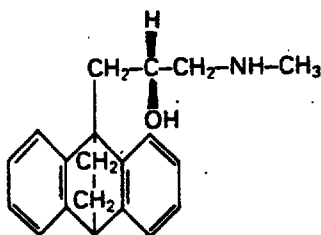


- 1 -

New laevorotatory, basic derivative of 9,10-ethanoanthracene, process for its preparation, and pharmaceutical products containing it

The present invention relates to a new laevorotatory, basic derivative of 9,10-ethanoanthracene and its acid addition salts, to process for the preparation of these substances, and to pharmaceutical products which contain these substances.

The compound according to the invention is R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I



(I)

the (-) antipode of the racemic α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10)-ethanol (sic) which is described in U.S. Patent Specification 4,017,542 and corresponding patents in other countries with Swiss Priority date 23.2.1971. Acid addition salts of the compound of the formula I are, in particular, pharmaceutically acceptable salts, such as the hydrobromide, phosphate, methanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, acetate, lactate, malonate, succinate, fumarate, maleate, malate, tartrate, citrate, benzoate, salicylate, phenylacetate, mandelate or embonate and, especially, the hydrochloride, as well as, quite generally, readily crystallizing salts with optically active acids, in addition to those already mentioned, for example including the (1:1) salt with bis-0,0'-(p-toluoyl)-L-tartaric acid. As a consequence of the close relationships between the free base and its acid addition salts, the base and its acid addition salts are analogously understood to include the acid addition salts and the free base respectively.

R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and its acid addition salts have valuable

pharmacological properties which differ in a surprising manner from those of the known racemate and its acid addition salts. In contrast to the known racemate, they show in animal experiments virtually no reserpine-antagonistic and tetrabenazine-antagonistic activity, nor do they have an inhibitory action on noradrenaline uptake in the rat heart and brain or the noradrenadrenaline (sic) depletion in the rat brain brought about by H77/77 (3-hydroxy-4,~~X~~-dimethylphenethylamine). On the other hand, the compound of the formula I and its acid addition salts have sedative, anti-aggressive and antihistaminic activity of a similar order of magnitude to that of the known racemate. The equieffective doses of the hydrochloride of the compound of the formula I in the potentiation of the narcosis of the mouse brought about by G 29505 [2-(4-allyl-2-methoxyphenoxy)-N,N-diethylacetamide, [W. Theobald and R. Domenjoz, *Arzneimittelforsch.* 9, 285-286 (1959)] which is measured to determine the sedative activity are about one half those of the hydrochloride of the racemate, and thus the compound of the formula I is approximately twice as potent as is the racemate, whereas the equieffective doses on intraperitoneal administration of the hydrochlorides of the compound of the formula I and of the racemate for the fighting (sic) reaction of the male mouse induced by electric foot shock [Tedeschi et al., *J. Pharmacol. Exptl. Therap.* 125, 28-34, (1959)] are approximately the same, and for the antagonism of histamine toxicity in the guineapig, likewise on intraperitoneal administration, the hydrochloride of the racemate is somewhat more effective, with a ED₅₀ of about 0.1 mg/kg, than the hydrochloride of the compound of the formula I, with a ED₅₀ of about 0.25 mg/kg. The hydrochloride of the compound of the formula I showed, in the isolated, electrically stimulated left atrium of reserpinated, that is to say pretreated with reserpine, guineapigs, an approximately identical negative inotropic effect, but on the other hand the negative chronotropic effect on the isolated, spontaneously beating right atrium was clearly weaker than those (sic) of the racemate, and

comparison of the effects of 1 mg/ml on isolated atria of non-reserpinated and reserpinated guineapigs shows that the compound of the formula I has, in contrast to the racemate, no cardiostimulant action at this concentration.

The acute toxicity of the hydrochloride of the compound of the formula I in mice and rats is, on intravenous administration, approximately the same as, and, on oral administration, is somewhat lower than, that of the hydrochloride of the racemate. R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and its pharmaceutically acceptable acid addition salts can be used as active ingredients for medicaments having sedative, antiaggressive, tranquillizing, antihistaminic and antidepressant activity, in particular for the treatment of depressive states of an anxious, dysphoric or irritable slant and of neurovegetative or psychosomatic symptoms with depression and/or anxiety in the background, of the nature of masked depression.

R-(-)- α -[(Methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I and its acid addition salts are prepared according to the invention by

- a) fractionation of racemic α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10)-ethanol and isolation of R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, where appropriate in the form of an acid addition salt, or
- b) reaction of a compound of the formula II



with a compound of the formula III



one of the symbols X_1 and X_2 denoting the amino group and the other denoting a reactive esterified hydroxyl group, and Y_1 denoting a free hydroxyl group, and it also being possible for X_1 together with Y_1 to denote an epoxy group,

- 4 -

and A representing the 9,10-ethanoanthracen-9(10H)-yl radical, or

c) elimination of the radical(s) Z_1 and/or Z_2 in a compound of the formula IV

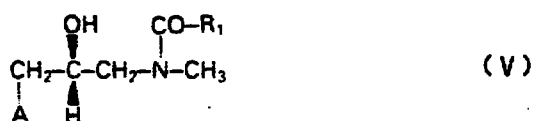


in which at least one of the symbols Z_1 and Z_2 denotes a radical which can be eliminated, and the other optionally denotes hydrogen, or Z_1 and Z_2 together denote a bivalent radical which can be eliminated, and A represents the 9,10-ethanoanthracen-9(10H)-yl radical, or

d) reduction of a compound which differs from the compound of the formula I only in that a carbon atom adjacent to the nitrogen atom in it is connected to the latter by a double bond or is substituted by a hydroxyl group or by an oxo radical, where appropriate together with lower alkoxy, or

e) addition of ethylene onto R-X-[(methylamino)methyl]-9(10H)-anthraceneethanol (sic), or

f) reaction of a compound of the general formula V



in which R_1 denotes an optionally substituted hydrocarbon radical or an optionally substituted heterocyclic radical, and A denotes the 9,10-ethanoanthracen-9(10H)-yl radical, with a strong, oxygen-containing inorganic or organic acid, or with a halide thereof, and hydrolysis of the resulting intermediate and, if desired, conversion of the R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, thus obtained, into an acid addition salt and/or liberation of the base from an acid addition salt obtained.

The fractionation and isolation according to process

- 5 -

a) is carried out in a manner known per se. For example, it is possible to convert the racemate into acid addition salts with optically active salt-forming acids, such as organic carboxylic or sulfonic acids, for example the (D)- and (L)-forms of tartaric acid, bis-O,O'-(p-toluoyl)-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid, quinic acid, lactic acid, glutamic acid or aspartic acid. The mixtures of the corresponding salts which are obtained can be fractionated into the diastereoisomeric salts on the basis of physicochemical differences, for example of solubility or crystallizability, and, where appropriate, the optically active (-) form can be liberated from the salt.

It is also possible to separate the (-) form of the racemate by fractional crystallization from a suitable solvent, where appropriate also from an optically active solvent, or by chromatography, in particular thin-layer chromatography, on an optically active support material.

