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PATENT SPECIFICATION

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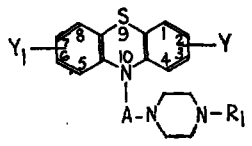
COMPLETE SPECIFICATION

Phenthiazine Derivatives and processes for their preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French Body Corporate, of 21 rue Jean-Goujon, Paris, France, 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:—

This invention relates to new phenthiazine derivatives of value as therapeutic agents and/or as intermediates for the production of such agents. It also concerns processes for the preparation of said derivatives.

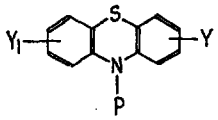
The new compounds of the present invention are those containing the structure:



I

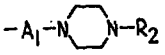
and include not only the bases conforming to this formula but also the corresponding acid addition and quaternary ammonium salts and addition compounds (such for example as those formed between the bases and 8-chlorotheophylline). In the foregoing formula, A represents a divalent saturated aliphatic hydrocarbon radical with a straight or branched chain containing from 2 to 6 carbon atoms, R_1 represents a hydrogen atom or a lower alkyl or an aryl or araliphatic group, Y and Y_1 are respectively a hydrogen or halogen atom or a lower alkyl, alkoxy or aryl or aryloxy group, preferably (in the case of Y) in the 1- or 3-position, the phenthiazine ring may contain substituents additional to Y and Y_1 and one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group. It should be understood that the term "lower alkyl" when used in this specification and in the appended claims means an alkyl group containing not more than 6 and preferably not more than 4 carbon atoms.

These new compounds may be prepared in a variety of different ways, of which the more important can be expressed generically as comprising the interaction of a phenthiazine compound having a structure represented by the formula:



II

with a compound Q, the group P and the compound Q being such that Q will react with the compound of the said formula to introduce or form at the 10-position of the ring a substituent grouping of the structure:



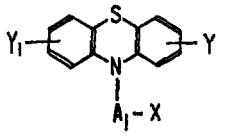
III

In the formulæ II and III, A_1 either represents the radical A (formula I) i.e. a divalent saturated aliphatic straight or branched chain hydrocarbon radical containing 2 to 6 carbon atoms or represents a divalent grouping convertible into the radical A by reduction, Y and Y_1 each represent a hydrogen or halogen atom or a lower alkyl, alkoxy, aryl or aryloxy group, and R_2 either represents the radical R_1 (formula I) i.e. a hydrogen atom or a lower alkyl, aryl or araliphatic group or represents a group convertible (as hereinafter defined) into the radical R_1. One or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group and the phenthiazine ring may contain substituents additional to Y and/or Y_1. Where either or both of the said starting materials contain one or more "convertible" groups as hereinafter defined, the process includes the step or steps of trans-

forming the convertible group or groups into the desired final atom and/or group.

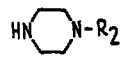
Specific embodiments of the generic process defined in the last preceding paragraph are as follows:—

(1) interaction of a phenthiazine of the general formula:



IV

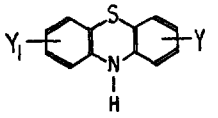
with a piperazine derivative of the general formula:



V

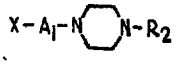
X representing the residue of a reactive ester (e.g. a halogen atom or a sulphuric or sulphonic ester radical such as a *p*-toluene sulphonate radical) and the other variables being as hereinbefore defined,

(2) interaction of a phenthiazine of the general formula:



VI

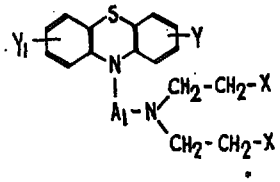
with a piperazine derivative of the general formula:



VII

wherein the stated variables are as hereinbefore defined,

(3) in the case of the production of compounds in which the piperazine ring contains no substituent on a carbon atom, interaction of a compound of the general formula:



VIII

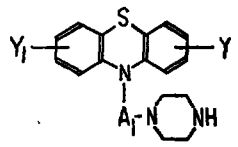
with an amine of the formula R_2NH_2, where the stated variables are as hereinbefore defined.

The aforesaid processes may be carried out by heating the reactants in the presence or absence of an organic diluent and, if desired, in the presence of an alkaline condensing agent, e.g. an alkali metal or derivative thereof such as the hydroxides, hydrides, amides or alcoholates, and more particularly sodium hydroxide or sodamide.

By the statement that R_2 may be a group convertible into the radical R_1 is meant the following possibilities:—

I. Where R_1 is other than a hydrogen atom. The following types of intermediates can be prepared by the aforesaid processes and converted as hereinafter stated:

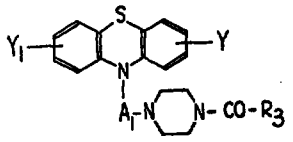
(a)



IX

convertible by alkylation into corresponding compounds in which R_1 represents an alkyl group (this process though being one of replacement of alkyl for hydrogen being classed as a "conversion" for simplicity of reference herein) and:

(b)

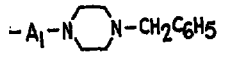


X

(where R_3 is an alkyl, aralkyl or aryl group) convertible by reduction into corresponding compounds containing as the group R_1 an alkyl or aralkyl group.

II. Where R_1 represents a hydrogen atom. Intermediate compounds can be prepared by the aforesaid processes containing the following groups and then converted as hereinafter stated:

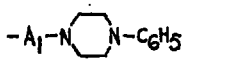
(a) compounds containing the structure:



XI

convertible by reduction (debenzylation),

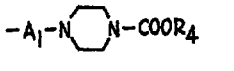
(b) compounds containing the structure:



XII

convertible by nitrosation and fission,

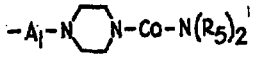
(c) compounds containing the structure:



XIII

where R_4 represents a hydrocarbon group, convertible by hydrolysis,

(d) compounds containing the structure:

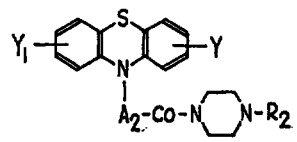


XIV

where R_5 represents any convenient radical such as a hydrocarbon group, convertible by hydrolysis.

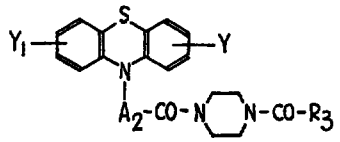
By way of illustration of the use of divalent groupings convertible into the grouping A, with or without groups convertible into an R_1 substituent, there may be prepared amide intermediates of the following types:

(a)



XV

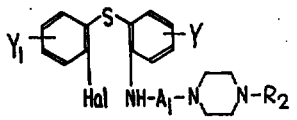
(b)



XVI

the group A_2 being an aliphatic hydrocarbon radical containing from 1 to 5 carbon atoms and the other variables being as hereinbefore defined, conversion being effected by methods of reduction known *per se* from the literature, e.g. by the use of lithium aluminium hydride.

An alternative process for the preparation of the compounds of general formula I comprises the cyclisation of the appropriate diphenyl sulphide of the general formula:



XVII

wherein Hal represents a halogen atom and the remaining symbols are as hereinbefore defined. This cyclisation is preferably carried out in a solvent of the class of N-substituted amides of fatty acids containing not more than 3 carbon atoms in the presence of an alkaline condensing agent such as an alkali metal hydroxide or carbonate and, if desired, also in the presence of a dehydrohalogenation catalyst such as copper powder. When either or both of A_1 and R_2 represents a "convertible" group, the process includes the subsequent step or steps of conversion to A and/or R_1 respectively.

The new compounds of the present invention containing a structure conforming to formula I possess interesting pharmacodynamic properties; in particular, they have been found to be very active anti-epileptics and anti-emetics. In consequence they have application in human or veterinary medicine.

Especially outstanding utility as anti-emetic agents is possessed by those of the said compounds in which Y represents a hydrogen or chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents a hydrogen atom or a methyl or ethyl group, and the piperazine ring is either unsubstituted or is substituted by a methyl group.

The invention is illustrated by the following Examples.

Example I

10-(2-Chloroethyl)phenthiazine (78.5 g.), anhydrous piperazine (76 g.) and methanol (75 cc.) are heated for four hours under reflux. The mixture is then treated with distilled water (100 cc.) and chloroform (2 × 100 cc.). The decanted chloroform is washed with water (2 × 50 cc.) and is shaken with 2N hydrochloric acid (150 cc.). A precipitate (10.5 g.) is formed which is filtered off and recrystallised from butanol (1 g. per 60 cc.) to give 1:4-di(10-phenthiazinylethyl)piperazine dihydrochloride, which melts at 220° C. (inst.).

The aqueous hydrochloric acid solution is treated with aqueous sodium hydroxide (d = 1.33; 100 cc.) and chloroform (4 × 50 cc.). The chloroform is then dried and concentrated *in vacuo* to give 10-(2-1¹-piperazinylethyl)phenthiazine (74 g.). This base when treated with alcohol and ethereal hydrogen chloride gives the dihydrochloride which, when recrystallised from 90% ethanol (1 g. per 25 cc.), melts at 260° C. (inst.).

Example II

Phenthiazine (10 g.) is converted to the sodium derivative by treatment with sodamide (2.25 g.) in xylene (75 cc.) and the product is condensed with a solution in xylene of 1-(2-chloroethyl)-4-benzyloxycarbonylpiperazine obtained from the corresponding hydrochloride (16 g.).

By treatment of the solution with water (100 cc.), extraction with 2N hydrochloric acid (2 × 50 cc.), treatment with aqueous sodium hydroxide, extraction with chloroform and preparation of the hydrochloride, there is obtained directly the same dihydrochloride of 10-(2-1¹-piperazinylethyl)-phenthiazine as described in Example I.

1-(2-Chloroethyl)-4-benzyloxycarbonylpiperazine hydrochloride, m.p. 130—132° C. (inst.), is obtained by the action of thionyl chloride upon 1-(2-hydroxyethyl)-4-benzyloxycarbonylpiperazine hydrochloride in benzene. 1-(2-Hydroxyethyl)-4-benzyloxycarbonylpiperazine, b.p. 286—288° C./1 mm.Hg., is obtained by condensing ethylene oxide with 1-benzyloxycarbonylpiperazine in methanol.

Example III

10-(2-Chloroethyl)phenthiazine (10.5 g.) is heated for 4 to 5 hours at 180° C. with 1-ethylpiperazine (22.8 g.). After cooling, water (25 cc.) is added and the mixture is extracted with ether (2 × 25 cc.). The ethereal solution is shaken with a normal solution of hydrochloric acid (60 cc.), the acidic layer is decanted and treated with concentrated sodium hydroxide solution (15 cc.). The base is extracted with ether (2 × 20 cc.) and the extract dried over sodium sulphate. Concentration *in vacuo* yields 10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine (11.4 g.), m.p.

(inst.) 72° C. The picrate of this base melts at 260° C. (inst.).

10 - (2-4¹-Ethyl-1¹-piperazinylethyl)phenthiazine (2 g.) is heated for two hours under reflux with methyl iodide (10 cc.). The excess methyl iodide is distilled off and the residual resin is dissolved in water (10 cc.). The solution is treated with charcoal, filtered and evaporated *in vacuo* at 20° C. The residue is recrystallised from 90% ethanol (50 cc.) to give 10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine dimethiodide (2.8 g.) which melts at 240° C. (inst.).

EXAMPLE IV

Proceeding as in Example III but commencing with 10-(2-chloroethyl)-phenthiazine (5.25 g.) and 1-methylpiperazine (10 g.), 10-(2 - 4¹-methyl-1¹-piperazinylethyl)phenthiazine (5.6 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 265° C. (inst.).

