NOVEL SPIRO[2H-1-BENZOPYRAN-2,4'-PIPERIDINE]-4(3H)-ONE DERIVATIVES, ACID ADDITION SALTS THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The invention relates to novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I),

wherein

R stands for halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, and their acid addition salts,

as well as their quaternary salts of formula (Ia),

wherein

R and R' are the same or different and are identical to the meaning of said (above) R or can mean also hydrogen; and

Z^- represents one equivalent of an anion.

The above compounds and salts exert a favourably influencing effect on dementias of various pathological origin or associated (accompanying) symptoms, respectively, thereof.

The invention also relates to pharmaceutical compositions containing as active ingredients novel or, wherein R means hydrogen, known spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I) and/or pharmaceutically acceptable salts, and/or quaternary salts thereof of formula (Ia). These compositions favourably influence the dementias of various pathological origin or accompanying symptoms, respectively, thereof.

Furthermore, the invention relates to the process of preparation of compounds of the formulas (I) and (Ia).

The invention relates also to a method of treatment, which comprises administering to a mammal, including man to be treated one or more effective dose(s) of a compound of formula (I) and/or pharmaceutically acceptable salts, and/or quaternary salts thereof of formula (Ia) for alleviating dementias of various pathological origin or the accompanying (associated) symptoms thereof.

Disturbances of various degree and progression of mental and cognitive functions (such as learning, memory, faculty of judgement and abstraction) are common characteristics of the dementias of various pathological origin, e.g.: Alzheimer's disease, multiinfarct dementias, states following stroke, dementias associated with Parkinson's disease or Huntington's chorea; or dementias occurring as sequels of hypoxia or poisonings. Since the life quality of both the

patient and his surroundings are decisively determined by the integrity of psychic, mental and cognitive functions (learning, memory), one of the most important targets of the therapy of dementias of various aetiology is to prevent the impairment of the cognitive functions and to reverse the disturbances established and their sequels.

It has surprisingly been found that the spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formulas (I) and (Ia) possess a significant antiamnesic effect.

1'-Benzylspiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (I) containing hydrogen as R as well as some of its derivatives were described [Chem. Pharm. Bull. 29, 3494-3497 (1981)]. These compounds were investigated as inhibitors of the release of histamine from mast cells in comparison to disodium chromoglycate [chemically 1,3-bis(2-carboxy-4-oxochromen-5-yloxy)propan-2-ol disodium salt]. 1'-Benzylspiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one was prepared by boiling 1-benzyl-4-piperidone with 2-hydroxy-acetophenone under reflux in methanolic medium in the presence of pyrrolidine. A reaction of similar type had previously been carried out between certain ketones and 2-hydroxyacetophenone in toluene by the addition of pyrrolidine [Synthesis 886 (1978)]. An advantageous feature of the method consists in that the water formed during the cyclocondensation may azeotropically be distilled off.

According to the Chem. Pharm. Bull. publication cited above, the melting point of 1'-benzylspiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (I) containing hydrogen as R is at 91-93°C. However, it has been shown in our reproduction experiments directed to the preparation of this compound, that its melting point was about by 10°C higher (103-104°C) in each case and indepedently thereof that it was prepared by process a) or b). This observation may be explained by a high-grade contamination or a chemical structure different from the published one of the compound described in the literature.

A much more wide scope of sprio[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives are concerned by the European patent application No. 0,431,943 A2 relating to antiarrhythmic agents of III. class. A very broad variety of target compounds according to this patent document are defined on the basis of general formulas; teachings by name are given only to a much more restricted scope of these compounds. Their compounds illustrated, which are structurally close to the target compounds of our invention, are characteristically distinct from those of our invention from the view point of substituents. In general, they are characterized by a substituent (e.g. methanesulfonylamino, methoxy, methylthio, dimethylamino or acetamido group) in position 6 of the ring system. They are similarly characterized thereof that the

aromatic substituent (if present) is connected to the nitrogen through an alkyl chain containing at least two atoms. The most closely related compound disclosed is 1'-[2-(p-nitrophenyl)ethyl]-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one hydrochloride hemihyd-rate (Example 68). No specific pharmacological results are described in this patent application. The really effective substances of the bulky content of this patent document are emphasized in J. Med. Chem. 35. 3973 (1992); these are common 6-methanesulfonylamino derivatives and bear 2-aryl-ethyl or 2-heteroarylethyl substituent on nitrogen in every case. Only one single derivative is nominated, which does not contain any substituent in position 6, which is however an 1'-2-(2-pyridyl)ethyl] derivative.

It can be stated from those described above that, from compounds of formula (I), 1'-benzylspiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one containing hydrogen as R is only known (if the melting point deviation mentioned above is not considered), but its quaternary derivative of formula (Ia) is also novel.

Based on the revealed therapeutical effects of known, structurally related compounds it could not be expected that compounds of formulas (I) and (Ia) could have a favourable influence on dementias of various pathological origin or the accompanying symptoms thereof.

According to the invention, the compounds of formulas (I) and (Ia) are prepared by

a) reacting o-hydroxyacetophenone with an N-(p-substituted benzyl)-4-piperidone of formula (II), wherein R stands for halogen or nitro group or a straight or branched chain C_{1-6} alkyl group in the presence of pyrollidine; or

b) alkylating spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV) with a p-substituted benzyl halide of formula (III), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group and X means chlorine or bromine, in the presence of an acid binding agent,

then if desired, converting a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, obtained as a base, to its acid addition salt by treating it with an acid; and/or, if desired, liberating the base form of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I) wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained as an acid addition salt, by treating it with a base; or

c) quaternizing a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (IV) or an acid addition salt thereof, or a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I) or an acid addition salt thereof. wherein R means

hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, with a benzyl halide of formula (III), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X represents chlorine or bromine,

to obtain quaternary salts of formula (Ia), wherein R and R' are the same or different and are identical to said R but can mean also hydrogen; and Z^- means one equivalent of an anion.

