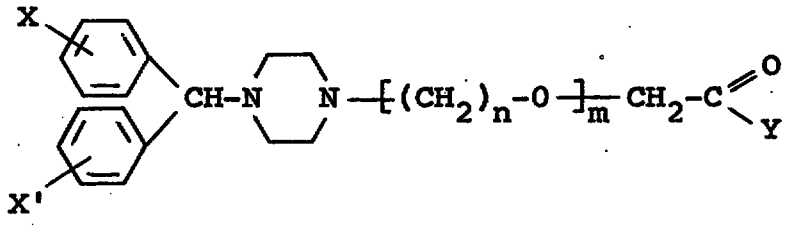
Description

The present invention relates to new 1-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids, to their amides, to their non-toxic, pharmaceutically acceptable salts, as well as to processes for the preparation thereof. It is also concerned with pharmaceutical compositions containing said compounds.

The new compounds according to the present invention have the general formula:



(I)

in which

Y is an -OH group or an $-NH_2$ group,

X and X', taken independently, represent a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,

m is equal to 1 or 2,

n is equal to 1 or 2, preferably 2,

as well as their non-toxic, pharmaceutically acceptable salts.

By the term "lower alkoxy", one understands the residues of straight or branched chain aliphatic alcohols having from 1 to 4 carbon atoms, such as

methoxy, ethoxy, propoxy etc. The halogen atom is preferably a chlorine or fluorine atom.

Within the scope of the present invention, one understands by "non-toxic, pharmaceutically acceptable salts" not only the addition salts of the acids and of the amides of formula I with pharmaceutically acceptable acids, such as acetic acid, citric acid, succinic acid, ascorbic acid, hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acid, but also the pharmaceutically acceptable salts of the acids of formula I, such as the salts of metals (for example sodium or potassium), the ammonium salts, the amine salts and the aminoacid salts.

These pharmaceutically acceptable salts may be prepared from compounds of formula I by per se known methods.

The preferred compounds according to the present invention are:-

- 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid and its dihydrochloride,
- the potassium salt of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid,
- 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetic acid and its dihydrochloride,
- 2-[2-[4-[(4-fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid and its hydrate.

The compounds of formula I possess interesting pharmacological properties; in particular, they are

useful as antiallergic, antihistaminic, broncho-dilatory and antispasmodic agents.

Furthermore, they are characterised by the fact that their secondary effects of stimulating or of depressing the central nervous system, frequently observed in the case of conventional antihistaminics, are minimal. In addition, they display interesting anaesthetic and antiinflammatory properties and prove to be active in cerebral or cardiovascular insufficiency.

In an article by H.B. WRIGHT and D.L. MARTIN (J.med.Chem. 11,(1968), 390-391), the activity of 2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-acetamide (formula I: Y = NH_2; X = p-Cl; X' = H; m = 0) as a hypocholesteremic agent is studied but the results obtained were not very encouraging.

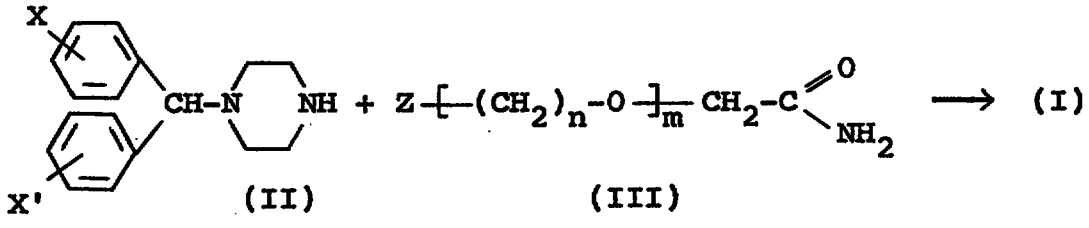
Furthermore, according to Belgian Patent Specification No. 763,609, 2-[4-(diphenylmethyl)-1-piperazinyl]-acetamide (formula I: Y = NH_2; X = X' = H; m = 0) possesses a diuretic activity. It also describes similar acetamides but in which the nitrogen atom of the amide group is substituted and which possess various other pharmacological properties.

The pharmacological tests carried out by the Applicant demonstrate that the antiallergic, antispasmodic and antihistaminic activities of these acetamides, as well as of the corresponding acids, are of little interest (see B. Pharmacology).

A. Processes of preparation.

I. The amides of formula I (Y = $-NH_2$) may be prepared by several methods, namely:

I.1. reacting a 1-(diphenylmethyl)-piperazine of formula II with an omega-haloacetamide of formula III according to the equation:



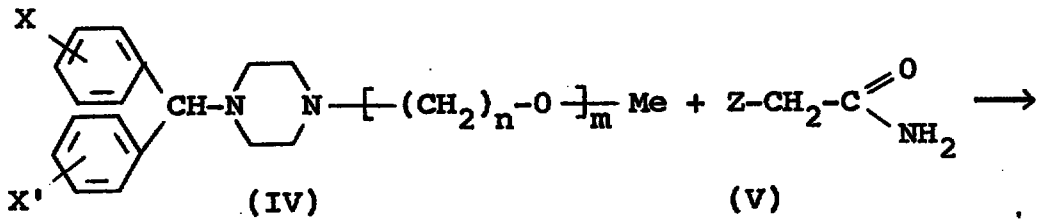
(II) (III) (I)

with Y = $-NH_2$

in which X, X', m and n have the meanings given above and Z represents a halogen atom.

