

wherein

X represents an oxygen atom or a NR group, wherein

R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl group, or a carbo
aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substituted on the arom
one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1 and R^2
represents a hydroxyl group and the other additionally represents a methyl group;

R^3 represents a hydrogen atom or a phenyl group optionally substituted by one or mo
atoms, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxyl group;

Ph represents a phenyl group unsubstituted or substituted by one or more halogen atoms
C_{1-4} alkoxy, hydroxyl or trihalomethyl groups; and

n is 1, 2, 3;

and all acid addition and quaternary ammonium salts thereof.

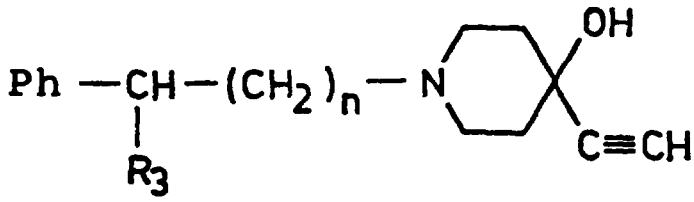
The compounds of the formula (I) may exist in various stereoisomeric forms such as geometric
as well as racemates, individual optical isomers and their mixtures, all of which may also occur in t
various solvates and hydrates. All these compounds and mixtures are within the scope of the present

According to another aspect of the invention, there is provided a process for the preparation of c
of the formula (I) and their acid addition and quaternary ammonium salts, which comprises

a) for the preparation of compounds of formula (I) wherein X is a group NR, reacting a 2-oxo-3
piro[4,5]decane derivative of formula (II),

wherein R^3, Ph and n are as herein before defined and Y represents a halogen atom or a
nyloxy or arylsulfonyloxy group; or

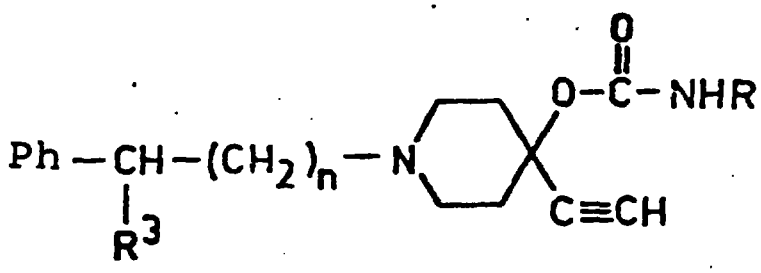
b) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a methy
acting a 4-ethynyl-4-hydroxypiperidine derivative of formula (IV),



(IV)

wherein R^3, Ph and n are as defined above with an isocyanate of formula R-NCO, wherein
above, and either

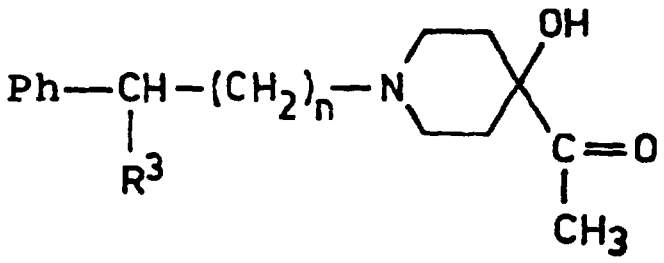
α) for compounds wherein X is an oxygen atom, cyclizing in an acidic medium the 4-
4-ethynylpiperdine derivative of the formula (V) as prepared above



(V)

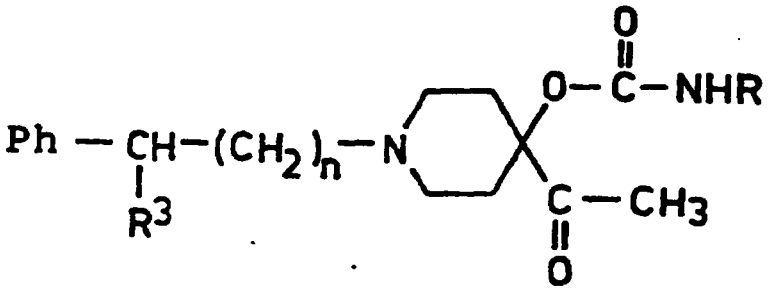
wherein R, R^3 Ph and n are as defined above and reacting the resulting salt of formula (V

mula (VII),



(VII

wherein R^3, Ph and n are as defined above, with an isocyanate of formula R-NCO where above, and cyclizing the thus formed compound of formula (VIII)



(VII

wherein R, R^3 Ph and n are as defined above;

or

f) for the preparation of compounds of formula (I) as defined for process (e) above, cyc 4carbamoyloxypiperidine derivative of the formula (VIII) as defined above;

followed if desired or necessary,

by reacting a compound of formula (I) as prepared above wherein X is an oxygen atom and R are a methylene group with an amine of formula $R\text{-}NH_2$ wherein R is as defined above, in c compound of the formula (I), wherein X is a group NR and one of R^1 and R^2 is a hydroxyl gro

Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)] to give a 4-carbamoyl
piperidine derivative of the formula (V). For preparing compounds of the formula (I) wherein X
atom, the compound of the formula (V) is cyclized in an acidic medium according to step α),
formed 2-imino-1,3-dioxolane derivative of the formula (VI) obtained as a salt is reacted with
paring compounds of the formula (I) where X is a >NR group, the compound of formula (V)
basic medium according to step β).

The cyclization of step α) may be carried out in an inert organic solvent (i.e. in a solvent
under the reaction conditions), in the presence of a suitable acid, preferably in the presence of
halide. Aliphatic or alicyclic ethers such as diethyl ether, dipropyl ether, diisopropyl ether, dibu
hydrofuran or dioxane as well as lower aliphatic carboxylic acids, e.g. acetic or propionic aci
ployed.

As a hydrogen halide hydrogen chloride, bromide, iodide or fluoride, preferably hydrogen
mide, may be used. Following the reaction with water, the 1-oxa-2-oxo-8-aza-spiro[4,5]decan
the formula (I) is obtained as an acid addition salt from which, if desired, the base can be liberat
known per se.

The cyclization of step β) may be realized in the presence of a base. Alkaline metal acetate
alkoxides, hydroxides and/or tertiary organic bases, e.g. pyridine, tripropylamine or picoline, n
basic catalysts in the cyclization; the organic bases may also serve as solvents for the reactio
able solvents are aliphatic alcohols, e.g. methanol, ethanol, propanol or butanol; aliphatic, alicy
hydrocarbons, e .g. hexane, cyclohexane, benzene, toluene or xylene; acid amides, e.g. dime
or N-methyl-2-pyrrolidone; ethers such as dibutyl ether or dioxane; nitriles such as acetonitrile;
dimethylsulfoxide; etc. and any mixture of the above solvents. The reaction may also be carr
any solvent, e.g. in a molten state. In order to accelerate the cyclization the temperature may
creased. The reaction is preferably accomplished between 40 °C and the boiling point of the re
It is preferable to work under an inert gas such as argon or nitrogen. According to a preferred
the present invention the 4-carbamoyloxy-4-ethynylpiperidine derivative of the formula (V), fo
action of the 4-ethynyl-4-hydroxypiperidine derivative of the formula (IV) with the isocyanate
R-NCO, is directly cyclized in the same reaction mixture, in the presence of a suitable base, i.e
of formula (V) is not isolated prior to cyclization.

In the processes c) and d) above the procedures as discussed for steps α) and β) above m

In the process e) above, a 4-acetyl-4-hydroxypiperidine derivative of the formula (VII) is
isocyanate of the formula R-NCO and the obtained 4-acetyl-4-carbamoyloxypiperidine deriva
mula (VIII) is cyclized. The condensation reaction according to the first step may be realised in a
per se [Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)
4-acetyl-4-carbamoyloxypiperidine derivative of the formula (VIII) is preferably cyclized in the
base. The cyclization may be carried out under the same reaction conditions as described for st

ates, aliphatic carboxylic acids, aliphatic or aromatic carboxylic acid anhydrides, Lewis acid
aromatic sulfonic acids may be employed for the dehydration. This reaction is preferably pe
ganic solvent. Suitable solvents are e.g. aromatic hydrocarbons such as benzene, toluene
such as dioxane, di-n-butyl ether; or aliphatic carboxylic acids such as acetic acid. Optionally,
in the reaction may be removed by azeotropic distillation.