The hydrogen maleate salt of the known compound of formula (I) containing hydrogen as R is novel. The advantage of this salt over the free base form appears in the higher stability.

A common and definitive feature of cognition-enhancing, i.e. nootropic drugs occurs in their capability to enhance the resistance of learning and memory processes against influences inducing anterograde and retrograde amnesia. Impairment of learning and memory induced by various ways, e.g. by anticholinergic drugs (such as scopolamine), carbon dioxide poisoning, a high dose of an anxiolytic agent (such as diazepam) or electroshock are commonly accepted experimental animal models of memory and learning deficiencies developed in human disorders of various aetiology (such as Alzheimer's disease, parkinsonism, Huntington's chorea or vascular dementias and states after stroke accompanied by neurodegenerative injuries). It has been found that compounds of formulas (I) and (Ia) exert an excellent antiamnesic effect in these animal models and therefore, they are useful for the treatment of cognitive disturbances occurring in the diseases mentioned above.

The biological activity of the compounds of formulas (I) and (Ia) was studied by using passive avoidance test. This test is one of the most widely used animal experimental model for investigating the effects of substances on the cognitive functions (learning and memory processes). This is based on inhibition of the genetically determined behaviour of rodents (mice and rats) that they prefer dark space to light one. A single electric shock given in the dark box is employed as a memory trace, the retention and retrieval of which can be controlled after a shorter or longer period.

1. Diazepam (DIA) induced anterograde amnesia

The passive avoidance test was carried out on NMRI mice with a body weight of 25-28 g. During the learning, preselected animals (mice entering into a dark space from an illuminated space within 30 s) were placed into an illuminated space. After entering into the dark space, the animal received within 30 s onto his plant an electric shock (1 mA for 3 s) causing an unpleasant sensation. The time of entry into the dark space (latency period) was measured. During the check, after 24 hours, the animals were again put back to the illuminated space and

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

the time elapsed until entry into the dark space (retention time) was measured (limit time = 300 s). The animals were intraperitoneally (i.p.) treated with 3 mg/kg of diazepam (chemically, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) 30 minutes before learning in order to induce anterograde amnesia. The compounds were orally (p.o.) administered in doses of 0.1 or 10 mg/kg, respectively one hour before the learning. The protective effect was calculated as percentage value (p%) by using the following formula:

$$p\% = \frac{T_{treated - DIA} - T_{placebo + DIA}}{T_{placebo} - T_{placebo - DIA}} \times 100$$

2. Electroshock (ECS) induced retrograde amnesia

In this test, the retrograde amnesia was induced on NMRI mice having a body weight of 24-26 g by using an auricular electroshock treatment of 20 mA for 0.2 s at one hour following the learning. The compounds to be tested were administered 2 hours after learning. The protective effect was calculated as percentage value (p%) by using the following formula:

$$p\% = \frac{T_{treated - ECS} - T_{placebo + ECS}}{T_{placebo} - T_{placebo - ECS}} \times 100$$

In the above formulas, T means the measured retention time of animals treated as shown in the index or the measured retention time of untreated animals, respectively. The results of experiments are summarized in the following Tables.

Table 1

Effect of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives on the diazepam induced anterograde amnesia

Compound	Dose (mg/kg p.o.)	Prevention %
4600592	0.1	144*
	10	92
4610351	0.1	78
	10	176*
4611109	0.1	92
	10	0
4610282	0.1	131*
	10	24

4610350	0.1	170*
	10	29
4611265	0.1	86*
	10	134*
4611266	0.1	159*
	10	105*
4611267	0.1	47
	10	67*
Vinpocetine	0.1	0
	10	123

* = $p < 0.05$ by the Mann-Whitney test in comparison to the diazepam control group.

Table 2

Effect of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives on the electroshock induced retrograde amnesia

Compound	Dose (mg/kg)	Route of administration	Prevention %
TRH	1	i.p.	77
	10	i.p.	35
4600592	1	p.o.	48
	10	p.o.	44
4610351	1	p.o.	81
	10	p.o.	108*
4610282	1	p.o.	77
	10	p.o.	29
4610350	1	p.o.	0
	10	p.o.	8

It can be seen from data of the Tables that the compounds of formulas (I) and (Ia) proved to be very effective in the diazepam-induced anterograde amnesia test of the so-called "one trial step-through passive avoidance" experiment, a method useful for measuring cognitive functions. The effects of compounds of the present invention were compared to those of drugs successfully employed in the therapy. From the compounds, those of code numbers 4600592, 4610282, 4610351, 4610350, 4611265 and 4611266 significantly (in a percentage of 105-176

%) antagonized the amnesic effect of diazepam. Analogues containing bromine or nitro group as substituent (compounds 4611109 and 4610350) showed an antiamnesic action in lower doses (0.1 mg/kg) but were inactive in higher doses; while both lower doses (0.1 mg/kg) as well as higher doses (10 mg/kg) of the compounds of formulas (I) and (Ia) containing tertiary butyl group (compounds 4611266 and 4611265) provided nearly the same protection against the amnesic effect of diazepam.

Three substances exhibited antiamnesic effectivity in the ECS-induced retrograde amnesia test. The compound 4610351 could significantly reverse the ECS-cauesed amnesia in both doses: a significant value (108 %) was obtained by the higher dose. A dose of 0.1 mg/kg of compound 4610282 provided 77 % protection. No considerable protection was afforded in this test by the known compound 4600592 containing hydrogen as R.