This reaction is generally carried out by heating to 80 to 150°C for several hours in an inert solvent selected from aliphatic alcohols, aliphatic ketones (e.g. methyl ethyl ketone), aromatic hydrocarbons (e.g. toluene or xylene) and in the presence of an acid acceptor, such as a tertiary organic base (e.g. triethylamine) or a mineral base (e.g. sodium carbonate).

I.2. reacting an alkali metal salt of an omega-[4-(diphenylmethyl)-1-piperazinyl]-alkanol of formula IV with a 2-haloacetamide of formula V according to the equation:



(IV) (V)

(I) with Y = $-NH_2$

in which X, X', m and n have the meaning given above, Z represents a halogen atom and Me is an alkali metal.

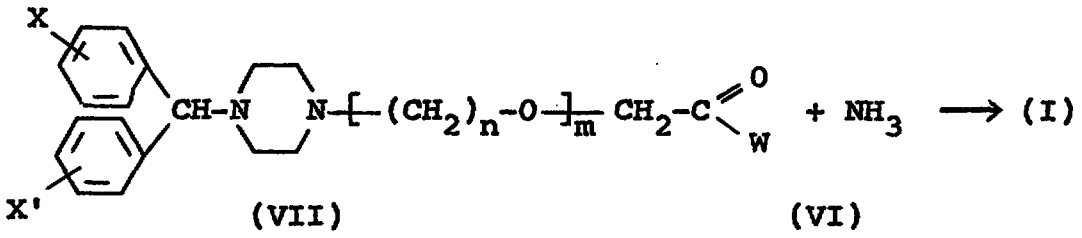
The reaction between the alkali metal salt of formula IV and the haloacetamide of formula V is carried out in an inert solvent (e.g. toluene, xylene or dimethylformamide) at a temperature of from 0°C to the reflux temperature of the reaction mixture.

The alkali metal salt of formula IV used in this reaction is prepared in situ by reacting the appropriate omega-[4-(diphenylmethyl)-1-piperazinyl]-alkanol with an alkali metal hydride, generally sodium hydride, in an inert solvent, such as toluene, xylene or dimethylformamide.

Regarding the preparation of the alcohols of formula IV (Me = H), this is described in U.S. Patent Specification No. 2,899,436 in the name of the Applicant.

I.3. reacting ammonia with a functional derivative of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid, namely a halide or a lower alkyl ester of formula

VII, according to the equation:



(VII) (VI)

with Y = $-NH_2$

in which X, X', m and n have the meanings given above and W represents a halogen atom or an -OR' radical, in which R' represents a lower alkyl radical.

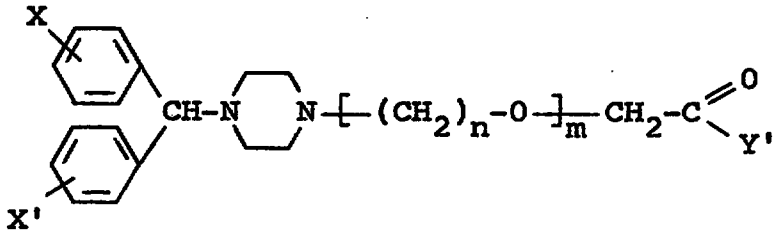
The halogen atom may be, for example, chlorine or bromine and the alkyl radical a methyl or ethyl radical.

In the case in which W represents a halogen atom, one commences by preparing an acid of formula I (Y = OH) by the method II described hereinafter and one converts it into its corresponding halide by known methods for the preparation of this type of compound. Subsequently, one reacts the acid halide obtained with ammonia in an inert solvent.

In the case in which W represents an -OR' radical, one commences by preparing an ester of formula VII by one of the methods described hereinafter. Subsequently, one reacts this ester with ammonia in an inert solvent at a temperature between 0°C and ambient temperature. This reaction may possibly

be carried out in the presence of a catalyst, such as sodium methoxide.

II. The acids of formula I, in which Y = OH, are prepared by hydrolysis, in a basic medium, of a functional derivative of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid, namely, an amide or a lower alkyl ester of the formula:



(VIII)

in which X, X', m and n have the meaning given above and Y' represents an $-NH_2$ group or an -OR' group, in which R' represents a lower alkyl radical (for example a methyl or ethyl radical).

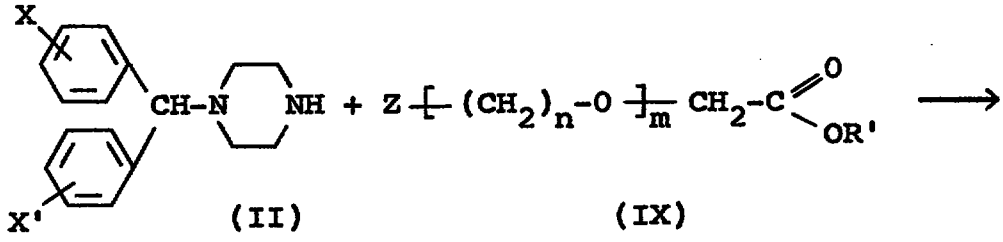
This hydrolysis is carried out by means of a mineral base, such as sodium or potassium hydroxide, in an aqueous or aqueous alcoholic medium (methanol, ethanol, etc.), at a temperature between 20°C and the reflux temperature of the reaction mixture.

