

975,705



PATENT SPECIFICATION

NO DRAWINGS

975,705

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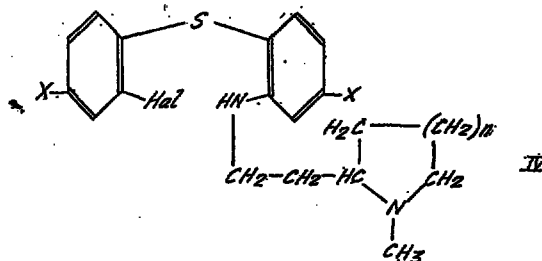
COMPLETE SPECIFICATION

Improvements in or relating to the preparation of 3-Alkylmercapto Phenothiazines and Intermediates Formed in the Process

We, WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2, a British Company, 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:—

5 The present invention relates to phenothiazine derivatives and to a process for their production.

The present invention provides compounds of the general formula IV,



wherein one of the two symbols

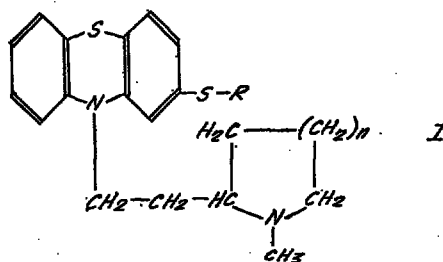
10 X represents a hydrogen atom, and the other symbol

X represents the grouping —S—R wherein R represents an alkyl group containing from 1—4 carbon atoms inclusive,

Hal represents a chlorine, bromine or iodine atom, and

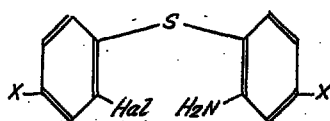
n represents 1 or 2.

15 The present invention also provides a process for the production of compounds having the general formula I,

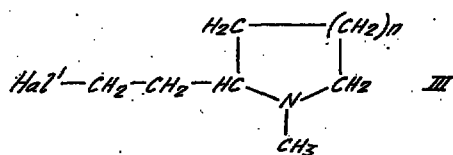


wherein R and n have the above significance, and their acid addition salts, characterised in that a compound of the general formula II,

[Price 4s. 6d.]



wherein Hal and X have the above significance, is condensed with a compound having the general formula III



wherein n has the above significance, and

Hal¹ represents a chlorine or bromine atom, the resulting compound IV above is then cyclised and, when it is desired to produce an acid addition salt of a compound I, salification is effected. Examples of acids for salifying are hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic acid.

On method of effecting the process of the invention consists in dissolving a compound II in an inert organic solvent, for example benzene, toluene or xylene, and reacting with a compound III in the presence of a basic condensation agent, for example sodium amide, by heating the reactants together. After the reaction has gone to completion, shaking out with water may be effected and the organic solution may be extracted with a dilute mineral or organic acid. The free base may be recovered from the acid extract by adding on alkali metal hydroxide solution or ammonia. Further purification of the compound IV, which is present in the form of an oily material, may be effected by taking up in a water-immiscible organic inert solvent, evaporation thereof and distillation of the residue at a reduced pressure.

Cyclisation of the purified material IV may be effected by heating with dimethyl formamide in the presence of a basic condensation agent (for example sodium or potassium carbonate) and a little powdered copper. Purification of the resulting compound I and/or conversion into an acid addition salt may be effected in manner known *per se*.

In British patent specification No. 863,552, there are described and claimed, *inter alia*, compounds of the formula I above.

It has previously been proposed to produce the compounds I above by condensing a 3-alkyl (C_1-C_4) mercaptophenthiazine with a compound having the general formula III above, the said alkyl-mercaptophenthiazine itself being obtained by cyclisation with sulphur in the presence of iodine as a catalyst at a temperature from 100–200° C. of the corresponding alkyl-mercapto-phenylaniline. It is also possible, in this previously proposed method of producing the compounds I above, to reverse the order of condensation and cyclisation. However, whether cyclisation is preceded by condensation or not, this previous method is bound to lead to two products, only one of which will have the —S—alkyl (C_1-C_4) group in the 3-position, whereas the other one will have the said alkyl mercapto group in the 1-position.

It is clear that the method of the present invention of producing the compounds I above can only lead to the production of a 3-methyl mercaptophenthiazine derivative and this is a considerable advantage of the present method of obtaining the compounds I above over the aforementioned previous method using an alkyl mercapto phenylaniline as starting material. The process of the present invention thus allows the obtaining of a high yield and the end product is obtained with a high degree of purity.

