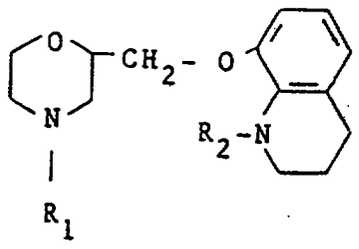
The present invention relates to new morpholine compounds, a process for the preparation thereof and pharmaceutical compositions containing them.

It relates especially to the morpholine compounds of the general formula I:



in which:

R_1 represents:

a hydrogen atom;

a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond;

an aralkyl radical of the general formula:

$$Ar-(CH_2)_m-$$

in which:

Ar represents an aryl radical optionally substituted by one or more halogen atoms, alkyl or alkoxy radicals each containing from 1 to 5 carbon atoms, or radicals of the formula $-O-(CH_2)_n-O-$ in which n has the value 1 or 2; and

m represents an integer from 1 to 3;

a cycloalkyl radical containing 5 or 6 carbon atoms;

or

an acyl radical of the formula: R′-CO- in which R′ represents an alkyl radical containing 1 or 2 carbon atoms; and

R_2 represents:

a hydrogen atom;

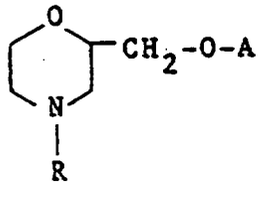
a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond;

an aralkyl radical of the general formula: $Ar-(CH_2)_m-$ in which Ar and m are as defined above; or

an acyl radical of the formula R′-CO- in which R′ is as defined above;

and their enantiomers.

The compounds of the prior art that are the closest to the compounds (I) correspond to the general formula



in which A represents:

a 2-ethoxyphenyl radical (see Belgian Patent No. 708557, the leading product of which is viloxazine);

a 2-(2-thienylmethyl)-phenyl radical (see British Patent No. 1,466,820, the leading product of which is sufoxazine);

an indenyl radical (see West German Patent No. 2,601,703, the leading product of which is indeloxazine);

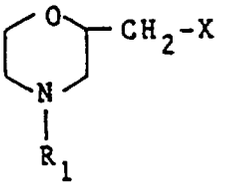
a benzofuranyl, benzothienyl or indolyl radical (see West German Patent No. 2,056,592, and Japanese Kokai No. 75-129575);

a quinolon-4-yl radical (see Japanese Kokai No. 77-116482).

The compounds of the present invention differ from those of the prior art not only in their chemical structure but also in their pharmacological behaviour. They possess an anti-ischaemic and antihypoxic activity superior to that of the compounds of the prior art cited above without manifesting their secondary effects. In particular, unlike the similar compounds of the prior art, they do not inhibit the uptake of serotonin. They are psychostimulating, which the closest products of the prior art are not, as is demonstrated by tests on narcoses. In those tests, a reduction in barbitone narcosis was observed with the compounds of the present invention while, for example, viloxazine, has no effect on that narcosis.

The present invention relates also to a process for the preparation of the compounds of the general formula I, characterised in that:

a substituted morpholine of the general formula II:



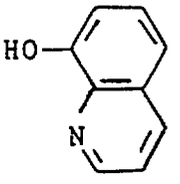
(II)

in which:

R_1 is as defined above, and

X represents a halogen atom or a tosyloxy radical,

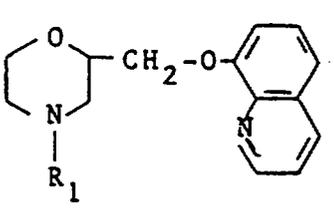
is reacted with a hydroxyquinoline of the formula III:



(III),

which has previously been converted into an alkali metal salt,

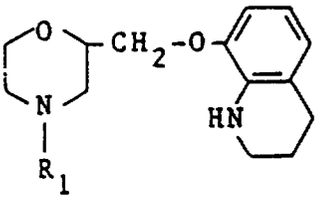
to obtain a compound of the general formula IV:



(IV)

in which R_1 is as defined above;

which is then hydrogenated to obtain a compound of the formula Ia:



(Ia)

in which R_1 is as defined above,

which is then condensed with a compound of the general formula V:

$$R'_2\text{-}X' \qquad (V)$$

in which:

R'_2 represents

a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond,

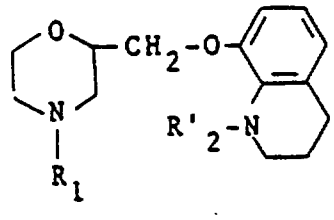
an aralkyl radical of the general formula: $Ar\text{-}(CH_2)_m\text{-}$, in which Ar and m are as defined above, and

at the same time, X' represents a bromine or iodine atom or a tosyloxy radical; or

R'_2 represents an acyl radical of the formula R'-CO- in which R' is as defined above, and,

at the same time, X' represents a chlorine atom;

to obtain a compound of the general formula Ib:



(Ib)

in which R_1 and R'_2 are as defined above.

Together the compounds (Ia) and (Ib) make up the entirety of the compounds (I).

The reaction of compounds (II) and (III) is carried out in an especially suitable manner by operating in a solvent selected from tertiary amides, such as, for example, dimethylformamide or dimethylacetamide, at a temperature of from 90 to 110°C in the presence of an acceptor of the compound HX formed; that acceptor being an alkaline agent, the most commonly used being sodium hydride as a 50 % suspension in oil.

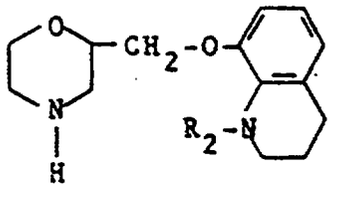
If desired, it is also possible to prepare the alkali metal salts of hydroxyquinoline by evaporating an aqueous ethanolic solution of the latter and of a strong base, such as potassium or sodium hydroxide, in an equimolar amount.

