APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 22.3.90

59 7326

AUSTRALIA

Patents Act 1952

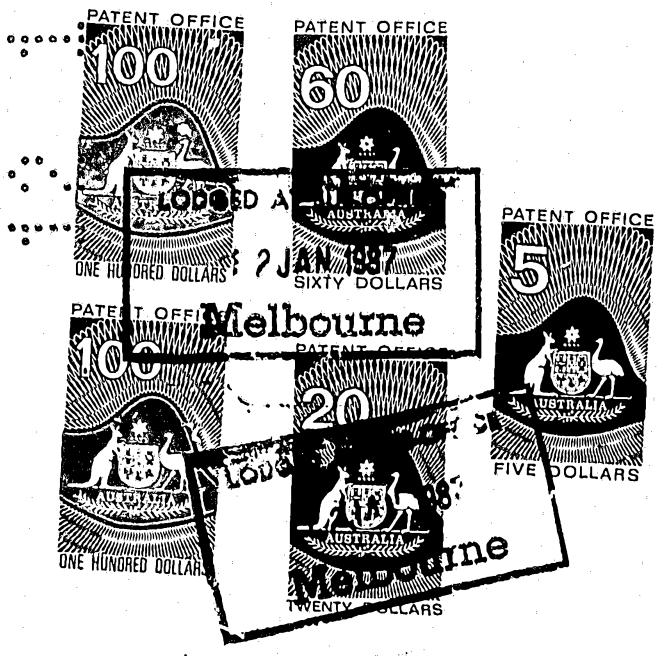
CONVENTION APPLICATION FOR A PATENT

We, ROUSSEL-UCLAF, a French Body Corporate, of 35, Boulevard des Invalides, 75007 Paris, France, hereby apply for the grant of a Patent for an invention entitled "NEW DERIVATIVES OF DECAHYDROQUINOLINE, THEIR PREPARATION PROCESS, THE PREPARATION INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM" which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered 86-00354 for a patent or similar protection made in France on 13th January, 1986.

Our address for service is: CALLINAN AND ASSOCIATES, Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

D A T E D this 12th day of January, 1987.



ROUSSEL-UCLAF
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

FEE STAMP TO VALUE OF 285 ATTACHED
MAIL OFFICER.....

LODGED AT SUB-OFFICE
12 JAN 1987
Melbourne

TO: The Commissioner of Patents

Form 6
Form 7

Regulation 11 (1)
Regulation 11 (2)

AUSTRALIA
Patents Act 1952-1973

Declaration in Support of
(a) A Convention Application
(b) ~~An Application~~
for a Patent ~~or Patent of Addition~~

(a) Delete for Non-Convention Application.

(b) Delete for Convention Application.

In support of the ~~Application~~/Convention Application made by

(c) Insert Full Name of Applicant

(c) ROUSSEL-UCLAF (hereinafter termed "the said Company")

for a patent/~~patent of addition~~ for an invention entitled:

(d) Insert Title of Invention.

(d) "NEW DERIVATIVES OF DECAHYDROQUINOLINE, THEIR PREPARATION PROCESS, THE PREPARATION INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM"

(e) Insert Full Names of Declarant(s).

I/~~We~~ (e) HUBERT FRITEL,
35, Boulevard des Invalides,

(f) Insert Address(es) of Declarant(s).

of (f) 75007 Paris, France

do solemnly and sincerely declare as follows:—

(g) Delete when Applicant is a Company.

1. (g) ~~I am/we are the applicant(s) for the patent/patent of addition~~
~~or~~

(h) Delete when Applicant is an Individual. Fill in Name of Applicant if a Company.

(h) I am/~~we are~~ authorised by the said Company

the applicant for the patent/~~patent of addition~~ to make this declaration on its behalf.

(i) For Non-Convention Application, delete. For Convention Application, fill in details of basic application.

2. (i) The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made in France on the 13th day of January 1986 by the said Company.

(j) Delete for Non-Convention Application by Assignee of Inventor and for Convention Application.

(k) Delete for Non-Convention Application by Inventor and for Convention Application by Assignee.

3. (j) ~~I am/we are the actual inventor(s) of the invention~~
~~or~~

(k) ~~I am/we are the actual inventor(s) of the invention referred to in the basic application.~~
~~or~~

FRANÇOIS CLEMENCE, of 2, rue Turgot, 75009 PARIS, France; MICHEL FORTIN, of 12, Passage Cottin, 75018 PARIS, France; ODILE LE MARTRET, of 42, Avenue de Versailles, 75016 PARIS, France; and FRANÇOISE DELEVALLEE, of 48-50, Avenue de la Dame Blanche, 94120 FONTENAY SOUS BOIS, France

(l) Delete for Application by Inventor. For Application by Assignee, insert name, address and occupation of Inventor.

(l)
~~of~~
~~is~~/are the actual inventor(s) of the invention and the facts upon which ~~I am/we are~~/the said Company is entitled to make the application are as follows:

(m) Insert details of Assignment, etc. Date of Assignment only is insufficient.

(m) The said Company would, if a patent were to be granted upon an application by the said actual inventors, be entitled to have the patent assigned to it.

(n) Delete for Non-Convention Application.

(n) The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the ~~Application~~.

(n) Insert place and date of signature.

(n) Declared at Paris, France this 19th day of December 19 86.

ROUSSEL-UCLAF
Société Anonyme à conseil d'administration
11B à 150 de la loi du 24 juillet 1966
Commerce de Paris
35, bd des Invalides
75007 PARIS

SIGN HERE X

Par procuration : Hubert FRITEL
Chef du Département

To: The Commissioner of Patents.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-67476/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 597326

(54) Title
DECAHYDROQUINOLINE DERIVATIVES

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C07D 409/14

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(71) Applicant(s)
ROUSSEL-UCLAF

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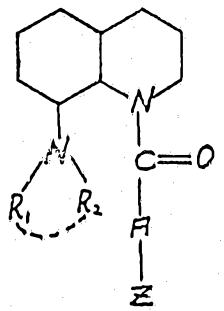
FRANCOIS CLEMENCE; ODILE LE MARTRET; MICHEL FORTIN; FRANCOISE DELEVALLEE

(74) Attorney or Agent
CALLINAN LAWRIE

(56) Prior Art Documents
US 3991065

(57) Claim

1. Compounds with the formula (I):



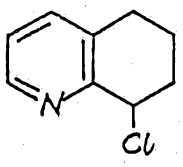
(I)

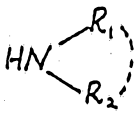
in which R_1 and R_2, identical or different, represent a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocycle having a 5- or 6- membered ring, optionally including another heteroatom being oxygen or nitrogen, said heterocycle optionally being substituted by an alkyl or alkoxy radical containing from 1 to 5 carbon atoms,

.../2

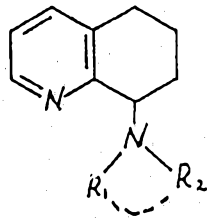
A represents a chain $(CH_2)_n$ in which n represents a numeral 0 to 5, or A represents an alkylene chain substituted by an alkyl radical containing in all from 2 to 8 carbon atoms,
Z represents a phenyl radical optionally substituted by one or more identical or different radicals chosen from the group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen atoms, hydroxyl, trifluoromethyl, nitro or amino radicals, and monoalkylamino or dialkylamino radicals in which the alkyl radicals contain from 1 to 5 carbon atoms, or Z represents a naphthyl radical, an indenyl radical, a heteromonocyclic radical being selected from the group made up of thiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl and thienyl radicals, or a heterobicyclic radical being chosen from the group made up of indolyl, quinolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzoxazolyl and benzothiazolyl radicals, all these radicals optionally being substituted by one or more identical or different radicals chosen from the group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, trifluoromethyl, nitro or amino radicals, monoalkylamino or dialkylamino radicals, of which the alkyl radicals contain from 1 to 5 carbon atoms, and phenyl radicals optionally substituted by one or more alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, or by one or more halogens,
the said compounds with the formula (I) being able to be in all their possible enantiomeric and diastereo-isomeric forms and in the form of addition salts with acids or quaternary ammonium salts.

6. Process for the preparation of compounds with the formula (I), as claimed in Claims 1 to 3, characterised in that 8-chloro-5,6,7,8-tetrahydroquinoline, with the formula :



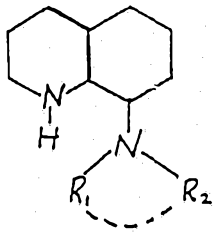
is condensed with an amine with the formula 

in which R^1 and R_2 have the significances indicated in Claim 1, so as to obtain a compound with the formula (II):



(II)

which is reduced so as to obtain a compound with the formula (III):



(III):

which is condensed with a compound with the formula (IV) or with a functional derivative of this compound:

(IV)

in which A and Z have the significance indicated in Claim 1, so as to obtain a compound with the formula (I) in all the enantiomeric and diastereo-isomeric forms possible, which is treated, if desired, with a mineral or organic acid, so as to obtain a salt or with an alkyl halogenide so as to obtain a quaternary ammonium salt.

9. 8-chloro-5,6,7,8-tetrahydroquinoline.

10. The products with the formulae (II) and (III) as defined in Claim 6, with the exception of the product of formula (II) in which R_1 and R_2 each represents an atom of hydrogen.

