

PATENT SPECIFICATION

(11) 1 484 986

1 484 986

(21) Application No. 14292/76 (22) Filed 8 April 1976

(31) Convention Application No. 2 516 046

(32) Filed 12 April 1975 in

(33) Fed. Rep. of Germany (DT)

(44) Complete Specification published 8 Sept. 1977

(51) INT CL² C07C 93/20; A61K 31/205

(52) Index at acceptance

C2C 220 227 22Y 29X 29Y 313 31Y 323 32Y 338 364 366

368 36Y 620 624 628 650 658 65X 662 790 79Y LQ

A5B 361 365 36X 36Y 381 383 38Y 421 42Y 431 43Y 480

481 482 483 48Y 586 58Y 644 64Y 77Y



(54) NEW SALTS OF THE DIMETHYLAMINOETHYL ESTER OF P-CHLOROPHENOXY ACETIC ACID

(71) We, BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH, a Company of the Federal Republic of Germany, of Byk-Gulden-Straße 2, D-775 Konstanz, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to new salts of dimethylamino-ethyl *p*-chlorophenoxyacetate, processes for their production and pharmaceutical products containing these salts.

Dimethylamino-ethyl *p*-chlorophenoxyacetate or its hydrochloride are known as psychiatric drugs. In addition to their excellent stimulant action on the central nervous system, however, they possess an unpleasant bitter taste which gives rise to great difficulties particularly in oral application, and this can sometimes lead to a refusal to take such forms of administration, for example tablets or suspensions. Furthermore, the said compounds are found to be not particularly suitable for processing and fairly long storage because, for example, they undergo decomposition reactions as a result of the presence of traces of moisture, which make it necessary to apply special precautions during the production and storage of the forms for oral application. There has therefore been an urgent need to do away with the said defects.

According to the invention this problem is solved in that salts of dimethylamino-ethyl *p*-chlorophenoxyacetate and hydroxybenzoylbenzoic acids are provided for the application, and these possess a neutral to pleasantly sweet taste and in addition display excellent stability.

The invention relates to salts of dimethylamino-ethyl *p*-chlorophenoxyacetate of the general formula I.



in which R signifies a hydrogen atom, an alkyl radical with 1 to 4 carbon atoms or a hydroxy group.

The alkyl radicals used are straight or branched alkyl groups, examples of which are methyl, ethyl, propyl, isopropyl, butyl, secondary butyl and tertiary butyl groups.

Preferred compounds of the general formula I are those in which R is located in the ortho position in relation to the hydroxy group and represents an ethyl or methyl group. Particularly preferred is the compound of formula I in which R represents a hydrogen atom.

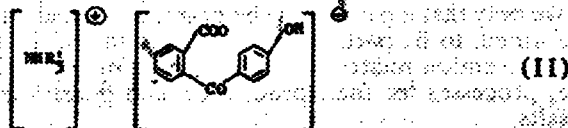
It is true that according to German laid open Application DT—OS 21 56 056 the bitter taste of a pharmacologically active amine can be improved by salt formation with *p*-hydroxybenzoylbenzoic acid.

In comparison with this, any other nitrogenous basic compounds with a bitter

taste have been reacted with 2-(*p*-hydroxybenzoyl)-benzoic acid to form the corresponding salts and their melting points and taste determined. The following table (page 4) shows the results. Whereas for the amines diethylamine, diisopropylamine and pyrrolidine a change in taste can be achieved by salt formation, leaving out of account whether a bitter after-taste or accompanying taste constitutes an improvement in taste, in the case of the alkanolamines 2-dimethylamino-ethanol, 3-dimethylamino-1-propanol and 1-dimethylamino-2-propanol, which are structurally well comparable with the basic component of the salts according to the invention or include same, no change in taste can be achieved by salt formation. In particular the taste of 2-dimethylaminoethanol, which is a structural component of dimethylamino-ethyl *p*-chlorophenoxyacetate is not improved at all by salt formation; the synthesised salt still shows a very unpleasant bitter taste. As against this, the 2-(*p*-hydroxybenzoyl)-benzoate of dimethylamino-ethyl *p*-chlorophenoxyacetate according to the invention is characterised by a particularly pleasant and faintly sweetish taste component, which in view of the abovementioned results—see also the following table—must be regarded as surprising.

