PATENT SPECIFICATION

NO DRAWINGS

890,912

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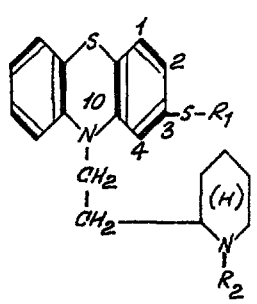
COMPLETE SPECIFICATION

3-Alkylmercapto-Phenthiazine Derivatives and their preparation

We, SANDOZ LTD., of Lichtstrasse 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 two novel acid addition salts of one of said derivatives.

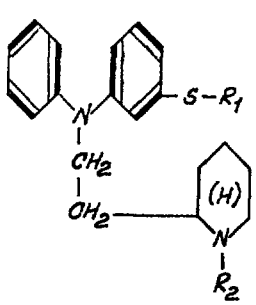
It has been found, in accordance with the present invention, that phenthiazine derivatives of the general formula I,



I

R_1=lower alkyl, aryl, aralkyl
R_2=lower alkyl,

can be obtained by treating a tertiary amine of the general formula II,



II

wherein R_1 and R_2 have the above significance, with a sulphur di-halide. It should be noted that the phrase "lower alkyl" as used herein means alkyl containing 6 or less carbon atoms; examples of such alkyl groups are those containing 4 or less carbon atoms, i.e. methyl, ethyl, propyl and butyl, it being permissible for the alkyl group to be a branched chain when it contains at least 3 carbon atoms.

According to Patent Specification No. 11049/57 (863,546), mercapto-phenthiazine derivatives of the formula I can be obtained by condensing an alkyl mercapto - phenthiazine with a 1 - halogeno - 2 - (N - alkyl - piperidyl - 2^1) - ethane; said specification contains claims to the derivatives of the formula I and their acid addition salts.

According to Patent Specification No. 10698/58 (Serial No. 863,549) it is possible to obtain alkyl mercapto - phenthiazine derivatives of the formula I by decarboxylating of the corresponding 10 - phenthiazine - carbonic acid ester derivatives.

The process of the present invention may be carried out, for example, by dissolving a N - [2 - (N^1 - alkyl - piperidyl - 2^1) - ethyl-1] - N - [mercapto - phenyl] - aniline derivative in an inert organic solvent (for example an aromatic solvent), e.g. benzene or toluene and adding a sulphur - dihalide whilst stirring, the reaction being effected at room temperature or at elevated temperature. After the reaction is complete the solvent is evaporated at a reduced pressure and the residue is taken up, after mixing with water and alkali metal hydroxide solution, in an inert organic solvent which is immiscible with water. The residue remaining after evaporation of the organic layer is then purified by high vacuum distillation and may be converted into an acid addition salt with an acid for the purpose of effecting further purification. This is especially necessary when the phenyl nuclei of the starting material are substituted, so that a mixture of various isomers is formed by the reaction, which isomers merely differ by the position

[*Price 4s. 6d.*]

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of the substituents. The separation of the components and their purification can then be effected by fractional crystallization of their acid addition salts.

The basic compounds produced according to the present process are oleaginous or crystalline at room temperature; they form stable acid addition salts with acids. Examples of such acids are:—hydrochloric acid, hydrobromic acid, sulphuric acid,, citric acid, maleic acid, tartaric acid, succinic acid, acetic acid, benzoic acid and hexahydrobenzoic acid.

The compounds produced in the examples given hereinafter have pharmacodynamic properties which may be used in therapy, for example, potentiating the effect of pharmaceuticals having a narcotic, hypnotic or analgesic action, and are therefore suitable for administration prior to giving anaesthetics. They can further be used for the treatment of allergies, or they may be used as sedatives, spasmolytics, antiemetics or neuroplegics. They may also be used in the treatment of various conditions of agitation.

In the following examples which illustrate the process of the invention without being limitative in any way, all temperatures are given in degrees Centigrade. The melting and boiling points are uncorrected.

EXAMPLE 1

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

340 g. of N - [*m* - methylmercapto - phenyl] - N - [2 - (N^1 - methylpiperidyl - 2^1) - ethyl] - aniline (boiling point 216°/0.01 mm of Hg) are dissolved in 5000 to 6000 cc of benzene to which is added whilst stirring, a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene. After a short while, ~~hydrochloride~~ separate out. The mixture is left to stand for 20 minutes at room temperature, the solvent is evaporated as soon as the reaction is complete at reduced pressure and the residue is then mixed with 2500 cc of water and 3N sodium hydroxide solution is added, until the mixture shows alkaline reaction. The precipitated material is extracted by shaking three times with 1000 cc of chloroform on each occasion. The chloroform extracts are reunited, dried over 300—400 g of potassium carbonate and evaporated at reduced atmospheric pressure. The residue from the evaporation is distilled in a high vacuum. After separating starting material distilling over at a temperature of up to 225° at a pressure of 0.06 mm of Hg, the main fraction, which distils at 225—235° at 0.02 mm of Hg is obtained containing 2 isomeric bases which are separated by fractional crystallization of the fumarate.