EXAMPLE V

Commencing with 10-(2-chloroethyl)phenthiazine (5.25 g.) and 1-benzylpiperazine (15.5 g.) there is obtained 10-(2-4¹-benzyl-1¹-piperazinylethyl)phenthiazine (8 g.), which is then treated with ethanol and ethereal hydrogen chloride to give the dihydrochloride which, on recrystallisation from water (1 g. per 7 cc.), melts at 230° C. (inst.).

EXAMPLE VI

Commencing with 10-(2-chloroethyl)phenthiazine (5.25 g.) and 1-phenylpiperazine (16.2 g.) a monohydrochloride (6.5 g.) is obtained which is then recrystallised from a mixture of dimethylformamide and water (1 g. per 20 cc. of dimethylformamide and 10 cc. of water). The 10-(2-4¹-phenyl-1¹-piperazinylethyl)phenthiazine monohydrochloride thus obtained melts at 245° C. (inst.).

EXAMPLE VII

Proceeding as in Example III but commencing with 10-(2-chloroethyl)-phenthiazine (5.25 g.) and 2:3:4:5:6-pentamethylpiperazine (15.6 g.), there is obtained 10-(2-2¹:3¹:4¹:5¹:6¹ - pentamethyl - 1¹ - piperazinylethyl) phenthiazine (5.2 g.) as a viscous resin. The picrate of this base melts at 228° C. (inst.).

EXAMPLE VIII

Proceeding as in Example III but commencing with 10-(3-chloropropyl)-phenthiazine (11 g.) and 1-ethylpiperazine (22.8 g.), 10-(3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine is obtained, m.p. (inst.) 52° C. The picrate of this base melts at 258° C. (inst.).

EXAMPLE IX

Proceeding as in Example III but commencing with 10-(3-chloropropyl)-phenthiazine (5.5 g.) and 4-ethyl-2:3:5:6-tetramethylpiperazine (5.1 g.), there is obtained 10-(3-4¹-ethyl-2¹:3¹:5¹:6¹ - tetramethyl - 1¹ - piperazinylpropyl)-phenthiazine (3 g.) as a viscous resin. The picrate of this base melts at 158° C. (inst.).

EXAMPLE X

Proceeding as in Example I but commencing with 10-(2-chloropropyl)-phenthiazine (11 g.) and 1-ethylpiperazine (21 g.), 10-(2-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (7.5 g.) is obtained, m.p. (inst.) 68° C. The picrate of this base melts at 250° C. (inst.).

EXAMPLE XI

10-(2-Chloropropyl)phenthiazine (5.5 g.) is heated for 5 hours at 200° C. with 1-phenylpiperazine (16.2 g.). The mixture is treated with water (50 cc.) and with ether (50 cc. followed by 20 cc.). The ethereal solutions are agitated with 7% hydrochloric acid (50 cc.) and a feebly soluble hydrochloride (4.5 g.) is obtained which is recrystallised from a 70% aqueous solution of dimethylformamide (50 cc.). 10 - (2 - 4¹ - Phenyl-1¹-piperazinylpropyl) phenthiazine monohydrochloride (3.5 g.) is obtained, m.p. 245° C. (inst.).

EXAMPLE XII

3-Chlorophenthiazine (9.3 g.) is converted to the sodium derivative with sodamide (2 g.) in xylene (75 cc.). The product is condensed with 1-(2-chloroethyl)-4-methylpiperazine (8 g.) in solution (45 cc.) in xylene by boiling for five hours. 3-Chloro-10-(2-4¹-methyl-1¹-piperazinylethyl)phenthiazine dihydrochloride (14.5 g.) is then obtained by the usual treatment, and may be recrystallised from absolute ethanol (1 g. per 10 cc.). The dihydrochloride melts at 253—255° C. (inst.).

1 - (2 - Chloroethyl) - 4-methylpiperazine dihydrochloride, m.p. 265° C. (inst.), is obtained by the action of thionyl chloride upon 1-(2-hydroxyethyl)-4-methylpiperazine in chloroform.

EXAMPLE XIII

3 - Chloro-10-(3-chloropropyl)phenthiazine (27 g.) is heated for 5 hours under reflux on the water-bath with anhydrous piperazine (22.4 g.) and methanol (25 cc.). The mixture is then treated with water (100 cc.) and chloroform (100 cc.), the chloroform solution is shaken with N hydrochloric acid (100 cc.) and the acid solution is made alkaline with sodium hydroxide (d = 1.33, 50 cc.). On extraction with chloroform (2 × 50 cc.), the base (15.2 g.) is obtained and is treated with maleic acid (10 g.) and ethyl acetate (200 cc.). The maleate is recrystallised from ethanol (750 cc.) and 3-chloro-10-(3-1¹-piperazinylpropyl)phenthiazine di-acid maleate (18 g.) is obtained, m.p. 186° C. (inst.).

EXAMPLE XIV

3-(3-Chloro-10-phenthiazinyl)propyl *p*-toluenesulphonate (20 g.) is heated under reflux for 5 hours with anhydrous piperazine (11.6 g.) and methanol (35 cc.). The mixture is treated with water (35 cc.) and chloroform (70 cc.) and the chloroform solution is agitated with 10% hydrochloric acid (50 cc.). The acid solution is made alkaline with sodium hydroxide (d = 1.33, 50 cc.) and the base is extracted with chloroform (50 cc.). The base (6.5 g.) is treated with maleic acid (5 g.) and ethyl acetate (100 cc.). 3 - Chloro - 10 - (3-1¹ - piperazinylpropyl)

phenthiazine dimaleate (8 g.) is obtained which, on recrystallisation from ethanol, melts at 186° C.

3-(3-Chloro-10-phenthiazinyl)propyl *p*-toluenesulphonate (20 g.) is prepared by treating 3-(3-chloro-10-phenthiazinyl)propanol (14.6 g.) in anhydrous pyridine (73 g.) with *p*-toluenesulphonylchloride (10.5 g.) added over 1 hour at a temperature in the neighbourhood of 5° C. The mixture is left at 0° C. for 48 hours and is then washed in the presence of ether with iced water, dilute hydrochloric acid and a 5% aqueous solution of sodium bicarbonate. It is then concentrated at 20° C.

EXAMPLE XV

Proceeding as in Example III but commencing with 3-chloro-10-(3-chforopropyl)phenthiazine (19 g.) and 1-methylpiperazine (15 g.), there is obtained 3-chloro-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine (15.8 g.), the dihydrochloride of which melts at 195° C. (inst.). The picrate of the base melts at 250° C. (inst.).

3 - Chloro - 10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine (2 g.) is heated for 1 hour under reflux with methyl iodide (10 cc.). The mixture is concentrated, dissolved in water, filtered and dried *in vacuo* and on recrystallisation from methanol 3-chloro-10-(3-4¹-methyl - 1¹-piperazinylpropyl)phenthiazine dimethiodide (2 g.), m.p. 266° C. (inst.), is obtained.

3 - Chloro - 10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine (1.6 g.), 8-chlorotheophylline (0.8 g.) and methanol (2.5 cc.) are heated for one hour under reflux. Methanol (5 cc.) and water (1 cc.) are then added and the mixture is boiled for half an hour and then filtered hot to remove insoluble matter.

The alcoholic solution crystallises on cooling and the crystals are filtered off, washed with ethanol and dried *in vacuo* to give 3-chloro-10-(3 - 4¹ - methyl-1¹-piperazinylpropyl)phenthiazine 8-chlorotheophyllinate which melts at 175° C. (inst.).

EXAMPLE XVI

By treating 3-(3-chloro-10-phenthiazinyl) propyl *p*-toluenesulphonate (20 g.) with 1-methylpiperazine (13.5 g.) in a manner similar to that described in Example XIV, 3-chloro-10 - (3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine dimaleate (16 g.) m.p. 228° C. is obtained.

Proceeding as in Example XV but using ethyl iodide instead of methyl iodide, 3-chloro-10 - (3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine diethiodide is obtained, m.p. 268° C. (inst.).

EXAMPLE XVII

Proceeding as in Example III but commencing with 3-chloro-10-(3-chloropropyl)phenthiazine (11.7 g.) and 1-ethylpiperazine (20 g.), 3 - chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl) phenthiazine (10.6 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 265° C. (inst.).

The base when treated with ethanol and ethereal hydrogen chloride gives the dihydrochloride which is recrystallised from absolute ethanol (1 g. per 25 cc.). The dihydrochloride melts at 220° C. (inst.).

3 - Chloro - 10 - (3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (1.2 g.) is heated with ethyl iodide (10 cc.) for two hours under reflux. The mixture is concentrated on the water-bath and the resin obtained is dissolved in water (10 cc.). On cooling, a crystalline product (1.5 g.) is obtained, which is then recrystallised from 80% ethanol (25 cc.) to give 3 - chloro - 10 - (3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine diethiodide (0.8 g.), m.p. 260° C. (inst.).

By treating 3-chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (3.4 g.) with theophylline acetic acid (4 g.) and ethanol (15 cc.), 3 - chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl) phenthiazine di-theophylline acetate (7.4 g.) is obtained which is water-soluble and melts at 100° C. (inst.) (not sharp).

3 - Chloro - 10 - (3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (2 g.) is heated for 2 hours under reflux with 8-chlorotheophylline (1.6 g.) in methylethylketone (9 cc.) and water (1 cc.). The solution is concentrated and then treated with ethanol (10 cc.). The solution crystallises slowly and 3-chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine di - 8 - chlorotheophyllinate (2.3 g.) is obtained, m.p. 185° C. (inst.).

3 - Chloro - 10 - (3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (2 g.) is heated for 1½ hours under reflux with methyl iodide (3 g.) and acetone (10 cc.). The mixture is concentrated, dissolved in water, filtered and dried *in vacuo* at 20° C. and the product is recrystallised from methanol (10 cc.). 3-Chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine dimethiodide (0.6 g.) is obtained, m.p. 260—265° C. (inst.).

EXAMPLE XVIII

Proceeding as in Example III but commencing with 3-chloro-10-(2-chloropropyl)phenthiazine (12.4 g.) and 1-ethylpiperazine (22.8 g.), 3 - chloro-10-(2-4¹-ethyl-1¹-piperazinylpropyl) phenthiazine (8.3 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 254° C. (inst.).

EXAMPLE XIX

Proceeding as in Example XI but commencing with 3-chloro-10-(2-chloropropyl) phenthiazine (6.2 g.), 3-chloro-10-(2-4¹-phenyl-1¹ - piperazinylpropyl) - phenthiazine monohydrochloride (3.4 g.) is obtained, m.p. 225° C.

EXAMPLE XX

A mixture of phenthiazine (6.65 g.), 85% sodamide (2 g.) and xylene (40 cc.) is heated for 1 hour under reflux. With continued reflux, 1 - (2 - phenylallyl) - 4-(3-chloropropyl)piperazine (11 g.) is added and heating is continued

for 4 hours. The mixture is treated with water (80 cc.) and the xylene is decanted. The xylene layer is treated with N hydrochloric acid (90 cc.) and 10-[3-4¹-(2-phenylallyl)-1¹-piperazinylpropyl]phenthiazine hydrochloride precipitates as an oil. It is converted to the base by adding sodium hydroxide ($d = 1.33$, 10 cc.) and ethanol (25 cc.) and the base is extracted with ether (2 × 80 cc.). The ethereal extract is dried over sodium sulphate and the ether is removed on the water-bath. 10-[3-4¹-(2-phenylallyl)-1¹-piperazinylpropyl]-phenthiazine (14 g.) is thus obtained and is purified by conversion to the oxalate in acetone. The hydrochloride of the pure base melts at 200—202° C.