TABLE

The taste of salts of the general formula II of different bases and 2-(*p*-hydroxybenzoyl)-benzoic acid



Base	NR', in formula II	Mp of salt	Taste of salt
Diethylamine	$\text{HN} \begin{cases} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{cases}$	181–183°	Sweetish, bitter after-taste
Diisopropylamine	$\text{HN} \begin{cases} \text{CH}(\text{CH}_3)_2 \\ \text{CH}(\text{CH}_3)_2 \end{cases}$	221–223°	sweetish, bitter accompanying taste
Pyrrolidine		228–230°	unpleasantly sweet bitter accompanying taste
2-dimethylamino-ethanol	$\text{N} \begin{cases} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{cases} \text{---} \text{CH}_2\text{---CH}_2\text{---OH}$	114–115°	very unpleasant bitter taste

3-dimethylamino-1-propanol	$\begin{array}{c} \text{H}_3\text{C} \\ \diagup \\ \text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2\text{OH} \\ \diagdown \\ \text{H}_3\text{C} \end{array}$	172-174°	unpleasant bitter taste
1-dimethylamino-2-propanol	$\begin{array}{c} \text{H}_3\text{C} \quad \text{OH} \\ \diagup \quad \diagdown \\ \text{N}-\text{CH}_2-\text{CH}-\text{CH}_3 \\ \diagdown \\ \text{H}_3\text{C} \end{array}$	156-158°	unpleasant bitter taste
Dimethylamino-ethyl p-chlorophenoxy acetate	$\text{Cl}-\text{C}_6\text{H}_4-\text{O}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OCH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$	146-148°	faintly sweet pleasant taste

The compounds according to the invention can be produced by known processes. A further object of the invention is therefore a process for the production of the compounds of the general formula I, which is characterised by the fact that dimethylamino-ethyl p-chlorophenoxyacetate is reacted with a suitably substituted 2-(p-hydroxy-benzoyl)-benzoic acid.

The reaction can be carried out, for example, by dissolving the dimethylamino-ethyl ester and the relevant hydroxybenzoylbenzoic acid separately in inert solvents, possibly accompanied by heating, and the two solutions are then mixed together. Suitable as solvents are, for example alcohols such as methanol, ethanol, isopropanol, or ethers, such as glyme, diglyme, tetrahydrofuran, or ketones such as preferably acetone. After they have been added together, the salt crystallises out almost quantitatively and can then be easily filtered at the pump, washed and dried. It has been found that the salt occurs in the pure state even if one starts off from initial products which are not quite pure or are coloured. Undissolved impurities can be filtered off, if desired, prior to the crystallisation.

It is also possible to start off from an easily accessible inorganic salt of the dimethylamino-ethyl ester, for example the hydrochloride, in which case this is preferably reacted in aqueous solution with an alkali metal salt, for example the sodium salt, of the hydroxybenzoylbenzoic acids. In this case, too, the desired salt of formula I crystallises out in the pure state straight away.

As a result of the additional purification effects achieved during the production of the compounds according to the invention, the requirements imposed on the synthesis of the initial products are considerably simplified.

The initial compounds for the production of the new salts are known. The production of dimethylamino-ethyl p-chlorophenoxyacetate and its hydrochloride are described in German Patent Specification DT-PS 1 300 955. Details regarding the production and use of hydroxybenzoylbenzoic acids are to be found inter alia in Ber. 26 (1893) 2263, Ann. de Chimie 11 (1940) 317-99 and in Finnish Patent Specification SF-PS 42 721 (abstracted in C.A. 74 (1971) 14183 r).