The amides of formula VIII, in which Y' is $-NH_2$, may be prepared by one of methods I.1 to I.3 described above.

With regard to the esters of formula VII, in which W = -OR', and the esters of formula VIII, in which

Y' = -OR', these may be prepared by various methods, for example:

a) reacting a 1-(diphenylmethyl)-piperazine of formula II with a lower alkyl omega-haloacetate of formula IX, according to the equation:



(II) (IX)

(VII) with W = -OR' or

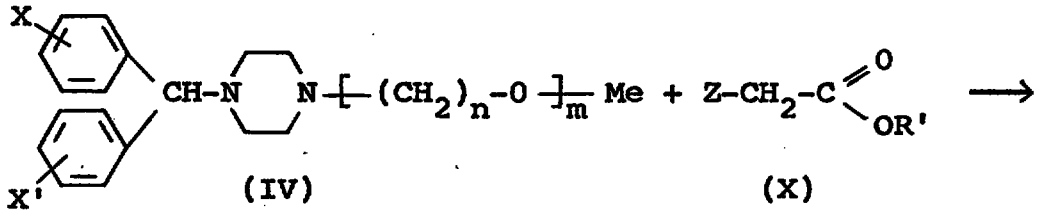
(VIII) with Y' = -OR'

in which X, X', m and n have the meaning given above, R' represents a lower alkyl radical and Z a halogen atom. Thus, R' is, for example, a methyl or ethyl radical and Z a chlorine or bromine atom.

This reaction is generally carried out by heating between 80 and 150°C for several hours in an inert solvent, such as benzene, toluene or xylene, and in the presence of an acid acceptor, such as a tertiary organic base (for example triethylamine) or a mineral base (for example sodium carbonate);

b) reacting an alkali metal salt of an omega-[4-(diphenylmethyl)-1-piperazinyl]-alkanol of formula IV with a lower alkyl ester of a 2-halo-

acetic acid of formula X according to the equation:



(IV) (X)

(VII) with W = -OR' or

(VIII) with Y' = OR'

in which R', X, X', m and n have the meaning given above, Z represents a halogen atom and Me is an alkali metal.

The reaction between the alkali metal salt of formula IV and the halogenated ester of formula X is carried out in an inert solvent at a temperature between 0°C and the reflux temperature of the reaction mixture.

The following Examples illustrate the invention without limiting it.

Example 1.

Preparation of amides of formula I (Y = $-NH_2$).

1.1. 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]-ethoxy]-acetamide dihydrochloride. (method I.1)

One heats between 90 and 120°C a mixture of 37.8 g (0.15 mole) of 1-(diphenylmethyl)-piperazine, 27.5 g (0.2 mole) of 2-(2-chloroethoxy)-acetamide and 26.5 g of anhydrous sodium carbonate in 120 ml of xylene.

Thereafter, one adds 120 ml of benzene, one filters off the precipitate formed and one extracts the organic phase with a dilute solution of hydrochloric acid (30 ml of concentrated hydrochloric acid + 100 ml of water). After the addition of 40 ml of a concentrated solution of sodium hydroxide and extraction with benzene, one washes the benzene solution with water, one dries over anhydrous sodium carbonate and one evaporates the benzene to dryness. One triturates the evaporation residue with diethyl ether and leaves to crystallise. One obtains 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetamide in a yield of 73%; m.p. 119-120°C.

The dihydrochloride, prepared in ethanol, melts at 230°C, with decomposition.

Analysis for $C_{21}H_{27}N_3O_2.2\ HCl$ in %

calc.: C 59.15 H 6.85 N 9.85 Cl^- 16.63

found: C 58.99 H 6.80 N 9.79 Cl^- 16.46

The following compounds were prepared by the method described above:

- 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide. Yield: 47%; m.p. 111-112°C (ethanol).

  Analysis for $C_{21}H_{26}ClN_3O_2$ in %

  calc. : C 65.02 H 6.71 N 10.83 Cl 9.14

  found : C 64.59 H 7.00 N 10.82 Cl 9.54

- 2-[2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetamide. The product, obtained in a crude state in a practically quantitative yield, was used as such, without further purification, for preparing the

corresponding acid (Example 2.2).

- 2-[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetamide. The product, obtained in a crude state in a practically quantitative yield, was used as such, without further purification, for preparing the corresponding acid (Example 2.2).
- 2-[2-[4-[(4-fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide. Yield: 54.7%; m.p. 105-107°C, (acetonitrile).

Analysis for $C_{21}H_{26}FN_3O_2$ in %

calc. : C 67.90 H 7.09 N 11.31

found : C 68.3 H 7.40 N 11.21

- 2-[2-[4-[(2-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide. Yield: 57%; m.p. 129-130°C, (benzene).

