

PATENT SPECIFICATION

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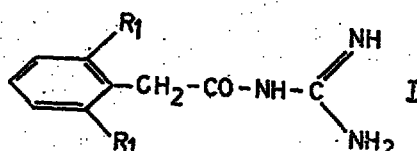
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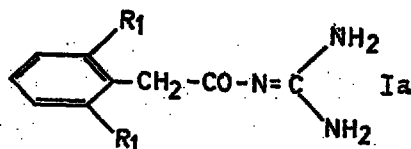
(54) PHENACETYL GUANIDINES AND THEIR PREPARATION

(71) We, DR. A. WANDER S.A., 115
 Monbijoustrasse, 3001 Berne, Switzerland, a
 Swiss Body Corporate, do hereby declare the
 invention, for which we pray that a patent
 5 may be granted to us, and the method by
 which it is to be performed, to be particularly
 described in and by the following state-
 ment:—

This invention relates to phenyl acetyl-
 10 guanidines and their preparation. The pre-
 sent invention provides compounds of general
 formula I,



15 in which R₁ signifies a chlorine atom or
 the methyl radical, and their tautomeric com-
 pounds of general formula Ia,

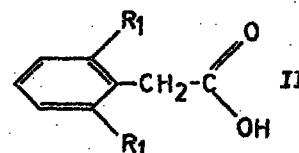


20 in which R₁ has the above significance,
 and their acid addition salts.

In the following description for the sake
 of brevity, a reference to compounds of
 general formula I is intended also to embrace
 the tautomeric compounds of formula Ia.

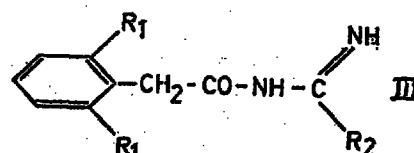
25 The compounds of general formula I and
 their acid addition salts may be obtained by
 a process characterized either by

a) reacting a compound of general formula
 II,



30 in which R₁ has the above significance,
 or a reactive, functional acid derivative there-
 of, with guanidine, or

b) reacting with ammonia a compound of
 general formula III,



35 in which R₁ has the above significance and
 R₂ signifies a reactive radical capable
 of being split off together with one of
 the hydrogen atoms in ammonia,
 and when the resulting compound of formula
 I is obtained in the form of an acid addition
 salt, optionally liberating the free base there-
 from, and/or when the resulting compound
 of formula I is obtained in the free base
 form, optionally salifying it.

40 In the process described under section a),
 suitable reactive, functional acid derivatives
 of the compounds of formula II include
 halides preferably chlorides or bromides, and
 esters with alkanols of 1 to 4 carbon atoms.
 45 When a halide is used and it is desired to
 obtain the compound of formula I in the
 form of a free base directly, the reaction
 may be effected in the presence of an acid
 binding agent e.g. triethylamine, or by using
 55 at least a 100% excess of guanidine. It will

be appreciated that in the absence of such an acid binding agent or excess of guanidine, an acid addition salt of the compound of formula I may be obtained, from which the free base may be liberated in manner known *per se* e.g. by treatment with dilute aqueous alkali metal hydroxide solutions.

The reaction described under section a) is preferably carried out in the presence of an organic solvent which is inert under the reaction conditions e.g. isopropanol or toluene. It may be carried out at a temperature between room temperature (20—25°C) and the reflux temperature of the reaction medium, preferably between room temperature and 80°C. The progress of reaction may be followed by, for example, thin layer chromatography.

In the process described under section b) suitable starting materials include, for example, those wherein the reactive radical is an alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or a substituted or unsubstituted aralkylthio radical, especially a methoxy, methylthio, or *p*-nitrobenzylthio radical. The reaction is preferably effected in an organic solvent which is inert under reaction conditions e.g. isopropanol. The ammonia reactant is suitably in the form of a concentrated aqueous solution and the reaction mixture may be stirred at a temperature between 20° and 80°C for 6 to 24 hours in order to complete the reaction.

The compounds of formula I produced in accordance with the above processes may be isolated in manner known *per se* e.g. by extraction, precipitation or salt formation, and may be purified in manner known *per se* e.g. by recrystallization.