Because of their good stability, their excellent pharmacological properties and their pleasant taste, the compounds according to the invention are suitable for the treatment of symptoms or diseases which require the use of a psychiatric drug. One may mention by way of example insufficiency of cerebral performance as a result of organic changes in the brain caused by age, sequelae and late sequelae after damage to the brain of traumatic, apoplectic, toxic or infectious aetiology with disorders of the consciousness and a restriction of mental performances, post-apoplectic and post-traumatic disorders of speech and paralyses, disorders of the

mental development of children and infants, restriction of the power of concentration and attention during school age.

Mammals which suffer from one or more symptoms of the type mentioned above may be treated by the process of the invention. The process is characterised by the fact that one administers to the sick mammal a therapeutically active and pharmacologically tolerable quantity of one or more salts of the general formula I.

The invention also comprises medicaments which are characterised by their containing one or more of the new active substances. If necessary the new medicaments contain, in addition to the new active substances, pharmaceutical supports for these active substances. The active substance content of these medicaments is from 1 to 95, preferably 10 to 85, percent by weight, reckoned on the final medicament.

The medicaments are preferably applied orally, but they can also be injected as solutions parenterally, for example intravenously. More advantageously, the pharmaceutical preparation of the active substance occurs in the form of unit doses which are calibrated for the type of administration desired. A unit dose can be, for example, a tablet, a capsule or a measured volume of powder, a granulate, a solution, an emulsion or a suspension or an ointment. Within the meaning of the present invention the term "unit dose" signifies a physically determined unit which contains an individual quantity of the active component mixed with a pharmaceutical support. The quantity of the active substance is then chosen in such a way that one or more units are usually required for a single therapeutical administration. However, it is also possible for a unit dose to be sub-divisible, for example in the case of tablets with a notch, if only a fraction such as a half or a quarter, of the sub-divisible unit is required for an individual therapeutical administration.

The pharmaceutical preparations according to the invention, if they occur in unit doses, contain from 1 to 1000 mg, particularly advantageously 50 to 750 mg and especially 100 to 500 mg of active substance. The therapeutical administration of the pharmaceutical preparations can be carried out from 1 to 4 times a day, for example after meals and/or in the evening. The dose administered depends upon the frequency of administration, the duration of the treatment, the nature and severity of the disease and upon the weight, age and condition of health of the patient. The daily dose for mammals is generally between 1 and 50 mg/kg body weight.

The pharmaceutical preparations consist as a rule of active substances according to the invention and non-toxic pharmacologically acceptable medicament supports, which are used as an admixture in the solid, semi-solid or liquid state, or as encapsulating media, for example in the form of a capsule, a tablet coating, a bag or other container for the therapeutically active component. A support can serve, for example, as a means of encouraging the absorption of the drug by the body, as an aid in formulation, as a sweetener, as a flavour, as a colouring material or as a preservative.

For oral application one may use, for example, tablets, pills, hard and soft capsules, for example of gelatin, dispersible powders, granulates, suspensions, emulsions, solutions or syrups.

Tablets can contain inert diluents, for example calcium carbonate, calcium phosphate, sodium phosphate or lactose; granulating and distributing agents, for example maize starch or alginates; binders, for example starch, gelatin or acacia gum; and lubricants, for example aluminium or magnesium stearate, talc or silicone oil.

Aqueous suspensions can contain suspension agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth or acacia gum; dispersants and wetting agents, for example polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyethylenesorbitol mono-oleate, polyethylenesorbitan mono-oleate or lecithin; preservatives, for example methyl or propyl hydroxybenzoates; flavourings; sweeteners, for example saccharose, lactose, dextrose, invert sugar syrup.

Oily suspensions may contain, for example, ground nut oil, olive oil, sesame oil, kojooil or liquid paraffin and thickeners, such as for example beeswax, hard paraffin wax or cetyl alcohol; also sweeteners, flavourings and anti-oxidants.

Emulsions may contain, for example, olive oil, ground nut oil or liquid paraffin as well as emulsants, such as for example acacia gum, gum tragacanth,

phosphatides, sorbitan mono-oleate, polyoxyethylenesorbitan mono-oleate, and sweeteners and flavourings.