The 1-(2-phenylallyl)-4-(3-chloropropyl) piperazine which serves as starting material is prepared by the action of 1-chloro-3-bromopropane upon 1-2¹-phenylallylpiperazine in ether.

EXAMPLE XXI

A mixture of phenthiazine (7.6 g.), 85% sodamide (4.5 g.) and anhydrous xylene (150 cc.) is heated for 2 hours under reflux. The mixture is cooled to 30° C., 1-(4-bromobutyl)-4-ethylpiperazine monohydrobromide (15 g.) is added, the mixture is reheated gradually until reflux commences and refluxing is continued for 8 hours. The excess sodamide is decomposed, after cooling, with water (20 cc.) and the xylene layer is extracted with N hydrochloric acid (2 × 50 cc.). The hydrochloric acid extracts are made alkaline with caustic soda ($d = 1.33$, 15 cc.), and the oily base which separates is extracted with ether (3 × 100 cc.). After drying over sodium sulphate, the ether is removed under normal pressure and the residue is distilled *in vacuo*. 10-(4-4¹-ethyl-1¹-piperazinylbutyl)phenthiazine (5.5 g.), b.p. 210—215° C./0.4 mm.Hg., is thus obtained. Its dihydrochloride melts at 218—220° C.

The 1-(4-bromobutyl)-4-ethylpiperazine monohydrobromide which serves as starting material in the preceding preparation is obtained by the bromination with thionyl bromide in chloroform of 1-(4-hydroxybutyl)-4-ethylpiperazine, b.p. 110—115° C./10.3 mm. Hg., itself prepared by heating 1 mole of 4-chlorobutanol with 2 moles of ethylpiperazine by heating for 10 hours at 100° C.

EXAMPLE XXII

Proceeding as in Example XII but commencing with 3-chlorophenthiazine and 1-(2-chloroethyl)-4-ethylpiperazine, there is obtained 3-chloro-10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine dihydrochloride, which melts at 228—230° C. (inst.).

3-Chloro-10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine (1.7 g.) and methyl iodide (10 cc.) are heated for four hours under reflux. The excess methyl iodide is distilled off and the resin so obtained is dissolved in water (20 cc.). The solution is treated with charcoal, filtered and concentrated *in vacuo* at 20° C., and the product is recrystallised from 80% ethanol (12 cc.) to give 3-chloro-10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine dimethiodide, which melts at 262° C. (inst.).

EXAMPLE XXIII

3-Chlorophenthiazine (7 g.) is converted to the sodium derivative with sodamide (1.4 g.) in xylene (50 cc.). 1-(2-Chloroethyl)-4-butylpiperazine (7 g.) in xylene (30 cc.) is then added over 10 minutes and the mixture is heated for 2 hours under reflux. The usual treatment yields 3-chloro-10-(2-4¹-butyl-1¹-piperazinylethyl)phenthiazine dihydrochloride (11.9 g.), m.p. 208° C. (inst.).

1-(2-Chloroethyl)-4-butylpiperazine dihydrochloride, m.p. 245° C. (inst.), is obtained by the action of thionyl chloride upon the hydroxy compound in chloroform.

1-(2-Hydroxyethyl)-4-butylpiperazine, b.p. 98—100° C./1mm.Hg., is obtained by heating 1-(2-hydroxyethyl)piperazine with *n*-butyl *p*-toluenesulphonate for 2 hours on a water-bath, treating the mixture with aqueous sodium hydroxide and chloroform and then distilling.

EXAMPLE XXIV

Sodamide (8.2 g.) is added to a solution of 3-chlorophenthiazine (44 g.) in toluene (250 cc.) maintained at about 120° C. and 1-(3-chloropropyl-4-methylpiperazine (37 g.) is then added gradually over 40 minutes. After being heated for a further 40 minutes under reflux, the mixture is cooled, treated with water (200 cc.) and acidified with hydrochloric acid ($d = 1.19$, 40 cc.). The organic layer is separated and the aqueous layer is washed with ether (200 cc.), made alkaline with aqueous sodium hydroxide ($d = 1.33$, 50 cc.) and extracted with ether (300 cc.). The ethereal extract is dried over sodium sulphate, the ether is evaporated and the residue is distilled yielding 3-chloro-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine (57 g.), b.p. 260—275° C./2 mm.Hg., the hydrochloride of which melts at 200—210° C.

3-Chloro-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine (6.9 g.) is heated under reflux with theobromine acetic acid (8.75 g.) and ethanol (20 cc.). The alcohol is distilled off *in vacuo* and the residue is dried *in vacuo* in the presence of sulphuric acid. 3-Chloro-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine di-theobromine acetate (15.5 g.) is obtained which is soluble in water and melts at about 130° C. (inst.).

1-(3-Chloropropyl)-4-methylpiperazine, b.p. 82—83° C./3 mm.Hg., may be prepared by the action of 1-chloro-3-bromopropane on 1-methylpiperazine.

EXAMPLE XXV

Sodamide (12.9 g.) is added to a solution of 3-chlorophenthiazine (23.4 g.) in toluene (300 cc.) maintained at 80° C. The mixture is heated in the neighbourhood of its boiling point (110° C.) and 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride (27.5 g.) is added gradually (over 1 hour). After addition

is completed, heating is continued for 3 hours. After cooling, the mixture is treated with water (250 cc.) and is made acid to Congo Red with hydrochloric acid ($d = 1.19$, 30 cc.). The toluene layer is separated and the aqueous layer is washed with ether (250 cc.) and is then made alkaline to phenolphthalein with sodium hydroxide ($d = 1.33$, 35 cc.). The base which separates is extracted with ether. The ether is evaporated and the residue is distilled. 3-Chloro - 10-(3-4¹-methyl-1¹-piperazinylpropyl) phenthiazine (27.3 g.) is thus obtained, the dihydrochloride of which melts at about 195° C.

By treating 3 - chloro - 10 - (3-4¹-methyl-1¹-piperazinylpropyl)-phenthiazine (5 g.) with theophylline acetic acid (6.3 g.) and ethanol (20 cc.) as described in Example XXIV, 3-chloro - 10-(3-4¹-methyl-1¹-piperazinylpropyl) phenthiazine ditheophylline acetate (11.2 g.) is obtained which is water-soluble and melts at 100° C. (inst.) (not sharp).

EXAMPLE XXVI

3 - Chlorophenthiazine (8 g.), anhydrous xylene (35 cc.) and 95% sodamide (1.52 g.) are heated under reflux for ½ hour. A solution of 1-(3-chloropropyl)-4-butylpiperazine (9 g.) in anhydrous xylene (18 cc.) is run gradually over 15 minutes into the boiling suspension of the sodium derivative of 3-chlorophenthiazine thus obtained and heating under reflux is continued for 2½ hours.

The excess sodamide is decomposed with water (30 cc.), the aqueous layer is decanted and the xylene layer is extracted with approximately normal hydrochloric acid (2 × 50 cc.). The hydrochloric acid extracts are made alkaline with sodium hydroxide (d = 1.33, 15 cc.) and the oily base which separates is extracted with ether (3 × 80 cc.). After drying over sodium sulphate the ether is removed under normal pressure and the residue is distilled. 3 - Chloro-10-(3-4¹-butyl-1¹-piperazinylpropyl) phenthiazine (9.45 g.), b.p. 237—246° C./0.6 mm.Hg., is thus obtained, the dihydrochloride of which melts at 232—234° C. (inst.).

The 1 - (3 chloropropyl)-4-butylpiperazine which serves as starting material in the preceding preparation is obtained by the action of 1-chloro-3-bromopropane on 1-butylpiperazine in ether under reflux. It boils at 85—87° C./0.8 mm.Hg.

EXAMPLE XXVII

Proceeding as in Example XII but commencing with 1-chlorophenthiazine and 1-(2-chloroethyl)-4-ethylpiperazine, there is obtained 1-chloro-10-(2-4¹-ethyl-1¹-piperazinylethyl)phenthiazine dihydrochloride, which melts at 238—240° C. (inst.).

EXAMPLE XXVIII

Proceeding as in Example XXVI but commencing with 1-chlorophenthiazine and 1-(3-chloropropyl)-4-ethylpiperazine, 1-chloro-10-(3 - 4¹-ethyl-1¹-piperazinylpropyl)phenthiazine, b.p. 213—230° C./0.25 mm.Hg., is obtained in 55% yield. Its dihydrochloride melts at 200—202° C.

EXAMPLE XXIX

Proceeding as in Example XXVI but commencing with 1-chlorophenthiazine, 1-chloro-10 - (3 - 4¹-butyl-1¹-piperazinylpropyl)phenthiazine (b.p. 236—245° C./0.4 mm.Hg.) is obtained in a 71% yield. Its dihydrochloride melts at 255—256° C.

EXAMPLE XXX

Proceeding as in Example XXI but commencing with 1-chlorophenthiazine, 1-chloro-10 - (4 - 4¹-ethyl-1¹-piperazinylbutyl)phenthiazine (b.p. 180—210° C./0.3 mm.Hg.) is obtained in a 40% yield. Its dihydrochloride melts at 225—230° C.

EXAMPLE XXXI

Proceeding as in Example XXVI but commencing with 3-methylphenthiazine (27 g.), sodamide (5.4 g.), 1-(3-chloropropyl)-4-methyl piperazine (24.5 g.) and xylene (270 cc.), 3-methyl - 10-(3-4¹-methyl-1¹-piperazinylpropyl) phenthiazine (40 g.), b.p. 230—245° C./0.9 mm.Hg., is obtained, the dihydrochloride of which melts at about 200° C.

EXAMPLE XXXII

3-Methylphenthiazine (21.3 g.) is converted to the sodium derivative with sodamide (4.5 g.) in boiling xylene (180 cc.) and the product is condensed with 1-(3-chloropropyl)-4-ethyl-piperazine (22.9 g.) by heating under reflux for 3 hours. The mixture is treated with water, the xylene layer is extracted with 2N hydrochloric acid and the aqueous layer is made alkaline and extracted with ether. The ethereal extract is dried, the ether is evaporated and the residue is distilled to yield 3-methyl-10-(3 - 4¹-ethyl-1¹-piperazinylpropyl)phenthiazine (30 g.), b.p. 233—235° C./0.2 mm.Hg., the dihydrochloride of which melts at 242—244° C.

1 - (3-Chloropropyl)-4-ethylpiperazine, b.p. 83—84° C./1 mm.Hg., may be prepared by the action of 1-chloro-3-bromopropane on 1-ethylpiperazine.

EXAMPLE XXXIII

Proceeding as in Example XXVI but commencing with 3-methoxyphenthiazine (23.4 g.) sodamide (4.4 g.) 1-(3-chloropropyl)-4-methyl-piperazine (20 g.) and xylene (230 cc.), 3-methoxy - 10 - (3-4¹ - methyl - 1¹-piperazinyl-propyl)phenthiazine (28 g.), b.p. 245—255° C./1 mm.Hg., is obtained, the dihydrochloride of which melts at about 225° C.

EXAMPLE XXXIV

Proceeding as in Example XXVI but commencing with 3-methoxyphenthiazine (12 g.) and 1-(3-chloropropyl)-4-ethylpiperazine (11.5 g.), 3 - methoxy - 10-(3-4¹-ethyl-1¹-piperazinyl-propyl)phenthiazine (12.5 g.) b.p. 238—243° C./0.7 mm.Hg., is obtained, the dihydrochloride of which melts at 229° C.

EXAMPLE XXXV

Proceeding as in Example XXVI but commencing with 3-methoxyphenthiazine, 3-meth-

oxy - 10-(3-4¹-butyl-1¹-piperazinylpropyl)phenthiazine, b.p. 230—243° C./0.35 mm.Hg., is obtained in 56% yield. Its hydrochloride melts at 252—254° C.