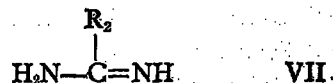
The compounds of general formula I are basic compounds, solid at room temperature. They may be converted into their acid addition salts by reacting with suitable organic or inorganic acids. Suitable organic acids for acid addition salt formation include toluene sulphonic acid, acetic acid, malonic acid, succinic acid, malic acid, maleic acid, and tartaric acid and suitable inorganic acids include hydrohalic acids, sulphuric acid, nitric acid and phosphoric acid.

The compounds of general formula II used as starting materials in section a) are known; the functional acid derivatives of compounds of general formula II used in accordance with the invention are known or may be produced in manner known *per se*.

The compounds of general formula III used as starting materials in section b) are new.

The compounds of formula III may be

prepared by reacting a halide preferably a chloride or bromide, or a compound of formula II with a compound of formula VII,



in which R₂ has the above significance.

The process may be carried out in an organic solvent which is inert under the reaction conditions e.g. acetone, preferably at room temperature. Preferred reactants of formula VII are compounds wherein the carbon atom carries an alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or a substituted or unsubstituted aralkylthio radical, especially a methoxy, methylthio, or *p*-nitrobenzylthio radical as substituent. When said substituent is a substituted or unsubstituted aralkylthio radical, an excess of the reactant is preferably used.

The resulting compounds of general formula III may be isolated in manner known *per se*, e.g. by precipitating with a precipitant, and may subsequently be purified in manner known *per se*, e.g. by recrystallization.

The compounds of general formula VII used as starting materials for the above process are known or may be produced in manner known *per se*.

The compounds of general formula I and their pharmaceutically acceptable acid addition salts are characterized by valuable pharmacodynamic properties, especially however by an antihypertensive effect. They are therefore indicated for use in the treatment of hypertonia in general and particularly in the treatment of essential and renal hypertonia.

The antihypertensive effect is demonstrated pharmacologically by a subsiding of the contraction of the nictitation membrane in cats in the case of preganglionic and postganglionic stimulus of the cervical part of the sympathetic nervous system. In order to measure this effect the dose of active compound (ED₅₀) is ascertained with which a 50% reduction of the nictitation membrane contraction occurs [Caviezel R. et al., Archiv Internat. de Pharmacodynamic et de Therapie 141, 331 (1963)]. The following table gives a comparison of the values ascertained for the 2,6-disubstituted phenyl-acetyl-guanidines, produced in accordance with the invention, with those of guanethidine known as the most effective antihypertensive, whereby the superiority of the compounds produced in accordance with the invention is demonstrated.

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Active compound		Reduction in the stimulation of the cervical part of the sympathetic nervous system ED ₅₀ mg/kg i.v. (cats)
5	2,6-dichlorophenyl-acetyl-guanidine	0.3
	2,6-dimethylphenyl-acetyl-guanidine	1.0
	guanethidine	2.0

The indicated total daily dose of compounds of general formula I is 1 to 10 mg. A suitable unit dose may contain 1—2 mg of the compounds of general formula I.

The compounds of general formula I and their pharmaceutically acceptable acid addition salts produced in accordance with the invention may be used as pharmaceuticals on their own or in the form of appropriated medicinal preparations for oral administration, e.g. in the form of tablets, dragées, or for parenteral administration, e.g. in the form of injectable solutions.

The invention also provides a pharmaceutical composition comprising a compound of formula I or Ia, stated above, or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable carrier.

The following non-limitative Examples, all temperatures are uncorrected.

EXAMPLE 1

2, 6 - dichlorophenyl - acetyl - guanidine.

A solution of 3.245 g (0.055 moles) of guanidine in isopropanol is added to a solution of 11.7 g (0.05 moles) of 2, 6 - dichlorophenyl - acetic acid ethyl ester (B.P. 142—143°C/12 mm of Hg) in 20 cc of isopropanol. The reaction mixture is allowed to stand over night and is subsequently concentrated by evaporation. After recrystallizing the residue from methanol/ether 2, 6 - dichlorophenyl - acetyl - guanidine is obtained in the form of white grains having a melting point of 225—227°C.

EXAMPLE 2

2, 6 - dichlorophenyl - acetyl - guanidine hydrochloride.

