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PATENT SPECIFICATION

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789,811

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International Classification:—C07d.

COMPLETE SPECIFICATION

New Phenthiazine Derivatives and Processes for their Preparation

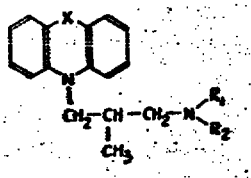
We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

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

It is known that various 10-aminoalkylphenthiazine possess interesting therapeutic properties. Thus Specification No. 608,208 describes phenthiazines substituted in 10-position by a grouping $(CR_1R_2)_n—NR_3R_4$ in which R_1 and R_2 are hydrogen or alkyl, R_3 and R_4 are alkyl and n is an integer greater than 1 and optionally containing also alkyl or alkoxy substituents in the benzene rings of the phenthiazine nucleus; Specification No. 632,277 describes analogous compounds in which the $—NR_3R_4$ grouping is replaced by a heterocyclic nitrogen nucleus; and Specifications Nos. 673,005 and 701,741 describe specific processes for the production of these compounds. Extensive research and experimentation has shown, however, that both the size of the therapeutic index and the nature of the therapeutic effect exhibited by certain compounds of this type can radically be changed (even all therapeutic effect eliminated) by even small changes in chemical structure. Especially is this the case with variations in the nature and length of the side chain attached to the 10-position nitrogen atom and with substitution in the phenthiazine nucleus. More particularly, it is known that certain 10-amino-alkyl-phenthiazines substituted in positions 1- or 3- of the phenthiazine nucleus (Beilstein numbering) by various atoms or groups (and in particular by halogen atoms or alkyl, alkoxy, aryl, aryloxy, aralkyl or aralkoxy groups) are active as potentiators of analgesics, hypnotics or anaesthetics while the corresponding nuclearly-unsubstituted compounds have this activity only to a considerably lesser degree. This fact points to the conclusion that the potentiating properties of the phenthiazine derivatives is associated with the presence of such substituents.

It has now unexpectedly been discovered that certain hitherto unknown nuclearly-unsubstituted phenthiazine derivatives containing a specific form of side chain, together with their salts and their quaternary ammonium derivatives, not only possess potentiating properties to a very high degree but also, in comparison with the known compounds hereinbefore referred to, exhibit a more favourable relationship between therapeutic and secondary effects. These new compounds also possess outstanding properties as antihistaminics and spasmolytics.

The aforesaid new phenthiazine derivatives of the invention, together with new primary amines from which some of them may be prepared, conform to the general formula:—



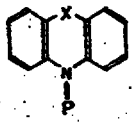
I

[Price 3s. 6d.]

In the above formula, X represents a sulphur atom or an SO or SO_2 group, and R_1 and R_2 are the same or different and either represent hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino. It should be understood that, as shown by formula I, the phenthiazine ring of the compounds of the invention contains no substituent in any of the 1- to 8-positions.

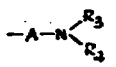
These compounds of general formula I can exist in optically active forms and the invention includes within its scope the racemates as well as the corresponding optically active isomers.

The new compounds of the present invention 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 containing a structure represented by the formula:—



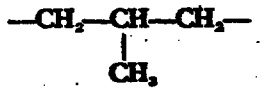
II

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

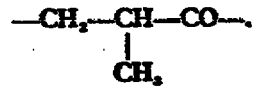


III

In formula II, X is as hereinbefore defined; in formula III, A either represents the branched chain



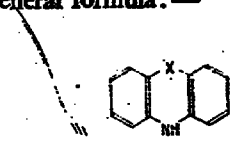
or a group convertible by reduction into said branched chain, such a convertible group being, for example, the group



and R_3 and R_4 represent either the radicals R_1 and R_2 as hereinbefore defined or radicals convertible into the radicals R_1 and R_2 by reduction (for example R^1—CO—, where R^1 is an alkyl group). Where A is other than said branched chain and/or R_3 and R_4 are other than R_1 and R_2 respectively, the process includes the subsequent step or steps of transforming the convertible group or radical using known methods of reduction, such as chemical reduction using lithium aluminium hydride or catalytic hydrogenation. By the expression "known methods" as used in this specification and in the accompanying claims is meant methods heretofore used or described in the chemical literature.

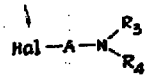
Specific embodiments of the general process defined in the last preceding paragraph are as follows:—

(1) Interaction of a phenthiazine compound of the general formula:—



IV

with a halogenoamine of the formula:—

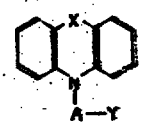


V

where Hal represents a halogen atom and the other variables are as hereinbefore defined.

This reaction is carried out with or without the use of a solvent and, if desired, in the presence of a condensing agent. It is advantageous to operate in an aromatic hydrocarbon solvent (for example, toluene or xylene) in the presence of a condensing agent, preferably in the form of an alkali metal or derivative thereof (such as, for example, hydride, amide, hydroxide, alcoholate or metal alkyl or aryl) and especially metallic sodium, sodamide, powdered sodium or potassium hydroxide, lithium hydride, sodium *tert*-butylate, butyllithium or phenyllithium. The reaction is preferably carried out at the boiling temperature of the solvent. It is advantageous to use the halogenoamine in the form of the free base in solution in, for example, benzene, toluene, or xylene, and to add this solution to the mixture of the other reactants in which the phenthiazine may already be present, at least in part, in the form of an alkali metal salt. The reaction may also be carried out using a salt of the halogenoamine but in this case a greater proportion of the condensing agent must clearly be used in order to neutralise the acid of the salt employed.

(2) Condensation of an amine HNR_3R_4 with a phenthiazine derivative of the type:—



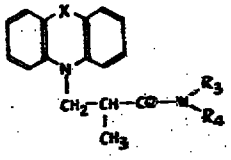
VI

where Y represents a residue of a reactive ester such as a halogen atom or a sulphuric or sulphonic ester group and the other symbols are as hereinbefore defined.

The reaction may be carried out with or without the use of a solvent and, if desired, in the presence of an alkali metal condensing agent. It is particularly advantageous to use a solvent in the form of an alcohol and an excess of the amine. When the amine is a volatile substance, e.g. dimethylamine, it is advantageous to effect the reaction in an autoclave.

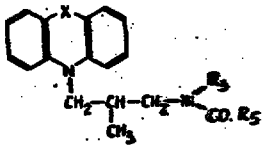
(3) In the case of compounds in which the groups R_1 and R_2 each represent an alkyl group, alkylation by known methods (for example, methylation with formaldehyde and hydrogen in the presence of a hydrogenation catalyst) of the corresponding primary or secondary amines. It is sometimes more advantageous to carry out the alkylation in two stages, by acylation followed by reduction, and these two operations may be carried out simultaneously in certain cases.

(4) Reduction of the corresponding amides:



VII

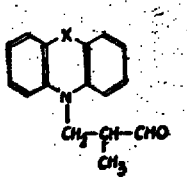
and



VIII

where R_5 is such that the group R_5CH_2— represents the group R_4 and the other symbols are as hereinbefore defined, by known methods, preferably using lithium aluminium hydride in a solvent such as tetrahydrofuran.