EXAMPLE XXXVI

Proceeding as in Example XXVI but commencing with 3-phenylphenthiazine (20 g.), xylene (200 cc.), sodamide (3.1 g.) and 1-(3-chloropropyl)-4-methylpiperazine (14 g.), 3-phenyl - 10-(3-4¹-methyl-1¹-piperazinylpropyl)-phenthiazine (25 g.), b.p. 275—285° C./0.9 mm.Hg., is obtained, the dihydrochloride of which melts at about 220° C.

EXAMPLE XXXVII

Sodamide (0.9 g.) is added to a solution of 1-phenylphenthiazine (5.5 g.) in xylene (55 cc.) heated to 100° C. The mixture is then heated in the neighbourhood of its boiling point (120—130° C.) and a solution of 1-(3-chloropropyl)-4-methylpiperazine (3.9 g.) in xylene (8 cc.) is added slowly. After the addition is completed, heating is continued for 1½ hours. After cooling, the mixture is treated with water (55 cc.) and then it is made acid to Congo Red with hydrochloric acid ($d = 1.19$, 6 cc.). The organic layer is separated and the aqueous solution is washed with ether (50 cc.) and then made alkaline to phenolphthalein with sodium hydroxide ($d = 1.33$, 6.5 cc.).

The base which separates is extracted with ether (3 × 150 cc.), the ether is evaporated and the residue is distilled *in vacuo*. 1-Phenyl-10-(3 - 4¹ - methyl - 1¹-piperazinylpropyl)phenthiazine (5.2 g.), b.p. 275—285° C./1 mm.Hg., is thus obtained the dihydrochloride of which melts at about 210° C.

EXAMPLE XXXVIII

Proceeding as in Example XXVI but commencing with 2:3-dimethylphenthiazine (22.7 g.) 85% sodamide (5 g.) xylene (210 cc.) and 1 - (3 - chloropropyl)-4-methylpiperazine (19.4 g.) in xylene (50 cc.), 2:3-dimethyl-10-(3-4¹-methyl - 1¹ - piperazinylpropyl)phenthiazine (24.75 g.), b.p. 215—225° C./0.2 mm.Hg., is obtained, the dihydrochloride of which melts at 238° C.

The 2:3-dimethylphenthiazine (m.p. 204° C.) which serves as starting material is prepared by the action of sulphur upon 3:4-dimethyldiphenylamine in the presence of iodine.

EXAMPLE XXXIX

10-(2-1¹-Piperazinylethyl)phenthiazine (9.3 g.) is heated with agitation under reflux with *n*-propyl *p*-toluenesulphonate (9.6 g.), anhydrous sodium carbonate (2.4 g.) and absolute ethanol (15 cc.). After 6 hours heating, the alcohol is distilled off and the residue is treated with N sodium hydroxide (45 cc.) and ether (100 cc.). The ethereal layer is decanted, the aqueous layer is washed with ether (60 cc.) and the combined ethereal solutions are treated with N hydrochloric acid (50 cc.). The acid solution is shaken with sodium hydroxide ($d = 1.33$, 20 cc.) and then with ether (2 × 50 cc.).

On drying and concentrating, the base (6 g.) is obtained. The hydrochloride is prepared in alcohol-ether and 10-(2-4¹-propyl-1¹-piperazinylethyl)phenthiazine dihydrochloride (7.7 g.) is obtained which melts at 240° C. (inst.) after crystallisation from ethanol (5 parts).

EXAMPLE XL

10-(2-1¹-piperazinylethyl)phenthiazine (6.2 g.), *n*-butyl *p*-toluenesulphonate (6.9 g.), anhydrous sodium carbonate (1.6 g.) and ethanol (10 cc.) are heated for five hours under reflux. The mixture is treated with N sodium hydroxide (30 cc.) and ether (2 × 50 cc.), and the ethereal solution is extracted with N hydrochloric acid (2 × 20 cc.). The acid layer is then treated with aqueous sodium hydroxide ($d =$ 1.33, 10 cc.) and is extracted with ether (2 × 50 cc.). After concentration, the base is treated with alcohol and ethereal hydrogen chloride to give 10-(2-4¹-butyl-1¹-piperazinylethyl)phenthiazine dihydrochloride (4.5 g.), which melts at 226° C. (inst.).

EXAMPLE XLI

3 - Chloro-10-(3-1¹-piperazinylpropyl)phenthiazine (0.4 g.) is hydrogenated for 1 hour at normal pressure and at 20° C. with 30% formaldehyde (0.3 g.) and acetic acid (10 cc.) in the presence of pre-reduced Adams' platinum catalyst (0.2 g.).

The mixture is filtered and, after washing the solid with water (4 × 10 cc.), is made alkaline with sodium hydroxide ($d = 1.33$) and extracted successively with ether (3 × 25 cc.) and chloroform (3 × 25 cc.). After drying, the solvents are distilled off and, on treatment with ethereal hydrogen chloride 3-chloro-10-(3-4¹-methyl - 1¹-piperazinylpropyl)phenthiazine dihydrochloride is obtained, m.p. 195—200° C. (inst.).

EXAMPLE XLII

A solution of 10-(2-4¹-propionyl-1¹-piperazinylethyl)phenthiazine (1.5 g.) in tetrahydrofuran (8 cc.) is added over 15 minutes to a 2% ethereal solution of lithium aluminium hydride (10 cc.).

The mixture is heated with agitation under reflux for 6 hours and, after standing overnight, is treated successively with water (0.25 cc.), 15% sodium hydroxide (0.25 cc.), water (7 cc.) and chloroform (20 cc.). The precipitate is filtered off and washed with chloroform (5 × 5 cc.). The liquors are dried over sodium sulphate and concentrated, and on the addition of ethereal hydrogen chloride give 10-(2-4¹-propyl - 1¹ - piperazinylethyl)-phenthiazine dihydrochloride (1.5 g.) melting at 240° C. (inst.) as in Example XXXIX.

10 - (2 - 4¹ - Propionyl-1¹-piperazinylethyl) phenthiazine hydrochloride, m.p. 165° C. (inst.), is obtained by the action of propionyl chloride on 10-(2-1¹-piperazinylethyl)phenthiazine in the presence of pyridine.

EXAMPLE XLIII

A solution of 3-chloro-10-(3-4¹-acetyl-1¹-piperazinylpropyl)phenthiazine (0.6 g.) in tetrahydrofuran (8 cc.) is added over ½ hour to a 2% ethereal solution of lithium aluminium hydride (10 cc.) and the mixture is heated for 7 hours under reflux with agitation. 3-chloro-10-(3-4¹-ethyl-1¹-piperazinylpropyl)phenthiazine dihydrochloride, m.p. 220—225° C. (inst.) is thus obtained.

3-Chloro-10-(3-4¹-acetyl-1¹-piperazinylpropyl)phenthiazine hydrochloride, m.p. 215° C. (inst.), is obtained by the action of acetyl chloride and pyridine upon 3-chloro-10-(3-1¹-piperazinylpropyl)phenthiazine.

EXAMPLE XLIV

3-Chloro-10-[3-(di-N-2-chloroethyl)aminopropyl]phenthiazine hydrochloride (1.8 g.) is heated in a sealed tube for 4 hours at 140° C. with a 290 g./l. aqueous solution (9 cc.) of monomethylamine. The contents of the tube are treated with chloroform (40 cc.). The aqueous layer is decanted and the chloroform layer is shaken with N hydrochloric acid (15 cc. followed by 2 cc.). The aqueous solution is treated with sodium hydroxide ($d = 1.33$, 10 cc.) and chloroform (20 cc.). After evaporation of the solvent, the base (1.5 g.) is obtained. A solution of maleic acid (1 g.) in ethanol (5 cc.) is added and after recrystallisation from water, 3-chloro-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine dimaleate is obtained, m.p. 228° C. (inst.).

EXAMPLE XLV

10-(2-4¹-Benzyl-1¹-piperazinylethyl)phenthiazine dihydrochloride (0.4 g.) is hydrogenated in acetic acid (7 cc.) with palladised charcoal (0.5 g., 10% palladium) at 20° C. and at atmospheric pressure. The hydrogenation is complete after 2 hours. After filtering and washing with water made alkaline with concentrated aqueous sodium hydroxide, the base so obtained is extracted with ether (4 × 10 cc.). Treatment of the base with ethereal hydrogen chloride yields 10-(2-1¹-piperazinylethyl)phenthiazine dihydrochloride (0.2 g.) which, after recrystallisation from absolute ethanol, melts at 260° C. (inst.).

EXAMPLE XLVI

10-(2-4¹-Phenyl-1¹-piperazinylethyl)phenthiazine hydrochloride (1.15 g.) agitated with dimethylformamide (20 cc.) and hydrochloric acid ($d = 1.19$, 2 cc.), is treated with a solution of sodium nitrite (0.2 g.) in water (2 cc.) the temperature being kept below 0° C. After 1 hour, sodium bisulphite ($d = 1.33$, 3 cc.) is added, and after standing overnight, the mixture is treated with sodium hydroxide ($d = 1.33$, 6 cc.) and water (20 cc.). It is then shaken with chloroform (2 × 25 cc.) and, on the addition of ethereal hydrogen chloride, 10-(2-1¹-piperazinylethyl)phenthiazine dihydrochloride (0.9 g.) is obtained, m.p. 260° C. (inst.).

EXAMPLE XLVII

10-(2-4¹-Ethoxycarbonyl-1¹-piperazinylethyl)phenthiazine (1 g.) is heated for 24 hours under reflux with alcoholic potassium hydroxide (250 g. per litre; 15 cc.). The solution is concentrated and treated with water (5 cc.) and ether (4 × 10 cc.). The addition of ethereal hydrogen chloride yields 10-(2-1¹-piperazinylethyl)phenthiazine dihydrochloride (0.7 g.) which, after recrystallisation from ethanol, melts at 260° C. (inst.).

10-(2-4¹-Ethoxycarbonyl-1¹-piperazinylethyl)phenthiazine may be obtained by heating 10-(2-chloroethyl)phenthiazine (10.5 g.) with 1-ethoxycarbonylpiperazine (31.6 g.) for 4 hours at 195° C. and then treating the mixture with water (30 cc.) and ether (2 × 20 cc.). The ethereal solution is shaken with 10% hydrochloric acid (35 cc.), and treatment with sodium hydroxide and ether yields 10-(2-4¹-ethoxycarbonyl-1¹-piperazinylethyl)phenthiazine (16.5 g.), m.p. 95° C. (inst.).

EXAMPLE XLVIII

10-(2-4¹-Diethylcarbamyl-1¹-piperazinylethyl)phenthiazine hydrochloride (0.3 g.) is heated for 30 hours under reflux with hydrochloric acid ($d = 1.19$, 7 cc.). Water (20 cc.) is then added, a small quantity of insoluble matter is filtered off and the aqueous solution is treated with sodium hydroxide solution ($d = 1.33$, 8 cc.). Extraction with chloroform (2 × 20 cc.), drying over sodium sulphate, concentration and treatment with ethereal hydrogen chloride yields 10-(2-1¹-piperazinylethyl)phenthiazine dihydrochloride (0.15 g.) which, after recrystallisation from ethanol, melts at 260° C. (inst.).

10-(2-4¹-Diethylcarbamyl-1¹-piperazinylethyl)phenthiazine may be obtained by heating 10-(2-chloroethyl)phenthiazine (5.2 g.) with 1-diethylcarbamylpiperazine (18.5 g.) for 5 hours at 200° C. 10-(2-4¹-diethylcarbamyl-1¹-piperazinylethyl)phenthiazine hydrochloride (6 g.) m.p. 182—184° C. (inst.) is thus obtained.