It can be seen that particularly compounds 4610282, 4610350, 4610351 and 4611266 from the substances of formula (I) as well as 4611265 from the derivatives of formula (Ia) possess a significant antiamnesic effect. Compound 4610351 has been investigated in detail both under *in vitro* and *in vivo* conditions. This compound exerted 36 % protection in an oral dose of 10 mg/kg in the normobaric hypoxia-induced memory deficiency model on rats; this surpassed the protective effect of 21 % provided by 10 mg/kg oral dose of vinpocetine. The same compound significantly inhibited the K^+ - or veratrine-induced uptake of $^{45}Ca^{++}$ by synaptosome preparation, a fact indicating the inhibitory action of the compound on the neuronal calcium uptake with the IC_{50} values of 45.6 μM (K^+-induced $^{45}Ca^{++}$ uptake) and 4,5 μM (veratrine-induced $^{45}Ca^{++}$ uptake), respectively. On the basis of these investigations, compounds of formulas (I) and (Ia) can be utilized for the treatment of diseases and dementias accompanied by the impairment of cognitive processes (learning, memory), such as multiinfarct and Alzheimer type dementias, states following stroke, ischaemic injuries, sequels of trauma of the central nervous system, parkinsonism, Huntington's chorea or multiple sclerosis. The therapeutical doses of compounds of formulas (I) and (Ia) can be expected between 0.1 and 40 mg/kg of body weight given orally, daily once or several times.

Based on the statement of the prior art European patent application No. 0,431,943 A2 and J. Med. Chem. 35. 3973 (1992), according to which compounds of similar structure showed an antiarrhythmic action, our target compounds have also been tested from this viewpoint.

These experiments were carried out on rats (with a body weight of 180-200 g) anaesthetized by uretane (1.25 g/kg i.p.) in such a way that 50 μg/kg of aconitine [chemically

acetyl benzoyl aconine] was injected to the tail vein then, the arrhythmic disturbances were observed on ECG II. lead after 5 minutes [J. Med. Exp. 10, 93 (1964)].

The compounds to be tested for antiarrhythmic effect were intravenously (i.v.) administered 2 minutes, or orally one hour before aconitine. (The route of administration is shown in the following Table.)

The aconitine arrhythmia was evaluated in such a manner that the severity of arrhythmia was characterized by an increasing number and, after average calculation both in the control as well as in the tested group, the average of treated group was expressed as percentage of the control. The arrhythmia was characterized by the following scores:

Score	Symptoms
0	complete protection
1	sporadical ventricular extrasystoles
2	serial ventricular extrasystoles
3	bi- and trigeminy
4	ventricular tachycardia
5	ventricular fibrillation, death

Table 3

Results of investigations on the antiarrhythmic effect

Compound	Dose (mg/kg)	Route of administration	Inhibition (%)	ED_{50} (mg/kg)
Control	-	-	average score=3.9	-
Bisaramil	0.3	i.v.	20	0.49
	0.5	i.v.	48	
	1.0	i.v.	91	
Quinidine	0.3	i.v.	34	6.66
	10.0	i.v.	55	
	30.0	i.v.	83	
Mexiletine	1.0	i.v.	29	2.51
	3.0	i.v.	68	
	10.0	i.v.	62	

Amiodarone	3.0	i.v.	13	
	5.0	i.v.	29	7.04
	10.0	i.v.	70	
4600592	10	i.v.	3	
	30	i.v.	19	-
	30	p.o.	0	
4611265	10	i.v.	21	
	30	i.v.	10	-
	30	p.o.	0	
4611267	10	i.v.	0	
	30	i.v.	29	-
	30	p.o.	0	
4610351	10	i.v.	16	
	30	i.v.	16	-
	30	p.o.	5	
4611266	10	i.v.	21	
	30	i.v.	3	-
	30	p.o.	0	

Note: Code numbers shown in the Tables stand for the following compounds:

4600592: known compound of formula (I) containing hydrogen as R

4610351: compound of formula (I) containing chlorine as R

4611109: compound of formula (I) containing bromine as R

4610282: compound of formula (I) containing fluorine as R

4610350 compound of formula (I) containing nitro group as R

4611265 compound of formula (Ia) containing tertiary butyl groups as R and R'

4611266 compound of formula (I) containing tertiary butyl groups as R

4611267 compound of formula (Ia) containing hydrogen as R and R'

Amiodarone: (2-butyl-3-benzofuranyl)-{4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl}-ketone

Bisaramil: 3-methyl-7-ethyl-9α-(4-chlorobenzoyloxy)-3,7-diazabicyclo[3.3.1]nonane hydrochloride

Quinidine: (S)-(6-methoxy-4-quinolinyl)-[(2R,4S,5R)-5-vinyl-2-quinuclidinyl]methanol

Mexiletine: 1-methyl-2-(2,6-xylyloxy)ethylamine

TRH: 5-oxo-L-prolyl-L-histidyl-L-proline amide

Vinpocetine: ethyl apovincaminate

Evaluation of the results

When administered intravenously, aconitine elicites a well-reproducible arrhythmia concerning both the time (duration) and severity of effect. According to the evaluations (average score = 3.9), the aconitine dose employed induced a very severe arrhythmia (ventricular tachycardia, fibrillation). Known antiarrhythmic agents inhibited the development of arrhythmia in a dose-dependent manner. The results obtained were in a good agreement with the previously published values [Orvostudomány 33, 347-361 (1982)]. The compounds according to the invention did not prevent the development of aconitine arrhythmia either through oral or intravenous application, i.e. the compounds of the invention did not exert any antiarrhythmic effect in the present model.

1-(4'-substituted benzyl)-4-piperidones (II), used as starting materials can be prepared by the reactions known from the literatuere:

a) Starting out of 4-substituted benzylamines the addition of this compound on two moles acrylic acid esters, the intramolecular ester condensation and the hydrolytic decarboxylation results in compound (II). [Helv. Chim. Acta, 41, 1188. (1958); J.Am. Chem.Soc., 68, 2108. (1946)]

b) Starting from 4-substituted benzylhalides the alkylating reaction of 4-piperidone monohydrate hydrochloride in the presence of acid binding agent yields the compound (II). [Synth. Comm., 20, 3537. (1990)]

The invention is illustrated in detail by the following non-limiting Examples.