The compounds I above have valuable pharmacodynamic properties. In particular the compound of example 2 is a pharmaceutical compound which may be used in the treatment of various psychoses, neuroses and similar disorders.

The following examples illustrate the invention without, however, limiting it; the melting points are corrected and temperatures stated in degree Centigrade.

EXAMPLE 1:

3-Methylmercapto-10-[2¹-(1¹¹-methylpiperidyl-2¹¹)-ethyl-1¹]-phenthiazine.

a) S - methyl - S¹ - (2¹ - bromophenyl) - 3 - [1¹¹ - methylpiperidyl - (2¹¹) - ethyl] - amino - dithiohydroquinone

5 22.0 g of S-methyl-S¹-(2¹-bromophenyl)-3-amino-dithiohydroquinone and 3.15 g of finely powdered sodium amide in 125 cc of abs. toluene are refluxed for 1 hour on an oil bath maintained at 150°, the mixture being continuously stirred. Without interrupting the boil a solution of 13.1 g of 2-[1¹-methyl-piperidyl-(2¹)]-1-chlorethane in 15 cc of toluene is added dropwise in the course of 1½ hours. After another 3 hours boiling the reaction mixture is cooled, 5 g of ammonium chloride are added, and the mixture is then shaken out three times each with 30 cc of water. The toluene solution is extracted with 120 cc of a 15% aqueous tartaric acid solution, the tartaric acid extract being washed with 50 cc of benzene and adjusted with 30 cc of concentrated caustic soda solution to give an alkaline phenolphthalein reaction. The separated oily base is taken up in a total of 100 cc of benzene, the benzene extract is washed out with 25 cc of water, dried over potassium carbonate, filtered, and boiled down under reduced pressure. The residue is distilled in a high vacuum. The first runnings which at 0.02 mm Hg come over up to 222° are discarded, the principal fraction distilling at this pressure between 222 and 226° being collected. The analytically pure S-methyl-S¹-(2¹-bromophenyl)-3-[1¹¹-methyl-piperidyl - (2¹¹)-ethyl]-amino-dithiohydroquinone boils at 224°/0.02 mm Hg.

25 The hydrochloride is obtained by adding an ethanolic hydrochloric acid solution to a solution of 12.79 g of the free base in 100 cc of abs. ethanol until an acid Congo reaction ensues, causing the hydrochloride of the S-methyl-S¹-(2¹-bromophenyl)-3-[1¹¹-methyl-piperidyl-(2¹¹)-ethyl]-amino-dithiohydroquinone to precipitate in crystalline form. After recrystallisation from abs. ethanol the hydrochloride melts at 194—196°.

30 The initially used S-methyl-S¹-(2¹-bromophenyl)-3-amino-dithiohydroquinone of m.p. 115—117° is prepared by condensing 2-bromothiophenol with 5-methylmercapto-2-chloro-nitrobenzene (m.p. 73—75°) and then reducing the S-methyl-S¹-(2¹-bromophenyl)-3-nitro-dithiohydroquinone (m.p. 90—92°) which has formed with sodium sulphide.

b) 3-Methylmercapto-10-[2¹-(1¹¹-methyl-piperidyl-2¹¹)-ethyl-1¹]-phenthiazine

35 A mixture of 3.1 g of S-methyl-S¹-(2¹-bromophenyl)-3-[1¹¹-methyl-piperidyl-(2¹¹)-ethyl]-aminodithiohydroquinone (b.p. 224°/0.02 mm Hg), 1.9 g. of finely powdered potassium carbonate, 0.15 g of powdered copper and 40 cc of dimethyl formamide is boiled under reflux for 48 hours on an oil bath kept at 210°. After having cooled, the mixture is filtered and the solvent driven out of the filtrate in a vacuum. The solution of the residue in 50 cc of xylene is then shaken out with 25 cc of a 15% aqueous tartaric acid solution. The tartaric acid extract is washed out with 20 cc of benzene and, after addition of 6.5 cc of a concentrated caustic soda solution to give an alkaline phenolphthalein reaction, the separated oily base is taken up in 45 cc of benzene, the benzene extract being washed with 20 cc of water, dried over potassium carbonate, filtered and concentrated. The residue is distilled in a high vacuum and the principal fraction which, at a pressure of 0.02 mm Hg, comes over between 228 and 232° is collected. After crystallisation from acetone the pure 3-methylmercapto-10-[2¹-(1¹¹-methyl-piperidyl-2¹¹)-ethyl-1¹]-phenthiazine of m.p. 72—74° is obtained.

