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COMPLETE SPECIFICATION

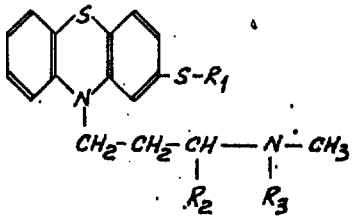
3-Mercapto-Phenthiazine Derivatives and their preparation

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 the production of compounds having the formula I below and their acid addition salts.

It has been found that phenthiazine derivatives containing sulphur having the general formula I

I



$R_1 = CH_3$, C_2H_5, C_3H_7

R_2 together with $R_3 = -(CH_2)_3-$, $-(CH_2)_4-$

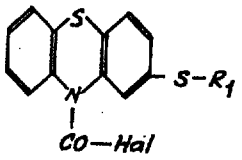
or

$R_1 = C_2H_5$, C_3H_7

$R_2 = H$

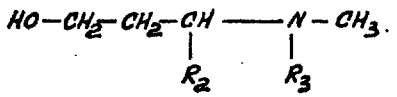
$R_3 = CH_3$

can be obtained by reacting phenthiazine-10-carboxylic acid halide derivatives having the general formula II



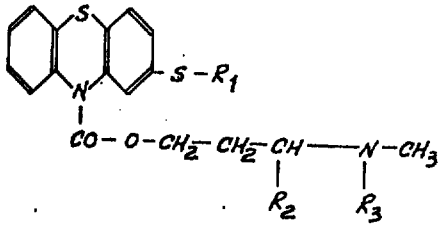
II

in which Hal represents a chlorine, bromine or iodine atom, with an amino alkanol having the general formula III



III

and decarboxylating the resulting ester having the general formula IV



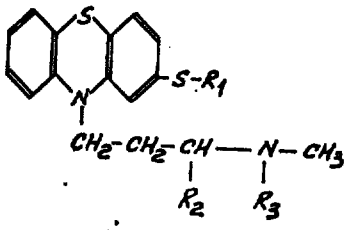
IV

without thereby decomposing the molecule; R_1, R_2 and R_3 in formulæ II, III and IV have the same significance as in formula I.

Specific compounds having the general formula I above are 3-methylmercapto-10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1] - phenthiazine, 3 - isopropylmercapto - 10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1] - phenthiazine, 3 - ethylmercapto - 10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1] - phenthiazine and 3 - ethylmercapto - 10-[2^1 - (N - methylpyrrolidyl - 2^{11}) - ethyl-1^1] - phenthiazine.

The present invention thus provides a process for the production of phenthiazine derivatives containing sulphur having the general formula I

I



Price 4s 6d

$R_1 = CH_3$, C_2H_5, C_3H_7

R_2 together with $R_3 = -(CH_2)_3-$, $-(CH_2)_4-$

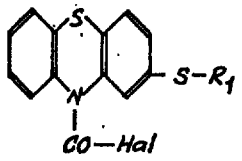
or

$R_1 = C_2H_5$, C_3H_7

$R_2 = H$

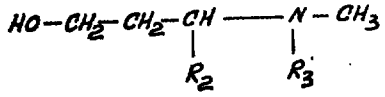
$R_3 = CH_3$

characterized in that a phenthiazine-10-carboxylic acid halide derivative having the general formula II



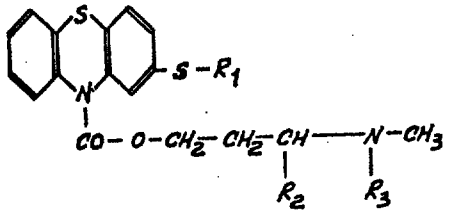
II

in which Hal represents a chlorine, bromine or iodine atom, is reacted with an aminoalkanol having the general formula III



III

the ester having the general formula IV



IV

obtained in this way is decarboxylated so as to produce the compounds having the general formula I, and the last mentioned compound is isolated, R_1, R_2 and R_3 in formulæ II, III and IV having the same significance as in formula I.

The invention further provides compounds having the general formula IV above and their acid addition salts.

It is obvious that the compounds of the general formula IV may be obtained, in accordance with the invention, by omitting the last step in the above process of the invention, i.e. the treatment for decarboxylating the ester having the general formula IV above.

The process may be carried into effect, for example, in such a manner that an alkylmercapto - phenthiazine - 10 - carboxylic acid halide of formula II is dissolved in an inert organic solvent (e.g. benzene, toluene, xylene, dichlorobenzene, nitrobenzene or another aromatic organic solvent) and reacted with an aminoalcohol of formula III, optionally dissolved in one of the above solvents, at room temperature or at an elevated temperature and the reaction product of formula IV isolated. The alkyl - mercapto - phenthiazine - 10-carboxylic acid ester of formula IV is then heated, e.g. to a temperature of about 150—220°C, whereby carbon dioxide is given off to produce the compound of formula I. The last mentioned reaction may be carried out in an inert organic solvent (e.g. dichlorobenzene or nitrobenzene).