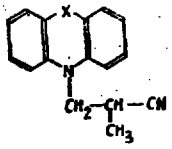
(5) Reduction in the presence of an amine HNR_3R_4 of a derivative of the type:—



IX

(where the symbols are as hereinbefore defined) which may be effected with molecular hydrogen in the presence of a hydrogenation catalyst.

(6) Reduction by standard methods of a nitrile of the general formula:—

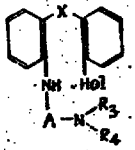


X

The reaction may be carried out in the presence or absence of a primary or secondary amine according to whether a primary, secondary or tertiary amine of the general formula I is required.

Alternative processes for the preparation of the compounds of this invention are:—

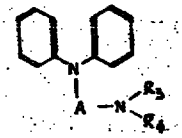
(7) Cyclisation, preferably in a solvent in the form of a substituted amide of a lower aliphatic acid (such as a dialkyl formamide or acetamide) in the presence of an alkali condensing agent (e.g. alkali metal hydroxide or carbonate) and, if desired, in the presence of a dihydrohalogenation catalyst such as copper powder, of a derivative of the type:—



XI

(wherein Hal represents a halogen atom).

(8) In the cases where X represents a sulphur atom, cyclisation with sulphur in the presence of iodine of a diphenylamine of the type:—



XII

(9) In the cases where X represents an SO or SO_2 group, oxidation of the corresponding phenthiazine compounds (X=S) of general formula I. This oxidation may be effected, for example, by means of hydrogen peroxide in the presence of acetic acid or with nitric acid.

When, in the foregoing various methods, one of the groups A, R_3 or R_4 represents a convertible group, the process includes the subsequent operation or operations of reduction to the final atoms or groups required.

The optically active isomers may be obtained by resolution of the racemates or by synthesis from optically active starting materials or intermediates.

The compounds of general formula I wherein R_1 and R_2 represent hydrogen atoms are, as hereinbefore mentioned, useful intermediates for the preparation of other compounds of said formula. The bases of formula I (save when R_1 and R_2 each represent a hydrogen atom) have the therapeutic properties hereinbefore described and, for therapeutic purposes, are preferably employed in the form of acid addition salts containing pharmaceutically acceptable anions (such as hydrochlorides and other hydrohalides and 8-chlorotheophyllinates) or of quaternary ammonium salts obtained by reaction with organic halides (e.g. methyl iodide) or other reactive esters. Of particularly outstanding utility as regards antihistaminic and potentiating properties are 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (in the form of the racemate or of either active isomer, especially the *l*-isomer) and 3-(9-9-dioxy-10-phenthiazinyl) - 2 - methyl - 1 - dimethylaminopropane.

The following non-limitative Examples show how the invention may be put into practice (the melting points are those determined on the Kofler bench).

EXAMPLE I

95% Sodamide (2.27 g.) is added to a solution of phenthiazine (9.6 g.) in xylene (140 cc.) at a temperature of 130°C. and the mixture is heated with reflux for 2 hours.

An 0.61 N solution (90 c.c.) of 1-chloro-2-methyl-3-dimethylaminopropane in xylene is then added over 50 minutes and heating with reflux is continued for 20 hours. After cooling, the mixture is treated with water (40 c.c.) and N methanesulphonic acid (70 c.c.). The aqueous layer is washed with ether, treated with aqueous sodium hydroxide (d=1.33; 10 c.c.) and extracted with ether. The extract is dried over potassium carbonate and evaporated and the residue is distilled *in vacuo*. 3 - (10 - Phenthiazinyl) - 2 - methyl - 1 - dimethylaminopropane (12.6 g.) is collected, distilling between 150° and 175°C. under a pressure of about 0.3 mm.Hg. By dissolving this base in acetone and adding ethereal hydrogen chloride, a hydrochloride is obtained, m.p. 216—217°C.

EXAMPLE II

Proceeding as described in Example I but commencing with phenthiazine (15.7 g.), technical sodamide (4.5 g.) and 1-chloro-2-methyl-3-dimethylaminopropane (15.6 g.), 3-(10 - phenthiazinyl) - 2 - methyl - 1 - diethylaminopropane (23 g.), b.p. 180—182°C./0.5 mm.Hg., is obtained. On the addition of dry hydrogen chloride to a solution of the last-mentioned base in acetone, a hydrochloride crystallises which, after recrystallisation from a mixture of acetone and *iso*propanol, melts at 158°C.

1 - Chloro - 2 - methyl - 3 - diethylaminopropane is obtained as the hydrochloride by the action of thionyl chloride on 3-diethylamino-2-methylpropane-1-ol, b.p. 81°C./12 mm.Hg., in boiling benzene solution. The last mentioned product is prepared by reducing with lithium aluminium hydride methyl 3-diethylamino-2-methylpropionate, itself obtained according to Bieber, *C.R. Acad. Sci. Paris 231*, 291 (1950).

EXAMPLE III

Proceeding as described in Example II but commencing with phenthiazine (15.7 g.), technical sodamide (4.5 g.) and 1-chloro-2-methyl-3-piperidinopropane (16.7 g.), 3-(10-phenthiazinyl) - 2 - methyl - 1 - piperidinopropane (22 g.), b.p. about 215°C./1 mm.Hg., is obtained. On the addition of hydrogen chloride to a solution of the last-mentioned base in acetone, a hydrochloride crystallises, which, after recrystallisation from a mixture of acetone and *iso*propanol, melts at 186°C.

1-Chloro-2-methyl-3-piperidinopropane is obtained as the hydrochloride by the action of thionyl chloride in boiling benzene upon 3-piperidino-2-methyl-propan-1-ol, b.p. 104° C./12 mm.Hg., itself prepared by reducing with lithium aluminium hydride methyl 3-piperidino-2-methyl-propionate, b.p. 97—98° C./13 mm.Hg. The last-mentioned product may be obtained by condensing piperidine with methyl methacrylate.

EXAMPLE IV

Proceeding as described in Example II but commencing with phenthiazine (11.5 g.), technical sodamide (3.3 g.) and 1-chloro-2-methyl-3-1^1-pyrrolidinylpropane, 3-(10-phenthiazinyl) - 2 - methyl - 1 - 1^1 - pyrrolidinylpropane (18 g.) is obtained. On the addition of oxalic acid to a solution of the last-mentioned base in *iso*propanol, an acid oxalate crystallises which, after recrystallisation from 50% ethanol, melts at 188°C.

1 - Chloro - 2 - methyl - 3 - 1^1 - pyrrolidinylpropane is obtained as the hydrochloride by the action of thionyl chloride in boiling benzene solution upon 3-1^1-pyrrolidinyl-2-methylpropan-1-ol, b.p. 91°C./15 mm.Hg. The last-mentioned product is obtained by reducing with lithium aluminium hydride methyl 3-1^1-pyrrolidinyl-2-methylpropionate, b.p. 92—93° C./15 mm.Hg., itself obtained by the condensation of pyrrolidine with methyl methacrylate.

