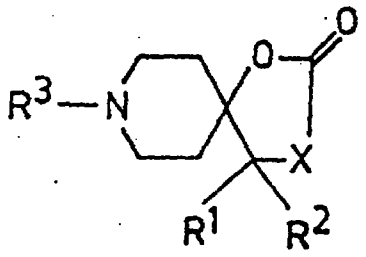
Description

The invention relates to 2-oxo-1-oxa-8-azaspiro[4,5]decane derivatives, processes for their preparation and pharmaceutical compositions thereof.

A number of therapeutically useful 2-oxo-1-oxa-3,8-diazaspiro[4,5]decane derivatives have been described in the literature, e.g. CA. 71, 91359d (1969); C.A. 78, 719668t (1973); C.A. 78, 23876g (1973); C.A. 81, 33153a and 105368b (1974); C.A. 95, 161765e (1981); as well as in the DE patent specifications Nos. 2,013,729, 2,013,668 and 2,163,000; in the BE patent specifications Nos. 775,984, 774,170, 786,631 and 825,444; in the GB patent specification No. 1,100,281; in the published NL patent application No. 7,214,689 as well as in the US patent specifications Nos. 3,555,033, 3,594,386, 4,244,961 and 4,255,432 and EP-A-292400.

We have now found a novel range of compounds wherein the nature of the substituents bound the 4-position and optionally in the 3-position of the spirodecane skeleton are substantially different.

According to one aspect of the present invention, there are provided compounds of formula (I)



(I)

wherein

X represents an oxygen atom or a >NR group, wherein

R represents a hydrogen atom or a C_{1-12}alkyl, C_{3-6}cycloalkyl or a tosyl group, or a carbocyclic C_{6-10} aryl or carbocyclic C_{6-10}aryl -C_{1-4}alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or trihalomethyl 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 may additionally represent a hydroxyl group whilst the other one is a methyl group; and

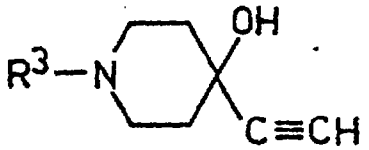
R^3 represents a hydrogen atom or a benzyl, (C_{1-4}alkoxy)carbonyl, phenoxycarbonyl, formyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl, 2-chloro-3-nicotinoyl-carbamoyl, C_{1-6}alkylcarbamoyl group or benzyloxy-carbonyl and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof,

and the compound of formula (I) wherein X is >NR in which R is a 2-(3,4-dihydroxyphenyl) ethyl] group, R^1 is a hydroxy group, R^2 is a methyl group and R^3 is a benzyl group, and optical isomers and mixtures thereof.

The compounds of the formula (I) may contain one or more asymmetric carbon atom(s) and consequently, they may exist in various stereoisomeric forms. Furthermore, the compounds of the formula (I) may also be in the form of bases, acid addition or quaternary ammonium salts, racemates, individual optical isomers and their mixtures, all of which may occur in the form of various solvates such as hydrates. All these compounds and mixtures are within the scope of the present invention.

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

a) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a methylene group, reacting a 4-ethynyl-4-hydroxypiperidine derivative of formula (III),

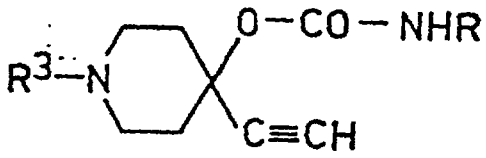


(III)

wherein R^3 is as hereinbefore defined, with an isocyanate of the formula R-NCO, wherein R is as herein-

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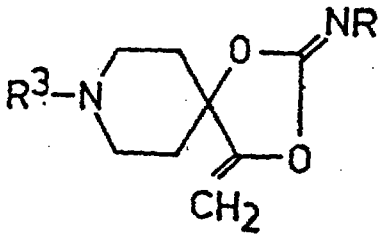
before defined, and cyclizing the thus obtained 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II),



(II)

wherein R and R^3 are as defined above, either

α) for compounds wherein X is an oxygen atom, in an acidic medium and reacting the resultant compound of formula (VI),



(VI)

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

β) for compounds wherein X is a group NR, in a basic medium;

or

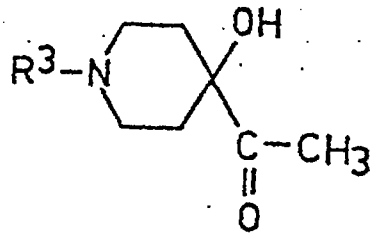
b) for the preparation of compounds of formula (I) as defined in process (a) (α) above, cyclizing in an acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, and reacting the resultant compound of formula (VI) as defined above with water,

or

c) for the preparation of compounds of formula (I) as defined in process (a) (β) above, cyclizing a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, in a basic medium;

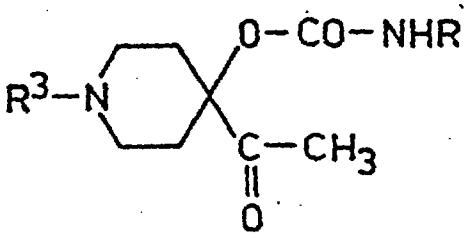
or

d) for the preparation of compounds of formula (I) wherein X is a >NR group and one or R^1 and R^2 is a hydroxyl group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypiperidine derivative of formula (IV),



(IV)

wherein R^3 is as defined above, with an isocyanate of the formula R-NCO, wherein R is as defined above, and cyclizing the thus formed 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V),



(V)

wherein R and R^3 are as defined above;

or

e) for the preparation of compounds of formula (I) wherein X is a >NR group, and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group, cyclizing a 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V) 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^1 and R^2 together are a methylene group, with an amine of formula $R\text{-}NH_2$, wherein R is as defined above, in order to prepare a compound of the formula (I), wherein X is a >NR group and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group;

and/or if desired or necessary,

transforming a compound of formula (I) as prepared above into another compound of the formula (I) as hereinbefore defined in a known manner;

and/or if desired or necessary,

reacting a compound of the formula (I), as prepared above, with an acid to obtain the acid addition salt thereof and/or reacting a salt of a compound of the formula (I) as prepared above with a base to liberate the base form thereof and/or converting a thus prepared compound of the formula (I) into its quaternary ammonium salt.

In the first step of process a) above a 4-ethynyl-4-hydroxypiperidine derivative of the formula (III) is brought into reaction with an isocyanate of the formula R-NCO in a manner known per se [Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)] to give a 4-carbamoyloxy-4-ethynylpiperidine derivative of the formula (II), which is cyclized in an acidic medium according to step α) or in a basic medium according to step β).

According to step α), the obtained 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) is cyclized in an acidic medium and then the thus formed salt of a 2-imino-1,3-dioxolane derivative of formula (VI) is reacted with water. The cyclization may be carried out in an inert organic solvent (i.e. in a solvent which is inert under the reaction conditions), in the presence of a suitable acid, preferably in the presence of a dry hydrogen halide. Aliphatic or alicyclic ethers such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tetrahydrofuran or dioxane as well as lower aliphatic carboxylic acids, e.g. acetic or propionic acid, may be employed as solvents.

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

The cyclization of the obtained 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) according to the step β)may be realized in the presence of a base. Alkaline metal acetates, carbonates, alkoxides, hydroxides and/or tertiary organic bases, e.g. pyridine, tripropylamine or picoline, may be used as basic catalysts in the cyclization; the organic bases may also serve as solvents for the reaction. Further suitable solvents are aliphatic alcohols, e.g. methanol, ethanol, propanol or butanol; aliphatic, alicyclic or aromatic hydrocarbons, e.g. hexane, cyclohexane, benzene, toluene or xylene; acid amides, e.g. dimethyl formamide or N-methyl-2-pyrrolidone; ethers such as dibutyl ether or dioxane; nitriles such as acetonitrile; sulfoxides, e.g. dimethyl sulfoxide, etc.; and any mixture of the above solvents. The reaction may also be carried out without any solvent, e.g. in a molten state. In order to accelerate the cyclization the temperature may be suitably increased: the reaction is preferably accomplished between 40 °C and the boiling point of the reaction mixture. It is suitable to work under an inert gas such as argon or nitrogen. According to a preferred embodiment of the present invention, when R^3 is other than a 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl or 2-chloro-3-nicotinoylcarbamoyl group, the 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) resulting from the reaction of a 4-ethynyl-4-hydroxypiperidine derivative of formula (III) with an isocyanate of formula R-NCO is not isolated but directly cyclized in the same reaction mixture in the presence of a suitable base.

In the processes b) and c) above the procedures. as discussed under steps α) and β) above may be followed.

In the process d) above, a 4-acetyl-4-hydroxypiperidine derivative of the formula (IV) is reacted with an isocyanate of the formula R-NCO and the obtained 4-acetyl-4-carbamoyloxypiperidine derivative of the formula (V) is cyclized. The condensation reaction according to the first step may be realised in a manner known per se [Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)]. The obtained 4-acetyl-4-carbamoyloxypiperidine derivative of the formula (V) is preferably cyclized in the presence of a base. The cyclization may be carried out under the same reaction conditions as described for step β) of process a) above. Alternatively, according to a preferred embodiment of process (a) (β) of this invention, the 4-acetyl-

4-carbamoyloxypiperidine derivative of the formula (V), created in the reaction of the 4-acetyl-4-hydroxypiperidine derivative of the formula (IV) with the isocyanate of formula R-NCO, may be cyclized directly in the same reaction mixture, and in the presence of a suitable base ,i.e. the derivative of formula (VIII) is not isolated from its reaction mixture before its cyclization.

For process e)above, the procedure in the second step of process d) above may be followed.

If desired or necessary, the compounds of formula (I) as prepared in any one of the processes a) to e) above may be transformed into other compounds within the scope of the formula (I) in a manner known per se.

Thus, on reacting a compound of the formula (I) as prepared above wherein X is an oxygen atom and R^1 together with R^2 are a methylene group with an amine of formula R-NH_2 wherein R is as defined above, a compound of formula (I) may be prepared wherein X is a >NR group and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group. This reaction may be carried out in a suitable solvent or without any solvent. Convenient solvents are e.g. aliphatic, alicyclic or araliphatic alcohols such as ethanol, butanol, cyclohexanol, benzyl alcohol; aliphatic or aromatic hydrocarbons such as hexane, heptane, xylene, chlorobenzene or nitrobenzene; ethers, e.g. dioxane; ketones, e.g. di-n-butyl ketone; tertiary organic bases, e.g. picoline, triethylamine or pyridine. An excess of the R-NH_2 amine may also serve as a solvent for this reaction. This procedure may be carried out at a temperature between room temperature and the boiling point of the reaction mixture, preferably under an inert gas, e.g. argon or nitrogen.

If desired or necessary, a fund of the formula (I) wherein R^1 an a R^2 are a hydroxyl and a methyl group may be dehydrated into a compound of formula (I) wherein R^1 and R^2 together are a methylene group. The dehydration may be achieved under normal or reduced pressure using well-known procedures. Isocyanates, aliphatic carboxylic acids, aliphatic or aromatic carboxylic acid anhydrides, Lewis acids, sulfuric acid or aromatic sulfonic acids may be employed for the dehydration. This reaction is preferably performed in an organic solvent. Suitable solvents are e. g. aromatic hydrocarbons such as benzene, toluene or xylene; ethers such as dioxane, di-n-butyl ether; or aliphatic carboxylic acids such as acetic acid.

According to a preferred embodiment of this reaction, a mixture of glacial acetic acid and acetic anhydride is used or the dehydration is carried out in xylene in the presence of p-toluenesulfonic acid while the water formed in the reaction is azeotropically distilled out.

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

From the obtained compounds of formula (I), wherein R^3 represents a benzyl or benzyloxycarbonyl group, these groups can be removed by e.g. a reductive cleavage to obtain compounds of the formula (I), wherein R^3 is hydrogen. This reduction may preferably be carried out by catalytic hydrogenation. As hydrogenating catalysts metals such as ruthenium, palladium, platinum, nickel, iron, cobalt, chromium, zinc, tungsten, molybdenum as well as their oxides and sulfides may be employed. The catalytic hydrogenation may also be carried out by using a catalyst previously precipitated onto the surface of a carrier. Such carriers may be e.g. carbon, silicon dioxide, aluminum oxide as well as carbonates and sulfates of the alkaline-earth metals. This reduction may be suitablyaccomplished in the presence of palladium-on-charcoal by hydrogenation in an inert solvent. Lower aliphatic alcohols, ethers, esters as well as aliphatic, cycloaliphatic or aromatic hydrocarbons or their mixtures may be used as solvents. The hydrogenation may be accomplished under atmospheric or higher pressure at a temperature between 20 °C and the boiling point of the reaction mixture. After termination of the reaction the catalyst is filtered off, the filtrate is evaporated and, if desired, the product obtained is purified e.g. by recrystallization. According to a preferred embodiment of the reduction, this process is performed by the means of catalytic transfer hydrogenation which is well known in the literature by using a hydrogen donor substance such as formic acid, hydrazine in the presence of palladium-on-charcoal catalyst. A formyl group as R^3 can reductively be cleaved or it can be removed by using hydrazine or hydroxylamine in the presence of a weak acid such as acetic acid. This reaction may be carried out in inert organic solvents such as e.g.: lower alkanols, e.g. methanol or ethanol; or in acid amides, e.g. dimethylacetamide; or in ethers such as dioxane; or in the mixtures of the above solvents. The reaction medium may also contain water. The temperature is preferably increased for accelerating the reaction. Thus, this reaction is preferably carriedlout at a temperature between 40 °C and the boiling point of the reaction mixture.