Example 1

Preparation of the compounds of formula (I) in their free base form by spirocyclisation

a) A solution containing 0.22 mole of a 4-piperidone of formula (II) and 27.2 g (0.2 mole) of 2-hydroxyacetophenone in 100 ml of toluene was weighed into a round-bottom flask equipped with stirrer, reflux condenser and water separator device. After starting the stirring, 4 g (56 mmole) of pyrrolidine were dropped to the above mixture at room temperature. After addition, the reaction mixture was heated to the boiling point and the boiling was continued for additional 2-24 hours following the gradual separation of water. Then, the reaction mixture was cooled and poured into 150 ml of water. After separation of the phases, the aqueous layer was re-extracted with 50 ml of toluene. The combined toluene extract was washed with 10 ml of water and evaporated. The evaporation residue of the toluene phase was thoroughly mixed

with diisopropyl ether until crystallization and, if desired, recrystallized from a protic polar solvent, e.g. ethanol to yield 60-75 % of purified product.

b) 0,1 mmole of 4-piperidone of formula (II), 0,1 mole 2-hydroxy-acetophenone, 0,1 mole pirrolidine are refluxed in methanol (25 ml) solution for 3-8 hours. The progress of the reaction is controlled by TLC. After cooling the reaction mixture the compound (I) crystallize (if it does not occour during the heating period), which can be increased by colling it in the refrigerator during a night. Filtration and careful washing the filtrate cake by cold methanol yields product (I) in 80-92 % of the theoretical amount.

Example 2

Preparation of the compounds of formula (I) in free base form by alkylating the acid addition salt of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one

A mixture of 25.4 g (0.1 mole) of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one hydrochloride was boiled under reflux with 0.105 mole of a compound of formula (III) and 17 g of sodium hydrogen carbonate in 50 ml of methanol. The boiling was continued until the starting spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one was consumed from the reaction mixture [as detected by thin layer chromatography (TLC)], which required 4-8 hours.

The compounds of formula (I) obtained could preferably be recovered from the reaction mixture as follows:

1) After filtering the hot reaction mixture, the filter cake was thoroughly washed once with 20 ml, then twice with 10 ml of water each. The methanolic mother liquor was not combined with the washings. The target compound of formula (I) was obtained in two generations: one as the solid phase washed on the filter and the other one as the substance precipitating from the methanolic mother liquor in crystalline form.

2) After evaporation of the methanolic mother liquor, the residue was thoroughly mixed with water. If the target compound of formula (I) precipitated in crystalline form, it was filtered; if precipitation did not occur, the aqueous mixture was extracted with an organic solvent (such as dichloromethane) and the extract was evaporated.

The target compound of formula (I) was recrystallized in each case. A C_{1-3} alcohol (such as methanol, ethanol or isopropanol), an ether (e.g. diisopropyl ether), an ester (such as ethyl acetate) or acetonitrile could preferably be used for this purpose.

The same reagents can be used to carry out the alkylating reaction in other solvents as well; among them acetonitrile, ans isopropanol has proved the most suitable. Usually the compound of formula (I) crystallizes out of these solvents and it can be separated contaminated

by inorganic salts, by filtration. As compounds of formula (I) in form of free base are rather insoluble in water, the purification can be done easily. The cold organic solvents (methanol, isopropanol, acetonitrile) contain only a very limited quantity of compounds of formula (I), which can be isolated after the evaporation of the solvent and recrystallizing the remainder.

Example 3

Preparation of acid addition salts of the compounds of formula (I)

a) Preparation of hydrochlorides

One mmole of a compound of formula (I) as free base was stirred in 6 ml of hydrochloric acid solution of 0.5 mol/litre concentration at 50°C for 15 minutes. After cooling (by keeping in a refrigerator for the higher yield) and filtering the solution, if desired, the precipitated hydrochloride was recrystallized from a protic solvent.

b) Preparation of hydrochlorides

One mmole of a compound of formula (I) as free base is dissolved in organic solvent, i.e. in ethyl acetate (20 ml) or C_{1-3} alcohol (10 ml) at boiling temperature. To the sharp solution of compound (I) free base a small excess of solution gaseous hydrogen chloride in the same solvent is added. The precipitate is increased by cooling the solution, and filtered. If it is desired the precipitate is crystallized out of organic solvents, mostly C_{1-3} alcohol.

c) Preparation of hydrogen maleate salts

One mmol of compound of formula (I) as free base was dissolved in an organic solvent (preferably ethanol or ether) and an ethereal solution containing 1.2 mmol of maleic acid was added. After filtering off the precipitated hydrogen maleate was preferably recrystallized from ethanol.

The following compounds of formula (I) were prepared as described above:

R	Salt/free base	Solvent of recrystallization	M.p. °C
Cl	free base	methanol	82-84
Cl	hydrogen maleate	ethanol	190-192
Cl	hydrochloride	ethanol	274-275
H	free base	diisopropyl ether	103-104*
H	hydrochloride	according a)	275 (decomp.)
Br	free base	methanol	[illegible]
F	free base	ethanol	117-119
[illegible]	[illegible]	[illegible]	[illegible]

$(CH_3)_3C$-	free base	diisopropyl ether	149-151
$(CH_3)_3C$-	hydrochloride	according Example 3.b.	282-285 (decomp.)
$(CH_3)_3C$-	hydrogen maleate	ethanol	175-178
$(CH_3)_3C$-	hydrogen fumarate	ethanol	255-258 (decomp.)

* The melting point of the known compound of formula (I) containing hydrogen as R is 103-104°C in opposition to 91-93°C published in the literature. This compound could not be purified by using the method described in the literature since the aimed product did not crystallize out of benzene or of a mixture of benzene and cyclohexane.

Example 4

Simultaneous preparation of compounds of formula (I) and quaternary salts of formula (Ia) from spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV)

A mixture containing 2.54 g (0.01 mole) of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one hydrochloride, 10 ml of methanol, 1.7 g of sodium hydrogen carbonate and 2.02 ml (0.011 mole) of 4-tertiary-butylbenzyl bromide was boiled under reflux for about 3 hours. In the course of boiling the solid phase was first dissolved, then a new solid phase precipitated. Subsequently, the reaction mixture was left to stand overnight in a refrigarator, then it was filtered in a cooled state. The obtained solid phase (3.10 g, which melted in a wide range) was mixed with 30 ml of toluene and again filtered. The obtained solid phase (1 g) was recrystallized from 25 ml of methanol to obtain 0.64 g of pure 1',1'-bis(4-tert-butylbenzyl)-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium]bromide, m.p.: 255-258°C.