597326

Australia

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

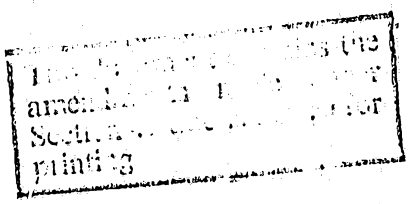
Int. Cl:

Application Number: 67476/87.
Lodged:

Complete Specification—Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:



TO BE COMPLETED BY APPLICANT

Name of Applicant: ROUSSEL-UCLAF

Address of Applicant: 35, Boulevard des Invalides, 75007 Paris, France.

Actual Inventor: FRANÇOIS CLEMENCE, MICHEL FORTIN, ODILE LE MARTRET and FRANÇOISE DELEVALLEE.

Address for Service: CALLINAN AND ASSOCIATES, Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

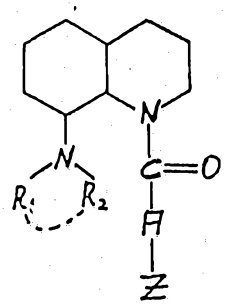
Complete Specification for the invention entitled: "NEW DERIVATIVES OF DECAHYDROQUINOLINE, THEIR PREPARATION PROCESS, THE PREPARATION INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, including the best method of performing it known to me:—*

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

The invention is concerned with the derivatives of decahydroquinoline, the process for their preparation, their use as medicaments, the pharmaceutical compositions containing them and the intermediates obtained.

The subject of the invention is compounds with the formula (I):



(I)

in which R_1 and R_2, identical or different, represent a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocycle having a 5- or 6- membered ring, optionally including another heteroatom being oxygen or nitrogen, said heterocycle optionally being substituted by an alkyl or alkoxy radical containing from 1 to 5 carbon atoms,

A represents a chain $(CH_2)_n$ in which n represents a numeral 0 to 5, or A represents an alkylene chain substituted by an alkyl radical containing in all from 2 to 8 carbon atoms,

Z represents a phenyl radical optionally substituted by one or more identical or different radicals chosen from the group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen atoms, hydroxyl, trifluoromethyl, nitro or amino radicals, and monoalkylamino or dialkylamino radicals in which the alkyl radicals contain from 1 to 5 carbon atoms, or Z represents a naphthyl radical, an indenyl radical, a heteromonocyclic radical being selected from the group made up of thiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl and thienyl radicals, or a heterobicyclic radical being chosen from the group made up of indolyl, quinolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzoxazolyl and benzothiazolyl radicals, all these radicals optionally being substituted by one or more identical or different radicals chosen from the

group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, trifluoromethyl, nitro or amino radicals, monoalkylamino or dialkylamino radicals, of which the alkyl radicals contain from 1 to 5 carbon atoms, and phenyl radicals optionally substituted by one or more alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, or by one or more halogens,
the said compounds with the formula (I) being able to be in all their possible enantiomeric and diastereo-isomeric forms and in the form of addition salts with acids or quaternary ammonium salts.

When R_1 and R_2 represent an alkyl radical, it is preferred to be a methyl, ethyl, n-propyl or isopropyl radical.

When R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocycle, it is preferred to be a pyrrolidinyl, piperazinyl, piperidinyl or morpholinyl radical. This heterocyle can be substituted, for example by an alkyl or alkoxy radical containing from 1 to 5 carbon atoms.

By alkyl, alkoxy or halogen substituent, it is preferred to understand methyl, ethyl, linear or branched propyl or butyl, methoxy, ethoxy, linear or branched propoxy or butoxy, fluoro, chloro, bromo or iodo.

In the monoalkylamino acid and dialkyamino values, the alkyl radicals are preferably methyl or ethyl radicals.

When A represents a $(CH_2)_n$ chain, n is preferably 0 or 1.

When A represent an alkylene chain substituted by an alkyl radical, methyl or ethyl are preferably understood and A is then preferably a 1,1-ethanediyl, 1-methyl-1,2-ethanediyl, 1-methyl- or 2-methyl-1,3-propanediyl, or 1-ethyl-1,2-ethanediyl radical.

Furthermore, a compound with the formula (I) can exist in the form of four racemates, or pairs of enantiomers. The enantiomers of each pair can be separated by standard processes. The invention covers therefore all the enantiomeric and diastereo-isomeric forms of the compounds with the formula (I).

The addition salts with mineral or organic acids can be, for example, the salts formed with hydrochloric, hydrobromic, nitric, sulphuric, phosphoric, acetic, propionic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic and aspartic acids, alkanesulphonic acids such as

methanesulphonic acid and arylsulphonic acids such as benzenesulphonic acid.

The invention is concerned also with compounds with the formula (I) in the form of salts of quaternary ammonium.

By salts of quaternary ammonium, there are understood compounds with the formula (I), quaternised by products of the type R-Y, R being an alkyl radical having from 1 to 4 carbon atoms such as a methyl, ethyl, n-propyl or isopropyl radical and Y a halogenide anion, for example, a chloride, bromide or iodide.

The invention has particularly as its subject the compounds with the formula (I) in which R_1 and R_2 represent a methyl or ethyl radical, or form together with the nitrogen atom to which they are bonded, a pyrrolidinyl or pyridinyl radical, A represents a $(CH_2)_n$ chain where n is 0 or 1, or a 1,1-ethanediyl chain, Z represents a radical; phenyl, optionally substituted as hereinbefore disclosed, naphthyl, indenyl, pyridinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, quinolyl, benzofuranyl, benzo[b]-thienyl, benzimidazolyl, benzoxazolyl or benzothiazolyl, optionally substituted by one or more identical or different substituents as hereinbefore disclosed, as well as their addition salts with acids and their quaternary ammonium salts.

More particularly, the subject of the invention is the compounds with the formula (I) in which R_1 and R_2 and A are defined as above, and Z represents a phenyl, optionally substituted as hereinbefore disclosed, naphthyl, pyridinyl, thienyl, indolyl or benzo[b]thienyl radical, optionally substituted as hereinbefore disclosed,

or different substituents, as well as their addition salts with acids and their quaternary ammonium salts.

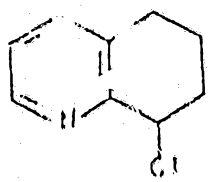
Quite particularly, the subject of the invention is the compounds with the formula (I) in which R_1 and R_2, together with the nitrogen atom to which they are bonded, form a pyrrolidinyl radical, A represents a $(CH_2)_n$ chain where n is 0 or 1, or a 1,2-ethanediyl chain, Z represents a phenyl radical substituted by one or more substituents chosen from the group made up of the halogen atoms and the trifluoromethyl radical or Z represents a naphthyl or benzo[b]-thienyl radical, as well as their addition salts with acids and their quaternary ammonium salts.

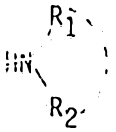
Quite particularly, the invention has as its subject the compounds with the formula (I) of which the names follow :

- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(3,4-dichloro-phenyl)acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[[4-(trifluoro-methyl)phenyl]acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[4-(bromophenyl)-acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[2-(3,4-dichloro-phenyl)1-oxopropyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-(3,4-dichloro-benzyl)-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[benzo[b]-thienyl)acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(1-naphthalenyl)-acetyl]-8-(1-pyrrolidinyl) quinoline,

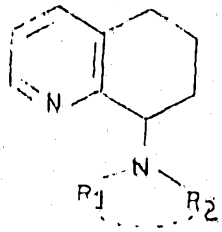
as well as their addition salts with acids and the quaternary ammonium salts.

The invention is concerned also with a process characterized in that 8-chloro-5,6,7,8-tetrahydro-quinoline, with the formula :

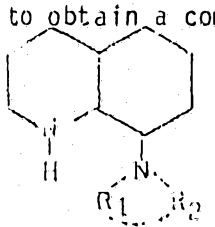


is condensed with an amine with the formula : 

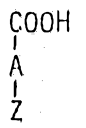
in which R_1 and R_2 have the previously indicated significances, in order to obtain a compound with the formula (II) :

 (II)

which is reduced in order to obtain a compound with the formula (III) :

 (III)

which is condensed with a compound with the formula (IV) or a functional derivative of this compound :

 (IV)

in which A and Z have the previously indicated significances, in order to obtain a compound with the formula (I) in all the possible enantiomeric and stereo-isomeric forms, which is treated, if desired, with a mineral or organic acid in order to obtain a salt or with an alkyl halogenide in order to obtain a quaternary ammonium salt.

More particularly, the invention has as its subject a process as previously defined, characterized in that if the reduction of the compound with the formula (II) is chemical, compounds with the formula (I) are preferentially obtained in which the junction of the ring is trans, and if the reduction of the compound with the formula (II) is catalytic, compounds with the formula (I) are preferentially obtained in which the junction of the ring is cis.

In a preferred method of carrying out the invention process :

- the chemical reduction agent used to reduce the compound with the formula (II) and enabling the compounds with the formula (I) in which

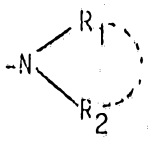
the junction of the ring is trans to be obtained preferentially is sodium in ethanol.

An alcoholate in another alcohol can also be used.

- The catalytic reduction of the compounds with the formula (II), in order to obtain preferentially the compounds with the formula (I) in which the junction of the ring is cis, is a catalytic hydrogenation. The catalyst preferably used is platinum oxide.

- The activation of the carboxyl function of the compound with the formula (IV) in order to carry out the condensation with the compound with the formula (III), is done in the presence of carbonyl diimidazole or of dicyclohexylcarbodiimide. The acid with the formula (IV) can also be activated in the form of an acid chloride or a mixed anhydride.

