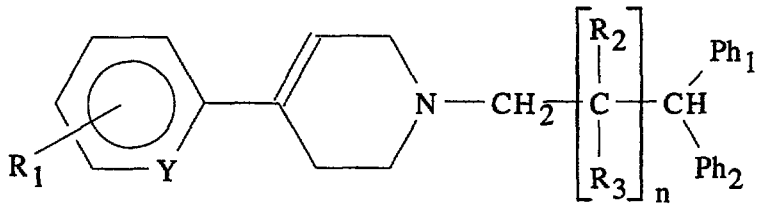
Diphenylalkyl-tetrahydropyridines, process for their preparation and pharmaceutical composition containing them

The present invention relates to novel 4-substituted gem-diphenylalkyl-1,2,3,6-tetrahydropyridines with neurotrophic and neuroprotective activity, to a process for their preparation and to pharmaceutical compositions containing them.

EP-0 458 696 describes the use of a 1-(2-naphthylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine for the preparation of drugs intended for the treatment of cerebral and neuronal disorders.

It has now been found that certain gem-diphenylalkyl-1,2,3,6-tetrahydropyridines substituted by a phenyl or pyridyl group exert a neurotrophic action on the nervous system which is similar to the action of nerve growth factor (NGF), and can restore the function of damaged cells or cells exhibiting anomalies in their physiological functions.

According to one of its features, the present invention therefore relates to the gem-diphenylalkyl-1,2,3,6-tetrahydropyridines of formula (I):



(I)

in which:

Y is -CH- or -N-;

R_1 is a halogen or a CF_3, (C_1-C_4)alkyl or (C_1-C_4)alkoxy group;

R_2 and R_3 are each hydrogen or a (C_1-C_3)alkyl;

n is 0 or 1; and

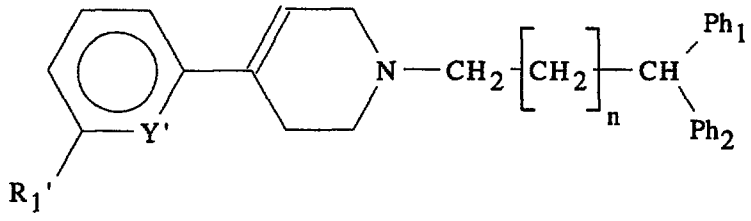
Ph_1 and Ph_2 are each independently an unsubstituted, monosubstituted or polysubstituted phenyl group;

and their salts and solvates and their quaternary ammonium salts.

Advantageous compounds according to the present invention are those of formula (I) in which Y is CH and R_1 is CF_3 and those of formula (I) in which Y is N and R_1 is Cl.

Among these compounds, those of formula (I) in which, in addition, R_2 and R_3 are both hydrogens and n is 0 or 1 are particularly advantageous.

Particularly advantageous compounds are represented by formula (I'):



(I')

in which R_1' is CF_3 and Y' is CH, or R_1' is Cl and Y' is N, and n is zero or 1, Ph_1 and Ph_2 being as defined above.

In formulae (I) and (I'), Ph_1 and Ph_2 are preferably identical but they can also be different, implying the existence of a chiral carbon atom.

Advantageously Ph_1 and Ph_2 are each independently a phenyl group; a phenyl group monosubstituted in the 2-, 3- or 4-position by a fluorine or chlorine atom or by a methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, trifluoromethyl, cyano, methoxy, methylthio, methylsulfonyl, ethoxy, ethylthio, ethylsulfonyl, (C_1-C_3)alkoxycarbonyl or di(C_1-C_3)alkylaminocarbonyl group; a phenyl group disubstituted in the 2,4-, 3,4-, 3,5- or 2,6-positions by a fluorine or chlorine atom or by a methyl, ethyl, trifluoromethyl, cyano or methoxy group; or a phenyl group trisubstituted in the 3,4,5-, 2,4,5- or 2,4,6-positions by a chlorine or fluorine atom or by a methyl, ethyl, trifluoromethyl, cyano or methoxy group.

If Ph_1 and Ph_2 are different, one of the phenyl groups is preferably unsubstituted and the other is preferably monosubstituted in the 2-, 3- or 4-position as indicated above.

In the present description the term "(C_1-C_3)alkyl" denotes methyl, ethyl, *n*-propyl and *i*-propyl groups.

The term "alkoxy" denotes a hydroxyl group substituted by a (C_1-C_4)alkyl group.