The hydrogenation of compound (IV) is carried out at low pressure in the presence of a catalyst belonging to the metals of group VIII, such as rhodium or palladium (the latter preferably being in the form of the hydroxide) in a solvent, such as the water-miscible low-molecular-weight alcohols, such as methanol or ethanol. It is especially recommended that the operation be carried out at a temperature of from 20 to 60°C, under a hydrogen pressure of from $1x10^5$ to $6x10^5$ Pa in the presence of a catalyst, such as Rh/C or $Pd(OH)_2/C$. The condensation of compounds (Ia) and (V) in order to prepare the compounds (Ib) is carried out in an especially suitable manner in a solvent which, depending on the meaning of R'_2, may be an aromatic hydrocarbon, tetrahydrofuran or a polar solvent, such as the low-molecular-weight alcohols, acetonitrile or dimethylformamide. It is recommended that the operation be carried out at a temperature of from 20 to 80°C in the presence of an acceptor of the compound HX'

formed. That acceptor may be a tertiary base, such as, for example, triethylamine, pyridine or dimethylamino-pyridine.

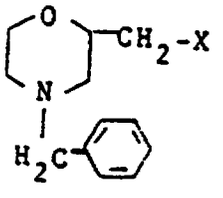
This synthesis scheme can be used especially well for the preparation of the enantiomers of the compounds (I) starting from a morpholine of formula II, in which X is a tosyloxy radical, the R and S forms of which can be prepared according to the method of R. HOWE et al., J. Med. Chem. (1976), 19, 1674-1676.

The compounds of the formula (I) in which R_1 represents a hydrogen atom, thus corresponding more specifically to the general formula I':



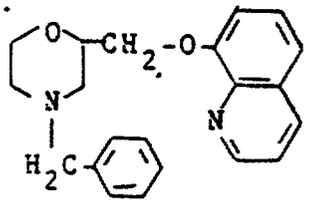
(I')

in which R_2 is as defined in formula I are preferably prepared starting from a morpholine of the general formula II'



(II')

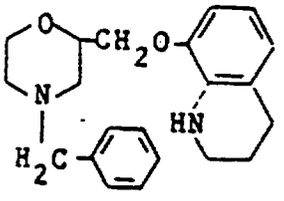
which is condensed with a hydroxyquinoline (III) to obtain a compound of the formula IV':



(IV')

which is subjected to catalytic hydrogenation under low pressure

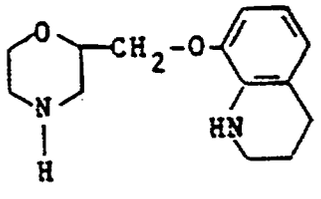
(operating preferably under a pressure of from $2x10^5$ to $5x10^5$ Pa with a rhodium catalyst) to obtain a compound of the formula IV":



(IV")

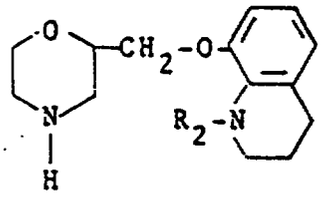
which is:

either debenzylated directly by hydrogenolysis at pressures of from $2x10^5$ to $5x10^5$ Pa to give the compound of the formula I'a:



(I'a)

or is first alkylated or acylated by means of R'_2X', which is as defined above, and then debenzylated by catalytic hydrogenation under low pressure (operating preferably at from $2x10^5$ to $5x10^5$ Pa in the presence of a palladium catalyst) to obtain the compound of the formula I'b



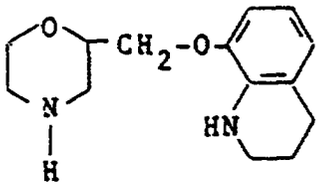
(I'b).

Together the compounds (I'a) and (I'b) represent the

entirety of the compounds (I').

This second method is also valuable in the preparation of the compounds of the general formula I in which R_1 and R_2 are different and, especially, when R_1 is a radical having a double bond sensitive to the hydrogenation conditions.

Finally, this second method also enables compounds of the general formula I to be prepared in which R_1 and R_2 are identical and other than hydrogen, by alkylation or acylation of the compound of the formula I'a:



(I'a)

according to the process described above.

All those preparation variants are included in the present invention.

The compounds of the present invention can be purified by flash chromatography on a SiO_2 support (35-70μ) and separated in systems such as CH_2Cl_2-CH_3OH, benzene-CH_3OH, under nitrogen pressures of from 0.5×10^5 to 1×10^5 Pa.

Those compounds give salts with physiologically tolerable acids and are normally in the amorphous state, both when in the form of a base and when in the form of a salt. Those salts are also included in the present invention.

The compounds of the present invention possess valuable pharmacological and therapeutic properties. They are effective against cerebral function disorders caused by circulatory deficiency or by a reduction in oxygenation,

which are two of the pathological components closely linked with cerebral vascular accident and ageing. These properties are manifested thanks to a mechanism of action which aims to maintain catecholaminergic neurotransmission, the dysfunction of which has also been widely demonstrated and implicated in depressive and amnesic phenomena associated with those cerebral pathologies. Those properties are exhibited in a more intense and more specific manner and with fewer secondary effects than in the case of the most recent anti-ischaemic and anti-geriatric reference compound, the effect of which is to improve the intrasynaptic bioavailability of catecholamines: bifemelane.

The compounds of the present invention are tested in respect of their capacity to prolong the cerebral survival of mice subjected to acute circulatory arrest by the intravenous injection of magnesium chloride. When administered intraperitoneally, the compounds of the invention increase the survival time very significantly at a dose of 3 mg/kg and above, while under the same conditions bifemelane exerts a 3 to 5 times lesser effect.

Likewise, the compounds of the invention exhibit their protective cerebral effects in mice subjected to acute global hypoxia (reduction in barometric pressure with inhaled oxygen fraction = 3.3). That protection is demonstrated by the increase in the survival time of the brain. The anti-hypoxic effect is very significant at a dose of 3 mg/kg and above, both in the case of i.p. administration (where an increase in the survival time of up to 30 % is observed) and in the case of p.o. administration (where that increase reaches 20 %) which indicates the very good bioavailability on digestion of the compounds tested (especially of the products forming the

subject of Examples 2 and 7a). Bifemelane, when administered under the same conditions, exhibits a slight protective effect (20 %) only at a dose of 10 mg/kg i.p. and 30 mg/kg orally. At a dose of 30 mg/kg per os, an increase in the survival time of 62 % and 52 % in the case of the products of Examples 2 and 7a, respectively, and an increase in the survival time of 20 % in the case of bifemelane and of 32 % in the case of viloxazine were observed.

