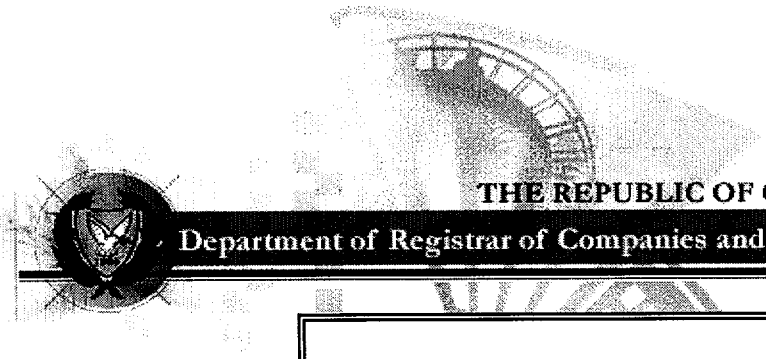

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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(54) Process for the 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-[4-[(4-chlorophenyl-phenylmethyl]-1-piperazinyl]1-1ethanol is reacted with an alkali metal halogenoacetate in the presence of an alkali metal alcoholate, the alkali metal salt thus obtained is converted into the corresponding acid and, if appropriate, into its dihydrochloride.

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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 and its dihydrochloride.

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. When used in therapy, this product has proved to be remarkably free from side effects on the central nervous system, such as drowsiness, reduced mental performance etc.(c.f. D.P.TASHKIN et al., Annals of Allergy, Part II, 59, (1987),49-52, and F.M. GENGO et al., Annals of Allergy, Part II, 59, (1987),53-57).

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 (potassium or sodium 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-[(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]-acetic acid and its dihydrochloride are prepared by a process which is characterized in that 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol is reacted with an alkali metal haloacetate in the presence of an alkali metal

alcoholate and in that the alkali metal salt thus obtained is converted into the corresponding acid and, if appropriate, into its dihydrochloride.

The 2-[4-[(4-chlorophenyl)phenylmethyl-1-piperazinyl)-ethanol used as the starting substance in the process of the invention is a product which is known per se. Its synthesis by reaction of 1-piperazineethanol with (4-chlorophenyl)phenylmethyl chloride has already been described in U.S. Patent No.2,899,436. This product can also be prepared in a higher yield (90%) by reaction of 1-[(4-chlorophenyl)phenylmethyl]-piperazine with a 2-haloethanol in the presence of an acid acceptor, such as an inorganic base (for example sodium or potassium carbonate) or a tertiary organic base (for example triethylamine), in an inert solvent, such as toluene, xylene or another aromatic solvent.

In accordance with the invention, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid is obtained by reaction of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol and an alkali metal haloacetate, such as sodium chloroacetate. This reaction is generally carried out by heating at between 60 and 100°C for several hours in the presence of an alkali metal alcoholate, such as, for example, potassium tert-butoxide, and in an organic solvent, preferably an aliphatic alcohol of low reactivity, such as, for example, tert-butanol.

To achieve optimum yields, its is advisable to use potassium tert-butoxide and tert-butanol and to resupply the reaction medium regularly with the two reactants (alkali metal alcoholate and alkali metal haloacetate) in smaller and smaller amounts and at regular intervals until the reaction is as complete as possible.

By way of example, each reactant can be added to the reaction mixture every half hour for a total duration of four hours. Each of the total molar amounts of alcoholate and haloacetate used is advantageously 25 to 75% higher than the molar amount of the starting 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol.

For reasons of economy, it is of interest to recover and recycle the starting alcohol. To this effect, the solvent is removed from the reaction medium, the latter is taken up in acidified water (to bring the pH to a weakly basic value) and the starting alcohol is extracted with diethyl ether. The 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid which is formed in the course of the

reaction is present in the reaction mixture in the form of an alkali metal salt. After the reaction mixture is acidified to pH 5 by addition of an inorganic acid (such as hydrochloric acid), the corresponding acid can be recovered from the reaction mixture by extraction by means of an organic solvent (dichloromethane, toluene etc.). The desired acid can also be isolated in the form of well-crystallized salts. This acid can be converted into the corresponding dihydrochloride of the acid by a conventional process.

This new synthesis process gives yields of 44% or more of cetirizine dihydrochloride, calculated on the basis of the 1-[(4-chlorophenyl)phenylmethyl]-1-piperazine employed. With recycling of the 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol in the reaction, the overall yield can even reach values close to 50%. This higher yield starting from 1-[(4-chlorophenyl)phenylmethyl]-1-piperazine constitutes a considerable technical advance with respect to the process described in European Patent No.58,146.

The following example is given for the purpose of illustrating the invention.

Example. Preparation of 2-[2-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

1. 2-[4-[4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol.

325 ml of dry toluene, 131.2 g (0.458 mole) of 1-[(4-chlorophenyl)phenylmethyl]-piperazine and 125 ml (0.9 mole) of triethylamine are introduced successively into a three-necked round-bottomed flask of 2 litres capacity equipped with a mechanical stirrer, a condenser and a thermometer. 41.5 g (0.516 mole) of 2-chloroethanol are added to this solution and the mixture is brought to the reflux temperature, while stirring. After heating for six hours, a further 20 g (0.248 mole) of 2-chloroethanol are added and reflux is maintained for an additional six hours.