The following compounds are particularly preferred:

- 1-(2,2-diphenylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine;
- 1-[2,2-(4,4'-dichlorodiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine;
- 1-[2,2-(3,3'-bistrifluoromethyldiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-

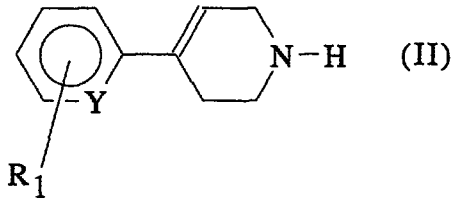
1,2,3,6-tetrahydropyridine;

- 1-[2,2-(4,4′-dimethoxydiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine;
- 1-[2-(4-fluorophenyl)-2-phenylethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine;
- 1-(3,3-diphenylpropyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine;
- 1-[2,2-(4,4′-dichlorodiphenyl)ethyl]-4-(6-chloropyrid-2-yl)-1,2,3,6-tetrahydropyridine;

and their salts, solvates or quaternary ammonium salts.

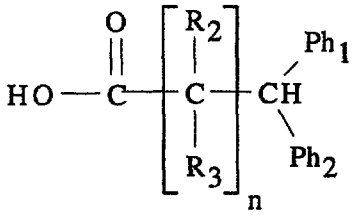
According to another of its features, the present invention relates to a process for preparing the compounds of formula (I), their salts or solvates and their quaternary ammonium salts, characterized in that:

(a) an aryl-1,2,3,6-tetrahydropyridine of formula (II):



(II)

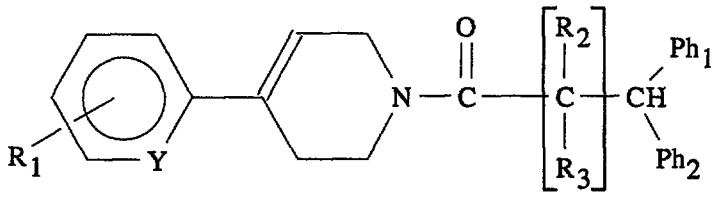
in which Y and R_1 are as defined above, is reacted with an acid of formula (III):



(III)

in which n, R_2, R_3, Ph_1 and Ph_2 are as defined above, or one of its functional derivatives;

(b) the intermediate carbonyl of formula (IV):



(IV)

is reduced; and

(c) the resulting compound of formula (I) is isolated and optionally converted to one of its salts or solvates or one of its quaternary ammonium salts.

The reaction of step (a) can conveniently be carried out in an organic solvent at a temperature between -10°C and the reflux temperature of the reaction mixture; the reaction is preferably carried out at low temperature.

The reaction solvent used is preferably a halogenated solvent such as methylene chloride, dichloroethane, 1,1,1-trichloroethane, chloroform or the like, or an alcohol such as methanol or ethanol, but it is also possible to use other organic solvents compatible with the reactants employed, for example dioxane, tetrahydrofuran or a hydrocarbon such as hexane.

The reaction can conveniently be carried out in the presence of a proton acceptor, for example an alkali metal carbonate or a tertiary amine. Appropriate functional derivatives of the acid of formula (III) which can be used are the free acid, which may be activated (for example with BOP), the anhydride, a mixed anhydride, an activated ester or an acid halide, preferably the chloride or bromide. Among the activated esters, the *p*-nitrophenyl ester is particularly preferred, but the methoxyphenyl, trityl, benzhydryl and similar esters are also convenient.

The reduction of step (b) can conveniently be carried out by means of appropriate reducing agents such as aluminum hydrides or a complex hydride of lithium and aluminum, in an inert organic solvent, at a temperature between 0°C and the reflux temperature of the reaction mixture, according to the customary techniques.

"Inert organic solvent" is understood as meaning a solvent which does not interfere with the reaction. Examples of such solvents are ethers such as diethyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane.

The compound of formula (I) obtained is isolated by the conventional techniques and optionally converted to one of its acid addition salts; alternatively, if an acid group is present, the amphoteric character of the compound enables the salts to be separated either with acids or with bases.

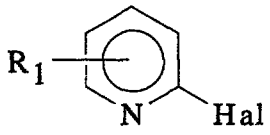
If the salts of the compound of formula (I) are prepared for administration as drugs, the acids or bases employed must be pharmaceutically acceptable; if salts of the compound of formula (I) are prepared for another purpose, for example to improve the purification of the product or to better carry out analytical assays, any acid or base may then be used.

Examples of the salts with pharmaceutically acceptable acids are those with mineral acids, such as the hydrochloride, hydrobromide, borate, phosphate, sulfate, hydrogensulfate, hydrogenphosphate and dihydrogenphosphate, and those with organic acids, such as the citrate, benzoate, ascorbate, methylsulfate, naphthalene-2-sulfonate, picrate, fumarate, maleate, malonate, oxalate, succinate, acetate, tartrate, mesylate, tosylate, isethionate, α-ketoglutarate, α-glycerophosphate, glucose-1-phosphate, etc.

Examples of the salts with pharmaceutically acceptable bases are those with alkali metals or alkaline earth metals such as sodium, potassium, calcium and magnesium, and those with organic bases such as amines, basic amino acids (lysine, arginine, histidine), trometamol, N-methylglutamine, etc.