An examination of the dose-effect relationships in respect of that same cerebral hypoxia test demonstrates, with increasing doses of the compounds of the invention, a perfect progression of the intensity of protection without any neurological symptoms in the animals after the administration of the compound to be tested.
For example, at oral doses of 10, 30, 50 and 100 mg/kg, the product of Example 7a exhibits a protective effect of 29, 52, 73 and 118 %, respectively.
In the case of bifemelane administered orally, that linearity is not observed and the protective effect (20 % at 30 mg/kg; 68 % at 100 mg/kg; 179 % at 300 mg/kg) is due to the appearance of secondary effects (apathy, drowsiness) and then of toxic effects proper.
In this test, the therapeutic index ($LD/_{50}/ED_{50}$) is very much in favour of the compounds of the invention because there is associated with a protective activity 3 to 5 times greater a toxicity 2.5 times lower, especially in the case of i.p. administration (the $LD/_{50}$ being 270 mg/kg in the case of the compounds of Examples 2 and 7a, for example, while it is 110 mg/kg in the case of bifemelane).

In addition, the compounds of the present invention are tested in respect of their capacity to facilitate noradrenergic neurotransmission. Thus, it is demons-

trated in mice that those compounds induce mortality in animals receiving a non-lethal dose of yohimbine (30 mg/kg) intraperitoneally. For example, at an oral dose of 100 mg/kg, the mortality, which is zero in the case of control animals receiving the solvent, is 50 % in the case of the compound of Example 6, 90 % in the case of the compounds of Examples 7a and 3, and 100 % in the case of the compound of Example 2, while it is 20 % in the case of bifemelane. This potentiation of toxicity is exhibited at a lower dose with the compounds of the invention. Thus, it varies from 20 to 60 % at a dose of 10 mg/kg, while no effect is manifested at that dose in the case of bifemelane.

Finally the compounds of the invention were studied in respect of experimental narcoses. The sleeping time induced by hexobarbitone at a dose of 75 mg/kg i.p. in mice is potentiated by 62 % by bifemelane administered beforehand at a dose of 30 mg/kg orally, and by 86 % by viloxazine administered beforehand at a dose of 30 mg/kg intraperitoneally. This potentiation is 18 and 41 % in the case of the compounds of Examples 7a and 2, respectively, administered beforehand at a dose of 30 mg/kg per os. Despite a more intense activity of facilitation of noradrenergic neurotransmission, the compounds of the present invention are less active, and therefore less sedative, than the reference products. That essential difference is greater in the case of sleep induced in mice by sodium barbitone (at 270 mg/kg i.p.). The compounds of the invention reduce significantly the sleeping time by from 10 to 30 % at a dose of 30 mg/kg i.p. or p.o., while bifemelane at the same dose increases barbitone narcosis systematically by 30 %, and viloxazine, administered at a dose of 30 mg/kg i.p., increases that barbitone narcosis by 6 %. Thus the compounds of the present invention can be used in the case of ischaemic

syndrome or in the case of cerebral ageing, because they act against the consequences of a reduction in blood flow or oxygenation, two of the pathological components weakening the brain. Their protective effect, being due, inter alia, to an improvement in noradrenergic neurotransmission, permits them to ameliorate the phenomena of reduction in attention, alertness and vigilance, and also the depressive and amnesic states which always accompany cerebral vascular accident and ageing.

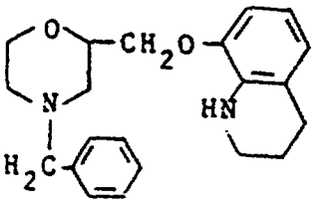
The present invention relates also to pharmaceutical compositions containing as active ingredient a compound of the general formula I or one of its physiologically tolerable salts, mixed or associated with a suitable pharmaceutical excipient, such as, for example, glucose, lactose, starch, talc, ethylcellulose, magnesium stearate or cocoa butter.

The pharmaceutical compositions so obtained are generally presented in dosage form and may contain from 1 to 100 mg of active ingredient. They may, for example, be in the form of tablets, dragées, gelatin capsules, suppositories, or injectable or drinkable solutions and may be administered orally, rectally or parenterally, as appropriate, at a dose of from 1 to 100 mg/kg, from 1 to 3 times per day.

The following Examples illustrate the present invention; the NMR constants of the products obtained being grouped in Table 1.

EXAMPLE 1:

R,S-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



2.75 g of 50 % sodium hydride in oil, which have previously been washed with benzene, are added to a solution of 7.25 g of 8-hydroxyquinoline in 200 ml of anhydrous dimethylformamide and then the mixture is heated for 2 hours at 60°C. 13 g of 2-chloromethyl-4-benzylmorpholine (b.p./$_{0.05}$=120-124°C; n_D^{20} = 1.5355) are then added and heating is continued for 16 hours at 110°C. The mixture is then cooled and concentrated to dryness. The residue is taken up in 50 ml of methylene chloride and 20 ml of water, decanting is carried out and the organic layer is evaporated. 6.9 g of oily product are obtained which are purified by flash chromatography on 1250 g of SiO_2 using the system CH_2Cl_2-CH_3OH (95:5). 4.9 g of 8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline are finally obtained in amorphous form (the NMR constants of which are given in Table 2). A solution of 16.2 g of the product obtained previously in solution in 486 ml of ethanol is hydrogenated for 24 hours under a hydrogen pressure of approximately $5x10^5$ Pa in the presence of 97.2 ml of N HCl and 1.7 g of 5 % Rh/C as catalyst. When reduction is complete, the catalyst is filtered off and the solvent is evaporated off under reduced pressure. The oily residue is treated with 50 ml of CH_2Cl_2 and 50 ml of 10 % Na_2CO_3. After decanting and evaporating the organic portion, the oily residue is purified by flash chromatography on 550 g of SiO_2 using the system CH_2Cl_2-$CH_3COOC_2H_5$ (90:10).