25 g of the base mixture and 8.3 g of fumaric acid are dissolved in 300 cc of boiling ethanol, filtered and left to stand at room temperature, whereby the fumarate of 3 - methylmercapto 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine (a new compound included in the present invention) separates out in crystalline form and the isomeric compound remains in solution. After recrystallizing from 100 cc of boiling ethanol, the salt has a melting point of 158—160° (decomposition). The fumarate of a preparation produced according to the Patent Specification 863,546 (Serial No. 11049/57) shows no depression of melting point when mixed with the fumarate of the compound of the present example. Melting point of 3 - methylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is 72—74°. Melting point of the hydrochloride (a new compound included in the present invention) is 158—160°, sintering above 153°. The tartrate crystallizes with 1 molecule of water of crystallization, melting point 130° (decomposition), sintering above 70°.

EXAMPLE 2

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

354 g of N - [*m* - ethylmercapto - phenyl] - N - [2-(N^1-methyl-piperidyl-2^1)-ethyl] - aniline (boiling point 206°/0.005 mm of Hg) are dissolved in 5000 to 6000 cc of benzene, and a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene is added whilst stirring. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature, after the reaction is complete the solvent is evaporated at reduced pressure and the residue is then mixed with 2500 cc of water and 3N sodium hydroxide solution is added until the mixture shows alkaline reaction. The mixture of the precipitated bases is extracted by three times shaking with 1000 cc of chloroform on each occasion, the reunited chloroform extracts are dried over 300—400 g of potassium carbonate and are evaporated at reduced pressure. The residue of the evaporation is then distilled in a high vacuum. After first runnings distilling over at a temperature up to 220° at a pressure of 0.008 mm of Hg have been separated, the main fraction which distils at 220—228° at the same pressure is collected.

A solution of 20 g of free base mixture in acetic acid-ethyl ester is added to a solution of a calculated quantity of tartaric acid in acetic acid-ethyl ester, whereby the tartrate of 3 - ethyl - mercapto - 10 - [2^1 - (N - methyl-piperidyl - 2^{11}) - ethyl - 1^1] -phenthiazine precipitates. After leaving to stand at room temperature filtration is effected. Melting point 135° (decomposition), sintering above 70°. The mixed melting point with a similar compound obtained according to Patent Specification 863,546 (Serial No. 11049/57) does not show depression. Boiling point of 3 - ethylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is

hydrochlorides

225° at 0.008 mm of Hg, melting point 57—59°.

EXAMPLE 3

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

368 g of N - [*m* - *n* - propylmercapto - phenyl] - N - [2 - (N^1 - methylpiperidyl - 2^1) - ethyl] - aniline (boiling point 198°/0.01 mm of Hg) are dissolved in 5000 to 6000 cc of benzene and 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene are added whilst stirring. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature. After the reaction is complete, the solvent is evaporated at reduced pressure and the residue is mixed with 2500 cc of water and 3N sodium hydroxide solution added until the mixture shows an alkaline reaction. The mixture of the precipitated bases is then extracted by shaking three times with 1000 cc of chloroform on each occasion and the united chloroform extracts are dried over 300—400 g of potassium carbonate and evaporated at reduced pressure. The residue of the evaporation is fractionally distilled in a high vacuum. After first runnings distilling over at a temperature of 242° at a pressure of 0.01 mm of Hg have been separated, the main fraction, which distils at 242—250° at the same pressure, is collected.

A solution of 25 g of the mixture of the free bases in 200 cc of acetic acid-ethyl ester is added to a solution of a calculated quantity of tartaric acid in acetic acid - ethyl ester, whereby the tartrate of 3 - *n* - propylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine precipitates. After leaving to stand at room temperature, filtration is effected. Melting point 120° (decomposition), sintering above 70°. The mixed melting point with a similar material produced according to Patent Specification 863,546 (Serial No. 11049/57) does not show depression. Boiling point of 3 - *n* - propyl - mercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is 247° at 0.01 mm Hg.