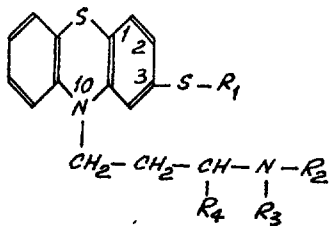
After elimination of the carbon dioxide, the phenthiazine derivatives of formula I are isolated, and, as mentioned above, they may be converted into acid addition salts.

The basic phenthiazine derivatives of the general formula I are oleaginous or crystalline at room temperature and form stable crystalline addition salts with organic and inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, succinic acid, maleic acid, fumaric acid, oxalic acid, acetic acid, benzoic acid and hexahydrobenzoic acid.

The exemplified compounds of the formula I above have pharmacodynamic properties. Their great adrenolytic action is characteristic of these properties; they may therefore be used for the control of excitement and stress in psychical illnesses. It has become apparent that the adrenolytic action is most strongly marked with phenthiazine derivatives having an ethylmercapto group in the 3-position of the phenthiazine nucleus.

The substances of the formula I above can be dispensed either *per os* as tablets or lozenges or parenterally (e.g. subcutaneously).

In Patent Specification No. 863,546 (11049/57) there are described and claimed phenthiazine derivatives of the general formula



in which

R_1 = a methyl group,

each of R_2 and R_3 = hydrogen or an alkyl group containing up to 4 carbon atoms, and

R_4 = hydrogen.

In Patent Specification No. 853,552 (22979/60) there are described and claimed phenthiazine derivatives of the general formula given in the preceding paragraph

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.

In Patent Specification No. 863,551 (22978/60) there are described and claimed phenthiazine derivatives of the general formula referred to in the preceding paragraph in which

either

R_1 = hydrogen, an alkyl group containing 2 to 4 carbon atoms, a phenyl group or a benzyl group,

each of R_2 and R_3 = hydrogen or an alkyl group containing up to 4 carbon atoms, and R_4 = hydrogen,

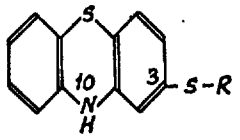
or

R_1 = hydrogen, an alkyl group containing 2 to 4 carbon atoms, a phenyl group or a benzyl 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.

In Patent Specification No. 863,550 (17380/60) there are described and claimed phenthiazine derivatives of the general formula



in which R is hydrogen, an alkyl group containing 2 to 4 carbon atoms, a phenyl group or a benzyl group.

In Patent Specification No. 863,547 (11050/57) 3-methylmercapto-phenthiazine is described and claimed.

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 given are uncorrected.

EXAMPLE 1.

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

(a) *3 - methylmercapto - phenthiazine - 10-carboxylic acid chloride.*

A solution of 93 g of phosgene in 450 cc of toluene is added in one batch at room temperature to a solution of 115 g of 3-methylmercapto-phenthiazine (melting point 138—140°) in 2,250 cc benzene. The reaction mixture is heated to boiling point in a water bath for 1 hour. After boiling at reflux for a further 3 hours, the solvent is evaporated at reduced pressure and the evaporation residue rapidly recrystallised from 1,000 cc of boiling absolute ethanol, cooled and filtered with suction. The resulting analytically pure 3 - methylmercapto - phenthiazine - 10 - carboxylic acid chloride has a melting point of 122—124°.

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

A mixture of 25.0 g of 3-methylmercapto-phenthiazine-10-carboxylic acid chloride (melting point 122—124°), 23.2 g of 1-methyl-2-(β-hydroxy-ethyl)-piperidine (boiling point 233°/760 mm of Hg) and 200 cc of benzene is boiled at reflux for 15 hours at a bath temperature of 120°. The reaction mixture, after cooling, is extracted by shaking twice with 70 cc of water in each case and then with 80 cc of 15% tartaric acid. The combined extracts are again extracted by shaking with 100 cc of benzene and finally made alkaline to phenolphthalein with 30 cc of concentrated sodium hydroxide solution. The precipitated base is taken up in 300 cc of benzene, the benzene layer washed with 100 cc of water, dried over potassium hydroxide and evaporated at reduced pressure. The evaporation residue is dissolved in 180 cc of isopropanol and isopropanolic hydrochloric acid solution added until the material is acid to Congo red. The precipitated acid addition salt is filtered with suction and recrystallised from 1,600 cc of boiling isopropanol. The resulting analytically pure hydrochloride of 3 - methylmercapto - phenthiazine - 10 - carboxylic acid - [2^1 - (N - methyl - piperidyl-2^{11})-ethyl-1^1]-ester has a melting point of 197—199° (with decomposition) and contains half a molecule of water of crystallisation.

The base is produced by dissolving 5.7 g of the hydrochloride in 100 cc of water, making the solution alkaline to phenolphthalein with 3N ammonia and taking up the precipitated base in 50 cc of benzene. After washing the benzene solution with 25 cc of water, it is dried over potassium carbonate, filtered and ~~free~~ freed of solvent in a vacuum. The evaporation residue is recrystallised from 300 cc of boiling petroleum ether (boiling point range 40—60°). The resulting analytically pure base, 3-methylmercapto-phenthiazine-10-carboxylic acid-[2^1-(N-methyl-piperidyl-2^{11})-ethyl-1^1]-ester has a melting point of 77—79°.