If desired or necessary, the reverse reaction to the dehydration process described abov
out by adding water to a compound of formula (I) wherein R^1 and R^2 together are a methyl
a compound of the formula (I) wherein R_1 and R_2 are a hydroxyl and a methyl group. This
may be accomplished in an aqueous medium, in the presence of mineral and/or organic ac
hydrogen halides, sulfuric, phosphoric, formic acid, aromatic sulfonic acids, oxalic or trifluo
be employed. This reaction may be carried out between 5 °C and the boiling point of the re

The compounds of the formula (I) may be converted into their acid addition salts or quate
salts by using methods known per se. For the preparation of acid addition salts, inorganic or o
as hydrogen halides, e.g. hydrochloric acid and hydrobromic acid, sulfuric acid, phosphoric
formic, acetic, propionic, oxalic, glycolic, maleic, fumaric, succinic, tartaric, ascorbinic, citri
lactic, benzoic, cinnamic, aspartic, glutamic, N-acetyl-aspartic or N-acetylglutamic acid as
fonic acids such as methanesulfonic acid or arenesulfonic acids, e.g. p-toluenesulfonic acid

Salt formation may be carried out e.g. in such a way that the relevant acid is added to t
compound of formula (I) in an inert solvent, e.g. ethanol, and the salt formed is precipitated by
a water-immiscible organic solvent, e.g. ethyl ether. For the preparation of quaternary ammo
alkyl, alkenyl or benzyl halide or an alkyl sulfate may preferably be employed. The quaterniz
formed in an organic solvent such as acetone, acetonitrile, ethanol or their mixtures, at a te
range from room temperature up to the boiling point of the solvent. The acid addition or quate
salt obtained may be isolated e.g. by filtration and, when necessary, purified by recrystalliz

Conversely, the corresponding bases can be liberated from their salts by an alkaline tr

The compounds of formula (III) may be prepared according to e.g. Collection Czechoslov.
38, 3879 (1973); as well as Chim. Ther. 3, 185 (1969).

The preparation of compounds of formula (II) is described in our EP-A-0412820 of even
ority from our Hungarian patent application No. 4092/89.

This preparation comprises the reduction of compounds of formula (X)



(XI)

wherein R^3 is as defined above with an isocyanate of formula RNCO wherein R is as hereinb
followed by cyclizing the resulting compound in a basic medium in order to prepare compoun
(X) wherein R_1 and R_2 together represent a methylene group; and, if necessary;

(ii) hydrating a compound as prepared in reaction (a) above in order to obtain compounds c
wherein one of R_1 and R_2 is a hydroxy group and the other a methyl group.

Compounds of formula (XI) may be prepared by a procedure analogous to the preparation c
of formula (IV) as described below.

The substances of formula (IV) may be synthesized e.g. by the ethynylation reaction of suitab
4-piperidone derivatives as described in e.g. Hungarian patent specification No. 166,769 or in Far
Ed. Sci. 12, 34 (1957).

The 4-acetyl-4-hydroxypiperidine derivatives of formula (VII) may be prepared by e.g. hydr
responding 4-ethynyl-4-hydroxypiperidine derivatives of formula (IV) as defined above, as e.g. H
Methoden der Organischen Chemie Vol. VII/2 a, pages 826 to 835 (1973) or by the alkaline tre
corresponding 1,3-dioxa-2-oxo-4-methylene-8-azaspiro[4,5]decane derivatives of formula (I).

The compounds of formulae (IV), (V), (VII) and (VIII) as defined above are all novel compou
valuable intermediates in the synthesis of the compounds according to the present invention, an
they are also biologically active.

The compounds of formula (I) as well as their stereoisomers and salts exhibit valuable pha
properties such as calcium uptake-inhibiting, antihypoxic and antianoxic effects. Thus they are
systemic (i.e. oral, rectal or parenteral) treatment of warm-blooded mammals (including man).
favourably employed for the prevention or therapeutic treatment of hypoxic brain damages of
such as senile dementia, Alzheimer's disease, ischemic lesions, disturbances of the cognitive fu
infarctual dementia, hypoxia following atheroschlerosis and the like.

The calcium uptake-inhibiting action of the compounds of formula (I) was studied on a rat b
somal preparation by using the method of P. H. Wu et al. [J. Neurochem. 39, 700 (1982)].

Wistar rats weighing 180 to 200 g were decapitated, their brains were collected in an ice-cold
saline solution, the cortex was removed and purified from the white substance. The tissue was
in 10 volumes of 0.32 M sucrose solution by using a glass-teflon potter. After centrifuging the h
a rate of 1000 × g at 4 °C for 10 minutes, the supernatant was further centrifuged at 10000 × g fo
The sediment was taken up in a 0.32 M sucrose solution in such a way that the protein content of th
was adjusted to 20 mg/ml.

Table I

Compound No.	IC_{50} /uM
1	5.8
2	5.9
3	2.1
4	5.3
5	6.1

Numbers for the chemical names and abbreviations used in the Tables:

1 1-Oxa-2-oxo-3-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]dec
2 1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5
3 1-Oxa-2-oxo-3-phenyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]d
4 1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,
5 1-Oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspi
hydrochloride
6 1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]deca
7 1-Oxa-2-oxo-3-propyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]
8 1-Oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro
9 1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]d

Abbreviations:

8	60	10
9	60	10

The average survival time of the control group was 23.5 ± 2.51 sec (X±S.E.)

The potassium cyanide test method was used for determination of the protective effect a toxic hypoxia. A hypoxia of this type can be developed by a rapid intravenous injection of 5.0 mg/ cyanide inducing abdominal contractions within and clonic convulsions of the animals and lea the animals within 2 minutes.

Male Hannover-Wistar rats weighing 160 to 170 g were used in this experiment. Animals by 30% than the average survival time of the control group were considered to be protecte stances were orally administered in various doses 60 minutes before starting the test. The E the dose protecting 50% of the treated animals from the hypoxia, were calculated from the pe protected animals relating to various doses (i.e. from the dose-response curve) by using prob results are summarized in Table III.

treatment of antihypoxic and antianoxic damage of mammals. They are also useful in inhibiting
in mammals.

The compounds according to the invention can be formulated into pharmaceutical composit
manner. The pharmaceutical compositions may be administered in oral, rectal and/or parentera
administration, the composition may be formulated e.g. as a tablet, dragée or capsule. In order
compositions, e.g. lactose or starch may be used as carriers. Gelatine, sodium carboxymethy
thylcellulose, polyvinylpyrrolidone or starch gum are suitable binding or granulating agents. A
agents, potato starch or microcrystalline cellulose may be added though ultra-amylopectin or
casein are also useful. Talc, colloidal silicic acid, stearin, calcium or magnesium stearate an
adhesive and sliding agents. The liquid oral compositions of the invention may be prepared in
a suspension, syrup or elixir which may contain water, glycols, oils, alcohols as well as colouring
additives.

Tablets may be prepared e.g. by compression following wet granulation. The mixture of the a
with the carriers and optionally with a part of the disintegrating additive is granulated with an
holic or aqueous-alcoholic solution of the binding agents , then the granulate is dried.

Subsequently, after mixing the other disintegrating, sliding and anti-adhesive additives to
ulate, the mixture is compressed into tablets. If desired, the tablets may be provided with a gro
facilitate their administration. Tablets may also directly be prepared from a mixture containing t
dient and suitable additives. The tablets may optionally be converted to dragées by employing
used pharmaceutical additives, e.g. protective, flavouring or colouring agents such as sugar,
atives (methyl- or ethylcellulose, sodium carboxymethylcellulose), polyvinylpyrrolidone, calci
calcium carbonate, food dyes, dyeing lacquers, aromatizing agents, iron oxide pigments. Caps
sitions may be prepared by filling a mixture of the active ingredient with the additives into cap

For rectal administration, the composition of the invention may be formulated as a supposi
a carrier mass, the so-called "adeps pro suppositorio", in addition to the active ingredient. As
able fats such as hardened vegetable oils, or triglycerides of C_{12-18} fatty acids (preferably the c
the trade name Witepsol) may be used. The active ingredient is uniformly distributed in the molte
then suppositories are prepared by moulding.

For parenteral administration, the composition of the invention may be formulated as an inje
For preparing these injectable solutions, the active ingredients are dissolved in distilled water
organic solvents, e.g. glycol ethers, if desired, in the presence of solubilizing agents such as p
sorbitan monolaurate or monooleate or monostearate (Tween 20, Tween 60, Tween 80), respe
jectable solution may further contain various additives (auxiliary agents), e.g. preservatives
nediamine tetraacetate as well as p-modifying and buffering substances or, if desired, a local ana
such as lidocaine. Before filling into the ampouls, the injectable solution containing the compo

pressure, the residue is extracted with benzene. The benzene solution is washed with water, drie
drous magnesium sulfate and evaporated under reduced pressure. After taking up the residue in
hydrochloride is precipitated by adding hydrogen chloride in diisopropyl ether solution. The title h
is obtained in 91.0% yield, m.p. : 166-168 °C.

Analysis for the base:

Calculated for $C_{23}H_{25}F_2NO$

C 74.77; H 6.82; F 10.28; N 3.79%;

found: C 74.85; H 6.66; F 10.15; N 4.00%.

Preparation 2

4-butylcarbamoyloxy-4-ethynyl-1-[4,4-bis(4-fluorophenyl)butyl]piperidine hydrochloride

6.4 ml of butyl isocyanate dissolved in 19 ml of benzene are dropwise added to a mixture of
ethynyl-4-hydroxy-1-[4,4-bis(4-fluorophenyl)butyl]-piperidine, 0.35 g of anhydrous powdered pot
bonate and 74 ml of benzene in a nitrogen atmosphere under reflux and stirring. The mixture is
an hour thereafter,

then cooled down and water is added. After separating the phases the benzene solution is
water to neutral, dried over anhydrous magnesium sulfate, the solution is filtered through a silica
and evaporated under reduced pressure. After taking up the residue in diisopropyl ether, the h
salt is precipitated by adding hydrogen chloride in diisopropyl ether solution. The title hydrochloride
in 87.5% yield, m.p.: 84-89°C. Analysis of the base:

Calculated for $C_{28}H_{34}F_2NO_2$

C 71.77; H 7.31; F 8.11; N 5.98%;

found: C 71.88; H 7.50; F 8.28; N 5.83%.