Furthermore, the two isomers corresponding to the alpha or beta orientations of the group :



with respect to the ring are separated by chromatography or by fractional crystallization of the salts for the products of formulae (II) and (III).

Each of the racemics obtained can be resolved by the usual methods, for example, by separation of the salts of the diastereoisomers obtained from optically active acids.

The compounds with the formula (I) as defined above as well as their addition salts with acids offer useful pharmacological properties. They present, in particular, a strong affinity for the opiate receptors and particularly for the K receptors and they are endowed with central analgesic properties.

They are also endowed with diuretic properties.

Furthermore, certain of them possess anti-arythmic, anti-ischemic and hypotensive properties.

These properties justify their use in therapeutics and the invention also has as its subject as medicaments, the products as defined by the formula (I) above, as well as their addition salts with pharmaceutically acceptable acids and their salts of quaternary ammonium.

The present invention has quite particularly as its subject, as medicaments, the previously mentioned preferred products, and notably :

- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(3,4-dichlorophenyl)acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[[4-(trifluoromethyl)phenyl]acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[4-(bromophenyl)-acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[2-(3,4-dichlorophenyl)1-oxopropyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-(3,4-dichlorobenzyl)-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[benzo[b]-thienyl)acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(1-naphthalenyl)-acetyl]-8-(1-pyrrolidinyl) quinoline,

as well as their addition salts with pharmaceutically acceptable acids and their salts of quaternary ammonium.

The medicaments which are the subject of the invention, enable in particular a pain to be alleviated, whatever its origin, for example, a pain of muscular, articular or nervous nature.

They can also be used in the treatment of dental pains, migraines, shingles, in the treatment of intense pains, in particular those resistant to peripheral antalgics, for example in the course of neoplasia processes, in the treatment of pancreatitis, nephritic or biliary colics, in the treatment of post-operation and post-traumatic pains.

The invention is extended to the pharmaceutical compositions containing the medicaments defined above as active principle.

These pharmaceutical compositions can be administered by oral, rectal or parenteral route, or by local route by topical application on the skin and the mucosa.

These compositions can be solid or liquid, and are presented in the pharmaceutical forms currently used in human medicine, for example, plain or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, ointments, creams, gels and preparations in aerosols; they are prepared according to the usual methods. The active principle can be incorporated in the excipients usually employed in

these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, the various wetting, dispersing or emulsifying agents, and preservatives.

The posology varies notably as a function of the administration route, the affection treated and the subject concerned.

For example, in an adult, it can vary between 20 and 400 mg of active principle per day by oral route, and between 5 and 100 mg per day by parenteral route.

The 8-chloro-5,6,7,8-tetrahydroquinoline, used as starting product in the invention process, is prepared by chlorination of 5,6,7,8-tetrahydroquinoline N-oxide according to the method indicated in the US patent 3,991,065.

This compound, however, is not described. The invention therefore has as its subject 8-chloro-5,6,7,8-tetrahydroquinoline, as a new industrial product.

The compounds with the formulae (II)(apart from that in which R_1 and R_2 each represents an atom of hydrogen) and (III) are new chemical products: the invention therefore has as its subject these products as new industrial products, particularly as necessary intermediate products for the operation of the process.

The following examples illustrate the invention, nevertheless without limiting it.

Example 1 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(3,4-dichlorophenyl)acetyl]-8-(1-pyrrolidinyl)quinoline hydrochloride

Stage A: 8-pyrrolidinyl-5,6,7,8-tetrahydroquinoline.

Over a period of 7 minutes, under agitation, and while allowing it to heat up, 50 ml of pyrrolidine is added to a solution containing 20 g of 8-chloro-5,6,7,8-tetrahydroquinoline (preparation given at the end of example 1) in 50 ml of water.

The temperature reaches 57° C at the end of the introduction and agitation is continued for 1 hour at this temperature. The temperature is then allowed to return to 20°C, the reactional medium is saturated

with sodium chloride, then extracted with ether. The organic phases are put together and dried, the solvents are eliminated under reduced pressure, and 20.22 g of the expected product is obtained in the form of an oil.

Stage B : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-8-(1-pyrrolidinyl) quinoline.

This product is obtained mixed with other diastereoisomers by reduction of the product obtained in the preceding stage A, either by catalytic hydrogenation or by a sodium-ethanol mixture.

The description of these two reductions is given at the end of Example 4.

Stage C : [4aRS(4a alpha, 8 alpha, 8a alpha)] (±)decahydro-1-[(3,4-dichlorophenyl)acetyl]-8-(1-pyrrolidinyl) quinoline.

A solution containing 873 mg of 3,4-dichlorophenyl acetic acid and 690 mg of carbonyldiimidazole in tetrahydrofuran is agitated for 1 hour at 20 - 25° C, then 645 mg of the product obtained at stage B in solution in 3 ml of tetrahydrofuran is added.

After agitating this for 4 hours at ambient temperature, the tetrahydrofuran is eliminated under reduced pressure at less than 40° C and the residue is taken up with 20 ml of ether. The solution is washed with a saturated solution of sodium bicarbonate, then with water saturated with sodium chloride, the ethereal phase is dried and distilled to dryness under reduced pressure.

1.39 g of the crude product is obtained.

Preparation of the hydrochloride

1.298 g of this last is dissolved in 5 ml of ether, filtered and rinsed with ether. 2 ml of ethanol is added to the filtrate and then 1.25 ml of a 5.75N solution in ethanol of hydrochloric acid is added until a pH of 1.2 is obtained.

Crystallization is initiated, and after leaving for 2 hours at 20-22° C, the crystals are separated, rinsed with a mixture of ethanol-ether (3-1) and then with ether. After drying under reduced pressure at 60° C, 852 mg of the hydrochloride is obtained. 825 mg of this latter is recrystallized from ethanol, and 722 mg of the expected product is obtained, melting at 233° C.

Analysis :

Calculated :	C% 58.41	H % 6.77	N % 6.48	Cl % 24.63
Found :	58.7	7.0	6.5	24.6

Preparation of the 8-chloro-5,6,7,8-tetrahydroquinoline (hydrochloride).

At ambient temperature, 3 ml of methane sulphonyl chloride is added slowly to 1.49 g of 5,6,7,8-tetrahydroquinoline N-oxide with agitation and under an inert atmosphere.

The mixture is heated for 4 hours at 80-82° C, then cooled to 20° C. and poured on to 20 ml of a saturated solution of sodium bicarbonate, then sodium bicarbonate is added until an alkaline pH is obtained. After extracting with methylene chloride, washing with water, drying the re-united organic solutions and distilling to dryness under reduced pressure, 1.53 g of the expected product is obtained in the form of an oil.

Preparation of the hydrochloride.

The above oil is dissolved in 2 ml of ethanol and 2 ml of a 5.75N solution in ethanol of hydrochloric acid is added. The hydrochloride crystallizes out, and after diluting slowly at 20-25° C with 4 ml of ether, the crystals are separated, rinsed first with a mixture of ethanol-ether (1-1) then with ether, and dried under reduced pressure at 20° C. After re-crystallizing from ethanol, 0.893 g of the expected product is obtained, m.p. 240° C.

Example 2 : [4aRS(4a alpha, 8 beta, 8a alpha)](±)decahydro-1-[(3,4-dichlorophenyl)acetyl]-8-(1-pyrrolidinyl) quinoline oxalate.

By operating as indicated at stage C of example 1, starting with 876 mg of [4aRS(4a alpha, 8 beta, 8a alpha)](±)decahydro-8-(1-pyrrolidinyl) quinoline (preparation given at the end of Example 4) 1.660 g of product is obtained. After chromatographing on silica, (eluent : ethyl acetate with 1 % of triethylamine), 316 mg of the expected product is obtained, melting at 90° C in the form of a base.

Preparation of the oxalate

280 mg of the above product is dissolved in 1.5 ml of 100 % ethanol, filtered, rinsed with ethanol, and 130 mg of oxalic acid is added to the filtrate. The solution obtained is diluted slowly with ml of ether, crystallization is initiated, and after leaving f hour at ambient temperature, separating, and drying under red

pressure at 65° C., 319 mg of product is obtained. 286 mg of this is re-crystallized from ethanol and 223 mg of the expected product is obtained, melting at 140° C.

Analysis :

Calculated :	C %	54.34	H %	5.89	N %	5.28	Cl % 13.37
Found :		54.5		5.9		5.4	13.2

Example 3 : [4aRS(4a alpha, 8 alpha, 8a beta)](±)decahydro-1-[(3,4-dichlorophenyl)acetyl]-8-(1-pyrrolidinyl) quinoline hydrochloride

A solution containing 1.98 g of 3,4-dichlorophenyl acetic acid, and 1.56 g of carbonyldiimidazole in 17 ml of tetrahydrofuran is agitated at 20-22° C for one hour. then 1.679 g of [4aRS(4a alpha, 8 alpha, 8a beta)] (±)decahydro-8-(1-pyrroli nyl) quinoline (preparation given at the end of Example 4) is added in solution in 5 ml of tetrahydrofuran.

The solution is agitated for 4 hours at 20-22° C, then the tetrahydrofuran is eliminated under reduced pressure at less than 45° C. The residue obtained is triturated in 15 ml of ether and in 5 ml of a saturated solution of sodium bicarbonate, then separated and rinsed, first with water then with ether. After drying under reduced pressure, 2.320 g of the expected product is obtained in the form of a base, melting at 138° C.