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

4.99 g of 3-methylmercapto-phenthiazine-10 - carboxylic acid - [2^1 - (N - methyl-piperidyl-2^{11})-ethyl-1^1]-ester are heated on an oil bath for 1 hour at 180° and then for 4 hours at 200° in the vacuum of a water pump. After evolution of carbon dioxide has ceased, the residue in the flask is distilled at 228—232° in a high vacuum of 0.02 mm of Hg. The resulting analytically pure base, 3-methylmercapto - 10 - [2^1 - (N - methyl - piperidyl-

2^{11})-ethyl-1^1]-phenthiazine has a boiling point of 230° at 0.02 mm of Hg. The base has a constant melting point of 72—74° after recrystallisation from four times the amount of boiling isopropanol.

The hydrochloride of 3-methylmercapto-10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1]-phenthiazine has a melting point of 158—160° after sintering at 153°.

EXAMPLE 2.

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

(a) *3 - isopropylmercapto - phenthiazine-10 - carboxylic acid chloride.*

A solution of 106 g of phosgene in 450 cc of toluene is added in one batch at room temperature to a solution of 46 g of 3-isopropylmercapto-phenthiazine (melting point 118—120°) in 1000 cc of benzene. The reaction mixture is heated to boiling point in a water bath for 1 hour. After boiling at reflux for a further 3 hours, the solvent is evaporated at a reduced pressure and the evaporation residue taken up by warming in 5 litres of petroleum ether (boiling point range 40—60°) and the solution is filtered. After reducing the filtrate to a volume of about 1 litre, this solution is allowed to stand overnight in a refrigerator. The resulting crystals are filtered with suction, rapidly recrystallised from 150 cc of warm absolute ethanol and cooled. The resulting analytically pure 3-isopropyl-mercapto-phenthiazine-10-carboxylic acid chloride has a melting point of 62—64° (with decomposition).

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

A mixture of 22.46 g of 3-isopropylmercapto-phenthiazine-10-carboxylic acid chloride (melting point 62—64°), 19.1 g of 1-methyl-2-(β-hydroxy-ethyl)-piperidine (boiling point 233°/760 mm of Hg) and 175 cc of benzene is refluxed for 15 hours at a bath temperature of 120°. The reaction mixture, after cooling, is extracted by shaking twice with 70 cc of water in each case and then with 75 cc of 15% tartaric acid. The combined extracts are extracted by shaking with 75 cc of benzene and finally made alkaline to phenolphthalein with 30 cc of concentrated sodium hydroxide solution.

The precipitated base is taken up in 250 cc of benzene, the benzene layer washed with 75 cc of water, dried over potassium carbonate and evaporated at a reduced pressure. The evaporation residue is dissolved in 150 cc isopropanol and isopropanolic hydrochloric acid solution added until the material is acid to Congo red. The resulting precipitated salt is filtered with suction and recrystallised from 225 cc of boiling isopropanol. The resulting analytically pure hydrochloride of 3-isopropyl-mercapto - phenthiazine - 10 - carboxylic acid-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1]-ester has a melting point of 115—117° (with decomposition) after sintering at 100°.

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

24.31 g of 3 - isopropylmercapto - phenthiazine - 10 - carboxylic acid [2^1 - (N - methyl-piperidyl-2^{11})-ethyl-1^1]-ester, produced from the hydrochloride resulting at 2(b) above, is heated in an oil bath for 1 hour at 180° and then for 4 hours at 200° in the vacuum of a water pump. After evolution of carbon dioxide has ceased, the residue is distilled at 222—225° in a high vacuum of 0.005 mm of Hg. The resulting analytically pure base, 3 - isopropylmercapto - 10 - [2^1 - (N - methyl-piperidyl - 2^{11}) - ethyl - 1^1] - phenthiazine, has a boiling point of 223° at 0.005 mm Hg. The base has a constant melting point of 73—75° after recrystallisation from 3 times its weight of isopropanol.

EXAMPLE 3.

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

A mixture of 32.1 g of 3-ethylmercapto-phenthiazine-10-carboxylic acid chloride (melting point 95—97°), 28.6 g 1-methyl-2-(β-hydroxy-ethyl)-piperidine (boiling point 233°/760 mm of Hg) and 200 cc of benzene is boiled at reflux for 15 hours at a bath temperature of 120°. The reaction mixture, after cooling, is extracted by shaking with 70 cc of water and then twice with 150 cc of 15% aqueous tartaric acid in each case. The combined extracts are extracted by shaking with 40 cc of benzene and finally made alkaline to phenolphthalein with 60 cc of concentrated sodium hydroxide solution. The resulting precipitated base is taken up in 450 cc of benzene, the benzene layer washed with 60 cc water, dried over sodium sulphate and evaporated in a vacuum. The evaporation residue is dissolved in 70 cc of isopropanol and ispropanolic hydrochloric acid solution added until the material is acid to Congo red indicator. The resulting precipitated hydrochloride is filtered off and recrystallised from 20 cc of boiling isopropanol. The analytically pure hydrochloride of 3 - ethylmercapto - 10 - carboxylic acid - [2^1 - (N - methyl - piperidyl-2^{11})-ethyl-1^1]-ester melts at 147—149° (with decomposition) and contains half a molecule of water of crystallisation.