EXAMPLE V

Racemic 3 - (10 - phenthiazinyl)-2-methyl-1-aminopropane (5 g.), m.p. 100—104°C., is agitated in acetic acid (150 c.c.) under an atmosphere of hydrogen in the presence of a 30% aqueous solution (10 g.) of formaldehyde and 5% palladised charcoal (1 g.). The theoretical volume of hydrogen is absorbed in 2 hours. The catalyst is filtered off, the filtrate is evaporated to dryness under reduced pressure and the oily residue is treated with aqueous sodium hydroxide and ether. The aqueous layer is separated out and, on evaporation of the ethereal solution, there is obtained the 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (5.4 g.) already described in Example I. The hydrochloride prepared in acetone melts at 216—218°C. and the base obtained from this hydrochloride melts at 68°C.

The initial primary amine is obtained by hydrogenation under pressure of 3-(10-phenthiazinyl)-2-methylpropiontrile, m.p. 104°C., with Raney nickel in the presence of ammonia. The nitrile is prepared by the action of potassium cyanide in boiling aqueous ethanolic solution upon 10'-phenthiazinyl*iso*propyl toluene-*p*-sulphonate, m.p. 150—151°C. The last mentioned product is obtained by the action of toluene-*p*-sulphonyl chloride upon 1-(10-phenthiazinyl)-propan-2-ol in pyridine.

EXAMPLE VI

3 - (10 - Phenthiazinyl) - 2 - methylpropyl toluene-*p*-sulphonate (3 g.), m.p. 134—135° C., is heated in a sealed tube at 100°C. for 4 hours with dimethylamine (1.5 g.) dissolved in propanol (30 c.c.). From the residue obtained by evaporation of the solvent 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane acid maleate, m.p. 187°C., is prepared. The free base obtained from this salt has already been described in Example I and melts at 68°C.

The initial toluene-*p*-sulphonate is obtained by the action of toluene-*p*-sulphonyl chloride upon 3-(10-phenthiazinyl)-2-methylpropan-1-ol, m.p. 115°C., in pyridine. This alcohol is obtained by reducing methyl 3-(10-phenthiazinyl)-2-methylpropionate with lithium aluminium hydride. The ester is reduced in the crude oily state as obtained by the action of diazomethane upon the acid, m.p. 148°C., which is itself obtained by the hydrolysis of 3-(10 - phenthiazinyl) - 2 - methylpropionitrile, already described in Example V, with sodium hydroxide in a boiling mixture of methanol and water.

EXAMPLE VII

3 - (10 - Phenthiazinyl) - 2 - methyl - 1-aminopropane (5 g.), m.p. 100°C., $[\alpha]_D^{15} = -6.3°$ (c=3.7, acetic acid), is agitated in acetic acid (150 c.c.) under an atmosphere of hydrogen at normal temperature in the presence of a 30% aqueous solution (10 g.) of formaldehyde and Adams' platinum catalyst (0.25 g.). The theoretical volume of hydrogen is absorbed in 2 hours. The catalyst is filtered off, the filtrate is evaporated to dryness under reduced pressure and the oily residue is treated with aqueous sodium hydroxide and ether. The aqueous layer is separated and, on evaporation of the ethereal solution, an oily residue (4.5 g.) is obtained which is converted in ethyl acetate into an acid maleate, m.p. 175°C., $[\alpha]_D^{17} = +10.7°$ (c=4.4, methanol). The 3 - (10 - phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane liberated from this maleate is oily and has the optical activity, $[\alpha]_D^{17} = +5.5°$ (c=3.0, ethanol).

The initial primary amine is obtained by hydrogenation of 3-(10-phenthiazinyl)-2-methylpropionitrile (m.p. 119—120°C., $[\alpha]_D^{13} = -11.2°$ (c=4.5, tetrahydrofuran)) in tetrahydrofuran with lithium hydride. The nitrile is prepared by the action of potassium cyanide in aqueous ethanol upon optically active 1-(10-phenthiazinyl)prop-2-yl toluene-*p*-sulphonate obtained from 1-bromopropan-2-ol (Levene and Walti, *J. Biol. Chem. 68*, 415 (1928)) which is itself prepared from propane-1:2-diol by fermentation (Levene and Walti, *Org. Synth. 10*, 84 (1930)).

EXAMPLE VIII

Proceeding as described in Example VII but commencing with 3-(10-phenthiazinyl)-2-methyl-1-aminopropane (6 g.), m.p. 100°C., which is dextrorotatory in acetic acid, oily 3-(10 - phenthiazinyl) - 2 - methyl - 1 - dimethylaminopropane (2.3 g.) is obtained, which is laevorotatory in ethanol and the acid maleate (2.1 g.) of which melts at 174—175° C. and has the optical activity, $[\alpha]_D^{17} = -12.5°$ (c=4.0, methanol).

The necessary starting materials are obtained as previously described but commencing with dextrorotatory propane-1:2-diol obtained by the degradation of mannitol according to Baer & Fischer, *J. Amer. Chem. Soc. 70*, 609 (1948).

EXAMPLE IX

3 - (10 - Phenthiazinyl) - 2 - methylpropyl toluene-*p*-sulphonate (7 g.), monomethylamine (2 g.) and propanol (35 c.c.) are heated in a sealed tube at 120°C. for 6 hours. After evaporation of the propanol under reduced pressure, the residue is treated with dilute hydrochloric acid and the acid solutions are washed with ether and then made alkaline with an excess of aqueous sodium hydroxide (d=1.33). The product which separates is extracted with ether and, on evaporation of the ether, 3-(10-phenthiazinyl) - 2 - methyl - 1 - methylaminopropane (4 g.) is obtained as a crude oily base. The corresponding hydrochloride melts at 195—196°C. after recrystallisation from a mixture of acetone (8 vols.) and *iso*propanol (2 vols.).

3 - (10 - Phenthiazinyl) - 2 - methylpropyl toluene-*p*-sulphonate, m.p. 134—135°C., is obtained by the action of toluene-*p*-sulphonyl chloride upon 3-(10-phenthiazinyl)-2-methyl-

propan-1-ol, m.p. 115°C., in pyridine. This alcohol is obtained by reducing the methyl ester of 3-(10-phenthiazinyl)-2-methylpropionic acid with lithium aluminium hydride. The acid, m.p. 148°C., may itself be obtained by alkaline hydrolysis of the corresponding nitrile described in Example V.

EXAMPLE X

Proceeding as described in Example IX but commencing with 3-(10-phenthiazinyl)-2-methylpropyl toluene-*p*-sulphonate (5 g.) and monoethylamine (6 g.), 3-(10-phenthiazinyl)-2-methyl-1-ethylaminopropane (3 g.) is obtained as a crude oily base. The corresponding hydrochloride melts at 200—201°C. after recrystallisation from *iso*propanol.

EXAMPLE XI

3 - (10 - Phenthiazinyl) - 2 - methyl - N:N-dimethylpropionamide (7 g.) dissolved in anhydrous ether (250 c.c.) is added slowly to lithium aluminium hydride (0.5 g.) in ether (100 c.c.). The mixture is heated under reflux for 3 hours and is then decomposed with water and sodium hydroxide. It is then filtered, the ether is evaporated from the filtrate and the residual oil is taken up in dilute acetic acid. The acid solution is washed with ether and made alkaline with an excess of sodium hydroxide. The product which separates is extracted with ether and, on evaporation of the solvent, 3 - (10 - phenthiazinyl) - 2 - methyl-1-dimethylaminopropane (1 g.) is obtained, the hydrochloride of which melts at 217—218°C. after crystallisation from acetone and whose acid maleate melts at 187—188°C. after crystallisation from ethanol.