Preparation of the hydrochloride

2.309 g of crude base is dissolved at reflux in 2 ml of ether, 2 ml of a 5.75N solution in ethanol of hydrochloric acid is added, and after filtering hot, the product crystallizes out on cooling of the filtrate. The crystals are separated, rinsed with ethanol and ether, dried under reduced pressure at 65-70° C. and 1.816 g of the expected product is obtained, melting at 214° C.

Analysis	:	C %	H %	N %	Cl %
Calculated	:	58.41	6.77	6.48	24.63
Found	:	58.6	6.8	6.6	24.6

Example 4 : [4aRS(4a alpha, 8 beta, 8a beta)](±)decahydro-1-[(3,4-dichlorophenyl)-acetyl]-8-(1-pyrrolidinyl) quinoline fumarate

1.384 g of the product is obtained by operating as indicated at stage C of example 1, starting with 707 mg of [4aRS(4a alpha, 8 beta, 8a beta)](±)-decahydro-8-(1-pyrrolidinyl) quinoline (preparation given at the end of Example 4).

The oil obtained is then triturated in 10 ml of n-hexane. Crystallization is initiated, followed by separating, rinsing with n-hexane and drying under reduced pressure at 20° C. 746 mg of the expected product is obtained in the form of a base. m.p. = 82-84°C.

Preparation of fumarate.

At 60° C, 817 mg of product obtained as above is dissolved in 8 ml of ethanol, then filtered and rinsed with boiling ethanol. 285 mg of fumaric acid is added to the filtrate and the whole is taken to reflux under agitation. Crystallization takes place on cooling, the crystals are separated, rinsed with ethanol and ether, then dried under reduced pressure at 70° C, and 9.49 mg of product is obtained, melting at 220° C.

Analysis	:	C %	H %	N %	Cl %
Calculated	:	58.71	6.31	5.48	13.86
Found	:	58.4	6.3	5.4	13.7

Preparation of the 4 following diastereoisomers to be used for the preparation of examples 1 to 4.

- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-8-(1-pyrrolidinyl) quinoline = diastereo-isomer (cis A),
- [4aRS(4a alpha, 8 beta, 8a alpha)](±)decahydro-8-(1-pyrrolidinyl) quinoline = diastereo-isomer (cis B),
- [4aRS(4a alpha, 8 alpha, 8a beta)](±)decahydro-8-(1-pyrrolidinyl) quinoline = diastereo-isomer (trans A),
- [4aRS(4a alpha, 8 beta, 8a beta)](±)decahydro-8-(1-pyrrolidinyl) quinoline = diastereo-isomer (trans B).

These 4 diastereoisomers are obtained by reduction of the 8-pyrrolidinyl-tetrahydro-5,6,7-8-quinoline prepared at stage A of example 1.

1) Catalytic reduction.

There is introduced into a hydrogenating apparatus :

6.24 g of 8-pyrrolidinyl-tetrahydro-5,6,7,8-quinoline,

62 ml of methanol

6.2 ml of hydrochloric acid,

690 mg of platinum oxide.

Hydrogenation is carried out at 22-25° C. at a pressure of 1850 mbars over 17 hours ; the absorption of hydrogen lasts about 4 hours 30 minutes.

The catalyst is filtered off and after rinsing and distilling to dryness under reduced pressure, 8.67 g of the product of reduction is obtained.

a) Crystallization of the hydrochloride of the diastereo-isomer cis A.

The resin previously obtained is dissolved at 50-60° C. in 16 ml of isopropanol and crystallization is initiated at 20° C. After diluting with 12.5 ml of ether, the crystals are separated and rinsed with a mixture of isopropanol and ethyl ether (1-1), then with ether, then dried under reduced pressure at 50° C. The product obtained is recrystallized from 42.5 ml of isopropanol with 2 % of water; the crystals are separated, rinsed with isopropanol, then with ether, and 2.150 g of the expected product is obtained in the form of the hydrochloride, melting at 210°C.

b) Return to the base

1 g of the hydrochloride is dissolved in 10 ml of water, then 2 ml of 2N sodium hydroxide is added, followed by extraction with ether, decanting, and washing with water saturated with sodium chloride. The ethereal solution is dried and distilled to dryness under reduced pressure, and 0.680 g of the expected product is obtained in the form of the base.

c) Preparative chromatography of the mother-liquors of crystallization of the hydrochloride of the diastereo-isomer cis A.

The mother-liquors of crystallization of the hydrochloride of isomer cis A are put together and the return to the base is carried out in water and ethyl acetate by sodium hydroxide. After extraction, washing with water saturated with sodium chloride, drying and distilling to dryness under reduced pressure, chromatography is carried out on silica at ambient pressure. (eluent : ethyl acetate, 85 - methanol 10 - triethylamine 5).

The diastereoisomers cis B, trans A and cis A are recovered successively.

- diastereoisomer cis B.

The homogeneous elution fractions are taken to dryness under reduced pressure, and 2.059 g of the expected product is obtained.

- diastereoisomer trans A

The following fractions are taken to dryness under reduced pressure and 0.564 g of product is obtained. The hydrochloride is made and is crystallized from an ethanol-ether (1-1) mixture, then the return to the base is carried out on 201 mg of hydrochloride in water, ether and 2N sodium hydroxide. 139 mg of the expected product is obtained..

- diastereoisomer cis A

The corresponding eluents are taken to dryness under reduced pressure and 0.686 g of a brown resin is obtained which gives a hydrochloride melting at 210° C.

2) Chemical reduction

Under a pressure of 2.5 to 3 cm of mercury, a solution containing 10.14 g of 8-pyrrolidinyl-tetrahydro-5,6,7,8-quinoline in 400 ml of ethanol is taken to reflux at 20° C, then, at reflux and over about 7 hours, 18 g of sodium is introduced in small portions. After bringing back to 20° C under nitrogen, allowing to rest for one night, then taking to reflux again, 14 g of sodium is introduced in small portions over 5 hours. The reactional mixture is brought back to 20° C under nitrogen, then poured on to 400 ml of iced water under agitation; the ethanol is eliminated by distilling under reduced pressure at less than 50° C. The residual medium is saturated with 28 g of sodium chloride, then extracted with ether, and the ethereal phases are washed with water saturated with sodium chloride. After drying and distilling to dryness under reduced pressure, 6.68 g of the crude expected product is obtained, in the form of a mixture.

After this a :

preparative chromatography to separate the trans B, trans A and cis-A diastereo-isomers

is carried out.

A chromatography is carried out on silica (eluent : ethyl acetate 85 - methanol 10 - triethylamine 5).

- diastereo-isomer trans B

The fractions containing the first isomer are taken to dryness under reduced pressure, and 1.183 g of an oil is obtained. 1.163 g of this oil is dissolved in 2 ml of ethanol, filtered and rinsed with ethanol, then 830 mg of oxalic acid is added to the filtrate. The solution obtained is diluted slowly with 40 ml of ether and a precipitate forms.

The supernatant solution is decanted, the gum is washed with ether, then dissolved in 7 ml of water and 20 ml of ether and 2 ml of sodium hydroxide is added. The mixture is shaken in a flask, decanted, and washed with water saturated with sodium chloride; the ethereal solutions are dried, rinsed and distilled to dryness under reduced pressure.

1.010 g of the expected product is obtained.

- diastereoisomer trans A

Under reduced pressure, the homogeneous fractions from chromatography corresponding to the isomer trans A are taken to dryness and 2.332 g of an oil is obtained. 2.322 g of this oil is dissolved in 2.5 ml of ethanol, the filtrate is diluted with 9.5 ml of ether, and 5 ml of a 5.75N solution of hydrochloric acid in ethanol is added. The hydrochloride obtained is separated, washed with a mixture of ethanol and ether (1-1), then with ether, dried under reduced pressure at 60° C, and 2.569 g of diastereo-isomer is obtained in the form of the hydrochloride.

The return to the base is carried out by treating 2.464 g of the hydrochloride with 10 ml of water and 2 ml of 32 % sodium hydroxide, then agitating, decanting and re-extracting with ether.

The ethereal phases are washed with water saturated with sodium chloride, dried, and distilled to dryness under reduced pressure, and 1.679 g of the expected product is obtained.

- diastereoisomer cis A

Under reduced pressure, the homogeneous fractions from chromatography corresponding to the diastereoisomer cis A are taken to dryness and 0.579 g of the expected product is obtained.

This is dissolved in 5 ml of isopropanol and 2 ml of a 4.4M solution of

dry hydrochloric acid in isopropanol is added. After diluting with 7 ml of ether, 0.15 ml of water is added, and crystallization is initiated. The crystals are separated, rinsed with a mixture of isopropanol - ether (1-1) and with ether, then dried under reduced pressure at 60° C, and 504 mg of the cis A diastereoisomer is obtained in the form of the hydrochloride. m.p. = 210° C.

The return to the base is carried out on 64 mg of the hydrochloride as indicated for the hydrochloride of the diastereoisomer trans A. 42 mg of the expected product is obtained.

Example 5 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(4-chlorophenylacetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride.

The operation is done as at stage C of example 1, starting with 554 mg of 4-chlorophenyl acetic acid, 527 mg of carbonyldiimidazole and 520 mg of the product obtained at stage A of example 1, keeping the reactional medium under agitation for 5 hours. After crystallization of the hydrochloride from a mixture of isopropanol and ether (1-1), 752 mg of the expected product is obtained. m.p. ≃ 222° C. (decomposes).

Analysis : $C_{21}H_{29}ClN_2O$, HCl = 397.391.

	C %	H %	N %	Cl %
Calculated :	63.47	7.61	7.05	17.84
Found :	63.6	7.6	6.8	17.8

Example 6 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(4-trifluoromethyl)phenyl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride.