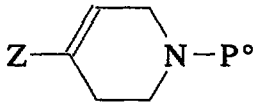
The starting amines of formula (II) in which Y is CH are known compounds or they can be prepared by methods analogous to those used to prepare the known compounds.

The starting amines of formula (II) in which Y is N can be prepared by reacting the appropriate 2-halogenopyridine of formula (p):



(p)

in which R_1 is as defined above and Hal is a halogen atom, with a 1,2,3,6-tetrahydropyridine of formula (q):



(q)

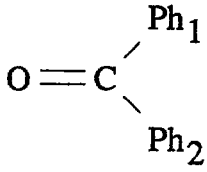
in which P° is a protecting group, for example the benzyl group, and Z is a substituent which allows the nucleophilic substitution of the pyridine halogen.

Examples of such substituents are trialkylstannanes such as tributylstannane, or Grignard compounds.

The 1,2,3,6-tetrahydropyridine is then deprotected by cleavage of the protecting group under suitable conditions.

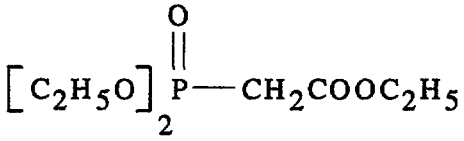
The acids of formula (III) in which n is 1 can be prepared by a Wittig reaction in which:

a) an appropriate benzophenone of formula (r):



(r)

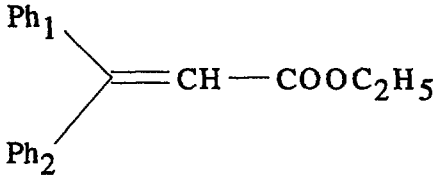
in which Ph_1 and Ph_2 are as defined above, is reacted with a compound of formula (s):



(s)

according to the Wittig reaction (as described for example in J. Med. Chem., 1996, 39(11), 2197 - 2206),

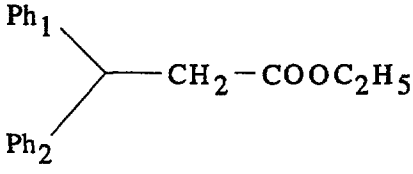
b) the intermediate of formula (t):



(t)

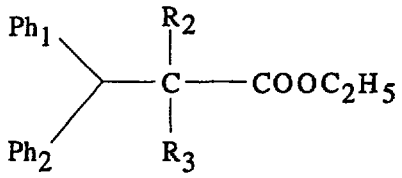
is then catalytically reduced in the presence of a catalyst such as Pd/C, and

c) the intermediate of formula (u):



(u)

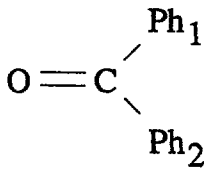
is optionally alkylated in the α-position relative to the ester carbonyl, according to the known methods, if it is desired to prepare compounds of formula (I) in which R_2 and R_3 are other than hydrogen, and the ester of formula (v):



(v)

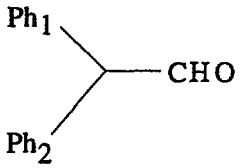
is hydrolyzed to give the acid of formula (III) in which n is 1.

The acids of formula (III) in which n is 0 can be prepared from the appropriate benzophenone of formula (r):



(r)

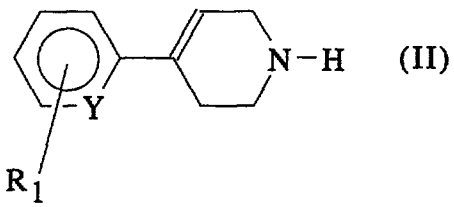
in which Ph_1 and Ph_2 are as defined above, by reaction with trimethylsulfoxonium iodide and oxidation of the intermediate aldehyde of formula (w):



(w)

according to the method described in J. Am. Chem. Soc., 1990, 112(18), 6690 - 6695, to give the corresponding acid.

In another procedure the compounds of formula (I) in which n is 0 can also be prepared by reacting an aryl-1,2,3,6-tetrahydropyridine of formula (II):



(II)

in which R_1 and Y are as defined above,
with an aldehyde of formula (w) above in the presence of a reducing agent such as sodium cyanoborohydride, according to the known techniques.

The activity of the compounds of formula (I) on the nervous system was demonstrated in *in vitro* and *in vivo* studies according to the methods described in EP-0 458 696 and, for evaluation of the neuronal survival, with the aid of an *in vitro* survival test carried out using neurons isolated from dissections of the septal region of rat embryos.

In this test the septal region of 17- to 18-day-old rat embryos is removed under a dissecting microscope under sterile conditions, is then dissociated in a trypsin/EDTA medium. The cellular suspension is placed in a culture flask in a DME/Ham's F12 (v:v) medium (Dulbecco Modified Eagle's medium/Ham's F12 nutrient mixture - R.G. Ham, Proc. Nat. Sci., 1965, 53, 288) containing 5% of calf serum and 5% of horse serum, and is kept at 37°C for 90 minutes. This treatment makes it possible to remove the non-neuronal cells.

