PATENT SPECIFICATION

NO DRAWINGS

863,552

Date of Application and filing Complete Specification: April 4, 1957.
No. 22979/60.
Application made in Switzerland on April 19, 1956.
Application made in Switzerland on Jan. 29, 1957.
(Divided out of No. 863,546).
Complete Specification Published: March 22, 1961.

Index at acceptance:—Classes 2(3), C1G(5B:6A1), C5(A4:E2); **and 81(1),** B1(G:S), B2(G:S).

International Classification:—C07d. A61k.

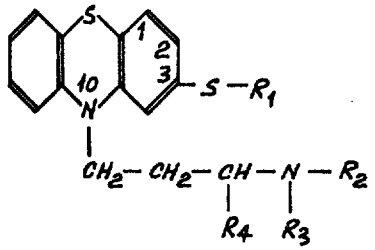
COMPLETE SPECIFICATION

3-Mercapto-Phenthiazine Derivatives and Salts thereof

We, SANDOZ LTD., of Lichstrasse 35, Basle, Switzerland, a Swiss Body Corporate, 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 present invention relates to a process for the production of phenthiazine derivatives substituted in the 3-position by a monovalent sulphur function; it also relates to said derivatives themselves and acid addition salts thereof.

The present invention consists in a process for the production of phenthiazine derivatives substituted in the 3-position by a monovalent sulphur function, said phenthiazine derivatives having the general formula I



I

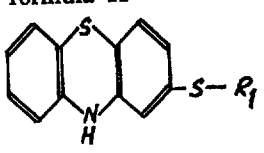
in which

R_1 = a methyl group,

R_2 = hydrogen or an alkyl group containing up to 4 carbon atoms, and

$R_3 + R_4$ = $-(CH_2)_3-$ or $-(CH_2)_4-$, thus forming a 5 or 6 membered ring with the carbon and the nitrogen atoms adjacent R_4 and R_3 respectively,

characterized in that a phenthiazine having the general formula II

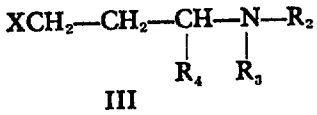


II

in which

R_1 has the above significance,

is condensed with a primary, secondary or tertiary ω-halogen alkyl amine of the general formula III



III

in which

R_2, R_3 and R_4 have the above significance, and

X represents chlorine or bromine.

The present invention also consists in the above mentioned phenthiazine derivatives, said phenthiazine derivatives being new compounds, and their acid addition salts.

The process of the invention may, for example, be carried into effect in such manner that a phenthiazine derivative of formula II is dissolved in an organic solvent therefor, for example an aromatic solvent (e.g. benzene, toluene or xylene), and is condensed with an ω-halogen-alkylamine of formula III at room temperature or at an elevated temperature in the presence of an alkaline condensation agent, for example an alkali metal (e.g. metallic sodium), or compounds thereof; suitable alkali metal compounds are alkali metal hydroxides, amides, hydrides or alcoholates, specific examples being sodium hydroxide, potassium hydroxide, sodium amide, lithium hydride and sodium *tert*-butylate.

The condensation reaction in the process of the invention can also be carried out without solvent by melting the reactants together; in this case it is possible to dispense with the presence of a condensation agent. However, this procedure results in a lower yield of the required phenthiazine of the general formula I.

After completing the condensation reaction, the reaction mixture should be extracted, e.g. by shaking with water, and the solvent evap-

[*Price 3s. 6d.*]

orated at a pressure below atmospheric pressure; it should be noted, however, that the compounds of the present invention can be extracted from the reaction mixture by dilute mineral acids or organic acids and can be separated out from the aqueous phase by adding an alkaline solution (e.g. potassium or sodium hydroxide solution) or ammonia. When the compounds of the invention are precipitated in the process of the invention as solids, they can be filtered off, whereas when they precipitate in the form of an oil, they can be taken up in benzene or another solvent which is immiscible with water and can then be freed from the solvent by evaporation. The compounds of the invention in the form of free bases can be purified by high vacuum distillation and converted by methods known *per se* into acid addition salts with organic or inorganic acids.

As already indicated above, the phenthiazine derivatives of the general formula I are bases which have not hitherto been described; these phenthiazine derivatives differ from all prior known phenthiazine derivatives by having a monovalent sulphur function in the 3-position, are oleaginous or crystalline at room temperature and form stable crystalline salts with organic or inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, succinic acid, maleic acid, acetic acid, benzoic acid and hexahydrobenzoic acid.