A reactive esterified hydroxyl group in the compound of the formula II or III is, in particular, a hydroxyl group which is esterified with a strong organic or inorganic acid, especially with a hydrohalic acid, such as hydrochloric, hydrobromic or hydriodic acid, or with an arylsulfonic acid, such as a benzenesulfonic acid which is substituted once, twice or several times by lower alkyl or alkoxy radicals, for example the abovementioned, or by halogen atoms, such as chlorine or bromine atoms, for example p-toluenesulfonic acid or p-bromobenzenesulfonic acid, or with a lower alkane-sulfonic acid, for example methanesulfonic acid, or, especially as X_2 , also a hydroxyl group which is esterified by sulfuric acid or methylsulfuric acid. It is also possible for X_1 together with Y_1 to be in the form of an epoxy bridge.

The reaction according to b) is carried out in a customary manner, preferably in the presence of a solvent and, where appropriate, in the presence of a condensing agent, for example of a basic condensing agent, preferably at elevated temperature and, where appropriate, in a closed vessel under

- 6 -

pressure. An example of a basic condensing agent is an alkali metal hydroxide or carbonate, for example sodium hydroxide or potassium carbonate, or a tertiary amine, for example triethylamine or pyridine.

The radicals Z_1 and Z_2 which can be eliminated in the starting materials of the general formula IV for process c) are, just as are bivalent radicals which are formed by Z_1 and Z_2 together and can be eliminated, radicals which can be eliminated by, for example, solvolysis, in particular hydrolysis, or by reduction, for example hydrogenolysis.

Examples of suitable radicals Z_1 and Z_2 which can be eliminated by solvolysis, in particular hydrolysis, are acyl radicals, such as alkanoyl radicals, especially optionally halogenated, for example, fluorinated, lower alkanoyl radicals, such as the acetyl radical or the trifluoroacetyl radical, furthermore, for example, aroyl and aryl-lower-alkanoyl radicals, such as the benzoyl and phenylacetyl radical, or acyl radicals of hemiesters of carbonic acid, for example lower alkoxy-carbonyl radicals, such as the methoxy-carbonyl, ethoxycarbonyl or tert.-butoxycarbonyl radical, or aralkoxy-carbonyl radicals, such as the benzyloxycarbonyl radical, as well as, for example, silyl radicals, such as the trimethylsilyl radical.

A bivalent radical formed by Z_1 and Z_2 is, for example, a geminal bivalent hydrocarbon radical, in particular a lower alkylidene radical, such as the methylene, ethylidene or 1-methylethylidene radical (isopropyl)-idene radical) (sic), or an aralkylidene radical, such as the benzylidene radical, furthermore, for example, a phosphorylidene group, in particular a lower alkoxyphosphorylidene group, such as the methoxy- or ethoxyphosphorylidene group.

The hydrolytic elimination of Z_1 and/or Z_2 is carried out with hydrolysing agents, for example in the presence of acidic agents such as, for example, dilute mineral acids, such as sulfuric acid or hydrohalic acids, especially hydrochloric acid, or, in the case of acyl radicals, preferably in the presence of basic agents, for example alkali

- 7 -

metal hydroxides, such as sodium hydroxide, in suitable organic or organic-aqueous solvents, in the cold, for example at room temperature, or, preferably, with heating. The hydrolytic elimination of a bivalent radical formed by Z_1 and Z_2 can be carried out analogously.

Radicals Z_1 and Z_2 which can be eliminated by reduction are, for example, 1-aryl-lower-alkyl radicals, such as the benzyl radical, or 1-aryl-lower-alkoxycarbonyl radical (sic), such as the benzyloxycarbonyl radical, all of which can be eliminated by, for example, hydrogenolysis, for example by reduction with catalytically activated hydrogen, such as hydrogen in the presence of a hydrogenation catalyst, such as a palladium or platinum catalyst. It is likewise possible to eliminate by hydrogenolysis aralkylidene radicals formed by Z_1 and Z_2 together, such as the benzylidene radical. However, Z_1 or Z_2 can also be a 2-halogeno-alkoxycarbonyl radical such as, for example, the 2,2,2-trichloroethoxycarbonyl radical or the 2-iodoethoxycarbonyl radical, both of which can be eliminated by reduction. Particularly suitable for the reduction is metallic reduction (so-called nascent hydrogen) such as, for example, the action of metal or metal alloys, as well as amalgams, preferably in the presence of hydrogen-releasing agents, such as carboxylic acids, alcohols or water. Zinc or zinc alloys in acetic acid are preferably used. Furthermore, chromium(II) compounds, such as chromium(II) chloride or chromium(II) acetate, are also suitable. Z_2 can also be an arylsulfonyl group, such as the toluenesulfonyl group, which can be eliminated in a customary manner by reduction with nascent hydrogen, for example by an alkali metal, such as lithium or sodium, in liquid ammonia. The elimination of an arylsulfonyl group can also be carried out with a hydride, for example one of the simple or complex hydrides mentioned below in connection with process c), preferably lithium aluminium hydride, advantageously in the presence of an inert solvent, such as an ether-like organic solvent, for example tetrahydrofuran.

Starting materials for process d) having a double

bond between the nitrogen atom and an adjacent carbon atom are R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and R-X-[(methylinino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol. The compounds substituted by hydroxyl in the position adjacent to the nitrogen atom are R-X-[(hydroxymethylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and R-1-(methylamino)-9,10-ethanoanthracene-9(10H)-propane-1,2-diol. The reduction of the abovementioned 4 compounds can be carried out in a customary manner, preferably using a simple or complex hydride, for example a borane, or a di-light-metal hydride, for example an alkali metal-earth metal hydride, such as sodium borohydride or lithium aluminium hydride, or an alkoxyaluminium hydride or alkoxyborohydride, for example one of those mentioned below.

However, it is also possible to accomplish the reduction as a hydrogenation with hydrogen in the presence of a catalyst, such as a platinum, palladium or nickel catalyst, or of a homogeneous catalyst, for example a complex rhodium compound, such as a rhodium-chloro-triphenyl-phosphine (sic) complex.

If a carbon atom adjacent to the nitrogen atom is substituted by an oxo radical, then the appropriate starting materials are, on the one hand, R-N-methyl-9,10-ethanoanthracene-9(10H)-lactamide and, on the other hand, N-[3-(9,10-ethanoanthracen-9(10H)-yl)-2(R)-hydroxypropyl]-formamide, as well as lower alkyl esters of carbamic acid which are substituted on the nitrogen atom by the same radical, such as the methyl and the ethyl ester. Their reduction can be carried out by the customary processes of amide reduction, for example using a simple or complex hydride, such as a borane, for example diborane, or using a complex di-light-metal hydride, in particular an alkali metal aluminium hydride, such as lithium or sodium aluminium hydride, in an ether-like solvent, such as diethyl ether or tetrahydrofuran, or using an alkali metal alkoxyaluminium hydride or -borohydride, for example sodium dibutoxyaluminium hydride or sodium trimethoxyborohydride, or using an alkaline earth metal aluminium hydride, such as

(241)

- 9 -

magnesium aluminium hydride, or using sodium borohydride in a tertiary amine, such as pyridine or triethylamine, or using aluminium hydride/aluminium chloride.