The neuroblasts are then inoculated at a rate of 17 x 10^4 cells/cm^2 into a non-serum culture medium consisting of DME/Ham's F12 medium containing selenium (30 nM) and transferrin (1.25 µM) in the wells of a titer plate. Each well has been treated with poly-L-lysine beforehand. The inoculated plates are placed in an incubator in the oven (37°C; 5% CO_2).

The test compounds are dissolved in DMSO and diluted with the culture medium as required.

The neuroblasts are kept in plates containing the test compound or the corresponding solvent for 4 days without changing the medium.

After 4 days the medium is replaced with a tetrazolium salt dissolved in the culture medium (0.15 mg/ml). The cells are then placed in the oven at 37°C for 4 hours. The mitochondrial succinate dehydrogenases of the living cells reduce the tetrazolium salt to formazan blue, whose optical density is measured at 540 nm after dissolution in DMSO. This density has a linear correlation with the number of living cells (Manthorpe et al., Dev. Brain Res., 1988, 25, 191 - 198).

The difference between the groups containing the test compounds and the controls was evaluated by statistical analysis using the two-tailed Dunnett t-test.

In said test the compounds of formula (I) were found to be as active as or more active than the compounds described in EP-0 458 696, the efficacy of certain compounds of formula (I) in respect of neuronal survival being twice that of

compound A described in EP-0 458 696.

By virtue of this potent neuroprotective activity and their low toxicity compatible with use as drugs, the compounds of formula (I) and their pharmaceutically acceptable addition salts, their solvates and their quaternary ammonium salts can be used for the preparation of pharmaceutical compositions indicated in the treatment and/or prophylaxis of all diseases involving neuronal degeneration. More particularly, the compounds of the invention can be used, either by themselves or in co-administration or association with other active principles acting on CNS, for example acetylcholinesterase inhibitors, selective M1 cholinomimetics, NMDA antagonists and nootropics such as piracetam, especially in the following indications: memory disorders, vascular dementia, postencephalitic disorders, postapoplectic disorders, post-traumatic syndromes due to a cranial traumatism, disorders deriving from cerebral anoxia, Alzheimer's disease, senile dementia, subcortical dementia such as Huntington's chorea and Parkinson's disease, dementia caused by AIDS, neuropathies deriving from morbidity or damage to the sympathetic or sensory nerves, and brain diseases such as cerebral edema, and spinocerebellar degenerations and motor neuron degenerations, for example amyotrophic lateral sclerosis.

The compounds of the invention can conveniently be administered orally, parenterally, sublingually or transdermally. The amount of active principle to be administered in the treatment of cerebral and neuronal disorders by the method of the present invention depends on the nature and severity of the complaints to be treated and on the weight of the patients. Nevertheless the preferred unit doses will generally comprise from 0.25 to 700 mg, advantageously from 0.5 to 300 mg and preferably from 1 to 150 mg, for example between 2 and 50 mg, i.e. 2, 5, 10, 15, 20, 25, 30, 40 or 50 mg of product. These unit doses will normally be administered one or more times a day, for example 2, 3, 4 or 5 times a day and preferably one to three times a day, the overall dose in man varying between 0.5 and 1400 mg per day, advantageously between 1 and 900 mg per day, for example from 2 to 500 mg and more conveniently from 2 to 200 mg per day.

According to another of its features, the present invention relates to a pharmaceutical composition containing, as active principles, a compound of formula (I) above and a compound indicated in the symptomatic treatment of senile dementia of the Alzheimer type (DAT), or their pharmaceutically acceptable salts.

The expression "compound indicated in the symptomatic treatment of

senile dementia of the Alzheimer type (DAT)" indicates a product which is capable of improving the symptomatological picture of patients suffering from DAT, without acting on the causes of the disease.

Examples of such compounds are acetylcholinesterase inhibitors, M_1 muscarinic agonists, nicotinic agonists, NMDA receptor antagonists and nootropics.

Preferred acetylcholinesterase inhibitors are donepezil and tacrine.

Examples of other acetylcholinesterase inhibitors which can be used are rivastigmine (SDZ-ENA-713), galanthamine, metrifonate, eptastigmine, velnacrine and physostigmine (Drugs, 1997, 53(5), 752 - 768; The Merck Index, 12th edition).

Other acetylcholinesterase inhibitors are 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[3,2-f]-1,2-benzisoxazol-6-one, also called icopezil (J. Med. Chem., 1995, 38, 2802 - 2808), MDL-73,745 or zifrosilone (Eur. J. Pharmacol., 1995, 276, 93 - 99) and TAK-147 (J. Med. Chem., 1994, 37, 2292 - 2299).

