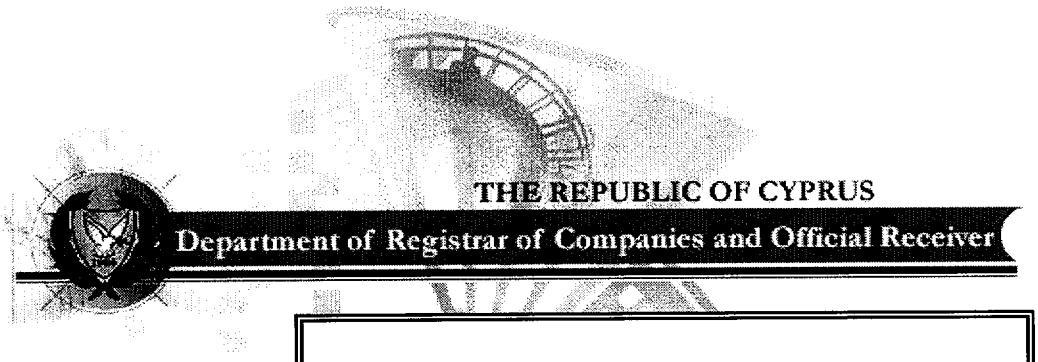

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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PUBLICATION NUMBER

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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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(56) Documents cited
EP 0058146 A
LF Fieser and M Fieser, Advanced organic chemistry, (New York, 1961) p.365

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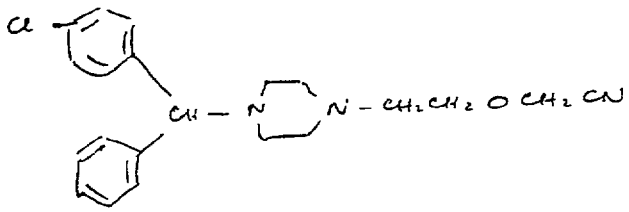
(54) Process for preparation of a 1-piperazine-ethoxyacetic acid

(57) A process for the preparation of 2-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride, wherein 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium by a base or by an acid, and, if desired, the acid thus obtained is converted into its dihydrochloride.

The compound



is claimed *per se*.

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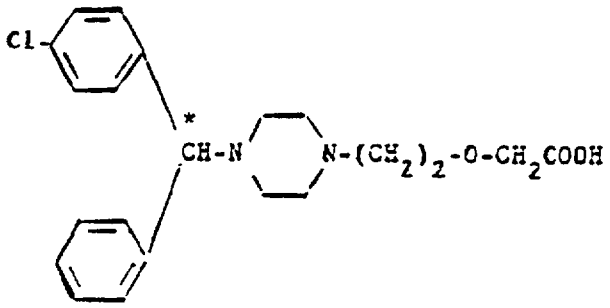
2225321

A process for the preparation of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride.

The present invention relates to a new process for the preparation of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy-acetic acid of the formula



(I)

in wich the asterisk indicates the centre of asymmetry of the molecule, and its dihydrochloride.

The compound of the formula I may exist in the levorotatory form, the dextrorotatory form or a mixture of the levorotatory and dextrorotatory forms.

The present invention relates to the synthesis of the compound of the formula I in these various forms.

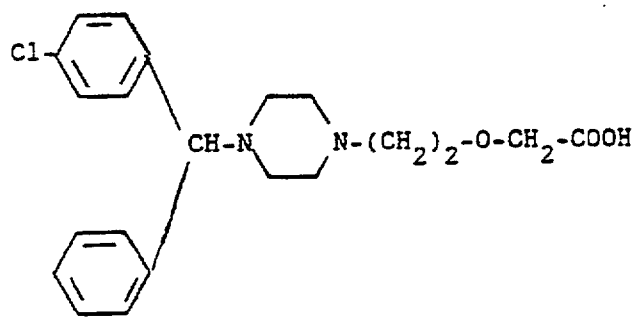
The dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid, also known by the generic name of cetirizine, has recently been introduced as a new medicament for the treatment of allergic syndromes, such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria etc..