Hydrogen as R^3 in the compounds of formula (I) may be replaced by an other group by using methods known per se; it can be replaced by e.g. a benzyl group on reacting it with a benzyl halide, preferably benzyl chloride or bromide, suitably in the presence of a convenient base such as an alkaline metal or alkaline earth

metal carbonate or hydrogen carbonate, a tertiary organic base or an excess of the compound of formula (I) which are useful for binding the acid formed in the reaction. A little amount of an alkaline metal iodide, e.g. potassium iodide may be used for promoting this reaction.

Hydrogen as R^3 may be replaced by a (C_{1-4}alkoxy)carbonyl, phenoxycarbonyl or benzyloxycarbonyl group by its reaction with a reactive carboxylic acid derivative containing such a group. A suitable chloroformate ester may be used as a reactive carboxylic acid derivative. This reaction is conveniently carried out in the presence of a base which is useful for binding the acid formed in the reaction. For this purpose the bases listed above may be employed. The reaction is accomplished by using methods commonly known from the literature.

Hydrogen as R^3 may be replaced by a formyl group by using a reactive formic acid derivative. Chloride, imidazolide or preferably a mixed anhydride of formic acid may be used as reactive derivatives for instance. For theformylation of compounds of the formula (I) the mixed anhydride of formic acid with acetic acid may be used. However, this reaction may also be carried out by using any other commonly known N-acylating process.

Hydrogen as R^3 may be replaced by a C_{1-6}alkylcarbamoyl, piperidin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 2-chloro-3-nicotinoylcarbamoyl group as a result of reaction with a suitably substituted chloroformic acid amide or isocyanate. This reaction may be carried out in an appropriate inert solvent, preferably in the presence of a base, under an inert gas, e.g. argon or nitrogen. Aromatic hydrocarbons such as benzene, toluene or xylene; ethers such as diethyl ether, diisopropyl ether or dioxan ; halogenated hydrocarbons such as methylene chloride, 1,2-dichloroethane or chloroform; nitriles, e.g. acetonitrile; acid amides such as N-methyl-2-pyrrolidone; tertiary organic bases, e.g. picolines, triethylamine or pyridine, may be used as solvents. The above mentioned inorganic and tertiary organic bases are useful acid binding agents. The reaction may be carried out at a temperature between 0 °C and the boiling point of the reaction mixture. The reaction with an acyl isocyanate, e.g. 2-chloro-3-nicotinoyl isocyanate may be realized in such a way that the isocyanate compound is prepared in situ and the compound of the formula (I) to be acylated is added to the reaction mixture containing the isocyanate. Thus, 2--chloro-3-nicotinoyl isocyanate can be prepared by e.g. reacting 2-chloronicotinic acid amide with oxalyl chloride in an inert solvent such as 1,2-dichloroethane.

Compounds containing a phenoxycarbonyl group as R^3may also be prepared from the compounds of formula (I) containing a benzyl group as R^3 by reacting the latter compounds with phenyl chloroformate. On reacting compounds of the formula (I) containing a phenoxycarbonyl group as R^3 with N-(2-hydroxyethyl)piperazine, compounds of the formula (I) containing a 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl group as R^3 are obtained.

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

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

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

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

The compounds of the formulae (II) and (V) may be obtained by reacting the 4-hydroxypiperidine derivatives of the formula (III) or (IV) respectively with isocyanates of the formula R-NCO by using a method known per se [see e.g. Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)].

The compounds of the formula (III) may be prepared by e.g. the ethynylation reaction of the appropriately substituted 4-piperidine derivatives according to e.g. Hungarian patent specification No. 166,769 or by using a method described in: Farmaco (Pavia) Ed. Sci. 12 34 (1957).

The 4-acetyl-4-hydroxypiperidine derivatives of the formula (IV) may be obtained by e.g. the hydration of the corresponding 4-ethynyl-4-hydroxypiperidine derivatives of the formula (III) [see e.g.: Houben-Weyl: Methoden der Organischen Chemie Vol. VII/2a, pages 826 to 835 (1973)] or by the alkaline treatment of the corresponding 4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane derivatives of the formula (I).

The novel compounds of formula (I) according to the invention are useful intermediates in the synthesis of other therapeutically active spirodecane derivatives e.g. as described in EP-A-0414422 EP-A-0413516, EP-A-0412821 and EP-A-0414421 of even date claiming priority from Hungarian patent applications Nos. 4093/89, 4094/89 and 4095/89). However, they do have their own biological (such as anticonvulsive, antiallergic and lipid level lowering) activities.

The present invention therefore also relates to a use of a compound of formula (I) as hereinbefore defined in the manufacture of a medicament for the treatment of epileptic and allergic diseases and high (increased) lipid levels in mammals.

The invention is illustrated by way of the following Examples.

Example 1

8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane

Dry gaseous hydrogen chloride is introduced at 20 to 50 °C during 2.5 to 3 hours into a solution containing 31.4 g of 1-benzyl-4-butylcarbamoyloxy-4-ethynylpiperidine in 157 ml of anhydrous dioxan. After standing overnight the reaction mixture is evaporated in a water bath of 40 to 50 °C temperature under reduced pressure. After adding 200 ml of water to the evaporation residue the base is liberated by sodium hydrogen carbonate. After filtration the solid precipitate is washed to chloride-free with water and dried. The crude product obtained is recrystallized from n-hexane under clarifying by activated carbon to give the title compound in 80.6%. yield, m.p.: 65-67 °C.

Analysis:

Calculated for $C_{15}H_{17}NO_3$			
	C 69.48;	H 6.61;	N 5.40%;
found:	C 69.65;	H 6.51;	N 5.63%.

Example 2

8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane

5.16 g of 1-benzyl-4-carbamoyloxy-4-ethynylpiperidine are stirred in 30 ml of 30% by weight solution of hydrogen bromide in acetic acid at room temperature for 6 hours. After evaporating the solvent under reduced pressure and adding 50 ml of water to the residue the base is liberated by sodium hydrogen carbonate. The solid product obtained is filtered, washed to bromide-free with water, dried and recrystallized from n-hexane to give the title compound in 59.3% yield the physical characteristics of which are in agreement with those given in Example 1 above.

Example 3

3-[2-(3,4-dimethoxyphenyl)ethyl]-8-benzyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro-[4,5]decane

19.9 g of 2-(3,4-dimethoxyphenyl)ethylamine are portion-wise added to a solution of 25.9 g of 8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane in 35 ml of anhydrous xylene under stirring. Meanwhile the temperature of the reaction mixture increases to 35 to 40 °C. The reaction mixture is left to stand at room temperature overnight, then the crystalline reaction mixture is diluted with n-heptane and filtered. The solid precipitate obtained is recrystallized from ethanol to obtain the title compound in 94% yield, m.p.: 181-183 °C.

Analysis:

Calculated for $C_{25}H_{32}N_2O_5$

C 68.16; H 7.32; N 6.36%;

found: C 68.35; H 7.18; N 6.50%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process as described in the above Example.

8-Benzyl-3-decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 111-112 °C;

8-Benzyl-3-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 116-117 °C;

8-Benzyl-3-butyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 122-123 °C (the hydrochloride is precipitated by using an ethereal hydrogen chloride solution, it melts about 260 °C); and

8-Benzyl-4-hydroxy-4-methyl-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. 203-205 °C [hydrochloride m.p.: 284-286 °C (with decomposition)].

Example 4

8-benzyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A solution containing 13.2 g of 8-benzyl-4-methylene-2-oxol,3-dioxa-8-azaspiro[4,5]decane in 130 ml of anhydrous ether is portionwise added to 130 ml of liquid ammonia under stirring and after stirring the reaction mixture for an additional 30 minutes, the ammonia is evaporated. The crystalline precipitate is filtered, washed with ether and dried to give the title product in 97.2% yield, m.p.: 162-164 °C.

Analysis:

Calculated for $C_{15}H_{20}N_2O_3$

C 65.19; H 7.29; N 10.14%;

found: C 65.24; H 7.43; N 10.28%.

The above reaction may be carried out also by using 25% aqueous ammonium hydroxide solution where appropriate. The physical characteristics of the product thus obtained are identical to those given above.

Example 5

3,8-dibenzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A solution containing 34.8 g of 1-benzyl-4-benzylcarbamoyloxy-4-ethynylpiperidine and 1.1 g of sodium methoxide in 350 ml of anhydrous methanol is refluxed for 4 hours. After cooling down and maintaining the reaction mixture at 0 °C for 30 to 60 minutes the crystalline precipitate is filtered and recrystallized from methanol to obtain the title compound in 83% yield, m.p.: 113-114 °C.

Analysis:

Calculated for $C_{22}H_{24}N_2O_2$

C 75.83; H 6.94; N 8.04%;

found: C 75.71; H 7.03; N 8.20%.

Example 6

8-benzyl-3-tert-butyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

8.3 g of 4-acetyl-1-benzyl-4-tert-butylcarbamoyloxypiperidine are refluxed in 100 ml of an ethanolic sodium ethoxide solution of 0.1 mole/litre concentration under stirring for 3 to 4 hours. After cooling down and adding 10% by weight aqueous ammonium chloride solution to the reaction mixture the greater part of the solvent is distilled off under reduced pressure. After adding water to the residue the precipitate is filtered off, wash-

ed to chloride-free with water, dried and finally recrystallized from benzene to give the title compound in 78% yield, m.p.: 179-181 °C.
Analysis:

Calculated for $C_{19}H_{28}N_2O_3$			
	C 68.64;	H 8.49;	N 8.43%;
found:	C 68.75;	H 8.57;	N 8.65%.

Example 7

8-benzyl-3-n-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

The solution of 18.7 g of 8-benzyl-3-n-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 40 ml of benzyl alcohol is heated at 160 °C for 5 hours while the water formed in the reaction is azeotropically distilled off. Thereafter, the mixture is evaporated under reduced pressure. After taking up the residue in chloroform the solution is dried over anhydrous magnesium sulfate, filtered off and evaporated under reduced pressure. The crude product obtained is recrystallized from n-hexane under clarifying by activated carbon to obtain the title compound in 81% yield, m.p.: 47-48°C.
Analysis:

Calculated for $C_{22}H_{32}N_2O_2$			
	C 74.12;	H 9.05;	N 7.86%;
found:	C 74.33;	H 9.14;	N 7.68%.

Example 8

3-benzyl-8-benzyloxycarbonyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

72 ml of aqueous hydrochloric solution of 3 mol/litre concentration are portionwise added over 20 to 30 minutes to a solution of 3.92 g of 3-benzyl-8-benzyloxycarbonyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 8 ml of 99%, formic acid under stirring. The precipitate is filtered off, washed with water and dried. After recrystallization from ethanol the title compound is obtained in a yield of 89%., m.p.: 155-157 °C.
Analysis:

Calculated for $C_{23}H_{26}N_2O_5$			
	C 67.30;	H 6.38;	N 6.82%;
found:	C 67.35;	H 6.19;	N 6.72%.

Example 9

8-(2-chloronicotinoylcarbamoyl)-3-ethyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]-decane

A solution of 11 g of 8-(2-chloronicotinoylcarbamoyl)-3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 116 ml of hydrochloric acid of 1 mol/litre concentration is stirred at room temperature for 2 hours and then cooled down to 3 to 5 °C. After adjusting the pH value of the reaction mixture to 6 to 7 by adding aqueous sodium hydrogen carbonate solution the precipitate is filtered and washed to chloride-free with water. The product obtained is recrystallized from a mixture of dimethylformamide and methylene chloride to give the title compound in 75% yield, m.p.: 195-196 °C.
Analysis:

Calculated for $C_{17}H_{21}ClN_4O_5$

C 51.45; H 5.33; Cl 8.93; N 14.12%;

found: C 51.60; H 5.51; Cl 8.84; N 14.25%.

Example 10

8-benzyl-3-cyclohexyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrochloride and free base

A solution of 10 g of 8-benzyl-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 100 ml of aqueous hydrochloric acid of 0.03 mol/litre concentration is vigorously stirred at room temperature for 20 minutes. The precipitate is filtered, washed with ice-cold eater and then dried at room temperature over solid potassium hydroxide under reduced pressure to obtain the title hydrochloride in 97% yield, m.p.: 308-310 °C (with decomposition).

After adding an equivalent amount of aqueous N sodium hydroxide solution to the hydrochloride, the base liberated is extracted into methylene chloride, the organic phase is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue is recrystallized from a mixture of chloroform and benzene to give the title base in 95% yield, m.p.: 207-208 °C.

Analysis:

Calculated for $C_{21}H_{30}N_2O_3$

C 70.36; H 8.43; N 7.81%;

found: C 70.30; H 8.61; N 7.97%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the processes described in Examples 8, 9 or 10 above.

8-(2-Chloronicotinoylcarbamoyl)-3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 191-193 °C;

3-tert-Butyl-4-hydroxy-4-methyl-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 164-165 °C;

8-Benzyl-3-(4-chlorophenyl)-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrochloride, m.p.: 298-299 °C;

8-Benzyl-4-hydroxy-4-methyl-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane hydrochloride, m.p.: 256-257 °C;

3-Benzyl-8-tert-butylcarbamoyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 222-224 °C;

8-Ethylcarbamoyl-4-hydroxy-4-methyl-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 234-236 °C;

3-Cyclohexyl-4-hydroxy-4-methyl-2-oxo-8-propylcarbamoyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 210-212 °C;

3-Butyl-4-hydroxy-4-methyl-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 136-137 °C;

8-Benzyl-3-ethyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrochloride, m.p.: 268-269 °C.