4-methylene-2-oxa-3-n-propyl-1-oxa-3,8 diazaspiro [4,5] decane

(a) 8-benzyl-3-n-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

21.5 g of 1-benzyl-4-ethynyl-4-hydroxypiperidine are boiled under reflux with 12.9 g of n- in the presence of 0.4 g of anhydrous potassium acetate in 66 ml of 2-picoline under nitrogen evaporating 2-picoline under reduced pressure and dissolving the residue in benzene, the o washed with water and dried over anhydrous magnesium sulfate. After filtration on an alum the benzene solution is evaporated under reduced pressure. The crude product obtained is re n-heptane to give the pure title substance in 78.5% yield, m.p.: 57-58 °C.

Analysis:

Calculated for $C_{19}H_{26}N_2O_2$

C 72.58; H 8.33; N 8.91%;

found: C 72.55; H 8.53; N 9.06%.

Using the appropriate starting materials the following compounds may be prepared in an ner;

8-Formyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 171-1

8-Benzyloxycarbonyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, °C;

4-Methylene-2-oxo-3-phenoxycarbonyl-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m

8-Benzyl-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 12 drogen fumarate salt melts at 207-208 °C);

8-Benzyl-3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 103-10 maleate salt m.p. : 184-186 °C);

8-Benzyl-3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 116- citrate salt m.p. : 132-133 °C);

8-Benzyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 134-13

8-Benzyl-3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 96-9

8-Benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrogen ma

found: C 66.33; H 7.10; N 8.10%.

Using the appropriate starting materials the following compounds may be prepared in an anal
ner.
3-Benzyl-8-benzyloxycarbonyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
8-benzyloxycarbonyl-3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 47-48 °C
8-ethoxycarbonyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 121-122 °
3-(3,4-dichlorophenyl)-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane,
222 °C;
3-methyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 118-119
4-methylene-2-oxo-8-phenoxycarbonyl-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 96-98 °C

(c) 4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro[4,5]decane

A suspension containing 0.5 g of 10% by weight palladium-on-carcoal catalyst in 5 ml of water
the solution of 5.0 g of 8-benzyloxycarbonyl-4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro
in 45 ml of methanol at 0 °C under argon while stirring. To this mixture 1 ml of 45.8% aqueous hydraz
is introduced and the reaction mixture is refluxed for 10 to 15 minutes. After cooling down to room t
and filtering off the catalyst the solvent is evaporated under reduced pressure and the crude eva
sidue is recrystallized from benzene to give the title compound in 95% yield, m.p.: 96-97 °C.

Using the appropriate starting materials the following compounds may be prepared in an anal
ner;
3-Ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 106-108 °C;
3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 151-152 °C;
4-methylene-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 208-209 °C;
3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 185-186 °C;
3-tert-Butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 138-139 °C;
3-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 139-140 °C;
3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.
°C;
3-benzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 77-79 °C;
3-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;

Example 1

1-oxa-2-oxo-3-propyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

A mixture containing 8.4 g of 1-oxa-2-oxo-3-propyl-4-methylene-3,8-diazaspiro[4,5]decan bis(4-fluorophenyl)butyl chloride, 16.6 g of anhydrous potassium carbonate and 0.3 g of pota 90 ml of methyl isobutyl ketone is boiled under reflux and stirring for 8 hours, then the solver under reduced pressure. After adding benzene and water to the residue, the organic phase is se ed with water to neutral, dried over anhydrous magnesium sulfate and evaporated under red The crude product obtained is purified by chromatography on a silica gel column by using e elution. The eluates are combined, evaporated and the residue is recrystallized from diisoprop the title compound in 89% yield, m.p.: 107-108 °C.

Analysis:

Calculated for $C_{27}H_{32}F_2N_2O_2$

C 71.34; H 7.10; F 8.36; N 6.16%;

found: C 71.50; H 7.23; F 8.28; N 6.07%.

Example 2

1-oxa-2-oxo-3-benzyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4.5]decane

A mixture containing 10.3 g of 1-oxa-2-oxo-3-benzyl-4-methylene-3,8-diazaspiro[4,5]deca (4-fluorophenyl)ethyl bromide and 11.2 ml of triethylamine in 100 ml of methyl isobutyl ketone is argon while stirring for 2.5 hours. After cooling down and adding water to the reaction mixtu phase is separated, washed with saturated sodium chloride solution, dried over anhydrous sod evaporated under reduced pressure. The residue is recrystallized under clarifying by activat hexane and then from diisopropyl ether to obtain the title compound in 31.8% yield, m.p.: 100

Analysis of the base:

Calculated for $C_{25}H_{30}N_2O_2$

C 76.89; H 7.74; N 7.17%;

found: C 76.95; H 7.89; N 7.24%.

Example 4

1-oxa-2-oxo-3-decyl-4-hydroxy-4-methyl-8- [4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5 chloride

5.5 g of 1-oxa-2-oxo-3-decyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspir dissolved in 11 ml of formic acid and after dropping 100 ml of a 3 mol/litre hydrochloric aci under stirring, the reaction mixture is stirred for additional 30 minutes. The crystals precipit washed with water and dried to give the title hydrochloride in 97.2% yield, m.p.: 109-111 °C. erated by adding aqueous sodium carbonate solution to the hydrochloride, extracted into ch ganic phase is washed with water to neutral, dried over anhydrous sodium sulfate and evap duced pressure. After recrystallization from diisopropyl ether the base melts at 89-90 °C.

Analysis:

Calculated for $C_{34}H_{48}F_2N_2O_3$

C 71.54; H 8.48; F 6.66; N 4.91%

found: C 71.54; H 8.31; F 6.73; N 4.99%

Example 6

1-oxa-2-oxo-3-methyl-4-methylene-8-(3-phenylpropyl)-3,8-diazaspiro[4.5]decane

A solution of 7.5 g of 4-ethynyl-4-methylcarbamoyl-oxy-1-(3-phenylpropyl)piperidine in 100 nolic sodium ethoxide solution of 0.09 mol/litre concentration is refluxed under argon for 3 to cooling down and adding aqueous ammonium chloride solution to the reaction mixture, the major is distilled off under reduced pressure. The residue is diluted with water and extracted with benz zene phase is washed with water to neutral, dried over anhydrous magnesium sulfate and eva reduced pressure. After recrystallizing the residue from hexane, the title compound is obtained m.p.: 35-36 °C.

Analysis:

Calculated for $C_{18}H_{24}N_2O_2$

C 71.97; H 8.05; N 9.33%;

found: C 71.88; H 8.19; N 9.52%.

Example 7

1-oxa-2-oxo-4-methylene-3-phenyl-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane

A mixture containing 6.2 g of 4-acetyl-4-hydroxy-1-(2-phenylethyl)-piperidine, 2 ml of triethyl ml of phenylisocyanate in 20 ml of xylene is refluxed under argon for 6 hours. After cooling dow with xylene the reaction mixture is filtered and the filtrate is evaporated under reduced pressure. tallizing the crude product from ethanol under clarifying by activated carbon, the title product 49.4% yield, m.p.: 137-138 °C.

After recrystallization of the residue from hexane, the base is converted to the hydrochloric
drogen chloride in diisopropyl ether solution. Thus, the title hydrochloride is obtained in 58.4%
composition point of 310-315 °C.

Analysis of the base:

Calculated for $C_{22}H_{31}ClN_2O_3$

C 63.93; H 7.68; Cl 8.71; N 6.88

found: C 65.10; H 7.53; Cl 8.60; N 7.00

Using the appropriate starting materials the following compounds may be prepared in an
ner to the processes described in Examples 1 to 3 or 8.
1-Oxa-2-oxo-3-methyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 119-
1-Oxa-2-oxo-4-methylene-3-phenyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m
1-Oxa-2-oxo-3-ethyl-4-methylene-8-[2-(4-methylphenyl)ethyl]-3,8-diazaspiro[4,5]decane hy
comp. at 280-282 °C;
1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m
1-Oxa-2-oxo-4-methylene-3-phenyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.:
1-Oxa-2-oxo-3-ethyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 121-12
1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]de
92 °C;
1-Oxa-2-oxo-3-isopropyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]de
119 °C;
1-Oxa-2-oxo-3-methyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane,
1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 10
1-Oxa-2-oxo-3-isopropyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.
1-Oxa-2-oxo-3-methyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m
1-Oxa-2-oxo-3-ethyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m
1-Oxa-2-oxo-3-isopropyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.
1-Oxa-2-oxo-4-methylene-3-phenyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]deca
126 °C;
1-Oxa-2-oxo-4-methylene-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m
1-Oxa-2-oxo-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-methylene-8-(2-phenylethyl)-3,8-diazaspir

After recrystallizing the residue from ethanol the title compound is obtained in 65% yield, m.

