dextro-rotatory d-form. Such resolution procedure may be carried out according to methods which are suitable for the separation of a racemate. For example, to a solution of the free base of a racemate (a d,l-compound) in a suitable inert solvent or solvent mixture is added one of the optically active forms of an acid, containing an asymmetric carbon atom, or a solution thereof. Especially useful as optically active forms of salt-forming acids, having an asymmetric carbon atom, are the d-tartaric acid (L-tartaric acid) and the l-tartaric acid (D-tartaric acid); the optically active forms of di-benzoyl tartaric, di-p-toluyl-tartaric, malic, mandelic, 10-camphor sulfonic acid, quinic acid and the like, may also be used. Salts, which are formed by the optically active forms of the base with the optically active forms of the acid may then be isolated, primarily on the basis of their different solubilities. The free and optically active base may be obtained from a resulting salt according to methods known for the conversion of a salt into a base, for example, as is outlined hereinbefore. An optically active base may be converted into a therapeutically useful acid addition salt with one of the acids mentioned hereinbefore, or may be converted into a quaternary ammonium compound as will be described hereinbefore. The optically active forms may also be isolated by biochemical methods.

This invention also comprises any modification of the process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is (are) carried out. It also includes any new intermediates, which

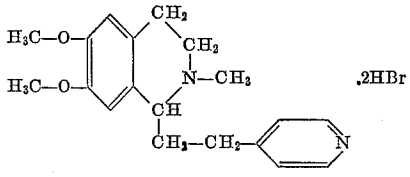
may be formed in one of the procedures outlined hereinbefore.

In the process of this invention such starting materials preferably used with lead to final products mentioned in the beginning as preferred embodiments of the invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

Example 1

A solution of 6.8 g. of 6,7-dimethoxy-1-[2-(4-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline in 250 ml. of ethanol and 125 ml. of a 37 percent aqueous solution of formaldehyde is treated with hydrogen in the presence of palladium on charcoal (10 percent). After on equivalent of hydrogen has been absorbed, the catalyst is filtered off, the solution is concentrated, and the residue is dissolved in benzene. The organic solution is treated with hydrogen bromide gas, the resulting 6,7-dimethoxy-2-methyl - [2 - (4-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline dihydrobromide of the formula:

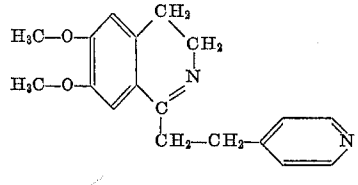


.2HBr

precipitates, is filtered off and recrystallized from ethanol, M.P. 234–236. The picrate obtained from a sample of the original reaction product melts at 172–173°.

The starting material may be prepared as follows: A solution of 40.0 g. of 2-(3,4-dimethoxy-phenyl)-ethylamine and 17.7 g. of ethyl 3-(4-pyridyl)-propionate in 150 ml. of ethylene glycol is refluxed for 48 hours in an atmosphere of nitrogen; small portions of solvent are distilled off during the reaction. The solvent is then evaporated under reduced pressure and the N-3-(4-pyridyl)-propionyl-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-amine is recrystallized from ethyl acetate, M.P. 109–110°; yield: 19.3 g.

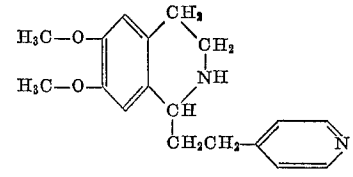
A mixture of 2.0 g. of N-3-(4-pyridyl)-propionyl-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-amine in 15 ml. of phosphorus oxychloride and 20 ml. of benzene is refluxed for two hours in an atmosphere of nitrogen. The reaction mixture is concentrated under reduced pressure, an excess of a 5 percent aqueous solution of sodium hydroxide is added, and the organic material is extracted with methylene chloride; the resulting 6,7-dimethoxy-1-[2-(4-pyridyl)-ethyl]-3,4-dihydro-isoquinoline of the formula:



is recrystallized from a mixture of methylene chloride and heptane, M.P. 115–116°; yield: 1.7 g.

To a solution of 1.3 g. of 6,7-dimethoxy-1-[2-(4-pyridyl)-ethyl]-3,4,dihydro-isoquinoline in 50 ml. of ethanol is added 1.5 g. of sodium borohydride. After 15 hours the reaction mixture is acidified with 5 percent aqueous hydrochloric acid, then made basic with a 5 percent aqueous solution of sodium hydroxide and diluted with water. The organic material extracted with methylene chloride, the organic layers is separated and evaporated, and the residue is crystallized from heptane to

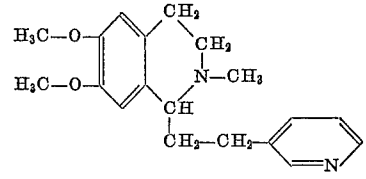
yield 0.95 g. of 6,7-dimethoxy-1-[2-(4-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline of the formula:



which melts at 82°; the picrate melts at 158–160°.