EXAMPLE 4

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

368 g of N - [*m* - isopropylmercapto - phenyl] - N - [2 - (N^1 - methyl - piperidyl-2^1) - ethyl] - aniline (boiling point 204° at 0.005 mm Hg) are dissolved in 5000 to 6000 cc of benzene and a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene is added whilst stirring. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature. After the reaction is complete the solvent is evaporated at reduced pressure and the residue is mixed with 2500 cc of water whilst stirring and 3N sodium hydroxide solution added until the mixture shows alkaline reaction. The mixture of the precipitated bases is extracted by shaking three times with 1000 cc of chloroform on each occasion and the united chloroform extracts are dried over 300—400 g of potassium carbonate and evaporated at reduced pressure. The residue of the evaporation is distilled in a high vacuum. After separating the first runnings which distil over at a temperature up to 220° at a pressure of 0.005 mm of Hg, the main fraction which distils at 220—226° at the same pressure, is collected.

A solution of 22 g of the mixture of the bases in acetic acid-ethyl ester is added to a solution of the calculated quantity of tartaric acid in acetic acid - ethyl ester, whereby the tartrate of 3 - isopropylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine precipitates. After standing at room temperature, filtration is effected. Melting point 120° (decomposition), sintering above 70°. The mixed melting point with a similar material produced according to Patent Specification 863,546 (Serial No. 11049/57) does not show depression. Boiling point of 3-isopropylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is 223° at 0.005 mm of Hg. Melting point 73—75°.

EXAMPLE 5

3 - *n* - butylmercapto - 10 - [2^1 - N - methyl-piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine.

382 g of N - [*m* - *n* - butylmercapto - phenyl] - N - [2-(N^1-methyl - piperidyl - 2^1)-ethyl] - aniline (boiling point 204° at 0.01 mm of Hg) are dissolved in 5000 to 6000 cc of benzene and a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene is added whilst stirring. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature. After reaction is complete the solvent is evaporated at reduced pressure and the residue mixed with 2500 cc of water and 3N sodium hydroxide solution is added until the mixture shows alkaline reaction. The mixture of the precipitated bases is extracted by shaking three times with 1000 cc of chloroform on each occasion and the united chloroform extracts are dried over 300—400 g of potassium carbonate and evaporated at reduced pressure. The residue resulting from the evaporation is distilled in a high vacuum. After separating first runnings which distil over up to 224° at a pressure of 0.005 mm of Hg, the main fraction distils at 224—230° at the same pressure and is collected. 3 - *n* - butylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine boils at 227°/0.005 mm of Hg.

EXAMPLE 6

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

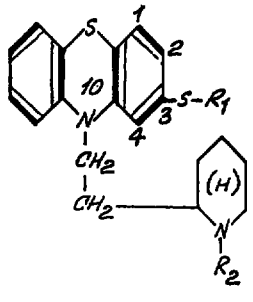
416 g of N - [*m*-benzylmercapto-phenyl]-

N - [2 - (N[1] - methyl - piperidyl - 2[1]) - ethyl] - aniline (boiling point 215° at 0.005 mm of Hg), are dissolved in 5000 to 6000 cc of benzene and, whilst stirring, a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene is added. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature, after reaction is complete the solvent is evaporated at reduced pressure and the residue mixed with 2500 cc of water. 3N sodium hydroxide solution is then added until the mixture shows alkaline reaction. The mixture of the precipitated ~~basis~~ bases is then extracted by shaking three times with 1000 cc of chloroform on each occasion and the united chloroform extracts are dried over 300 to 400 g of potassium carbonate and evaporated at reduced pressure. The residue of the evaporation is distilled in a high vacuum. After separating first runnings distilling over at a temperature up to 242° at a pressure of 0.01 mm of Hg, the main fraction which distils at 242—250° at the same pressure, is collected.

A solution of 22 g of the mixture of the bases in 200 cc of acetic acid-ethyl ester is added to a solution of the calculated quantity of tartaric acid in acetic acid - ethyl ester, whereby the tartrate of 3 - benzylmercapto - 10 - [2[1] - (N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine precipitates. After standing at room temperature, filtration is effected. The tartrate contains 1/2 mol of water of crystallization and melts at 105° (decomposition), sintering above 75°. The mixed melting point with a similar material produced according to Patent Specification 863,546 (Serial No. 11049/57) does not show depression. Boiling point of 3 - benzylmercapto - 10 - [2[1] - (N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine is 246°/0.01 mm of Hg.

WHAT WE CLAIM IS:—

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

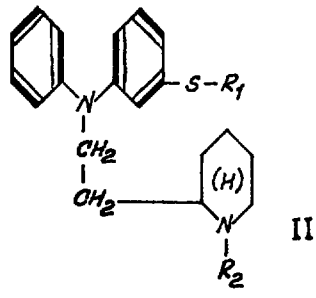


I

R_1=lower alkyl (as herein defined), aryl, aralkyl

R_2=lower alkyl (as herein defined),

characterized in that a tertiary amine of the general formula II,



II

wherein R_1 and R_2 have the above significance is treated with a sulphur di-halide.