The free base is obtained by adding to an aqueous solution of the above hydrochloride 3N ammonia until the material is alkaline to phenolphthalein, the resulting precipitate is taken up in benzene and the benzene solution dried and evaporated. By driving off carbon dioxide from the ester base using the method described in example 2(c) 3-ethylmercapto-10-[2^1 - (N - methyl - piperidyl - 2^{11}) - ethyl-1^1)-phenthiazine is obtained. The boiling point of the pure base is 225° at 0.008 mm of Hg; the tartrate melts at 135° (with decomposi-

tion) after sintering above 70°.

EXAMPLE 4.

3 - ethylmercapto - 10 - [2¹ - (N - methyl-pyrrolidyl-2¹¹)-ethyl-1¹]-phenthiazine.

A mixture of 12.9 g of 3-ethylmercapto-phenthiazine-10-carboxylic acid chloride (melting point 95—97°), 10.4 g of 1-methyl-2-(β-hydroxy-ethyl)-pyrrolidine (boiling point 95—96°/11 mm of Hg) and 100 cc of benzene is boiled at reflux for 15 hours at a bath temperature of 120° C. The reaction mixture, after cooling, is extracted by shaking with 70 cc of water and twice with 75 cc of 15% aqueous tartaric acid in each case. The combined extracts are extracted by shaking with 60 cc of benzene and the extract is made alkaline with 45 cc of 28% of aqueous ammonia. The precipitated base is taken up in 750 cc of benzene, the benzene layer washed with 40 cc of water, dried over sodium sulphate and evaporated in a vacuum. The evaporation residue is dissolved in 20 cc of isopropanol and isopropanolic hydrochloric acid solution added until the material is acid to Congo red. The resulting precipitated hydrochloride is filtered off and recrystallised from 100 cc of boiling isopropanol. The resulting analytically pure hydrochloride of 3 - ethylmercapto - phenthiazine - 10 - carboxylic acid - [2¹ - (N - methyl-pyrrolidyl-2¹¹)-ethyl-1¹]-ester melts at 75—77° with decomposition and contains 1 molecule of water of crystallisation. The salt melts at 146—148° after drying in a high vacuum. The free base is obtained by adding 3N ammonia to an aqueous solution of the hydrochloride until alkaline to phenolphthalein, the precipitated base is taken up in benzene and the benzene solution dried and evaporated. By driving off carbon dioxide from the ester base using the method described in Example 2(c), 3-ethyl-mercapto-10-[2¹-(N-methyl - pyrrolidyl - 2¹¹) - ethyl - 1¹] - phenthiazine is obtained. The pure base boils at 213° (0.01 mm of Hg); the tartrate melts at 90° with decomposition after sintering above 70°.

EXAMPLE 5.

3-methylmercapto-10-[2¹-(N-methyl-pyrrolidyl-2¹¹)-ethyl-1¹]-phenthiazine

A mixture of 21.5 g of 3-methylmercapto-phenthiazine-10-carboxylic acid chloride (m.p. 122—124°), 18.0 g 1-methyl-2-(β-hydroxy-ethyl)-pyrrolidine (b.p. 95—96° at 11 mm Hg) and 300 cc of benzene are heated for 15 hours at a bath temperature of 120° so as to effect boiling at reflux. After cooling the reaction mixture is extracted first with 150 cc of water and then with 100 cc of a 15% aqueous tartaric acid. The reunited extracts are further extracted with 100 cc of benzene and finally the extract is made alkaline to phenolphthaleine with 35 cc of concentrated sodium hydroxide solution. The precipitated base is taken up in a total of 250 cc of benzene, the benzene layer is washed with 150 cc of water, the material is dried over sodium sulphate and evaporated in a vacuum. The residue of evaporation is crystallised from 80 cc of 95% ethanol. After recrystallisation from 50 cc of 95% ethanol there is obtained analytically pure 3 - methylmercapto - phenthiazine - 10-carboxylic acid [2¹ - (N - methyl - pyrrolidyl-2¹¹)-ethyl-1¹]-ester having a melting point of 101—103°. 17.8 g of pure base are dissolved in 100 cc of absolute ethanol and the material is made acid to Congo red indicator by adding a solution in ethanol of hydrochloric acid. The precipitated hydrochloride is filtered with suction and recrystallised from 250 cc of boiling absolute ethanol. The analytically pure hydrochloride of 3-methylmercapto-phenthiazine - 10 - carboxylic acid [2¹ - (N - methyl-pyrrolidyl-2¹¹)-ethyl-1¹]-ester melts at 205—207° (with decomposition).