The following derivatives may also be treated in a similar manner:

10-(2-4¹-dimethylcarbamyl-1¹-piperazinylethyl)phenthiazine hydrochloride, m.p. 215° C. (inst.).

10-(2-4¹-phenylcarbamyl-1¹-piperazinylethyl)phenthiazine, m.p. 160° C. (inst.).

10-(2-4¹-carbamyl-1¹-piperazinylethyl)phenthiazine hydrochloride, m.p. 180° C. (inst.).

EXAMPLE IL

3-Chloro-10-(2-chloroethyl)phenthiazine (29.6 g.) is heated for 6 hours under reflux with anhydrous piperazine (26 g.) and methanol (30 cc.). The mixture is then treated with chloroform (100 cc.) and water (100 cc.) and filtered and the chloroform layer is agitated with 10% hydrochloric acid (100 cc.). The aqueous layer is treated with aqueous sodium hydroxide ($d = 1.33$, 40 cc.) and the base is extracted with chloroform (2 × 50 cc.). After the chloroform has been evaporated the crude base (27.7 g.) is obtained, to which is added

ethyl acetate (200 cc.) and a warm solution of maleic acid (20.8 g.) in ethyl acetate (600 cc.). A maleate is obtained which is recrystallised from ethanol (1,200 cc.) to give 3-chloro-10 - (2 - 1¹-piperazinylethyl)phenthiazine dimaleate (34.8 g.), m.p. 195° C.

EXAMPLE L

3-Ethylphenthiazine (5.7 g.) is heated for 1 hour under reflux with sodamide (3.6 g.) in xylene (150 cc.). 1-Methyl-4-(3-chloropropyl) piperazine dihydrochloride (7.5 g.), is added over ½ hour and heating under reflux is continued for 6 hours. Water (100 cc.) is then added and the xylene layer is agitated with 7% hydrochloric acid (50 cc. followed by 25 cc.). The aqueous layer is treated with aqueous sodium hydroxide ($d = 1.33$, 25 cc.) and the base is extracted with ether (2 × 25 cc.). On evaporating off the ether the crude base (9 g.) is obtained which is triturated with a warm solution of maleic acid (5.8 g.) in ethyl acetate (150 cc.) to give 3-ethyl-10-(3-4¹-methyl-1¹-piperazinylpropyl)phenthiazine dimaleate (12 g.) m.p. 200° C. which may be recrystallised from water.

EXAMPLE LI

2:5-Dimethylpiperazine (6.9 g.) is heated for 7 hours under reflux with 3-chloro-10-(3-hydroxypropyl)phenthiazine *p*-toluenesulphonate (8.9 g.) and methanol (10 cc.). The mixture is treated with chloroform (100 cc.) and water (100 cc.) and the chloroform layer is agitated with 10% hydrochloric acid (25 cc.). The aqueous layer is filtered and aqueous sodium hydroxide ($d = 1.33$, 10 cc.) is added. The base is extracted with chloroform (3 × 25 cc.) and on evaporation of the chloroform the crude base (4 g.) is obtained, which is treated with ethereal hydrogen chloride to give 3-chloro-10 - (3-2¹:5¹ - dimethyl-1¹-piperazinylpropyl)-phenthiazine dihydrochloride (2.7 g.), m.p. 195° C.

EXAMPLE LII

A mixture of 10-(2-chloropropyl)phenthiazine (13.8 g.) and anhydrous piperazine (13 g.) is fused by heating in an oil-bath for 7 hours at 160° C. The mixture is then treated with water (40 cc.) and chloroform (60 cc.), the chloroform layer is agitated with 10% hydrochloric acid (40 cc.) and the aqueous layer is then filtered and treated with aqueous sodium hydroxide ($d = 1.33$, 30 cc.). The base is extracted with chloroform (2 × 20 cc.) and on evaporation of the chloroform, the crude base (5.9 g.) is isolated and is treated with maleic acid (4.2 g.) in ethyl acetate (50 cc.) to give 10 - (2 - 1¹-piperazinylpropyl)phenthiazine dimaleate (8.1 g.), m.p. 160° C., which may be recrystallised from ethanol.

EXAMPLE LIII

10-(3-Chloropropyl)phenthiazine (7.5 g.) is heated for 5½ hours under reflux with anhydrous piperazine (7 g.) and methanol (10 cc.). Water (30 cc.) and chloroform (2 × 20 cc.) are then added and the chloroform layer is agitated with 9% hydrochloric acid (20 cc.). The aqueous acid layer is made alkaline with sodium hydroxide ($d = 1.33$, 10 cc.) and the base is extracted with chloroform (2 × 20 cc.).

After concentration, the base (6.7 g.) is isolated and is treated with maleic acid (6 g.) and ethyl acetate (150 cc.) to give 10-(3-1¹-piperazinylpropyl)phenthiazine dimaleate (7.7 g.), m.p. 185° C.

EXAMPLE LIV

Phenthiazine (8 g.) is heated for one hour under reflux with sodamide (1.8 g.) and xylene (100 cc.) and a solution of 1-(3-chloropropyl)-4-methylpiperazine (8.5 g.) in xylene (20 cc.) is then added dropwise over 2 hours. The mixture is heated under reflux for 5 hours and is then treated with water (100 cc.) and with ether (100 cc.). The ether-xylene layer is agitated with 7% hydrochloric acid (60 cc. followed by 2 × 20 cc.), the aqueous acid layer is made alkaline with sodium hydroxide ($d =$ 1.33, 40 cc.) and the base is extracted with ether (3 × 50 cc.).

After concentration, the base (13 g.) is isolated and is treated with maleic acid (9 g.) and ethyl acetate (230 cc.). The crude maleate is recrystallised from boiling water (750 cc.) and 10 - (3 - 4¹-methyl-1¹-piperazinylpropyl) phenthiazine dimaleate (15 g.) is obtained, m.p. 210° C.

EXAMPLE LV

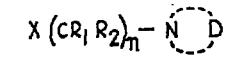
2 - Bromo - 2¹ - (3-4¹-methyl-1¹-piperazinyl-propylamino)-4¹-chlorodiphenyl sulphide (10.5 g.) is dissolved in dimethylformamide (80 cc.). Potassium carbonate (5 g.) and copper powder (0.4 g.) are added to this solution and the mixture is heated under reflux for 48 hours. After cooling, insoluble matter is filtered off and washed with dimethylformamide (20 cc.). The filtrates are treated with distilled water (200 cc.) and the base formed is extracted with ether (3 × 50 cc.) and dried over sodium sulphate. The ether is removed on the water-bath and the residue is distilled to give 3-chloro-10-(3 - 4¹ - methyl - 1¹ - piperazinylpropyl)phenthiazine, (5.05 g.), b.p. 224—234° C./0.5 mm.Hg. The maleate is prepared by the action of maleic acid upon the base dissolved in ethyl acetate and melts at about 220° C. The dimethiodide melts at 266° C. and the 8-chlorotheophyllinate at 175° C.

The 2-bromo-2¹-(3-4¹-methyl-1¹-piperazinyl-propylamino)-4¹-chlorodiphenyl sulphide (b.p. 234—245° C./0.5 mm.Hg., m.p. 75—77° C.) which is used as starting material is obtained by the action of 1-(3-chloropropyl)-4-methylpiperazine upon 2-bromo-2¹-amino-4¹-chlorodiphenyl sulphide in xylene solution in the presence of sodamide.

It should be noted that in the foregoing specification and in the appended claims the system of numbering of substituents in the phenthiazine ring is that of Beilstein.

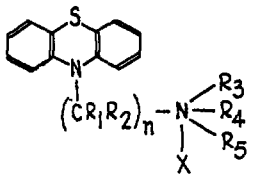
In our Specification No. 632,277 we have claimed a process for the production of phen-

thiazine derivatives, which comprises reacting a compound of the general formula:

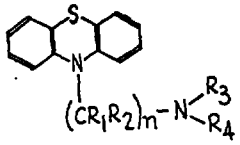


where X is halogen, R_1 and R_2 are the same or different in their various occurrences and are hydrogen atoms or alkyl groups, n is a small positive integer greater than 1 and D is the residue of a heterocyclic nucleus of which the N atom is one hetero atom and in which there may be another hetero atom, with phenthiazine itself or phenthiazine which is benzene-ring-substituted by alkyl or alkoxy groups, the said reaction being effected in the presence of an acceptor for hydrogen halide. We have further claimed the products when obtained by the said process.

Further in Specification No. 641,452 we have claimed a process for the production of compounds of the general formula:

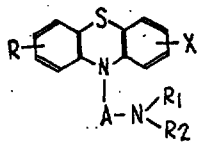


which comprises reacting a compound of the general formula R_5X, where R_5 is an alkyl or aralkyl group and X is an acid residue, with a compound of the general formula:



wherein R_1 and R_2 are the same or different and are hydrogen atoms or methyl groups, n is 2 or 3, the CR_1R_2 groups may be the same or different and the total number of carbon atoms in the $(CR_1R_2)_n$ grouping does not exceed three, R_3 and R_4 are the same and are methyl or ethyl groups or together represent a divalent saturated unsubstituted alkylene chain which may include a hetero atom, or with a corresponding compound in which the phenthiazine nucleus contains a methoxy substituent in the 3-position. We have further claimed the products when obtained by the said process.

Again, in Specification No. 716,206 we have claimed phenthiazine compounds of the general formula:



wherein:

R is in the 6- or 8-position and represents a hydrogen, chlorine or bromine atom or a methyl or methoxy group,

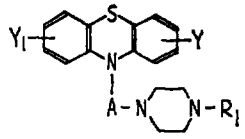
X is in the 1- or 3-position and represents either a chlorine or a bromine atom,

A represents a divalent, straight, or branched aliphatic chain containing from 2 to 5 carbon atoms, and

R_1 and R_2 represent either individual methyl or ethyl groups or divalent groups which together with the adjacent nitrogen atom form a mono-nuclear heterocyclic ring, with the exclusion of those compounds in which simultaneously R represents a hydrogen atom, X represents a chlorine atom, A represents *n*-propylene and R_1 and R_2 each represent methyl and of those compounds in which simultaneously R represents a hydrogen atom and R_1 and R_2 together represent the residue of a pyrrolidyl or piperidyl ring. We have further claimed processes for the production of such compounds.

What we claim is:—

1. Phenthiazine compounds containing the structure:



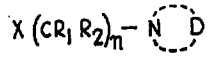
including not only the bases conforming to this formula but also the corresponding acid addition and quaternary ammonium salts and addition compounds, wherein A represents a divalent saturated aliphatic hydrocarbon radical with a straight or branched chain containing from 2 to 6 carbon atoms, R_1 represents a hydrogen atom or a lower alkyl or an aryl or araliphatic group, Y and Y_1 are respectively a hydrogen or halogen atom or a lower alkyl, alkoxy or aryl or aryloxy group, the phenthiazine ring may carry one or more substituents additional to Y and Y_1 and one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group.

2. Phenthiazine compounds as claimed in claim 1 where Y is a substituent in the 1- or 3-position.

3. Phenthiazine compounds as claimed in claim 1 in which Y represents a chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents a hydrogen atom and the piperazine ring is either unsubstituted or one of the ring carbon atoms carries a substituent in the form of a methyl group.