9.9 g of pure 8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are recovered, a portion of which is converted into the dihydrochloride by N HCl. The following products were prepared in the same manner:

a) R,S-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride, the m.p. of which (capillary) = 229-235°C

b) R,S-8-[(4-methyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

c) R,S-8-[(4-ethyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

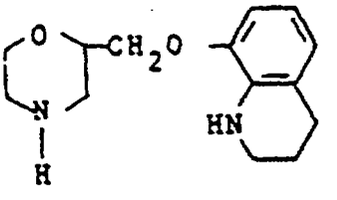
d) R,S-8-[(4-propyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

e) R,S-8-[(4-cyclopentyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, m.p. (capillary) of the corresponding dihydrochloride = 198-205°C

f) R,S-8-[(4-p-chlorobenzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

EXAMPLE 2:

R,S-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



A solution of 5 g of R,S-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (prepared according to Example 1) in 100 ml of ethanol is subjected to hydrogenolysis under a hydrogen pressure of approximately 4×10^5 Pa, in the presence of 0.4 g of 20 % $Pd(OH)_2$ on carbon, for 20 hours at 50°C. At the end of that period,

the catalyst is filtered off and the solvent is evaporated off under reduced pressure. The oily residue is chromatographed on 150 g of SiO_2 using the system CH_2Cl_2-CH_3OH (70:30). 3.9 g of pure 8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are finally obtained in amorphous form and are converted into the dihydrochloride using N HCl; m.p. (capillary): 228-231°C.

The following products were prepared in the same manner:

a) $S^{(+)}$-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride; the procedure being as follows:

α) A solution of 57 g of $S^{(+)}$-2-tosyloxymethyl-4-benzylmorpholine and 32 g of the potassium salt of 8-hydroxyquinoline (prepared when required from an equimolar solution of 8-hydroxyquinoline and potassium hydroxide, in ethanol) in 900 ml of dimethylformamide is heated at 110°C for 20 hours. At the end of the reaction, the solvent is evaporated off under reduced pressure and the residue is taken up in 300 ml of CH_2Cl_2. The organic solution is washed with 0.5N sodium hydroxide solution, washed with water and dried over Na_2SO_4. After evaporating the solvent, the oily residue is purified by flash chromatography on 1200 g of silica using ethyl acetate as eluant. After concentrating the fractions, 50.3 g of $S^{(+)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline are obtained, $\alpha_D^{25.5}$ = +6.5°[1] (c=2 MeOH).

By operating in the same manner and starting from $R^{(-)}$-2-tosyloxymethyl-4-benzylmorpholine, $R^{(-)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline is obtained, $\alpha_D^{25.5}$ = -6.4°[2] (c=2 MeOH).

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[1]Translator's note: the French text here (and in similar instances elsewhere) reads "+6°, 5" and presumably is a typing error and should read "+6.5°", although this is not entirely certain.

[2]Please see Translator's note 1.

ß) 48.2 g of the $S^{(+)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline obtained above are dissolved in 900 ml of methanol. 288 ml of N HCl are added and the quinoline ring structure is hydrogenated under $6x10^5$ Pa of hydrogen in the presence of 4.5 g of 5 % rhodium/C. After 2 hours, when the theoretical quantity of hydrogen has been absorbed, the catalyst is filtered off, 4.5 g of 10 % palladium/carbon are added and hydrogenation is carried out at 60°C under $6x10^5$ Pa of hydrogen. The theoretical quantity of hydrogen being absorbed after 6 hours, filtering is carried out and the solvent is evaporated off, the oily residue is taken up in 300 ml of CH_2Cl_2 and the whole is washed with a 10 % Na_2CO_3 solution. Decanting is carried out and the organic phase is dried over Na_2SO_4; evaporation is carried out and the residue is purified by flash chromatography on 1260 g of silica (eluant: CH_2Cl_2-methanol, 80:20). The fractions collected are concentrated under reduced pressure. 31 g of resinous base are obtained which are dissolved in 200 ml of ethanol. After adding dry HCl, to an acid pH, 600 ml of anhydrous ether are added. 38 g of amorphous product are dried and crystallised from 77.6 ml of propanol to which 3.88 ml of water have been added. 32.5 g of the dihydrochloride of $S^{(+)}$-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are finally obtained, m.p. (capillary): 174-178°C; $\alpha_D^{25.5}$ = +8.4°[3] (c=2 pyridine).

b) $R^{(-)}$-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, and its dihydrochloride, the physical constants of which are: m.p. (capillary) = 173-175°C; $\alpha_D^{22.5}$ = -8.85° (c=2 pyridine), prepared in accordance with the procedure described in Example 2a from $R^{(-)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline, $\alpha_D^{25.5}$ = -6.4° (c=2 methanol), which was itself prepared from

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[3]Please see Translator's note 1.

$R^{(-)}$-2-tosyloxymethyl-4-benzylmorpholine.

The $S^{(+)}$- and $R^{(-)}$-2-tosyloxymethyl-4-benzylmorpholine, the starting materials of Examples 2a and 2b, were prepared from R,S-2-tosyloxymethyl-4-benzylmorpholine, the starting material of Example 2, which was itself prepared in the following manner:

62.15 g of R,S-2-hydroxymethyl-4-benzylmorpholine are dissolved in 1 litre of pyridine. The solution is cooled to +5°C and 57.2 g of tosyl chloride are added without the temperature exceeding +10°C. The solution is left in the refrigerator for 20 hours and then the pyridine is evaporated off under reduced pressure at 30°C.

The residue is taken up in CH_2Cl_2 and the whole is washed with a 10 % Na_2CO_3 solution and dried over Na_2SO_4, and the solvent is evaporated off under reduced pressure. The residue is taken up in heptane. The product crystallises. Drying is carried out and 90.7 g of white crystals melting (Kofler) at 74°C are obtained.

The enantiomers are separated in accordance with the method of R. HOWE et al., J. Med. Chem. (1976), 19, 1674-1676, starting from S-tosylglutamic acid, m.p. Kofler): 125°C.