The operation is done as in the preceding example, using 663 mg of 4-trifluoromethylphenyl acetic acid and maintaining agitation for 16 hours. After crystallization of the hydrochloride from ethanol, 921 mg of the expected product is obtained. m.p. ≃ 208° C. (decomposes).

Analysis : $C_{22}H_{29}F_3N_2O$, HCl = 430.944

	C %	H %	N %	Cl %	F %
Calculated :	61.32	7.02	6.50	8.23	13.22
Found :	61.4	7.1	6.4	8.1	12.9

Example 7 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(4-(bromophenyl) —— acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

The operation is done as in example 5, using 699 mg of 4-bromophenyl acetic acid and maintaining agitation for 20 hours. After crystallization of the hydrochloride from isopropanol, 685 mg of the expected product is obtained. m.p. ≃ 235° C. (decomposes).

Analysis : $C_{21}H_{29}BrN_2O$, HCl : 441,847

Calculated :	C % 57.09	H % 6.84	N % 6.34	Cl % 8.02	Br % 18.08
Found :	57.4	6.9	6.3	7.8	18.0

Example 8 ; [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(4-nitrophenyl)-acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

The operation is done as at stage C of example 1, starting with 471 mg of p-nitrophenyl acetic acid, 422 mg of carbonyldiimidazole and 417 mg of the product prepared as at stage B of example 1, maintaining agitation for 3 hours. After crystallization of the hydrochloride from ethanol, 606 mg of the expected product is obtained.

m.p. 249° C. (decomposes).

Analysis : $C_{21}H_{29}N_3O_3$, HCl : 407,944

Calculated :	C % 61.83	H % 7.41	N % 10.30	Cl % 8.67	
Found :	61.8	7.5	10.1	8.5	

Example 9 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(3,4-dimethoxyphenyl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

The operation is done as in example 8, using 510 mg of 3,4-dimethoxyphenyl acetic acid, maintaining agitation for 20 hours. 571 mg of the expected hydrochloride is obtained.

m.p. 250° C. (decomposes).

Analysis : $C_{23}H_{34}N_2O_3$, HCl : 422,999

Calculated :	C % 65.31	H % 8.34	N % 6.62	Cl % 8.38	
Found :	65.3	8.4	6.4	8.4	

Example 10 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(2,4-dichlorophenyl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

The operation is done as in example 9, using 533 mg of 2,4-dichlorophenyl acetic acid and maintaining agitation for 4 hours. The expected product is obtained, m.p. > 260° C.

Analysis : $C_{21}H_{28}Cl_2N_2O$, HCl : 431.836

Calculated :	C % 58.41	H % 6.77	N % 6.48	Cl % 24.63	
Found :	58.7	6.8	6.5	24.6	

Example 11 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(1-naphthalenyl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline

The operation is done as in example 8, using 484 mg of alpha-naphthyl acetic acid, and maintaining agitation for 20 hours. 769 mg of the expected product is obtained. m.p. ≃ 262° C.

Analysis : $C_{25}H_{32}N_2O$, HCl : 413.007

Calculated :	C % 72.70	H % 8.05	N % 6.78	Cl % 8.58
Found :	72.9	8.2	6.8	8.7

Example 12 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[2-(3,4-dichlorophenyl)-1-oxopropyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride (isomer A).

The operation is done as in example 8, using 482 mg of alpha-methyl-3,4-dichlorophenyl acetic acid, dl, and maintaining agitation for 24 hours. 334 mg of the expected hydrochloride is obtained. (decomposes).

Analysis : $C_{22}H_{30}Cl_2N_2O$, HCl : 445.863

Calculated :	C % 59.26	H % 7.01	N % 6,28	Cl % 23.85
Found :	59,2	7.0	6.3	23.6

Example 13 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[2-(3,4-dichlorophenyl)-1-oxopropyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride (isomer B).

570 mg of alpha-methyl-3,4-dichlorophenyl acetic acid, and 417 mg of the product prepared as at stage B of example 1 in 5 cm^3 of methylene chloride are agitated for 40 hours at ambient temperature in the presence of 20 mg of 4-dimethylaminopyridine and 635 mg of dicyclohexylcarbodiimide. The dicyclohexylurea formed is filtered off and the filtrate is concentrated to dryness under reduced pressure. The residue is taken up in 50 cm^3 of ether, washed with a saturated aqueous solution of sodium bicarbonate, then with water and dried.. The solvents are eliminated under reduced pressure, the residue is taken up in ether and the crystallized product is separated. The mother liquors of crystallization are concentrated to dryness, and 905 mg of crude product is obtained, which is chromatographed on silica (eluent : ethyl acetate with 2% of triethylamine). 378 mg of isomer A and 303 mg of isomer B are obtained in the form of a base. 287 mg of the isomer B base is dissolved in 1 cm^3 of ether, then filtered and rinsed with ether and with ethanol. 0.5 cm^3 of a 5.75N ethanol solution of hydrochloric acid is added to the filtrate, and after this is concentrated under reduced pressure to a volume of 0.5 cm^3, 10 cm^3 of ether is added. The crystallized product is separated and dried at 70° C under reduced pressure. 146 mg of the expected product is collected. m.p. ≃ 254° C (decomposes).

Analysis : $C_{22}H_{30}Cl_2N_2O$, HCl = 445.863

Calculated :	C % 59.26	H % 7.01	N % 6.28	Cl % 23.85	
Found :	59.3	7.0	6.3	23.7	

Example 14 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(benzo[b]-thien-4-yl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

The operation is done as in example 8, using 500 mg of 4-thia-naphthalene acetic acid, and maintaining agitation for 6 hours. 655 mg of the expected hydrochloride is obtained. m.p. > 260° C.

Analysis : $C_{23}H_{30}N_2OS$, HCl = 419.032

Calculated :	C % 65.93	H % 7.46	N % 6.68	S % 7.65	Cl % 8.46
Found :	65.8	7.6	6.6	7.3	8.7

Example 15 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(1H-indol--3-yl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline fumarate

The product is prepared in the form of the base by operating as in example 8, using 455 mg of 3-indole acetic acid and maintaining under agitation for 40 hours. The fumarate is prepared by operating as in example 4, and after recrystallizing from methanol, 233 mg of the expected product is obtained. m.p. > 260° C.

Analysis : $C_{23}H_{31}N_3O$ 1/2 $C_4H_4O_4$ = 423.560

Calculated :	C % 70.89	H % 7.85	N % 9.92
Found :	70.8	8	9.8

Example 16 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-(phenyl-acetyl)decahydro-8-(1-pyrrolidinyl) quinoline fumarate.

The operation is done as indicated in example 14, using 442 mg of phenyl acetic acid, 527 mg of carbonyldiimidazole and 521 mg of the product prepared at stage B of example 1, and maintaining the agitation for 16 hours. 641 mg of the expected fumarate is obtained after crystallization from ethanol. m.p. = 228° C.

Analysis : $C_{21}H_{30}N_2O$ = 442.56

Calculated :	C % 67.85	H % 7.74	N % 6.35
Found :	67.8	7.8	6.3

Example 17 : [4aRS(4a alpha, 8 alpha,8a alpha)](±)-1-[(4-methyl-phenyl)acetyl]decahydro-8-(1-pyrrolidinyl) quinoline fumarate.

The operation is done as in example 8, using 390 mg of p-tolyl acetic acid, and maintaining agitation for 6 hours. The product obtained in the form of a base is converted into a fumarate according to the method indicated in example 4. After recrystallizing

from isopropanol, 458 mg of the expected product is obtained.
m.p. = 198° C.

Analysis : $C_{22}H_{32}N_2O$, 1.5 $C_4H_4O_4$ = 514,624
Calculated : C % 65.35 H % 7.44 N % 5.4
Found : 65.1 7.5 5.3

Example 18 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-/(4-pyridinyl) acetyl)decahydro-8-(1-pyrrolidinyl) quinoline fumarate

The operation is done as in example 8, using 452 mg of 4-pyridyl acetic acid, maintaining agitation for 3 hours. The product obtained in the form of a base is converted into a fumarate according to the method indicated in example 4. 373 mg of the expected fumarate is obtained. m.p. = 232° C.

Analysis : $C_{20}H_{29}N_3O$, 1.5 $C_4H_4O_4$ * 501.585
Calculated : C % 62.26 H % 7.03 N % 8.38
Found : 62.2 7.1 8.4

Example 19 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-(2-thienyl-acetyl)decahydro-8-(1-pyrrolidinyl) quinoline fumarate

The operation is done as in example 13, using 512 mg of thiophene acetic acid, 521 mg of the product prepared as at stage B of example 1, 816 mg of dicyclohexylcarbodiimide and 10 mg of dimethylaminopyridine. After 42 hours of agitation at ambient temperature, the product is obtained in the form of the base which is converted into fumarate by the method indicated in example 4. 648 mg of the expected acid fumarate is obtained. m.p. = 252° C. (decomposes).

Analysis : $C_{19}H_{28}N_2OS$, $C_4H_4O_4$ = 448.585
Calculated : C % 61.58 H % 7.19 N % 6.24 S % 7.15
Found : 61.5 7.3 6.2 7.02

Example 20 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-(3,4,5-trimethoxybenzoyl)decahydro-8-(1-pyrrolidinyl) quinoline hydrochloride

510 mg of 3,4,5-trimethoxybenzoyl chloride and 417 mg of the product obtained at stage B of example 1 are made to react in ether for 40 hours at ambient temperature. The crude product is obtained in the form of the base which is converted into the hydrochloride as indicated in example 1. 319 mg of the expected product is obtained.
m.p. ≃ 260° C.