After evaporation of the toluene mother liquor and recrystallization of the evaporation residue (1.97 g) from 35 ml of diisopropyl ether, 1.5 g of pure 1'- (4-tert-butylbenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one were obtained, m.p.: 149-151°C.

Example 5

Preparation of quaternary salts of formula (Ia) from spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV)

A mixture containing 2.54 g (0.01 mole) of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one hydrochloride, 5 ml of methanol, 1.7 g of sodium hydrogen carbonate and 2.53 ml (0.02 mole) of benzyl chloride was boiled under reflux for 3 hours, to yield 3.66 g of 1',1'-dibenzyl-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium]hydrochloride which was recrystallized from methanol, m.p.: 262°C (with decomposition).

Example 6

Preparation of quaternary salts of formula (Ia) from 1'-benzyl-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-ones of formula (I)

A mixture containing 3.07 g (0.10 mole) of 1'-benzyl-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one, 15 ml of methanol and 1.3 g of benzyl chloride was boiled under reflux for 8 hours to result in 3.13 g of 1',1'-dibenzyl-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium] hydrochloride, which was identical to the product of Example 5. After recrystallization from methanol the product melted at 262°C with decomposition.

Example 7

Pharmaceutical compositions

a) Tablets of 100 mg weight containing 10 mg of active ingredient each

Components:	g
Active ingredient	50.0
Lactose	285.0
Potato starch	100.0
Sodium dodecyl sulfate	2.5
Polyvinylpyrrolidone (Kollidon-K 90®)	5.0
Microcrystalline cellulose (Avicel®)	50.0
Vegetable oil (Sterotex®)	7.5

The above components were usually wet-granulated and then compressed to tablets of 100 mg weight containing 10 mg of active ingredient each.

b) Dragées of 125 mg weight containing 10 mg of active ingredient each

The tablets prepared as described above were coated in a known way by a coat consisting of sugar and talc. The dragées were polished with a mixture of bee wax and carnauba wax.

c) Capsules containing 20 mg of active ingredient each

Components:	g
Active ingredient	40.0
Sodium lauryl sulfate	12.0
Lactose	102.0
Potato starch	102.0
[illegible]	[illegible]
[illegible]	1.6

After thoroughly mixing the above components, the mixture obtained was filled into hard gelatine capsules containing 20 mg of active ingredient each.

THIS SHEET HAS BEEN REPLACED

Claims

1. Spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein

R means halogen, nitro group or straight or branched chain C_{1-6} alkyl group, and their acid addition salts;

as well as their quaternary salts of formula (Ia),

wherein

the meanings of R and R' are the same or different and are identical with said meanings of R but can represent also hydrogen; and

Z^- means one equivalent of an anion,

exerting improving effect on dementias of various pathological origin or accompanying symptoms thereof.

2. A compound of formula (I) selected from the group consisting of

1'-(4-fluorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-chlorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-bromobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-nitrobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-tert-butylbenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

and the acid addition salts thereof; as well as

a compound of formula (Ia) selected from the group consisting of

1',1'-bis(4-tert-butylbenzyl)-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium]bromide and

1',1'-dibenzyl- spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium] chloride.

3. Pharmaceutical compositions exerting a improving effect on dementias of various pathological origin and accompanying symptoms thereof, containing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group or an acid addition salt thereof, and/or a quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meaning of R as defined for the present claim, and Z^- represents one equivalent of an anion, in an admixture with filling, diluting, savouring, aromatizing, stabilizing, pH-adjusting and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions.

4. Process for the preparation of novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I),

wherein

R means halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, and acid addition salts thereof;

as well as their quaternary salts of formula (Ia),

wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can represent also hydrogen, and Z^- means one equivalent of an anion,

exerting improving effect on dementias of various pathological origin and accompanying symptoms thereof, which comprises

a) reacting o-hydroxyacetophenone with an N-(p-substituted benzyl)-4-piperidone derivative of formula (II), wherein R stands for halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, in the presence of pyrrolidine; or

b) alkylating spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV) with a p-substituted benzyl halide of formula (III),

wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X stands for chlorine or bromine, in the presence of an acid binding agent, then if desired, converting a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained by process a) and/or b) in the base form thereof, to its acid addition salt by treating it with an acid; and/or, if desired, liberating the base form of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained as an acid addition salt by treating it with a base; or

c) quaternizing a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (IV) or an acid addition salt thereof, or a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I) or an acid addition salt thereof, wherein R means hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, with a benzyl halide of formula (III), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X represents chlorine or bromine,

to obtain quaternary salts of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can mean also hydrogen, and Z^- means one equivalent of an anion.

THIS SHEET HAS BEEN REPLACED

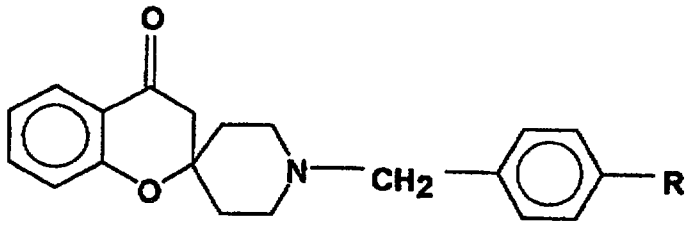
5. Process for the preparation of pharmaceutical compositions exerting an improving effect on dementias of various pathological origin and accompanying symptoms thereof, which comprises mixing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, or a pharmaceutically acceptable acid addition salt thereof, and/or of a quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R as defined for the present claim, with filling, diluting, savouring, aromatizing, stabilizing, pH-adjusting and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions and transforming them to a pharmaceutical composition.