2. A process according to claim 1, in which the reaction is effected in solution in an inert organic solvent.

3. A process according to claim 1, in which the solvent is an aromatic solvent.

4. A process according to claim 3, in which the aromatic solvent is benzene or toluene.

5. A process according to any one of the preceding claims, in which the reaction products are positional isomers and these are separated by fractional crystallization of their acid addition salts.

6. A process for the production of the compounds having the general formula I shown in claim 1 substantially as herein described with reference to any one of the examples.

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

8. Acid addition salts of the compounds claimed in the preceding claim.

9. 3 - methylmercapto - 10 - [2[1] - N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and their acid addition salts.

10. 3 - ethylmercapto - 10 - [2[1] - (N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

11. 3 - *n* - propylmercapto - 10 - [2[1] - (N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

12. 3 - isopropylmercapto - 10 - [2[1] - (N-methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

13. 3 - *n* - butylmercapto - 10 - [2[1] - (N-methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

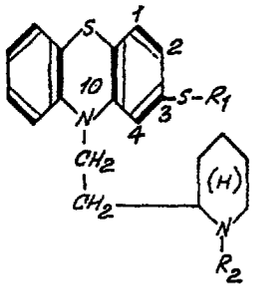
14. 3 - benzylmercapto - 10 - [2[1] - (N - methyl - piperidyl - 2[11]) - ethyl - 1[1]] - phenthiazine whenever produced according to the

N - [2 - (N^1 - methyl - piperidyl - 2^1) - ethyl] - aniline (boiling point 215° at 0.005 mm of Hg), are dissolved in 5000 to 6000 cc of benzene and, whilst stirring, a solution of 103 g of freshly distilled sulphur di-chloride in 1000 cc of benzene is added. After a short while hydrochlorides separate out. The mixture is left to stand for 20 minutes at room temperature, after reaction is complete the solvent is evaporated at reduced pressure and the residue mixed with 2500 cc of water. 3N sodium hydroxide solution is then added until the mixture shows alkaline reaction. The mixture of the precipitated ~~basis~~ bases is then extracted by shaking three times with 1000 cc of chloroform on each occasion and the united chloroform extracts are dried over 300 to 400 g of potassium carbonate and evaporated at reduced pressure. The residue of the evaporation is distilled in a high vacuum. After separating first runnings distilling over at a temperature up to 242° at a pressure of 0.01 mm of Hg, the main fraction which distils at 242—250° at the same pressure, is collected.

A solution of 22 g of the mixture of the bases in 200 cc of acetic acid-ethyl ester is added to a solution of the calculated quantity of tartaric acid in acetic acid - ethyl ester, whereby the tartrate of 3 - benzylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine precipitates. After standing at room temperature, filtration is effected. The tartrate contains 1/2 mol of water of crystallization and melts at 105° (decomposition), sintering above 75°. The mixed melting point with a similar material produced according to Patent Specification 863,546 (Serial No. 11049/57) does not show depression. Boiling point of 3 - benzylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine is 246°/0.01 mm of Hg.

WHAT WE CLAIM IS:—

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

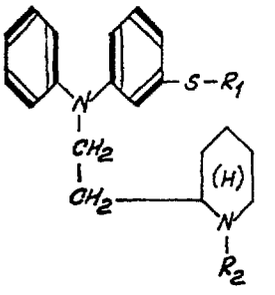


I

R_1 = lower alkyl (as herein defined), aryl, aralkyl

R_2 = lower alkyl (as herein defined),

characterized in that a tertiary amine of the general formula II,



II

wherein R_1 and R_2 have the above significance is treated with a sulphur di-halide.

2. A process according to claim 1, in which the reaction is effected in solution in an inert organic solvent.

3. A process according to claim 1, in which the solvent is an aromatic solvent.

4. A process according to claim 3, in which the aromatic solvent is benzene or toluene.

5. A process according to any one of the preceding claims, in which the reaction products are positional isomers and these are separated by fractional crystallization of their acid addition salts.

6. A process for the production of the compounds having the general formula I shown in claim 1 substantially as herein described with reference to any one of the examples.

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

8. Acid addition salts of the compounds claimed in the preceding claim.

9. 3 - methylmercapto - 10 - [~~2^1 N~~ - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and their acid addition salts.

10. 3 - ethylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

11. 3 - *n* - propylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

12. 3 - isopropylmercapto - 10 - [2^1 - (N-methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

13. 3 - *n* - butylmercapto - 10 - [2^1 - (N-methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the process claimed in any one of claims 1 to 6 and its acid addition salts.

14. 3 - benzylmercapto - 10 - [2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine whenever produced according to the

process claimed in any one of claims 1 to 6 and its acid addition salts.

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

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

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