Analysis : $C_{23}H_{34}N_2O_4$, HCl : 438,999
Calculated : C% 62.93 H% 8.04 N% 6.38 Cl% 8.07
Found : 62.7 8.1 6.3 8.0

Example 21 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-(4-bromobenzoyl)decahydro-8-(1-pyrrolidinyl) quinoline fumarate

The operation is done as in example 20, using 483 mg of bromobenzoyl chloride, and maintaining the reaction for 22 hours at ambient temperature. The crude product is obtained in the form of the base which is converted into the fumarate by the method indicated in example 4. 457 mg of the expected product is recovered.
m.p. = 206° C (decomposes).

Analysis : $C_{20}H_{27}BrN_2O$, $C_4H_4O_4$: 507.434

	C %	H %	N %	Br %
Calculated	56.80	6.16	5.52	15.74
Found	56.6	6.2	5.5	15.6

Example 22 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-(3,4-dichlorobenzoyl)decahydro-8-(1-pyrrolidinyl) quinoline fumarate

The operation is done as in example 20, using 461 mg of 3,4-dichlorobenzoyl chloride, and maintaining the reaction for 20 hours at ambient temperature. The crude product is obtained in the form of a base which is converted into the fumarate by the method indicated in example 4. 547 mg of the expected product is recovered. m.p. = 202° C.

Analysis : $C_{20}H_{26}Cl_2N_2O$, $C_4H_4O_4$: 497.423

	C %	H %	N %	Cl %
Calculated	57.95	6.08	5.63	14.25
Found	57.7	6.2	5.6	14.1

Example 23 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(3,4-dichlorophenyl)acetyl]decahydro-8-dimethylamino quinoline hydrochloride

Stage A : N,N-dimethyl-5,6,7,8-tetrahydro-8-quinolinamine.

4.08 g of 8-chloro-5,6,7,8-tetrahydroquinoline hydrochloride, prepared as indicated at the end of example 1, is mixed under agitation for 75 minutes in 20 cm^3 of a 40% aqueous solution of dimethylamine. This is heated for 1 hour at 65° C ± 2° C, then allowed to cool to ambient temperature, the reactional medium is saturated with sodium chloride and 0.3 cm^3 of 2N sodium hydroxide is added. After extracting with ether, the extracts are washed with water, dried, and

the solvent is eliminated under reduced pressure. 3.35 g of the expected product is obtained which is used as it is for the following stage.

Stage B : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-N,N-dimethyl-decahydro-8-quinolinamine (isomer cis A) and /4aRS(4a alpha, 8 beta, 8a alpha)/ (±) N,N-dimethyl-decahydro-8-quinolinamine (isomer cis B).

1) Catalytic reduction

3.35 g of the product obtained at stage A, 33 cm^3 of methanol and 3.3 cm^3 of hydrochloric acid are introduced into a hydrogenation apparatus in the presence of 0.37 g of 80% platinum oxide. Hydrogenation is continued for 7 hours at 22°-24° C at a pressure of 1840 mbars. The catalyst is filtered off, and after rinsing and concentrating to dryness under reduced pressure, 4.85 g of the expected product is obtained.

2) Crystallization of the hydrochloride of the isomer cis A

The dried extract is taken up in 15 cm^3 of isopropanol, and crystallization is initiated. After leaving for 1 hour at ambient temperature, the crystals are filtered off, rinsed with isopropanol and with ether, then dried under reduced pressure at 50° C. After re-crystallizing from ethanol, 1.27 g of the expected product is recovered in the form of the hydrochloride. m.p. > 260° C.

3) Return to the base

1.237 g of the product obtained above is dissolved in 5 cm^3 of water which is then saturated with sodium chloride and 2 cm^3 of 2N sodium hydroxide is added. Extraction is done with ether, the extracts are dried and the solvent is eliminated under reduced pressure. 0.952 g of the expected product is obtained in the form of the base.

4) Preparation of the cis B isomer

The mother liquors of crystallization of the hydrochloride of the cisA isomer are put together and concentrated to dryness under reduced pressure. The residue is taken up in 10 cm^3 of water, saturated with sodium chloride and alkalized with 2N sodium hydroxide. Extraction is done with ether, the extracts are dried and the solvent is eliminated under reduced pressure. After chromatography on silica (eluent : ethyl acetate - methanol - triethylamine 85-10-5), 384 mg of the expected product is recovered.

Stage C : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(3,4-dichlorophenyl)acetyl]decahydro-8-dimethylamino quinoline.

1.160 g of dicyclohexylcarbodiimide is added to a solution comprising 855 mg of the cis A isomer in the form of the base prepared at stage B 3) and 1.160 g of 3,4-dichlorophenyl acetic acid in 15 cm^3 of methylene chloride. The whole is agitated for 18 hours, the urea formed is eliminated by filtering, and the filtrate is concentrated to dryness under reduced pressure. The residue is taken up in 50 cm^3 of ether, washed with a saturated aqueous solution of sodium bicarbonate, and extracted with ether. The extracts are dried and the solvent is eliminated under reduced pressure. 2.5 g of product is recovered in the form of the base which is dissolved in 15 cm^3 of ethanol. 2 cm^3 of a 5.75N solution in ethanol of hydrochloric acid is added, and crystallization is allowed for 1 hour. The crystals are filtered off and dried, rinsed with ethanol and then with ether and dried at 50° C under reduced pressure. 1.064 g of the expected product is obtained. m.p. ≃ 256° C.

Analysis : $C_{19}H_{26}Cl_2N_2O$, HCl : 405.798

	C %	H %	N %	Cl %
Calculated :	56.24	6.70	6.90	26.21
Found :	56.1	6.7	6.8	25.8

Example 24 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[3,4-dichlorophenyl)acetyl]decahydro-8-dimethylamino quinoline oxalate

The operation is done as at stage C of example 23, starting with 844 mg of the isomer cis B prepared at stage B 4) of example 23. 2.065 g of product is obtained in the form of the base. 1.22 g of this base and 0.7 g of dihydrated oxalic acid are dissolved in 5 cm^3 of ethanol, then filtered, rinsed with ethanol, and 30 cm^3 of ether is added to the filtrate. The crystals are separated, rinsed with an ethanol-ether (1-3) mixture and then with ether, and dried under reduced pressure at 70° C. 1.132 g of the expected oxalate is obtained. m.p. = 159° C.

Analysis : $C_{19}H_{26}Cl_2N_2O$: 459.373

	C %	H %	N %	Cl %
Calculated :	54.90	6.14	6.10	15.44
Found :	54.8	6.0	6.9	15.2

Example 25 : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[3,4-dichlorophenyl)acetyl]decahydro-8-(1-piperidinyl) quinoline hydrochloride

Stage A : 8-(1-piperidinyl)-5,6,7,8-tetrahydroquinoline.

3.9 cm^3 of piperidine is introduced into a solution comprising 2 g of 8-chloro-5,6,7,8-tetrahydroquinoline hydrochloride in 5 cm^3 of water, agitated for 15 minutes, heated for two-and-a-half hours at 57° ± 2° C, then cooled to ambient temperature. The medium is saturated with sodium chloride, then extracted with ether. The solvent is eliminated under reduced pressure, and 2.07 g of the expected product is obtained.

Stage B : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-8-(1-piperidinyl) quinoline (isomer cisA) ; [4aRS(4a alpha, 8 beta, 8a alpha)](±)decahydro-8-(1-piperidinyl) quinoline (isomer cis B) and [4aRS(4a alpha, 8 alpha, 8a beta)](±)decahydro-8-(1-piperidinyl) quinoline (isomer trans A).

1.974 g of the product obtained at stage A in 30 cm^3 of ethanol is hydrogenated for 6 hours at a pressure of 1850 mbars and at ambient temperature in the presence of 3 cm^3 of hydrochloric acid and 0.2 g of platinum oxide: the catalyst is filtered off, and the filtrate is rinsed and concentrated to dryness under reduced pressure. The residue is taken up by 10 cm^3 of water, 12 cm^3 of sodium hydroxide is added, and extraction is done with ethyl acetate. The extracts are driedand the solvent is eliminated under reduced pressure. 2.04 g of crude product is obtained which is chromatographed on silica (eluent : ethyl acetate - methanol - triethylamine 85-10-5). 551 mg of isomer cis A, 733 mg of isomer cis B and 353 mg of isomer trans A are obtained.

Stage C : [4aRS(4a alpha, 8 alpha, 8a alpha)](±)-1-[(3,4-dichlorophenyl)acetyl]decahydro-8-(1-piperidinyl) quinoline hydrochloride.

479 mg of 3,4-dichlorophenyl acetic acid and 467 mg of cis A isomer prepared at stage B are made to react for 6 hours in 7.2 cm^3 of methylene chloride in the presence of 482 mg of dicyclohexylcarbodiimide. The dicyclohexylurea formed is filtered off, the filtrate is concentrated to dryness under reduced pression, and the residue is taken up by 30 cm^3 of etnyl acetate. The organic phase is washed with a saturated aqueous solution of sodium bicarbonate, then with water, then dried, and the solvent is eliminated under reduced pressure. 1.117 g of crude product is obtained in the form of the base which is converted into the hydrochloride by the method indicated in example 1. 600 mg of the expected product is recovered. m.p. > 260° C.