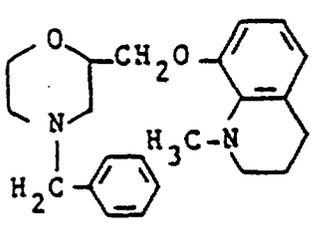
The physical constants of the enantiomers obtained are:

$S^{(+)}$ isomer: m.p. $_{(K)}$:71°C, α_D^{21} = +21° (c=2 methanol)

$R^{(-)}$ isomer: m.p. $_{(K)}$: 70°C, α_D^{21} = -19.8° (c=2 methanol)

EXAMPLE 3:

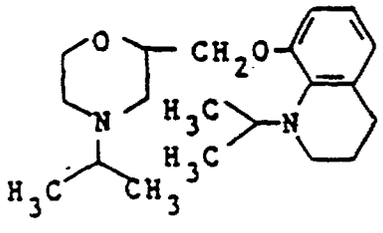
R,S-1-methyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



4.5 g of methyl iodide and 4.3 g of K_2CO_3 are added to a solution of 9.6 g of R,S-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (prepared according to Example 1) in 100 ml of acetone, and the mixture is heated under reflux for 3 hours. The salt is then filtered off and the solvent is evaporated off under reduced pressure. The residue is taken up in 50 ml of CH_2Cl_2 and 50 ml of water. After decanting, the organic portion is evaporated off and the oily residue is chromatographed on 850 g of SiO_2 using the system CH_2Cl_2-CH_3OH (97-3). 4 g of R,S-1-methyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are isolated in amorphous form and are converted into the dihydrochloride using N HCl.

The following products were prepared in the same manner:
a) R,S-1-isopropyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride
b) R,S-1-isopropyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline
c) R,S-1-isobutyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline
d) R,S-1-methyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride, the m.p. (capillary) of which = 228-231°C.

EXAMPLE 4:
R,S-1-isopropyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



A solution of 8.1 g of R,S-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (prepared according to Example 2) in 170 ml of ethanol is heated under reflux for 20 hours with 19.5 g of isopropyl iodide and 10 ml of triethylamine.

At the end of that period, the solvent is removed under reduced pressure and the residue is taken up in 50 ml of CH_2Cl_2 and 50 ml of water. After decanting, the solvent is evaporated off. The oily residue is chromatographed on 600 g of SiO_2 using the system CH_2Cl_2-CH_3OH (96:4). 7.5 g of 1-isopropyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are isolated in amorphous form and are converted into the dihydrochloride (also amorphous) using N HCl.

The following products were prepared in the same manner:

a) R,S-1-methyl-8-[(4-methyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

b) R,S-1-ethyl-8-[(4-ethyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

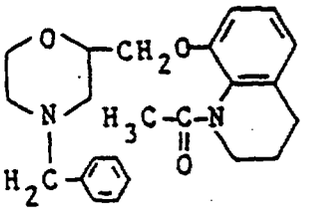
c) R,S-1-isobutyl-8-[(4-isobutyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

d) R,S-1-benzyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

e) R,S-1-allyl-8-[(4-allyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

EXAMPLE 5:

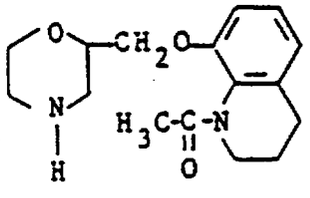
R,S-1-acetyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



2.86 g of acetyl chloride are added at 5°C to a solution of 12.5 g of R,S-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (prepared according to Example 1) in 100 ml of anhydrous tetrahydrofuran containing 5.5 ml of triethylamine. The whole is stirred for 1 hour at that temperature and then heated at 45°C for one and a half hours. The solvent is then evaporated off and the residue is taken up in 50 ml of CH_2Cl_2 and 50 ml of 10 % sodium carbonate. After decanting, the organic portion is evaporated off. The residue, which weighs 14.3 g, is purified by flash chromatography on 2.50 g of SiO_2 using the system CH_2Cl_2-CH_3OH (95:5). Finally, 13.3 g of R,S-1-acetyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are isolated in the form of a resin and are converted into the amorphous hydrochloride.
The following products were prepared in the same manner:

a) R,S-1-acetyl-8-[(4-acetyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline
b) R,S-1-acetyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its hydrochloride
c) R,S-8-[(4-acetyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its hydrochloride

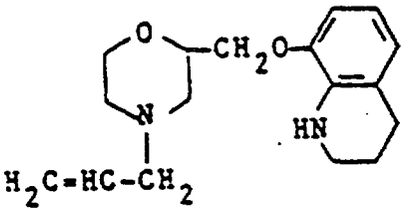
EXAMPLE 6:
R,S-1-acetyl-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



A solution of 8.6 g of R,S-1-acetyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (prepared according to Example 5) in 170 ml of ethanol are subjected to hydrogenation at ambient temperature in the presence of 0.86 g of 20 % $Pd(OH)_2/C$, under a hydrogen pressure of approximately $6x10^5$ Pa. After 20 hours, the theoretical quantity of hydrogen has been absorbed. The catalyst is filtered off and the solution is concentrated under reduced pressure. The residue is chromatographed on 235 g of SiO_2 using the system CH_2Cl_2-CH_3OH (85:15). 5.7 g of R,S-1-acetyl-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline are obtained in the form of a resin and are converted into the amorphous hydrochloride.

EXAMPLE 7:

R,S-8-[(4-allyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline



By proceeding as in Example 4 and starting from 1-acetyl-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline (according to Example 6) and from allyl bromide there is obtained 1-acetyl-8-[(4-allyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline which is hydrolysed with NaOH in ethanolic solution to give R,S-8-[(4-allyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline; m.p. (Kofler) of the corresponding dihydrochloride = 188°C.