Analysis:

Calculated for $C_{26}H_{25}FN_2O_2$

C 74.98; H 6.05; F 4.56; N 6.73%;

found: C 75.10; H 6.25; F 4.37; N 6.55%.

Example 10

1-oxa-2-oxo-3-n-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decan

3.3 g of n-butyl isocyanate dissolved in 11 ml of benzene are added portionwise to a ge pension containing 11 g of 4-ethynyl-4-hydroxy-1-[4,4-bis(4-fluorophenyl)butyl]piperidine and methoxide in 45 ml of benzene under argon while stirring, then the mixture is refluxed for additio After cooling down the benzene solution is washed with water, dried over anhydrous sodium and the solvent is distilled off under reduced pressure. After recrystallizing the residue from d the title compound is obtained in 79,5% yield, m.p.: 94-95 °C

Analysis

Calculated for $C_{28}H_{34}F_2N_2O_2$

C 71.77; H 7.31; F 8:11; N 5.98%;

found: C 71.98; H 7.40; F 8.24; N 6.13%.

in Examples 9, 10 or 11, using the appropriate starting materials.

1-Oxa-2-oxo-4-methylene-3-propyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane,

1-Oxa-2-oxo-3-ethyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, r

1-Oxa-2-oxo-4-methylene-3-(1-naphthyl)-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,
127-128 °C;

1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]d
92 °C;

1-Oxa-2-oxo-3-heptyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]dec
maleate, m.p.: 121-122 °C;

1-Oxa-2-oxo-3-(3,4-dichlorophenyl)-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspir
drochloride, decomp. at 292-295 °C;

1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.:

1-Oxa-2-oxo-4-methylene-3-propyl-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 97-

1-Oxa-2-oxo-3-butyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, r

Example 12

1-oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5
chloride

3 ml of butylamine dissolved in 3 ml of benzene are dropped to a solution of 8.3 g of 1
methylene-8-[4,4-bis(4-fluorophenyl)butyl]-8-azaspiro[4,5]decane in 17 ml of anhydrous b
ring. Meanwhile the temperature of the reaction mixture raises to 38 - 45 °C. Thereafter th
is stirred at room temperature for additional 16 hours, then evaporated under reduced pres
of the residue in anhydrous ether the title hydrochloride salt is precipitated by adding ethere
ide solution. The title salt is obtained in 87% yield, m.p.: 218-221 °C.

The base is obtained from the hydrochloride by adding ammonium hydroxide solution.

A solution of 16.0 g of 1-[4,4-bis(4-fluorophenyl)butyl]-4-butyl-carbamoyloxy-4-ethynyl
of anhydrous dioxane is saturated by dry gaseous hydrogen chloride at 15 to 20 °C, then th
is left to stand overnight. The solvent is evaporated at 40 to 50 °C under reduced pressure.
to the residue, the base is liberated with sodium hydrogen carbonate and extracted into benz
solution is dried over anhydrous magnesium sulfate, then the solvent is evaporated under
After dissolving the residue in ethyl acetate, the solution is filtered through a silica gel colun
thus obtained is evaporated under reduced pressure. After taking up the residue in acetone
maleate salt is precipitated by maleic acid. The title salt is obtained in 55% yield, m.p.: 149

Analysis for the base:

Calculated for $C_{24}H_{25}F_2NO_3$

C 69.72; H 6.09; F 9.19; N 3.39

found: C 69.85; H 6.17; F 9.35; N 3.12

Example 15

1-oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane

A solution containing 9.1 g of 4-acetyl-4-methyl-carbamoyloxyl-1-(2-phenylethyl)piperi
dium methoxide in 100 ml of methanol is refluxed under argon for 4 to 5 hours. After cooling
methoxide is decomposed by adding aqueous ammonium chloride solution, the mixture is
and methanol is distilled off under reduced pressure. After filtration the precipitate obtaine
from ethanol to give the title product in 72.1% yield, m.p.: 184-185 °C.

Calculated for $C_{23}H_{27}FN_2O_3$

C 69.32; H 6.83; F 4.77; N 7.03%;

found: C 69.40; H 6.64; F 4.85; N 7.16%.

The following compounds may be prepared in an analogous manner using the processes Examples 12 or 16 and using the appropriate starting materials:

1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 1

1-Oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]d 189-190 °C;

1-Oxa-2-oxo-3-tert-butyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]de chloride, decomp. at 286-288 °C;

1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane ide, decomp. at 220-223 °C;

1-Oxa-2-oxo-3-benzyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]d chloride, decomp. at 177-179 °C;

1-Oxa-2-oxo-4-hydroxy-3-isopropyl-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]dec 157-158 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-phenyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]d chloride, decomp. at 274-276 °C;

1-Oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[2-4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, 156 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decan ide, decomp. at 248 °C; the base melts at 138-139 °C;

1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]de chloride, decomp. at 235 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-(1-naphthyl)-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro hydrochloride, decomp. at 180-182 °C;

1-Oxa-2-oxo-3-heptyl-4-hydroxy-4-methyl-8-[4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]dec 128-129 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-(1-naphthyl)-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5] drochloride, decomp. at 288-290 °C;

1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane 140 °C;

The tablets prepared as described above are covered in a manner known per se wit
sisting of sugar and talc. The dragées are polished by using a mixture of bees wax and
Each dragée weighes 250 mg;

c) Preparation of capsules

100 mg of active ingredient, 30 g of sodium lauryl sulfate, 280 g of starch, 280 g o
colloidal silicon dioxide (Aerosil) and 6 g of magnesium stearate are thoroughly mixed to
sieving, the mixture obtained is filled into hard gelatine capsules containing 20 mg of the
each ;

d) Preparation of suppositories

30.0 mg of active ingredient are thoroughly mixed with 60.0 mg of lactose. Simulta
mg of suppository base (e.g. Witepsol 4) are made molten (all weights are calculated for o
cooled to 35 °C and the mixture of the active ingredient and lactose are mixed thereinto
enizer. The product obtained is poured into cooled conic moulds. Each suppository weig

e) Preparation of a suspension

Components in 100 ml of the suspension:

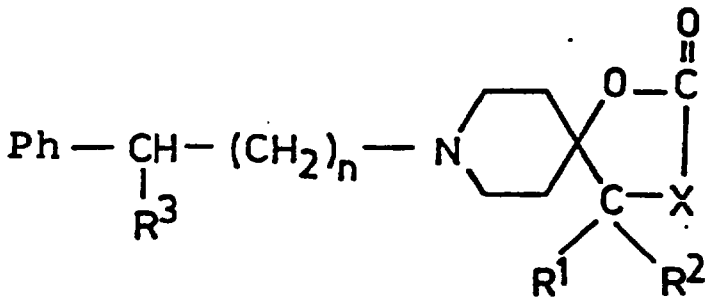
"Aerosil", "Witepsol", "Nipagin" and "Carbopol" are all Trade Marks.

After adding carbopol in little portions to the solution of nipagin and citric acid in 20 m
under vigorous stirring, the solution obtained is left to stand for 10 to 12 hours. Subsequently,
above of sodium hydroxide dissolved in 1 ml of distilled water, the aqueous solution of sorbi
ethanolic solution of the raspberry flavour are dropped in under stirring. The active ingredien
portions to this mixture and suspended by using a submerged homogenizer. Finally, the s
plemented to 100 ml by adding sufficient distilled water and the syrupy suspension is led
mill.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, L

1. A compound of formula (I),



(I

wherein

X represents an oxygen atom or an NR group, wherein

R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl grou
C_{6-10} aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substitut
ring by one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1

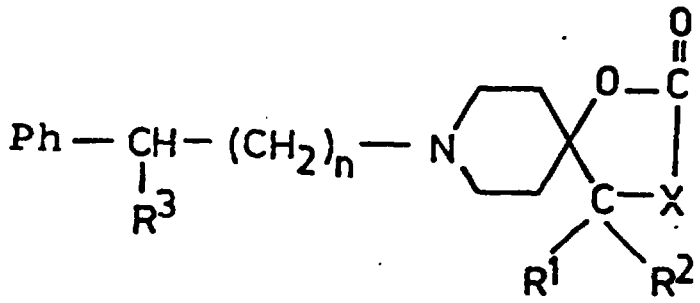
"Aerosil", "Witepsol", "Nipagin" and "Carbopol" are all Trade Marks.

After adding carbopol in little portions to the solution of nipagin and citric acid in 20 m under vigorous stirring, the solution obtained is left to stand for 10 to 12 hours. Subsequently above of sodium hydroxide dissolved in 1 ml of distilled water, the aqueous solution of sort ethanolic solution of the raspberry flavour are dropped in under stirring. The active ingredie portions to this mixture and suspended by using a submerged homogenizer. Finally, the plemented to 100 ml by adding sufficient distilled water and the syrupy suspension is le mill.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, L

1. A compound of formula (I),



(I

wherein

X represents an oxygen atom or an NR group, wherein

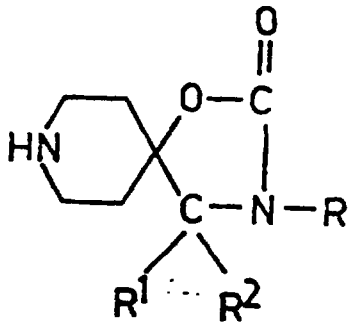
R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl grou C_{6-10} aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substitut ring by one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1



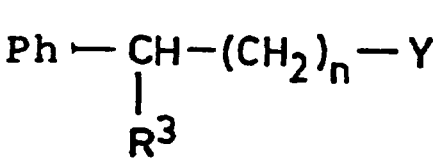
ceutically acceptable carrier and/or additive.