Analysis for $C_{21}H_{26}ClN_3O_2$ in %

calc. : C 65.0 H 6.75 N 10.8 Cl 9.4

found : C 66.3 H 7.0 N 10.6 Cl 9.7

The dihydrochloride of this amide was also prepared; it proved to contain monohydrochloride. M.p. 218-220°C, (isopropyl alcohol).

Analysis for $C_{21}H_{26}ClN_3O_2.2\ HCl$ in %

calc. : C 54.72 H 6.12 N 9.11 Cl^- 15.38 Cl^{tot} 23.08

found : C 55.69 H 6.52 N 9.20 Cl^- 11.86 Cl^{tot} 20.27

- 2-[2-[4-[(4-methoxyphenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide dihydrochloride. Yield: 20%; m.p. 175-176°C (acetonitrile).

Analysis for $C_{22}H_{29}N_3O_3.2\ HCl$ in %

calc. : C 57.8 H 6.8 N 9.2 Cl^- 15.5

found : C 57.8 H 7.2 N 9.5 Cl^- 15.9

- 2-[2-[2-[4-[[4-(trifluoromethyl)-phenyl]-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetamide.
- 2-[2-[2-[4-[bis-(4-fluorophenyl)-methyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetamide.

1.2. 2-[2-[2-[4-(Diphenylmethyl)-1-piperazinyl]-ethoxy]-ethoxy]-acetamide dihydrochloride.(method I.2).

One adds 24.2 g (0.53 mole) of sodium hydride to a solution of 172.9 g (0.508 mole) of 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-ethanol in 180 ml of dimethylformamide. When the addition is finished, one heats the reaction mixture to 40°C for 30 minutes. After cooling, one adds thereto 60 g (0.624 mole) of 2-chloroacetamide in 10 minutes. The temperature of the reaction mixture increases to 40°C and is maintained at this temperature for a further 30 minutes. One cools, one adds 30 ml of water and evaporates to dryness. One suspends the residue in 1 litre water and extracts the suspension obtained with benzene. The organic phase is dried over potassium carbonate, then evaporated. The residue is purified by chromatography on a column of silica (eluent: chloroform-ethanol 95:5). The product obtained is dissolved in 45 ml of ethanol, to which one adds 24 ml of a 5.1 N ethanolic solution of hydrochloric acid. One obtains 19 g of 2-[2-[2-[4-(diphenylmethyl)-

1-piperazinyl]-ethoxy]-ethoxy]-acetamide dihydrochloride in a yield of 8%. M.p. 196-197°C. (acetonitrile).

Analysis for $C_{23}H_{31}N_3O_3$.2 HCl in %

calc. : C 58.72 H 7.07 N 8.93 Cl^- 15.07

found : C 58.29 H 6.83 N 8.44 Cl^- 15.01

The following product was prepared by the method described above:

- 2-[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetamide dihydrochloride. The product recrystallises from isopropyl alcohol with one molecule of solvent. Yield: 11%; m.p. 100-102°C.

Analysis for $C_{23}H_{30}ClN_3O_3.C_3H_7OH.2$ HCl in %

calc.: C 55.27 H 7.16 N 7.43 Cl^- 12.55 $Cl^{tot.}$ 18.22

found: C 53.10 H 6.93 N 7.18 Cl^- 12.56 $Cl^{tot.}$ 18.79

1.3. 2-[2-[4-[(4-Chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide. (method I.3).

One dissolves 2.3 g (0.0057 mole) of methyl 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetate in 100 ml of anhydrous methanol. One cools this solution to a temperature of 5 to 10°C and then bubbles through ammonia for 20 hours. One evaporates the solvent in a vacuum, one triturates the residue with ether and leaves to crystallise. One obtains 1.2 g of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide. Yield: 54%; m.p. 109-110°C.

Analysis for $C_{21}H_{26}ClN_3O_2$ in %

calc. : C 65.02 H 6.71 N 10.83 Cl 9.54

found : C 65.13 H 6.59 N 10.95 Cl 9.14

The methyl 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetate used as starting product was prepared as follows:

One heats to reflux, with good stirring, a mixture of 87 g (0.30 mole) of 1-[(4-chlorophenyl)-phenylmethyl]-piperazine, 58 g (0.38 mole) of methyl (2-chloroethoxy)-acetate and 40.3 g (0.38 mole) of sodium carbonate in 500 ml anhydrous xylene. One cools, one filters and one washes the solid with benzene and one discards the washed solid. The filtrate is evaporated to dryness. One purifies the residue by chromatography on a column of silica (eluent: chloroform-methanol, 97:3). One thus obtains 34 g (yield 27.8%) of the desired methyl ester.

Analysis for $C_{22}H_{27}ClN_2O_3$ in %

calc. : C 65.60 H 6.70 N 6.95

found : C 63.87 H 6.55 N 6.59

Two addition salts of this ester were also prepared:

- the dihydrochloride; m.p. 123-125°C.

  Analysis for $C_{22}H_{27}ClN_2O_3 . 2\ HCl$ in %

  calc. : C 55.50 H 6.10 N 5.89 Cl^- 14.92

  found : C 55.20 H 6.23 N 5.65 Cl^- 13.2

- the dimaleate; m.p. 128-130°C.