Example 11

8-benzyl-4-hydroxy-3,4-dimethyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane trifluoroacetate and free base

The solution containing 1.4 g of 8-benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in the mixture of 10 ml of water and 1.14 g of trifluoroacetic acid is stirred at room temperature for 15 minutes. The crystalline precipitate is filtered, washed with water and dried to give the title substance in 97% yield, m.p.: 147-148 °C.

The base is liberated by adding sodium hydroxide solution to its trifluoroacetate salt and melts at 161-163 °C.

Analysis of the base

Calculated for $C_{16}H_{22}N_2O_3$						
	C	66.18;	H	7.64;	N	9.65%;
found:	C	66.32;	H	7.58;	N	9.78%.

Example 12

8-benzyl-3-(4-chlorophenyl)-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane and hydrogen fumarate salt

A mixture containing 12.90 g of 1-benzyl-4-ethynyl-4-hydroxypiperidine, 9.21 g of 4-chlorophenyl isocyanate and 0.4 g of anhydrous sodium acetate is stirred under argon. The reaction is exothermic, therefore the reaction mixture is cooled in such a way that the highest temperature reached is 140°C. After 2 hours the reaction mixture is cooled to room temperature, dissolved in 150 ml of chloroform, the chloroformic phase is washed with water, dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The crude product obtained as evaporated residue is recrystallized from acetonitrile to obtain the pure title substance in 84% yield, m.p.: 189-191 °C.
Analysis:

Calculated for $C_{21}H_{21}ClN_2O_2$								
	C	68.38;	H	5.74;	Cl	9.61;	N	7.59%;
found:	C	68.53;	H	5.81;	Cl	9.55;	N	7.63%.

An equimolar amount of fumaric acid dissolved in ethanol is added to a benzene solution of the base to obtain the hydrogen fumarate salt as a crystalline precipitate which is then filtered off and dried, m.p.: 230-232 °C.

Example 13

8-benzyl-3-n-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane and dihydrogen citrate salt

21.5 g of 1-benzyl-4-ethynyl-4-hydroxypiperidine are boiled under reflux with 12.9 g of n-butyl isocyanate in the presence of 0.4 g of anhydrous potassium acetate in 66 ml of 2-picoline under nitrogen for 6 hours. After evaporating 2-picoline under reduced pressure and dissolving the residue in benzene, the organic solution is washed with water and dried over anhydrous magnesium sulfate. After filtration on an aluminum oxide layer the benzene solution is evaporated under reduced pressure. The crude product obtained is recrystallized from 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%.

An equimolar amount of anhydrous citric acid dissolved in ethanol is added to the base dissolved in anhydrous ether and the solution is diluted with ether to give the dihydrogen citrate salt as a crystalline precipitate which is filtered off and dried, m.p.: 148-150 °C.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the processes described in Examples 12 or 13 above.

8-Formyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 171-172 °C;
8-Benzyloxycarbonyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 145-146 °C;
4-Methylene-2-oxo-8-phenoxycarbonyl-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 208-210 °C;

8-Benzyl-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 128-130 °C (the hydrogen 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.: 103-104 °C (hydrogen 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.: 116-117 (dihydrogen 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.: 134-135 °C;

8-Benzyl-3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 96-97 °C;

8-Benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrogen maleate, m.p.: 210-211 °C;

8-Benzyl-4-methylene-2-oxo-3-propyl-1-oxa3,8-diazaspiro[4,5]decane dihydrogen citrate, m.p.: 168-171 °C.

Example 14

3,4-dimethyl-4-hydroxy-2-oxo-8-phenoxy-carbonyl-1-oxa-3,8-diazaspiro[4,5]decane

A solution of 1.6 g of methyl isocyanate in 5 ml of pyridine is dropwise added to a solution containing 5.3 g of 4-acetyl-4-hydroxy-1-phenoxycarbonylpiperidine and 0.2 g of sodium methoxide in 10 ml of pyridine under argon while stirring. The reaction is exothermic. After the addition the reaction mixture is refluxed for 2 to 3 hours, then the solvent is evaporated under reduced pressure. After taking up the evaporation residue in benzene the solution is washed with water to neutral and evaporated under reduced pressure to give the crude title product which is then recrystallized from ethyl acetate under clarifying by activated carbon to give the crystalline title compound in 61% yield, m.p.: 166-168 °C.

Analysis:

Calculated for $C_{16}H_{20}N_2O_5$

C 59.99; H 6.29; N 8.74%;

found: C 60.17; H 6.18; N 8.86%.

Example 15

3-tert-butyl-8-ethoxycarbonyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A mixture containing 4.3 g of 4-acetyl-1-ethoxycarbonyl-4-hydroxypiperidine, 6.0 g of tert-butyl isocyanate and 1 ml of triethylamine is refluxed under nitrogen for 6 hours. After cooling down and adding 50 ml of chloroform to the reaction mixture the organic phase is washed with water to neutral, then the solvent is evaporated under reduced pressure. The crude product obtained as evaporation residue is recrystallized from isopropyl ether to give the title substance in 44% yield, m.p.: 104-105 °C.

Analysis:

Calculated for $C_{15}H_{24}N_2O_4$

C 60.79; H 8.16; N 9.45%;

found: C 60.66; H 8.23; N 9.61%.

Example 16

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

2 g of catalyst containing 10% by weight of palladium on charcoal are suspended in 20 ml of water and added to the solution of 20.0 g of 8-benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 180 ml of methanol at 0 to 5 °C under nitrogen while stirring. Thereafter, 4.9 ml of an aqueous hydrazine solution of 48 g/100 ml concentration are introduced to the mixture which is then gently boiled under reflux. The progress of the reaction is followed by thin layer chromatography (TLC). After termination of the reaction (10 to 15 minutes) the mixture is cooled down, the catalyst is filtered off and washed with methanol. The methanolic wash-

ings are combined with the methanolic solution and the solvent is evaporated under reduced pressure. After recrystallizing the evaporation residue from a mixture of ethyl acetate with isopropyl ether the title compound is obtained in 94% yield, m.p.: 92-93 °C.

Analysis:

Calculated for $C_9H_{14}N_2O_2$				
	C 59.32;	H 7.74;	N 15.37%;	
found:	C 59.55;	H 7.76;	N 15.49%.	

Example 17

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 is added to the solution of 5.0g of 8-benzyloxycarbonyl-4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro[4,5]decane in 45 ml of methanol at 0 °C under argon while stirring. To this mixture 1 ml of 45.8% aqueous hydrazine solution is introduced and the reaction mixture is refluxed for 10 to 15 minutes. After cooling down to room temperature and filtering off the catalyst the solvent is evaporated under reduced pressure and the crude evaporation residue is recrystallized from benzene to give the title compound in 95% yield, m.p.: 96-97 °C.

Analysis:

Calculated for $C_{11}H_{18}N_2O_2$				
	C 62.83;	H 8.63;	N 13.32%;	
found:	C 63.00;	H 8.57;	N 13.47%.	

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process described in Example 17 above.

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.p.: 190-191 °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;
3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]-decane, m.p.: 141-142 C;
3-[2-(3, 4-dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 107-109 °C.

Example 18

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

A solution containing 5.4 g of 8-formyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, 3.0 g of hydrazine monohydrate and 3.6 g of acetic acid in 54 ml of aqueous ethanol of 60% by volume concentration is stirred under argon at a temperature of 62 to 65 °C. The reaction is followed by TLC. After termination of the reaction the mixture is evaporated under reduced pressure. After taking up the residue in chloroform and saturated aqueous sodium hydrogen carbonate solution, the chloroformic phase is separated, washed to neutral, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product obtained is recrystallized from ethyl acetate under clarifying by activated carbon to give the title compound in

41.0% yield, m.p.: 185-186 °C
Analysis:

Calculated for $C_{14}H_{16}N_2O_2$

C 68.83; H 6.60; N 11.47%;

found: C 68.85; H 6.71; N 11.35%.

Example 19

4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A solution containing 4.2 g of 8-benzyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3 8-diazaspiro[4,5]decane in 42 ml of 95% methanol is refluxed in the presence of 0.75 g of hydrazine hydrate and 0.42 g of 10% by weight palladium-on-charcoal catalyst under vigorous stirring for 30 minutes. After cooling the reaction mixture to room temperature the catalyst is filtered off, washed with methanol and after combining the filtrate with the washings, the solution is evaporated under reduced pressure. After thoroughly triturating the residue with acetone the crystalline product obtained is filtered off and dried to give the title compound in 9.5% yield, m.p.: 192-194 °C.
Analysis:

Calculated for $C_8H_{14}N_2O_3$

C 51.60; H 7.58; N 15.04%;

found: C 51.58; H 7.55; N 15.2%.

Example 20

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

A solution of 5.44 g of 8-benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 40 ml of N hydrochloric acid is hydrogenated in the presence of 5.4 g of palladium-on-charcoal catalyst until the theoretical amount of hydrogen is consumed. After filtering off the catalyst the filtrate is evaporated to a volume of about 10 ml under reduced pressure and 40 ml of acetone are added. The crystalline precipitate is filtered off and dried to obtain the title compound in 87% yield, m.p.: 272-274 °C.
Analysis of the base:

Calculated for $C_9H_{16}N_2O_3$

C 53.98; H 8.05; N 13.99%;

found: C 54.16; H 8.15; N 14.20%.

Example 21

3-decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

4.0 g of 8-benzyl-3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane are stirred together with 4.0 g of 10% by weight palladium-on-carbon catalyst in 40 ml of 50% aqueous formic acid for 2 hours at room temperature. After filtering off the catalyst the solution is evaporated under reduced pressure, the residue is treated with aqueous sodium hydrogen carbonate solution and the solid product is filtered off. After recrystallizing this product from a mixture of chloroform with n-hexane the title substance is obtained in 78.0%. yield, m.p.: 139-140 °C.
Analysis:

Calculated for $C_{18}H_{34}N_2O_3$

C 66.22; H 10.50; N 8.58%;

found: C 66.31; H 10.64; N 8.41%.

Example 22

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

A mixture of 11.8 9 of 4-methylene3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, 5.8 ml of benzyl chloride, 4.2 g of anhydrous sodium hydrogen carbonate, 0.5 g of potassium iodide and 177 ml of methyl ethyl ketone is refluxed under argon while stirring for 18 hours. After termination of the reaction the mixture is cooled down and the solvent is evaporated under reduced pressure. After adding chloroform and water to the residue and separating the phases, the organic layer is washed with water to chloride-free, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. After recrystallizing the residue under clarifying by activated carbon the title substance is obtained in 84% yield, m.p.: 130-131 °C.
Analysis:

Calculated for $C_{25}H_{24}N_2O_2$

C 78.10; H 6.29; N 7.29%;

found: C 78.19; H 6.37; N 7.37%.

Example 23

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

A mixture containing 3.2 g of 4-methylene-2-oxo-3-(4-toluenesulfonyl)-1-oxo-3,8-diazaspiro[4,5]decane, 2.1 g of benzyl bromide and 1.7 g of anhydrous potassium carbonate in 32 ml of methyl isobutyl ketone is refluxed under nitrogen while stirring for 8 hours. After cooling down the reaction mixture to room temperature the inorganic salts are filtered off and the filtrate is evaporated under reduced pressure. The residue is dissolved in 50 ml of benzene, washed to bromide-free and neutral with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. After recrystallizing the crude product obtained from ethanol the title substance is obtained in 84% yield, m.p.: 157-158 °C.
Analysis:

Calculated for $C_{22}H_{24}N_2SO_4$

C 64.05; H 5.86; N 6.79; S 7.77%;

found: C 64.15; H 5.84; N 6.88; S 7.64%.

Example 24

8-benzyloxycarbonyl-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

3.5 ml of benzyl chloroformate dissolved in 5 ml of chloroform are portionwise added to a solution containing 5.0 g of 3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane and 3.4 ml of triethylamine in 50 ml of chloroform with cooling under nitrogen, then the reaction mixture is stirred at room temperature for an additional 30 minutes. After adding water to the reaction mixture and separating the phases the chloroformic layer is washed to neutral with water, dried over anhydrous sodium sulfate, then the solvent is evaporated under reduced pressure. After recrystallization of the residue from ethanol the title compound is obtained in 83% yield, m.p.: 104-105 °C.
Analysis:

Calculated for $C_{22}H_{28}N_2O_4$

C 68.72; H 7.34; N 7.29%;

found: C 68.66; H 7.44; N 7.33%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process described in the preceding Example.
3-Ethyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 98-99 °C;
3-cyclohexyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 188-189 °C; and
3-butyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 94-95 °C.

Example 25

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

A solution containing 4.6 g of 4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro[4,5]decane in 35 ml of chloroform is dropwise added to a formic acid-acetic acid mixed anhydride prepared from 4.4 ml of acetic anhydride and 2.2 ml of formic acid in situ, then the reaction mixture is stirred at room temperature for additional 30 minutes. After neutralizing the reaction mixture by adding 8.4% by weight aqueous sodium hydrogen carbonate solution under stirring and separating the phases, the organic layer is washed with water, dried over anhydrous potassium carbonate and evaporated under reduced pressure. The residue is mixed with ether and filtered off to give the title substance in 96% yield, m.p.: 150-151 °C.
Analysis:

Calculated for $C_{12}H_{18}N_2O_3$

C 60.48; H 7.61; N 11.76%;

found: C 60.54; H 7.73; N 11.80%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process described in Example 25.
3-tert-Butyl-8-formyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 141-142 °C; and
3-cyclohexyl-8-formyl-4-methylene2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 212-213 °C.