The following products were prepared in the same manner:

a) R,S-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-

tetrahydroquinoline and its dihydrochloride

b) R,S-8-[(4-isobutyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

c) R,S-8-[(4-p-chlorobenzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline

d) R,S-1-methyl-8-(2-morpholinylmethoxy)-1,2,3,4-tetrahydroquinoline and its dihydrochloride, the m.p. (capillary) of which = 193-198°C.

e) R,S-8-[(4-piperonyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride (amorphous)

f) $S^{(+)}$-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride, of which the m.p. (capillary) = 140-145°C and α_D^{22} = +30.7° (c=2 pyridine) prepared according to the method of Example 7 starting from $S^{(+)}$-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1-acetyl-1,2,3,4-tetrahydroquinoline, α_D^{22} = +13.9° (c=2 pyridine), which was itself prepared from isopropyl iodide and $S^{(+)}$-8-(2-morpholinylmethoxy)-1-acetyl-1,2,3,4-tetrahydroquinoline, α_D^{22} = +13.5° (c=2 pyridine), which was itself prepared, according to the method of Example 6, by debenzylation of $S^{(+)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-1-acetyl-1,2,3,4-tetrahydroquinoline, α_D^{22} = +24.7° (c=2 pyridine), which was itself prepared according to the method of Example 5, starting from acetyl chloride and $S^{(+)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, α_D^{22} = +21° (c=2 pyridine), which was itself prepared according to the method of Example 1.

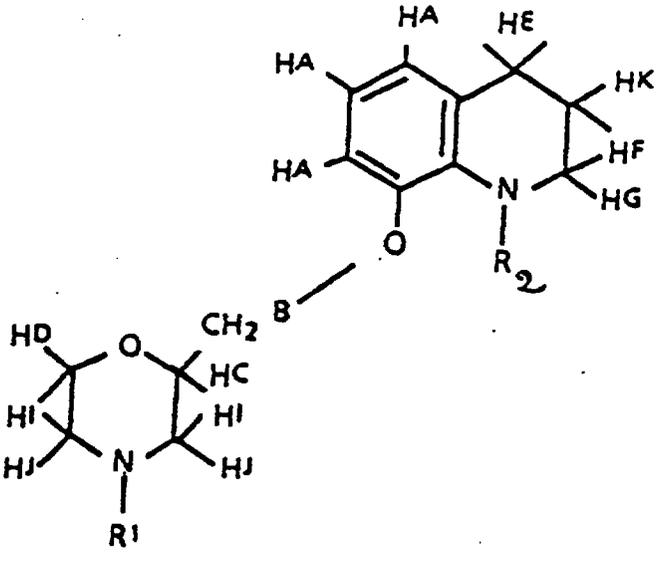
g) $R^{(-)}$-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline and its dihydrochloride, the m.p. (capillary) of which = 135-140°C and α_D^{22} = -29.5° (c=2 pyridine) prepared according to the method of Example 7 starting from $R^{(-)}$-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1-acetyl-1,2,3,4-tetrahydroquinoline, α_D^{22} = -14°C (c=2 pyridine), which was itself prepared

from isopropyl iodide and $R^{(-)}$-8-(2-morpholinylmethoxy)-1-acetyl-1,2,3,4-tetrahydroquinoline, $\alpha_D^{22} = -14.9°$ (c=2 pyridine), which was itself prepared according to the method of Example 6, by debenzylation of $R^{(-)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-1-acetyl-1,2,3,4-tetrahydroquinoline, $\alpha_D^{22} = -24.7°$ (c=2 pyridine), itself prepared according to the method of Example 5, starting from acetyl chloride and $R^{(-)}$-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, $\alpha_D^{22} = -21°$ (c=2 pyridine), which was itself prepared according to the method of Example 1.

The NMR constants of the products exemplified above are grouped in the following Table.

TABLE 1

NMR of the products forming the subject of the preceding Examples



R_2=H; R_1=$CH_2C_6H_5$ (Example 1)

($CDCl_3$)
δ = 7.3 (s, 5H, $CH_2C_6\underline{H}_5$); 6.3 to 6.8 (m, 3H, H^A); 3.6 to 4.3 (m, 5H, H^B, H^C, H^D) 3.5 (s, 2H, $\underline{CH}_2$, C_6H_5) 3.25 (t, 2H, H^F, H^G); 1.7 to 3.1 (m, 8H, H^E, H^I, H^J, H^K); 1 proton N$\underline{H}$ exchangeable with D_2O at approximately 3.4 ppm

R_2=R_1=H (Example 2)

($CDCl_3$)
δ = 6.4 to 6.8 (m, 3H, H^A); 3.6 to 4.2 (m, 5H, H^B, H^C, H^D); 2.4 to 3.6 (m, 10H of which two exchangeable with D_2O: R_2 and R_1; H^E, H^F, H^G, H^I, H^J); 1.9 (m, 2H, H^K)

R_2=CH_3; R_1=$CH_2CH_6H_5$ (Example 3)

($CDCl_3$)
δ = 7.3 (s, 5H, $CH_2C_6\underline{H}_5$) 6.5 to 7.1 (m, 3H, H^A) 3.5 to 4.4 (m, 5H, H^B, H^C, H^D) 3.5 (s, 2H, $C\underline{H}_2C_6H_5$) 2.5 to 3.4 (m, 6H, H^E, H^F, H^G, H^I) 2.7 (s, 3H, N-$C\underline{H}_3$) 1.4 to 2.5 (m, 4H, H^K, H^J)

R_2=R_1=$(CH(CH_3)_2$ (Example 3a)

($CDCl_3$)
δ = 6.6 to 7.1 (m, 3H, H^A) 3.6 to 4.5 (m, 5H, H^B, H^C, H^D); 2.1 to 3.6 (m, 10H, H^E, H^F, H^G, H^I, H^J; 2$\underline{CH}(CH_3)_2$) 1.9 (m, 2H, H^K) 1.15 - 1.05 (two doublets, 12H, 2CH($\underline{CH}_3)_2$)

R_2=$COCH_3$; R_1=$CH_2C_6H_5$ (Example 5)

($CDCl_3$)
δ = 7.4 (s, 5H, $CH_2C_6\underline{H}_5$) 6.6 to 7.3 (m, 3H, H^A) 4.6 (m, 1H, H^G) 3.6 to 4.2 (m, 5H, H^B, H^C, H^D) 3.6 (s, 2H, $\underline{CH}_2C_6H_5$) 1.4 to 3.2 (m, 9H, H^E, H^F, H^I, H^J, H^K) 2.0 (s, 3H, CO$\underline{CH}_3$)