Analysis : $C_{22}H_{30}Cl_2N_2O$, HCl : 445.863

Calculated : C % 59.26 H % 7.01 N % 6.28 Cl % 23.85

Found 59.4 7.2 6.2 24.0

Example 26 : [4aRS(4a alpha, 8 beta, 8a alpha)](+)-1-[(3,4-dichlorophenyl)acetyl]decahydro-8-(1-piperidinyl) quinoline fumarate

The operation is done as in stage C of example 25, using 550 mg of 3,4-dichlorophenyl acetic acid and 537 mg of cis B isomer prepared at stage B of example 25 and by allowing reaction for 20 hours at ambient temperature. 1.296 g of crude product is obtained in the form of the base which is converted into the fumarate as indicated at example 4. 202 mg of the expected product is collected. m.p. ≃ 227° C.

Analysis : $C_{22}H_{30}Cl_2N_2O$, $C_4H_4O_4$: 525.177

Calculated : C % 59.43 H % 6.52 N % 5.33 Cl % 13.49

Found : 59.3 6.8 5.1 13.5

Example 27 : [4aRS(4a alpha,8alpha, 8a alpha)](±)-1-[1-[(3,4-dichlorophenyl)acetyl]decahydro-8-quinolenyl]-1-methyl-pyrrolidinium

6 g of methyl bromide is added to a solution comprising 401 mg of product from example 1 in the form of the base in 6 cm^3 of tetrahydrofuran. This is agitated for 24 hours at ambient temperature, then separated; the crystallized product is rinsed with tetrahydrofuran, then with ether, and dried under reduced pressure at 70° to 80° C. 455 mg of the expected product is obtained, m.p. ≃ 170° C.

Analysis : $C_{22}H_{31}BrCl_2N_2O$: 490.319

Calculated : C % 53.89 H % 6.37 N % 5.71 Cl % 14.46 Br % 16.3

Found : 53.8 6.5 5.5 13.7 14.9

Example 28 :

Tablets responding to the following formula have been prepared :

- Product of example 1 ..... 200 mg
- excipient q.s. for ..... 800 mg

(detail of excipient : lactose, talc, starch, magnesium stearate.

Example 29 :

An injectable solution (intramuscular route) has been prepared responding to the following formula :

- product of example 1 ..... 50 mg
- sterile solvent q.s. for ..... 5 ml.

PHARMACOLOGICAL STUDY

1) Bond with the opiate receptor K in vitro

Membrane residues are used, kept at -30° C for about 30 days, and prepared from the cerebella of guinea-pigs.

These residues are put back into suspension in Tris buffer pH7.7. 2 ml fractions are distributed in hemolysis tubes and 9^3H ethylketo-cyclazocine InM and the product under test are added. (The product is first tested at $5x10^{-6}M$ (in triplicate). When the product tested displaces by more than 50 % the radio-activity bonded specifically to the receptor, it is tested again over a range of 7 doses in order to determine the dose which inhibits by 50 % the radio-activity bonded specifically to the receptor. In this way, the 50 % inhibiting concentration is determined).

The non-specific bonding is determined by the addition of the product known under the name U-50488 H at $10^{-5}M$ (in triplicate). After incubating at 25° C for 40 minutes, returning to the water-bath at 0° C for 5 minutes, filtering under vacuum, and rinsing with Tris buffer pH 7.7, the radio-activity is counted in the presence of scintillating Trition.

The results are expressed directly as the 50 % inhibiting concentration (IC_{50}), (that is to say, in concentration of the product studied, expressed in nM, necessary in order to displace 50 % of the specific radio-activity fixed on the receptor studied,

Results :

Product of example	IC_{50} in nM
1	2.7
6	5
7	9.5
8	17
10	12
11	6
12	5.4
14	4.1
22	7.4

2) Analgesic activity

-Hot plate test.

Female mice weighing 22 to 24 g were placed one by one on a copper plate maintained at 56° C. : the reaction to the pain was shown by the animal licking its front paws ; the time of this reaction is noted and only the mice reacting in less than 8 seconds were retained.

The animals were distributed in homogeneous groups and treated with the product under study administered by sub-cutaneous route, one group receiving only the vehicle. The time of reaction to the pain is again measured 30 to 60 minutes after the treatment. The active dose, or AD_{100} is the dose which increases the reaction time by 100 %, 30 minutes after the treatment, taking account of the variations in the reaction time of the control animals.

For the product of example 1, the AD_{100} is 20 mg/kg.

-Stretchings Test

The test employed is based on the fact remarked by R. KOSTER et Coll.,(Fed. Proc., 1959, 18 412) according to which the intra-peritoneal injection of acetic acid in mice causes repeated movements of stretching and twisting which can persist for more than 6 hours. Analgesics prevent or diminish this syndrome which can be considered as

the exteriorisation of a diffuse abdominal pain. A 1 % solution of acetic acid in water is used. The dose which in these conditions causes the syndrome is 0.01 cm^3 per g, or 100 mg/kg of acetic acid.

The product studied is administered by oral route half-an-hour before the acetic acid injection, the mice having fasted since the day before the test.

The stretchings are observed and counted for each mouse during an observation period of 15 minutes beginning immediately after the injection of the acetic acid.

The results are expressed by the AD_{50}, that is to say, the dose which enables a reduction of 50% in the number of stretching in comparison with the control animals.

Results :

Product of example	DA_{50} in mg/kg
1	18
6	21
8	20

3) Anti-arrhythmic action in the rat

Male rats weighing 300 - 350 g, anaesthetized by intraperitoneal route with 1.20 g/kg of urethane are tracheotomized and submitted to an artificial respiration (40-50 breaths of 3 ml per minute).

Needles are implanted sub-cutaneously so as to record the electrocardiogram of the rats on the DII derivation signal.

The products under test are administered intravenously.

Five minutes after the product is administered, the jugular vein of the rats is perfused with 10 µg/mn from 0.2 ml of a solution of aconitrine and the time of appearance of disturbances of the cardiac rhythm is noted.

The results are expressed as a percentage of the extension of the time of appearance of the disturbances of the cardiac rhythm in comparison with controls and as a function of the dosage of the product

under test.

The results appearing in the following table show that certain of the products of the present application are endowed with good anti-arrhythmic properties.

Product of example	Dose mg/kg	Percentage of extension of time
1	10	+ 113.5
	5	+ 56.5
	2.5	+ 31.5
	1	+ 17.5
2	2.5	+ 182
	1	+ 93
	0.5	+ 46
	0.25	+ 26
3	10	+ 35.5
	5	+ 36
	2.5	+ 17
4	10	+ 112
	1	+ 38.5
	0.5	+ 10.5
20	1	+ 141
	0.5	+ 85
	0.25	+ 45

4) Test of asphyxic anoxia

The study is carried out on male rats (Charles River CD) (250-300 g), anaesthetized with ether, tracheotomized, paralysed with d-tubocuranine hydrochloride, 0.5 mg/kg IV, and submitted to artificial respiration with a mixture of 70% of nitrogen protoxide and 30% of oxygen. The body temperature is maintained at 37° C by an automatic temperature controller. Two silver-silver chloride electrodes were implanted on the cranium and fixed with dental cement, in the regions

of the visual cortex and the cerebellum, in order to record the E.E.G. (electro-encephalogram). A common carotid artery is catheterized in order to record the arterial pressure and the cardiac frequency. The values of paO_2, $paCO_2$ and of pH are measured before the anoxia and the frequency of the respiratory pump is adjusted in order to obtain the normal values.

The anoxia is obtained by disconnecting the respiratory pump, according to the technique described by I. ROSNER, J.LEGROS and C.BERGER, Arch. Int. Pharmacodyn. 194, 375 (1971).

After 3 minutes, the respiratory pump is restarted and the ventilation is maintained for 30 minutes.

Before the anoxia, at the end of the anoxia and 2, 10 and 30 minutes after restarting the ventilation the E.E.G. is recorded on an encephalograph and the power spectra of the E.E.G. are analysed by a PDP 11/34 digital computer. During the recording of the E.E.G. precautions are taken to avoid visual and acoustic stimulations.

5 periods of 10 seconds are selected by visual control each minute, in order to exclude artefacts and the analysis is made by Fourier transformation. The power spectrum is evaluated between 0 and 25 Hz with a resolution of 0.2 Hz.

The product under test is dissolved in Methocel at 0.5 %, and is administered by intravenous route at 1 and 5 mg/kg, 3 minutes before stopping the pump.

The values of paO_2, $paCO_2$ and of the pH are again measured 30 minutes after the anoxia. The mean arterial pressure (P.A.M.) and the cardiac frequency (F.C.) have been recorded.

Groups of 10 animals were used.

The results are given in table 1.

The total power and the energies of the different frequency bands are expressed as percentages of those recorded during the check before the anoxia. The standard deviations are shown just in order to indicate the dispersion of the data. The Mann Whitney U test is used in order to calculate the degree f significance of the differences between the controls (physiological serum) and the treated group.

ns = $P > 0.05$; * = $P < 0.05$; ** = $P < 0.01$.

The results obtained with the product of example 1 are shown in table 1.

TABLE 1

Spectral analysis of electroencephalogram of anaesthetized rats after 3 minutes of asphyxic anoxia.