6. A method of treatment for improving dementias of various pathological origin and accompanying symptoms thereof on mammals including man, characterized by administering to the mammal including man to be treated an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, or a pharmaceutically acceptable acid addition salt thereof, and/or of a quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R as defined for the present claim, alone or in the form of a pharmaceutical composition.

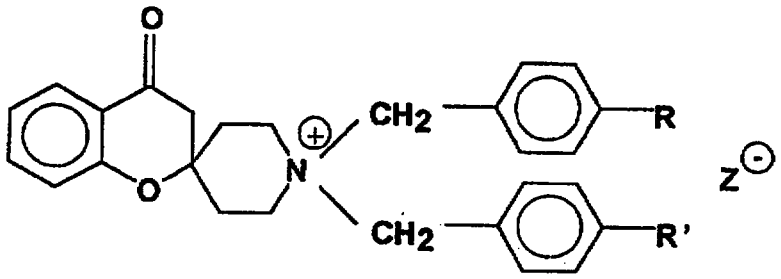
This Sheet Has Been Replaced



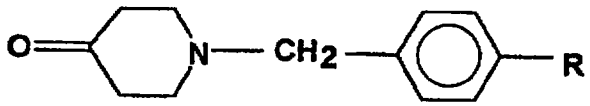




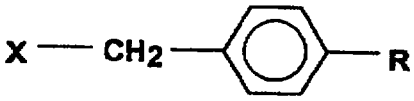
(I)



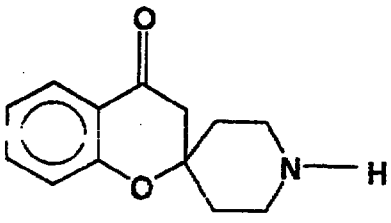
(Ia)



(II)



(III)



(IV)

hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, with a benzyl halide of formula (III), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X represents chlorine or bromine,

to obtain quaternary salts of formula (Ia), wherein R and R' are the same or different and are identical to said R but can mean also hydrogen; and Z^- means one equivalent of an anion.

The hydrogen maleate salt of the known compound of formula (I) containing hydrogen as R is novel. The advantage of this salt over the free base form appears in the higher stability.

A common and definitive feature of cognition-enhancing, i.e. nootropic drugs occurs in their capability to enhance the resistance of learning and memory processes against influences inducing anterograde and retrograde amnesia. Impairment of learning and memory induced by various ways, e.g. by anticholinergic drugs (such as scopolamine), carbon dioxide poisoning, a high dose of an anxiolytic agent (such as diazepam) or electroshock are commonly accepted experimental animal models of memory and learning deficiencies developed in human disorders of various aetiology (such as Alzheimer's disease, parkinsonism, Huntington's chorea or vascular dementias and states after stroke accompanied by neurodegenerative injuries). It has been found that compounds of formulas (I) and (Ia) exert an excellent antiamnesic effect in these animal models and therefore, they are useful for the treatment of cognitive disturbances occurring in the diseases mentioned above.

The biological activity of the compounds of formulas (I) and (Ia) was studied by using passive avoidance test. This test is one of the most widely used animal experimental model for investigating the effects of substances on the cognitive functions (learning and memory processes). This is based on inhibition of the genetically determined behaviour of rodents (mice and rats) that they prefer dark space to light one. A single electric shock given in the dark box is employed as a memory trace, the retention and retrieval of which can be controlled after a shorter or longer period.

1. Diazepam (DIA) induced anterograde amnesia

The passive avoidance test was carried out on NMRI mice with a body weight of 25-28 g. During the learning, preselected animals (mice entering into a dark space from an illuminated space within 30 s) were placed into an illuminated space. After entering into the dark space, the animal received within 30 s onto his paw an electric shock (1 mA for 3 s) causing an unpleasant sensation. The time of entry into the dark space (latency period) was measured. During the check, after 24 hours, the animals were again put back to the illuminated space and

REPLACEMENT SHEET
02 FEB 1998

the time elapsed until entry into the dark space (retention time) was measured (limit time = 300 s). The animals were intraperitoneally (i.p.) treated with 3 mg/kg of diazepam (chemically, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) 30 minutes before learning in order to induce anterograde amnesia. The compounds were orally (p.o.) administered in doses of 0.1 or 10 mg/kg, respectively one hour before the learning. The protective effect was calculated as percentage value (p%) by using the following formula:

$$P\% = \frac{T_{treated \pm DIA} - T_{placebo + DIA}}{T_{placebo} - T_{placebo \pm DIA}} \times 100$$

2. Electroshock (ECS) induced retrograde amnesia

In this test, the retrograde amnesia was induced on NMRI mice having a body weight of 24-26 g by using an auricular electroshock treatment of 20 mA for 0.2 s at one hour following the learning. The compounds to be tested were administered 2 hours after learning. The protective effect was calculated as percentage value (p%) by using the following formula:

$$P\% = \frac{T_{treated \pm ECS} - T_{placebo + ECS}}{T_{placebo} - T_{placebo \pm ECS}} \times 100$$

In the above formulas, T means the measured retention time of animals treated as shown in the index or the measured retention time of untreated animals, respectively. The results of experiments are summarized in the following Tables.

Table 1

Effect of spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives on the diazepam induced anterograde amnesia

Compound	Dose (mg/kg p.o.)	Prevention %
4600592	0.1	144*
	10	92
4610351	0.1	78
	10	176*
4611109	0.1	92
	10	0
4610282	0.1	131*
	10	24

REPLACEMENT SHEET
26 FEB 1999

REPLACEMENT SHEET
This Sheet Has Been Replaced
THIS SHEET HAS BEEN REPLACED

Claims

1. Spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein

R means halogen, nitro group or straight or branched chain C_{1-6} alkyl group, and their pharmacologically acceptable acid addition salts;

as well as their quaternary salts of formula (Ia),

wherein

the meanings of R and R' are the same or different and are identical with said meanings of R but can represent also hydrogen; and

Z^- means one equivalent of a pharmacologically acceptable anion,

exerting a favourably influencing effect on dementias of various pathological origin or accompanying symptoms thereof.