At least some of the compounds of the invention have pharmacodynamic properties which can be made use of in therapy, for example in order to increase the effect of drugs having a narcotic, hypnotic or analgesic action, and are consequently suitable for the treatment of patients prior to the administration of anaesthetics in order to achieve potentiation; a further possible use is for the treatment of allergies and also as spasmolytics or neuroplegics.

Furthermore, the compounds of the invention have a strong fungicidal action. It is known that infection of the skin by hyphomycetes, especially in its most common form, which is interdigital mycosis, is widespread. About 20% of children between 6 and 7 years old and more than 80% of people between 17 and 19 years old are affected thereby. Most known fungicides commercially available for treatment of humans are intended for combating these dermatomycoses or dermatophytes. The therapeutic success so far achieved by means of these known fungicides is however so low that the development of preparations with a powerful fungicidal action while being non-toxic to the human organism when administered in therapeutic doses is an urgent requirement of modern therapy. It has now surprisingly been found that the compounds of the aforementioned formula I have a strong fungicidal action with low toxicity. The action of the compounds of the invention on, for example, candida albicans, which is the irritant causing most dermatophytes is superior to the previously known fungicides. The new compounds can be dispensed *per os* (e.g. in the form of tablets) or parenterally, but also locally, for example by brushing on the affected skin portions their solutions in an organic solvent (e.g. in ethanol) or aqueous solutions of their acid addition salts. The present invention thus also includes pharmaceutical preparations containing, in addition to an inert diluent or carrier, the above phenthiazine derivatives.

In the following examples which illustrate the process of the invention, but are in no way limitative, all temperatures are stated in degrees Centigrade. The melting and boiling points are uncorrected.

It should be noted that 3-methylmercaptophenthiazine is described and claimed in Patent Specification No. 11050/57 (Serial No. 863,547) and also No. 802,726.

EXAMPLE 1.

3 - methylmercapto - 10 - [2^1 - N - methylpyrrolidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

59.0 g of thionyl chloride are added dropwise at 10° while stirring and within 10 minutes to a solution of 31.0 g of 2 - (N-methylpyrrolidyl-2^1)-ethane-1-ol in 200 cc of chloroform, the solution being saturated with hydrogen chloride. While continuing stirring, the reaction mixture is heated under reflux for 2 hours at a water bath temperature of 70° and is then freed as far as possible from the excess thionyl chloride and from the chloroform in a partial vacuum. The evaporation residue is taken up in 160 cc of ice-cold 3N sodium hydroxide solution and covered with 100 cc of ether. After adding 30 g of potassium hydroxide, the material is extracted by shaking three times with 200 cc of ether on each occasion. The ether extracts which are reunited are dried over a small amount of sodium sulphate, filtered and the solvent is distilled off in a water bath at a temperature of approximately 40—50°.

The residue resulting from evaporation is distilled *in vacuo*. The resulting 2-(N-methylpyrrolidyl - 2^1) - 1 - chloroethane has the boiling point of 65°/13 mm of Hg.

16.65 g of 3-methylmercapto-phenthiazine, 3.18 g of finely powdered sodium amide and 100 cc of absolute xylene are heated to boiling point while stirring and during three hours under reflux at a bath temperature of 180°. Without interrupting the heating, a solution of 10.0 g of 2-(N-methyl-pyrrolidyl-2^1)-1-chloroethane in 10 cc of absolute xylene is added dropwise within 1 and a half hours. After heating for another 3 hours, the reaction mixture is cooled and, after adding 5 g of ammonium chloride, it is extracted by shaking three times with 50 cc of water on each

occasion. The xylene solution is extracted once with 75 cc of 15% tartaric acid and then twice with the said acid, using 20 cc on each occasion. The tartaric acid extracts are washed with 100 cc of benzene and made alkaline to phenolphthalein with 35 cc of concentrated sodium hydroxide solution. The resulting precipitated oleaginous base is taken up in a total of 175 cc of benzene. The benzene layer is dried over potassium hydroxide, filtered and concentrated by evaporation at reduced pressure. The evaporation residue is distilled in a high vacuum; after first runnings distilling over at a temperature up to 208° with a pressure of 0.008 mm of Hg have been separated, the main fraction, which distils at 208—210° at the same pressure and which is 3 - methylmercapto - 10 - [2^1 - (N - methyl - pyrrolidyl - 2^{11}) - ethyl - 1^1]-phenthiazine, is collected. The boiling point of the analytically pure base is 209°/0.008 mm of Hg.