The amide starting material is the crude product obtained by condensing with dimethylamine the product obtained by the action of thionyl chloride upon 3-(10-phenthiazinyl)-2-methylpropionic acid, m.p. 148°C. already described in Example IX.

EXAMPLE XII

3 - (10 - Phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane (19.35 g.) is dissolved with agitation in glacial acetic acid (120 c.c.). Sulphuric acid (d=1.83; 1.5 c.c.) is then added with cooling to 10—15°C. and a mixture of glacial acetic acid (30 c.c.) and hydrogen peroxide (6 c.c. of a solution containing 38 g. of hydrogen peroxide in 100 c.c.) is then run in over 1 hour with agitation, the internal temperature being kept at 15°C. The mixture is left for 16 hours at 20°C. and water (200°C.) is added and, with cooling, sodium hydroxide (d=1.33; 300 c.c.) until a strongly alkaline reaction is obtained. The resulting mixture is shaken with ethyl acetate (3 x 100 c.c.), the ethyl acetate solution is concentrated on a water bath and petroleum ether (100 c.c.) is added. 3 - (9 - Oxy - 10 - phenthiazinyl) - 2 - methyl-1-dimethylaminopropane (19.7 g.) is obtained, m.p. 98°C.

The corresponding acid maleate, prepared in ethyl acetate and recrystallised from a mixture of ethanol and ether, melts at 160°C.

EXAMPLE XIII

3 - (10 - Phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane (11.9 g.) is dissolved with agitation in glacial acetic acid (120 c.c.). Pure sulphuric acid (d=1.83; 0.5 c.c.) is added and a mixture of glacial acetic acid (10 c.c.) and hydrogen peroxide (8.5 c.c. of a solution containing 38 g. of hydrogen peroxide in 100 c.c.) is then run in over 20 minutes. The temperature rises from 25—35°C. and is then kept at 60°C. for 18 hours. The mixture is cooled and water (150 c.c.) is added and, with cooling, aqueous sodium hydroxide (d=1.33; 220 c.c.). The resulting mixture is extracted with ethyl acetate (3 x 100 c.c.), the solvent is evaporated on a water bath and the residue is recrystallised from heptane (150 c.c.). 3-(9:9 - Dioxy - 10 - phenthiazinyl) - 2-methyl-1-dimethylaminopropane (7.8 g.) is obtained, m.p. 115°C.

The corresponding hydrochloride prepared in ethyl acetate and recrystallised from a mixture of ethanol and *iso*propanol melts at 250°C.

EXAMPLE XIV

3 - (10 - Phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane (5.96 g.) and ethyl iodide (2.5 c.c.) are dissolved in acetone (5 c.c.). The mixture is left to stand for 24 hours at room temperature and, on seeding, the mass crystallises. The product is filtered off, washed with acetone and ether and dried *in vacuo* over sulphuric acid. [3 -(10-Phenthiazinyl)-2-methylpropyl]-dimethylethylammonium iodide (7.9 g.) is thus obtained, m.p. 180—190°C. (not sharp).

EXAMPLE XV

Racemic 3 - (10 - phenthiazinyl) - 2-methylpropionitrile (5.3 g.), m.p. 104°C., is dissolved in methanol (300 c.c.) and dimethylamine (10 g.) and a 10% palladium on barium sulphate catalyst (15 g.) are added. The mixture is agitated under a hydrogen pressure of 2—3kg./cm² until absorption of hydrogen is complete. The catalyst is filtered off, the methanol is evaporated and the residue is treated with ether. The ethereal solution is extracted with dilute hydrochloric acid, the aqueous layer is made alkaline with sodium hydroxide and the oil which separates is extracted with ether. On evaporation of the ether, there is obtained 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane, the hydrochloride of which melts at 216—218°C.

EXAMPLE XVI

A mixture of 2-bromo-2¹-(3-dimethylamino-2-methylpropylamino) diphenyl sulphide (14.5 g.), dimethyl formamide (130 c.c.), potassium carbonate (8 g.) and copper powder (0.7 g.) is heated under reflux for 56 hours with agitation. After cooling, insoluble mineral matter is filtered off and the filtrate is poured into water (350 c.c.). The oily base which is precipitated is extracted with ether (2 x 100

c.c. followed by 2 x 50 c.c.) and the combined ethereal extracts are washed with water (50 c.c.), dried over sodium sulphate and the ether distilled off on the water bath.

There is obtained crude 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (12.5 g.), which is purified by conversion in ethanol to the neutral tartrate (4.05 g.), m.p. 162—163°C. (Kofler block).

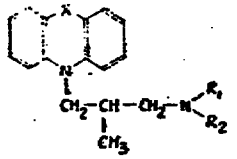
The 2 - bromo - 2¹ - (3 - dimethylamino-2 - methylpropylamino) - diphenyl sulphide employed as starting material is prepared as follows:—

A mixture of 2-bromo-2¹-aminodiphenyl sulphide (20 g.), anhydrous xylene (125 c.c.) and 96% sodamide (3.16 g.) is heated for 1½ hours under reflux with agitation. A 31% solution (35 c.c.) of 3-dimethylamino-2-methyl-1-chloropropane in xylene is run over 25 minutes into the boiling suspension of the sodium derivative of bromoaminodiphenyl sulphide obtained and heating under reflux is continued for 5 hours. After cooling, the reaction mixture is washed with water (50 c.c.) and the xylene solution is extracted with N hydrochloric acid (2 x 75 c.c.). The combined hydrochloric acid extracts are washed with ether (30 c.c.) and made alkaline with aqueous sodium hydroxide (d=1.33; 16 c.c.). The oily base which is precipitated is extracted with ether (3 x 50 c.c.) and, after washing with water (50 c.c.), the combined ethereal extracts are dried over sodium sulphate and the ether is distilled off on a water bath. The oily residue is distilled *in vacuo*.

There is thus obtained 2-bromo-2¹-(3-dimethylamino-2-methylpropylamino) diphenyl sulphide (15.5 g.), b.p. 179—187°C./0.25 mm.Hg.

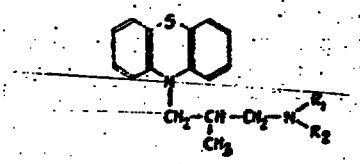
What we claim is:—

1. The racemic and optically active phenthiazine derivatives of the general planar formula:—



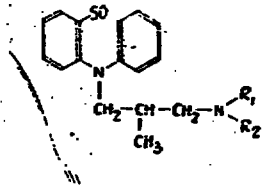
and their salts and their quaternary ammonium derivatives, wherein X represents a sulphur atom or an SO or SO_2 group and R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

2. Phenthiazine derivatives of the general formula:—



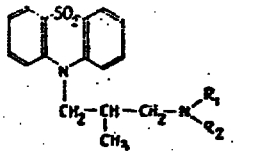
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4. Phenthiazine derivatives of the general formula:—



and their salts and quaternary ammonium derivatives, wherein R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

5. 3 - (10 - Phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane and its salts and quaternary ammonium derivatives.