The introduction of the 9,10-ethano radical according to e) can be carried out in a customary manner, for example by reaction of the said anthracene derivative with ethylene by the Diels-Alder method, advantageously in a suitable solvent, such as an aromatic hydrocarbon, for example benzene or toluene; and at elevated temperature such as, for example, from 5 to 250°C, and/or under pressure, such as, for example, at 2 to 150 at.

Examples of an optionally substituted hydrocarbon radical R₁ in the starting materials of the general formula V for process f) are lower alkyl, such as ethyl, propyl, isopropyl, butyl or tert-butyl (sic) and, especially, methyl, furthermore, for example, phenyl-lower alkyl, such as benzyl or 2-phenylethyl, or phenyl, it being possible in these or other radicals R₁ for, for example, halogen up to atom number 35, lower alkyl, for example methyl, lower alkoxy, for example methoxy or aryloxy, for example phenoxy, to be present as substituents. Examples of heterocyclic radical R₁ are furyl, such as 2-furyl, thienyl, such as 2-thienyl, or pyridinyl, such as 3- or 4-pyridinyl.

The corresponding starting materials of the formula V can be prepared from the free S-(+)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, which results, for example, as a by-product of the fractionation of racemic α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, by customary acylation methods, in particular using carbonyl halides or lower alkyl esters or, in particular for the preparation of the compound which is particularly suitable as starting material and has methyl as R₁, anhydrides, such as acetic anhydride.

Strong, oxygen-containing inorganic or organic acids which are suitable in process f) are, in particular, concentrated sulfuric acid or phosphoric acid, furthermore, for example, strong organic sulfonic acids, possibly aliphatic

(42)

sulfonic acids, for example methanesulfonic acid, or aromatic sulfonic acids, such as an optionally substituted phenyl-sulfonic acid, possibly 4-methyl-, 4-bromo-, 4-nitro- or 2,4-dinitrophenylsulfonic acid or naphthalenesulfonic acid, for example 1-naphthalenesulfonic acid; and their halides which are suitable are, primarily, the chlorides or bromides such as, especially, thionyl chloride, furthermore, for example, thionyl bromide, sulfuryl chloride, chlorosulfonic acid, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride or methanesulfonyl chloride. Furthermore, it is also possible for mixed ester halides corresponding to the said halides of polybasic acids to be used, such as, possibly, a lower alkoxysulfonyl halide, for example methoxysulfonyl or ethoxysulfonyl chloride, or phosphoric acid lower alkyl ester halides, for example phosphoric acid dimethyl ester chloride.

The reactions with strong acids, especially concentrated sulfuric acid or phosphoric acid, are carried out in the presence or absence of solvents or diluents such as, for example, acetic anhydride, at temperatures from about -50 to +200°C, and the reactions with acid halides such as, for example, thionyl chloride, are likewise carried out in the presence or absence of solvents or diluents, for example hydrocarbons or, in particular, chlorinated hydrocarbons, such as methylene chloride, in a temperature range from about -10 to +70°C, preferably from about +10 to +50°C. The reaction products of these reactions can be assumed to be 2-R-5-(9,10-ethanoanthracen-9(10H)-yl)-4,5-dihydro-3-methyloxazolium (sic) salts, whose anion corresponds to the acid used for the reaction or, in the case of reactions with acid halides, is the corresponding halogen ion.

The hydrolysis of the intermediates is carried out in acid or basic medium. Examples of suitable acid agents are aqueous acids, possibly aqueous mineral acids, for example aqueous hydrochloric acid, sulfuric acid or phosphoric acid. The acid hydrolysis is carried out in a temperature range from 0 to +120°C, advantageously at +10 to

+50°C. Examples of suitable basic media are aqueous alkaline solutions, possibly those of the alkali metals or alkaline earth metals, such as sodium hydroxide or potassium hydroxide or the hydroxides of calcium or magnesium, it being advantageous to use the said reagents at elevated temperature, possibly in a range from 50 to 150°C.

The hydrolysis can also be carried out stepwise by hydrolysis of an intermediate, where appropriate via the corresponding free base as intermediate step, in aqueous medium to give the corresponding N-acyl compound of the general formula V with the opposite steric configuration to that of the starting material of the formula V used in each case, and then hydrolysis of the latter compound to give a compound corresponding to the formula I.

It is also possible, advantageously, to carry out the process according to f) in such a manner that a starting material of the general formula V, which has been prepared immediately beforehand but not isolated in pure form, is reacted, in the same reaction mixture, with a suitable acid or with a halide thereof, and the resulting intermediate is likewise subjected to hydrolysis without further purification.

The optically active starting materials required for processes b) to e) can be prepared either by fractionation of known racemic, in particular basic, starting materials in a manner known per se, or, in analogy to the racemic starting materials required for the preparation of the known racemate, by use of optically active in place of racemic precursor compounds.

Acid addition salts, in particular pharmaceutically acceptable acid addition salts, of the compound of the formula I, for example those mentioned above, can be prepared in a customary manner. For example, a solution of the base in an organic solvent, such as, for example, methylene chloride, ethyl acetate, ethanol or isopropanol, is mixed with the acid desired as salt component, or a solution thereof in the same or other organic solvents, such as ethyl acetate or diethyl ether, and the precipitated salt is filtered off, if

44

necessary after cooling or concentration or after addition of a solvent with poorer solvent properties for salts, such as, for example, diethyl ether.

The present invention also relates to the compound of the formula I and its pharmaceutically acceptable acid addition salts for use as medicaments, in particular as anti-depressants, sedatives or antihistaminics, for example for use for the abovementioned indications, and to their use for the preparation of corresponding pharmaceutical products.

The dosage of the compound of the formula I and of its pharmaceutically acceptable acid addition salts in warm-blooded animals depends on the species, the body weight and age and on the individual condition, as well as on the mode of administration. The doses administered each day are between about 0.05 and about 3 mg/kg, preferably between about 0.08 and 1.5 mg/kg of body weight. On average, a daily dose from about 10 to about 150 mg, preferably from about 30 to about 75 mg, of active compound is administered to a warm-blooded animal of about 70 kg body weight.

The present invention likewise relates to pharmaceutical products which contain the compound of the formula I or pharmaceutically acceptable acid addition salts of this compound. The pharmaceutical products according to the invention are, in particular, those for enteral, such as oral or rectal, and for parenteral administration, which contain the pharmacological active compound alone or, preferably, together with at least one pharmaceutically acceptable vehicle. Products of this type contain the active compound, that is to say the compound of the formula I or a pharmaceutically acceptable acid addition salt thereof, in an amount and concentration suitable for the administration of the abovementioned daily doses in one or more, preferably three, single doses.

Pharmaceutical compositions in unit dose forms, which can be used according to the invention, such as coated tablets, tablets, capsules, suppositories or ampoules, contain as active compound preferably 2.5-50 mg, in particular 5-25

mg, of the compound of the formula I or, preferably, of a pharmaceutically acceptable acid addition salt of this base, together with at least one pharmaceutical vehicle, per unit dose.