  Analysis for $C_{30}H_{35}ClN_2O_{11}$ in %

  calc. : C 56.70 H 5.51 N 4.41

  found : C 57.01 N 5.22 N 4.45

Example 2.

Preparation of the acids of formula I (Y = OH).

2.1. 2-[2-[4-[(4-Chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid. (method II).

One dissolves 16.8 g (0.0417 mole) of methyl 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetate (prepared as described above in Example 1.3) in 65 ml. of absolute ethanol. One adds thereto 42 ml of a 1 N ethanolic solution of potassium hydroxide. One heats the mixture under reflux for 4 hours. One cools and one removes the precipitate by filtration, after washing with diethyl ether. The filtrate is evaporated to dryness. One triturates the residue in diethyl ether and allows to crystallise. One obtains 10.5 g potassium 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetate (hygroscopic). Yield: 59%, m.p. 161-163°C.

Analysis for $C_{21}H_{24}ClN_2O_3K$ in %

calc. : C 59.0 H 5.63 N 6.56

found : C 57.97 H 5.77 N 6.48

One dissolves the potassium salt in 100 ml of water and neutralises with 10% hydrochloric acid to pH = 4. One extracts the solution with chloroform and dries the organic phase over magnesium sulphate. One evaporates to dryness. One triturates the residue with diethyl ether and leaves to crystallise. One obtains 7.5 g of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-

ethoxy]-acetic acid. Yield: 81%, m.p. 110-115°C.

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

calc. : C 64.80 H 6.48 N 7.20

found : C 62.3 H 6.48 N 6.92

The corresponding dihydrochloride, prepared in toluene in a yield of 80%, melts at 225°C.

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

calc.: C 54.60 H 5.85 N 6.07 Cl^- 15.38 $Cl^{tot.}$ 23.07

found: C 54.42 H 5.60 N 6.01 Cl^- 15.29 $Cl^{tot.}$ 23.08

2.2. 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]-ethoxy]-acetic acid. (method II).

One heats under reflux for 3 hours a mixture of 19 g (0.054 mole) of 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetamide (obtained as described in Example 1.1) in 200 ml of ethanol and 27 ml of a 4 N ethanolic solution of sodium hydroxide. One neutralises with 29.7 ml of hydrochloric acid (3.61 N) to pH 6.3. One evaporates the ethanol in a vacuum. One filters off the precipitate. After evaporation of solvent, one obtains 17.4 g of crude 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetic acid. Yield: 91%; m.p. 100°C.

Analysis for $C_{21}H_{26}N_2O_3$ in %

calc. : C 71.1 H 7.39 N 7.90

found : C 69.1 H 7.07 N 7.12

Dihydrochloride: m.p. 217-218°C (isopropyl alcohol)

Analysis for $C_{21}H_{26}N_2O_3.2\ HCl$ in %

calc. : C 59.02 H 6.60 N 6.55 Cl^- 16.59

found : C 58.83 H 6.94 N 6.33 Cl^- 15.90

The following products were prepared by the method described above:

- 2-[2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid dihydrochloride. Yield: 57%; m.p. 85°C (lyophilised; decomposition).
  Analysis for $C_{23}H_{30}N_2O_4 \cdot 2\ HCl$ in %
  calc. : C 58.60 H 6.84 N 5.94 Cl^- 15.04
  found : C 56.82 H 7.82 N 6.02 Cl^- 16.76
- 2-[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid dihydrochloride. Yield: 82%; m.p. 112°C (lyophilised).
  Analysis for $C_{23}H_{29}ClN_2O_4 \cdot 2\ HCl$ in %
  calc. : C 54.6 H 5.78 N 5.54 $Cl^{tot.}$ 21.03
  found : C 52.48 H 6.10 N 5.72 $Cl^{tot.}$ 22.19
- 2-[2-[4-[(4-fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid hydrate. Yield 100%; m.p. not sharp (from 70°C onwards the product softens gradually).
  Analysis for $C_{21}H_{25}FN_2O_3 \cdot 3/2\ H_2O$ in %
  calc. : C 63.1 H 7.0 N 7.0
  found : C 63.7 H 7.6 N 6.9
- 2-[2-[4-[(4-methoxyphenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid dihydrochloride. Yield: 35%; m.p. 214-217°C (acetonitrile; decomposition).
  Analysis for $C_{22}H_{28}N_2O_4 \cdot 2\ HCl$ in %
  calc. : C 57.7 H 6.6 N 6.1 Cl^- 15.5
  found : C 53.2 H 6.5 N 6.0 Cl^- 17.5

- 2-[2-[4-[(2-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid. Yield: 50%; m.p. 96-100°C (lyophilised).

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

  calc. : C 64.8 H 6.5 N 7.2 Cl 9.1

  found : C 62.3 H 6.9 N 6.9 Cl 10.2

- 2-[2-[2-[4-[[4-(trifluoromethyl)-phenyl]-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid.
- 2-[2-[2-[4-[bis-(4-fluorophenyl)-methyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid.