Examples of other acetylcholinesterase inhibitors are those described in patent applications JP 09-095483, WO 97/13754, WO 97/21681, WO 97/19929, ZA 96-04565, US 5,455,245, WO 95-21822, EP 637 586, US 5,401,749, EP 742 207, US 5,547,960, WO 96/20176, WO 96/02524, EP 677 516, JP 07-188177, JP 07-133274, EP 649 846, EP 648 771, JP 07-048370, US 5,391,553, WO 94/29272 and EP 627 400.

According to another of its features, the present invention relates to a pharmaceutical composition containing, as active principles, a compound of formula (I) and an M_1 receptor agonist or their pharmaceutically acceptable salts.

Examples of M_1 receptor agonists are milameline, besipiridine, talsaclidine, xanomeline, YM-796 and YM-954 (Eur. J. Pharmacol., 1990, 187, 479 - 486), 3-[N-(2-diethylamino-2-methylpropyl)-6-phenyl-5-propyl]pyridazinamine, also called SR-46559 (Biorg. Med. Chem. Let., 1992, 2, 833 - 838), AF-102, CI-979, L-689,660, LU 25-109, S-99 77-2, SB 202,026, thiopilocarpine and WAL 2014 (Pharmacol. Toxicol., 1996, 78, 59 - 68).

According to another of its features, the invention relates to a pharmaceutical composition containing, as active principles, a compound of formula (I) and a nicotinic agonist or their pharmaceutically acceptable salts.

Examples of advantageous nicotinic agonists are MKC-231 (Biorg. Med. Chem. Let., 1995, 5(14), 1495 - 1500), T-588 (Japan J. Pharmacol., 1993, 62, 81 -

86) and ABT-418 (Br. J. Pharmacol., 1997, 120, 429 - 438).

According to another of its features, the invention relates to a pharmaceutical composition containing, as active principles, a compound of formula (I) and an NMDA receptor antagonist or their pharmaceutically acceptable salts.

An example of an advantageous NMDA receptor antagonist is memantine (Arzneim. Forsch., 1991, 41, 773 - 780).

According to another of its features, the invention relates to a pharmaceutical composition containing, as active principles, a compound of formula (I) and a nootropic agent or their pharmaceutically acceptable salts.

Examples of nootropic agents which can be used according to the invention are netiracetam and nebracetam (Merck Index, 12th edition).

The doses of the two associated active principles are generally chosen from the doses of each drug which would be administered in monotherapy.

According to a further feature, the present invention also relates to a method of treating senile dementia of the Alzheimer type, which consists in administering, to a patient suffering from this disease, an effective dose of a compound of formula (I) or one of its pharmaceutically acceptable salts and an effective dose of a compound indicated in the symptomatic treatment of DAT, or one of its pharmaceutically acceptable salts, said compounds being administered simultaneously, sequentially or spread over a period of time and it being possible for the effective doses of the active principles to be contained in separate unit forms of administration; alternatively, if the two active principles are administered simultaneously, they are advantageously contained in a single pharmaceutical form.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal or rectal administration, the active principle can be administered to animals and humans in unit forms of administration, either as such, for example in lyophilized form, or mixed with conventional pharmaceutical carriers, for the treatment of the above-mentioned complaints. The appropriate unit forms of administration include oral forms such as tablets, which may be divisible, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, sublingual and buccal forms of administration, subcutaneous, intramuscular or intravenous forms of administration, local forms of administration and rectal forms of administration.

When a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose,

magnesium stearate, talcum, gum arabic or the like. The tablets can be coated with sucrose or other appropriate substances or they can be treated so as to have a sustained or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir can contain the active ingredient together with a sweetener, which is preferably calorie-free, methylparaben and propylparaben as antiseptics, a flavoring and an appropriate color.

Water-dispersible powders or granules can contain the active ingredient mixed with dispersants or wetting agents, or with suspending agents such as polyvinylpyrrolidone, and with sweeteners or taste correctors.

Rectal administration is effected using suppositories, which are prepared with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, saline solutions or injectable sterile solutions containing pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

The active principle can also be formulated as microcapsules, optionally with one or more carriers or additives.

In the pharmaceutical compositions according to the present invention, the active principle can also be in the form of an inclusion complex in cyclodextrins, their ethers or their esters.

The Examples which follow illustrate the invention more clearly without however limiting it.

EXAMPLE 1

1-(2,2-Diphenylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

1a/ 1-(α,α-Diphenylacetyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine

8 g of α,α-diphenylacetyl chloride in 50 ml of methylene chloride are added dropwise at a temperature of 0/+5°C to a mixture of 8 g (0.035 mol) of 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine, 50 ml of methylene chloride and 4.96 ml of triethylamine. The reaction mixture is stirred for one

hour at room temperature, the solvent is evaporated off under reduced pressure and the residue is taken up with ethyl ether and washed with a 0.2 M aqueous hydrochloric acid solution, with water, with an aqueous sodium carbonate solution and again with water. It is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to give 5 g of the title compound.