6. Laevorotatory 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane.

7. 3 - (9:9 - Dioxy - 10 - phenthiazinyl)-2-methyl-1-dimethylaminopropane and its salts and quaternary ammonium derivatives.

8. A process for the preparation of a phen-

c.c. followed by 2 x 50 c.c.) and the combined ethereal extracts are washed with water (50 c.c.), dried over sodium sulphate and the ether distilled off on the water bath.

There is obtained crude 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane (12.5 g.), which is purified by conversion in ethanol to the neutral tartrate (4.05 g.), m.p. 162—163°C. (Kofler block).

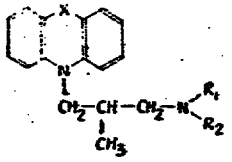
The 2 - bromo - 2¹ - (3 - dimethylamino-2 - methylpropylamino) - diphenyl sulphide employed as starting material is prepared as follows:—

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There is thus obtained 2-bromo-2¹-(3-dimethylamino-2-methylpropylamino) diphenyl sulphide (15.5 g.), b.p. 179—187°C./0.25 mm.Hg.

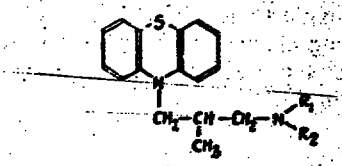
What we claim is:—

1. The racemic and optically active phenthiazine derivatives of the general planar formula:—



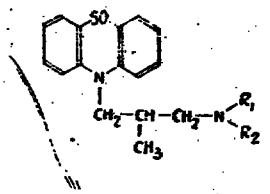
and their salts and their quaternary ammonium derivatives, wherein X represents a sulphur atom or an SO or SO_2 group and R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

2. Phenthiazine derivatives of the general formula:—



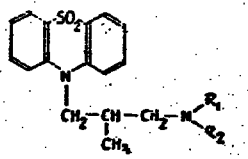
and their salts and quaternary ammonium derivatives, wherein R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

3. Phenthiazine derivatives of the general formula:—



and their salts and quaternary ammonium derivatives, wherein R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mono-nuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

4. Phenthiazine derivatives of the general formula:—



and their salts and quaternary ammonium derivatives, wherein R_1 and R_2 are the same or are different and represent individual hydrogen atoms or alkyl groups containing not more than four carbon atoms or together with the nitrogen atom to which they are attached collectively represent a mononuclear heterocyclic group such as pyrrolidino, piperidino or morpholino.

5. 3 - (10 - Phenthiazinyl) - 2 - methyl - 1-dimethylaminopropane and its salts and quaternary ammonium derivatives.

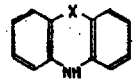
6. Laevorotatory 3-(10-phenthiazinyl)-2-methyl-1-dimethylaminopropane.

7. 3 - (9:9 - Dioxy - 10 - phenthiazinyl)-2-methyl-1-dimethylaminopropane and its salts and quaternary ammonium derivatives.

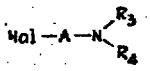
8. A process for the preparation of a phen-

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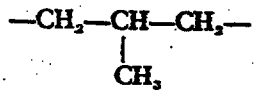
thiazine compound as claimed in any one of the preceding claims which comprises the interaction of a phenthiazine compound of the general formula:—



with a halogenoamine of the type:—

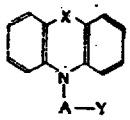


or an acid addition salt thereof, where Hal represents a halogen atom, X is as hereinbefore defined, A represents either the branched chain

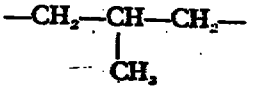


or a group convertible by reduction into this branched chain and R_3 and R_4 either represent R_1 and R_2 or represent groups convertible by reduction into R_1 and R_2 respectively and, where one or more convertible groups is or are present, the subsequent step or steps of transforming the convertible group(s) by reduction.

9. A process for the preparation of a phenthiazine compound as claimed in any of claims 1—7 which comprises the condensation of an amine HNR_3R_4 with a phenthiazine derivative of the type:—



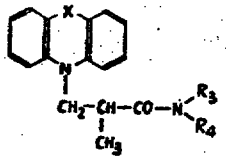
where Y represents the residue of a reactive ester, X is as hereinbefore defined, A represents either the branched chain



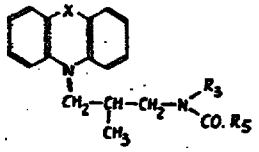
or a group convertible by reduction into this branched chain and R_3 and R_4 either represent R_1 and R_2 or represent groups convertible by reduction into R_1 and R_2 respectively and, where one or more convertible groups is or are present, the subsequent step or steps of transforming the convertible group(s) by reduction.

10. A process for the preparation of a phenthiazine compound as claimed in any of claims 1—7 in which the symbols R_1 and R_2 represent alkyl groups, which comprises alkylating by known methods as hereinbefore defined (for example, methylation with formaldehyde and hydrogen in the presence of a hydrogenating catalyst) the corresponding primary or secondary amines.

11. A process for the preparation of a phenthiazine compound as claimed in any of claims 1—7 which comprises the reduction of a corresponding amide of either of the formulae:—

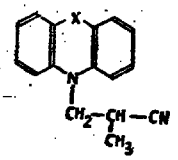


and



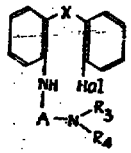
(where R_5 is such that the group R_5CH_2— represents the group R_4 and the other symbols are as hereinbefore defined).

12. A process for the preparation of a phenthiazine compound as claimed in any of claims 1—7 which comprises reduction of a nitrile of the general formula:—



(where X is as hereinbefore defined) in the presence or absence of a primary or secondary amine according to whether a primary, secondary or tertiary amine is required.

13. A process for the preparation of a phenthiazine compound as claimed in any of claims 1—7 which comprises the cyclisation, preferably in a solvent in the form of a substituted amide of a lower aliphatic acid (such as a dialkyl-formamide or -acetamide) in the presence of an alkali condensing agent (e.g. alkali metal hydroxide or carbonate) and, if desired, in the presence of a dehydrohalogenation catalyst, such as copper powder, of a derivative of the type:—



(wherein Hal represents a halogen atom and the other symbols are as hereinbefore defined).

* C L M S *

14. A process for the preparation of an oxophenthiazine compound as claimed in any of claims 1, 3, 4 and 7 in which X represents an SO or SO_2 group, which comprises the oxidation of the corresponding phenthiazine compound wherein X represents a sulphur atom.

J. A. KEMP & CO.,
Chartered Patent Agents,
9, Staple Inn,
London, W.C.1.

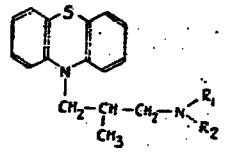
PROVISIONAL SPECIFICATION
No. 34589 A.D. 1954.