Unit dose forms for oral administration preferably contain as active compound between 1 and 50% of the compound of the formula I or of a pharmaceutically acceptable acid addition salt thereof. To prepare them, the active compound is combined with, for example, solid vehicles in the form of powders, such as lactose, sucrose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, furthermore powdered laminaria or powdered citrus pulp; cellulose derivatives or gelatine, where appropriate with the addition of lubricants, such as magnesium or calcium stearate, or polyethylene glycols, to form tablets or to form cores of coated tablets. The cores of coated tablets are coated with, for example, concentrated sugar solutions which, for example, may also contain gum arabic, talc and/or titanium dioxide, or with a lacquer which is dissolved in volatile organic solvents or mixtures of solvents. Pigments may be added to these coatings, for example to identify various doses of active compound.

Other oral unit dose forms which are suitable are hard gelatine capsules, and soft, closed capsules made of gelatine and a softening agent, such as glycerol. The hard gelatine capsules preferably contain the active compound as granules, for example mixed with fillers, such as maize starch, and/or lubricants, such as talc or magnesium stearate, and, where appropriate, stabilizers, such as sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$) or ascorbic acid. The active compound in soft capsules is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols, it likewise being possible to add stabilizers.

Examples of suitable unit dose forms for rectal administration according to the invention are suppositories which are composed of a combination of an active compound with a suppository base. Examples of suitable suppository

46

- 14 -

bases are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatine rectal capsules which are composed of a combination of the active compound with a base are also suitable. Examples of suitable bases are liquid triglycerides (sic), polyethylene glycols or paraffin hydrocarbons.

Ampoules for parenteral, in particular intramuscular, administration preferably contain a water-soluble, pharmaceutically acceptable salt of the compound of the formula I in a concentration of, preferably, 0.5-5%, where appropriate together with suitable stabilizers and buffer substances, in aqueous solution.

The examples which follow illustrate the preparation of the compound of the formula I and of some typical unit dose forms, but are not intended to restrict the scope of the invention in any way.

Example 1

184.8 g (0.63 mole) of racemic α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and 127.5 g (0.315 mole) of (-)-bis-(0,0'-(p-toluoyl)-L-tartaric acid are dissolved in 2,500 ml of methanol to 40°C and then allowed to stand at room temperature for 24 h. The precipitated crystals are filtered off with suction and washed twice with 50 ml of ice-cold methanol each time. The filtrate can, if desired, be used to obtain the other antipode. The material on the filter is dissolved in 2,500 ml of hot methanol, and the solution is concentrated to 800 ml by distilling off methanol. This solution is allowed to stand at room temperature for 24 h, during which R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol (-)-bis-0,0'-(p-toluoyl)-L-tartrate (1:1) crystallizes out. This is filtered off with suction, washed twice with 40 ml of ice-cold methanol each time, and dried under waterpump vacuum at 50°C.

Melting point 180°C with decomposition;

$[\alpha]_D^{20} = -64^\circ\text{C}$ (sic) (c = 1.135 in methanol).

To obtain the free base, 4.9 g (0.01 mole) of the above salt are dissolved in 50 ml of methylene chloride, and

the solution is extracted twice with 15 ml of 1 N sodium hydroxide solution each time, and subsequently washed twice with 15 ml of water each time, and evaporated at about 14 mbar. The remaining crystallized R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol melts at 107-108°C $[\alpha]_D^{20} = -9.1$ (sic) (c = 1.01 in methanol). If desired, the base can also be recrystallized from ether.

To prepare the hydrochloride, 56.9 g of R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol (-)-bis-O,O'-(p-toluoyl)-L-tartrate (1:1) are dissolved in 200 ml of methylene chloride and, while stirring at room temperature, mixed with an ethereal solution of hydrogen chloride until the overlying vapours permanently colour Congo paper blue. R-(-)-X-[(Methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride crystallizes out during this. After addition of 300 ml of ether, the crystals are filtered off with suction and then recrystallized once from ethanol/methanol.

The hydrochloride thus purified melts at 231-232°C, $[\alpha]_D^{20} = -9^\circ$ (sic) (c = 1.37 in methanol).

Example 2

a) 1.9 ml of acetic anhydride are added dropwise to a solution of 2.93 g (0.010 mole) of S-(+)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol in 8 ml of dimethylformamide at 5-10°C. The solution is stirred at room temperature for 4 h, then poured onto 60 ml of water and extracted with 100 ml of ethyl acetate. The ethyl acetate solution is washed with saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated in vacuo. The remaining crude S-(+)-X-[(N-methylacetamido)methyl]-9,10-ethanoanthracene-9(10H)-ethanol can be immediately processed further.

b) The crude product from a (2.5 g) is dissolved in 6 ml of methylene chloride. While stirring at 5-10°C, a solution of 0.77 ml of thionyl chloride in 4 ml of methylene chloride is added within 15 min. The reaction solution is stirred at 20°C for 2 h and then at 35°C for one hour, and is then evaporated to dryness at about 14 mbar (waterpump vacuum).

- 16 -

c) The evaporation residue from b) is dissolved in 10 ml of ethanol, mixed with 2.5 ml of water and 1.6 g of sodium hydroxide, and boiled under reflux for 3 h. The reaction mixture is then concentrated at about 14 mbar, mixed with 50 ml of ice-water, and then extracted with 100 ml of ethyl acetate. The ethyl acetate solution is washed to neutrality with water, dried over sodium sulfate and evaporated at about 14 mbar, whereupon the crude inverted base remains.

The residue is dissolved in 10 ml of methylene chloride and mixed with ethereal hydrogen chloride solution, whereupon the R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride crystallizes out. The crystals are filtered off with suction and recrystallized from isopropanol. Melting point 229-231°C, $[\alpha]_D^{20} = -9 \pm 1^\circ\text{C}$ (sic) (c = 1.6 in methanol).

The starting material for section a) is prepared as follows:

The filtrate which was mentioned in Example 1 and contains the antipode is evaporated at about 14 mbar.

The residue is dissolved in 500 ml of methylene chloride, and this solution is extracted by shaking three times with 100 ml of 2 N sodium hydroxide solution each time and then, additionally, twice with 100 ml of water each time. After removal of the methylene chloride by evaporation, 132.5 g of base which is partially enriched in S-(+)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol are obtained. This base (0.452 mole) and 91.4 g (0.226 mole) of (+)-bis-O,O'-(p-toluoyl)-D-tartaric acid are dissolved in 1,800 ml of methanol at 40°C and then allowed to stand at room temperature for 24 h. The crystals which have separated out are filtered off with suction, dissolved in methanol, and the resulting solution is concentrated to about one-third of its volume and again allowed to stand at room temperature for 24 h. The crystals which have separated out are filtered off with suction and washed with a little cold methanol, whereupon S-(+)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol (+)-bis-O,O'-(p-toluoyl)-D-tartrate (1:1) is

49

- 17 -

obtained, which melts at 178°C with decomposition; $[\alpha]_D^{20} = +63^\circ$ (sic) ($c = 0.774$ in methanol). To liberate the base, 88.4 g (0.18 mole) of the above salt are dissolved in 500 ml of methylene chloride, and this solution is extracted by shaking three times with 100 ml of 2 N sodium hydroxide solution each time and then, additionally, twice with 100 ml of water each time. The S-(+)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol (melting point 106-107°C) which remains after removal of the methylene chloride by evaporation can be immediately used for the acetylation according to a).