Example 26

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

2.25 ml of n-butyl isocyanate are dropped to a suspension of 3.64 g of 3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 18 ml of acetonitrile while stirring under argon. Since the reaction is exothermic, the temperature is maintained at 25 to 30 °C by cooling. After 15 minutes the reaction mixture is evaporated under reduced pressure. The white solid evaporation residue is recrystallized from ethyl acetate to obtain the title compound in 91.3% yield, m.p.: 129-130 °C.
Analysis:

Calculated for $C_{14}H_{23}N_3O_3$

C 59.76; H 8.24; N 14.94%;

found: C 59.63; H 8.28; N 15.04%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process described in Example 26.
3-Cyclohexyl-4-methylene-2-oxo-8-propylcarbamoyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 157-158;
8-ethylcarbamoyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 196-197 °C;

3-benzyl-8-tert-butylcarbamoyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 158-159 °C; and 8-butylcarbamoyl-3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 152-153 °C.

Example 27

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

A solution of 3.9 g of 4-methylpiperazin-1-yl-carbonyl chloride in 5 ml of chloroform is dropwise added at a temperature between 0 and 5 °C to a solution containing 4.9 g of 4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]-decane and 7.4 ml of triethylamine in 74 ml of chloroform under stirring. Thereafter, the reaction mixture is stirred at room temperature for an additional 30 minutes. After termination of the reaction the chloroform phase is washed to chloride-free with water, dried over anhydrous sodium sulfate, then the solvent is evaporated under reduced pressure. After recrystallization of the crude product obtained from ethanol under clarifying by activated carbon the title compound is obtained in 83% yield, m.p.: 198-199 °C.

Analysis:

Calculated for	$C_{20}H_{26}N_4O_3$				
	C 64.84;	H 7.07;	N 15.12%;		
found:	C 64.88;	H 7.23;	N 15.01%.		

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process described in Example 27.

3-Methyl-4-methylene-8-(4-methylpiperazin-1-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 139-140 °C;

3-cyclohexyl-4-methylene-8-(4-methylpiperazin-1-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 191-192 °C;

4-methylene-2-oxo-3-(piperidin-1-ylcarbonyl)-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 105-106 °C;

3-tert-butyl-4-methylene-2-oxo-8-(piperidin-1-ylcarbonyl)-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 149-150 °C;

3-(4-chlorophenyl)-4-methylene-8-(morpholin-4-ylcarbony)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 214-215 °C;

4-methylene-8-(4-methylpiperazin-ylcarbonyl)-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 146-147 °C; and

3-butyl-4-methylene-8-(4-methylpiperazin-1-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 113-114 °C.

Example 28

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

5.8 g of oxalyl chloride are portionwise added to a solution of 6.2 g of 2-chloronicotinic acid amide in 150 ml of anhydrous 1,2-dichloroethane under stirring, then the reaction mixture is heated at 85 °C for 90 minutes. After cooling the mixture to 0 to 5 °C first 12.6 ml of triethylamine and then a solution of 8.4 g of 3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 42 ml of anhydrous 1,2-dichloroethane are portionwise added while maintaining the temperature between 20 and 30 °C. The reaction mixture is stirred at room temperature for additional 30 minutes, then extracted with 200 ml of N sodium hydroxide solution and then with 100 ml of water. After combining, the aqueous extract is acidified to a pH value of 5.5 to 6 by adding acetic acid and the mixture is extracted with 1,2-dichloroethane: The organic solution is washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue is recrystallized from ethanol to give the title compound in 54% yield, m.p.: 186-188 °C.

Analysis:

Calculated for	$C_{18}H_{21}ClN_4O_4$				
	C 55.03;	H 5.39;	Cl 9.02;	N 14.26%;	
found:	C 55.15;	H 5.57;	Cl 9.14;	N 14.12%.	

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process as described in Example 28.
8-(2-Chloronicotinoylcarbamoyl)-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 196-198 °C;
8-(2-chloronicotinoylcarbamoyl)-3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 202-204 °C;
8-(2-chloronicotinoylcarbamoyl)-4-methylene-3-propyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 183-184 °C;
3-tert-butyl-8-(2-chloronicotinoylcarbamoyl)-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 179-181 °C;
3-n-butyl-8-(2-chloronicotinoylcarbamoyl)-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 166-168 °C;
8-(2-chloronicotinoylcarbamoyl)-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 217-218 °C; and
8-(2-chloronicotinoylcarbamoyl)-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 190-192 °C.

Example 29

3-(4-chlorophenyl)-8-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A mixture containing 4.0 g of 3-(4-chlorophenyl)-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]-decane and 6.13 ml of N-(2-hydroxyethyl)piperazine in 20 ml of ortho-xylene is refluxed under nitrogen for 60 hours. After cooling down the reaction mixture is diluted with 20 ml of xylene and the organic solution is washed first with an aqueous saturated sodium chloride solution containing 5% by weight of sodium hydroxide and then with aqueous saturated sodium chloride solution. After drying over anhydrous magnesium sulfate and then evaporating the solvent under reduced pressure the crude product obtained is recrystallized from a mixture of benzene and hexane under clarifying by activated carbon to give the title compound in 67% yield, m.p.: 185-186 °C.
Analysis:

Calculated for $C_{21}H_{27}ClN_4O_4$								
	C	57.99;	H	6.27;	Cl	8.15;	N	12.88%;
found:	C	57.78;	H	6.35;	Cl	8.30;	N	13.05%.

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process as described in Example 29.
3-Butyl-8-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 101.5-102.5 °C;
8-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 177-178 °C;
3-tert-butyl-8-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 159-160 °C;
3-cyclohexyl-4-methylene-2-oxo-8-piperidin-1-ylcarbonyl)-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 170-171 °C;
3-ethyl-4-methylene-8-(morpholin-4-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 160-162 °C;
4-methylene-8-(morpholin-4-ylcarbonyl)-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 215-216 °C;
3-tert-butyl-4-methylene-8-(morpholin-4-ylcarbony)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 174-175 °C;
3-cyclohexyl-4-methylene-8-(morpholin-4-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 202-203 °C;
4-methylene-8-(morpholin-4-ylcarbonyl-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 146-147 °C;
3-butyl-4-methylene-8-(morpholin-4-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 113-114 °C;
3-ethyl-4-methylene-8-(4-methylpiperazin-1-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 140-141 °C; and
3-tert-butyl-4-methylene-8-(4-methylpiperazin-1-ylcarbonyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 143-144 °C.

Example 30

3-tert-butyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane

A solution of 3.6 g of phenyl chloroformate in 5 ml of methylene chloride are dropped into a solution of 6.3 g of 8-benzyl-3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro-[4,5]decane in 30 ml of methylene chloride under argon at 0 °C while stirring, then the reaction mixture is stirred sat room temperature for one additional hour. After termination of the reaction the mixture is diluted with 35 ml of methylene chloride, extracted with 4 N sodium hydroxide solution and washed to neutral with water. After drying over anhydrous magnesium sulfate the solvent is evaporated under reduced pressure. After adding n-hexane to the residue the solid precipitate is filtered off and recrystallized from isopropanol to obtain the title substance in 82% yield, m.p.: 125-126 °C.

Analysis:

Calculated for $C_{19}H_{24}N_2O_4$

C 66.26; H 7.02; N 8.13%;

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

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process as described in Example 30.

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 °C;

3-(3,4-dichlorophenyl)-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 220-222 °C;

3-methyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[-4,5]decane, m.p.: 118-119 °C; and

4-methylene-2-oxo-8-phenoxycarbonyl-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 96-98 °C.

Example 31

8-benzyl-3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane and hydrochloride salt

A suspension containing 5.2 g of 8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane, 2.1 g of methylamine hydrochloride and 2.1 g of anhydrous powdered potassium carbonate in 11 ml of ethanol is stirred under nitrogen for 2 hours, then left to stand overnight. After adding water to the reaction mixture the crystalline precipitate is filtered off and washed with water. The crude product obtained is recrystallized from a mixture of acetone and diisopropyl ether to give the title compound in 88% yield with the same physical characteristics as given for the base in Example 10.

The hydrochloride is obtained by treating the base with an ethereal hydrogen chloride solution, m.p.: 277-279 °C.

Using the appropriate starting materials the follow-ing compound may be prepared in a manner analogous to the process as described in Example 31.

8-Benzyl-3-[2-(3,4-dihydroxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 105-106 °C;

the hydrogen maleate salt melts at 77 °C.

Example 32

8-benzyl-3-decyl-4-methylene-2-oxo-1-oxa-3,8 diazaspiro[4,5]decane

A mixture containing 6.2 g of 8-benzyl-3-decyl-3-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane and 0.6 g of p-toluenesulfonic acid monohydrate in 63 ml of xylene is boiled by using a Dean-Stark device while azeotropically distilling out the water formed in the reaction. After termination of the reaction the mixture is cooled down, then the organic solution is extracted with a 5% by weight aqueous sodium hydroxide solution and with water up to neutral. The xylene phase is dried over anhydrous sodium sulfate and evaporated under reduced pressure. After recrystallization the evaporation residue from n-hexane under clarifying by activated carbon the title compound is obtained in 91% yield, m.p.: 51-52 °C.

Analysis:

Calculated for $C_{25}H_{38}N_2O_2$				
	C 75.33;	H 9.61;	N 7.03%;	
found:	C 75.41;	H 9.69;	N 7.15%.	

Using the appropriate starting materials the following compounds may be prepared in a manner analogous to the process as described in Example 32.
8-Benzyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro]4,5]decane, m.p. : 91-92 °C; and
3,8-dibenzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane.

Example 33

8-benzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

A solution containing 14.0 g of 8-benzyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 210 ml of dioxan is boiled under nitrogen while azeotropically distilling out the water formed in the reaction. After termination of the reaction dioxan is evaporated under reduced pressure. The residue is recrystallized from ethanol under clarifying by activated carbon to give the title compound in 62% yield, m.p.: 169-170 °C.
Analysis:

Calculated for $C_{15}H_{18}N_2O_2$				
	C 69.74;	H 7.02;	N 10.84%;	
found:	C 69.92;	H 7.18;	N 10.78%.	

Example 34

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

A solution of 1.6 g of methylamine in 35 ml of xylene prepared at 0 °C is added to a solution of 13.0 g of 8-benzyl4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5]decane in 30 ml of xylene under stirring. The reaction is exothermic, thus the temperature of the reaction mixture increases up to 55 to 60 °C. Thereafter, the heterogeneous reaction mixture is heated to a temperature of 100 to 102 °C, maintained at the same temperature for 10 minutes, then 0.2 g of p-toluenesulfonic acid monohydrate is added to the solution and the reaction mixture is boiled while the water formed in the reaction is azeotropically distilled out. After termination of the reaction the mixture is cooled down to room temperature, washed with 5% by weight aqueous sodium hydroxide solution and after separation the xylene phase is washed to neutral with water. The organic phase is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue is recrystallized from a mixture of ethanol and diisopropyl ether under clarifying by activated carbon to obtain the title compound in 96.7% yield, m.p.: 96-97 °C.

Calculated for $C_{16}H_{20}N_2O_2$				
	C 70.56;	H 7.40;	N 10.29%;	
found:	C 70.58;	H 7.55;	N 10.14%.	

Example 35

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

After refluxing a solution containing 9.6 g of 8-benzyl-4-hydroxy-4-methyl-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]-decane in a mixture of 96 ml of acetic acid and 5.7 ml of acetic anhydride under argon for 5 hours

the solvent is evaporated under reduced pressure. After adding 5% by weight aqueous sodium hydroxide solution to the residue until the pH value is 10, the mixture is extracted with benzene and the organic phase is washed to neutral with water. After drying the organic phase over anhydrous sodium sulfate benzene is evaporated under reduced pressure. After recrystallizing the residue from diisopropyl ether the title compound is obtained in 86.4% yield, m.p.: 70-71 °C.

Analysis:

Calculated for $C_{18}H_{24}N_2O_2$				
	C 71.97;	H 8.05;	N 9.33%;	
found:	C 72.18;	H 8.16;	N 9.12%.	

Examples of pharmaceutical compositions that may be prepared using the compounds according to the present invention include:

a)Preparation of tablets

50.0 g of active ingredient are mixed together with 92 g of lactose, 40 g of potato starch, 4 g of polyvinylpyrrolidone, 6 g of talc, 1g of magnesium stearate, 1 g of colloidal silicon dioxide (Aerosil) and 6 g of ultra-amylopectin and, after wet granulation, the product obtained is compressed into tablets containing 50 mg of the active ingredient each;

b) Preparation of dragées

The tablets prepared as described above are covered in a manner known per se with a coating consisting of sugar and talc. The dragées are polished by using a mixture of beeswax and carnaube wax. 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 of lactose, 4 g of colloidal silicon dioxide (Aerosil) and 6 g of magnesium stearate are thoroughly mixed together and after sieving, the mixture obtained is filled into hard gelatine capsules containing 20 mg of the active ingredient each.

d) Preparation of suppositories

100.0 mg of active ingredient and 200.0 mg of lactose calculated for one suppository are thoroughly mixed together. 1700.0 mg of suppository base (e.g. Witepsol 4) are made molten, cooled to 35 °C and the mixture of the active ingredient and lactose is mixed thereinto by using a homogenizer. The product obtained is poured into cooled conic moulds. Each suppository weighes 2000 mg.

e) Preparation of a suspension

Components in 100 ml of the suspension:

Active ingredient	1.00 g
Sodium hydroxide	0.26 g
Citric acid	0.30 g
Nipagin (methyl 4-hydroxybenzoate sodium salt)	0.10 g
Carbopol 940 (polyacrylic acid)	0.30 g
96% Ethanol	1.00 g
Raspberry flavour	0.60 g
Sorbitol (aqueous solution of 70%)	71.00 g
Distilled water for injection purpose	up to 100.00 ml

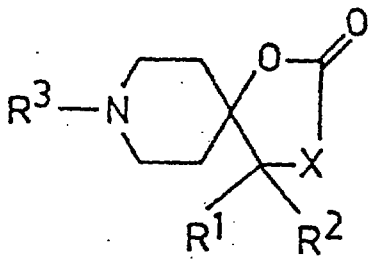
"Aerosil", "Witepsol", "Nipagin" and "Carbopol" are all Trade Marks.