European Patent No.58,146 in the name of the Applicant describes the synthesis of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy-acetic acid and its dihydrochloride. In this synthesis, the starting substance is 1-[(4-chlorophenyl)phenylmethyl]-piperazine, which is reacted with methyl (2-chloroethoxy)-acetate to give methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetate in a yield of 27.8%. This methyl ester is then subjected to hydrolysis with an inorganic base (sodium or potassium hydroxide) to give the sodium or potassium salt, which is easily converted into the free acid, and then into cetirizine dihydrochloride.

The major disadvantage of this synthesis is that the overall yield of 2-[2-[4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride is only 10.6%, based on the amount of 1-[(4-chlorophenyl)-phenylmethyl]-piperazine employed.

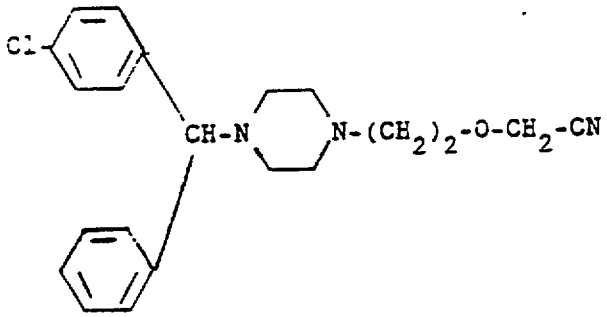
According to the present invention, a new process for the synthesis is provided, which enables 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride to be prepared with better yields.

According to the present invention, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid of the formula



(I)

and its dihydrochloride are prepared by a process which is characterized in that 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula

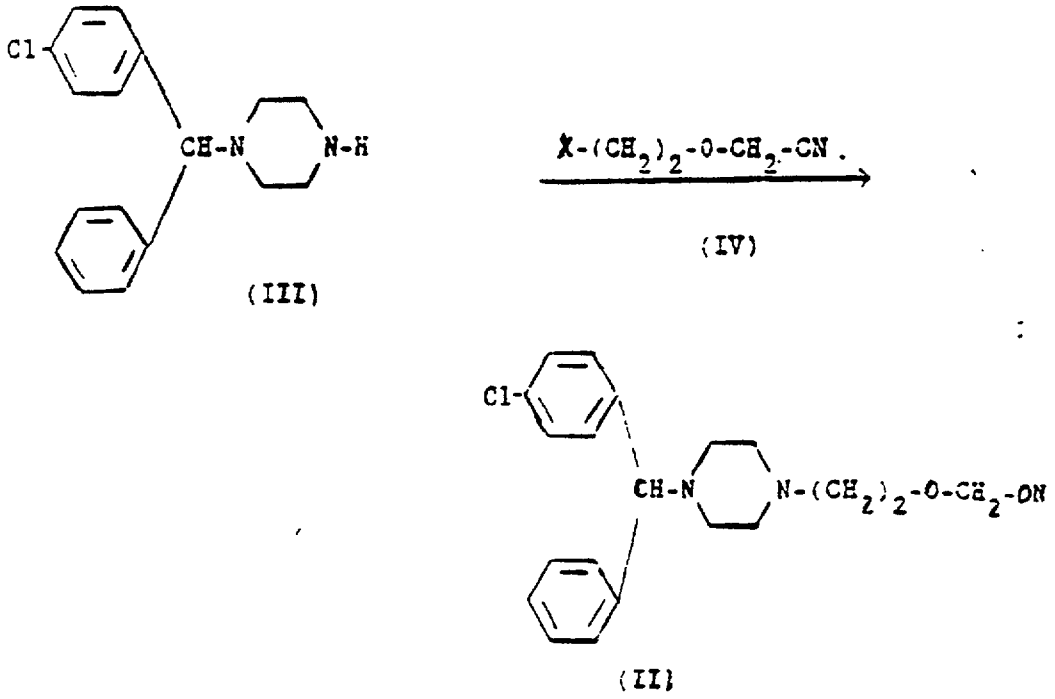


(II)

is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium by a base or by an acid, and in that, if desired, the acid of the formula I thus obtained is converted into its dihydrochloride.