20.0 g of 3-methylmercapto-phenthiazine-10-carboxylic acid [2¹-(N-methyl-pyrrolidyl-2¹¹)-ethyl-1¹]-ester are heated in an oil bath at a pressure of 15 mm Hg for one hour to a temperature of 180° and thereafter for four hours at 200°. After the evolution of carbon dioxide had ceased, the residue is distilled in a high vacuum at a pressure of 0.008 mm Hg at a temperature of 208—210°. The analytically pure base, 3-methylmercapto-10-[2¹-(N-methyl - pyrrolidyl - 2¹¹) - ethyl - 1¹] - phenthiazine has a boiling point of 209° at 0.008 mm Hg. The tartrate of 3-methylmercapto-10 - [2¹ - (N - methyl - pyrrolidyl - 2¹¹)-ethyl-1¹]-phenthiazine produced by a method known *per se* has a melting point of 115° (with decomposition) after sintering above 70° C.

EXAMPLE 6.

3-ethylmercapto-10-(3¹-dimethylamino-propyl-1¹)-phenthiazine.

32.1 g of 3-ethylmercapto-phenthiazine-10-carboxylic acid chloride (m.p. 95—97°), 20.6 g 3-dimethylaminopropanol-1 (b.p. 163—164° at 760 mm Hg) and 300 cc benzene are heated for 15 hours at a bath temperature of 120° C to effect boiling at reflux. After cooling the reaction mixture is extracted with 100 cc of water, then twice with 100 cc of 15% aqueous tartaric acid on each occasion. The extracts are shaken with a total of 40 cc of benzene and then made alkaline with 40 cc of 28% ammonia. The precipitated base is taken up in a total of 900 cc of benzene, the benzene solution is washed with 60 cc of water, dried over sodium sulphate and evaporated in a vacuum. The residue of evaporation is boiled with the calculated amount of fumaric acid in absolute ethanol, whereupon the acid addition salt crystallises on cooling. The precipitated salt is filtered off and recrystallised quickly from absolute ethanol. The analytically pure fumarate of 3-ethylmercapto-phenthiazine-10-carboxylic acid (3¹-dimethylamino-propyl-1¹)-ester has a melting point of 133—135° and contains one molecule of water.

4.45 g of 3-ethylmercapto-phenthiazine-10-carboxylic acid (3^1-dimethylamino-propyl-1^1)-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for 4 hours to 200°. After the carbon dioxide evolution has ceased the residue is distilled in a high vacuum at a pressure of 0.008 mm Hg at 199—201°. The analytically pure base, 3 - ethylmercapto - 10 - (3^1 - dimethylamino-propyl-1^1)-phenthiazine, has a boiling point of 200° at 0.008 mm Hg. The tartrate of 3-ethylmercapto - 10 - (3^1 - dimethylamino-propyl-1^1)-phenthiazine has a melting point of 117—119° (with decomposition) after sintering above 110°.

EXAMPLE 7.

3-isopropylmercapto-10-(3^1-dimethylamino-propyl-1^1)-phenthiazine.

A mixture of 15.0 g of 3-isopropylmercapto-phenthiazine-10-carboxylic acid chloride (m.p. 62—64°), 9.2 g 3-dimethylamino-propanol-1 and 150 cc benzene are heated for 15 hours at a bath temperature of 120° at reflux to the boil. After cooling the reaction mixture is extracted first with 120 cc water then with 75 cc of a 15% aqueous solution of tartaric acid. The reunited extracts are shaken with 80 cc of benzene and finally made alkaline to phenolphthaleine with 25 cc of concentrated sodium hydroxide solution. The precipitated base is taken up in a total of 250 cc of benzene, the benzene layer is washed with 120 cc of water, dried over sodium sulphate and evaporated in a vacuum. The evaporation residue is dissolved in 60 cc of ethanol and an ethanolic solution of hydrochloric acid is added until the material is acid to Congo red indicator. The precipitated hydrochloride is filtered off and recrystallised from boiling absolute ethanol. The analytically pure hydrochloride of 3-isopropylmercapto-phenthiazine-10 - carboxylic acid - (3^1 - ~~dimethylamine~~ - propyl-1^1)-ester melts at 180—182° (with decomposition).

15.0 g of 3-isopropylmercapto-phenthiazine-10-carboxylic acid-(3^1-dimethyl-amino-propyl-1^1)-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for four hours to 200°. After evolution of carbon dioxide has ceased the residue is distilled in a high vacuum at 0.01 mm Hg at a temperature of 197—199°. The analytically pure base, 3 - isopropylmercapto - 10 - (3^1-dimethylamino-propyl-1^1)-phenthiazine, has a boiling point of 198° at 0.01 mm Hg. After adding to a solution of 15.0 g of the base in 150 cc of absolute ethanol a solution of 5.3 g of oxalic acid in 150 cc of absolute ethanol there is obtained the oxalate of 3-isopropyl-mercapto - 10 - (3^1 - dimethylamino - propyl-1^1)-phenthiazine. After recrystallising from 900 cc of methanol there is obtained the analytically pure oxalate of 3-isopropylmercapto - 10 - (3^1 - dimethylamine - propyl-1^1)-phenthiazine decomposing at 206—208°C. The hemihydrate of the tartrate of 3-isopropylmercapto - 10 - (3^1 - dimethylamino - propyl-1^1)-phenthiazine has a melting point of 90° (with decomposition) after sintering above 60°.