4. A process for the preparation of a compound of formula (I) as defined in Claim 1 which c
a) for the preparation of compounds of formula (I) wherein X is a group NR, reacting a
zaspiro[4,5]decane derivative of formula (II),



(II)

wherein R, R^1 and R^2 are as defined in claim 1, with a phenylalkane derivative of form



(III)

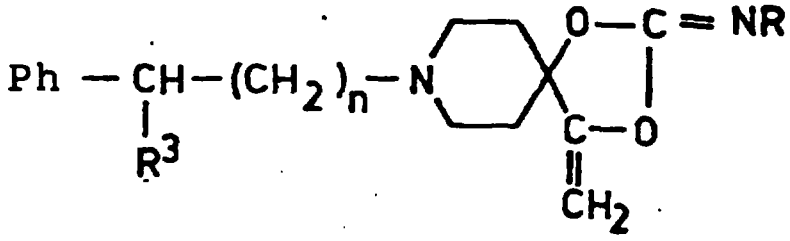
wherein R^3, Ph and n are as defined in claim 1 and Y represents a halogen atom or a
nyloxy or arylsulfonyloxy group; or
b) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a m
reacting a 4-ethynyl-4-hydroxypiperidine derivative of formula (IV),

* C L M



(V)

wherein R, R^3 Ph and n are as defined above and reacting the resulting salt of formula (



(VI)

wherein R, R^3 Ph and n are as defined above, with water; or

β) for compounds wherein X is a group NR, cyclizing in a basic medium the com
formula (V) as defined and prepared above;

or

c) for the preparation of compounds of formula (I) as defined in process (b) (α) above, c
acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of the formula (V) as d
and reacting the obtained salt of formula (VI) as defined above with water;

or

d) for the preparation of compounds of formula (I) as defined in process (b) (β) above, cy
presence of a base a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (V) as de

or

e) for the preparation of a compound of formula (I) wherein is X is a group NR and one of
a hydroxy group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypipridine
formula (VII),



wherein R, R^3 Ph and n are as defined above;

or

f) for the preparation of compounds of formula (I) as defined for process (e) above, c
4-carbamoyloxypiperidine derivative of formula (VIII) as defined above;

followed if desired or necessary,

by reacting a compound of formula (I) as prepared above wherein X is an oxyge
R^2 together are a methylene group with an amine of formula R-NH_2 wherein R is as defi
to prepare a compound of the formula (I) wherein X is a group NR and one of R^1 ar
group and the other is a methyl group,

and/or if desired or necessary,

transforming a compound of the formula (I) as prepared above into another co
mula (I) as defined in Claim 1,

and/or desired or necessary,

reacting a compound of formula (I) as prepared above with an acid to obtain the acid a
and/or treating a salt of a compound of the formula (I) as prepared above with a base t
form thereof and /or converting a thus prepared compound of the formula (I) into its
nium salt.

5. A process as claimed in claim 4 process a) wherein Y is either a chlorine or bromine
nesulphonyloxy group.

6. A process as claimed in claim 4 process (b) (β) wherein the reaction is carried out as a
separating the compound of formula (V).

7. A process as claimed in claim 4 process e) which comprises carrying out the reaction
triethylamine at the boiling point of the reaction mixture.

8. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a m
treatment of hypoxic brain damage in mammals.

9. The use of a compound of formula (I) as defined in claim 1 for the manufacture of a m
in inhibiting calcium-uptake in mammals.

10. A process for the preparation of a pharmaceutical composition as defined in Claim
admixing a compound of formula (I) or a pharmaceutically acceptable acid addition or
nium salt thereof as defined in Claim 1 with a pharmaceutically acceptable carrier an

* C L M S

tionally represent a hydroxyl group and the other additionally represents a

R^3 represents a hydrogen atom or a phenyl group optionally substituted by o
logen atoms, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxyl group;

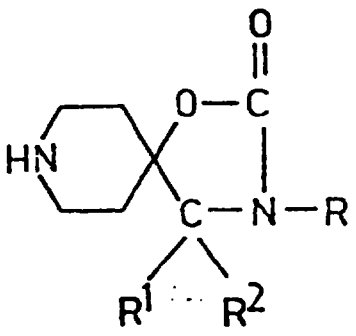
Ph represents a phenyl group unsubstituted or substituted by one or more h
C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or trihalomethyl groups; and

n is 1, 2, 3;

and optical isomers and mixtures thereof and all acid addition and quaternary ammonium

which comprises

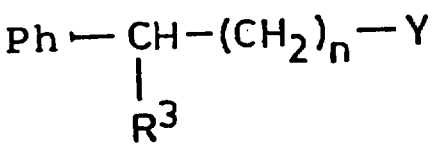
a) for the preparation of compounds of formula (I) wherein X is a group NR, reacting a
zaspiro[4,5]decane derivative of formula (II),



(II)

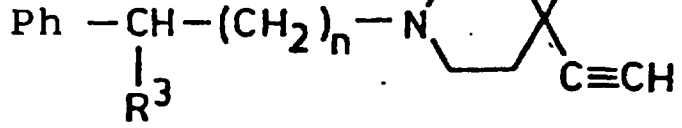
wherein R, R^1 and R^2 are as defined above, with a phenylalkane derivative of formula

(III)



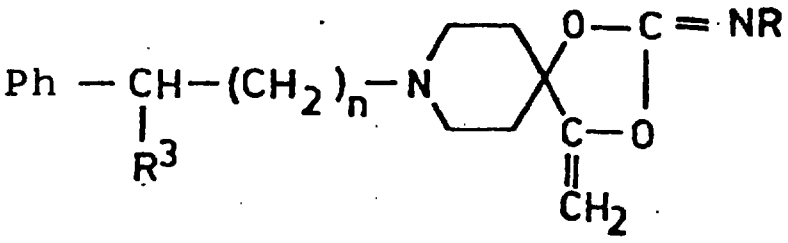
wherein R^3, Ph and n are as defined above and Y represents a halogen atom or a C_{1-4} a
or arylsulfonyloxy group; or

* C L M



(V)

wherein R, R^3 Ph and n are as defined above and reacting the resulting salt of form



(VI

wherein R, R^3 Ph and n are as defined above, with water; or

β) for compounds wherein X is a group NR, cyclizing in a basic medium the formula (V) as defined and prepared above;

or

c) for the preparation of compounds of formula (I) as defined in process (b) (α) abov acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of the formula (V) a and reacting the obtained salt of formula (VI) as defined above with water;

or

d) for the preparation of compounds of formula (I) as defined in process (b) (β) above presence of a base a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (V) a

or

e) for the preparation of a compound of formula (I) wherein is X is a group NR and on a hydroxy group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypipric formula (VII),



wherein R, R^3 Ph and n are as defined above;
or
f) for the preparation of compounds of formula (I) as defined for process (e) above, cyclizin
4carbamoyloxypiperidine derivative of formula (VIII) as defined above;
followed if desired or necessary,
by reacting a compound of formula (I) as prepared above wherein X is an oxygen aton
R^2 together are a methylene group with an amine of formula R-NH_2 wherein R is as defined al
to prepare a compound of the formula (I) wherein X is a group NR and one of R^1 and R^2 i
group and the other is a methyl group,
and/or if desired or necessary,
transforming a compound of the formula (I) as prepared above into another compou
mula (I) as defined above,
and/or desired or necessary,
reacting a compound of formula (I) as prepared above with an acid to obtain the acid additio
and/or treating a salt of a compound of the formula (I) as prepared above with a base to liber
form thereof and /or converting a thus prepared compound of the formula (I) into its quate
nium salt.

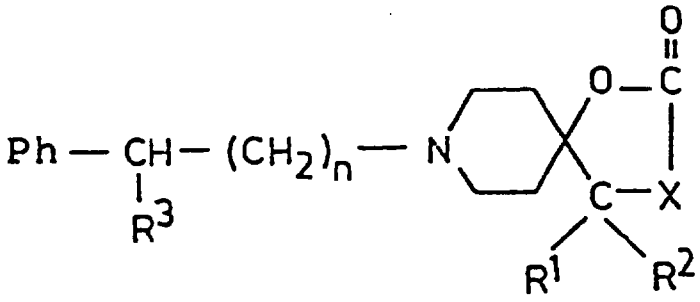
2. A process as claimed in claim 1 process a) wherein Y is either a chlorine or bromine atom
nesulphonyloxy group.

3. A process as claimed in claim 1 process (b) (β) wherein the reaction is carried out as a single
separating the compound of formula (V).

4. A process as claimed in claim 1 process e) which comprises carrying out the reaction in the
triethylamine at the boiling point of the reaction mixture.