Example 3

2.93 g (0.010 mole) of S-(+)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol are dissolved, in portions, in 14 ml of acetic anhydride. This solution is mixed, with stirring, with a solution of 1.75 g of 96% strength sulfuric acid in 6 ml of acetic anhydride, and then the mixture is boiled under reflux for 3 h. The resulting solution is then concentrated at about 14 mbar, and the remaining reaction product which has resulted from N-acetylation and cyclization is taken up in 30 ml of 1 N sulfuric acid and boiled under reflux for 2 h. Then 50 g of ice are added, and the resulting mixture is adjusted to pH 9 with aqueous ammonia solution, and is extracted twice with 50 ml of ethyl acetate each time. The combined organic phases are dried over sodium sulfate and evaporated to dryness. The remaining crude base is dissolved in 10 ml of methylene chloride and mixed with ethereal hydrogen chloride solution, whereupon the R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride crystallizes out. It is filtered off with suction and recrystallized from isopropanol; melting point 228-230°C.

Example 4

3.9 g of the crude 5-(R)-[(9,10-ethanoanthracen-9(10H)-yl)methyl]-3-methyl-oxazolidine obtained according to a) (sic) are heated with 60 ml of 2 N hydrochloric acid at 90°C for 3 h. Then 5 N sodium hydroxide solution is added

until the reaction is alkaline, and the mixture is extracted with methylene chloride, and the organic phase is evaporated. The remaining crude R- -(-)-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is dissolved in 10 ml of ethanol, and 1 ml of a 10% strength ethanolic hydrogen chloride solution is added. The hydrochloride of the above base is induced to crystallize by mixing with ether. The crystallized hydrochloride is filtered off with suction and, if desired, purified further in analogy to Example 1 or Example 2.

The starting material can be prepared as follows:

a) 20.0 g of R-~~X~~-[aminomethyl]-9,10-ethanoanthracene-9(10H)-ethanol (sic) (from the corresponding racemic compound, described in U.S. Patent Specification 4,017,542, Example 1, of melting point 176-177°C, for example obtainable similar to the present Example 1) are heated in a mixture of 10 ml of 35% strength aqueous formaldehyde solution and 150 ml of formic acid at 95°C for one hour. The reaction mixture is evaporated in vacuo, the residue is made alkaline by addition of 2 N sodium hydroxide solution, and the mixture is extracted with methylene chloride. The organic phase is evaporated, whereupon the 5(R)-[(9,10-ethanoanthracen-9(10H)-yl)methyl]-3-methyl-oxazolidine remains.

Example 5

A solution of 1.5 g of N-[3-(9,10-ethanoanthracen-9(10H)-yl)-2(R)-hydroxypropyl]-formamide in 20 ml of tetrahydrofuran is added to a suspension of 0.7 g of lithium aluminium hydride in 20 ml of tetrahydrofuran, and the mixture is boiled under reflux for 4 hours. It is then cooled and mixed with 1.4 ml of water and then with 1.4 ml of 15% strength sodium hydroxide solution and with a further 5 ml of water. The precipitate which has separated out is filtered off, and the filtrate is evaporated and the residue is dissolved in 2N acetic acid. The acid solution is washed with ether, then mixed with 10% strength sodium hydroxide solution until the reaction is alkaline, and the solution is extracted with methylene chloride. The solvent is evaporated off, and the remaining crude R-(-)-~~X~~-[(methylamino)methyl]-9,10-

ethanoanthracene-9(10H)-ethanol is converted into the hydrochloride of melting point 231-232 (sic) in analogy to Example 1 or 2.

The substituted formamide used as starting material can be prepared as follows:

a) 5 g of (R)-~~X~~-(aminomethyl)-9,10-ethanoanthracene-9(10H)-ethanol (compare Example 4a) in 75 ml of ethyl formate are boiled under reflux for 2 h. The cooled solution is evaporated to dryness at about 14 mbar. The residue is dissolved in 75 ml of methylene chloride, and the solution is washed with 40 ml of 1 N hydrochloric acid, dried over sodium sulfate and again evaporated to dryness at about 14 mbar. The remaining N-[3-(9,10-ethanoanthracen-9(10H)-yl)-2(R)-hydroxypropyl]-formamide can be used immediately for the reduction.

Example 6

A solution of 10 g of R-~~X~~-[(methylamino)methyl]-anthracene-9(10H)-ethanol in 200 ml of benzene is heated in an autoclave with ethylene under a pressure of 70 at. and at 70°C for 6 h. The mixture is then extracted with 200 ml of 2 N hydrochloric acid. The acid extract is made alkaline and extracted with methylene chloride. The organic phase is evaporated, and the remaining crude R-~~X~~-(-)-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is converted into its hydrochloride in analogy to Example 1.

Example 7

a) 100 g of R-(-)-~~X~~-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride are mixed with 202 g of lactose and 195 g of potato starch, and the mixture is moistened with an alcoholic solution of 10 g of stearic acid and is granulated through a screen. After drying, 200 g of potato starch, 250 g of talc, 3.0 g of magnesium stearate and 40 g of colloidal silica are admixed, and the mixture is compressed to form 10,000 tablets each weighing 100 mg and containing 10 mg of active compound, which, if desired, can be provided with dividing grooves for more accurate adjustment of the dosage.

- b) 50 g of R-(-)-~~X~~-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride, 228.40 g of lactose and the alcoholic solution of 7.5 g of stearic acid are used to prepare granules which, after drying, are mixed with 56.60 g of colloidal silica, 200 g of talc, 20 g of potato starch and 2.50 g of magnesium stearate and compressed to form 10,000 coated tablet cores. These are then coated with a concentrated syrup of 417.3 g of crystalline sucrose, 6 g of shellac, 10 g of gum arabic, 0.2 g of pigment and 1.5 g of titanium dioxide and are dried. The resulting coated tablets each weigh 120 mg and each contain 5 mg of active compound.
- c) In order to prepare 1,000 capsules each containing 10 mg of active compound, 10 g of R-(-)-~~X~~-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride are mixed with 263 g of lactose, and the mixture is uniformly moistened with an aqueous solution of 2 g of gelatine and is granulated through a suitable screen (for example screen III according to Ph. Helv. V). The granules are mixed with 10 g of dried maize starch and 15 g of talc, and are uniformly dispensed into 1,000 size 1 hard gelatine capsules.
- d) A suppository base is prepared from 2.0 g of R-(-)-~~X~~-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride and 168.0 g of hard fat, and this is used to cast 100 suppositories each containing 20 mg of active compound.
- e) A solution of 25 g of R-(-)-~~X~~-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol hydrochloride in one litre of water is dispensed into 1,000 ampoules and sterilized. One ampoule contains a 2.5% strength solution of 25 mg of active compound.



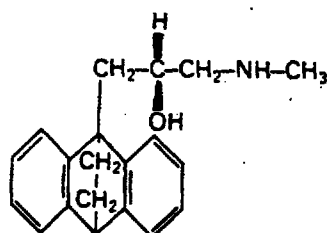
53

- 21 -

Patent Claims

for the contracting states BE, CH, DE, FR, GB, IT, LU, NL, SE

1. R-(-)-X-[(Methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I



(I)

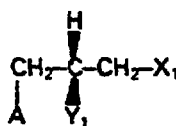
and its acid addition salts.