50 *Salicylate*: 100 g of the free base and 38.5 g of salicylic acid are dissolved in 700 cc of boiling abs. ethanol. As the solution cools the salicylate crystallises slowly and, after recrystallisation from abs. ethanol, the pure salicylate melts at 66—68° (small bubbles).

55 *Gallate*: 5.0 g of the free base and 2.54 g of gallic acid (containing 1 mol of water of crystallisation) are dissolved in 25 cc of a boiling mixture of abs. ethanol and acetone (1:1). After filtration the solution is allowed to stand in the cold for some time and the gallate then crystallises. Recrystallisation from abs. ethanol/acetone (1:1) yields the pure gallate, m.p. 145—147° (decomp. sintering above 135°).

Hydrochloride: M.p. 158—160°;
Tartrate: M.p. 130° (decomp; sintering above 70°).
Fumarate: M.p. 158—160° (forming bubbles).

EXAMPLE 2:

3-Methylmercapto-10-[2¹-(1¹¹-methylpyrrolidyl-2¹¹)-ethyl-1¹]-phenothiazine.

- a) S - methyl - S¹ - (2¹ - bromophenyl) - 3 - [1¹¹ - methylpyrrolidyl - (2¹¹) - ethyl] - amino-dithiohydroquinone.

35.0 g of S-methyl-S¹-(2¹-bromophenyl)-3-aminodithiohydroquinone (m.p. 115—117°) and 5.02 g of finely powdered sodium amide in 200 cc of abs. toluene are refluxed for 1 hour, whilst being continuously stirred, on an oil bath kept at a temperature of 150°. Without interrupting the boil a solution of 19.0 g of 2-[1¹-methylpyrrolidyl-(2¹)]-1-chlorethane (b.p. 65°/13 mm Hg) in 20 cc of toluene is added dropwise in the course of 1½ hours. After continuing the boil for another 3 hours the reaction mixture is cooled, 10 g of ammonium chloride are added, and it is shaken out three times each with 40 cc of water. The toluene solution is extracted with 165 cc of a 15% aqueous tartaric acid solution, the tartaric acid extract is washed with 75 cc of benzene and then adjusted by addition of 45 cc of a concentrated caustic soda solution to give an alkaline phenolphthalein reaction. The separated oily base is taken up in a total of 150 cc of benzene, the benzene extract is washed out with 50 cc of water and then dried over potassium carbonate, filtered, and boiled down under reduced pressure. The residue is distilled in a high vacuum and, the first runnings which at 0.01 mm Hg come over up to 215° are discarded; the main fraction which at the same pressure distils between 215 and 219° is collected. At 0.01 mm Hg the analytically pure S-methyl - S¹ - (2¹ - bromophenyl) - 3 - [1¹¹ - methyl - pyrrolidyl - (2¹¹) - ethyl]-amino-dithiohydroquinone boils at 217°.

The tartrate is produced by dissolving 29.7 g of the free base and 10.7 g of tartaric acid in 500 cc of distilled water at 80°, filtering and cooling. After crystallisation of the salt from water, the crystalline, analytically pure tartrate of S-methyl-S¹-(2¹-bromophenyl) - 3 - [1¹¹ - methyl - pyrrolidyl-(2¹¹)-ethyl] - amino - dithiohydroquinone, m.p. 86—88° is obtained (bubbles, sintering above 80°).

- b) 3 - Methylmercapto - 10 - [2¹ - (1¹¹ - methyl - pyrrolidyl - 2¹¹) - ethyl - 1¹] - phenothiazine.

A mixture of 4.8 g of S-methyl-S¹-(2¹-bromophenyl)-3-[1¹¹-methyl-pyrrolidyl-(2¹¹)-ethyl]-amino - dithiohydroquinone (m.p. 217°/0.01 mm Hg), 3.03 g of finely powdered potassium carbonate, 0.22 g of powdered copper and 65 cc of dimethyl formamide is refluxed for 48 hours, whilst being stirred, on an oil bath kept at a temperature of 210°. After cooling and filtration the solvent is removed from the filtrate in a vacuum. The solution of the residue in 50 cc of xylene is then shaken out with 25 cc of a 15% aqueous tartaric acid solution. After the tartaric acid extract has been washed out with 20 cc of benzene, 6.5 cc of a concentrated caustic soda solution are added until the phenolphthalein reaction is alkaline. The separated oily base is taken up in 45 cc of benzene, the benzene extract is washed out with 20 cc of water, dried over potassium carbonate, filtered and concentrated. The residue is distilled in a high vacuum and the main fraction which, at a pressure of 0.008 mm Hg comes over between 208 and 210° is collected.