A solution of 5.6 g (0.025 moles) of 2, 6 - dichlorophenyl - acetic acid chloride (B.P. 137—138°C/12 mm of Hg) in 10 cc of toluene is added dropwise to a mixture of 4.5 g (0.076 moles) of guanidine and 60 cc of toluene. The reaction mixture is allowed to stand at room temperature for 20 minutes, is then heated on a steam bath for 2 hours and is subsequently cooled. The resulting precipitate is filtered off and washed twice with 25 cc amounts of water in order to dissolve the guanidine hydrochloride. The residue (2, 6 - dichlorophenyl - acetyl - guanidine) is washed with chloroform for further purification and is then dissolved in 50 cc of isopropanol. The pH-value of the solution is adjusted to 6 with

ethanolic hydrochloric acid and the solution is cooled. The resulting white needles are again washed with chloroform. The resulting 2, 6 - dichlorophenyl - acetyl - guanidine hydrochloride has a melting point of 213—216°C.

EXAMPLE 3

2, 6 - dimethylphenyl - acetyl - guanidine hydrochloride.

A solution of 17.8 g (0.1 mole) of 2, 6 - dimethylphenyl - acetic acid methyl ester (B.P. 122—123°C/11 mm of Hg) in 100 cc of isopropanol is added at room temperature to a stirred solution of 6.5 g (0.11 moles) of guanidine in 100 cc of isopropanol. The reaction mixture is subsequently stirred for a further hour and is then concentrated by evaporation in a vacuum. The resulting rubber-like residue, consisting of 2, 6 - dimethylphenyl - acetyl - guanidine, is dissolved in isopropanol and the pH value of the solution is adjusted to 2 with ethanolic hydrochloric acid. White needles are obtained, which are separated and re washed with isopropanol. 2, 6 - dimethylphenyl - acetyl - guanidine hydrochloride, having a melting point of 229—231°C (with decomposition) is obtained.

EXAMPLE 4

2, 6 - dichlorophenyl - acetyl - guanidine hydrochloride.

A solution of 65.7 g (0.3 moles) of 2, 6 - dichlorophenyl - acetic acid methyl ester (B.P. 149°C/17 mm of Hg) in 200 cc of isopropanol is added to a solution of 19.5 g (0.33 moles) of guanidine in 150 cc of isopropanol. The resulting reaction mixture is stirred for 15 minutes and is then concentrated by evaporation in a vacuum. The resulting white residue, consisting on 2, 6 - dichlorophenyl - acetyl - guanidine, is suspended in 100 cc of isopropanol, whereupon acidification is effected with ethanolic hydrochloric acid. The resulting precipitate is crystallized from isopropanol/ethanol and recrystallized from ethanol. 2, 6 - dichlorophenyl - acetyl - guanidine hydrochloride is obtained in the form of white needles having a melting point of 215—217°C.

EXAMPLE 5

2, 6 - dichlorophenyl - acetyl - guanidine.

10 cc of a concentrated aqueous ammonia solution are added to a solution of 1.4 g

- (0.005 moles) of S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea in 40 cc of isopropanol and the resulting reaction mixture is stirred at 60°C for 15 hours. Upon cooling a precipitate is formed which is filtered off and washed with water. 2, 6 - dichlorophenyl - acetyl - guanidine is obtained in the form of white needles having a melting point of 220—226°C.
- 10 The S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea, used as starting material in the above Example, is produced as follows:

- a) S-methyl-isothiurea.
- 15 29.4 g (0.105 moles) of dried pulverized S-methyl-isothiuronium sulphate are added to a solution cooled to 0°C of 4.6 g (0.2 moles) of sodium in 150 cc of methanol and the suspension is stirred for 2 hours. The precipitated sodium sulphate is filtered off and the filtrate concentrated by evaporation in a vacuum and ether is added thereto, whereby S - methyl - isothiurea, having a melting point of 75—78°C (with decomposition) is obtained.

- b) S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea.
- A solution of 5.6 g (0.025 moles) of 2, 6 - dichlorophenyl - acetyl chloride (B.P. 137—138°C/12 mm of Hg) in 10 cc of acetone is slowly added to a solution of 4.7 g (0.052 moles) of S-methyl-isothiurea in 120 cc of acetone, whereby the temperature of the mixture rises to 35°C. The resulting white precipitate (S - methyl - isothiurea hydrochloride) is filtered off. The filtrate is evaporated to dryness, whereby S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea, having a melting point of 108—112°C, results. After recrystallizing twice from di-isopropyl ether the melting point rises to 125—127°C.