5. A process as claimed in Claim 1 for the preparation of a compound of formula (I) as defin
selected from the group comprising:
1-oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl-3,8-diazaspiro [4,5] d
1-oxa-2-oxo-3-cyclohexyl-4-methylene-8-[,4,4-bis(4-fluorophenyl)butyl] -3,8-diazaspiro [4,
1-oxa-2-oxo-3-butyl-4-hydroxy-methyl-8 [4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro [4,5]
1-oxa-2-oxo-4-methylene-3-phenyl-8 [4,4-bis(4-fluorophenyl)-butyl]-3,8-diazaspiro [4,5] de
1-oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro [4,5] d

1. Verbindung der Formel (I)



(I)

worin

X ein Sauerstoffatom oder eine NR-Gruppe darstellt, wobei

R ein Wasserstoffatom oder eine C_{1-12}-Alkyl- oder C_{3-6}-Cycloalkylgruppe oder eine C_{6-10}-Aryl- oder carbocyclische C_{6-10}-Aryl-C_{1-14}-Alkylgruppe darstellt, welche wahlweise schen Ring mit einem oder mehreren Halogenatomen, C_{1-4}-Alkyl- oder C_{1-4}-Alkoxygrup sind;

R^1 und R^2 zusammen eine Methylengruppe darstellen, oder wenn X eine NR-G Gruppe von R^1 und R^2 außerdem eine Hydroxylgruppe und die andere außerdem eine Me stellt;

R^3 ein Wasserstoffatom oder eine Phenylgruppe, wahlweise substituiert mit einem Halogenatomen, C_{1-4}-Alkyl-, C_{1-4}-Alkoxy- oder Hydroxylgruppen, darstellt;

Ph eine Phenylgruppe darstellt, die unsubstituiert oder substituiert mit einem ode logenatomen, $C1_{-4}$-Alkyl-, C_{1-6}-Alkoxy-, Hydroxyl- oder Trihalomethyl-Gruppen ist; und

n 1, 2 oder 3 ist;

und deren optische Isomere und Mischungen und alle ihre Säureadditions- und q moniumsalze.

2. Verbindung der Formel (1) gemäß Anspruch 1, ausgewählt aus der Gruppe, welche umf

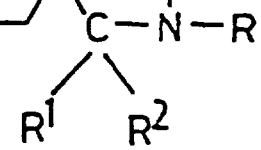
1-Oxa-2-oxo-3-tert-butyl-4-methylen-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspi

1-Oxa-2-oxo-3-cyclohexyl-4-methylen-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazasp

1-Oxa-2-oxo-3-butyl-4-hydroxy-methyl-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazas

1-Oxa-2-oxo-4-methylen-3-phenyl-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspiro[

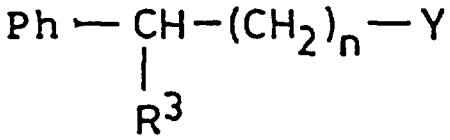
* C L M



(II)

worin R, R^1 und R^2 wie in Anspruch 1 definiert sind, mit einem Phenylalkan-Deriv

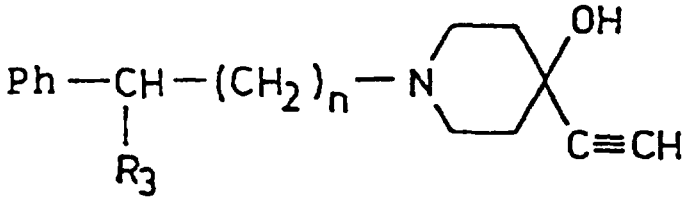
(III)



(III)

worin R^3, Ph und n wie in Anspruch 1 definiert sind und Y ein Halogenatom oder kylsulfonyloxy- oder Arylsulfonyloxy-Gruppe darstellt; oder

b) zur Herstellung von Verbindungen der Formel (I), in denen R^1 und R^2 zusammen eine M pe sind, Umsetzung eines 4-Ethinyl-4-hydroxypiperidin-Derivats der Formel (IV)



(IV)

worin R^3, Ph und n wie oben definiert sind, mit einem Isocyanat der Formel R-I wie oben definiert ist, und entweder

(α) für Verbindungen, in denen X ein Sauerstoffatom ist, Cyclisierung des wie oben 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der Formel (V) in einem sauren Medium

β) für Verbindungen, in denen X eine NR-Gruppe ist, Cyclisierung der wie oben d
hergestellten Verbindung der Formel (V) in einem basischen Medium;

oder

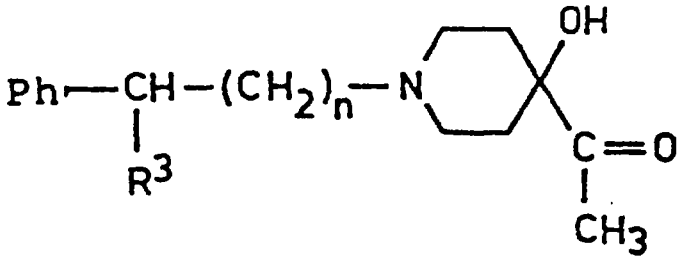
c) zur Herstellung von Verbindungen der Formel (I), die wie in Verfahren (b) (α) oben
cyclisierung eines 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der obigen Formel (V),
rem Medium und Umsetzung des erhaltenen Salzes der obigen Formel (VI) mit Wasse

oder

d) zur Herstellung von Verbindungen der Formel (I), die wie in obigem Verfahren (b) (β)
Cyclisierung eines 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der obigen Formel (V) in
ner Base;

oder

e) zur Herstellung einer Verbindung der Formel (I), in der X eine NR-Gruppe ist und ein
R_1 und R_2 eine Hydroxygruppe und die andere eine Methylgruppe ist, Umsetzung ein
hydroxypiperidin-Derivats der Formel (VII)



(VII)

worin R^3, Ph und n wie oben definiert sind, mit einem Isocyanat der Formel R-
wie oben definiert ist, und Cyclisierung der so gebildeten Verbindung der Formel (VIII)

* C L M S

Umwandlung einer wie oben hergestellten Verbindung der Formel (I) in

der Formel (I) gemäß Anspruch 1,

und/oder falls gewünscht oder erforderlich,

Umsetzung einer wie oben hergestellten Verbindung der Formel (I) mit einer Säure

Säureadditionssalzes und/oder Behandlung eines Salzes einer wie oben hergestellten

Formel (I) mit einer Base zur Freisetzung der Baseform und/oder Umwandlung einer so h

bindung der Formel (I) in ihr quaternäres Ammoniumsalz.

5. Verfahren gemäß Anspruch 4, Verfahren a), dadurch **gekennzeichnet**, daß Y entweder Bromatom oder eine p-Toluolsulfonyloxygruppe ist.

6. Verfahren gemäß Anspruch 4, Verfahren (b) (β) dadurch **gekennzeichnet**, daß die Rea fenreaktion ohne Abtrennung der Verbindung der Formel (V) ausgeführt wird.

7. Verfahren gemäß Anspruch 4, Verfahren e), dadurch **gekennzeichnet**, daß die Reaktio von Triethylamin am Siedepunkt der Reaktionmischung durchgeführt wird.

8. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 bei der Herstellung ein zur Behandlung von hypoxischen Hirnschäden bei Säugetieren.

9. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 zur Herstellung eines M Verwendung bei der Inhibierung der Calciumaufnahme bei Säugetieren.

10. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung gemäß Anspru die Mischung einer Verbindung der Formel (I) oder eines ihrer pharmazeutisch Säureadditions- oder quaternären Ammoniumsalze gemäß Anspruch 1 mit einem pha nehmbaren Träger und/oder Zusatzstoff.

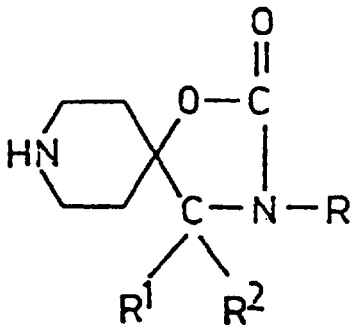
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I)

* C L M S *

Halogenatomen, C_{1-4}-Alkyl-, C_{1-4}-Alkoxy- oder Hydroxylgruppen;
Ph eine Phenylgruppe darstellt, die unsubstituiert oder substituiert mit einem oder mehr
men, C_{1-4}-Alkyl-, C_{1-4}-Alkoxy-, Hydroxyl- oder Trihalomethyl-Gruppen ist; und
n 1, 2 oder 3 ist;
und deren optischen Isomeren und ihren Mischungen und allen ihren Säureadditions-
Ammoniumsalzen, welches umfaßt:

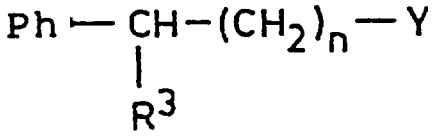
a) zur Herstellung von Verbindungen der Formel (I), in denen X eine NR-Gruppe ist,
2-Oxo-3,8-diazaspiro[4,5]decan-Derivats der Formel (II)



(II)

worin R, R^1 und R^2 wie oben definiert sind, mit einem Phenylalkan-Derivat der Form

(III)