2. A compound of fclaim 1 selected from the group consisting of

1'-(4-fluorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-chlorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-bromobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-nitrobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-tert-butylbenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

and the pharmacologically acceptable acid addition salts thereof; as well as

a compound of formula (Ia) selected from the group consisting of

1',1'-bis(4-tert-butylbenzyl)-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium]bromide and

1',1'-dibenzyl- spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium] chloride.

3. Pharmaceutical compositions exerting a improving effect on dementias of various pathological origin and accompanying symptoms thereof, containing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I),

wherein R means halogen, nitro group or a straight or branched chain C_{1-6} alkyl group or a pharmacologically acceptable acid addition salt thereof, and/or a pharmacologically acceptable quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meaning of R as defined for the present claim but can represent also hydrogen, and Z^- represents one equivalent of a pharmacologically acceptable anion, in an admixture with filling, diluting, savouring, aromatizing, stabilizing, pH-adjusting

REPLACEMENT SHEET
26 FEB 1999

RE
This Sheet Has Been Replaced
THIS SHEET REPLACED

and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions.

4. Process for the preparation of novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein R means halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, and pharmacologically acceptable acid addition salts thereof as well as their quaternary salts of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can represent also hydrogen, and Z^- means one equivalent of a pharmacologically acceptable anion, exerting improving effect on dementias of various pathological origin and accompanying symptoms thereof, which c o m p r i s e s

a) reacting o-hydroxyacetophenone with an N-(p-substituted benzyl)-4-piperidone derivative of formula (II), wherein R stands for halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, in the presence of pyrrolidine; or

b) alkylating spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV) with a p-substituted benzyl halide of formula (III), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X stands for chlorine or bromine, in the presence of an acid binding agent, then if desired, converting a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained by process a) and/or b) in the base form thereof, to its pharmacologically acceptable acid addition salt by treating it with a pharmacologically acceptable acid; and/or, if desired, liberating the base form of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained as a pharmacologically acceptable acid addition salt by treating it with a base; or

c) quaternizing a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (IV) or an acid addition salt thereof, or a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I) or an acid addition salt thereof, wherein R means hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, with a benzyl halide of formula (III), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X represents chlorine or bromine, to obtain a pharmacologically acceptable quaternary salts of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can mean also hydrogen, and Z^- means one equivalent of a pharmacologically acceptable anion.

REPLACEMENT SHEET
26 FEB 1999

REPLACEMENT SHEET

THIS SHEET HAS BEEN REPLACED

5. Process for the preparation of pharmaceutical compositions exerting an improving effect on dementias of various pathological origin and accompanying symptoms thereof, which c o m p r i s e s mixing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means _____ halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, or a pharmaceutically acceptable acid addition salt thereof, and/or of a pharmaceutically acceptable quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R as defined for the present claim but can mean also hydrogen, and Z^- represents one equivalent of a pharmacologically acceptable anion, with filling, diluting, savouring, aromatizing, stabilizing, pH-adjusting and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions and transforming them to a pharmaceutical composition.

6. Use of formula (I) for improving dementias of various pathological origin and accompanying symptoms thereof on mammals including man, c h a r a c t e r i z e d b y administering to the mammal including men to be treated an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means _____ halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, or a pharmaceutically acceptable acid addition salt thereof; and/or a pharmacologically acceptable quaternary salts thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R as defined in the present claim but can mean also hydrogen, and Z^- represents one equivalent of a pharmacologically acceptable anion, alone or in the form of a pharmaceutical composition.

This Sheet Has Been Replaced

* C L M S *

REPLACEMENT SHEET
30 APR 1999

Claims

1. Spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein

R means halogen, nitro group or straight or branched chain C_{1-6} alkyl group, and their pharmacologically acceptable acid addition salts;

as well as their quaternary salts of formula (Ia),

wherein

the meanings of R and R' are the same or different and are identical with said meanings of R but can represent also hydrogen; and

Z^- means one equivalent of a pharmacologically acceptable anion,

exerting a favourably influencing effect on dementia's of various pathological origin or accompanying symptoms thereof.

2. A compound of claim 1 selected from the group consisting of

1'-(4-fluorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-chlorobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-bromobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-nitrobenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

1'-(4-tert-butylbenzyl)-spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one,

and the pharmacologically acceptable acid addition salts thereof; as well as

a compound of formula (Ia) selected from the group consisting of

1',1'-bis(4-tert-butylbenzyl)-spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium]bromide and

1',1'-dibenzyl- spiro[2H-4(3H)-oxo-1-benzopyran-2,4'-piperidinium] chloride.

3. Pharmaceutical compositions exerting a improving effect on dementia's of various pathological origin and accompanying symptoms thereof, containing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I),

wherein R means halogen, nitro group or a straight or branched chain C_{1-6} alkyl group or a pharmacologically acceptable acid addition salt thereof, and/or a pharmacologically acceptable quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meaning of R as defined for formula (I) but can represent also hydrogen, and Z^- represents one equivalent of a pharmacologically acceptable anion, in an admixture with filling, diluting, savouring, aromatizing, stabilising, pH-

REPLACEMENT SHEET
30 APR 1999

REPLACEMENT SHEET

adjusting and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions.

4. Process for the preparation of novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein R means halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, and pharmacologically acceptable acid addition salts thereof as well as their quaternary salts of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can represent also hydrogen, and Z^- means one equivalent of a pharmacologically acceptable anion, exerting improving effect on dementia's of various pathological origin and accompanying symptoms thereof, which c o m p r i s e s

a) reacting o-hydroxyacetophenone with an N-(p-substituted benzyl)-4-piperidone derivative of formula (II), wherein R stands for halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, in the presence of pyrrolidine; or

b) alkylating spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one of formula (IV) with a p-substituted benzyl halide of formula (III), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X stands for chlorine or bromine, in the presence of an acid binding agent, then if desired, converting a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained by process a) and/or b) in the base form thereof, to its pharmacologically acceptable acid addition salt by treating it with a pharmacologically acceptable acid; and/or, if desired, liberating the base form of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group obtained as a pharmacologically acceptable acid addition salt by treating it with a base; or

c) quaternizing a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (IV) or an acid addition salt thereof, or a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I) or an acid addition salt thereof, wherein R means hydrogen, halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, with a benzyl halide of formula (III), wherein R means hydrogen, halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, and X represents chlorine or bromine, to obtain a pharmacologically acceptable quaternary salts of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R but can mean also hydrogen, and Z^- means one equivalent of a pharmacologically acceptable anion.