EXAMPLE 8.

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

A mixture of 15.0 g 3-isopropylmercapto-phenthiazine-10-carboxylic acid chloride, 11.5 g 1 - methyl - 2 - (β - ~~hydroxyl~~ - ethyl)-pyrrolidine and 250 cc benzene is heated for 15 hours at 120° bath temperature at reflux to the boil. After cooling the reaction mixture is extracted with 120 cc water and then with 75 cc of a 15% aqueous solution of tartaric acid. The reunited extracts are shaken with 80 cc of benzene and finally made alkaline with 25 cc of concentrated sodium hydroxide solution until the material gives an alkaline reaction with phenolphthaleine. The precipitates base is taken up in a total of 250 cc of benzene, the benzene layer is washed with water, dried over sodium sulphate and evaporated in a vacuum. The residue from the evaporation is dissolved in 60 cc of absolute ethanol, the material has added to it until it is acid to Congo red indicator some ethanolic hydrochloric acid solution and then 60 cc of ether are added. The resulting crystalline hydrochloride is dissolved in 35 cc of warm ethanol, filtered off and the warm filtrate has added to it 70 cc of ether. The resulting analytically pure hydrochloride of 3-isopropyl-mercapto - phenthiazine - 10 - carboxylic acid-[2^1 - (N - methyl - pyrrolidyl - 2^{11})- - 1^1]-ester melts at 179—181° (with decomposition).

20.0 g of 3-isopropylmercapto-phenthiazine-10 - carboxylic acid - [2^1 - (N - methyl-pyrrolidyl-2^{11})-ethyl-1^1]-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for four hours to 200°. After evolution of carbon dioxide has ceased the residue is distilled in a high vacuum at a pressure of 0.008 mm Hg at 216—218°. The resulting analytically pure base, 3-isopropyl-mercapto - 10 - [2^1 - (N - methyl - pyrrolidyl-2^{11})-ethyl-1^1]-phenthiazine, has a boiling point of 217° at 0.008 mm Hg. The hemihydrate of the tartrate of 3-isopropylmercapto-10-[2^1-(N - methyl - pyrrolidyl - 2^{11}) - ethyl - 1^1]-phenthiazine has a melting point of 90° (with decomposition) after sintering above 70°.

WHAT WE CLAIM IS:—

1. A process for the production of phenthiazine derivatives containing sulphur having the general formula I

4.45 g of 3-ethylmercapto-phenthiazine-10-carboxylic acid (3^1-dimethylamino-propyl-1^1)-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for 4 hours to 200°. After the carbon dioxide evolution has ceased the residue is distilled in a high vacuum at a pressure of 0.008 mm Hg at 199—201°. The analytically pure base, 3 - ethylmercapto - 10 - (3^1 - dimethylamino-propyl-1^1)-phenthiazine, has a boiling point of 200° at 0.008 mm Hg. The tartrate of 3-ethylmercapto - 10 - (3^1 - dimethylamino-propyl-1^1)-phenthiazine has a melting point of 117—119° (with decomposition) after sintering above 110°.

EXAMPLE 7.

3-isopropylmercapto-10-(3^1-dimethylamino-propyl-1^1)-phenthiazine.

A mixture of 15.0 g of 3-isopropylmercapto-phenthiazine-10-carboxylic acid chloride (m.p. 62—64°), 9.2 g 3-dimethylamino-propanol-1 and 150 cc benzene are heated for 15 hours at a bath temperature of 120° at reflux to the boil. After cooling the reaction mixture is extracted first with 120 cc water then with 75 cc of a 15% aqueous solution of tartaric acid. The reunited extracts are shaken with 80 cc of benzene and finally made alkaline to phenolphthaleine with 25 cc of concentrated sodium hydroxide solution. The precipitated base is taken up in a total of 250 cc of benzene, the benzene layer is washed with 120 cc of water, dried over sodium sulphate and evaporated in a vacuum. The evaporation residue is dissolved in 60 cc of ethanol and an ethanolic solution of hydrochloric acid is added until the material is acid to Congo red indicator. The precipitated hydrochloride is filtered off and recrystallised from boiling absolute ethanol. The analytically pure hydrochloride of 3-isopropylmercapto-phenthiazine-10 - carboxylic acid - (3^1 - ~~dimethylamine~~ - propyl-1^1)-ester melts at 180—182° (with decomposition).