2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula II used as the starting material is a new compound which is easily obtained by reacting 1-[(4-

chlorophenyl)phenylmethyl]-piperazine of the formula III with 2-haloethoxyacetonitrile of the formula IV in accordance with the equation:



(III) (IV) (II)

in which X represents a halogen atom.

This reaction is carried out in the presence of an acid acceptor, such as an alkali metal carbonate, and optionally in the presence of a small amount of an alkali metal iodide to accelerate the reaction, in an inert organic solvent, such as an alcohol (for example n-butanol etc.), preferably at a temperature close to the reflux temperature.

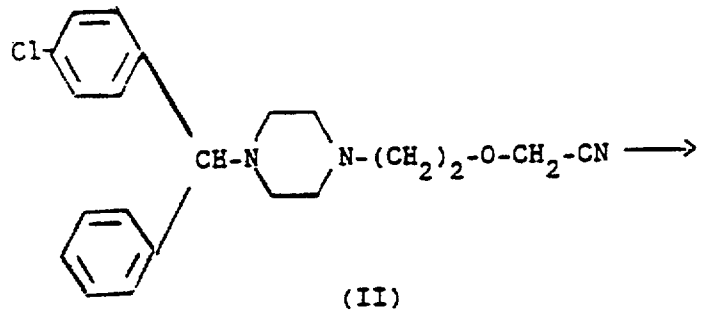
When an optically active 1-[(4-chlorophenyl)phenylmethyl]-piperazine of the formula III instead of the racemate is used in this reaction, the starting enantiomer can be obtained by resolution of the corresponding racemic compound by methods which are known per se.

Of the optically active acids which can be used for this resolution, tartaric acid is preferably used.

As regards the 2-haloethoxyacetonitriles of the formula IV, and more particularly 2-chloroethoxyacetonitrile, these products can be prepared in accordance with the method described by E.J. SALMI et al., Suomen Kemistilehti, 17B,(1944),17-19 (Chem. Abstr. 40,(1946),6491).

The 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-

acetic acid of the formula I is obtained by hydrolysis of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula II in accordance with the equation:



(II) (I)

This hydrolysis can be carried out by two operating methods, one in a basic medium and the other in an acid medium.

1. Hydrolysis of the nitrile in a basic medium

The nitrile of the formula II is heated in the presence of an inorganic base, such as an alkali metal hydroxide, in an aqueous, alcoholic or aqueous-alcoholic medium (methanol, ethanol etc.), at a temperature between 60°C and the reflux temperature of the reaction mixture.

The acid of the formula I formed is present in the reaction mixture in the form of its alkali metal salt, from which the acid is liberated by acidification of the reaction mixture by means of an inorganic acid (such as hydrochloric acid). The acid of the formula I is then extracted by means of an organic solvent (dichloromethane, toluene etc.) and crystallized for isolation.

Finally, the acid of the formula I is converted into the dihydrochloride by a process which is known per se.

2. Hydrolysis of the nitrile in an acid medium

The nitrile of the formula II is heated in the presence of an inorganic acid, such as hydrochloric acid, preferably in an aqueous medium, at a temperature between 60°C and the reflux temperature of the reaction mixture. The acid of the formula I formed is then extracted from the reaction mixture by means of an organic solvent (dichloromethane, toluene etc.) and purified by crystallization.

The free acid of the formula I is then converted into the dihydrochloride by a process which is known per se.