New Phenthiazine Derivatives and Processes for their Preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris 8e, France, do hereby declare this invention to be described in the following statement:—

This invention provides new phenthiazine derivatives and their salts, quaternary ammonium derivatives and addition compounds (for example with 8-chlorotheophylline) and processes for their preparation.

These new phenthiazine derivatives are of the general planar formula:—



I

and include the optically active isomers, mixtures, thereof and the corresponding racemates.

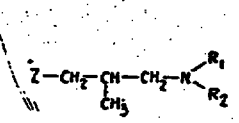
In the foregoing formula either R_1 represents an alkyl group containing not more than 4 carbon atoms and R_2 represents an alkyl group containing not more than 4 carbon atoms or R_1 and R_2 together with the adjacent nitrogen atom collectively represent a heterocyclic group such as pyrrolidino, piperidino or morpholino.

It is known that certain 10-aminoalkylphenthiazines substituted in the 1- or 3-position of the phenthiazine nucleus (Beilstein numbering) by various atoms or groups (in particular by halogen atoms or alkyl, alkoxy, aryl, aryloxy, aralkyl or aralkoxy groups) are active as potentiators of analgesics, hypnotics or anaesthetics while the corresponding derivatives that are not substituted in the nucleus are active in this way only to a much lesser degree. This led to the conclusion that the potentiating properties of phenthiazine derivatives are linked with the presence of such substituents. It has now been found that, contrary to expectation, on the basis of the known facts, the aforesaid new compounds in which the phenthiazine nucleus is substituted solely in the 10-position by the chain $—CH_2—CH(CH_3)—CH_2—N(R_1R_2)$ possess these potentiating activities to at least as great an extent as the most active di-substituted substances previously known.

Consequently these new products find application in human and veterinary medicine.

They may be obtained according to a feature of the invention:—

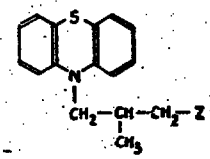
(a) By the action of a reactive ester of an aminoalcohol of the formula:—



II

(wherein Z represents the residue of a reactive ester, e.g. a halogen atom or a residue of a sulphonic or sulphuric ester) upon phenthiazine the reaction being carried out in the presence or absence of a solvent and/or alkaline condensing agent. It is, however, preferable to operate in a solvent medium selected from the group of aromatic hydrocarbons (e.g. toluene and xylene) in the presence of a condensing agent selected from the group of alkali metals and their derivatives, and in particular sodamide, at the boiling point of the solvent employed.

(b) By the condensation of a phenthiazine derivative of the general formula:—



III

upon an amine



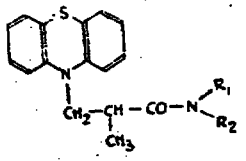
(wherein Z, R_1 and R_2 are as hereinbefore defined) this reaction being preferably carried out in the presence of a solvent in the form of an alcohol and in the presence of an excess of said amine. In the case of a volatile amine, it is advantageous to effect the reaction in an autoclave.

(c) By the alkylation by known methods of

* C L M S *

the corresponding primary amines ($R_1=R_2=H$ in formula I).

(d) By the reduction by known methods of the corresponding amides:—



IV

The following Example shows how the invention may be put into practice:—

EXAMPLE

95% Sodamide (2.27 g.) is added to a solution of phenthiazine (9.6 g.) in xylene (140 c.c.) at a temperature of 130°C. and the mixture is heated with reflux for 2 hours.

An 0.61 N solution (90 c.c.) of 1-chloro-2-methyl-3-dimethylaminopropane in xylene is then added over 50 minutes and heating with reflux is continued for 20 hours. After cooling, the mixture is treated with water (40 c.c.) and N methanesulphonic acid (70 c.c.). The aqueous layer is washed with ether, treated with aqueous sodium hydroxide (d=1.33; 10 c.c.) and extracted with ether. The extract is dried over potassium carbonate and evaporated and the residue is distilled *in vacuo*. 10 - (2^1 - Methyl - 3^1 - dimethylaminopropyl)-phenthiazine (12.6 g.) is collected, distilling between 150° and 175°C. under a pressure of about 0.3 mm.Hg. By dissolving this base in acetone and adding ethereal hydrogen chloride, a hydrochloride is obtained, m.p. 216—217° C. (Kofler bench).

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

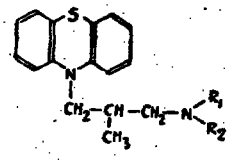
PROVISIONAL SPECIFICATION
No. 5348 A.D. 1955.

New Phenthiazine Derivatives and Processes for their Preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French Body Corporate of 21, rue Jean-Goujon, Paris 8e, France, do hereby declare this invention to be described in the following statement:—

This invention is for improvements in or relating to phenthiazine compounds and to processes for their preparation.

In the specification of our co-pending Application No. 34589/54 we have disclosed new phenthiazine derivatives of the general planar formula:—



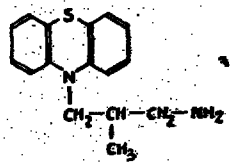
I

including the optically active isomers, mixtures thereof and the corresponding racemates.

In the foregoing formula either R_1 represents an alkyl group containing not more than 4 carbon atoms and R_2 represents an alkyl group containing not more than 4 carbon atoms or R_1 and R_2 together with the adjacent nitrogen atom collectively represent a heterocyclic group such as pyrrolidino, piperidino or morpholino.

According to a feature of the present invention, an optically-active isomer within the scope of the aforesaid general formula, being the 10-(2-methyl-3-dimethylaminopropyl)-phenthiazine isomer which is laevorotatory in ethanol and of which the acid maleate melts at 174—175°C. (Kofler), has been found to possess outstanding physiological activity as compared to its enantiomorph and to the corresponding racemate.

According to a further feature of the present invention, new intermediates are provided for the production of racemates, but more especially optically active isomers, of the aforesaid general formula in the form of the racemates and corresponding isomers respectively of the planar formula:—



II

These intermediates may be prepared by the process hereinafter exemplified and can be converted into compounds of general formula I by the application of methods known *per se* for the conversion of primary amines into tertiary amines of the type



where A represents an organic radical and R_1 and R_2 are each as hereinbefore defined,

The results of further research and experimentation carried out since the aforesaid prior specification was filed are given in the following Examples.

EXAMPLE I

Proceeding as described in the Example of Application No. 34589/54 but commencing with phenthiazine (15.7 g.), technical sodamide (4.5 g.) and 1-chloro-2-methyl-3-diethylaminopropane (15.6 g.), 10-(2-methyl-3-diethylaminopropyl)phenthiazine (23 g.), b.p. 180—182°C./0.5 mm.Hg., is obtained. On the addition of dry hydrogen chloride to a solution of the last mentioned base in acetone, a hydrochloride crystallises which, after recrystallisation from a mixture of acetone and *iso*propanol, melts at 158°C. (Kofler bench).

1 - Chloro - 2 - methyl - 3 - diethylaminopropane is obtained as the hydrochloride by the action of thionyl chloride on 3-diethylamino-2-methylpropan-1-ol, b.p. 81°C./1 mm.Hg. in boiling benzene solution. The last-mentioned product is prepared by reducing with lithium aluminium hydride methyl 3-diethylamino - 2 - methylpropionate, itself obtained according to Bieber, *C.R. Acad. Sci. Paris 231*, 291 (1950).