1b/ 1-(2,2-Diphenylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

A solution of 5 g (0.012 mol) of the product of the previous step in 50 ml of ethyl ether is added dropwise at 25°C to a mixture of 0.7 g of lithium aluminum hydride in 10 ml of ethyl ether. The reaction mixture is stirred at room temperature for one hour and 5 ml of water are added dropwise. The two phases are separated, the organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to give 1-(2,2-diphenylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine. The hydrochloride is prepared with a saturated solution of hydrochloric acid in ethyl ether. It is crystallized from 150 ml of ethyl acetate. M.p. (hydrochloride) 207 - 210°C.

EXAMPLE 2

1-[2,2-(4,4'-Dichlorodiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its oxalate

2a/ α,α-(4,4'-Dichlorodiphenyl)acetaldehyde

0.75 g (0.025 mol) of an 80% dispersion of sodium hydride in oil is added in portions to a mixture of 5.5 g (0.025 mol) of trimethylsulfoxonium iodide in 10 ml of anhydrous tetrahydrofuran. The reaction mixture is heated at 55°C for 6 hours and 6 g (0.025 mol) of 4,4'-dichlorobenzophenone in 10 ml of anhydrous tetrahydrofuran are added. The mixture is stirred at 55°C overnight, poured into water and extracted with ethyl ether, the organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure. The residue is dissolved in 32 ml of toluene, and 3 ml of BF_3-EtO are added. The mixture is stirred for 2 minutes and then left to stand for 3 minutes. It is washed twice with an aqueous sodium bicarbonate solution, the organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to give an oil, which is purified by chromatography on a silica gel column using a 9/1 hexane/ethyl acetate mixture as the eluent

to give the title compound.

2b/ 1-[2,2-(4,4'-Dichlorodiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its oxalate

1.3 g (0.0045 mol) of the product of the previous step, 1.2 g (0.0053 mol) of 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine, 21 ml of methanol, 0.8 ml of glacial acetic acid and 0.5 g of anhydrous sodium acetate are mixed at a temperature of 0/+5°C. 0.76 g (0.0121 mol) of sodium cyanoborohydride is added to the mixture at the same temperature and the resulting mixture is stirred at low temperature for 1.5 hours and then at room temperature overnight. 5 ml of concentrated hydrochloric acid are added dropwise, the mixture is stirred for 10 minutes, the methanol is evaporated off and the residue is taken up with a mixture of ethyl acetate and dilute aqueous NH_4OH solution. The two phases are separated, the organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to give an oil, which is purified by chromatography on a silica gel column using a 9/1 hexane/ethyl acetate mixture as the eluent to give the title compound in the form of the base. The oxalate is prepared with oxalic acid in isopropanol. M.p. (oxalate) 187 - 189°C.

EXAMPLE 3

1-[2,2-(3,3'-Bistrifluoromethyldiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its oxalate

3a/ α,α-(3,3'-Bistrifluoromethyldiphenyl)acetaldehyde

The title compound is obtained by the procedure described in Example 2a/ except that 3,3'-bistrifluoromethylbenzophenone is used.

3b/ 1-[2,2-(3,3'-Bistrifluoromethyldiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its oxalate

The title compounds are obtained by the procedure described in Example 2b/ except that the product of the previous step is used instead of α,α-(4,4'-dichlorodiphenyl)acetaldehyde. M.p. (oxalate) 194 - 196°C.

EXAMPLE 4

1-[2,2-(4,4'-Dimethoxydiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

4a/ α,α-(4,4'-Dimethoxydiphenyl)acetaldehyde

The title compound is obtained by the procedure described in Example 2a/ except that 4,4'-dimethoxybenzophenone is used.

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4b/ 1-[2,2-(4,4'-Dimethoxydiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

The title compounds are obtained by the procedure described in Example 2b/ except that the product of the previous step is used instead of α,α-(4,4'-dichlorodiphenyl)acetaldehyde. M.p. (hydrochloride) 214 - 216°C.

EXAMPLE 5

1-[2-(4-Fluorophenyl)-2-phenylethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

5a/ α-4-Fluorophenyl-α-phenylacetaldehyde

The title compound is obtained by the procedure described in Example 2a/ except that 4-fluorobenzophenone is used.

5b/ 1-[2,2-(4-Fluorophenyl)-2-phenylethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

The title compounds are obtained by the procedure described in Example 2b/ except that the product of the previous step is used instead of α,α-(4,4'-dichlorodiphenyl)acetaldehyde. M.p. (hydrochloride) 206 - 208°C.

EXAMPLE 6

1-(3,3-Diphenylpropyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

The title compounds are obtained by the procedure described in Example 1b/ except that commercial 3,3-diphenylpropionic acid (Aldrich, reference D21,165-6) is used instead of 2,2-diphenylacetic acid. M.p. (hydrochloride) 176 - 178°C.