Treatment	dose mg/kg i.v.	Before	End of Anoxia	Time in minutes after anoxia 2	10	30
				DELTA		
Controls	-	100 ± 0	1 ± 0	3 ± 1	902 ± 250	278 ± 44
Product of	5	100 ± 0	1 ± 0	243 ± 68**	127 ± 25**	123 ± 14**
example 1	1	100 ± 0	1 ± 0	214 ± 60**	404 ± 123 *	225 ± 32
				THETA		
Controls	-	100 ± 0	0 ± 0	1 ± 0	40 ± 7	71 ± 5
Product of	5	100 ± 0	0 ± 0	6 ± 2**	63 ± 11	94 ± 14 *
example 1	1	100 ± 0	0 ± 0	6 ± 2**	57 ± 8 *	72 ± 6
				ALPHA		
Controls	-	100 ± 0	0 ± 0	1 ± 0	69 ± 10	83 ± 11
Product of	5	100 ± 0	0 ± 0	25 ± 5**	55 ± 4	80 ± 8
example 1	1	100 ± 0	0 ± 0	19 ± 6**	73 ± 5	79 ± 6
				BETA		
Controls	-	100 ± 0	0 ± 0	1 ± 0	90 ± 11	90 ± 10
Product of	5	100 ± 0	0 ± 0	33 ± 5**	103 ± 14	102 ± 9
example 1	1	100 ± 0	0 ± 0	21 ± 7**	96 ± 11	87 ± 5
				TOTAL POWER		
Controls	-	100 ± 0	0 ± 0	1 ± 0	252 ± 76	117 ± 9
Product of	5	100 ± 0	0 ± 0	68 ± 14**	79 ± 6 **	100 ± 8
example 1	1	100 ± 0	0 ± 0	70 ± 22**	173 ± 41	120 ± 9

* = $P < 0,05$ ** = $P < 0,001$ (Test Of Mann-Whitney U)

Results

The product, administered by intravenous route at a dose of 5 mg/kg, causes a remarkable anticipation of the recuperation of the electro-cortical activity in all the frequency bands.

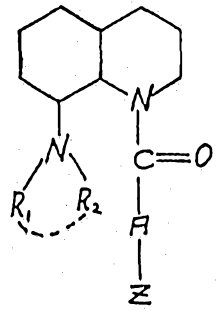
Thirty minutes after the anoxia, the values of the different bands of frequency of the group treated with 5 mg/kg are almost equal to the base values, while in the controls, there persists a large slow component (delta band) which indicates that a state of cerebral suffering is still present.

Even at a dose of 1 mg/kg, an anticipation of the recuperation of the electro-cortical activity is observed, while the effect on the normalisation of the trace is less evident.

In fact, after 30 minutes from the end of the anoxia, the value of the delta band is still about twice the base value.

The claims defining the invention are as follows:

1. Compounds with the formula (I):



(I)

in which R_1 and R_2, identical or different, represent a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocycle having a 5- or 6- membered ring, optionally including another heteroatom being oxygen or nitrogen, said heterocycle optionally being substituted by an alkyl or alkoxy radical containing from 1 to 5 carbon atoms,

A represents a chain $(CH_2)_n$ in which n represents a numeral 0 to 5, or A represents an alkylene chain substituted by an alkyl radical containing in all from 2 to 8 carbon atoms,

Z represents a phenyl radical optionally substituted by one or more identical or different radicals chosen from the group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, halogen atoms, hydroxyl, trifluoromethyl, nitro or amino radicals, and monoalkylamino or dialkylamino radicals in which the alkyl radicals contain from 1 to 5 carbon atoms, or Z represents a naphthyl radical, an indenyl radical, a heteromonocyclic radical being selected from the group made up of thiazolyl, pyridinyl, oxazolyl, isoxazolyl, imidazolyl and thienyl radicals, or a heterobicyclic radical being chosen from the group made up of indolyl, quinolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzoxazolyl and benzothiazolyl radicals, all these radicals optionally being substituted by one or more identical or different radicals chosen from the group made up of alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, trifluoromethyl, nitro or amino radicals, monoalkylamino or dialkylamino

radicals, of which the alkyl radicals contain from 1 to 5 carbon atoms, and phenyl radicals optionally substituted by one or more alkyl or alkoxy radicals containing from 1 to 5 carbon atoms, or by one or more halogens,
the said compounds with the formula (I) being able to be in all their possible enantiomeric and diastereo-isomeric forms and in the form of addition salts with acids or quaternary ammonium salts.

2. Compounds with the formula (I) as claimed in Claim 1, in which R_1 and R_2 represent a methyl or ethyl radical or together with the nitrogen atom to which they are bonded form a pyrrolidine or pyridinyl radical,
A represents a chain $(CH_2)_n$ where n is 0 or 1, or a 1,1-ethanediyl chain,
Z represents one of the following radicals, phenyl, optionally substituted in the manner disclosed in Claim 1, naphthyl, indenyl, pyridinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, quinolyl, benzofuranyl, benzo[b]-thienyl, benzimidazolyl, benzoxazolyl, or benzothiazolyl, optionally substituted in the manner disclosed in Claim 1, as well as their addition salts with acids and their quaternary ammonium salts.

3. Compounds with the formula (I) as claimed in Claim 2, in which R_1, R_2 and A have the significance indicated in Claim 2, and Z represents a phenyl, naphthyl, pyridinyl, thienyl, indolyl, or benzo[b]thienyl radical, optionally substituted in the manner disclosed in Claim 2, as well as their addition salts with acids and their quaternary ammonium salts.

4. Compounds with the formula (I) as claimed in any one of the claims 1 to 3, in which R_1 and R_2 together with the nitrogen atom to which they are bonded, form a pyrrolidinyl radical,
A represents a $(CH_2)_n$ chain where n is 0 or 1, or a 1,2-ethanediyl chain,
Z represents a phenyl radical substituted by one or more substituents chosen from the group constituted by the halogen atoms and the trifluoromethyl radical or Z represents a naphthyl or benzo[b]thienyl radical, as well as their addition salts with acids and their quaternary ammonium salts.

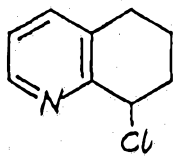
5. Any one of the compounds with the formula (I) as defined in Claim 1, the names of which follow:

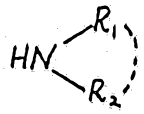
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±) decahydro-1-[(3,4-dichloro-phenyl)acetyl]-8-(1-pyrrolidinyl) quinoline,

- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[[(4-trifluoromethyl)phenyl]acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[4-bromophenyl)acetyl-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[2-(3,4-dichlorophenyl)-1-oxopropyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-(3,4-dichlorobenzyl)-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(benzo[b]-thienyl)acetyl]-8-(1-pyrrolidinyl) quinoline,
- [4aRS(4a alpha, 8 alpha, 8a alpha)](±)decahydro-1-[(1-naphthalenyl)acetyl]-8-(1-pyrrolidinyl) quinoline,

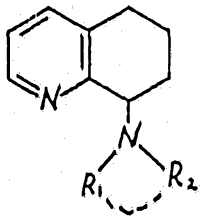
as well as their addition salts with acids and their quaternary ammonium salts.

6. Process for the preparation of compounds with the formula (I), as claimed in Claims 1 to 3, characterised in that 8-chloro-5,6,7,8-tetrahydroquinoline, with the formula :



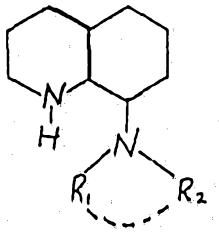
is condensed with an amine with the formula 

in which R^1 and R_2 have the significances indicated in Claim 1, so as to obtain a compound with the formula (II):



(II)

which is reduced so as to obtain a compound with the formula (III):



(III):

which is condensed with a compound with the formula (IV) or with a functional derivative of this compound:

(IV)

in which A and Z have the significance indicated in Claim 1, so as to obtain a compound with the formula (I) in all the enantiomeric and diastereo-isomeric forms possible, which is treated, if desired, with a mineral or organic acid, so as to obtain a salt or with an alkyl halogenide so as to obtain a quaternary ammonium salt.

7. Process for the preparation of compounds with the formula (I) as defined in Claim 6, characterised in that the reduction of the compound with the formula (II) is effected by either sodium in ethanol or an alcoholate in another alcohol, and there is obtained preferentially the compounds with the formula (I) in which the junction of the ring is trans and in that the reduction of the compound with the formula (II) is done by the catalytic method and there is obtained preferentially the compounds with the formula (I) in which the junction of the cycle is cis.

8. A pharmaceutical composition containing as active principle, one at

least of the compounds claimed in any one of Claims 1 to 5 or their addition salts with pharmaceutically acceptable acids or their salts of quaternary ammonium, in association with a pharmaceutically acceptable excipient.

9. 8-chloro-5,6,7,8-tetrahydroquinoline.

10. The products with the formulae (II) and (III) as defined in Claim 6, with the exception of the product of formula (II) in which R_1 and R_2 each represents an atom of hydrogen.

11. A method of treatment for alleviating pain, whatever its origin, wherein is administered, either by oral, rectal or parenteral route, or by local route by topical application on the skin and the mucosa, a pharmaceutical composition containing, as active principle, one or more compounds of formula (I) as claimed in any one of Claims 1 to 5 or their addition salts with pharmaceutically acceptable acids or their salts of quaternary ammonium.

12. A compound of formula (I) as claimed in any one of Claims 1 to 5, substantially as hereinbefore described, with reference to any one of Examples 1 to 27.

13. A preparation process as claimed in either Claim 6 or Claim 7, substantially as hereinbefore described, with reference to any one of Examples 1 to 27.

14. A pharmaceutically composition as claimed in Claim 8, substantially as hereinbefore described, with reference to either Example 28 or Example 29.

DATED this 14th day of March, 1990.

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