2. The pharmaceutically acceptable acid addition salts of the compound of the formula I indicated in claim 1.

3. The hydrochloride of the compound of the formula I indicated in claim 1.

4. Process for the preparation of R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I indicated in claim 1 and of its acid addition salts, characterized by

- a) fractionation of racemic X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and isolation of R-(-)-X-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, where appropriate in the form of an acid addition salt, or
- b) reaction of a compound of the formula II



(II)

with a compound of the formula III.

X₂ - CH₃

(III)

one of the symbols X₁ and X₂ denoting the amino group and the other denoting a reactive esterified hydroxyl group, and Y₁ denoting a free hydroxyl group, and it also being possible for X₁ together with Y₁ to denote an epoxy group, and A representing the 9,10-ethanoanthracen-9(10H)-yl radical,



54

- 22 -

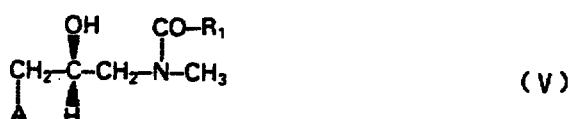
or

c) elimination of the radical(s) Z_1 and/or Z_2 in a compound of the formula IV



in which at least one of the symbols Z_1 and Z_2 denotes a radical which can be eliminated, and the other optionally denotes hydrogen, or Z_1 and Z_2 together denote a bivalent radical which can be eliminated, and A represents the 9,10-ethanoanthracen-9(10H)-yl radical, or

d) reduction of a compound which differs from the compound of the formula I only in that a carbon atom adjacent to the nitrogen atom in it is connected to the latter by a double bond or is substituted by a hydroxyl group or by an oxo radical, where appropriate together with lower alkoxy, or
e) addition of ethylene onto R-~~K~~[(methylamino)methyl]-9(10H)-anthraceneethanol, or
f) reaction of a compound of the general formula V



in which R denotes an optionally substituted hydrocarbon radical or an optionally substituted heterocyclic radical, and A denotes the 9,10-ethanoanthracen-9(10H)-yl radical, with a strong, oxygen-containing inorganic or organic acid, or with a halide thereof, and hydrolysis of the resulting intermediate and, if desired, conversion of the R-(-)-~~K~~[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, thus obtained, into an acid addition salt and/or liberation of the base from an acid addition salt obtained.

5. Pharmaceutical products characterized by a content of the compound of the formula I indicated in claim 1 or of



- 23 -

a pharmaceutically acceptable acid addition salt thereof, and of at least one pharmaceutical vehicle.

6. Pharmaceutical products according to claim 5 in unit dose form, characterized by a content of 2.5 to 50 mg of the compound of the formula I indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, per unit dose.

7. Pharmaceutical products according to claim 5 in unit dose form, characterized by a content of 5 to 25 mg of the compound of the formula I indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, per unit dose.

8. Pharmaceutical products according to one of claims 5, 6 and 7, characterized by a content of the hydrochloride of the compound of the formula I indicated in claim 1.

9. The compound of the formula I indicated in claim 1, or a pharmaceutically acceptable acid addition salt thereof, for use as a sedative.

10. The compound of the formula I indicated in claim 1, or a pharmaceutically acceptable acid addition salt thereof, for use as an antihistaminic.

11. The compound of the formula I indicated in claim 1, or a pharmaceutically acceptable acid addition salt thereof, for use as an antidepressant.

12. Use of the compound of the formula I indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, for the preparation of pharmaceutical products having sedative, antihistaminic and antidepressant activity.

Patent Claims

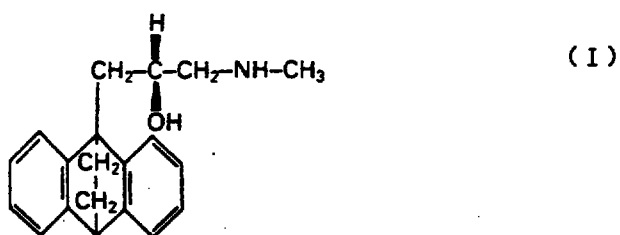
for the contracting state AT

1. Process for the preparation of R-(-)-X-[(methyl-amino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I

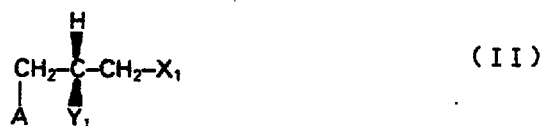


56

- 24 -



and of its acid addition salts, characterized in that
a) racemic κ -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is fractionated, and R-(-)- κ -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is isolated, where appropriate in the form of an acid addition salt, or
b) a compound of the formula II



is reacted with a compound of the formula III



one of the symbols X_1 and X_2 denoting the amino group and the other denoting a reactive esterified hydroxyl group, and Y_1 denoting a free hydroxyl group, and it also being possible for X_1 together with Y_1 to denote an epoxy group, and A representing the 9,10-ethanoanthracen-9(10H)-yl radical, or

c) the radical(s) Z_1 and/or Z_2 in a compound of the formula IV



in which at least one of the symbols Z_1 and Z_2 denote a



57

- 25 -

radical which can be eliminated, and the other optionally denotes hydrogen, or Z₁ and Z₂ together denote a bivalent radical which can be eliminated, and A represents the 9,10-ethanoanthracen-9(10H)-yl radical, is/are eliminated, or d) a compound which differs from the compound of the formula I only in that a carbon atom adjacent to the nitrogen atom in it is connected to the latter via a double bond, or is substituted by a hydroxyl group or by an oxo radical, where appropriate together with lower alkoxy, is reduced, or e) ethylene is added onto R- α -[(methylamino)methyl]-9(10H)-anthracene-ethanol and, if desired, the R-(-)- α [(methylamino)methyl]-9,10-ethano-anthracene-9(10H)-ethanol (sic), thus obtained, is converted into an acid addition salt, or the base is liberated from an acid addition salt obtained.

2. Modification of the process according to claim 1, characterized in that a compound of the general formula V



in which R denotes an optionally substituted hydrocarbon radical or an optionally substituted heterocyclic radical, and A denotes the 9,10-ethanoanthracen-9(10H)-yl radical, is reacted with a strong oxygen-containing inorganic or organic acid, or with a halide thereof, and the resulting intermediate is hydrolysed and, if desired, the R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol thus obtained, is converted into an acid addition salt, or the base is liberated from an acid addition salt obtained.

3. Process according to claim 1, characterized in that a pharmaceutically acceptable acid addition salt of R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is prepared.

4. Process according to claim 1, characterized in that the hydrochloride of R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol is prepared.

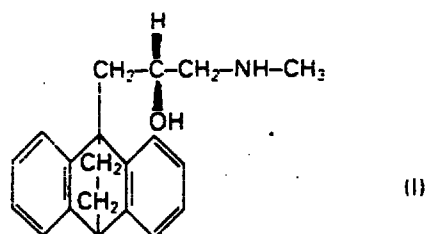


58

Claims

(for the Contracting states: BE, CH, DE, FR, GB, IT, LU, NL, SE) (as printed)

1. R-(-)- α -[(Methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I



or an acid addition salt thereof.