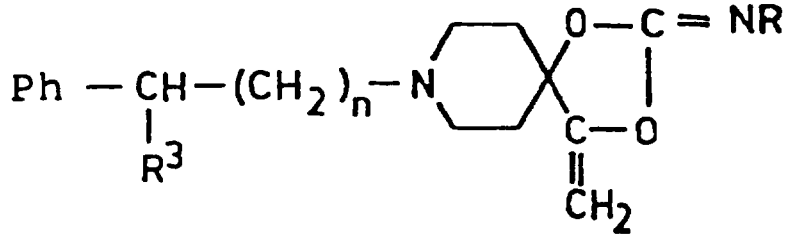
worin R^3, Ph und n wie oben definiert sind und Y ein Halogenatom oder eine C_{1-4}-Alky
Arylsulfonyloxy-Gruppe darstellt; oder

b) zur Herstellung von Verbindungen der Formel (I), in denen R^1 und R^2 zusammen ei
pe sind, Umsetzung eines 4-Ethinyl-4-hydroxypiperidin-Derivats der Formel (IV)

* C L M S *

worin R, R^3, Ph und n wie oben definiert sind, und Umsetzung des resultierenden Sa

(VI)



(VI

worin R, R^3, Ph und n wie oben definiert sind, mit Wasser;

oder

β) für Verbindungen, in denen X eine NR-Gruppe ist, Cyclisierung der Verbindung der oben definiert und hergestellt, in einem basischen Medium;

oder

c) zur Herstellung von Verbindungen der Formel (I), wie in obigem Verfahren (I Cyclisierung eines 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der obigen Formel (V rem Medium und Umsetzung des erhaltenen Salzes der obigen Formel (VI) mit Wass

oder

d) zur Herstellung von Verbindungen der Formel (I), die wie in obigem Verfahren (b) (Cyclisierung eines 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der obigen Formel (V) ner Base;

oder

e) zur Herstellung einer Verbindung der Formel (I), in der X eine NR-Gruppe ist und e R_1 und R_2 eine Hydroxygruppe und die andere eine Methylgruppe ist, Umsetzung e hydroxypiperidin-Derivats der Formel (VII)



in der R, R^3, Ph und n wie oben definiert sind;
oder
f) zur Herstellung von Verbindungen der Formel (I), die wie für obiges Verfahren (e)
Cyclisierung eines 4-Acetyl-4-carbamoyloxypiperidin-Derivats der obigen Formel (VIII)
gefolgt, falls gewünscht oder erforderlich,
von Umsetzung einer wie oben hergestellten Verbindung der Formel (I), worin X ein Sau
und R^1 und R^2 zusammen eine Methylengruppe sind, mit einem Amin der Formel R-NH
oben definiert ist, um eine Verbindung der Formel (I) herzustellen, in der X eine NR-Grup
Gruppe aus R^1 und R^2 eine Hydroxylgruppe und die andere eine Methylgruppe ist;
und/oder, falls gewünscht oder erforderlich,
Umwandlung einer Verbindung der wie oben hergestellten Verbindung der Formel (I) in ei
bindung der obigen Formel (I),
und/oder, falls gewünscht oder erforderlich,
Umsetzung einer wie oben hergestellten Verbindung der Formel (I) mit einer Säure zum Er
readditionssalzes und/oder Behandlung eines Salzes einer wie oben hergestellten Verbind
(I) mit einer Base zur Freisetzung ihrer Baseform und/oder Umwandlung einer so herge
dung der Formel (I) in ihr quaternäres Ammoniumsalz.

2. Verfahren gemäß Anspruch 1, Verfahren (a), dadurch **gekennzeichnet**, daß Y entweder
Bromatom oder eine p-Toluolsulfonyloxygruppe ist.

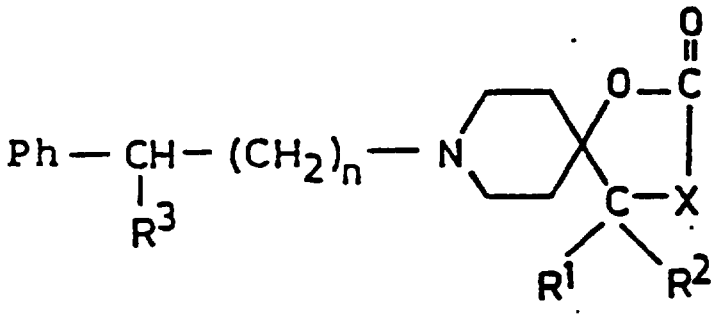
3. Verfahren gemäß Anspruch 1, Verfahren (b) (β), dadurch **gekennzeichnet**, daß die Reak
fenreaktion ohne Abtrennung der Verbindung der Formel (V) ausgeführt wird.

4. Verfahren gemäß Anspruch 1, Verfahren (e), dadurch **gekennzeichnet**, daß die Reaktio
von Triethylamin am Siedepunkt der Reaktionmischung ausgeführt wird.

5. Verfahren gemäß Anspruch 1 zur Herstellung einer Verbindung der Formel (I) gemäß Ansp
gewählt ist der Gruppe, welche umfaßt:
1-Oxa-2-oxo-3-tert-butyl-4-methylen-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspiro[4,5]d
1-Oxa-2-oxo-3-cyclohexyl-4-methylen-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspiro[4,5]
1-Oxa-2-oxo-3-butyl-4-hydroxy-methyl-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspiro[4,5
1-Oxa-2-oxo-4-methylen-3-phenyl-8-[4,4-bis(4-fluorphenyl)butyl]-3,8-diazaspiro[4,5]dec
1-Oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[2-(4-fluorphenyl)ethyl]-3,8-diazaspiro[4,5]d

* C L M S *

1. Composé de formule (I)



(I)

dans laquelle

X représente un atome d'oxygène ou un groupe NR, où

R représente un atome d'hydrogène ou un groupe alkyle en C_{1-12} ou un g
en C_{3-6}, ou un groupe carbocyclique aryle en C_{6-10} ou un groupe carbo
C_{6-10}-alkyle en C_{1-14}, éventuellement substitués sur le cycle aromatiq
sieurs atomes d'halogènes, des groupes alkyle en C_{1-4} ou alcoxy en C

R^1 et R^2 représentent ensemble un groupe méthylène ou, lorsque X est un groupe
R^2 représente en outre un groupe hydroxyle et l'autre représente en outre u

R^3 représente un atome d'hydrogène ou un groupe phényle éventuellement s
plusieurs atomes d'halogènes,un groupe alkyle en C_{1-4}, un groupe alcoxy e
pe hydroxyle;

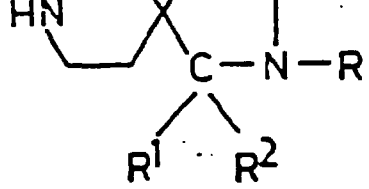
Ph représente un groupe phényle non substitué ou substitué par un ou plusi
logènes, des groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, hydroxyle ou trihalor

n est 1,2,3;

et leurs isomères optiques et mélanges et tous leurs sels d'addition d'acides et d'ammo

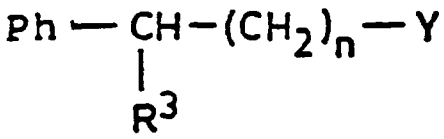
2. Composé de formule (I) telle que définie dans la revendication 1, ce composé étant ch
comportant:
le 1-oxa-2-oxo-3-tert.butyl-4-méthylène-8-[4,4-bis(4-fluorophényl)butyl-3,8-diazaspir
le 1-oxa-2-oxo-3-cyclohexyl-4-méthylène-8-[4,4-bis(4-fluorophényl)butyl]-3,8-diazasp
le 1-oxa-2-oxo-3-butyl-4-hydroxy-méthyl-8-[4,4-bis(4-fluorophényl)butyl]-3,8-diazasp

* C L M S *



(II)

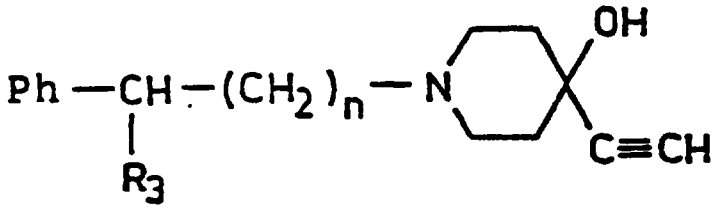
où R, R^1 et R^2 sont tels que définis dans la revendication 1, avec un dérivé phénylal (III),



(III)

où R^3, Ph et n sont tels que définis dans la revendication 1 et Y représente un atom un groupe alkylsulfonyloxy en C_{1-4} ou un groupe arylsulfonyloxy; ou

b) pour la préparation de composés de formule (I) où R^1 et R^2 ensemble sont un gr on fait réagir un dérivé de la 4-éthynyl-4-hydroxypipéridine de formule (IV),