When a solution of 14.40 g of the free base in 125 cc of acetic ester is added to a solution of 6.06 g of tartaric acid in 900 cc of acetic ester, the latter solution being cooled to 0°, the tartrate of 3-methylmercapto-10-[2^1-(N-methyl-pyrrolidyl-2^{11})-ethyl-1^1]-phenthiazine is precipitated. M.p. 115°, after sintering above 70°.

EXAMPLE 2.

3 - methylmercapto - 10 - [2^1 - (N - methylpiperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

m - Methylmercapto - aniline (b.p. 163—165°/16 mm of Hg) is condensed with the potassium salt of *o*-chlorobenzoic acid and the N - (*m*-methylmercapto-phenyl) - anthranilic acid (m.p. 139—141°) which is formed is decarboxylated by heating and subsequently distilling to form N - (*m*-methylmercapto-phenyl)-aniline (m.p. 59—61°).

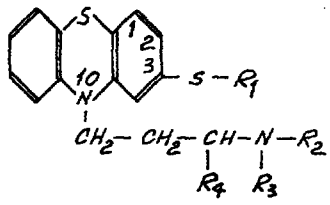
9.87 g of N - (*m*-methylmercapto-phenyl)-aniline are heated with 2.93 g of sulphur and 0.15 g of powdered iodine for 15 minutes in a bath at a temperature of about 160°. When the evolution of hydrogen sulphide has ended, the reaction mixture, with addition of animal charcoal, is first dissolved and recrystallized from 40 cc of chlorobenzene, and then from 25—30 cc of benzene at boiling temperature. The resulting lemon yellow 3-methylmercapto-phenthiazine has a melting point of 138—140°.

17.82 g of 3-methylmercapto-phenthiazine, 3.4 g of finely powdered sodium amide and 80 cc of absolute xylene are heated to boiling point while stirring during 2 hours under reflux with a bath temperature of 180°. Without interrupting the heating, a solution of 13.2 g of 2 - (N-methylpiperidyl - 2^1) - 1 - chloroethane in 40 cc of absolute xylene is added dropwise within 1 and a half hours. After heating for another 3 hours, the reaction mixture is cooled and, after adding 5 g of ammonium chloride, it is extracted by shaking three times with 25 cc of water in each case. The xylene solution is extracted once with 35 cc of 3N acetic acid, and then three times with 15 cc of said acid each time, the reunited acetic acid extracts are washed with 60 cc of ether and made alkaline to phenolphthalein with 25 cc of concentrated potassium hydroxide solution. The oleaginous base which separates out is taken up in a total of 100 cc of benzene. The benzene layer is dried over potassium hydroxide, filtered and concentrated by evaporation at reduced pressure. The residue resulting from evaporation is distilled in a high vacuum; after separating first runnings which distil over at a temperature up to 228° at a pressure of 0.02 mm of Hg, the main fraction distilling at 228—232° at the same pressure is collected, this being 3 - methylmercapto - 10 - [2^1 - (N - methylpiperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine. The analytically pure base has a boiling point of 230°/0.02 mm of Hg.

When a solution of 15.3 g of the free base in 125 cc of acetic ester is added to a solution of 6.78 g of tartaric acid in 1150 cc of acetic ester, this latter solution being cooled to 0°, the tartrate of 3 - methylmercapto - 10 - [2^1 - (N - methylpiperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is precipitated. The salt containing 1 mol of water of crystallization is decomposed at a temperature above 130° after sintering above 70°.

WHAT WE CLAIM IS:—

1. A process for the production of phenthiazine derivatives substituted in the 3-position by a monovalent sulphur function, said phenthiazine derivatives having the general formula I