R_1=R_2=$COCH_3$ (Example 5a)

($CDCl_3$)
δ = 6.6 to 7.6 (m, 3H, H^A); 4.5 (m, 3H, H^G, H^J) 3.35 to 4.2 (m, H, H^B, H^C, H^D) 2.2 to 3.35 (m, 5H, H^E, H^F, H^I) 2.0 and 2.1 (two singlets 6H; $2COC\underline{H}_3$) 1.8 (m, 2H, H^K)

R_2=$COCH_3$;R_1=$CH(CH_3)_2$ (Example 5b)

($CDCl_3$)
δ = 6.3 to 7.4 (m, 3H, H^A) 4.5 (m, 1H, H^G) 3.3 to 4.1 (m, 5H, H^B, H^C, H^D) 2.0 to 3.3 (m, 8H, H^E, H^F, H^I, H^J; $\underline{CH}(CH_3)_2$) 2.0 (s, 3H, $CO\underline{CH}_3$) 1.9 (m, 2H, H^K); 1.1 (d, 6H, $CH(\underline{CH}_3)_2$)

R_2=H; R_1=$COCH_3$ (Example 5c)

($CDCl_3$)
δ = 6.4 to 6.9 (m, 3H, H^A); 4.5 (m, 2H, H^J) 2.9 to 4.1 (m, 9H, H^B, H^C, H^D, H^I, H^F, H^G) 2.8 (t, 2H, H^E) 2.1 (s, 3H, $CO\underline{CH}_3$) 1.9 (m, 2H, H^K) 1 proton NH, not detected.

R_2=$COCH_3$; R_1=H (Example 6)

($CDCl_3$)
δ = 6.3 to 7.5 (m, 3H, H^A); 4.5 (m, 1H, H^G); 3.5 to 4.1 (m, 5H, H^B, H^C, H^D); 2.2 to 3.5 (m, 8H of which one exchangeable with D_2O: R_1; H^E, H^F, H^G, H^I, H^J); 2.0 (s, 3H, $CO\underline{CH}_3$) 1.9 (m, 2H, H^K)

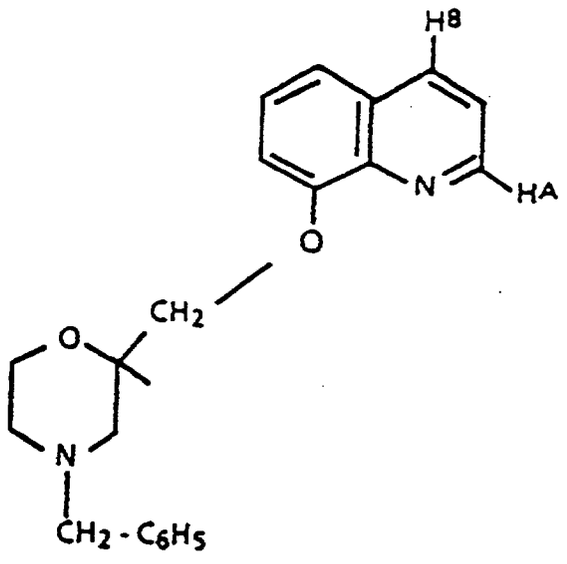
R_2=H; R_1=$CH(CH_3)_2$ (Example 7a)

($CDCl_3$)
δ = 6.5 to 7.1 (m, 3H, H^A); 4.6 (m, 1H exchangeable with D_2O R_2= $\underline{H}$); 3.6 to 4.4 (m, 5H, H^B, H^C, H^D); 3.4 (t, 2H,

H^F, H^G) 1.6 to 3.1 (m, 9H, H^I, H^J, H^E, H^K; $C\underline{H}(CH_3)_2$) 1.1 (d, 6H, $CH(\underline{CH_3})_2$)

TABLE 2

NMR of 8-[(4-benzyl-2-morpholinyl)-methoxy]-quinoline (intermediate product in Example 1)



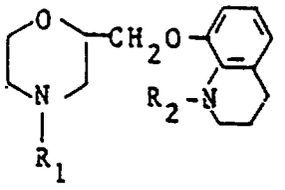
($CDCl_3$)

δ = 8.9 (d, resolved 1H, H^A) 8.1 (d, resolved, 1H, H^B) 7.3 (s, 5H, $CH_2C_6\underline{H}_5$) 6.9 to 7.3 (m, 4H aromatic) 3.6 to 4.5 (m, 5H, $2C\underline{H}_2$-O and $C\underline{H}$-O) 3.5 (s, 2H, $C\underline{H}_2C_6H_5$) 1.9 to 3.2 (m, 4H, $2N-C\underline{H}_2$)

* C L M S *

CLAIMS

1. Morpholine compounds of the general formula I:



in which:

R_1 represents:

a hydrogen atom;

a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond;

an aralkyl radical of the general formula:

$$Ar-(CH_2)_m-$$

in which:

Ar represents an aryl radical optionally substituted by one or more halogen atoms, alkyl or alkoxy radicals each containing from 1 to 5 carbon atoms, or radicals of the formula $-O-(CH_2)_n-O-$ in which n has the value 1 or 2; and

m represents an integer from 1 to 3;

a cycloalkyl radical containing 5 or 6 carbon atoms; or

an acyl radical of the formula: R'-CO- in which R' represents an alkyl radical containing 1 or 2 carbon atoms; and

R_2 represents:

a hydrogen atom;

a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond;

an aralkyl radical of the general formula: $Ar-(CH_2)_m-$ in which Ar and m are as defined above; or

an acyl radical of the formula R'-CO- in which R' is as defined above;

and their enantiomers.