This new synthesis process gives yields of cetirizine dihydrochloride,

calculated with respect to the amount of 1-[(4-chlorophenyl)phenylmethyl]-piperazine employed, of 60% or more by acid hydrolysis and 65% or more by basic hydrolysis. Moreover, very high yields of the optically active forms of this compound can be obtained by this process. These higher yields starting from 1-[4-chlorophenyl)phenylmethyl]-piperazine constitute a considerable technical advance with respect to the process described in European Patent No.58,146.

The following examples are given for the purpose of illustrating the invention.

Example 1. Preparation of racemic 2-[2-[4[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethoxy]-acetic dihydrochloride of the formule I.

1. Racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula II.

200 ml of n-butanol, 43.05 g (0.15 mole) of racemic 1-[(4-chlorophenyl)phenylmethyl]-piperazine, 24 g (0.174 mole) of 2-chloroethoxyacetonitrile, 26.1 g (0.246 mole) of sodium carbonate and 0.78 g (0.0047 mole) of potassium iodide are introduced successively into a three-necked round-bottomed flask equipped with a mechanical stirrer, a condenser and a thermometer. The mixture is heated at 110°C for 11 hours while stirring, cooled, filtered and concentrated on a rotary evaporator. 60 g of a yellow-brown oil are isolated and are chromatographed over a column containing 1 kg of silica using a mixture containing, by volume, 98% dichloromethane and 2% methanol. This desired nitrile is collected in two fractions, from which the solvents are removed and the purity of which is measured by high performance liquid chromatography.

Racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile is thus obtained in two fractions, one of which of 33.6 g has a purity of 100% and the other of which of 14.4 g has a purity of 97.4%.

Yield: 86.4%

The product obtained can be characterized in the form of its dihydrochloride prepared from an ethanolic solution of gaseous hydrochloric acid.

M.P.: 201-202°C.

Analysis for $C_{21}H_{24}ClN_3O.2HCl$ in %

calc.: C 56.96 H 5.91 N 9.48 Cl^- 16.01 $Cl^{tot.}$ 24.02

found: C 57.21 H 6.00 N 9.49 Cl^- 15.78 $Cl^{tot.}$ 23.76

2. Racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid of the formula I (by hydrolysis in a basic medium)

250 ml of ethanol, 23 g (0.062 mole) of racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile and 31 ml of a 4N ethanolic solution of potassium hydroxide are introduced successively into a three-necked round-bottomed flask equipped with a mechanical stirrer, a condenser and a thermometer. The reaction mixture is refluxed for 10 hours, while stirring. The reaction mixture is allowed to cool and its pH is brought to 6 by addition of 37% concentrated hydrochloric acid. The ethanol is evaporated and the reaction mixture is diluted with 100 ml of water and extracted three times with 200 ml of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and concentrated in a rotary evaporator. An oil is obtained and is allowed to crystallize by addition of 100 ml of 2-butanone, while hot. The solid formed is filtered, washed and dried. 18.9 g of racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid are thus obtained.

18.9 g of the acid thus obtained are resuspended in 150 ml of water; the pH is brought to 0.8 by addition of concentrated hydrochloric acid. The aqueous solution is concentrated on a rotary evaporator and the residue is then diluted by addition of 75 ml of 2-butanone and concentrated again. The addition of 150 ml of 2-butanone to the residue thus obtained causes crystallization of racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. The crystals are filtered off and dried, 21.7 g being obtained.

Yield: 75.9%. M.P.:220.15°C (Differential Scanning Calorimetry; DSC) (decomposition on melting)

Analysis for $C_{21}H_{25}ClN_2O_3.2HCl$ in %

Calc.: C 54.56 H 5.84 N 6.06 Cl^- 15.37 $Cl^{tot.}$ 23.05

found: C 54.60 H 5.86 N 6.02 Cl^- 15.33 $Cl^{tot.}$ 23.26

The overall yield of dihydrochloride of the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid,

calculated with respect to the amount of 1-[(4-chlorophenyl)-phenylmethyl]-piperazine employed, is 65.6%.

3. Racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid of the formula I (by hydrolysis in an acid medium)

45.3 g (0.123 mole) of racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile are introduced into a reactor equipped with a mechanical stirrer, a condenser, a thermometer and a dropping funnel and are heated to 45°C, while stirring. 41 ml of 37% concentrated hydrochloric acid are then introduced dropwise. The temperature of the reaction mixture rises to 92°C; the reaction mixture is heated at 95°C for 90 minutes, while stirring. The reaction mixture is allowed to cool and is concentrated on a rotary evaporator, the residue is taken up in 150 ml of toluene and the reaction mixture is concentrated again on a rotary evaporator. The residue is dissolved in 200 ml of water and the aqueous solution obtained is brought to pH 5 by addition of sodium hydroxide. The solution is extracted three times with 300 ml of dichloromethane. The organic phases are combined and the solvent is removed on a rotary evaporator. The oil thus obtained is allowed to crystallize by being dispersed in 250 ml of 2-butanone, while hot.

The mixture is cooled and filtered and the crystals are dried. 34 g of racemic 2-[2-[4-[(4-chlorophényl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid are thus isolated.

34 g of the acid thus obtained are resuspended in 300 ml of water; the pH is brought to 0.8 by addition of concentrated hydrochloric acid. The aqueous solution is concentrated on a rotary evaporator, the residue is then diluted by addition of 150 ml of 2-butanone and the mixture is concentrated again. The addition of 300 ml of 2-butanone to the residue thus obtained causes crystallization of racemic 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride. The crystals are filtered off and dried, 39.7 g being obtained.

Yield: 70%. M.P.: 227.02°C (DSC) (decomposition on melting).

Analysis for $C_{21}H_{25}ClN_2O_3.2HCl$ in %

Calc.: C 54.56 h 5.84 N 6.06 Cl^- 15.37 $Cl^{tot.}$ 23.05

found: C 54.30 H 5.88 N 6.83 Cl^- 15.56 $Cl^{tot.}$ 23.06

The overall yield of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride, calculated with

respect to the amount of 1-[4-chlorophenyl)phenylmethyl]-piperazine employed, is 60.5%.

Example 2. Preparation of dextrorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride of the formula I.

1. Levorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine of the formula III.

A solution of 300 g (2 moles) of (2R,3R)-tartaric acid in 2 litres of ethanol is heated at 72-74°C and a solution of 286.5 (1 mole) of racemic 1-[(4-chlorophenyl)phenylmethyl]-piperazine in 1 litre of ethanol is added, while stirring. The mixture is refluxed for 5 minutes and then allowed to return to room temperature, while stirring (the desired salt starts to crystallize towards 57°C). The salt obtained is filtered off and recrystallized three times in succession, first in a mixture of 2 litres of ethanol and 0.8 litre of methanol, then in 1 litre of ethanol, and finally in a mixture of 0.5 litre of ethanol, 65 ml of methanol and 5 ml of water. After filtration and drying, 118 g of diastereoisomerically impure 1-[4-chlorophenyl)phenylmethyl]-piperazine (2R,3R)-tartrate are obtained. M.P.: 170.4°C (DSC). $[\alpha]_D^{25}$: + 7.8° (c = 1, methanol).

This salt is then decomposed by addition of a solution of 22 g (0.55 mole) of sodium hydroxide in 750 ml of water. Levorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine thus liberated is extracted several times with dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and concentrated on a rotary evaporator. 80 g of optically impure levorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine are obtained; this product is purified by successive recrystallizations from hexane, to give finally 18.2 g of levorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine. M.P.: 90-92°C.. M.P.: 90.35°C (DSC) $[\alpha]_D^{25}$: -19.4° (c = 1, toluene).