* C L M S *

REPLACEMENT SHEET
30 APR 1999

REPLACEMENT SHEET

5. Process for the preparation of pharmaceutical compositions exerting an improving effect on dementia's of various pathological origin and accompanying symptoms thereof, which c o m p r i s e s mixing as active agent an effective dose of a spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivative of formula (I), wherein R means halogen or nitro group or a straight or branched chain C_{1-6} alkyl group, or a pharmaceutically acceptable acid addition salt thereof, and/or of a pharmaceutically acceptable quaternary salt thereof of formula (Ia), wherein the meanings of R and R' are the same or different and are identical with the meanings of R as defined for formula (I) but can mean also hydrogen, and Z^- represents one equivalent of a pharmacologically acceptable anion, with filling, diluting, savouring, aromatizing, stabilising, pH-adjusting and isotonizing as well as formulation-facilitating additives and auxiliaries usually employed for the preparation of such compositions and transforming them to a pharmaceutical composition.

970566-2.
IPOS

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K — A2

(11) International Publication Number: **WO 97/37630**

(43) International Publication Date: 16 October 1997 (16.10.97)

(21) International Application Number: PCT/HU97/00012

(22) International Filing Date: 3 April 1997 (03.04.97)

(30) Priority Data:
P 96 00928 10 April 1996 (10.04.96) HU

(71) Applicant *(for all designated States except US)*: RICHTER GEDEON VEGYÉSZETI GYÁR RT. [HU/HU]; Gyömrői út 19-21, H-1103 Budapest X (HU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HARSÁNYI, Kálmán [HU/HU]; Túrista u. 7, H-1025 Budapest (HU). SZABADKAI, István [HU/HU]; Margó Tivadar u. 182, H-1186 Budapest (HU). BORZA, István [HU/HU]; Margó Tivadar u. 218, H-1185 Budapest (HU). KÁRPÁTI, Egon [HU/HU]; Tövis u. 7/b, H-1022 Budapest (HU). KISS, Béla [HU/HU]; Gergely u. 48, H-1103 Budapest (HU). PELLIONISZ, Margit [HU/HU]; Trencsényi u. 45, H-1125 Budapest (HU). FARKAS, Sándor [HU/HU]; Olajliget u. 42, H-1103 Budapest (HU). HORVÁTH, Csilla [HU/HU]; Dér u. 42, H-1105 Budapest (HU). CSOMOR, Katalin [HU/HU]; Nyár u. 99, H-1045 Budapest (HU). LAPIS, Erzsébet [HU/HU]; Abaliget u. 86, H-1172 Budapest (HU). LASZLOVSZKY, István [HU/HU]; Bartók Béla út 16, H-1111 Budapest (HU). SZABÓ, Sándor [HU/HU]; Liszt Ferenc tér 9.II.5, H-1061 Budapest (HU). KIS-VARGA, Ágnes [HU/HU]; Thököly i. u. 20, H-1184 Budapest (HU). LASZY, Judit [HU/HU]; Madách tér 1, H-2094 Nagykovácsi (HU). GERE, Anikó [HU/HU]; Egry J. u. 40, H-1111 Budapest (HU).

(74) Common Representative: RICHTER GEDEON VEGYÉSZETI GYÁR RT.; Gyömrői ut 19-21, H-1103 Budapest X (HU).

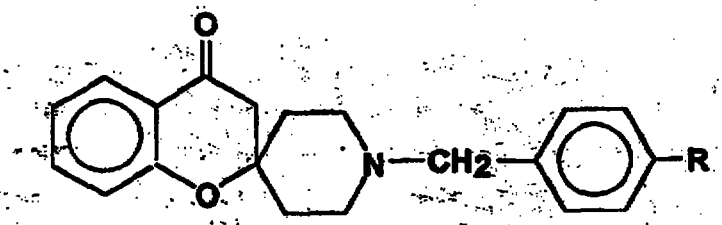
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

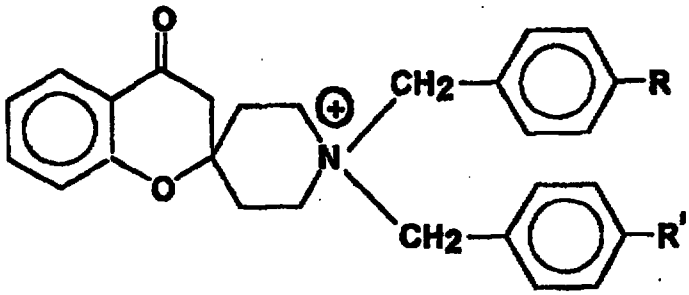
(54) Title: NOVEL SPIRO [2H-1-BENZOPYRAN-2,4'-PIPERIDINE]- 4(3H)-ONE DERIVATIVES, ACID ADDITION SALTS THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

The invention relates to novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivatives of formula (I), wherein R stands for halogen, nitro group or a straight or branched chain C_{1-6} alkyl group, and their acid addition salts, as well as their quaternary salts of formula (Ia), wherein R and R' are the same or different and are identical to the meaning of said (above) R or can mean also hydrogen; and Z^- represents one equivalent of an anion. The compounds of formulas (I) and (Ia) exert an improving effect on dementias of various pathological origin and accompanying symptoms thereof. Furthermore, the invention relates to a process for the preparation of compounds of formulas (I) and (Ia); to pharmaceutical compositions containing as active agents the above compounds of formulas (I) and (Ia); and to a method of treatment.



(I)



(Ia)