The fumarate is prepared by dissolving 2.73 g of the free base together with 0.93 g of fumaric acid in 15 cc of boiling abs. ethanol and then cooling. Crystallisation of the salt thus obtained from 17 cc of abs. ethanol yields the fumarate of 3-methylmercapto - 10 - [2¹ - (1¹¹ - methyl - pyrrolidyl - 2¹¹) - ethyl - 1¹] - phenothiazine having a constant m.p. of 139—141° (bubbles).

Tartrate: M.p. 115° (sinters above 70°).

EXAMPLE 3:

3-Ethylmercapto-10-[2¹-(1¹¹-methyl-piperidyl-2¹¹)-ethyl-1¹]-phenothiazine.

- a) S - Ethyl - S¹ - (2¹ - bromophenyl) - 3 - [1¹¹ - methyl - piperidyl - (2¹¹)-ethyl] - amino-dithiohydroquinone.

20 g of S-ethyl-S¹-(2¹-bromophenyl)-3-amino-dithiohydroquinone (m.p. 95—97°) and 2.75 g of finely powdered sodium amide in 115 cc of abs. xylene are refluxed, whilst being stirred, for one hour on an oil bath kept at a temperature of 180°. Without interrupting the boil a solution of 11.4 g of 2-[1¹-methyl-piperidyl-(2¹)]-1-chlorethane in 12 cc of abs. xylene is added dropwise in the course of 1½ hours. Heating is continued for another 3 hours, the reaction mixture is then cooled and, after addition of 5 g of ammonium chloride, shaken out three times each with 30 cc of water. The xylene solution is extracted with 120 cc of a 15% aqueous tartaric acid solution, the tartaric acid extract is washed with 50 cc of benzene and 30 cc of concentrated caustic soda solution are added until the phenolphthalein reaction is alkaline. The separated oily base is taken up in a total of 100 cc of benzene, the benzene extract is washed out with 25 cc of water, dried over potassium carbonate, filtered and boiled down

under reduced pressure. The residue is distilled in a high vacuum, the main fraction which, at 0.05 mm Hg, comes over between 230 and 240° and slightly decomposes being collected.

5 The maleinate is prepared by dissolving 8.3 g of the free base together with 2.17 g of maleic acid in 40 cc of boiling abs. ethanol and then cooling. After crystallisation from 20 cc of abs. ethanol and 20 cc of ether the pure crystalline maleinate of S-ethyl-S¹ - (2¹ - bromophenyl) - 3 - [1¹¹ - methyl - piperidyl - (2¹¹) - ethyl] - amino - dithiohydroquinone of m.p. 130—132° (bubbles) is obtained. 5

10 The S - ethyl - S¹ - (2¹ - bromophenyl) - 3 - aminodithiohydroquinone of m.p. 95—97° initially used is obtained by condensing 2-bromothiophenol with 5-ethylmercapto-2-chloronitrobenzene (m.p. 39—41°) and by then reducing the resultant S-ethyl - S¹ - (2¹ - bromophenyl) - 3 - nitro - dithiohydroquinone (m.p. 81—83°) with sodium sulphide. The 5-ethylmercapto-2-chloronitro-benzene is obtained by reducing 3,3¹ - dinitro - 4,4¹ - dichloro - diphenyl - disulphide (m.p. 116—117°) with sodium sulphide to the corresponding thiophenol whilst at the same time alkylating with diethyl sulphate. 15

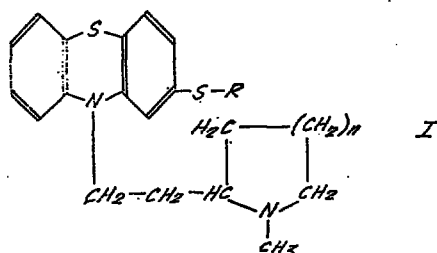
b) 3-Ethylmercapto - 10 - [2¹ - (1¹¹ - methyl - piperidyl - 2¹¹) - ethyl - 1¹] - phenothiazine.