Yield: 12.7%

2. Levorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]-acetonitrile of the formula II.

100 ml of n-butanol, 20 g (0.07 mole) of levorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine, 11.2 g (0.0937 mole) of 2-chloroethoxyacetonitrile, 12.18 g (0.115 mole) of sodium carbonate

and 0.36 g (0.002 mole) of potassium iodide are introduced successively into a three-necked round-bottomed flask equipped with a mechanical stirrer, a condenser and a thermometer. The mixture is heated at 110°C for 7 hours, while stirring, then cooled, filtered and concentrated on a rotary evaporator. 26 g of a yellow-brown oil are isolated and are chromatographed over a column containing 1 kg of silica using a mixture containing by volume, 98% dichloromethane and 2% methanol. 17.8 g of levorotatory 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile are obtained in the form of an oil.

$[\alpha]_{365}^{25}$: -31,8° (c = 1, methanol). Yield: 69%.

The product can be characterized in the form of its dihydrochloride prepared from an ethanolic solution of gaseous hydrochloric acid.

M.P.: 211-212°C $[\alpha]_{365}^{25}$: +7.18° (c = 1, methanol)

Analysis for $C_{21}H_{24}ClN_3O.2HCl$ in %

Calc.:	C 56.96	H 5.91	N 9.49	Cl^- 16.01	$Cl^{tot.}$ 24.02
found:	C 56.92	H 5.93	N 9.33	Cl^- 15.76	$Cl^{tot.}$ 23.65

3. Dextrorotatory 2-[2-[4-[(4-chlorophenyl-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid dihydrochloride of the formula I.

9.42 g (0.0255 mole) of levorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile are introduced into a reactor equipped with a mechanical stirrer, a condenser, a thermometer and a dropping funnel and are heated to 45°C, while stirring. 15 ml of 37% concentrated hydrochloric acid are then added. The temperature of the reaction mixture rises to 92°C. The reaction mixture is heated at 60°C for 60 minutes, while stirring. The reaction mixture is allowed to cool and is concentrated on a rotary evaporator, and the residue is taken up in 50 ml of water. The pH of the reaction mixture is brought to 5 by addition of sodium hydroxide and the mixture is extracted with several successive fractions of dichloromethane. The organic phases are combined and dried over magnesium sulphate and the solvent is removed on a rotary evaporator. 9.6 g of the free acid of the formula I are thus obtained in the form of a beige powder and are converted into the dihydrochloride by means of a solution of hydrochloric acid in acetone, and the dihydrochloride is crystallized. After filtration and drying, 9.8 g of dextrorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-

piperazinyl]ethoxy]-acetic acid dihydrochloride are obtained. The purity of this product, measured by high performance liquid chromatography with a chiral stationary phase of α_1-AGP (from the LKB Company) is 95% with respect to the dextrorotatory enantiomer.

M.P.: 199-201°C M.P.:224.4°C (DSC). $[\alpha]_{365}^{25}$: +9.4° (c = 1, water)

Yield: 83%

Analysis for $C_{21}H_{25}ClN_2O_3.2HCl$ in %

calc.: C 54.56 H 5.84 N 6.06 Cl^- 15.37 $Cl^{tot.}$ 23.05

found: C 54.00 H 5.88 N 5.91 Cl^- 15.55 $Cl^{tot.}$ 23.13

The overall yield of dextrorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride, calculated with respect to the amount of levorotatory 1-[4-chlorophenyl-phenylmethyl]-piperazine employed, is 57.3%.

Example 3. Preparation of levorotatory 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride of the formula I.

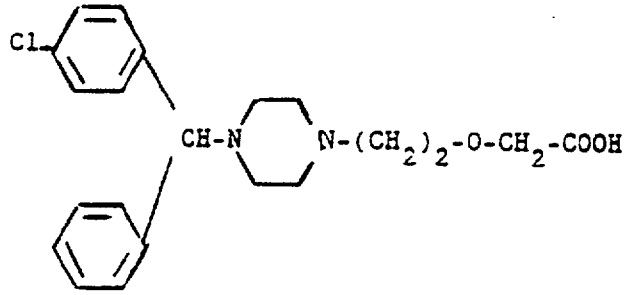
This product is obtained by the method described in example 2, but starting from dextrorotatory 1-[(4-chlorophenyl)phenylmethyl]-piperazine, the latter being obtained as in example 2.1 by treating the racemate with (2S,3S)-tartaric acid.