B. Pharmacology.

The following products of the present invention were subjected to pharmacological testings and gave the results described hereinafter:

- 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetamide dihydrochloride (compound A, prepared in Example 1.1);
- 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide (compound B, prepared in Examples 1.1 and 1.3);
- 2-[2-[4-[(4-fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide (compound C, prepared in Example 1.1);
- 2-[2-[4-[(2-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide dihydrochloride (compound D, prepared in Example 1.1);
- 2-[2-[4-[(4-methoxyphenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetamide dihydrochloride (compound E, prepared in Example 1.1);

- 2-[2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy-ethoxy]-acetamide dihydrochloride (compound F, prepared in Example 1.2);
- 2-[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetamide dihydrochloride (compound G, prepared in Example 1.2);
- potassium 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetate (compound H, prepared in Example 2.1);
- 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid (compound I, prepared in Example 2.1);
- 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid dihydrochloride (compound J, prepared in Example 2.1);
- 2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-acetic acid (compound K, prepared in Example 2.2);
- 2-[2-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid dihydrochloride (compound L, prepared in Example 2.2);
- 2-[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethoxy]-acetic acid dihydrochloride (compound M, prepared in Example 2.2);
- 2-[2-[4-[(4-fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid hydrate (compound N, prepared in Example 2.2).

The following products, which are not part of the invention (general formula I in which m = 0) were also submitted to the same pharmacological testings:

- 2-[4-(diphenylmethyl)-1-piperazinyl]-acetamide (product 1). This product was prepared according to the method described in Belgian Patent Specification No. 763,609; m.p. 204°C.
- 2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-acetamide (product 2; see H.B. WRIGHT and D.L. MARTIN, loc. cit.). This product was also prepared by the method described in Belgian Patent Specification No. 763,609; m.p. 145°C.
- 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid (product 3). This substance was prepared by method II (Example 2.2); m.p. 176°C.
- 2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-acetic acid (product 4). This substance was prepared by method II (Example 2.2); m.p. 106-108°C.

1. Antiallergic activity.

This activity was determined on the rat by means of the "passive cutaneous anaphylaxis (PCA)" test (see J. GOOSE and A.M.J.N. BLAIR, Immunology, 16, (1969), 749-760; and U. MARTIN and D. ROEMER, Arzneimittel-Forschung, 28, (1978) (5), 770-782).

One uses female rats, the sides of which have been partly shaved. Into the zone thus shaved one injects intradermally, for passive sensitisation of the animals,

0.05 ml of "IGE antiovalbumin" serum at a dilution such that, at the time of the PCA test, a distinct spot with a surface area of about 100 mm^2 appears at the point of injection.

72 Hours after the injection, one administers by the intravenous route 0.25 ml of a solution of allergen containing a colouring agent (5 mg of ovalbumin and 6 mg of Evans Blue in 0.25 ml of a 0.9% solution of sodium chloride). At the point of intradermal injection, one can see a distinct blue spot, and one measures the surface.

For testing the activity of the products of the invention, one operates in the same manner; however:

- the product to be tested is administered per os 72 hours after the injection of serum;
- minutes after this administration, one injects by the intravenous route 0.25 ml of the solution of allergen;
- 30 minutes after the administration of the allergen, one measures the surface of the blue spot.

In the Table below are given the immunological doses (ID 50 in μmol/kg) which bring about, on average of the total number of animals submitted to the test, a reduction of 50% of the surface area of the coloured spot.

From this Table, it is evident that the products of the invention are active per os, contrary to sodium

cromoglycate, a product the antiasthmatic activity of which is well known by the intravenous route. On the other hand, products 1, 2, 3 and 4 (not according to the invention; m = 0) prove to be of little interest.

products	ID 50 per os in mol/kg
sodium cromoglycate	inactive
B	36.5
C	18.9
F	10.6
N	10.2
1	> 320
2	> 320
3	> 320
4	> 320

2. Spasmolytic and antihistaminic activity.

These activities were measured on the guinea pig by the method of H. KONZETT and R. ROESSLER (Naunyn-Schmiedebergs Arch. exp. Path. Pharmakol. 195, (1940), 71-74) and compared with those of theophylline.

The unaesthetised and curarised guinea pig is artificially ventilated. The endotracheal pressure is recorded. Repetitive bronchial spasms are induced by successive and progressive intravenous injections of serotonin and histamine, respectively.

The test substances are also administered by the intravenous route. In the Table below are given the doses of products (ID 50 in μmol/kg) which inhibit 50%,

on average, of the total number of animals, of the induced bronchospasms:

products	Serotonin	Histamine
Theophylline	10	10
A	0.78	0.23
B	0.88	0.45
C	0.94	0.71
D	1.1	0.63
E	10.0	0.67
F	0.32	0.25
G	0.66	1.14
H	7.0	0.23
I	9.44	0.205
J	7.3	0.20
K	9.5	0.093
L	5.69	0.39
M	10.0	0.79
N	2.1	0.08
1	77	2.1
2	11	3.1
3	> 32	5
4	> 32	7.8

The compounds of the present invention are devoid of cholinergic activity. It can be seen from this Table that the products of the invention have a

remarkable activity with regard to bronchospasms induced by serotonin and histamine, respectively, with a very marked selectivity towards the latter. In contradistinction thereto, products 1, 2, 3 and 4 (not according to the invention; m = 0) prove to be considerably less active.