15.0 g of 3-isopropylmercapto-phenthiazine-10-carboxylic acid-(3^1-dimethyl-amino-propyl-1^1)-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for four hours to 200°. After evolution of carbon dioxide has ceased the residue is distilled in a high vacuum at 0.01 mm Hg at a temperature of 197—199°. The analytically pure base, 3 - isopropylmercapto - 10 - (3^1-dimethylamino-propyl-1^1)-phenthiazine, has a boiling point of 198° at 0.01 mm Hg. After adding to a solution of 15.0 g of the base in 150 cc of absolute ethanol a solution of 5.3 g of oxalic acid in 150 cc of absolute ethanol there is obtained the oxalate of 3-isopropyl-mercapto - 10 - (3^1 - dimethylamino - propyl-1^1)-phenthiazine. After recrystallising from 900 cc of methanol there is obtained the analytically pure oxalate of 3-isopropylmercapto - 10 - (3^1 - dimethylamine - propyl-1^1)-phenthiazine decomposing at 206—208°C. The hemihydrate of the tartrate of 3-isopropylmercapto - 10 - (3^1 - dimethylamino - propyl-1^1)-phenthiazine has a melting point of 90° (with decomposition) after sintering above 60°.

EXAMPLE 8.

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

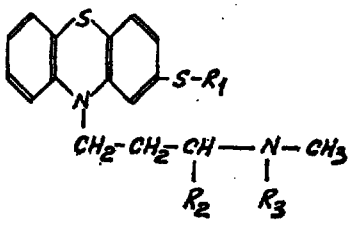
A mixture of 15.0 g 3-isopropylmercapto-phenthiazine-10-carboxylic acid chloride, 11.5 g 1 - methyl - 2 - (β - ~~hydroxyl~~ - ethyl)-pyrrolidine and 250 cc benzene is heated for 15 hours at 120° bath temperature at reflux to the boil. After cooling the reaction mixture is extracted with 120 cc water and then with 75 cc of a 15% aqueous solution of tartaric acid. The reunited extracts are shaken with 80 cc of benzene and finally made alkaline with 25 cc of concentrated sodium hydroxide solution until the material gives an alkaline reaction with phenolphthaleine. The precipitates base is taken up in a total of 250 cc of benzene, the benzene layer is washed with water, dried over sodium sulphate and evaporated in a vacuum. The residue from the evaporation is dissolved in 60 cc of absolute ethanol, the material has added to it until it is acid to Congo red indicator some ethanolic hydrochloric acid solution and then 60 cc of ether are added. The resulting crystalline hydrochloride is dissolved in 35 cc of warm ethanol, filtered off and the warm filtrate has added to it 70 cc of ether. The resulting analytically pure hydrochloride of 3-isopropyl-mercapto - phenthiazine - 10 - carboxylic acid-[2^1 - (N - methyl - pyrrolidyl - 2^{11})- 1^1]-ester melts at 179—181° (with decomposition).

20.0 g of 3-isopropylmercapto-phenthiazine-10 - carboxylic acid - [2^1 - (N - methyl-pyrrolidyl-2^{11})-ethyl-1^1]-ester are heated at 15 mm Hg in an oil bath for one hour to 180° and subsequently for four hours to 200°. After evolution of carbon dioxide has ceased the residue is distilled in a high vacuum at a pressure of 0.008 mm Hg at 216—218°. The resulting analytically pure base, 3-isopropyl-mercapto - 10 - [2^1 - (N - methyl - pyrrolidyl-2^{11})-ethyl-1^1]-phenthiazine, has a boiling point of 217° at 0.008 mm Hg. The hemihydrate of the tartrate of 3-isopropylmercapto-10-[2^1-(N - methyl - pyrrolidyl - 2^{11}) - ethyl - 1^1]-phenthiazine has a melting point of 90° (with decomposition) after sintering above 70°.

WHAT WE CLAIM IS:—

1. A process for the production of phenthiazine derivatives containing sulphur having the general formula I

I



$R_1 = CH_3$, C_2H_5 , C_3H_7

R_2 together with $R_3 = -(CH_2)_3-$, $-(CH_2)_4-$

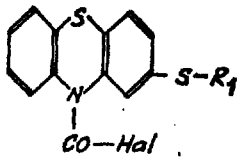
or

$R_1 = C_2H_5$, C_3H_7

$R_2 = H$

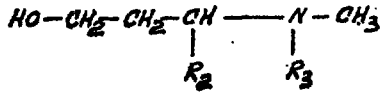
$R_3 = CH_3$

characterised in that a phenthiazine-10-carboxylic acid halide derivative having the general formula II



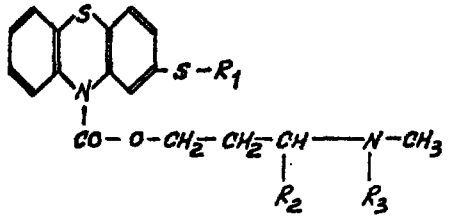
II

in which Hal represents a chlorine, bromine or iodine atom, is reacted with an aminoalkanol having the general formula III



III,

the ester having the general formula IV



IV

obtained in this way is decarboxylated so as to produce the compounds having the general formula I and the last mentioned compound is isolated, R_1, R_2 and R_3 in formulæ II, III and IV having the same significance as in formula I.