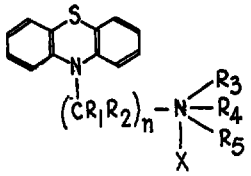
4. Phenthiazine compounds as claimed in claim 1 in which Y represents a chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents a methyl group and the piperazine ring is either unsubstituted or one of the ring carbon

thiazine derivatives, which comprises reacting a compound of the general formula:

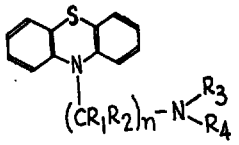


where X is halogen, R_1 and R_2 are the same or different in their various occurrences and are hydrogen atoms or alkyl groups, n is a small positive integer greater than 1 and D is the residue of a heterocyclic nucleus of which the N atom is one hetero atom and in which there may be another hetero atom, with phenthiazine itself or phenthiazine which is benzene-ring-substituted by alkyl or alkoxy groups, the said reaction being effected in the presence of an acceptor for hydrogen halide. We have further claimed the products when obtained by the said process.

Further in Specification No. 641,452 we have claimed a process for the production of compounds of the general formula:

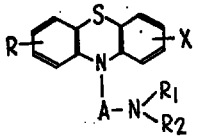


which comprises reacting a compound of the general formula R_5X, where R_5 is an alkyl or aralkyl group and X is an acid residue, with a compound of the general formula:



wherein R_1 and R_2 are the same or different and are hydrogen atoms or methyl groups, n is 2 or 3, the CR_1R_2 groups may be the same or different and the total number of carbon atoms in the $(CR_1R_2)_n$ grouping does not exceed three, R_3 and R_4 are the same and are methyl or ethyl groups or together represent a divalent saturated unsubstituted alkylene chain which may include a hetero atom, or with a corresponding compound in which the phenthiazine nucleus contains a methoxy substituent in the 3-position. We have further claimed the products when obtained by the said process.

Again, in Specification No. 716,206 we have claimed phenthiazine compounds of the general formula:



wherein:

R is in the 6- or 8-position and represents a hydrogen, chlorine or bromine atom or a methyl or methoxy group,

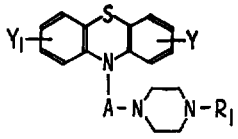
X is in the 1- or 3-position and represents either a chlorine or a bromine atom,

A represents a divalent, straight, or branched aliphatic chain containing from 2 to 5 carbon atoms, and

R_1 and R_2 represent either individual methyl or ethyl groups or divalent groups which together with the adjacent nitrogen atom form a mono-nuclear heterocyclic ring, with the exclusion of those compounds in which simultaneously R represents a hydrogen atom, X represents a chlorine atom, A represents *n*-propylene and R_1 and R_2 each represent methyl and of those compounds in which simultaneously R represents a hydrogen atom and R_1 and R_2 together represent the residue of a pyrrolidyl or piperidyl ring. We have further claimed processes for the production of such compounds.

What we claim is:—

1. Phenthiazine compounds containing the structure:



including not only the bases conforming to this formula but also the corresponding acid addition and quaternary ammonium salts and addition compounds, wherein A represents a divalent saturated aliphatic hydrocarbon radical with a straight or branched chain containing from 2 to 6 carbon atoms, R_1 represents a hydrogen atom or a lower alkyl or an aryl or araliphatic group, Y and Y_1 are respectively a hydrogen or halogen atom or a lower alkyl, alkoxy or aryl or aryloxy group, the phenthiazine ring may carry one or more substituents additional to Y and Y_1 and one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group.

2. Phenthiazine compounds as claimed in claim 1 where Y is a substituent in the 1- or 3-position.

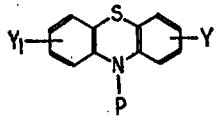
3. Phenthiazine compounds as claimed in claim 1 in which Y represents a chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents a hydrogen atom and the piperazine ring is either unsubstituted or one of the ring carbon atoms carries a substituent in the form of a methyl group.

4. Phenthiazine compounds as claimed in claim 1 in which Y represents a chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents a methyl group and the piperazine ring is either unsubstituted or one of the ring carbon

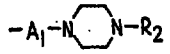
atoms carries a substituent in the form of a methyl group.

5. Phenthiazine compounds as claimed in claim 1 in which Y represents a chlorine atom in the 3-position, Y_1 represents a hydrogen atom, A represents $-(CH_2)_3-$, R_1 represents an ethyl group and the piperazine ring is either unsubstituted or one of the ring carbon atoms carries a substituent in the form of a methyl group.

6. A process for the production of phenthiazine compounds as claimed in any one of the preceding claims comprising the interaction of a phenthiazine compound having a structure represented by the formula:

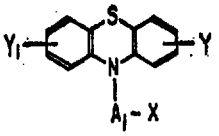


with a compound Q, the group P and the compound Q being such that Q will react with the compound of the said formula to introduce or form at the 10-position of the ring a substituent grouping of the structure:

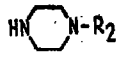


A_1 representing a divalent saturated aliphatic straight or branched chain hydrocarbon radical containing 2 to 6 carbon atoms or a divalent grouping which is convertible thereto by reduction, Y and Y_1 each representing a hydrogen or halogen atom or a lower alkyl, alkoxy, aryl or aryloxy group, and R_2 representing a hydrogen atom or a lower alkyl, aryl or araliphatic group or a group convertible (as hereinbefore defined) thereinto and, where either or both of the said starting materials contain one or more "convertible" groups as hereinbefore defined, transformation of the convertible group or groups into the desired final atom and/or group, as hereinbefore defined.

7. A process as claimed in claim 6 which comprises the interaction of a phenthiazine of the general formula:

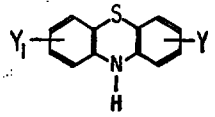


with a piperazine derivative of the general formula:

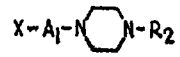


X representing the acid residue of a reactive ester.

8. A process as claimed in claim 6 which comprises the interaction of a phenthiazine of the general formula:

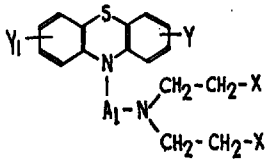


with a piperazine derivative of the general formula:



X representing the acid residue of a reactive ester.

9. A process as claimed in claim 6 which comprises the production of compounds in which the piperazine ring contains no substituent on a carbon atom, by interaction of a compound of the general formula:

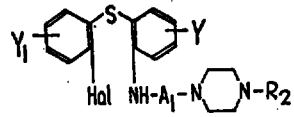


X representing the acid residue of a reactive ester, with an amine of the formula R_2NH_2.

10. A process as claimed in any one of claims 6 to 9 wherein the reaction is effected in the presence of an alkaline condensing agent.

11. A process as claimed in claim 10 wherein said agent is an alkali metal or derivative thereof such as hydroxide, hydride, amide or alcoholate.

12. A process for the production of phenthiazine compounds as claimed in any one of claims 1 to 5 which comprises the cyclisation of a diphenylsulphide of the general formula:



wherein Hal represents a halogen atom and the remaining symbols are as hereinbefore defined, followed when A_1 is other than A and/or R_2 is other than R_1 by conversion of A_1 into A and/or conversion of R_2 into R_1.

13. A process as claimed in claim 12 wherein the cyclisation is carried out in a solvent of the class of N-substituted amides of fatty acids containing not more than 3 carbon atoms in the presence of an alkaline condensing agent.

14. A process as claimed in claim 13 wherein the condensing agent is an alkali metal hydroxide or carbonate.

* C L M S *

15. A process as claimed in claim 12, 13 or 14 wherein the reaction is effected in the presence of a dehydrohalogenation catalyst such as copper powder.

16. Process for the production of phenthiazine compounds as claimed in claims 1 to 5 when carried out substantially in the manner described in any one of the foregoing Examples.

For the Applicants,
J. A. KEMP & CO.,
Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1.

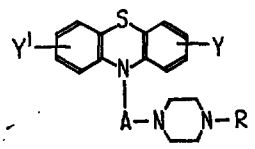
PROVISIONAL SPECIFICATION
No. 12225 A.D. 1954

Phenthiazine Derivatives and processes for their preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French Body Corporate, of 21 rue Jean-Goujon, Paris, France, do hereby declare this invention to be described in the following statement:—

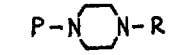
This invention relates to new phenthiazine derivatives and to processes for their production.

The new phenthiazine derivatives of the present invention are 10-(piperazinyl-alkyl) phenthiazines which conform to the formula:

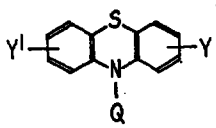


and their salts, including their quaternary ammonium salts. In this formula, A is a divalent saturated aliphatic hydrocarbon radical with a straight or branched chain containing from 2 to 6 carbon atoms, R represents a hydrogen atom or a lower alkyl or an aryl or aralkyl group and Y and Y^1 are respectively a hydrogen or halogen atom or a lower alkyl, alkoxy or aryl or aryloxy group, preferably (in the case of Y) in the 1- or 3-position. The piperazine nucleus may also be substituted by lower alkyl groups. It should be understood that the term "lower alkyl" when used in this specification means an alkyl group containing not more than 6 and preferably not more than 4 carbon atoms.

According to a feature of this invention, the aforesaid new phenthiazine derivatives are prepared by causing two compounds of the general formulæ:

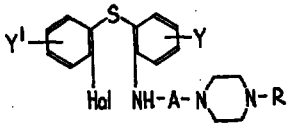


and



where Y, Y^1 and R are as hereinbefore defined and P and Q are atoms or atom groups which are jointly capable of providing the linkage —A—, to react with one another and isolating from the reaction mixture the compound of formula I or a salt thereof. By way of example, P may represent a group —A—Z (Z representing a residue of a reactive ester such as a halogen atom or a residue of a sulphuric or sulphonic ester) in which case Q represents a hydrogen atom. Conversely, P may represent a hydrogen atom and Q a chain —A—Z, Z being as hereinbefore defined. These reactions are carried out by heating the reactants with or without a solvent and, if desired, in the presence of an alkaline condensing agent, e.g. an alkali metal or derivative thereof such as the hydroxides, hydrides, amides or alcoholates, and more particularly sodium hydroxide or sodamide.

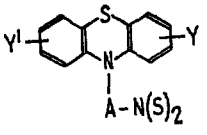
According to a further feature of this invention, a useful modification of the aforesaid process consists in cyclising a substance of the general formula:



wherein Y, Y^1, A and R are as indicated above and Hal represents a halogen atom.

This cyclisation is preferably carried out in a solvent of the class of substituted lower aliphatic acid amides in the presence of an alkaline condensing agent such as an alkali metal hydroxide or carbonate and, if desired, also in the presence of a dehydrohalogenation catalyst such as copper powder.

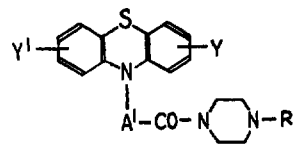
Alternatively, the piperazine nucleus may be synthesised by the action of an amine of the formula $R—N(T)_2$ upon the derivative:



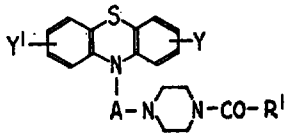
$R—N(T)_2$ and $N(S)_2$ representing atoms or groups of atoms capable of reacting to form a piperazine nucleus. Thus, for example, $—N(T)_2$ may be the group $—N(CH_2CH_2Cl)_2$ and in this case $—N(S)_2$ represents NH_2; conversely $—N(S)_2$ may be the group $—N(CH_2CH_2Cl)_2$ and $—N(T)_2$ then repre-

sents an NH_2 group.

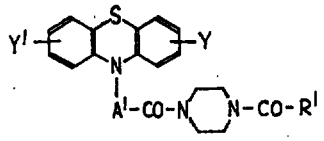
Another method comprises reducing by known methods (e.g. the use of lithium aluminium hydride) an amide of the formula:



or



or



A^1 and R^1 representing divalent hydrocarbon chains containing one carbon atom less than the chains A and R.