EXAMPLE 7

1-[2,2-(4,4'-Dichlorodiphenyl)ethyl]-4-(6-chloropyrid-2-yl)-1,2,3,6-tetrahydropyridine and its hydrochloride

The title compound is obtained by the procedure described in Example 2b/ except that 4-(6-chloropyrid-2-yl)-1,2,3,6-tetrahydropyridine is used instead of 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine. M.p. (hydrochloride) 230 - 32°C.

EXAMPLE 8

1-[2,2-(4,4'-Difluorodiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

1-[2,2-(4,4'-Difluorodiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine is obtained by the procedure described in Example 2

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except that 4,4'-difluorobenzophenone is used instead of 4,4'-dichlorobenzophenone. The hydrochloride is prepared with a solution of hydrochloric acid in isopropanol to give the title compound. M.p. 173 - 175°C.

EXAMPLE 9

1-[2,2-(4,4'-Dichlorodiphenyl)ethyl]-4-(2-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

9a/ 4-Hydroxy-4-(2-trifluoromethylphenyl)piperidine hydrochloride

3.25 g (0.135 mol) of Mg are mixed with a spatula tipfull of I_2, and a solution of 30.4 g (0.135 mol) of 2-bromo-1-trifluoromethylbenzene in 125 ml of THF is added dropwise. The mixture is stirred for one hour at room temperature and 10.1 g (0.041 mol) of benzylpiperidone are added dropwise. The mixture is stirred for 1 hour at room temperature and a saturated ammonium chloride solution is added. After extraction with ethyl ether, the organic phase is dried and the solvent is evaporated off under reduced pressure. The product is purified by chromatography on a silica gel column using a cyclohexane/ethyl acetate mixture as the eluent to give 6.8 g of 1-benzyl-4-hydroxy-4-(2-trifluoromethylphenyl)piperidine, which is hydrogenated with the aid of 0.7 g of 10% Pd/C in 75 ml of 95% ethanol which has been brought to acid pH by the addition of hydrochloric acid, the mixture being heated at a temperature of 60°C for 8 hours. The catalyst is filtered off to give 2.1 g of the title product. M.p. 247 - 251°C.

9b/ 4-(2-Trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

2.0 g (0.007 mol) of the product of the previous step are dissolved in 12 ml of glacial acetic acid. 3 ml of concentrated sulfuric acid are added dropwise and the mixture is heated at 100°C for two hours. It is poured onto ice, a concentrated NaOH solution is added until the pH is basic, and the mixture is extracted with methylene chloride. The organic phase is dried and the solvent is evaporated off under reduced pressure. The product is taken up with 15 ml of isopropanol to give 4-(2-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine. The hydrochloride is prepared with a solution of hydrochloric acid in isopropanol to give 0.9 g of the title compound. M.p. 213 - 215°C.

9c/ 1-[2,2-(4,4'-Dichlorodiphenyl)ethyl]-4-(2-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine hydrochloride

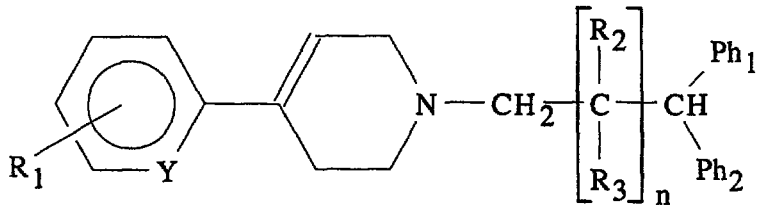
0.5 g (0.0022 mol) of the product of the previous step in the form of the base,

9 ml of methanol, 0.33 ml of glacial acetic acid and 0.2 g of anhydrous sodium acetate are mixed at a temperature of 0/+5°C. 0.5 g (0.0019 mol) of α,α-(4,4′-dichlorodiphenyl)acetaldehyde, prepared according to Example 2a/, and then 0.33 g of sodium cyanoborohydride are added to the mixture at the same temperature and the resulting mixture is stirred at low temperature for 1.5 hours and then at room temperature overnight. 2.1 ml of concentrated hydrochloric acid are added dropwise, the mixture is stirred for 15 minutes, the methanol is evaporated off and the residue is taken up with a mixture of ethyl acetate and dilute aqueous NH_4OH solution. The organic phase is dried, a saturated solution of hydrochloric acid in isopropanol is added and the solvent is evaporated off to give 0.48 g of the title compound, which is crystallized from ethyl acetate. M.p. 229 - 230°C.