After adding Carbopol in little portions to the solution of nipagin and citric acid in 20 ml of distilled water under vigorous stirring, the solution obtained is left to stand for 10 to 12 hours. Subsequently, the amount given above of sodium hydroxide dissolved in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic solution of the raspberry flavour are dropped in under stirring. The active ingredient is added in small portions to this mixture and suspended by using a submerged homogenizer. Finally, the suspension is supplemented to 100 ml by adding sufficient distilled water and the syrupy suspension is led through a colloid mill.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of formula (I),



(I)

wherein

X represents an oxygen atom or >NR group, wherein

R represents a hydrogen atom or a C_{1-12}alkyl, C_{3-6}cycloalkyl or a tosyl group, or a carbocyclic C_{6-10}aryl or carbocyclic C_{6-10}aryl-C_{1-4}alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or trihalomethyl 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 may additionally represent a hydroxyl group whilst the other one is a methyl group; and

R^3 represents a hydrogen atom or a benzyl, (C_{1-4}alkoxy)carbonyl, phenoxycarbonyl, formyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-hydroxyethyl)-piperazin-1-ylcarbonyl, 2-chloro-3-nicotinoyl-carbamoyl, C_{1-6}alkylcarbamoyl group or benzyloxycarbonyl and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof;

and the compound of formula (I) wherein X is >NR in which R is a 2-(3-4-dihydroxyphenyl) ethyl group, R^1 is a hydroxy group, R^2 is a methyl group and R^3 is a benzyl group, and optical isomers and mixtures thereof.

2. A compound of formula (I) as defined in Claim 1 selected from the group comprising:
3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-benzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-[2-(3,4dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,

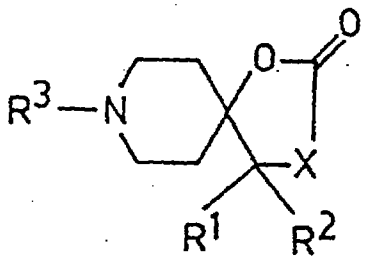
"Aerosil", "Witepsol", "Nipagin" and "Carbopol" are all Trade Marks.

After adding Carbopol in little portions to the solution of nipagin and citric acid in 20 ml of distilled water under vigorous stirring, the solution obtained is left to stand for 10 to 12 hours. Subsequently, the amount given above of sodium hydroxide dissolved in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic solution of the raspberry flavour are dropped in under stirring. The active ingredient is added in small portions to this mixture and suspended by using a submerged homogenizer. Finally, the suspension is supplemented to 100 ml by adding sufficient distilled water and the syrupy suspension is led through a colloid mill.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of formula (I),



(I)

wherein

X represents an oxygen atom or >NR group, wherein

R represents a hydrogen atom or a C_{1-12}alkyl, C_{3-6}cycloalkyl or a tosyl group, or a carbocyclic C_{6-10}aryl or carbocyclic C_{6-10}aryl-C_{1-4}alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or trihalomethyl 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 may additionally represent a hydroxyl group whilst the other one is a methyl group; and

R^3 represents a hydrogen atom or a benzyl, (C_{1-4}alkoxy)carbonyl, phenoxycarbonyl, formyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-hydroxyethyl)-piperazin-1-ylcarbonyl, 2-chloro-3-nicotinoyl-carbamoyl, C_{1-6}alkylcarbamoyl group or benzyloxycarbonyl and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof;

and the compound of formula (I) wherein X is >NR in which R is a 2-(3-4-dihydroxyphenyl) ethyl group, R^1 is a hydroxy group, R^2 is a methyl group and R^3 is a benzyl group, and optical isomers and mixtures thereof.

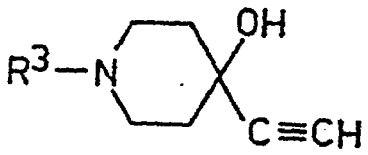
2. A compound of formula (I) as defined in Claim 1 selected from the group comprising:
3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-benzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-[2-(3,4dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,

* C L M S *

3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro[4,5] decane,
4-methylene-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof.

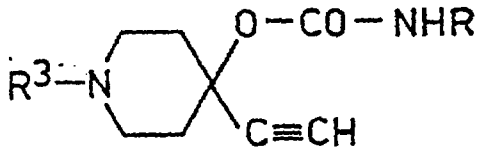
3. A pharmaceutical composition, which comprises as active ingredient a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof in admixture with a pharmaceutically acceptable carrier, diluent or excipient.

4. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises
a) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a methylene group, reacting a 4-ethynyl-4-hydroxypiperidine derivative of formula (III),



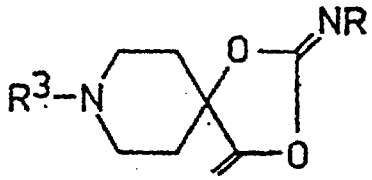
(III)

wherein R^3 is as defined in claim 1, with an isocyanate of the formula R-NCO, wherein R is as defined in claim 1, and cyclizing the thus obtained 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II),



(II)

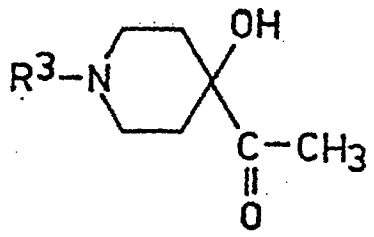
wherein R and R^3 are as defined above, either
α) for compounds wherein X is an oxygen atom, in an acidic medium and reacting the resultant compound of formula (VI),



(VI)

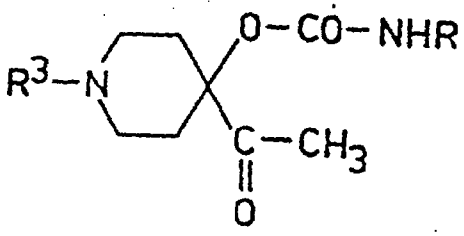
wherein R and R^3 are as defined above with water; or
β) for compounds wherein X is a group NR, in a basic medium;
or
b) for the preparation of compounds of formula (I) as defined in process (a) (α) above, cyclizing in an acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, and reacting the resultant compound of formula (VI) as defined above with water;
or
c) for the preparation of compounds of formula (I) as defined in process (a) (β) above, cyclizing a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, in a basic medium;
or
d) for the preparation of compounds of formula (I) wherein X is a >NR group and one or R^1 and R^2 is a hydroxyl group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypiperidine derivative of formula (IV),

* C L M S *



(IV)

wherein R^3 is as defined above, with an isocyanate of the formula R-NCO, wherein R is as defined above, and cyclizing the thus formed 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V),



(V)

wherein R and R^3 are as defined above;

or

e) for the preparation of compounds of formula (I) wherein X is a >NR group, and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group, cyclizing a 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V) 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^1 and R^2 together are a methylene group, with an amine of formula R-NH_2, wherein R is as defined above, in order to prepare a compound of the formula (I), wherein X is a >NR group and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group;

and/or if desired or necessary,

transforming a compound of formula (I) as prepared above into another compound of the formula (I) as defined in claim 1 in a known manner;

and/or if desired or necessary,

reacting a compound of the formula (I), as prepared above, with an acid to obtain the acid addition salt thereof and/or reacting a salt of a compound of the formula (I) as prepared above with a base to liberate the base form thereof and/or converting a thus prepared compound of the formula (I) into its quaternary ammonium salt.

5. A process as claimed in claim 4 process (a) (β) wherein R^3 is as defined in claim 1 except for the 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl and 2-chloronicotinoylcarbamoyl groups, which comprises carrying out the whole reaction in a single step without isolating the compound of formula (II).

6. A process as claimed in claim 4 process (b), wherein the reaction is carried out in an organic solvent in the presence of a hydrogen halide.

7. A process as claimed in claim 4 with process d), which comprises carrying out the reaction of the derivative of formula (IV) as defined in claim 4 with the isocyanate of formula R-NCO as defined in claim 4 and the cyclization of the thus formed derivative of formula (V) as defined in claim 4 in the same reaction mixture.

8. A process as claimed in claim 4, process e), which comprises carrying out the reaction in ethanol and in the presence of a sodium ethoxide.

9. The use of a compound of formula (I) as defined in claim 1 for the manufacture of a medicament for anticonvulsive (antiepileptic), antiallergic and/or lipid level lowering treatement of mammals.

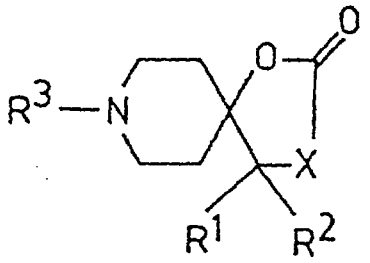
10. A process for the preparation of a pharmaceutical composition as defined in claim 3 which comprises admixing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition or

* C L M S *

quaternary ammonium salt thereof with a pharmaceutically acceptable carrier, diluent or excipient.

Claims for the following Contrating States : ES, GR

1. A process for the preparation of a compound of formula (I)



(I)

wherein

X represents an oxygen atom or >NR group, wherein

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

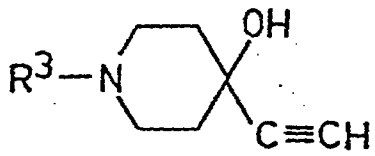
R^1 and R^2 together represent a methylene group or, when X is a >NR group, one of R^1 and R^2 may additionally represent a hydroxyl group whilst the other one is a methyl group; and

R^3 represents a hydrogen atom or a benzyl, (C_{1-4}alkoxy)carbonyl, phenoxycarbonyl, formyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl, 2-chloro-3-nicotinoylcarbamoyl, C_{1-6}alkylcarbamoyl group or benzyloxycarbonyl and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof;

and the compound of formula (I) wherein X is >NR in which R is a 2-(3,4-dihydroxyphenyl) ethyl group, R^1 is a hydroxy group, R^2 is a methyl group and R^3 is a benzyl group, and optical isomers and mixtures thereof,

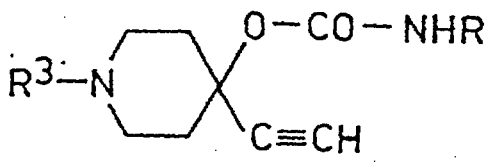
which comprises

a) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a methylene group, reacting a 4-ethynyl-4-hydroxypiperidine derivative of formula (III),



(III)

wherein R^3 is as defined above, with an isocyanate of the formula R-NCO, wherein R is as defined above, and cyclizing the thus obtained 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II),

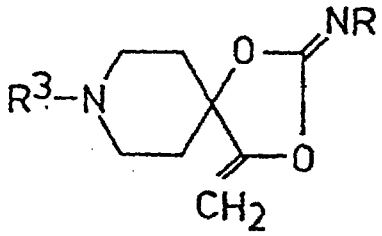


(II)

wherein R and R^3 are as defined above, either

α) for compounds wherein X is an oxygen atom, in an acidic medium and reacting the resultant compound of formula (VI),

* C L M S *



(VI)

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

β) for compounds wherein X is a group NR, in a basic medium;

or

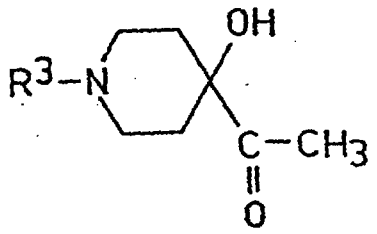
b) for the preparation of compounds of formula (I) as defined in process (a) (α) above, cyclizing in an acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, and reacting the resultant compound of formula (VI) as defined above with water;

or

c) for the preparation of compounds of formula (I) as defined in process (a) (β) above, cyclizing a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (II) as defined above, in a basic medium;

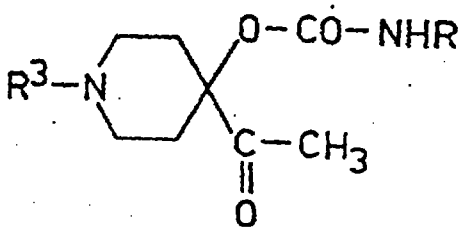
or

d) for the preparation of compounds of formula (I) wherein X is a >NR group and one or R^1 and R^2 is a hydroxyl group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypiperidine derivative of formula (IV),



(IV)

wherein R^3 is as defined above, with an isocyanate of the formula R-NCO, wherein R is as defined above, and cyclizing the thus formed 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V),



(V)

wherein R and R^3 are as defined above;

or

e) for the preparation of compounds of formula (I) wherein X is a >NR group, and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group, cyclizing a 4-acetyl-4-carbamoyloxypiperidine derivative of formula (V) 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^1 and R^2 together are a methylene group, with an amine of formula $R\text{-}NH_2$, wherein R is as defined above, in order to prepare a compound of the formula (I), wherein X is a >NR group and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group;

and/or if desired or necessary,

transforming a compound of formula (I) as prepared above into another compound of the formula (I) as defined above in a known manner;

and/or if desired or necessary,

* C L M S *

reacting a compound of the formula (I), as prepared above, with an acid to obtain the acid addition salt thereof and/or reacting a salt of a compound of the formula (I) as prepared above with a base to liberate the base form thereof and/or converting a thus prepared compound of the formula (I) into its quaternary ammonium salt.