Example 2

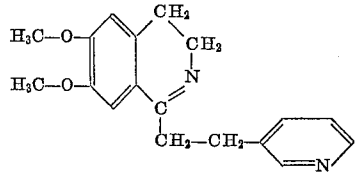
A solution of 5.1 g. of 6,7-dimethoxy-1-[2-(3-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline in 250 ml. of ethanol is treated with 125 ml. of a 37 percent aqueous solution of formaldehyde and hydrogen in the presence of palladium on charcoal (10 percent); the reaction is carried out as described in Example 1 to yield 7.4 g. of 6,7-dimethoxy - 2 - methyl-1-[2-(3-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline of the formula:



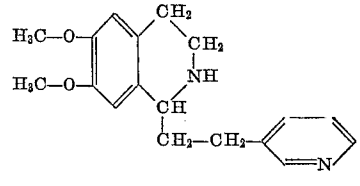
.2HBr

which melts at 225–226° after recrystallization from a mixture of methanol and diethyl ether.

The starting material may be prepared according to the procedure given in Example 1; the N-3-(3-pyridyl)-propionyl - N - [2 - (3,4-dimethoxy-phenyl)-ethyl]-amine melts at 104–105°; the 6,7-dimethoxy-1-[2-(3-pyridyl)-ethyl]-3,4-dihydro-isoquinoline of the formula:



prepared from that starting material, melts at 88–89°, and is converted into the 6,7-dimethoxy-1-[2-(3-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline of the formula:



which melts at 245–246° after recrystallization from methanol, by treatment with sodium borohydride as shown in Example 1.

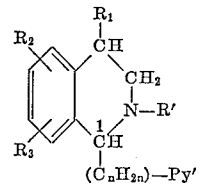
Example 3

A solution of 1.3 g. of 6,7-dimethoxy-2-methyl-1-[2-(4-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline in 10 ml. of methyl iodide is allowed to stand for 20 hours and is then concentrated; the crude dimethiodide of 6,7-dimethoxy - 2 - methyl-1-[2-(4-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline is recrystallized from methanol to yield 1.4 g. of the pure product, which melts at 167–169°.

The dimethiodide of 6,7-dimethoxy-2-methyl-1-[2-(3-pyridyl) - ethyl]-1,2,3,4-tetrahydro-isoquinoline, prepared according to the same procedure melts at 157° after recrystallization from ethanol.

What is claimed is:

1. A member selected from the group consisting of compounds of the formula:



in which Py′ is pyridyl, the letter *n* is one of the whole numbers 2 and 3, the group of the formula $—(C_nH_{2n})—$ separates pyridyl from the 1-position of the isoquinoline nucleus by at least two carbon atoms, R′ is lower alkyl, R_1 is a member selected from the group consisting of hydrogen and lower alkyl, and each of the groups R_2 and R_3 is a member selected from the group consisting of hydrogen, hydroxyl, lower alkoxy, phenyl-lower alkoxy, halogeno, and, when taken together, lower alkylenedioxy, a pharmacologically acceptable, non-toxic acid addition salt thereof and a lower alkyl quaternary ammonium compound thereof.

2. 6,7 - dimethoxy - 2 - lower alkyl-1-[2-(pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

3. A pharmacologically acceptable, non-toxic acid addition salt of 6,7-dimethoxy-2-lower alkyl-1-[2-(pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

4. 6,7 - dimethoxy - 2 - methyl - 1 - [2 - (3 - pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

5. 6,7 - dimethoxy - 2 - methyl - 1 - [2 - (4 - pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

6. A pharmacologically acceptable, non-toxic acid addition salt of 6,7-dimethoxy-2-methyl-1-[2-(3-pyridyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,133,926 May 19, 1964

Martin Eric Kuehne

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 52, for "them" read -- the same --; column 2, line 21, for "(such" read -- (such as --; lines 48 and 49, for "phospotungstic" read -- phosphotungstic --; column 5, lines 19 to 24, for the portion of the formula designated as

$$\begin{array}{c} | \\ A_1\text{-Fy} \end{array} \qquad \text{read} \qquad \begin{array}{c} | \\ A_1\text{-Py} \end{array}$$

column 9, line 4, for "with" read -- which --; line 17, for "on", second occurrence, read -- one --; same column 9, line 68, for "3,4," read -- 3,4- --.

Signed and sealed this 29th day of September 1964.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patent