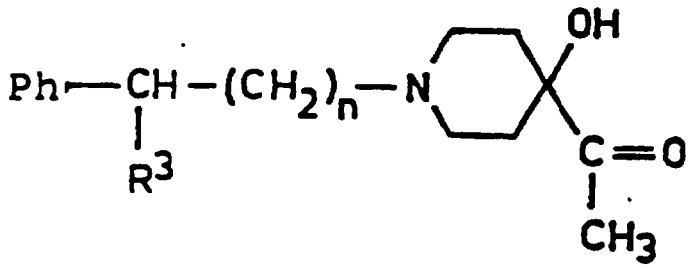
(IV)

où R^3, Ph et n sont tels que définis ci-dessus, avec un isocyanate de formule R-NCO, défini ci-dessus, et

* C L M S *



où R, R^3, Ph et n sont tels que définis ci-dessus;
ou
β) pour les composés où X est un groupe NR, on cyclise en milieu basique le composé tel que défini et préparé ci-dessus;
ou
c) pour la préparation des composés de formule (I) tels que définis dans le procédé (b) on cyclise dans un milieu acide un dérivé de la 4-carbamoyloxy-4-éthynylpipéridine de f que définie ci-dessus et on fait réagir le sel obtenu de formule (VI) telle que définie ci-d l'eau;
ou
d) pour la préparation des composés de formule (I) tels que définis dans le procédé (b) on cyclise en présence d'une base un dérivé de la 4-carbamoyl-oxy4-éthynylpipéridine telle que définie ci-dessus ;
ou
e) pour la préparation d'un composé de formule (I) où X est un groupe NR et un des groupe hydroxy et l'autre est un groupe méthyle, on fait réagir un dérivé de la 4-acétyl- ridine de formule (VII),



(VII)

où R^3, Ph et n sont tels que définis ci-dessus, avec un isocyanate de formule R-NCO d défini ci-dessus, et on cyclise le composé ainsi formé de formule (VIII)



tel que défini dans la revendication 1,
et/ou si on le désire ou si cela est nécessaire,
on fait réagir un composé de formule (I) tel que préparé ci-dessus avec un acide pour obtenir s
dition d'acide et/ou on traite un sel d'un composé de formule (I) tel que préparé ci-dessus ave
pour libérer de celui-ci la forme de base et/ou on transforme le composé ainsi préparé de for
son sel d'ammonium quaternaire.

5. Procédé tel que revendiqué dans la revendication 4 procédé a) où Y est soit un atome de cl
brome soit un groupe p-toluènesulfonyloxy.

6. Procédé tel que revendiqué dans la revendication 4 procédé (b) (β) où la réaction est mise en o
une étape unique sans séparer le composé de formule (V).

7. Procédé tel que revendiqué dans la revendication 4 procédé e) qui comporte le fait d'effectuer
en présence de triéthylamine au point d'ébullition du mélange réactionnel.

8. Emploi d'un composé de formule (I) tel que défini dans la revendication 1 pour la fabrication
cament pour le traitement de dommage hypoxique du cerveau chez les mammifères.

9. Emploi d'un composé de formule (I) tel que défini dans la revendication 1 pour la fabrication
cament destiné à être utilisé pour inhiber la prise de calcium chez les mammifères.

10. Procédé pour la préparation d'une composition pharmaceutique telle que définie dans la rev
3, qui comporte le fait de mélanger un composé de formule (I) ou un sel d'addition d'acide ou d'
quaternaire de celui-ci, acceptable en pharmacie, tel que défini dans la revendication 1, avec
et/ou un additif acceptables en pharmacie.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de formule (I)

* C L M S *

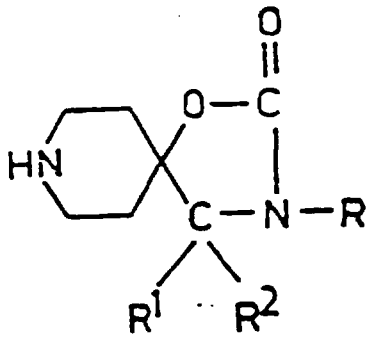
pe hydroxyle;

Ph représente un groupe phényle non substitué ou substitué par un ou plusieurs ato
logènes, des groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, hydroxyle ou trihalométhyle ;

n est 1,2,3;

et leurs isomères optiques et mélanges et tous leurs sels d'addition d'acides et d'ammonium qu
ce procédé comportant les points suivants

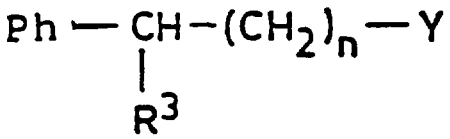
a) pour la préparation des composés de formule (I) où X est un groupe NR, on fait réagir un
2-oxo-3,8-diazaspiro[4,5]décane de formule (II),



(II)

où R, R^1 et R^2 sont tels que définis plus haut, avec un dérivé phénylalcane de formule (III),

(III)

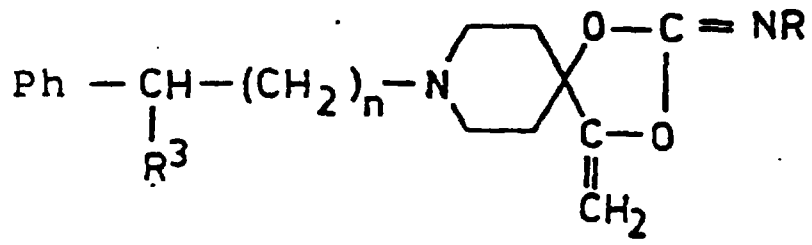


où R^3, Ph et n sont tels que définis ci-dessus et Y représente un atome d'halogène ou un gro
sulfonyloxy en C_{1-4} ou un groupe arylsulfonyloxy; ou

b) pour la préparation de composés de formule (I) où R^1 et R^2 ensemble sont un groupe m
on fait réagir un dérivé de la 4-éthynyl-4-hydroxypipéridine de formule (IV),

* C L M S *

où R, R^3, Ph et n sont tels que définis ci-dessus, et on fait réagir avec de l'eau le sel résult
(VI)



(VI

où R, R^3, Ph et n sont tels que définis ci-dessus;
ou

β) pour les composés où X est un groupe NR, on cyclise en milieu basique le comp
(V) tel que défini et préparé ci-dessus;
ou

c) pour la préparation des composés de formule (I) tels que définis dans le procédé (b)
on cyclise dans un milieu acide un dérivé de la 4-carbamoyloxy-4-éthynylpipéridine de fo
que définie ci-dessus et on fait réagir le sel obtenu de formule (VI) telle que définie ci-d
l'eau;
ou

d) pour la préparation des composés de formule (I) tels que définis dans le procédé (b)
on cyclise en présence d'une base un dérivé de la 4-carbamoyl-oxy-4-éthynylpipéridine
telle que définie ci-dessus ;
ou

e) pour la préparation d'un composé de formule (I) où X est un groupe NR et un des
groupe hydroxy et l'autre est un groupe méthyle, on fait réagir un dérivé de la 4-acétyl-
ridine de formule (VII),

* C L M S *

où R, R^3, Ph et n sont tels que définis ci-dessus;
ou
f) pour la préparation de composés de formule (I) comme définis pour le procédé
clise un dérivé de la 4-acétyl-4-carbamoyloxypipéridine de formule (VIII) comme
et ensuite, si on le désire ou si cela est nécessaire,
on fait réagir un composé de formule (I) tel que préparé ci-dessus, où X est un atom
R^2 ensemble sont un groupe méthylène, avec une amine de formule R-NH_2 où R
dessus, pour préparer un composé de formule (I), où X est un groupe NR et un des R
hydroxyle et l'autre est un groupe méthyle;
et/ou si on le désire ou si cela est nécessaire,
on transforme un composé de formule (I) tel que préparé ci-dessus en un autre con
tel que défini précédemment,
et/ou si on le désire ou si cela est nécessaire,
on fait réagir un composé de formule (I) tel que préparé ci-dessus avec un acide pour
dition d'acide et/ou on traite un sel d'un composé de formule (I) tel que préparé ci-de
pour libérer de celui-ci la forme de base et/ou on transforme le composé ainsi prépa
son sel d'ammonium quaternaire.

2. Procédé tel que revendiqué dans la revendication 1 procédé a) où Y est soit un ato
brome soit un groupe p-toluènesulfonyloxy.

3. Procédé tel que revendiqué dans la revendication 1 procédé (b)(β)où la réaction est
une étape unique sans séparation du composé de formule (V).

4. Procédé selon la revendication 1 procédé e) qui comporte le fait de mettre la réactio
sence de triéthylamine au point d'ébullition du mélange réactionnel.

5. Procédé selon la revendication 1 pour la préparation d'un composé de formule (I) te
la revendication 1, ce composé étant choisi dans le groupe comportant :
le 1-oxa-2-oxo-3-tert.butyl-4-méthylène-8-[4,4-bis(4-fluorophényl)butyl-3,8-diazasp
le 1-oxa-2-oxo-3-cyclohexyl-4-méthylène-8-[4,4-bis(4-fluorophényl)butyl]-3,8-diaza
le 1-oxa-2-oxo-3-butyl-4-hydroxy-méthyl-8-[4,4-bis(4-fluorophényl)butyl]-3,8-diazas
le 1-oxa-2-oxo-4-méthyl-3-phényl-8-[4,4-bis(4-fluorophényl)-butyl]-3,8-diazaspiro [4

* C L M S *

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