2. A process as claimed in claim 1 process (a) (β) wherein R^3 is as defined in claim 1 except for the 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl and 2-chloronicotinoylcarbamoyl groups, which comprises carrying out the whole reaction in a single step without isolating the compound of formula (II).

3. A process as claimed in claim 1 process (b), wherein the reaction is carried out in an organic solvent in the presence of a hydrogen halide.

4. A process as claimed in claim 1 with process d), which comprises carrying out the reaction of the derivative of formula (IV) as defined in claim 1 with the isocyanate of formula R-NCO as defined in claim 1 and the cyclization of the thus formed derivative of formula (V) as defined in claim 1 in the same reaction mixture.

5. A process as claimed in claim 1, process e), which comprises carrying out the reaction in ethanol and in the presence of a sodium ethoxide.

6. A process as claimed in Claim 1 for the preparation of a compound of formula (I) as defined in Claim 1 selected from the group comprising:
3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5] decane,
3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane,
3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-benzyl-4-methylene-2-oxo-1-oxa-diazaspiro[4,5]decane,
3-[2-(3,4dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1oxa-3,8-diazaspiro[4,5]decane,
3-decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3-8-diazaspiro[4,5]decane,
3-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
8-benzyl-4-methylene-2-oxo-1,3-dioxa-8-azaspiro-[4,5]decane,
4-methylene-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane,
and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof.

7. The use of a compound of formula (I) as defined in claim 1 for the manufacture of a medicament for anticonvulsive (antiepileptic), antiallergic and/or lipid level lowering treatement of mammals.

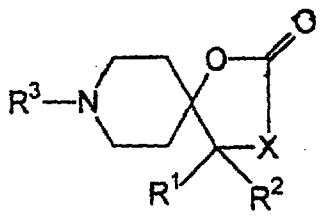
8. A process for the preparation of a pharmaceutical composition which comprises as active ingredient a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof, wherein the active ingredient is admixed with a pharmaceutically acceptable carrier, diluent or excipient.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel (I),

* C L M S *



(I)

worin

X ein Sauerstoffatom oder eine >NR-Gruppe darstellt, wobei

R ein Wasserstoffatom oder eine C_{1-12}-Alkyl-, C_3-C_6-Cycloalkyl- oder eine Tosylgruppe, oder eine carbocyclische C_{6-10}-Aryl- oder carbocyclische C_{6-10}-Aryl-C_{1-4}-alkylgruppe darstellt, die wahlweise am aromatischen Ring mit einem oder mehreren Halogenatomen, C_{1-4}-Alkyl-, C_{1-4}-Alkoxy- oder Trihalomethylgruppen substituiert sind;

R^1 und R^2 zusammen eine Methylengruppe darstellen oder, wenn X eine >NR-Gruppe ist, einer der Substituenten R^1 und R^2 außerdem eine Hydroxylgruppe darstellen kann, während der andere eine Methylgruppe ist; und

R^3 ein Wasserstoffatom oder eine Benzyl-, (C_{1-4}-Alkoxy)carbonyl-, Phenoxycarbonyl-, Formyl-, Piperidin-1-ylcarbonyl-, Morpholin-4-ylcarbonyl-, 4-Methylpiperazin-1-ylcarbonyl-, 4-(2-Hydroxyethyl)piperazin-1-ylcarbonyl-, 2-Chloro-3-nicotinoyl-carbamoyl-, C_{1-6}-Alkylcarbamoylgruppe oder Benzyloxycarbonyl darstellt,

und ihre optischen Isomere und Mischungen und alle ihre Säureadditions- und quaternären Ammoniumsalze,

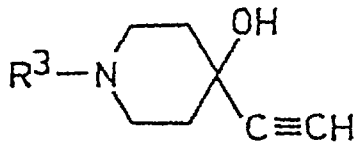
und die Verbindung der Formel (I), in der X >NR ist, wobei R eine 2-(3,4-Dihydroxyphenyl)ethylgruppe, R^1 eine Hydroxygruppe, R^2 eine Methylgruppe und R^3 eine Benzylgruppe ist, und deren optische Isomere und Mischungen.

2. Verbindung der Formel (I) gemäß Anspruch 1, ausgewählt aus der Gruppe, umfassend:
3-Methyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Ethyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Cyclohexyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Methylen-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decan,
3-Isoprcpyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Butyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-tert-Butyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Heptyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Methylen-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4, 5]decan,
3-Decyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Benzyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-[2-(3,4-Dimethoxyphenyl)ethyl]-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Hydroxy-4-methyl-2-oxo-1-oxy-3,8-diazaspiro[4,5]decan,
3,4-Dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-[2-(3,4-Dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
8-Benzyl-4-methylen-2-oxo-1,3-dioxa-8-azaspiro[4,5]decan,
4-Methylen-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
und deren optische Isomere und Mischungen und alle ihre Säureadditions- und quaternären Ammoniumsalze.

3. Pharmazeutische Zusammensetzung, umfassend als Wirkstoff eine Verbindung der Formel (I) gemäß Anspruch 1 oder eines ihrer pharmazeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalze in Mischung mit einem pharmazeutisch annehmbaren Träger, Verdünnungsmittel oder Korrigens.

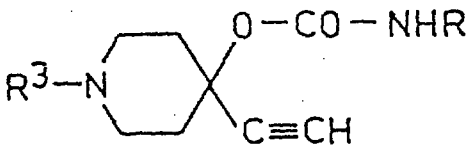
4. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, umfassend:
a) zur Herstellung von Verbindungen der Formel (I), in denen R^1 und R^2 zusammen eine Methylengruppe sind, Umsetzung eines 4-Ethinyl-4-hydroxypiperidin-Derivats der Formel (III)

* C L M S *



(III)

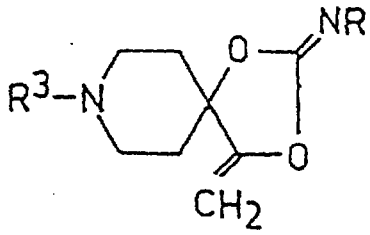
worin R^3 wie in Anspruch 1 definiert ist, mit einem Isocyanat der Formel R-NCO, wobei R wie in Anspruch 1 definiert ist, und Cyclisierung des so erhaltenen 4-Carbamoyloxy-4-ethinyl-piperidin-Derivats der Formel (II),



(II)

worin R und R^3 wie oben definiert sind, entweder

α) für Verbindungen, in denen X ein Sauerstoffatom ist, in einem saurem Medium und Umsetzung der resultierenden Verbindung der Formel (VI)



(VI)

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

β) für Verbindungen, in denen X eine NR-Gruppe ist, in einem basischen Medium;

oder

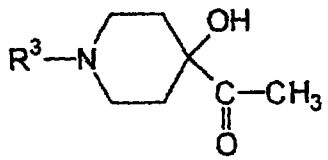
b) zur Herstellung von Verbindungen der Formel (I), gemäß dem obigen Verfahren (a) (α), cyclisierung eines wie oben definierten 4-carbamoyloxy-4-ethinylpiperidin-Derivats der Formel (II) in einem sauren Medium und Umsetzung der resultierenden, wie oben definierten Verbindung der Formel (VI) mit Wasser;

oder

c) zur Herstellung von Verbindungen der Formel (I), die wie in Verfahren (a) (β) oben definiert sind, cyclisierung eines wie oben definierten 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der Formel (II) in einem basischem Medium;

oder

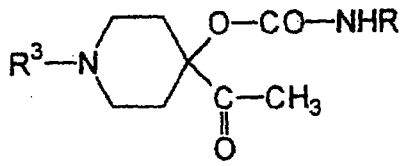
d) zur Herstellung von Verbindungen der Formel (I), in denen X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgruppe ist, Umsetzung eines 4-Acetyl-4-hydroxypiperidin-Derivats der Formel (IV)



(IV)

worin R^3 wie oben definiert ist, mit einem Isocyanat der Formel R-NCO, wobei R wie oben definiert ist, und Cyclisierung des so gebildeten 4-Acetyl-4-carbamoyloxypiperidin-Derivats der Formel (V)

* C L M S *



(V)

worin R und R^3 wie oben definiert sind;

oder

e) zur Herstellung von Verbindungen der Formel (I), in denen X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgrupe ist, Cyclisierung eines wie oben definierten 4-Acetyl-4-carbamoyloxypiperidin-Derivats der Formel (V);

gefolgt, falls gewünscht oder erforderlich,

von Umsetzung einer wie oben hergestellten Verbindung der Formel (I), worin X ein Sauerstoffatom ist und R^1 und R^2 zusammen eine Methylengruppe sind, mit einem Amin der Formel $R\text{-}NH_2$, wobei R wie oben definiert ist, um eine Verbindung der Formel I herzustellen, in der X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgruppe ist;

und/oder, falls gewünscht oder erforderlich,

Umwandlung einer wie oben hergestellten Verbindung der Formel (I) in eine andere Verbindung der Formel (I) gemäß Anspruch 1 in einer bekannten Weise;

und/oder, falls gewünscht oder erforderlich,

Umsetzung einer wie oben hergestellten Verbindung der Formel (I) mit einer Säure unter Erhalt ihres Säureadditionssalzes und/oder Umsetzung eines Salzes einer wie oben hergestellten Verbindung der Formel (I) mit einer Base zur Freisetzung ihrer Base-Form und/oder Umwandlung einer so hergestellten Verbindung der Formel (I) in ihr quaternäres Ammoniumsalz.

5. Verfahren gemäß Anspruch 4, Verfahren (a) (β), wobei R^3 wie in Anspruch 1 definiert ist, mit Ausnahme von 4-(2-Hydroxyethyl)piperazin-1-ylcarbonyl und 2-Chloronicotinoylcarbamoyl-Gruppen, umfassend die Ausführung der gesamten Reaktion in einer einzigen Stufe ohne Isolierung der Verbindung der Formel (II).

6. Verfahren gemäß Anspruch 4, Verfahren (b), dadurch **gekennzeichnet**, daß die Reaktion in einem organischen Lösungsmittel in Gegenwart eines Halogenwasserstoffs durchgeführt wird.

7. Verfahren gemäß Anspruch 4, Verfahren (d), umfassend die Ausführung der Reaktion des Derivats der in Anspruch 4 definierten Formel (IV) mit dem Isocyanat der in Anspruch 4 definierten Formel R-NCO und die Cyclisierung des so gebildeten Derivats der in Anspruch 4 definierten Formel (V) in derselben Reaktionsmischung.

8. Verfahren gemäß Anspruch 4, Verfahren (e), dadurch **gekennzeichnet**, daß die Reaktion in Ethanol und in Gegenwart von Natriumethoxid ausgeführt wird.

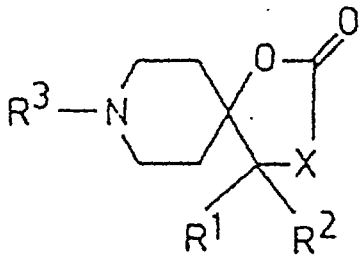
9. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 zur Herstellung eines Medikaments für antikonvulsive (antiepileptische), antiallergische und/oder lipidspiegelsenkende Behandlung von Säugetieren.

10. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung gemäß Anspruch 3, umfassend die Mischung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines ihrer pharmazeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalze mit einem pharmazeutisch annehmbaren Träger, Verdünnungsmittel oder Korrigens.