It will, of course, be appreciated that those of the new compounds in which R represents an alkyl or aralkyl group may also be prepared by alkylation or aralkylation of a corresponding derivative in which R represents a hydrogen atom, using methods known *per se*.

The new compounds of the present invention possess interesting pharmacodynamic properties; in particular, they have been found to be very active anti-epileptics. In consequence they have application in human or veterinary medicine.

The following non-limitative Examples show how the invention may be put into practice. The melting points indicated have been determined on the Kofler block.

EXAMPLE I

10-(2^1-Chloroethyl)phenthiazine (10.5 g.) is heated for 4 to 5 hours at 180° C. with N-ethylpiperazine (22.8 g.). After cooling, water (25 c.c.) is added and the mixture is extracted with ether (2 × 25 c.c.). The ethereal solution is shaken with a normal solution of hydrochloric acid (60 c.c.), the acidic layer is decanted and treated with concentrated sodium hydroxide solution (15 c.c.). The base is extracted with ether (2 × 20 c.c.) and the extract dried over sodium sulphate. Concentration *in vacuo* yields 10-(2^1-N-ethylpiperazinyl-ethyl)phenthiazine (11.4 g.), m.p. (inst.) 72° C. The picrate of this base melts at 260° C. (inst.).

EXAMPLE II

Proceeding as in Example I but commencing with 10-(3^1-chloropropyl)phenthiazine (11 g.) and N-ethylpiperazine (22.8 g.), 10-(3^1-N-ethylpiperazinyl - propyl)phenthiazine is obtained, m.p. (inst.) 52° C. The picrate of this base melts at 258° C. (inst.).

EXAMPLE III

Proceeding as in Example I but commencing with 10-(2^1-chloropropyl)phenthiazine (11 g.) and N-ethylpiperazine (21 g.), 10-(2^1-N-ethylpiperazinyl-propyl)phenthiazine (7.5 g.) is obtained, m.p. (inst.) 68° C. The picrate of this base melts at 250° C. (inst.).

EXAMPLE IV

Proceeding as in Example I but commencing with 3-chloro-10-(3^1-chloropropyl)phenthiazine (11.7 g.) and N-ethylpiperazine (20 g.), 3-chloro - 10 - (3^1 - N - ethylpiperazinyl-propyl) phenthiazine (10.6 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 256/265° C. (inst.).

EXAMPLE V

Proceeding as in Example I but commencing with 3-chloro-10-(2^1-chloropropyl)phenthiazine (12.4 g.) and N-ethylpiperazine (22.8 g.), 3-chloro - 10 - (2^1 - N - ethylpiperazinyl-propyl) phenthiazine (8.3 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 254° C. (inst.).

EXAMPLE VI

Proceeding as in Example I but commencing with 10-(2^1-chloroethyl)phenthiazine (5.25 g.) and N-methylpiperazine (10 g.), 10-(2^1-N-methylpiperazinyl-ethyl)phenthiazine (5.6 g.) is obtained in the form of a viscous resin. The picrate of this base melts at 256/265° C. (inst.).

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PROVISIONAL SPECIFICATION
No. 19366 A.D. 1954

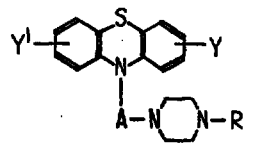
Phenthiazine Derivatives and processes for their preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French Body Corporate, of 21 rue Jean-Goujon, Paris, France, do hereby declare this invention to be described in the following statement:—

This invention relates to new chemical compounds and to process for their production.

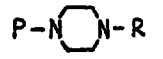
In the specification of our co-pending Application No. 12225/54 we have disclosed new and useful chemical compounds in the form of

the 10-(piperazinyl-alkyl)-substituted phenthiazines and analogues thereof which conform to the formula:

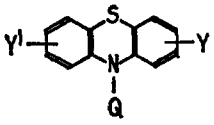


and their salts, including their quaternary ammonium salts and their addition compounds (for example with 8-chlorotheophylline). In this formula, A is a divalent saturated aliphatic hydrocarbon radical with a straight or branched chain containing from 2 to 6 carbon atoms, R represents a hydrogen atom or a lower alkyl or an aryl or aralkyl group and Y and Y^1 are respectively a hydrogen or halogen atom or a lower alkyl, alkoxy or aryl or aryloxy group, preferably (in the case of Y) in the 1- or 3- position. The piperazine nucleus may also be substituted by lower alkyl groups. It should be understood that the term "lower alkyl" when used in this Specification means an alkyl group containing not more than 6 and preferably not more than 4 carbon atoms.

According to a feature of the aforesaid invention, the said new compounds are prepared by causing two compounds of the general formulae:



and



where Y, Y^1 and R are as hereinbefore defined and P and Q are atoms or atom groups which are jointly capable of providing the linkage —A—, to react with one another and isolating from the reaction mixture the compound of formula I or a salt thereof, (the process is hereinafter referred to as "method I"). By way of example, P may represent a group —A—Z (Z representing a residue of a reactive ester such as a halogen atom or a residue of a sulphuric or sulphonic ester) in which case Q represents a hydrogen atom. Conversely, P may represent a hydrogen atom and Q a chain —A—Z, Z being as hereinbefore defined. These reactions are carried out by heating the reactants with or without a solvent and, if desired, in the presence of an alkaline condensing agent, e.g. an alkali metal or derivative thereof such as the hydroxides, hydrides, amides or alcoholates, and more particularly sodium hydroxide or sodamide.

According to a further feature of the said invention, those of the new compounds in which R represents an alkyl or aralkyl group may also be prepared by alkylation or aralkylation of a corresponding derivative in which R represents a hydrogen atom, using methods known *per se*.

Some results of their further experimental work are recorded in the following Examples; two of the specific compounds described in these Examples namely 3-chloro-10-(3^1-N-methylpiperazinyl-propyl)phenthiazine and 3-chloro-10-(3^1-N-ethylpiperazinyl-propyl)-phenthiazine have been shown to possess outstanding utility as anti-emetics.

EXAMPLE I.

10-(2^1-N-ethylpiperazinyl-ethyl)phenthiazine (2 g.) is heated for two hours under reflux with methyl iodide (10 c.c.). The excess methyl iodide is distilled off and the residual resin is dissolved in water (10 c.c.). The solution is treated with charcoal, filtered and evaporated *in vacuo* at 20° C. The residue is recrystallised from 90% ethanol (50 c.c.) to give 10-(2^1-N-ethylpiperazinyl-ethyl)phenthiazine dimethiodide (2.8 g.), which melts at 240° C. (inst.).

EXAMPLE II.

The base of Example IV of the said prior Specification when treated with ethanol and ethereal hydrogen chloride gives the dihydrochloride which is recrystallised from absolute ethanol (1 g. per 25 c.c.). The dihydrochloride melts at 220° C. (inst.).

EXAMPLE III.

Commencing with 10-(2^1-chloroethyl)phenthiazine (5.25 g.) and N-benzylpiperazine (15.5 g.) there is obtained 10-(2^1-N-benzylpiperazinylethyl)phenthiazine (8 g.), which is then treated with ethanol and ethereal hydrogen chloride to give the dihydrochloride which, on recrystallisation from water (1 g. per 7 c.c.), melts at 230° C. (inst.).

EXAMPLE IV.

Commencing with 10-(2^1-chloroethyl)phenthiazine (5.25 g.) and N-phenylpiperazine (16.2 g.) a monohydrochloride (6.5 g.) is obtained which is then recrystallised from a mixture of dimethylformamide and water (1 g. per 20 ccs. of dimethylformamide and 10 c.c. of water). The 10-(2^1-N-phenylpiperazinyl-ethyl)phenthiazine monohydrochloride thus obtained melts at 245° C. (inst.).

EXAMPLE V.

10-(2^1-Chloroethyl)phenthiazine (78.5 g.), anhydrous piperazine (76 g.) and methanol (75 c.c.) are heated for four hours under reflux. The mixture is then treated with distilled water (100 c.c.) and chloroform (2 × 100 c.c.). The decanted chloroform is washed with water (2 × 50 c.c.) and is shaken with 2N hydrochloric acid (150 c.c.). A precipitate (10.5 g.) is formed which is filtered off and recrystallised from butanol (1 g. per 60 c.c.) to give 1:4-di(10^1-phenylthiazinylethyl)piperazine dihydrochloride, which melts at 220° C. (inst.).

The aqueous hydrochloric acid solution is treated with aqueous sodium hydroxide (*d* 1.33; 100 c.c.) and chloroform (4 × 50 c.c.).

The chloroform is then dried and concentrated *in vacuo* to give 10-(2¹-N-piperazinylethyl)-phenthiazine (74 g.). This base when treated with alcohol and ethereal hydrogen chloride gives the dihydrochloride which, when recrystallised from 90% ethanol (1 g. per 25 c.c.), melts at 260° C. (inst.).

EXAMPLE VI.

Phenthiazine (10 g.) is converted to the sodium derivative by treatment with sodamide (2.25 g.) in xylene (75 c.c.) and the product is condensed with a solution in xylene of 1 - (2¹ - chloroethyl) - 4 - carbobenzyloxy-piperazine obtained from the corresponding hydrochloride (16 g.).

By treatment of the solution with water (100 c.c.), extraction with 2N hydrochloric acid (2 × 50 c.c.), treatment with aqueous sodium hydroxide, extraction with chloroform and preparation of the hydrochloride, there is obtained directly the same dihydrochloride of 10-(2¹-N-piperazinylethyl)phenthiazine as described in Example V.

1 - (*p* - Chloroethyl) - 4 - carbobenzyloxy-piperazine hydrochloride, m.p. 130—132° C. (inst.), is obtained by the action of thionyl chloride upon 1-(2¹-hydroxyethyl)-4-carbobenzyloxypiperazine hydrochloride in benzene. 1 - (2¹ - Hydroxyethyl) - 4 - carbobenzyloxy-piperazine, b.p. 286—288° C./1 mm. Hg., is obtained by condensing ethylene oxide with 1-carbobenzyloxypiperazine in methanol.

EXAMPLE VII.

10-(2¹-N-piperazinylethyl)phenthiazine (6.2 g.), *n*-butyl *p*-toluenesulphonate (6.9 g.), anhydrous sodium carbonate (1.6 g.) and ethanol (10 c.c.) are heated for five hours under reflux. The mixture is treated with N sodium hydroxide (30 c.c.) and ether (2 × 50 c.c.), and the ethereal solution is extracted with N hydrochloric acid (2 × 20 c.c.). The acid layer is then treated with aqueous sodium hydroxide (*d* 1.33; 10 c.c.) and is extracted with ether (2 × 50 c.c.). After concentration, the base is treated with alcohol and ethereal hydrogen chloride to give 10-(2¹-N-butyl-piperazinyl-ethyl)phenthiazine dihydrochloride (4.5 g.), which melts at 226° C. (inst.).

EXAMPLE VIII.

Proceeding as in Example I of the aforesaid prior specification but commencing with 10-(2¹-chloroethyl)phenthiazine (5.25 g.) and 1:2:3:5:6-pentamethylpiperazine (15.6 g.), there is obtained 10-[2¹-(1¹¹:2¹¹:3¹¹:5¹¹:6¹¹-pentamethylpiperazin - 4¹¹ - yl) - ethyl]-phenthiazine (5.2 g.) as a viscous resin.

The picrate of this base melts at 228° C. (inst.).

EXAMPLE IX.