I

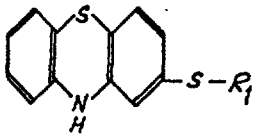
in which

R_1 = a methyl group,

R_2 = hydrogen or an alkyl group containing up to 4 carbon atoms, and

$R_3 + R_4$ = — $(CH_2)_3$— or —$(CH_2)_4$—, thus forming a 5 or 6 membered ring with the carbon and the nitrogen atoms adjacent R_4 and R_3 respectively,

characterized in that a phenthiazine having the general formula II



II

occasion. The xylene solution is extracted once with 75 cc of 15% tartaric acid and then twice with the said acid, using 20 cc on each occasion. The tartaric acid extracts are washed with 100 cc of benzene and made alkaline to phenolphthalein with 35 cc of concentrated sodium hydroxide solution. The resulting precipitated oleaginous base is taken up in a total of 175 cc of benzene. The benzene layer is dried over potassium hydroxide, filtered and concentrated by evaporation at reduced pressure. The evaporation residue is distilled in a high vacuum; after first runnings distilling over at a temperature up to 208° with a pressure of 0.008 mm of Hg have been separated, the main fraction, which distils at 208—210° at the same pressure and which is 3 - methylmercapto - 10 - [2^1 - (N - methyl - pyrrolidyl - 2^{11}) - ethyl - 1^1]-phenthiazine, is collected. The boiling point of the analytically pure base is 209°/0.008 mm of Hg.

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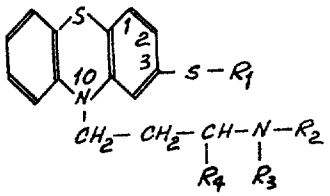
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I

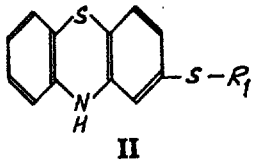
in which

R_1 = a methyl group,

R_2 = hydrogen or an alkyl group containing up to 4 carbon atoms, and

$R_3 + R_4$ = $-(CH_2)_3-$ or $-(CH_2)_4-$, thus forming a 5 or 6 membered ring with the carbon and the nitrogen atoms adjacent R_4 and R_3 respectively,

characterized in that a phenthiazine having the general formula II



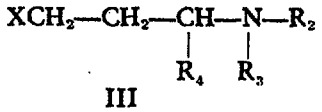
II

* C L M S *

in which

R_1 has the above significance,

is condensed with a primary, secondary or tertiary ω-halogen alkyl amine of the general formula III



III

in which

R_2, R_3 and R_4 have the above significance, and X represents chlorine or bromine.

2. A process according to claim 1, in which the condensation is effected in an organic solvent for the starting materials and in the presence of an alkaline condensation agent.

3. A process according to claim 2, in which the condensation agent is an alkali metal, an alkali metal hydroxide, an alkali metal amide, an alkali metal hydride or an alkali metal alcoholate, said solvent being an aromatic solvent.

4. A process according to claim 1, in which the condensation is effected in the absence of a solvent, the starting materials being reacted with one another to effect condensation at a temperature at which they are liquid.

5. A process for the production of the phenthiazine derivatives having the general formula I stated in claim 1, R_1, R_2, R_3 and R_4 being as defined in claim 1, substantially as herein described with reference to the example.

6. Phenthiazine derivatives having the general formula I stated in claim 1 whenever produced by the process claimed in any one of the preceding claims.

7. A process for the production of acid addition salts of the phenthiazine derivatives having the general formula I stated in claim 1, characterised in that the said phenthiazine derivatives are salified with an organic or inorganic acid.

8. A process according to claim 7, characterised in that the said acid for salifying is selected from hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, succinic acid, maleic acid, acetic acid, benzoic acid and hexahydrobenzoic acid.

9. 3 - methylmercapto - 10 - [2^1 - (N - methylpyrrolidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

10. The tartrate of 3 - methylmercapto-10 - [2^1 - (N - methyl - pyrrolidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

11. 3 - methylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

12. The tartrate of 3-methylmercapto-10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

13. Phenthiazine derivatives having the general formula I stated in claim 1, R_1, R_2, R_3 and R_4 having the significance stated in claim 1.

14. Acid addition salts of the compounds claimed in claim 13.

15. Salts according to claim 14, in which the acid portion is selected from hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, succinic acid, maleic acid, acetic acid, benzoic acid and hexahydrobenzoic acid.

16. Pharmaceutical preparations containing, in addition to an inert diluent, compounds claimed in any one of claims 9 to 15.

17. Pharmaceutical preparations according to claim 16, said preparations being in the form of tablets.

18. Pharmaceutical preparations according to claim 16, said preparations being in the form of injectable solutions.

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70, Chancery Lane, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

SPECIFICATION NO. 863,552

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of Westminster Bank Limited, of 41, Lothbury, London, E.C.2., a British Company.

THE PATENT OFFICE,
21st April, 1961

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