EXAMPLE II

Proceeding as described in the Example of Application No. 34589/54 but commencing with phenthiazine (15.7 g.), technical sodamide (4.5 g.) and 1-chloro-2-methyl-3-piperidinopropane (16.7 g.), 10-(2-methyl-3-piperidinopropyl)-phenthiazine (22 g.), b.p. about 215° C./1 mm.Hg., is obtained. On the addition of hydrogen chloride to a solution of the last-mentioned base in acetone, a hydrochloride crystallises, which, after recrystallisation from a mixture of acetone and *iso*propanol, melts at 186°C. (Kofler).

1 - Chloro - 2 - methyl - 3 - piperidinopropane is obtained as the hydrochloride by the action of thionyl chloride in boiling benzene upon 3-piperidino-2-methyl-propan-1-ol, b.p. 104°C./12 mm.Hg., itself prepared by reducing with lithium aluminium hydride methyl 3 - piperidino - 2 - methylpropionate, b.p. 97—98°C./13 mm.Hg. The last mentioned product may be obtained by condensing piperidine with methyl methacrylate.

EXAMPLE III

Proceeding as described in the Example of Application No. 34589/54 but commencing with phenthiazine (11.5 g.), technical sodamide (3.3 g.) and 1-chloro-2-methyl-3-1¹-pyrrolidinylpropane, 10 - (2 - methyl - 3 - 1¹-pyrrolidinylpropyl)phenthiazine (18 g.) is obtained. On the addition of oxalic acid to a solution of the last-mentioned base in *iso*propanol, an acid oxalate crystallises which, after recrystallisation from 50% ethanol, melts at 188°C. (Kofler bench).

1 - Chloro - 2 - methyl - 3 - 1¹ - pyrrolidinylpropane is obtained as the hydrochloride by the action of thionyl chloride in boiling benzene solution upon 3-1¹-pyrrolidinyl-2-methylpropan-1-ol, b.p. 91°C./15 mm.Hg. The last mentioned product is obtained by reducing with lithium aluminium hydride methyl-3-1¹-pyrrolidinyl - 2 - methylpropionate, b.p. 92—93° C./15 mm.Hg, itself obtained by the condensation of pyrrolidine with methyl methacrylate.

EXAMPLE IV

Racemic 10-(2-methyl - 3 - aminopropyl)-phenthiazine (5 g.), m.p. 100—104° C. (Kofler), is agitated in acetic acid (150 cc.) under an atmosphere of hydrogen in the presence of a 30% aqueous solution (10 g.) of formaldehyde and 5% palladised charcoal (1 g.). The theoretical volume of hydrogen is absorbed in 2 hours. The catalyst is filtered off, the filtrate is evaporated to dryness under reduced pressure and the oily residue is treated with aqueous sodium hydroxide and ether. The aqueous layer is separated and, on evaporation of the ethereal solution, there is obtained the 10-(2-methyl-3-dimethylaminopropyl)phenthiazine (5.4 g.) already described in the Example of Application No. 34589/54. The hydrochloride prepared in acetone melts at 216—218° C. (Kofler bench) and the base obtained from this hydrochloride melts at 68° C. (Kofler).

The initial primary amine is obtained by hydrogenation under pressure of 3-(10-phenthiazinyl)-2-methylpropionitrile, m.p. 104°C. (Kofler), with Raney nickel in the presence of ammonia. The nitrile is prepared by the action of potassium cyanide in boiling aqueous ethanolic solution upon 10¹-phenthiazinyl*iso*propyl toluene-*p*-sulphonate, m.p. 150—151° C. (Kofler). The last mentioned product is obtained by the action of toluene-*p*-sulphonyl chloride upon 1-(10 - phenthiazinyl)propan-2-ol in pyridine.

EXAMPLE V.

3-(10 - Phenthiazinyl) - 2 - methylpropyl toluene-*p*-sulphonate (3 g.), m.p. 134—135° C. (Kofler), is heated in a sealed tube at 100° C. for 4 hours with dimethylamine (1.5 g.) dissolved in propanol (30 cc.). From the residue obtained by evaporation of the solvent 10-(2 - methyl-3-dimethyl - aminopropyl)phenthiazine acid maleate, m.p. 187° C. (Kofler), is prepared. The free base obtained from this salt has already been described in Example IV and melts at 68° C. (Kofler).

The initial toluene-*p*-sulphonate is obtained by the action of toluene-*p*-sulphonyl chloride upon 3-(10-phenthiazinyl)- 2 -methylpropan-1-ol, m.p. 115° C. (Kofler), in pyridine. This alcohol is obtained by reducing methyl 3-(10-phenthiazinyl) - 2 - methylpropionate with lithium aluminium hydride. The ester is reduced in the crude oily state as obtained by the action of diazomethane upon the acid, m.p. 148° C. (Kofler), which is itself obtained by the hydrolysis of 3-(10-phenthiazinyl)-2-methylpropionitrile, already described in

Example IV, with sodium hydroxide in a boiling mixture of methanol and water.

EXAMPLE VI

10-(2 - Methyl - 3 - aminopropyl)phenthiazine (5 g.), m.p. 100° C. (Kofler), $[\alpha]_D^{15} = -6.3°$ (c=3.7, acetic acid), is agitated in acetic acid (150 cc.) under an atmosphere of hydrogen at normal temperature in the presence of a 30% aqueous solution (10 g.) of formaldehyde and Adams' platinum catalyst (0.25 g.). The theoretical volume of hydrogen is absorbed in 2 hours. The catalyst is filtered off, the filtrate is evaporated to dryness under reduced pressure and the oily residue is treated with aqueous sodium hydroxide and ether. The aqueous layer is separated and, on evaporation of the ethereal solution, an oily residue (4.5 g.) is obtained which is converted in ethyl acetate into an acid maleate. m.p. 175° C. (Kofler). $[\alpha]_D^{17} = +10.7°$ (c=4.4, methanol). The 10-(2-methyl - 3 - dimethylaminopropyl)phenthiazine liberated from this maleate is oily and has the optical activity, $[\alpha]_D^{17} = +5.5°$ (c=3.0, ethanol).

The initial primary amine is obtained by hydrogenation of 3-(10 - phenthiazinyl)-2-methylpropionitrile (m.p. 119—120° C. (Kofler), $[\alpha]_D^{15} = +11.2°$ (c=4.5, tetrahydrofuran)) in tetrahydrofuran with lithium hydride. The nitrile is prepared by the action of potassium cyanide in aqueous ethanol upon optically active 1-(10-phenthiazinyl)prop-2-yl toluene-*p*-sulphonate obtained from 1-bromopropan-2-ol (Levene and Walti, *J. Biol. Chem. 68*, 415 (1928)) which is itself prepared from propane-1:2-diol by fermentation (Levene and Walti, *Org. Synth. 10*, 84 (1930)).

EXAMPLE VII

Proceeding as described in Example VI but commencing with 10-(2-methyl-3-aminopropyl)phenthiazine, m.p. 100° C. (Kofler), which is dextrorotatory in acetic acid, oily 10-(2-methyl- 3 -dimethylaminopropyl)phenthiazine is obtained, which is laevorotatory in ethanol and the acid maleate of which melts at 174—175° C. (Kofler).