The levorotatory acid dihydrochloride of the formula I is obtained in yields and with a purity very close to those obtained for the dextrorotatory acid dihydrochloride: 95% measured by high performance liquid chromatography with a chiral stationary phase of α_1-AGP (from the LKB Company).

M.P.: 198-200°C M.P.: 220.7 (DSC) (decomposition on melting).

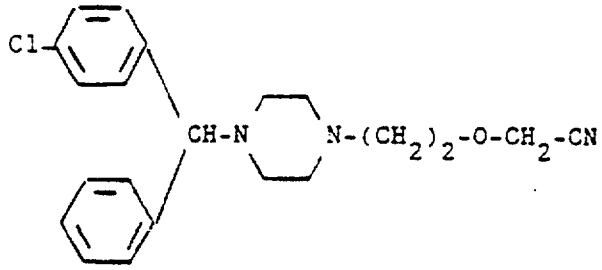
CLAIMS.

1. A process for the preparation of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid of the formula



(I)

and its dihydrochloride, characterized in that 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula



(II)

is hydrolysed in an aqueous, alcoholic or aqueous-alcoholic medium by a base or by an acid, and in that, if desired, the acid of the formula I thus obtained is converted into its dihydrochloride.

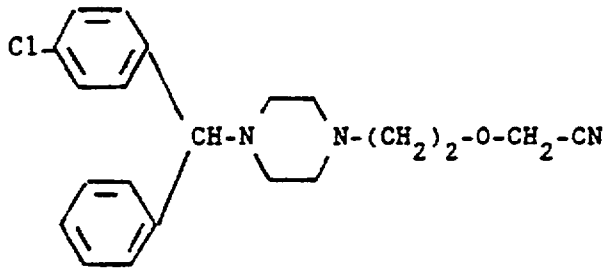
2. A process according to claim 1, characterized in that the hydrolysis is carried out at a temperature between 60°C and the reflux temperature of the reaction mixture.

3. A process according to any of claims 1 and 2, characterized in that the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid of the formula I is in the levorotatory or dextrorotatory form or in the form of a mixture of the levorotatory and

dextrorotatory forms.

4. A process according to any of claims 1 to 3, characterized in that the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula II is in the levorotatory or dextrorotatory form or in the form of a mixture of the dextrorotatory and levorotatory forms.

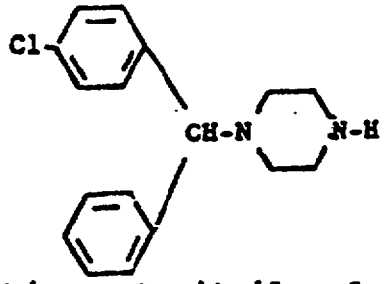
5. 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile of the formula



(II)

and its dihydrochloride in the levorotatory or dextrorotatory form or in the form of a mixture of the levorotatory and dextrorotatory forms.

6. A process for the preparation of 2-(2-(4-((4-chlorophenyl)-phenylmethyl)-1-piperazinyl)ethoxy)-acetonitrile as claimed in claim 5 comprising reacting 1-((4-chlorophenyl)phenyl-methyl)-piperazine of the formula III



(III)

with a 2-haloethoxyacetonitrile of formula $X-(CH_2)_2-O-CH_2-CN$, in which X represents a halogen atom.

7. A process as claimed in Claim 6 wherein the reaction is carried out in the presence of an acid acceptor such as an alkali metal carbonate and optionally, in the presence of an alkali metal iodide in an inert organic solvent such as an alcohol.

8. A process substantially as hereinbefore described in any one of examples 1-3.

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