Furthermore, this test provides evidence that some of the compounds, administered in a single dose, possess an antihistaminic activity of long duration. Thus, for example, compound J, administered by the intravenous route to the guinea pig at a dose of 1 µmol/kg, still retains an activity equal to 100% after 5 hours.

3. General behaviour of the mouse (Irwin's test).

This behaviour was studied by Irwin's test (S. IRWIN, "General philosophy and methodology of screening: a multidimensional approach"; Gordon Research Conference on Medicinal Chemistry, August 3-7 (1959) at Colby Junior College, New London).

Progressive doses of product submitted to the test are administered by the intra peritoneal route to groups of three male mice (weighing 18 to 22 g) and the general behaviour of the animals is observed according to known criteria.

One uses the following products as reference substances:

- hydroxyzine = 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-ethanol;

- oxazepam = 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one.

In the Table below are given the doses (in mg/kg) which induce the first manifestations of tranquilisation in the animals:

products	Tranquilising dose in mg/kg
A	> 255
B	38.7
C	115
D	> 460
E	136
F	94
G	34
H	46.2
J	138
K	106
L	141
M	505
N	372
Hydroxyzine	27
Oxazepam	2.6

It can be seen from this Table that the products of the invention have little sedative effect in comparison with the reference compounds.

Furthermore, in this test, the toxicity of the products of the invention proves to be very low.

In the Table below is given the lethal dose (two animals out of three) for the products of the invention which were administered by the intraperitoneal route to the mouse:

products	Lethal dose (2/3) in mg/kg
A	255
B	232
C	386
D	460
E	456
F	282
G	339
H	277
I	116
J	138
K	708
L	942
M	505
N	372

When one compares the two Tables (tranquilising dose and lethal dose), one can see that for certain products the sedative effect only appears at a dose which is near the lethal dose.

4. DL 50 Lethal dose.

The low toxicity of the products of the invention was confirmed by the measurement of the DL 50 per os.

Thus, for product J, on the Wistar rat, it is 703 mg/kg for the male rat and 865 mg/kg for the female rat.

On the mouse, the DL 50 for the same product are, respectively 600 mg/kg (male mouse) and 752 mg/kg (female mouse).

5. Posology and administration.

The pharmaceutical compositions containing the compounds of the invention may be administered by the oral, parenteral or rectal route. They may also be utilised by nasal instillation (aerosols) or in the form of unguents or creams.

The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example, in the form of tablets (coated or not), pills, dragees, gelatine capsules, solutions, syrups, etc. In the same way, the compositions which can be used for administration by the parenteral route are in the pharmaceutical forms known for this mode of administration, for example, aqueous or oily solutions, suspensions or emulsions.

For administration by the rectal route, the compositions containing the compounds of the invention are generally used in the form of suppositories.

The pharmaceutical forms, such as injectable solutions, injectable suspensions, tablets, drops, suppositories etc., are prepared by methods

conventionally used by pharmacists. One mixes the compounds of the invention with a solid or liquid, non-toxic, pharmaceutically acceptable vehicle and possibly with a dispersing agent, a disintegration agent, a stabilising agent, etc. If appropriate, one may also add preservatives, sweeteners, colouring agents, etc.

The percentage of active product in the pharmaceutical compositions may be varied within wide limits, according to the patient and the mode of administration, in particular, according to the frequency of administration.

With regard to the posology, it may be varied within a wide range of dosage units, for example from 0.5 to 250 mg of active product.

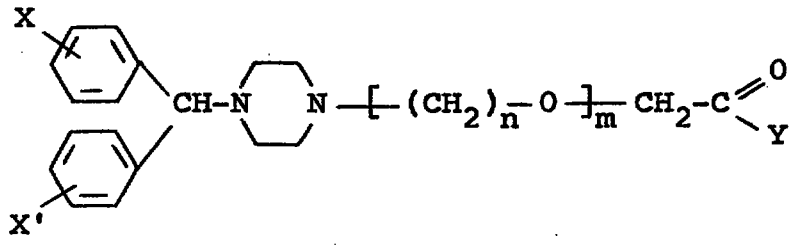
As non-limiting Example of a composition containing the compounds of the invention, there is given below an example of a gelatine capsule usable per os:

product J	100 mg
lactose	67 mg
magnesium stearate	1 mg
silicon dioxide (Aerosil)	2 mg

* C L M S *

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

1. 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides having the general formula



(I)

wherein

Y is an -OH group or an $-NH_2$ group,

X and X', taken separately, represent a hydrogen atom, a straight-chain or branched C_1-C_4-alkoxy radical or a trifluoromethyl radical,

m is 1 or 2,

n is 1 or 2,

as well as the non-toxic pharmaceutically acceptable salts thereof.

2. 2-[2-[4-[(4-Chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid and its dihydrochloride.