2. A process for the production of the compounds having the general formula I stated in claim 1, in which the ester having the general formula IV is produced by reacting the starting materials in an inert organic solvent.

3. A process according to claim 2, in which the inert solvent is benzene, toluene, xylene, dichlorobenzene or nitrobenzene.

4. A process according to any one of the preceding claims, in which the carbon dioxide is driven off by heating to a temperature in the range of 150—220° C.

5. A process according to any one of the preceding claims, in which the decarboxylation is effected by heating in an inert organic solvent.

6. A process according to claim 5, in which the solvent is dichlorobenzene or nitrobenzene.

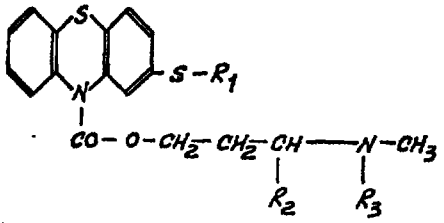
7. A process for the production of the compounds having the general formula I stated in claim 1 substantially as herein described.

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

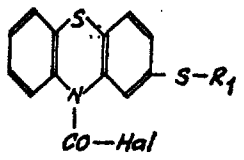
9. A process for the production of acid addition salts of the phenthiazine derivative having the general formula I stated in claim 1, characterised in that the said phenthiazine derivatives whenever obtained by the process of claim 1 are salified with an organic or inorganic acid.

10. A process according to claim 9, characterised in that the said acid for salifying is hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, succinic acid, maleic acid, fumaric acid, oxalic acid, acetic acid, benzoic acid or hexahydrobenzoic acid.

11. A process for the production of phenthiazine esters having the general formula IV



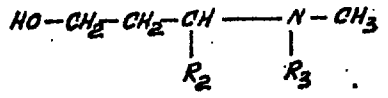
wherein R_1, R_2 and R_3 have the significance stated in claim 1, characterised in that a phenthiazine-10-carboxylic acid halide derivative having the general formula II



II

* C L M S *

in which Hal has the significance stated in claim 1, is reacted with an aminoalkanol having the general formula III



III

in which R_2 and R_3 have the significance stated in claim 1, and the resulting ester is isolated.

12. A process according to claim 11, in which the reaction is effected in the medium of an inert organic solvent.

13. A process according to claim 12, in which the inert organic solvent is benzene, toluene, xylene, dichlorobenzene or nitrobenzene.

14. A process according to claim 11 substantially as herein described.

15. A process according to claim 11 substantially as herein described with reference to any one of the examples.

16. Compounds having the general formula I stated in claim 1 whenever produced by the process claimed in any one of claims 1 to 8.

17. Acid addition salts of the compounds having the general formula I stated in claim 1 whenever produced by the process claimed in either of claims 9 and 10.

18. Compounds having the general formula IV stated in claim 1 whenever produced by the process claimed in any one of claims 11 to 15.

19. 3 methylmercapto - phenthiazine - 10-carboxylic acid [2^1 - (N - methyl - piperidyl-2^{11})-ethyl-1^1]-ester.

20. 3 - isopropylmercapto - phenthiazine-10 - carboxylic acid [2^1 - (N - methyl piperidyl - 2^{11}) - ethyl - 1^1] - ester.

21. 3 - ethylmercapto - phenthiazine - 10-carboxylic acid [2^1 - (N - methyl - piperidyl-2^{11})-ethyl-1^1]-ester.

22. 3 - ethylmercapto - phenthiazine - 10 - carboxylic acid [2^1 - (N - methyl - pyrrolidinyl-2^{11})-ethyl-1^1]-ester.

23. 3 - ethylmercapto - phenthiazine - 10-carboxylic acid (3^1 - dimethylamino - propyl-1^1)-ester.

24. 3 - isopropylmercapto-phenthiazine - 10-carboxylic acid (3^1-dimethylamino-propyl-1^1)-ester.

25. The acid addition salts of the compounds claimed in any one of claims 19 to 24.

26. Compounds having the general formula IV stated in claim 1 and their acid addition salts.

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70 & 72, Chancery Lane, London, W.C.2,
Chartered Patent Agents.

ERL

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SPECIFICATION NO. 863,549

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, E.C.2, a British Company.

THE PATENT OFFICE,
20th March, 1961

DS 88337/1(20)/R.153 200 3/61 PL

ERRATA

SPECIFICATION No. 863,549
Amendment No. 1

Page 3, line 104, *for* "free" *read* "freed"
Page 6, line 42, *for* "dimethylamine" *read* "dimethylamino"
Page 6, line 75, *for* "hydroxyl" *read* "hydroxy"
Page 6, line 100, *after* "-2'')" *insert* "-ethyl"

THE PATENT OFFICE
5th August 1966