For the parenteral application of the medicaments one uses sterile injectable aqueous suspensions, isotonic salt solutions or other solutions which can contain dispersants or wetting agents and/or pharmacologically compatible diluents, for example propyleneglycol or butyleneglycol.

Besides the new salts of dimethylamino-ethyl *p*-chlorophenoxyacetate, the pharmaceutical preparations can also contain one or more pharmacologically active components belonging to other groups of medicaments, for example substances which promote local circulation of the blood, such as derivatives of nicotinic acid and dimethylsulphoxide; and vitamins (such as vitamin B₁ chloride-hydrochloride, vitamin B₆ hydrochloride, vitamin B₁₂ cyanocomplex and thiamine disulphide).

The following examples illustrate the invention in greater detail without restricting it. The temperatures given are in degrees C. The abbreviation m.p. signifies melting point.

EXAMPLES

EXAMPLE 1.

Salt of dimethylamino-ethyl *p*-chlorophenoxyacetate and 2-(*p*-hydroxybenzoyl)-benzoic acid

22.4 g of 2-(*p*-hydroxybenzoyl)-benzoic acid are dissolved by heating in 100 mls of acetone and combined with a solution of 24 g of dimethylamino-ethyl *p*-chlorophenoxyacetate in 100 mls of acetone. After a short time the crystallisation of the salt takes place. It is filtered at the pump, washed with acetone and dried at 70°C. Yield 95% of theory. M.p. 147—149°.

EXAMPLE 2.

Salt of dimethylamino-ethyl *p*-chlorophenoxyacetate and 2-(*p*-hydroxy-*m*-methylbenzoyl)-benzoic acid

5.12 g of 2-(4'-hydroxy-3'-methylbenzoyl)-benzoic acid are dissolved at room temperature in 25 mls of acetone and combined with a solution of 5.14 g of dimethylamino-ethyl *p*-chlorophenoxyacetate in 10 mls of acetone. After allowing to stand for a short time, the salt crystallises out. It is filtered off, washed with acetone and dried at 70°C. Yield practically quantitative. M.p. 140—142°.

EXAMPLE 3.

Salt of dimethylamino-ethyl *p*-chlorophenoxyacetate and 2-(*m*, *p*-hydroxybenzoyl)-benzoic acid

0.205 g of dimethylamino-ethyl *p*-chlorophenoxyacetate are dissolved in 3 mls of acetone and mixed with a solution of 0.206 g of 2-(3',4'-dihydroxybenzoyl)-benzoic acid in acetone. The salt crystallises out straight away. After filtering, washing with acetone and drying at 70°C, one obtains the benzoate with a melting point of 164—166° in a practically quantitative yield.

EXAMPLE 4.

Salt of dimethylamino-ethyl *p*-chlorophenoxyacetate and 2-(*p*-hydroxybenzoyl)-benzoic acid

29.4 g of dimethylamino-ethyl *p*-chlorophenoxyacetate hydrochloride are dissolved in 80 mls of iced water and mixed with an aqueous solution of sodium 2-(4'-hydroxybenzoyl)-benzoate, produced from 24.2 g of 2-(4'-hydroxybenzoyl)-benzoic acid and 4 g of sodium hydroxide in 200 mls of water. After a short time the benzoate is precipitated. It is filtered at the pump, washed with water and dried at 90°. The yield amounts to 45 g. M.p. 144—146°.

EXAMPLE 5.

For the production of a granulate the following are processed in the usual way:

Dimethylamino-ethyl *p*-chlorophenoxyacetate 2-(4'-hydroxybenzoyl)-benzoate (prepared according to Example 1) 340.00 mg

Maize starch European Pharmacopoeia I 784.50 mg

	Glucose monohydrate German Pharmacopoeia 7	1,000.00 mg	
	Saccharose powder German Pharmacopoeia 7	837.00 mg	
	Vanillin German Pharmacopoeia 7	37.50 mg	
5	4-(4-sulpho-1-phenylazo)-1-(4-sulphophenyl)-5-hydroxypyrazolone-3-carboxylic acid (tri-sodium salt)	1.00 mg	5
		<u>3,000.00 mg</u>	

EXAMPLE 6.