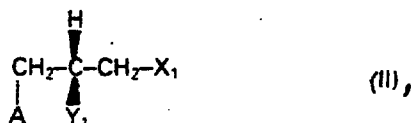
2. A pharmaceutically acceptable acid addition salt of the compound of the formula I as indicated in claim 1.

3. The hydrochloride of the compound of the formula I as indicated in claim 1.

4. A process for the production of R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I as indicated in claim 1, or of an acid addition salt thereof, which process comprises.

a) resolving the racemic α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and isolating R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, if desired in the form of an acid addition salt, or

b) reacting a compound of the formula II

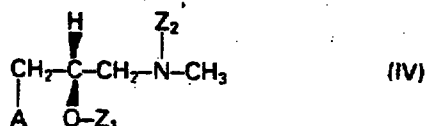


with a compound of the formula III



wherein one of X₁ and X₂ is the amino group and the other is a reactive esterified hydroxyl group, and Y₁ is a free hydroxyl group, and X₁ together with Y₁ can also be an epoxy group, and A is the 9,10-ethanoanthracene-9(10H)-yl-radical, or

c) in a compound of the formula IV

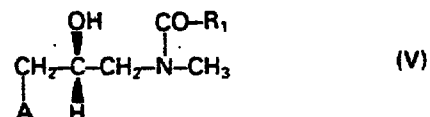


in which at least one of Z₁ and Z₂ is a removable radical and the other may be hydrogen, or Z₁ and Z₂ together are a divalent removable radical, and A is the 9,10-ethanoanthracene-9(10H)-yl radical, removing Z₁ and/or Z₂.

d) reducing a compound which differs from the compound of the formula I only in that, in said compound, a carbon atom adjacent to the nitrogen atom is attached to this latter through a double bond or is substituted by a hydroxyl group or an oxo radical, optionally together with lower alkoxy, or

e) adding ethylene to R- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, or

f) reacting a compound of the general formula V



in which R is an unsubstituted or substituted hydrocarbon radical or an unsubstituted or substituted heterocyclic radical, and A is the 9,10-ethanoanthracene-9(10H)-yl radical, with a strong oxygen-containing inorganic or organic acid or with a halide thereof, and hydrolysing the intermediate obtained, and, if desired, converting the resultant R-(-)- α -[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol into an acid addition salt and/or liberating the base from a resultant acid addition salt.

5. A pharmaceutical composition containing a compound of the formula I as indicated in claim 1, or a pharmaceutically acceptable acid addition salt thereof, and at least one pharmaceutical carrier.

6. A pharmaceutical composition according to claim 5 in dosage unit form, which contains, per dosage unit, from 2.5 to 50 mg of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof.

7. A pharmaceutical composition according to claim 5 in dosage unit form, which contains, per dosage unit, from 5 to 25 mg of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition according to any one of claims 5, 6 or 7, which contains the hydrochloride of the compound of the formula I as indicated in claim 1.

9. Use of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, as sedative.

10. Use of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, as antihistamine.

11. Use of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, as antidepressant.

12. Use of the compound of the formula I as indicated in claim 1, or of a pharmaceutically acceptable acid addition salt thereof, for the preparation of a pharmaceutical composition having sedative, antihistaminic or antidepressive properties.

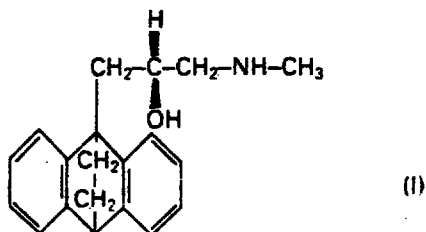


59

Revendications

(pour les Etats contractants: BE, CH, DE, FR, GB, IT, LU, NL, SE) (as printed)

1. R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol de formule I



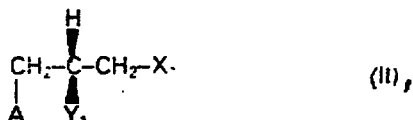
et ses sels d'addition d'acides.

2. Les sels d'addition d'acides pharmaceutiquement acceptables du composé de formule I donnée dans la revendication 1.

3. Le chlorhydrate du composé de la formule I donnée dans la revendication 1.

4. Procédé de préparation du R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol de formule I donnée dans la revendication 1 et de ses sels d'addition d'acides, caractérisé en ce que

- a) on sépare 1'-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol racémique et on isole le R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol, éventuellement sous la forme d'un sel d'addition d'acide, ou
- b) on fait réagir un composé de formule II

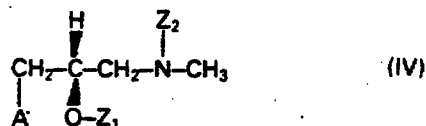


avec un composé de formule III



où l'un des symboles X_1 et X_2 représente le groupe amino et l'autre un groupe hydroxy estérifié réactif et Y_1 un groupe hydroxy libre, et X_1 peut également représenter avec Y_1 un groupe époxy, et A représente le radical 9,10-éthanoanthracène-9(10H)-yle, ou

c) dans un composé de formule IV

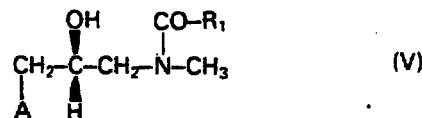


où au moins l'un des symboles Z_1 ou Z_2 représente un radical séparable et l'autre éventuellement un hydrogène, ou bien où Z_1 et Z_2 forment ensemble un radical bivalent séparable, et A représente le radical 9,10-éthanoanthracène-9(10H)-yle, on sépare le ou les radicaux Z_1 et/ou Z_2 , ou

d) on réduit un composé qui ne se différencie du composé de formule I qu'en ce qu'un atome de carbone voisin de l'atome d'azote est relié avec celui-ci par une double liaison ou est substitué par un groupe hydroxy ou par un radical oxo, éventuellement avec un alcoxy inférieur, ou

e) on fixe de l'éthylène sur le R-α-[(méthylamino)méthyl]-9(10H)-anthracène-éthanol, ou

f) on fait réagir un composé de formule V



où R représente un radical hydrocarboné éventuellement substitué ou un radical hétérocyclique éventuellement substitué et A représente un radical 9,10-éthanoanthracène-9(10H)-yle, avec un acide organique ou inorganique fort contenant de l'oxygène ou un halogénure d'un tel acide, et on hydrolyse le produit intermédiaire apparu, et si on le désire on transforme le R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol ainsi obtenu en un sel d'addition d'acide et/ou on libère la base à partir d'un sel d'addition d'acide obtenu.

5. Préparations pharmaceutiques caractérisées en ce qu'elles contiennent un composé de formule I donnée dans la revendication 1 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables, et au moins un support pharmaceutique.

6. Préparations pharmaceutiques selon la revendication 5 sous forme posologique unitaire, caractérisée en ce qu'elles contiennent par unité posologique de 2,5 à 50 mg du composé de formule I donné dans la revendication 1 ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables.

7. Préparations pharmaceutiques selon la revendication 5 sous forme posologique unitaire, caractérisées en ce qu'elles contiennent par unité posologique de 5 à 25 mg du composé de formule I donné dans la revendication 1 ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables.

8. Préparations pharmaceutiques selon l'une des revendications 5, 6 et 7, caractérisées en ce qu'elles contiennent le chlorhydrate du composé de formule I donnée dans la revendication 1.