Patentansprüche für folgende Vertragsstaaten ES, GR

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

* C L M S *



(I)

worin

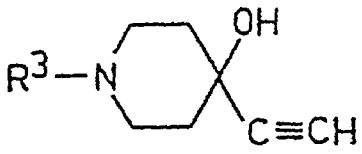
X ein Sauerstoffatom oder eine >NR-Gruppe darstellt, wobei

R ein Wasserstoffatom oder eine C_{1-12}-Alkyl-, C_{3-6}-Cycloalkyl- oder eine Tosylgruppe, oder eine carbocyclische C_{6-10}-Aryl oder carbocyclische C_{6-10}-Aryl-C_{1-4}-alkylgruppe darstellt, die am aromatischen Ring wahlweise mit einem oder mehreren Halogenatomen, C_{1-4}-Alkyl-, C_{1-4}-Alkoxy- oder Trihalomethylgruppen substituiert sind;

R^1 und R^2 zusammen eine Methylengruppe darstellen oder, wenn X eine >NR-Gruppe ist, einer der Substituenten R^1 und R^2 auch eine Hydroxylgruppe darstellen kann, während der andere eine Methylgruppe ist; und

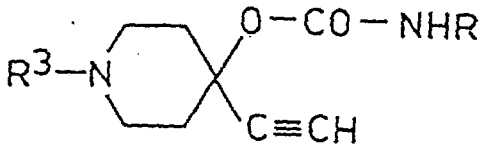
R^3 ein Wasserstoffatom oder eine Benzyl-, (C_{1-4}-Alkoxy)carbonyl-, Phenoxycarbonyl-, Formyl-, Piperidin-1-ylcarbonyl-, Morpholin-4-ylcarbonyl-, 4-Methylpiperazin-1-ylcarbonyl-, 4-(2-Hydroxyethyl)piperazin-1-ylcarbonyl-, 2-Chloro-3-nicotinoyl-carbamoyl-, C_{1-6}-Alkylcarbamoyl- oder Benzyloxycarbonylgruppe darstellt, und deren optischen Isomeren und Mischungen und aller ihrer Säureadditions- und quaternären Ammoniumsalzen, und der Verbindungen der Formel (I), in denen X >NR ist, wobei R eine 2-(3,4-Dihydroxyphenyl)ethylgruppe ist, R^1 eine Hydroxygruppe ist, R^2 eine Methylgruppe ist und R^3 eine Benzylgruppe ist, und deren optischen Isomeren und Mischungen, umfassend:

a) zur Herstellung von Verbindungen der Formel (I), in denen R^1 und R^2 zusammen eine Methylengruppe sind, Umsetzung eines 4-Ethinyl-4-hydroxypiperidin-Derivats der Formel (III)



(III)

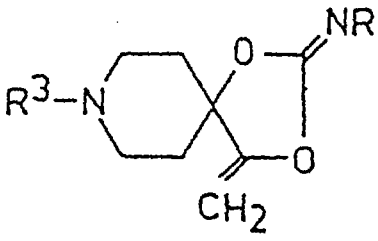
worin R^3 wie oben definiert ist, mit einem Isocyanat der Formel R-NCO, worin R wie oben definiert ist, und Cyclisierung des so erhaltenen 4-Carbamoyloxy-4-ethinyl-piperidin-Derivats der Formel (II),



(II)

worin R und R^3 wie oben definiert sind, entweder

α) für Verbindungen, in denen X ein Sauerstoffatom ist, in einem saurem Medium und Umsetzung der resultierenden Verbindung der Formel (VI)



(VI)

* C L M S *

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

β) für Verbindungen, in denen X eine NR-Gruppe ist, in einem basischen Medium;

oder

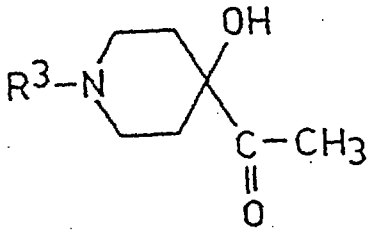
b) zur Herstellung von Verbindungen der Formel (I), gemäß obigen Verfahren (a) (α), Cyclisierung eines wie oben definierten 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der Formel (II) in einem sauren Medium und Umsetzung der resultierenden Verbindung der oben definierten Formel (VI) mit Wasser;

oder

c) zur Herstellung von Verbindungen der Formel (I), die wie in Verfahren (a) (β) oben definiert sind, Cyclisierung eines 4-Carbamoyloxy-4-ethinylpiperidin-Derivats der oben definierten Formel (II) in einem basischem Medium;

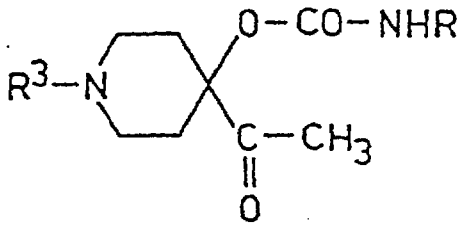
oder

d) zur Herstellung von Verbindungen der Formel (I), in denen X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgruppe ist, Umsetzung eines 4-Acetyl-4-hydroxypiperidin-Derivats der Formel (IV),



(IV)

worin R^3 wie oben definiert ist, mit einem Isocyanat der Formel R-NCO, wobei R wie oben definiert ist, und Cyclisierung des so gebildeten 4-Acetyl-4-carbamoyloxypiperidin-Derivats der Formel (V)



(V)

worin R und R^3 wie oben definiert sind;

oder

e) zur Herstellung von Verbindungen der Formel (I), in denen X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgrupe ist, Cyclisierung eines wie oben definierten 4-Acetyl-4-carbamoyloxypiperidin-Derivats der Formel (V);

gefolgt, falls gewünscht oder erforderlich, von Umsetzung einer wie oben hergestellten Verbindung der Formel (I), in der X ein Sauerstoffatom ist und R^1 und R^2 zusammen eine Methylengruppe sind, mit einem Amin der Formel $R\text{-}NH_2$, wobei R wie oben definiert ist, um eine Verbindung der Formel (I) herzustellen, worin X eine >NR-Gruppe ist und ein Rest aus R^1 und R^2 eine Hydroxylgruppe und der andere eine Methylgruppe ist;

und/oder, falls gewünscht oder erforderlich, Umwandlung einer wie oben hergestellten Verbindung der Formel (I) in eine andere Verbindung der wie oben definierten Formel (I) in einer bekannten Weise; und/oder, falls gewünscht oder erforderlich, Umsetzung einer wie oben hergestellten Verbindung der Formel (I) mit einer Säure zum Erhalt ihres Säureadditionssalzes und/oder Umsetzung eines Salzes einer wie oben hergestellten Verbindung der Formel (I) mit einer Base zur Freisetzung ihrer Base-Form und/oder Umwandlung einer so hergestellten Verbindung der Formel (I) in ihr quaternäres Ammoniumsalz.

2. Verfahren gemäß Anspruch 1, Verfahren (a) (β), worin R^3 wie in Anspruch 1 definiert ist, mit Ausnahme von 4-(2-Hydroxyethyl)piperazin-1-ylcarbonyl und 2-Chloronicotinoylcarbamoyl-Gruppen, dadurch gekennzeichnet, daß die gesamte Reaktion in einer einzigen Stufe ohne Isolierung der Verbindung der Formel (II) ausgeführt wird.

* C L M S *

3. Verfahren gemäß Anspruch 1, Verfahren (b), dadurch **gekennzeichnet**, daß die Reaktion in einem organischen Lösungsmittel in Gegenwart eines Halogenwasserstoffs durchgeführt wird.

4. Verfahren gemäß Anspruch 1, Verfahren (d), dadurch **gekennzeichnet**, daß die Reaktion des Derivats der in Anspruch 1 definierten Formel (IV) mit dem in Anspruch 1 definierten Isocyanat der Formel R-NCO und Cyclisierung des so gebildeten Derivats der in Anspruch 1 definierten Formel (V) in derselben Reaktionsmischung ausgeführt wird.

5. Verfahren gemäß Anspruch 1, Verfahren (e), dadurch **gekennzeichnet**, daß die Reaktion in Ethanol und in Gegenwart von Natriumethoxid ausgeführt wird.

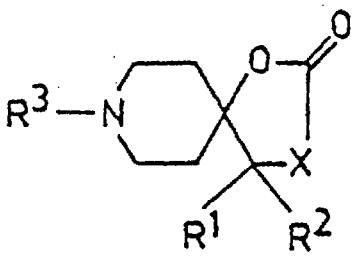
6. Verfahren gemäß Anspruch 1 zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, die ausgewählt ist aus der Gruppe, umfassend:
3-Methyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Ethyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Cyclohexyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Methylen-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decan,
3-Isopropyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Butyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-tert-Butyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Heptyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Methylen-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decan,
3-Decyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Benzyl-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-[2-(3,4-Dimethoxyphenyl)ethyl]-4-methylen-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
4-Hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3,4-Dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-[2-(3,4-Dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Decyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
3-Heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
8-Benzyl-4-methylen-2-oxo-1,3-dioxa-8-azaspiro[4,5]decan,
4-Methylen-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decan,
und ihre optischen Isomere und Mischungen und alle ihre Säureadditions- und quaternären Ammoniumsalze.

7. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 zur Herstellung eines Medikaments zur antikonvulsiven (antiepileptischen), antiallergischen und/oder lipidspiegelsenkenden Behandlung von Säugetieren.

8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, die als Wirkstoff eine Verbindung der wie in Anspruch 1 definierten Formel (I) oder eines ihrer pharmazeutisch annehmbaren Säureadditions- oder quaternären Ammoniumsalze umfaßt, dadurch **gekennzeichnet**, daß der Wirkstoff mit einem pharmazeutisch annehmbaren Träger, Verdünnungsmittel oder Korrigens gemischt wird.

Revendications

1. Composés de formule (I),



(I)

* C L M S *

dans laquelle

X représente un atome d'oxygène ou le groupe >NR, dans lequel R représente un atome d'hydrogène ou un groupe alkyle en C_{1-12}, cycloalkyle en C_{3-6} ou tosyle, ou un groupe carbocyclique aryle en C_{6-10} ou carbocyclique (aryl en C_{6-10})alkyle en C_{1-4} facultativement substitués sur le cycle aromatique par un ou plusieurs atomes d'halogène et groupes alkyles en C_{1-4}, alcoxy en C_{1-4} ou trihalogénométhyle ;

R^1 et R^2 représentent ensemble un groupe méthylène ou, lorsque X est un groupe >NR, un de R^1 et R^2 peut de plus représenter un groupe hydroxy, tandis que l'autre est un groupe méthyle ; et

R^3 représente un atome d'hydrogène ou un groupe benzyle, (alcoxy en C_{1-4})carbonyle, phénoxycarbonyle, formyle, pipéridine-1-ylcarbonyle, morpholine-4-ylcarbonyle, 4-méthylpipérazine-1-ylcarbonyle, 4-(2-hydroxyéthyl) pipérazine-1-ylcarbonyle, 2-chloro-3-nicotinoylcarbamoyle, (alkyle en C_{1-6})carbamoyle ou benzyloxycarbonyle et leurs isomères optiques et leurs mélanges et tous leurs sels d'addition d'acides et sels d'ammonium quaternaire ;

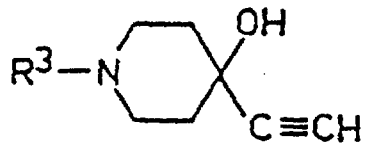
et le composé de formule (I) dans laquelle X est >NR où R est un groupe 2-(3,4-dihydroxyphényl)éthyle, R^1 est un groupe hydroxy, R^2 est un groupe méthyle et R^3 est un groupe benzyle, et ses isomères optiques et leurs mélanges.

2. Composé de formule (I) selon la revendication 1, choisi dans l'ensemble comprenant :
le 3-méthyl-4-methylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-éthyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5] décane,
le 3-cyclohexyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-méthylène-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-isopropyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-butyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-tert-butyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-heptyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-méthylène-2-oxo-3-phényl-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-décyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-benzyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-[2-(3,4-diméthoxyphényl)éthyl]-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3,4-diméthyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-[2-(3,4-diméthoxyphényl)éthyl]-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-décyl-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-heptyl-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 8-benzyl-4-méthylène-2-oxo-1,3-dioxa-8-azaspiro[4,5]décane,
le 4-méthylène-3-(1-naphtyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
et leurs isomères optiques et leurs mélanges et tous leurs sels d'addition d'acides et sels d'ammonium quaternaire.

3. Composition pharmaceutique qui comprend, comme ingrédient actif, un composé de formule (I) comme défini dans la revendication 1 ou un sel d'addition d'acide ou sel d'ammonium quaternaire pharmaceutiquement acceptables de celui-ci, en mélange avec un véhicule, diluant ou excipient pharmaceutiquement acceptables.

4. Procédé pour la préparation d'un composé de formule (I) comme défini dans la revendication 1, qui comprend

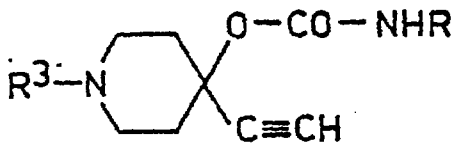
a) pour la préparation des composés de formule (I) dans laquelle R^1 et R^2 sont ensemble un groupe méthylène, la réaction d'un dérivé de 4-éthynyl-4-hydroxypipéridine de formule (III)



(III)

* C L M S *

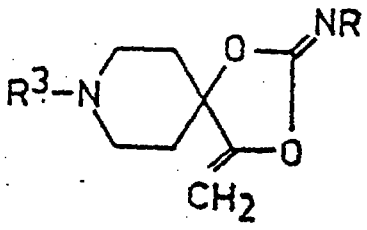
dans laquelle R^3 est défini comme dans la revendication 1, avec un isocyanate de formule R-NCO, dans laquelle R est défini comme dans la revendication 1, et la cyclisation du dérivé de 4-carbamoyloxy-4-éthynylpipéridine ainsi obtenu de formule (II),



(II)

dans laquelle R et R^3 sont définis ci-dessus, soit

α) pour les composés dans lesquels X est un atome d'oxygène, dans un milieu acide et réaction du composé obtenu de formule (VI),