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CLAIMS

1. Compound of formula (I):



(I)

in which:

Y is -CH- or -N-;

R_1 is a halogen or a CF_3, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy group;

R_2 and R_3 are each hydrogen or a $(C_1$-$C_3)$alkyl;

n is 0 or 1; and

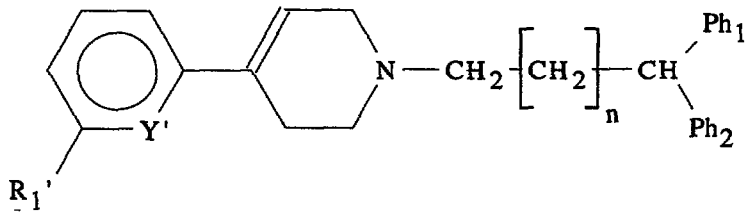
Ph_1 and Ph_2 are each independently an unsubstituted, monosubstituted or polysubstituted phenyl group;

and its salts and solvates and its quaternary ammonium salts.

2. Compound according to claim 1 in which Y is CH and R_1 is CF_3, or Y is N and R_1 is Cl.

3. Compound according to claim 1 or 2 in which R_2 and R_3 are both hydrogens.

4. Compound according to claim 1 of formula (I'):



(I')

in which R_1' is CF_3 and Y' is CH, or R_1' is Cl and Y' is N, and n, Ph_1 and Ph_2 are as defined for the compounds (I) in claim 1, and its salts and solvates and its quaternary ammonium salts.

5. Compound according to any one of claims 1 to 4 in which Ph_1 and Ph_2 are each a phenyl group; a phenyl group substituted in the 2-, 3- or 4-position by a fluorine or chlorine atom or by a methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl,

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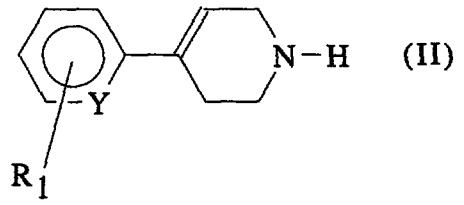
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s-butyl, *t*-butyl, trifluoromethyl, cyano, methoxy, methylthio, methylsulfonyl, ethoxy, ethylthio, ethylsulfonyl, (C_1-C_3)alkoxycarbonyl or di(C_1-C_3)alkylaminocarbonyl group; a phenyl group disubstituted in the 2,4-, 3,4-, 3,5- or 2,6-positions by a chlorine or fluorine atom or by a methyl, ethyl, trifluoromethyl, cyano or methoxy group; or a phenyl group trisubstituted in the 3,4,5-, 2,4,5- or 2,4,6-positions by a chlorine or fluorine atom or by a methyl, ethyl, trifluoromethyl, cyano or methoxy group.

6. Compound according to claim 5 in which Ph_1 and Ph_2 are identical.

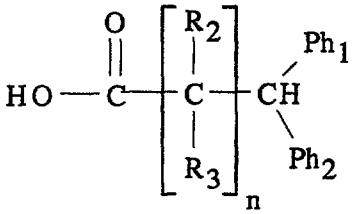
7. Compound according to claim 1 selected from 1-(2,2-diphenylethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-[2,2-(4,4′-dichlorodiphenyl)-ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-[2,2-(3,3′-bistrifluoromethyldiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-[2,2-(4,4′-dimethoxydiphenyl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-[2-(4-fluorophenyl)-2-phenylethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-(3,3-diphenylpropyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine; 1-[2,2-(4,4′-dichlorodiphenyl)ethyl]-4-(6-chloropyrid-2-yl)-1,2,3,6-tetrahydropyridine; and their salts, solvates or quaternary ammonium salts.

8. Method of preparing the compounds of formula (I) according to claim 1, their salts or solvates and their quaternary ammonium salts, characterized in that:
(a) an aryl-1,2,3,6-tetrahydropyridine of formula (II):



(II)

in which Y and R_1 are as defined for the compounds (I) in claim 1, is reacted with an acid of formula (III):



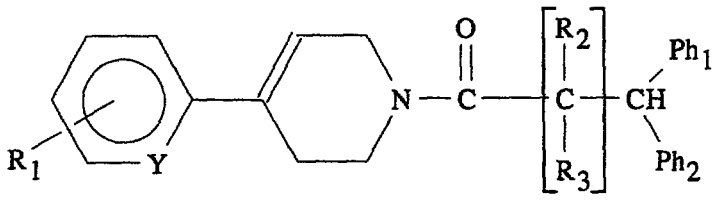
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in which n, R_2, R_3, Ph_1 and Ph_2 are as defined for the compounds (I) in claim 1, or one of its functional derivatives;

(b) the intermediate carbonyl of formula (IV):



(IV)

is reduced; and

(c) the resulting compound of formula (I) is isolated and optionally converted to one of its salts or solvates or one of its quaternary ammonium salts.

9. Pharmaceutical composition containing, as the active principle, a compound according to any one of claims 1 to 7.

10. Pharmaceutical composition containing, as the active principles, a compound according to one of claims 1 to 7 and a compound indicated in the symptomatic treatment of senile dementia of the Alzheimer type (DAT), or their pharmaceutically acceptable salts.

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