20 A mixture of 5.1 g of S-ethyl-S¹-(2¹-bromophenyl)-3-[1¹¹-methyl-piperidyl-(2¹¹)-ethyl]-amino-dithiohydroquinone (prepared from the pure maleinate, m.p. 130—132°, bubbles), 3.03 g of finely powdered potassium carbonate, 0.22 g of copper bronze and 65 cc of dimethyl formamide is refluxed for 48 hours, whilst being stirred, on an oil bath maintained at 210°. After having cooled, the mixture is filtered and the solvent driven off the filtrate in vacuum. The solution of the residue in 50 cc of xylene is then shaken out with 25 cc of a 15% aqueous tartaric acid solution. The tartaric acid extract 25 is washed out with 20 cc of benzene and alkalis to phenolphthalein alkalinity by adding 6.5 cc of a concentrated caustic soda solution. The separated oily base is taken up in 45 cc of benzene, the benzene extract is washed with 20 cc of water, dried over potassium carbonate, filtered and boiled down. The residue is distilled in a high vacuum and the main fraction which, at 0.008 mm Hg, comes over between 224 and 226° is collected. After crystallisation from isopropanol the pure 3-ethylmercapto-10- 30 [2¹-(1¹¹-methyl-piperidyl-2¹¹)-ethyl-1¹]-phenothiazine, m.p. 57—59° is obtained.

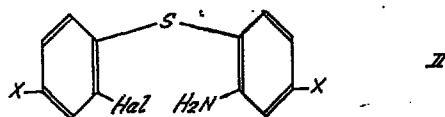
Tartrate: M.p. 135° (decomp. sinters above 70°).

WHAT WE CLAIM IS:—

35 1. A process for the production of compounds having the general formula I, 35



wherein R represents an alkyl group containing from 1—4 carbon atoms inclusive, and *n* represents 1 or 2, and their acid addition salts, characterised in that a compound of the general formula



wherein one of the two symbols

X represents a hydrogen atom, and the other symbol

X represents the grouping —S—R wherein R has the above significance, and

Hal represents a chlorine, bromine or iodine atom,

45 is condensed with a compound having the general formula III, 45

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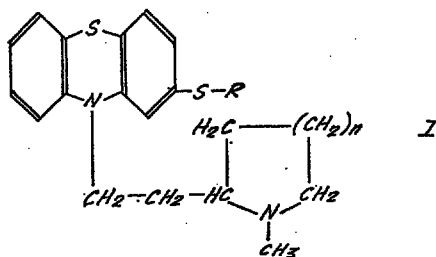
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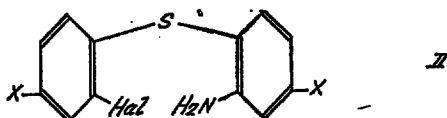
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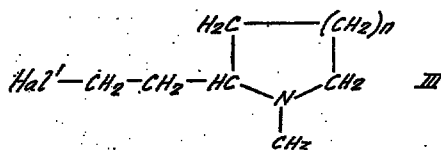


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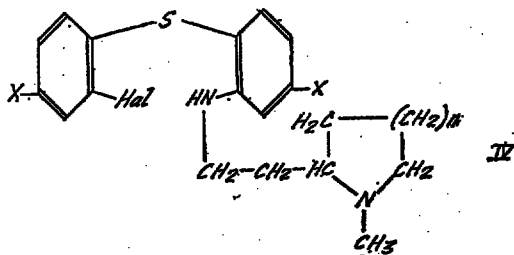
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Hal represents a chlorine, bromine or iodine atom, is condensed with a compound having the general formula III,



wherein n has the above significance, and

Hal^1 represents a chlorine or bromine atom, the resulting compound IV,



5 wherein X, n and Hal have the above significance, is then cyclised and, when it is desired to produce an acid addition salt of a compound I, salification is effected. 5

2. A process according to claim 1, wherein the condensation is effected by heating in the presence of a basic condensation agent.

3. A process according to claims 1 or 2, wherein the cyclisation is effected by heating in the presence of a basic condensation agent and copper. 10

4. A process for the production of the compounds having the formula I stated in claim 1 and their acid addition salts substantially as herein described with reference to any one of the Examples.

5. The compounds having the formula I stated in claim 1 and their acid addition salts whenever produced by the process claimed in any one of claims 1 to 4. 15

6. Compounds having the formula IV stated in claim 1.

7. The specific compounds having the formula IV stated in claim 1 mentioned in any one of the Examples.

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