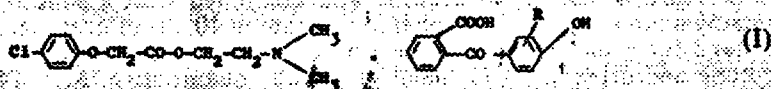
For the production of a tablet the following are processed in the usual way:

10	Dimethylamino-ethyl <i>p</i> -chlorophenoxyacetate 2-(4'-hydroxybenzoyl)-benzoate (prepared according to Example 1)	340.00 mg	10
	Maize starch European Pharmacopoeia I	160.00 mg	
	Milk sugar German Pharmacopoeia 7	100.00 mg	
	Talc German Pharmacopoeia 7	40.00 mg	
	Magnesium stearate U.S. Pharmacopoeia XVIII	10.00 mg	
15		<u>650.00 mg</u>	15

WHAT WE CLAIM IS:—

1. Dimethylamino-ethyl *p*-chlorophenoxyacetate salts of the general formula

I



20 in which

R signifies a hydrogen atom, an alkyl radical with 1 to 4 carbon atoms or a hydroxy group.

2. Compounds in accordance with claim 1, in which R signifies an ethyl or methyl group in the ortho position in relation to the hydroxy group.

25 3. Dimethylamino-ethyl-*p*-chlorophenoxyacetate 2-(*p*-hydroxybenzoyl)-benzoate.

4. Dimethylamino-ethyl-*p*-chlorophenoxyacetate 2-(*p*-hydroxy-*m*-methyl-benzoyl)-benzoate.

30 5. Dimethylamino-ethyl-*p*-chlorophenoxyacetate 2-(*m*, *p*-dihydroxy-benzoyl)-benzoate.

6. A process for the production of compounds of the general formula I according to claim 1, characterised by the fact that dimethylamino-ethyl *p*-chlorophenoxyacetate is reacted with the appropriate 2-(*p*-hydroxybenzoyl)-benzoic acid.

35 7. A process for the production of a compound of claim 2, characterised by the fact that dimethylamino-ethyl *p*-chlorophenoxyacetate is reacted with the appropriate 2-(*p*-hydroxybenzoyl)-benzoic acid.

8. A process for the production of the compound of claim 3, characterised by the fact that dimethylamino-ethyl *p*-chlorophenoxyacetate is reacted

40 9. A process as claimed in any one of claims 6, 7 or 8 wherein dimethylamino-ethyl *p*-chlorophenoxyacetate and the appropriate 2-(*p*-hydroxybenzoyl)-benzoic acid are dissolved separately in inert solvents, if desired with heating, and the two solutions are then mixed together.

45 10. A process as claimed in claim 9 wherein the solvent is an alcohol, an ether or a ketone.

11. A process for the production of compounds of the general formula I



15

according to claim 1 wherein an inorganic salt of dimethylamino-ethyl *p*-chloro-phenoxyacetate is reacted with an alkali metal salt of the 2-(*p*-hydroxybenzoyl)-benzoic acid.

5

12. Medicaments containing a compound according to any one of claims 1 to 5 in admixture with one or more solid or liquid non-toxic pharmaceutically acceptable inert carriers.

5

13. A pharmaceutical preparation comprising 1 to 95% by weight of a compound according to any one of claims 1 to 3 in admixture with one or more solid or liquid non-toxic pharmaceutically acceptable inert carriers.

10

14. A method for the preparation of compounds of the general formula I according to claim 1 substantially as described with reference to any one of Examples 1 to 4 hereinbefore set forth.

10

15. A compound of the general formula I according to claim 1 when prepared by the method claimed in any one of claims 6 to 11.

REID CLARKE & CO.,
Chartered Patent Agents,
Agents for the Applicants,
Craven House,
121 Kingsway,
London WC2B 6PJ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