The reaction mixture is cooled and filtered and the filtrate is concentrated under a vacuum on a rotary evaporator. 146.5 g of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol are thus isolated in the form of a yellow oil in a yield of 96.8%.

50 g of the alcohol obtained are distilled at 220°C under reduced pressure (0.0065 mbar) and collected in two separate fractions. The purity of each fraction is measured by high pressure liquid chromatography. One fraction of 24.5 g has a purity of 96.6%,

whereas the other fraction (of 22.2 g) has a purity of 99.6%. A yield of pure product of 90.4% is thus obtained.

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

M.P.: 222°C

Analysis for $C_{19}H_{23}ClN_2O.2HCl$ in %

calc :	C 56.50	H 6.19	N 6.94	Cl^- 17.59	$Cl^{tot.}$ 26.39
found:	C 56.63	H 6.28	N 6.86	Cl^- 17.48	$Cl^{tot.}$ 26.32

2. 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

50 g (0.15 mole) of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol and 225 ml of tert-butanol are introduced into a three-necked round bottomed flask equipped with a mechanical stirrer, a thermometer, a nitrogen inlet and a condenser. The mixture is stirred gently and heated to 45°C under a nitrogen atmosphere, and 21 g of potassium tert-butoxide are added. The temperature is raised to 75-80°C and the mixture is kept at this temperature. 11 g of sodium chloroacetate are then added to the mixture, taking the time of this addition as time zero. Sodium chloroacetate and potassium tert-butoxide are introduced successively into the reaction mixture, the temperature being kept at 75-80°C and while stirring under a nitrogen atmosphere, in the following manner: after 45 minutes 11 g of sodium chloroacetate are added; after 1 hour and a half 5.2 g of potassium tert-butoxide are added; after 2 hours 5.64 g of sodium chloroacetate are added; after 2 and a half hours 1.9 g of potassium tert-butoxide are added; after 3 hours 1.9 g of sodium chloroacetate are added; after 3 and a half hours 0.8 g of potassium tert-butoxide is added; after 4 hours the operation is ended by addition of 1.13 g of sodium chloroacetate. A total of 28.92 g (0.25 mole) of potassium tert-butoxide (97%) and 30.65 g (0.25 mole) of sodium chloroacetate (95%) has thus been added. The reactor is then converted into a distillation apparatus and about 150 ml of tert-butanol are distilled off; 190 ml of water are then added to the reaction mixture and the distillation of tert-butanol in the form of an azeotrope with water is continued until the temperature of the vapours reaches 100°C.

The reaction mixture is cooled, diluted with 60 ml of water and brought to pH 8 by addition of about 8 ml concentrated hydrochloric acid. The starting 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol which has not reacted is then carefully extracted with diethyl ether, which enables 7.3 g to be recovered after evaporation of the solvent.

The aqueous phase, which contains the sodium salt of the desired acid, is acidified to pH 5 by addition of hydrochloric acid and extracted three times with 200 ml of dichloromethane. The organic phases of the extraction are combined and dried over magnesium sulphate, filtered and concentrated in a rotary evaporator. An oil is obtained and is allowed to crystallize by addition of 150 ml of 2-butanone, while hot. The solid formed is filtered off and dried. 32.7 g of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acid are thus isolated.

Yield: 55.5%. M.P.:146-148°C.

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

calc.:	C 64.86	H 6.48	N 7.20	Cl^- 9.12
found:	C 64.67	H 6.46	N 7.19	Cl^- 9.39

A second crop of product can be obtained by concentration of the mother liquors (7.4 g).

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

32.7 g of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid are suspended in a mixture of 125 ml of water and 13.8 ml of 37% aqueous hydrochloric acid. This mixture is concentrated on a rotary evaporator. An oil is obtained and is crystallized by addition of 245 ml of 2-butanone. The crystals formed are filtered off, drained and dried. 34.2 g of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride are obtained.

Yield: 88%. M.P.: 228.22°C (Differential Scanning Calorimetry, DSC)

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 54.28	H 5.86	N 6.15	Cl^- 15.24	$Cl^{tot.}$ 23.22

A second crop of dihydrochloride can be obtained in the same way starting from the second crop of product obtained above under point 2 (4.5 g).

Taking into account the fact that the 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol is obtained in a yield of 90.4% from 1-[(4-chlorophenyl)phenylmethyl]-piperazine, the 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid dihydrochloride is thus obtained in three steps in an overall yield of 44.1% (or more than 48% if possible recycling of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol which has not reacted is taken into account), which constitutes a marked improvement with respect to the process according to European Patent No. 58,146.

WE CLAIM:

1. A process for the preparation of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride, characterized in that 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethanol is reacted with an alkali metal haloacetate in the presence of an alkali metal alcoholate, and in that the alkali metal salt thus obtained is converted into the corresponding acid and, if appropriate, into its dihydrochloride.

2. A process according to claim 1, characterized in that the alkali metal alcoholate is potassium tert-butoxide.

3. A process according to claim 1 or 2, characterized in that the reaction medium is resupplied regularly with the two reactants, the alkali metal alcoholate and the alkali metal haloacetate, in decreasing amounts and at regular intervals, until the reaction is as complete as possible.

4. A process according to any of claims 1 to 3, characterized in that the reaction is carried out at a temperature between 60°C and 100°C.

5. A process substantially as hereinbefore described in the foregoing example.

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