3. Potassium salt of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid.

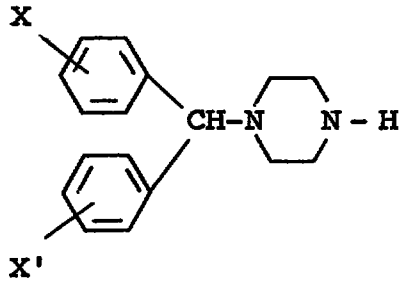
4. 2-[2-[4-(Diphenylmethyl)-1-piperazinyl]-ethoxy-acetic acid and its dihydrochloride.

5. 2-[2-[4-[(4-Fluorophenyl)-phenylmethyl]-1-piperazinyl]-ethoxy]-acetic acid and its hydrate.

6. Process for the preparation of 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids, their amides and their salts

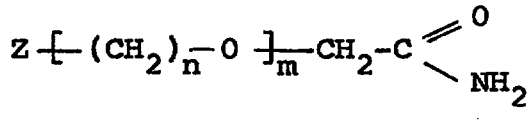
as defined in claim 1, characterised in that:

a) in order to prepare the amides of 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids having the general formula (I) given in claim 1 and wherein Y = NH_2, a 1-(diphenylmethyl)-piperazinyl of the formula



(II)

wherein X and X' have the meaning given in claim 1, is reacted, in an inert solvent and in the presence of an acid acceptor, with an omega-haloacetamide of the formula

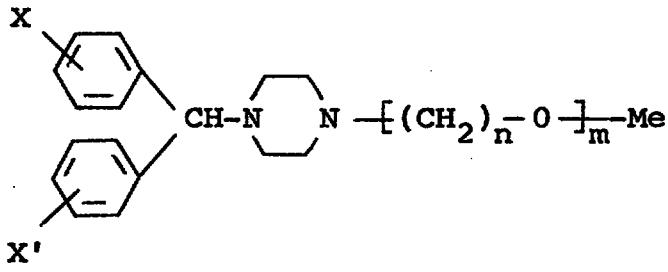


(III)

wherein m and n have the meaning given in claim 1 and Z represents a halogen atom; or

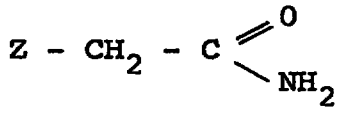
b) in order to prepare the amides of 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids having the general formula (I) given in claim 1 and wherein Y = NH_2, an alkali metal salt of an omega-[4-(diphenylmethyl)-piperazinyl]-alkanol of the formula

* C L M S *



(IV)

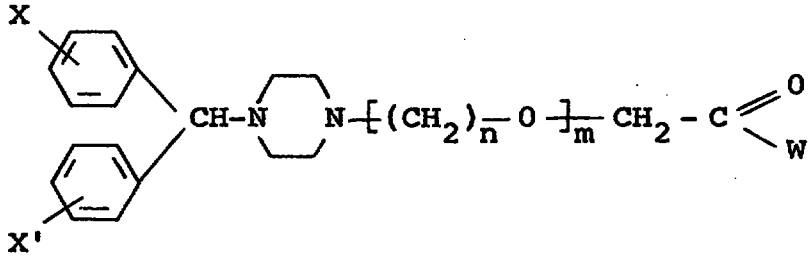
wherein X, X', m and n have the meaning given in claim 1 and Me represents an alkali metal, is reacted, in an inert solvent, with a 2-haloacetamide of the formula



(V)

wherein Z represents a halogen atom; or

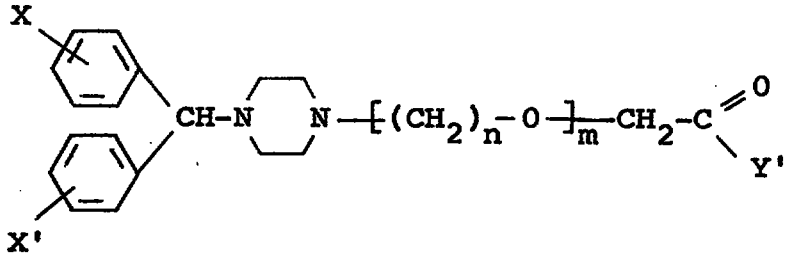
c) in order to prepare the amides of 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids having the general formula (I) given in claim 1 and wherein Y = NH_2, ammonia (VI) is reacted, in an inert solvent, with a functional derivative of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid of the formula



(VII)

wherein X, X', m and n have the meaning given in claim 1 and W represents a halogen atom or an -OR' group, wherein R' represents a lower alkyl radical; or

d) in order to prepare the 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids having the general formula (I) given in claim 1 and wherein Y = OH, a functional derivative of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid of the formula



(VIII)

wherein X, X', m and n have the meaning given in claim 1 and Y' represents an $-NH_2$ group or an -OR' group, wherein R' represents a lower alkyl radical, is hydrolysed, in an aqueous or hydroalcoholic medium and with an inorganic base; and

e) optionally, the 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids or amides thus obtained are converted into their non-toxic pharmaceutically acceptable salts.

7. Therapeutic compositions containing a therapeutically effective amount of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid or its amide according to claim 1 or a non-toxic pharmaceutically acceptable salt thereof, in association with solid or liquid pharmaceutical excipients.