3-Chlorophenthiazine (9.3 g.) is converted to the sodium derivative with sodamide (2 g.) in xylene (75 c.c.). The product is condensed with 1-(2¹-chloroethyl)-4-methylpiperazine (8 g.) in solution (45 c.c.) in xylene by boiling for five hours. 3-Chloro-10-(2¹-N-methyl-piperazinyl-ethyl)phenthiazine dihydrochloride (14.5 g.) is then obtained by the usual treatment, and may be recrystallised from absolute ethanol (1 g. per 10 c.c.). The dihydrochloride melts at 253—255° C. (inst.).

1-(2¹-Chloroethyl)-4-methylpiperazine dihydrochloride, m.p. 265° C. (inst.), is obtained by the action of thionyl chloride upon 1-(2¹-hydroxyethyl)-4-methylpiperazine in chloroform.

EXAMPLE X.

Proceeding as in Example IX but commencing with 3-chlorophenthiazine and 1-(2¹-chloroethyl) - 4 - ethylpiperazine, there is obtained 3-chloro-10-(2¹-N-ethylpiperazinyl-ethyl)phenthiazine dihydrochloride, which melts at 228—230° C. (inst.).

EXAMPLE XI.

3 - Chloro - 10 - (2¹ - N - ethylpiperazinyl-ethyl)phenthiazine (1.7 g.) and methyl iodide (10 c.c.) are heated for four hours under reflux. The excess methyl iodide is distilled off and the resin so obtained is dissolved in water (20 c.c.). The solution is treated with charcoal, filtered and concentrated *in vacuo* at 20° C., and the product is recrystallised from 80% ethanol (12 c.c.) to give 3-chloro-10-(2¹-N-ethylpiperazinyl-ethyl)phenthiazine dimethiodide. which melts at 262° C. (inst.).

EXAMPLE XII.

Proceeding as in Example IX but commencing with 1-chlorophenthiazine and 1-(2¹-chloroethyl) - 4 - ethylpiperazine, there is obtained 1 - chloro - 10 - (2¹ - N - ethyl-piperazinyl-ethyl)phenthiazine dihydrochloride, which melts at 238—240° C. (inst.).

EXAMPLE XIII.

Proceeding as in Example I of the aforesaid prior specification but commencing with 3-chloro-10-(3¹-chloropropyl)phenthiazine (19 g.) and N-methylpiperazine (15 g.), there is obtained 3-chloro-10-(3¹-N-methylpiperazinyl-propyl)phenthiazine (15.8 g.), the dihydrochloride of which melts at 195° C. (inst.). The picrate of the base melts at 250° C. (inst.).

EXAMPLE XIV.

3 - Chloro - 10 - (3¹ - N - methylpiperazinyl-propyl)phenthiazine (1.6 g.), 8-chlorotheophylline (0.8 g.) and methanol (2.5 c.c.) are heated for one hour under reflux. Methanol (5 c.c.) and water (1 c.c.) are then added and the mixture is boiled for half an hour and then filtered hot to remove insoluble matter.

The alcoholic solution crystallises on cooling and the crystals are filtered off, washed with ethanol and dried *in vacuo* to give 3-chloro-10 - (3¹ - N - methylpiperazinyl - propyl)-phenthiazine 8-chlorotheophyllinate which melts at 175° C. (inst.).

EXAMPLE XV.

3 - Chloro - 10 - (3¹ - N - ethylpiperazinyl-propyl)phenthiazine (1.2 g.) is heated with ethyl iodide (10 c.c.) for two hours under

reflux. The mixture is concentrated on the water-bath and the resin obtained is dissolved in water (10 c.c.). On cooling, a crystalline product (1.5 g.) is obtained, which is then recrystallised from 80% ethanol (25 c.c.) to give 3 - chloro - 10 - (3¹ - ethylpiperazinyl-propyl)phenthiazine diethiodide (0.8 g.), m.p. 260° C. (inst.).

EXAMPLE XVI.

Proceeding as in Example I of the aforesaid prior specification but commencing with 10-(3¹-chloropropyl)phenthiazine (5.5 g.) and 1-ethyl-2 : 3 : 5 : 6-tetramethylpiperazine (5.1 g.), there is obtained 10-[3¹-(1¹¹-ethyl-2¹¹ : 3¹¹ : 5¹¹ : 6¹¹ - piperazin - 4¹¹ - yl) - propyl]-phenthiazine (3 g.) as a viscous resin. The picrate of this base melts at 158° C. (inst.).

EXAMPLE XVII.

3-Chlorophenthiazine (7 g.) is converted to the sodium derivative with sodamide (1.4 g.) in xylene (50 c.c.). 1-(2¹-Chloroethyl)-4-butylpiperazine (7 g.) in xylene (30 c.c.) is then added over 10 minutes and the mixture is heated for 2 hours under reflux. The usual treatment yields 3 - chloro - 10 - (2¹ - N-butylpiperazinyl-ethyl)phenthiazine dihydrochloride (11.9 g.), m.p. 208° C. (inst.).

1 - (2¹ - Chloroethyl) - 4 - butylpiperazine dihydrochloride, m.p. 245° C. (inst.), is obtained by the action of thionyl chloride upon the hydroxy compound in chloroform.

1 - (2¹ - Hydroxyethyl) - 4 - butylpiperazine, b.p. 98—100° C./1 mm. Hg., is obtained by heating N-(2¹-hydroxyethyl)-piperazine with *n*-butyl *p*-toluenesulphonate for 2 hours on a water-bath, treating the mixture with aqueous sodium hydroxide and chloroform and then distilling.

EXAMPLE XVIII.

3-Methylphenthiazine (21.3 g.) is converted to the sodium derivative with sodamide (4.5 g.) in boiling xylene (180 c.c.) and the product is condensed with 1-(3¹-chloropropyl)-4-ethylpiperazine (22.9 g.) by heating under reflux for 3 hours. The mixture is treated with water, the xylene layer is extracted with 2N hydrochloric acid and the aqueous layer is made alkaline and extracted with ether. The ethereal extract is dried, the ether is evaporated and the residue is distilled to yield 3 - methyl - 10 - (3¹ - N - ethylpiperazinyl-propyl)phenthiazine (30 g.), b.p. 233—235° C./0.2 mm. Hg., the dihydrochloride of which melts at 242—244° C.

1-(3¹-Chloropropyl)-4-ethylpiperazine, b.p. 83—84° C./1 mm. Hg., may be prepared by the action of 1-chloro-3-bromopropane on N-ethylpiperazine.

EXAMPLE XIX.

Sodamide (8.2 g.) is added to a solution of 3-chlorophenthiazine (44 g.) in toluene (250 c.c.) maintained at about 120° C. and 1-(3¹-chloropropyl) - 4 - methylpiperazine (37 g.) is then added gradually over 40 minutes. After being heated for a further 40 minutes under reflux, the mixture is cooled, treated with water (200 c.c.) and acidified with hydrochloric acid (*d* 1.19; 40 c.c.). The organic layer is separated and the aqueous layer is washed with ether (200 c.c.), made alkaline with aqueous sodium hydroxide (*d* 1.33; 50 c.c.) and extracted with ether (300 c.c.). The ethereal extract is dried over sodium sulphate, the ether is evaporated and the residue is distilled yielding 3-chloro-10 - (3¹-N-methylpiperazinyl-propyl)phenthiazine (57 g.), b.p. 260—275° C./2 m.m. Hg., the hydrochloride of which melts at 200—210° C.

1-(3¹-Chloropropyl)-4-methyl phenthiazine, b.p. 82—83° C./3 mm. Hg., may be prepared by the action of 1-chloro-3-bromopropane on N-methylpiperazine.

The following Examples illustrate specific methods of manufacture for compounds of the present invention different from those hereinbefore described. Thus, Example XX illustrates the preparation of compounds of the formula first hereinbefore set out by the reductive fission of the corresponding compounds in which R represents a benzyl group, this reductive fission being effected by catalytic hydrogenation using a palladium catalyst. Examples XXI and XXII illustrate an alternative method of procedure in which a starting material of the aforesaid general formula, but in which R now represents the grouping CO.Z (Z being an alkoxy group or a primary, secondary or tertiary amino group), is subjected to hydrolysis resulting in the fission of group CO.Z and the consequent formation of a compound of the aforesaid general formula in which R now represents a hydrogen atom.

EXAMPLE XX.

10 - (2¹-N-benzylpiperazinyl-ethyl)phenthiazine dihydrochloride (0.4 g.) is hydrogenated in acetic acid (7 c.c.) with palladised charcoal (0.5 g.; 10% palladium) at 20° C. and at atmospheric pressure. The hydrogenation is complete after 2 hours. After filtering and washing with water made alkaline with concentrated aqueous sodium hydroxide, the base so obtained is extracted with ether (4 × 10 c.c.). Treatment of the base with ethereal hydrogen chloride yields 10 - (2¹ - N - piperazinyl-ethyl) phenthiazine dihydrochloride (0.2 g.) which, after recrystallisation from absolute ethanol, melts at 260° C. (inst.).

EXAMPLE XXI.

10 - (2¹-N-ethoxycarbonylpiperazinyl-ethyl) phenthiazine (1 g.) is heated for 24 hours under reflux with alcoholic potassium hydroxide (250 g. per litre; 15 c.c.). The solution is concentrated and treated with water (5 c.c.) and ether (4 × 10 c.c.). The addition of ethereal hydrogen chloride yields 10-(2¹-N-piperazinyl-ethyl)phenthiazine dihydrochloride (0.7 g.) which, after recrystallisation from ethanol, melts at 260° C. (inst.).

10 - (2¹-N-Ethoxycarbonylpiperazinyl-ethyl) phenthiazine may be obtained by heating 10-

(2¹-chloroethyl)phenthiazine (10.5 g.) with N-ethoxycarbonylpiperazine (31.6 g.) for 4 hours at 195° C. and then treating the mixture with water (30 c.c.) and ether (2 × 20 c.c.). The ethereal solution is shaken with 10% hydrochloric acid (35 c.c.), and treatment with sodium hydroxide and ether yields 10-(2¹-N-ethoxycarbonylpiperazinyl - ethyl)phenthiazine (16.5 g.), m.p. 95° C. (inst.).

EXAMPLE XXII.

10-(2¹-N-Diethylcarbamylpiperazinyl-ethyl) phenthiazine hydrochloride (0.3 g.) is heated for 30 hours under reflux with hydrochloric acid (*d* 1.19; 7 c.c.). Water (20 c.c.) is then added, a small quantity of insoluble matter is filtered off and the aqueous solution is treated with sodium hydroxide solution (*d* 1.33; 8 c.c.). Extraction with chloroform (2 × 20 c.c.), drying over sodium sulphate, concentration and treatment with ethereal hydrogen chloride yields 10-(2¹-N-piperazinyl-ethyl)phenthiazine dihydrochloride (0.15 g.) which, after recrystallisation from ethanol, melts at 260° C. (inst.).

10-(2¹-N-Diethylcarbamylpiperazinyl-ethyl) phenthiazine may be obtained by heating 10-(2¹-chloroethyl)phenthiazine (5.2 g.) with N-diethylcarbamylpiperazine (18.5 g.) for 5 hours at 200° C. The usual treatment yields 10-(2¹-N - diethylcarbamylpiperazinyl-ethyl)phenthiazine hydrochloride (6 g.), m.p. 182—184° C. (inst.).

The following derivatives may also be treated in a similar manner:

10 - (2¹ - N - dimethylcarbamylpiperazinyl-ethyl)phenthiazine hydrochloride, m.p. 215° C. (inst.).

10 - (2¹-N-phenylcarbamylpiperazinyl-ethyl) phenthiazine, m.p. 160° C. (inst.).

10 - (2¹-N-carbamylpiperazinyl-ethyl)phenthiazine hydrochloride, m.p. 180° C. (inst.).

The new compounds hereinbefore mentioned are useful not only as anti-epileptics but also as anti-emetics.

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