9. Composé de formule I donnée dans la revendication 1 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables aux fins d'application comme sédatif.

10. Composé de formule I donnée dans la revendication 1 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables aux fins d'application comme anti-histaminique.

11. Composé de formule I donnée dans la revendication 1 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables aux fins d'application comme agent anti-dépresseur.

12. Application du composé de formule I donnée dans la revendication 1 ou d'un de ses sels d'addition d'acides pharmaceutiquement acceptables à la préparation de préparations pharmaceutiques à action sédatif, anti-histaminique et anti-dépresseur.

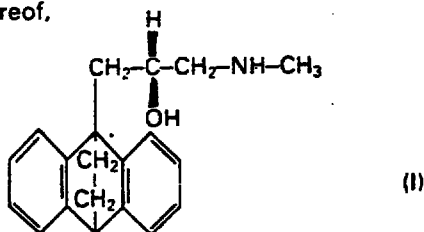
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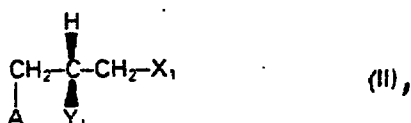
Claims for the designated state: AT
(as printed)

1. A process for the production of R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol of the formula I or of an acid addition salt thereof,



which process comprises

- a) resolving the racemic α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol and isolating R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol, if desired in the form of an acid addition salt, or
- b) reacting a compound of the formula II

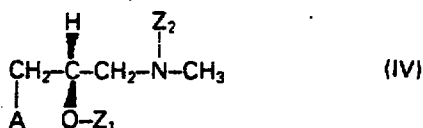


with a compound of the formula III



wherein one of X₁ and X₂ is the amino group and the other is a reactive esterified hydroxyl group, and Y₁ is a free hydroxyl group, and X₁ together with Y₁ can also be an epoxy group, and A is the 9,10-ethanoanthracene-9(10H)-yl radical, or

c) in a compound of the formula IV

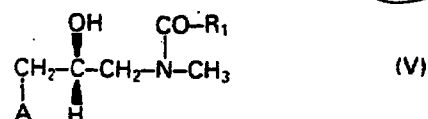


in which at least one of Z₁ and Z₂ is a removable radical and the other may be hydrogen, or Z₁ and Z₂ together are a divalent removable radical, and A is the 9,10-ethanoanthracene-9(10H)-yl radical, removing Z₁ and/or Z₂.

d) reducing a compound which differs from the compound of the formula I only in that, in said compound, a carbon atom adjacent to the nitrogen atom is attached to this latter through a double bond or is substituted by a hydroxyl group or an oxo radical, optionally together with lower alkoxy, or

e) adding ethylene to R-α-[(methylamino)methyl]-9(10H)-anthracene-ethanol, and, if desired, converting the resultant R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol into an acid addition salt and/or liberating the base from a resultant acid addition salt.

2. A modification of the process according to claim 1, which comprises reacting a compound of the general formula V



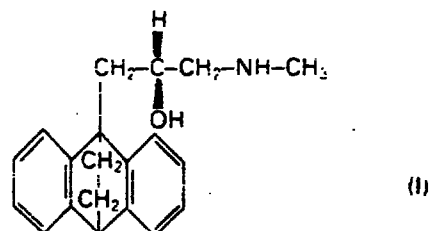
in which R₁ is an unsubstituted or substituted hydrocarbon radical or an unsubstituted or substituted heterocyclic radical, and A is the 9,10-ethanoanthracene-9(10H)-yl radical, with a strong oxygen-containing inorganic or organic acid or with a halide thereof, and hydrolysing the intermediate obtained, and, if desired, converting the resultant R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol into an acid addition salt and/or liberating the base from a resultant acid addition salt.

3. A process according to claim 1 for the production of a pharmaceutically acceptable acid addition salt of R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol.

4. A process according to claim 1 for the production of the hydrochloride of R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol.

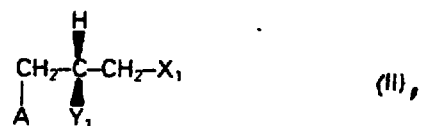
Revendications pour l'Etat contractant: AT
(as printed)

1. Procédé de préparation du R-(-)-α-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol de formule I



et de ses sels d'addition d'acides, caractérisé en ce que

- a) on sépare l'α-[(methylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol racémique et on isole le R-(-)-α-[(methylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol, éventuellement sous la forme d'un sel d'addition d'acide, ou
- b) on fait réagir un composé de formule II



avec un composé de formule III



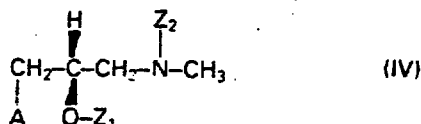
où l'un des symboles X₁ et X₂ représente le groupe amino et l'autre un groupe hydroxy estérifié réactif et Y₁ représente un groupe hydroxy



61

libre, et X₁ peut également représenter avec Y₁ un groupe époxy, et A représente le radical 9,10-éthanoanthracène-9(10H)-yle, ou

c) dans un composé de formule IV

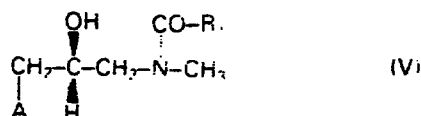


où au moins l'un des symboles Z₁ et Z₂ représente un radical separable et l'autre éventuellement un hydrogène, ou bien où Z₁ et Z₂ représentent ensemble un radical bivalent separable, et A représente le radical 9,10-éthanoanthracène-9(10H)-yle, on sépare le ou les radicaux Z₁ et ou Z₂, ou

d) on réduit un composé qui ne se différencie du composé de formule I qu'en ce qu'un atome de carbone voisin de l'atome d'azote est relié à celui-ci par une double liaison ou est substitué par un groupe hydroxy ou par un radical oxo, éventuellement avec un alcoxy inférieur, ou

e) on fixe de l'éthylène sur le R-α-[(méthylamino)méthyl]-9(10H)-anthracène-éthanol, et éventuellement on transforme le R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol ainsi obtenu en un sel d'addition d'acide ou on libère la base à partir d'un sel d'addition d'acide obtenu.

2. Modification du procédé selon la revendication 1, caractérisée en ce qu'on fait réagir un composé de formule générale V



où R représente un radical hydrocarboné éventuellement substitué ou un radical hétérocyclique éventuellement substitué et A représente un radical 9,10-éthanoanthracène-9(10H)-yle, avec un acide inorganique ou organique fort contenant de l'oxygène ou un halogénure d'un tel acide et on hydrolyse le produit intermédiaire apparu, et si on le désire on transforme le R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol ainsi obtenu en un sel d'addition d'acide ou on libère la base à partir d'un sel d'addition d'acide obtenu.

3. Procédé selon la revendication 1, caractérisé en ce qu'on prépare un sel d'addition d'acide pharmaceutiquement acceptable du R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol.

4. Procédé selon la revendication 1, caractérisé en ce qu'on prépare le chlorhydrate du R-(-)-α-[(méthylamino)méthyl]-9,10-éthanoanthracène-9(10H)-éthanol.