EXAMPLE 6

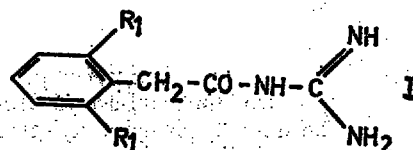
Description of a tablet composition.

45	2,6-dichlorophenyl-acetyl-guanidine hydrochloride	2 mg
	lactose	116 mg
	paraffin oil	2 mg
	gelatin	1 mg
	maize starch	13 mg
50	talcum	6 mg

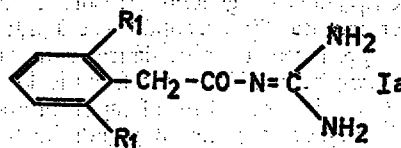
The weight of the tablets produced depends on the amount of active compound to be administered. The tablets may be provided with a breaking slit.

55 WHAT WE CLAIM IS:—

1. A process for the production of compounds of general formula I,

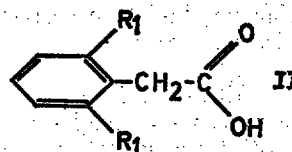


in which R₁ signifies a chlorine atom or a methyl radical, and/or their tautomeric compounds of general formula Ia,



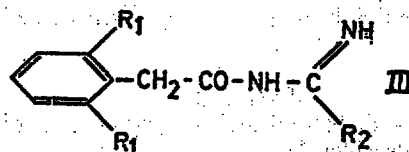
in which R₁ has the above significance, and their acid addition salts, characterized either by

a) reacting a compound of general formula II,



in which R₁ has the above significance, or a reactive, functional acid derivative thereof, with guanidine, or

b) reacting with ammonia a compound of general formula III,



in which R₁ has the above significance and R₂ signifies a reactive radical capable of being split off together with one of the hydrogen atoms in ammonia, and when the resulting compound of formula I and/or Ia is obtained in the form of an acid addition salt, optionally liberating the free base therefrom, and/or when the resulting compound of formula I and/or Ia is obtained in the free base form, optionally salifying it.

2. A process according to Claim 1 in which the compound of formula II, or a reactive functional acid derivative thereof, is reacted with guanidine in an organic solvent

- (0.005 moles) of S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea in 40 cc of isopropanol and the resulting reaction mixture is stirred at 60°C for 15 hours. Upon cooling a precipitate is formed which is filtered off and washed with water. 2, 6 - dichlorophenyl - acetyl - guanidine is obtained in the form of white needles having a melting point of 220—226°C.
- The S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea, used as starting material in the above Example, is produced as follows:

- a) S-methyl-isothiurea.
- 29.4 g (0.105 moles) of dried pulverized S-methyl-isothiuronium sulphate are added to a solution cooled to 0°C of 4.6 g (0.2 moles) of sodium in 150 cc of methanol and the suspension is stirred for 2 hours. The precipitated sodium sulphate is filtered off and the filtrate concentrated by evaporation in a vacuum and ether is added thereto, whereby S - methyl - isothiurea, having a melting point of 75—78°C (with decomposition) is obtained.

- b) S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea.

- A solution of 5.6 g (0.025 moles) of 2, 6 - dichlorophenyl - acetyl chloride (B.P. 137—138°C/12 mm of Hg) in 10 cc of acetone is slowly added to a solution of 4.7 g (0.052 moles) of S-methyl-isothiurea in 120 cc of acetone, whereby the temperature of the mixture rises to 35°C. The resulting white precipitate (S - methyl - isothiurea hydrochloride) is filtered off. The filtrate is evaporated to dryness, whereby S - methyl - N - 2, 6 - dichlorophenyl - acetyl - isothiurea, having a melting point of 108—112°C, results. After recrystallizing twice from di-isopropyl ether the melting point rises to 125—127°C.

EXAMPLE 6

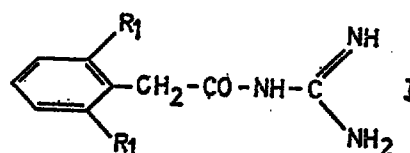
Description of a tablet composition.