2. The physiologically tolerable salts of the compounds of claim 1 with suitable acids.

3. R,S-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

4. R,S-8-[(4-cyclopentyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

5. R,S-8-[(4-p-chlorobenzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

6. R,S-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, its dihydrochloride and its enantiomers.

7. R,S-1-methyl-8-[(4-benzyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

8. R,S-1-isopropyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

9. R,S-1-acetyl-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

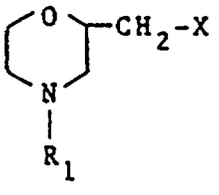
10. R,S-1-acetyl-8-[(2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

11. R,S-8-[(4-allyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline.

12. R,S-8-[(4-isopropyl-2-morpholinyl)-methoxy]-1,2,3,4-tetrahydroquinoline, its dihydrochloride and its enantiomers.

13. Process for the preparation of the compounds of claim 1, characterised in that:

a substituted morpholine of the general formula II:



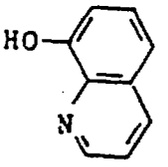
(II)

in which:

R_1 is as defined in claim 1, and

X represents a halogen atom or a tosyloxy radical,

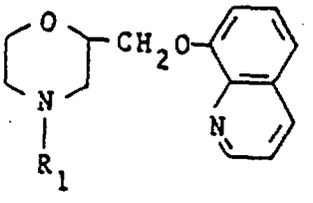
is reacted with a hydroxyquinoline of the formula III:



(III),

which has previously been converted into an alkali metal salt,

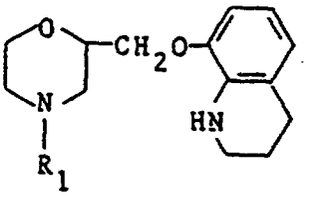
to obtain a compound of the general formula IV:



(IV)

in which R_1 is as defined in claim 1;

which is then hydrogenated to obtain a compound of the formula Ia:



(Ia)

in which R_1 is as defined in claim 1,

which is then condensed with a compound of the general formula V:

$$R'_2\text{-}X' \qquad (V)$$

in which:

R'_2 represents

a straight-chain or branched alkyl radical containing from 1 to 6 carbon atoms and optionally having a double bond,

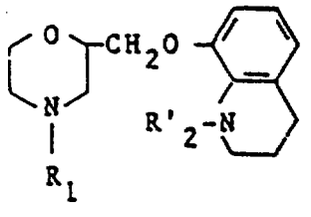
an aralkyl radical of the general formula: $Ar-(CH_2)_m-$, in which Ar and m are as defined in claim 1, and,

at the same time, X' represents a bromine or iodine atom or a tosyloxy radical; or

R'_2 represents an acyl radical of the formula R'-CO- in which R' is as defined in claim 1, and,

at the same time, X' represents a chlorine atom;

to obtain a compound of the general formula Ib:



(Ib)

in which R_1 and R'_2 are as defined above.

14. The preparation process according to claim 13, characterised in that the reaction of compounds II and III is carried out in a solvent selected from the tertiary amides, at a temperature of from 90 to 110°C in the presence of an acceptor of the hydracid formed in the course of the reaction.

15. A process according to claim 14, characterised in that the acceptor is sodium hydride.

16. A process according to claim 13, characterised in

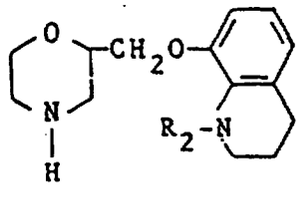
that the hydrogenation of compound IV is carried out under low pressure in the presence of a catalyst belonging to the metals of group VIII, in a solvent such as the low-molecular-weight alcohols, at a temperature of from 20 to 60°C.

17. Process according to claim 16, characterised in that the hydrogenation is carried out under a hydrogen pressure of from 1×10^5 to 6×10^5 Pa, in the presence of Rh/C or $Pd(OH)_2/C$ as catalyst.

18. Process according to claim 13, characterised in that the condensation of compounds (Ia) and V is carried out in a solvent selected from the aromatic hydrocarbons or polar solvents, at a temperature of from 20 to 80°C in the presence of an acceptor of the hydracid formed.

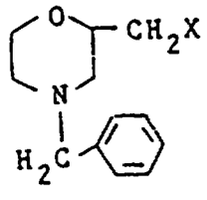
19. Process according to claim 18, characterised in that the acceptor is a tertiary amine.

20. Process for the preparation of the compounds of claim 1 corresponding to the general formula I':



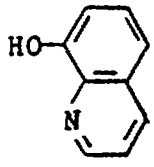
(I')

in which R_2 is as defined in claim 1, characterised in that a morpholine of the general formula II':



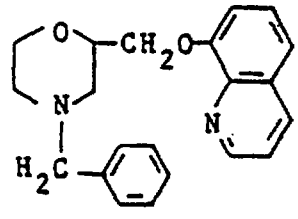
(II')

in which X is as defined in claim 13, is condensed with a hydroxyquinoline of the formula III:



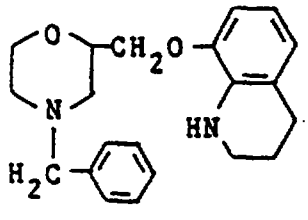
(III)

to obtain a compound of the formula IV':



(IV')

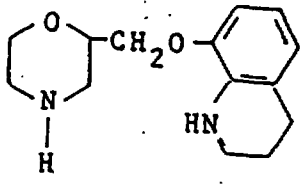
which is subjected to catalytic hydrogenation under low pressure to obtain a compound of the formula IV":



(IV")

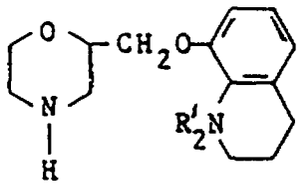
which is:

either debenzylated directly by hydrogenolysis to give the compound of the formula I'a:



(I'a)

or is first alkylated or acylated by means of R'_2X', which is as defined in claim 13, and then debenzylated by catalytic hydrogenation under low pressure to obtain the compound of the general formula I'b



(I'b)

in which R'_2 is as defined in claim 13.

21. Pharmaceutical compositions containing as active ingredient a compound according to claims 1 to 12, with suitable pharmaceutical excipients.

22. Pharmaceutical compositions according to claim 21, presented in a form suitable especially for the treatment of ischaemic syndromes and cerebral ageing.