(VI)

dans laquelle R et R^3 sont définis ci-dessus, avec de l'eau ; soit

β) pour les composés dans lesquels X est un groupe NR, dans un milieu basique ;

ou

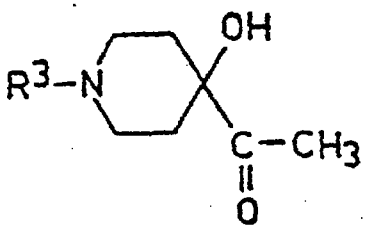
b) pour la préparation des composés de formule (I) comme défini dans le procédé (a) (α) ci-dessus, la cyclisation dans un milieu acide d'un dérivé de 4-carbamoyloxy-4-éthynylpipéridine de formule (II) comme défini ci-dessus et la réaction du composé obtenu de formule (VI), comme défini ci-dessus, avec de l'eau ;

ou

c) pour la préparation des composés de formule (I) comme défini dans le procédé (a) (β) ci-dessus, la cyclisation d'un dérivé de 4-carbamoyloxy-4-éthynylpipéridine de formule (II) comme défini ci-dessus, dans un milieu basique ;

ou

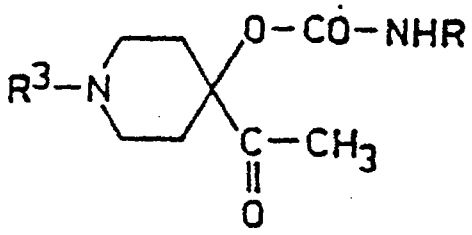
d) pour la préparation des composés de formule (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle, la réaction d'un dérivé de 4-acétyl-4-hydroxypipéridine de formule (IV),



(IV)

dans laquelle R^3 est défini comme ci-dessus, avec un isocyanate de formule R-NCO, dans laquelle R est défini comme ci-dessus, et la cyclisation du dérivé de 4-acétyl-4-carbamoyloxypipéridine ainsi forme de formule (V),

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(V)

dans laquelle R et R^3 sont définis comme ci-dessus ; ou

e) pour la préparation des composés de formule (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle, la cyclisation d'un dérivé de 4-acétyl-4-carbamoyloxypipéridine de formule (V) comme défini ci-dessus ;

puis, si on le désire ou si cela est nécessaire,

la réaction d'un composé de formule (I) préparé ci-dessus, dans lequel X est un atome d'oxygène et R^1 et R^2 ensemble sont un groupe méthylène, avec une amine de formule $R\text{-}NH_2$ dans laquelle R est défini comme ci-dessus, pour préparer un composé de formule (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle ;

et/ou, si on le désire ou si cela est nécessaire,

la transformation d'un composé de formule (I) préparé ci-dessus en un autre composé de formule (I) comme défini dans la revendication 1, de façon connue ;

et/ou, si on le désire ou si cela est nécessaire,

la réaction d'un composé de formule (I) préparé ci-dessus, avec un acide pour obtenir son sel d'addition d'acide et/ou la réaction d'un sel d'un composé de formule (I) préparé ci-dessus avec une base pour en libérer la base libre et/ou la conversion d'un composé ainsi préparé de formule (I) en son sel d'ammonium quaternaire.

5. Procédé selon le procédé a) (β) de la revendication 4, dans lequel R^3 est comme défini dans la revendication 1, à l'exception des groupes 4-(2-hydroxyéthyl)pipérazine-1-ylcarbonyle et 2-chloronicotinoylcarbamoyle, qui comprend la réalisation de la totalité de la réaction en une seule étape, sans isolement du composé de formule (II).

6. Procédé selon le procédé b) de la revendication 4, dans lequel la réaction est effectuée dans un solvant organique en présence d'un halogénure d'hydrogène.

7. Procédé selon le procédé d) de la revendication 4, qui comprend la réalisation de la réaction du dérivé de formule (IV) comme défini dans la revendication 4, avec l'isocyanate de formule R-NCO comme défini dans la revendication 4, et la cyclisation du dérivé ainsi formé de formule (V) comme défini dans la revendication 4, dans le même mélange réactionnel.

8. Procédé selon le procédé e) de la revendication 4, qui comprend la réalisation de la réaction dans l'éthanol et en présence d'éthylate de sodium.

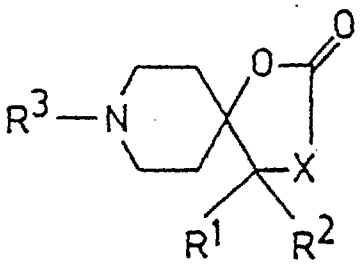
9. Utilisation d'un composé de formule (I) comme défini dans la revendication 1, pour la préparation d'un médicament pour un traitement anticonvulsif (antiépileptique), antiallergique et/ou abaissant le taux des lipides de mammifères.

10. Procédé pour la préparation d'une composition pharmaceutique selon la revendication 3, qui comprend le mélange d'un composé de formule (I) comme défini dans la revendication 1 ou d'un sel d'addition d'acide ou sel d'ammonium quaternaire pharmaceutiquement acceptables de celui-ci avec un véhicule, diluant ou excipient pharmaceutiquement acceptables.

Claims for the following Contracting States : ES, GR

1. Un procédé pour préparer un composé de formule (I),

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(I)

dans laquelle

X représente un atome d'oxygène ou le groupe >NR, dans lequel R représente un atome d'hydrogène ou un groupe alkyle en C_{1-12}, cycloalkyle en C_{3-6} ou tosyle, ou un groupe carbocyclique aryle en C_{6-10} ou carbocyclique (aryl en C_{6-10})alkyle en C_{1-4} facultativement substitués sur le cycle aromatique par un ou plusieurs atomes d'halogène et groupes alkyles en C_{1-4}, alcoxy en C_{1-4} ou trihalogénométhyle ;

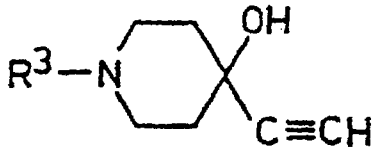
R^1 et R^2 représentent ensemble un groupe méthylène ou, lorsque X est un groupe >NR, un de R^1 et R^2 peut de plus représenter un groupe hydroxy, tandis que l'autre est un groupe méthyle ; et

R^3 représente un atome d'hydrogène ou un groupe benzyle, (alcoxy en C_{1-4})carbonyle, phénoxycarbonyle, formyle, pipéridine-1-ylcarbonyle, morpholine-4-ylcarbonyle, 4-méthylpipérazine-1-ylcarbonyle, 4-(2-hydroxyéthyl) pipérazine-1-ylcarbonyle, 2-chloro-3-nicotinoylcarbamoyle, (alkyle en C_{1-6})carbamoyle ou benzyloxycarbonyle et leurs isomères optiques et leurs mélanges et tous leurs sels d'addition d'acides et sels d'ammonium quaternaire ;

et le composé de formule (I) dans laquelle X est >NR où R est un groupe 2-(3,4-dihydroxyphényl)éthyle, R1 est un groupe hydroxy, R^2 est un groupe méthyle et R^3 est un groupe benzyle, et ses isomères optiques et leurs mélanges ;

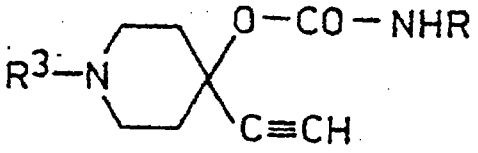
qui comprend

a) pour la préparation des composés de formule (I) dans laquelle R^1 et R^2 sont ensemble un groupe méthylène, la réaction d'un dérivé de 4-éthynyl-4-hydroxypipéridine de formule (III)



(III)

dans laquelle R^3 est défini comme ci-dessus, avec un isocyanate de formule R-NCO, dans laquelle R est défini comme ci-dessus, et la cyclisation du dérivé de 4-carbamoyloxy-4-éthynylpipéridine ainsi obtenu de formule (II),

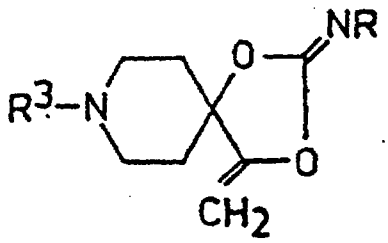


(II)

dans laquelle R et R^3 sont définis ci-dessus, soit

α) pour les composés dans lesquels X est un atome d'oxygène, dans un milieu acide et réaction du composé obtenu de formule (VI),

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(VI)

dans laquelle R et R^3 sont définis ci-dessus, avec de l'eau ; soit

β) pour les composés dans lesquels X est un groupe NR, dans un milieu basique ;

ou

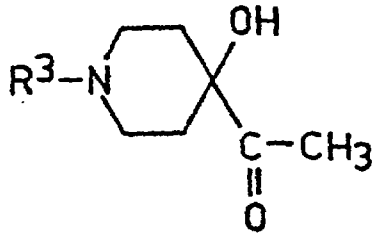
b) pour la préparation des composés de formule (I) comme défini dans le procédé (a) (α) ci-dessus, la cyclisation dans un milieu acide d'un dérivé de 4-carbamoyloxy-4-éthynylpipéridine de formule (II) comme défini ci-dessus et la réaction du composé obtenu de formule (VI), comme défini ci-dessus, avec de l'eau ;

ou

c) pour la préparation des composés de formule (I) comme défini dans le procédé (a) (β) ci-dessus, la cyclisation d'un dérivé de 4-carbamoyloxy-4-éthynylpipéridine de formule (II) comme défini ci-dessus, dans un milieu basique ;

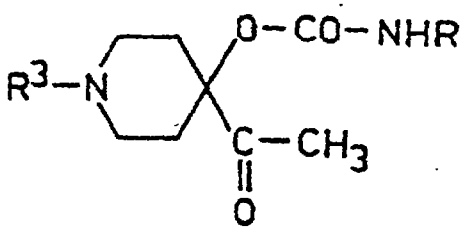
ou

d) pour la préparation des composés de formule (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle, la réaction d'un dérivé de 4-acétyl-4-hydroxypipéridine de formule (IV),



(IV)

dans laquelle R^3 est défini comme ci-dessus, avec un isocyanate de formule R-NCO, dans laquelle R est défini comme ci-dessus, et la cyclisation du dérivé de 4-acétyl-4-carbamoyloxypipéridine ainsi forme de formule (V),



(V)

dans laquelle R et R^3 sont définis comme ci-dessus ;

ou

e) pour la préparation des composés de formula (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle, la cyclisation d'un dérivé de 4-acétyl-4-carbamoyloxypipéridine de formule (V) comme défini ci-dessus ;

puis, si on le désire ou si cela est nécessaire,

la réaction d'un composé de formule (I) préparé ci-dessus, dans lequel X est un atome d'oxygène et R^1 et R^2 ensemble sont un groupe méthylène, avec une amine de formule $R\text{-}NH_2$ dans laquelle R est défini comme ci-dessus, pour préparer un composé de formule (I) dans laquelle X est un groupe >NR et un de R^1 et R^2 est un groupe hydroxyle et l'autre est un groupe méthyle ;

et/ou, si on le désire ou si cela est nécessaire,

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la transformation d'un composé de formule (I) préparé ci-dessus en un autre composé de formule (I) comme défini ci-dessus, de façon connue ;

et/ou, si on le désire ou si cela est nécessaire,

la réaction d'un composé de formule (I) préparé ci-dessus, avec un acide pour obtenir son sel d'addition d'acide et/ou la réaction d'un sel d'un composé de formule (I) préparé ci-dessus avec une base pour en libérer la base libre et/ou la conversion d'un composé ainsi préparé de formule (I) en son sel d'ammonium quaternaire.

2. Procédé selon le procédé a) (β) de la revendication 1, dans lequel R^3 est comme défini dans la revendication 1, à l'exception des groupes 4-(2-hydroxyéthyl)pipérazine-1-ylcarbonyle et 2-chloronicotinoylcarbamoyle, qui comprend la réalisation de la totalité de la réaction en une seule étape, sans isolement du composé de formule (II).

3. Procédé selon le procédé b) de la revendication 1, dans lequel la réaction est effectuée dans un solvant organique en présence d'un halogénure d'hydrogène.

4. Procédé selon le procédé d) de la revendication 1, qui comprend la réalisation de la réaction du dérivé de formule (IV) comme défini dans la revendication 1, avec l'isocyanate de formule R-NCO comme défini dans la revendication 1, et la cyclisation du dérivé ainsi formé de formule (V) comme défini dans la revendication 1, dans le même mélange réactionnel.

5. Procédé selon le procédé e) de la revendication 1, qui comprend la réalisation de la réaction dans l'éthanol et en présence d'éthylate de sodium.

6. Procédé selon la revendication 1, pour la préparation d'un composé de formule (I) comme défini dans la revendication 1, choisi dans l'ensemble comprenant :
le 3-méthyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-éthyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-cyclohexyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-méthylène-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-isopropyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-butyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-tert-butyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-heptyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-méthylène-2-oxo-3-phényl-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-décyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-benzyl-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-[2-(3,4-diméthoxyphényl)éthyl]-4-méthylène-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3,4-diméthyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-[2-(3,4-diméthoxyphényl)éthyl]-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-décyl-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 3-heptyl-4-hydroxy-4-méthyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
le 8-benzyl-4-méthylène-2-oxo-1,3-dioxa-8-azaspiro[4,5]décane,
le 4-méthylène-3-(1-naphtyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]décane,
et leurs isomères optiques et leurs mélanges et tous leurs sels d'addition d'acides et sels d'ammonium quaternaire.

7. Utilisation d'un composé de formule (I) comme défini dans la revendication 1, pour la préparation d'un médicament pour un traitement anticonvulsif (antiépileptique), antiallergique et/ou abaissant le taux des lipides de mammifères.

8. Procédé pour la préparation d'une composition pharmaceutique, qui comprend comme ingrédient actif un composé de formule (I) comme défini dans la revendication 1 ou d'un sel d'addition d'acide ou sel d'ammonium quaternaire pharmaceutiquement acceptables de celui-ci, dans lequel on mélange l'ingrédient actif avec un véhicule, diluant ou excipient pharmaceutiquement acceptables.

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