- | | |
|---|--------|
| 2,6-dichlorophenyl-acetyl-guanidine hydrochloride | 2 mg |
| lactose | 116 mg |
| paraffin oil | 2 mg |
| gelatin | 1 mg |
| maize starch | 13 mg |
| talcum | 6 mg |

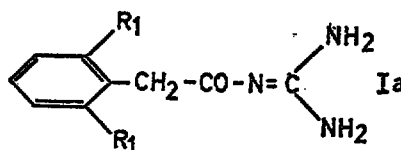
The weight of the tablets produced depends on the amount of active compound to be administered. The tablets may be provided with a breaking slit.

55, WHAT WE CLAIM IS:—

1. A process for the production of compounds of general formula I,

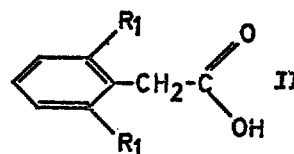


in which R₁ signifies a chlorine atom or a methyl radical, and/or their tautomeric compounds of general formula Ia,



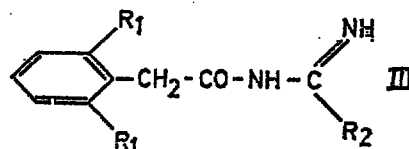
in which R₁ has the above significance, and their acid addition salts, characterized either by

- a) reacting a compound of general formula II,



in which R₁ has the above significance, or a reactive, functional acid derivative thereof, with guanidine, or

- b) reacting with ammonia a compound of general formula III,



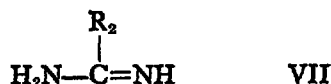
in which R₁ has the above significance and R₂ signifies a reactive radical capable of being split off together with one of the hydrogen atoms in ammonia, and when the resulting compound of formula I and/or Ia is obtained in the form of an acid addition salt, optionally liberating the free base therefrom, and/or when the resulting compound of formula I and/or Ia is obtained in the free base form, optionally salifying it.

2. A process according to Claim 1 in which the compound of formula II, or a reactive functional acid derivative thereof, is reacted with guanidine in an organic solvent



which is inert under the reaction conditions, at a temperature between room temperature and 80°C.

3. A process according to Claim 1 or 2 in which the reactive functional acid derivative of compound of formula II, is a halide or ester with an alkanol of 1 to 4 carbon atoms.
4. A process according to Claim 3 in which the reactive functional acid derivative is a halide, and the reaction is carried out in the presence of a acid binding agent or by using at least a 100% excess of guanidine to obtain a compound of formula I and/or Ia directly in free base form.
5. A process according to Claim 1 in which the compound of formula III is reacted with a concentrated aqueous solution of ammonia, in an organic solvent which is inert under the reaction conditions, at a temperature between 20° and 80°C for 6 to 24 hours.
6. A process according to Claim 1 or 5 wherein there is used a compound of formula III, in which R₂ signifies a alkylthio of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or a substituted or unsubstituted aralkylthio radical.
7. A process according to any one of Claims 1, 5 and 6 in which the compound of formula III is prepared by reacting a halide of a compound of formula II with a compound of formula VII,



- in which R₂ has the significance stated in Claim 1.

8. A process according to Claim 7 wherein there is used an excess of a compound of formula VII in which R₂ signifies an aralkylthio radical.

9. A process for the preparation of phenyl-acetyl guanidine derivatives substantially as herein described with reference to any one of Examples 1 to 5.

10. Compounds of formula I or Ia, stated in Claim 1, and their acid addition salts whenever prepared by the process of any one of the preceding claims.

11. Compounds of formula I or Ia, stated in Claim 1, and their acid addition salts.

12. 2, 6 - dichlorophenyl - acetyl - guanidine.

13. 2, 6 - dimethyl - phenyl - acetyl - guanidine.

14. Acid additions salts of the compounds claimed in Claims 12 and 13.

15. A pharmaceutical composition comprising a compound of formula I or Ia, stated in Claim 1, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition according to Claim 15, in unit dosage form containing from 1 to 2 mgs of the said compound or salt.

17. A pharmaceutical composition according to Claim 15 substantially as hereinbefore described.

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