The necessary starting materials are obtained as previously described but commencing with dextrorotatory propane-1:2-diol obtained by the degradation of mannitol according to Baer & Fischer, *J. Amer. Chem. Soc. 70*, 609 (1948).

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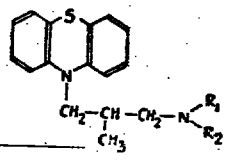
PROVISIONAL SPECIFICATION
No. 13952 A.D. 1955

New Phenthiazine Derivatives and Processes for their Preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate of 21, rue Jean-Goujon, Paris 8e, France, do hereby declare this invention to be described in the following statement:—

This invention relates to phenthiazine derivatives and to processes for their preparation.

In the specifications of our co-pending Applications Nos. 34589/54 and 5348/55 we have disclosed new phenthiazine derivatives of the general planar formula:



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including the optically active isomers, mixtures thereof and the corresponding racemates. In the foregoing formula either R_1 represents an alkyl group containing not more than 4 carbon atoms and R_2 represents an alkyl group containing not more than 4 carbon atoms or R_1 and R_2 together with the adjacent nitrogen atom collectively represent a heterocyclic group such as pyrrolidino, piperidino or morpholino. These phenthiazine derivatives in which the phenthiazine nucleus is substituted solely in the 10-position by the chain

$$-CH_2-CH(CH_3)-CH_2-N<^{R_1}_{R_2}$$

have been found to be at least as active as potentiators of analgesics, hypnotics or anaesthetics as certain 10 - aminoalkylphenthiazines substituted in the 1- or 3-position of the phenthiazine nucleus (Beilstein numbering) by various atoms or groups (in particular by halogen atoms or alkyl, alkoxy, aryl, aryloxy, aralkyl or aralkoxy groups).

The Applicants have continued their research and experimentation and have found that the hitherto unknown phenthiazine derivatives of general formula I in which R_1 now represents a hydrogen atom and/or the sulphur atom of the phenthiazine nucleus is replaced by an SO or SO_2 group also possess similar useful properties. As with the phenthiazine derivative of the said co-pending

Applications, these compounds may be employed in the form of their acid addition and quaternary ammonium salts.

The new phenthiazine derivatives of the present invention in which R_1 represents a hydrogen atom may be prepared by application of the methods described in Application No. 34589/54. Those new compounds of the present invention that contain an SO or SO_2 group as aforesaid may be prepared by the oxidation (by any known method for converting a sulphide into a sulphone or sulphoxide) of the corresponding phenthiazine compound.

The following Examples illustrate the preparation of the phenthiazine derivatives of the present invention and also record some further experimental work carried out with respect to the subject matter of application No. 34589/54.

EXAMPLE I

2. Methyl - 3 - (10 - phenthiazinyl)propyl toluene-*p*-sulphonate (7 g.), monomethylamine (2 g.) and propanol (35 cc.) are heated in a sealed tube at 120° C. for 6 hours. After evaporation of the propanol under reduced pressure, the residue is treated with dilute hydrochloric acid and the acid solutions are washed with ether and then made alkaline with an excess of aqueous sodium hydroxide (d=1.33). The product which separates is extracted with ether and, on evaporation of the ether, 10-(2-methyl- 3 -methylaminopropyl) phenthiazine (4 g.) is obtained as a crude oily base. The corresponding hydrochloride melts at 195—196° C. (Kofler) after recrystallisation from a mixture of acetone (8 vols.) and *iso*propanol (2 vols.).

EXAMPLE II

Proceeding as described in Example I but commencing with 2-methyl-3-(10-phenthiazinyl)propyl toluene-*p*-sulphonate (5 g.) and monoethylamine (6 g.), 10-(3-ethylamino-2-methylpropyl)phenthiazine (3 g.) is obtained as a crude oily base. The corresponding hydrochloride melts at 200—201°C. (Kofler) after recrystallisation from *iso*propanol.

EXAMPLE III

10 - (3 - Dimethylamino - 2 - methylpropyl)phenthiazine (19.35 g.) is dissolved with agitation in glacial acetic acid (120 c.c.). Sulphuric acid (d=1.83; 1.5 c.c.) is then added with cooling to 10—15°C. and a mixture of glacial acetic acid (30 c.c.) and hydrogen peroxide (6 c.c. of a solution containing 38 g. of hydrogen peroxide in 100 c.c.) is then run in over 1 hour with agitation, the internal temperature being kept at 15°C. The mixture is left for 16 hours at 20°C. and water (200°C.) is added and, with cooling, sodium hydroxide (d=1.33; 300 c.c.) until a strongly alkaline reaction is obtained. The resulting mixture is shaken with ethyl acetate (3 x 100 c.c.), the ethyl acetate solution is concentrated on a water bath and petroleum ether (100 c.c.) is added. 9-Oxy-10-(3-dimethylamino-2-methylpropyl)phenthiazine (19.7 g.) is obtained, m.p. 98°C. (Kofler).

The corresponding acid maleate, prepared in ethyl acetate and recrystallised from a mixture of ethanol and ether, melts at 160°C. (Kofler).

EXAMPLE IV

10 - (3 - Dimethylamino - 2 - methylpropyl)phenthiazine (11.9 g.) is dissolved with agitation in glacial acetic acid (120 c.c.). Pure sulphuric acid (d=1.83; 0.5 c.c.) is added and a mixture of glacial acetic acid (10 c.c.) and hydrogen peroxide (8.5 c.c. of a solution containing 38 g. of hydrogen peroxide in 100 c.c.) is then run in over 20 minutes. The temperature rises from 25-35°C. and is then kept at 60°C. for 18 hours. The mixture is cooled and water (150 c.c.) is added and, with cooling, aqueous sodium hydroxide (d=1.33; 220 c.c.) until a strongly alkaline reaction is obtained. The resulting mixture is extracted with ethyl acetate (3 x 100 c.c.), the solvent is evaporated on a water bath and the residue is recrystallised from heptane (150 c.c.). 9:9-Dioxy - 10 - (3 - dimethylamino - 2 - methylpropyl)phenthiazine (7.8 g.) is obtained, m.p. 115°C. (Kofler).

The corresponding hydrochloride prepared in ethyl acetate and recrystallised from a mixture of ethanol and isopropanol melts at 250°C. (Kofler).

EXAMPLE V

2 - Methyl - 3 - (10 - phenthiazinyl)propiondimethylamide (7 g.) dissolved in anhydrous ether (250 c.c.) is added slowly to lithium aluminium hydride (0.5 g.) in ether (100 c.c.). The mixture is heated under reflux for 3 hours and is then decomposed with water and sodium hydroxide. It is then filtered, the ether is evaporated from the filtrate and the residual oil is taken up in dilute acetic acid. The acid solution is washed with ether and made alkaline with an excess of sodium hydroxide. The product which separates is extracted with ether and, on evaporation of the solvent, 10-(3-dimethylamino-2-methylpropyl)-phenthiazine (1 g.) is obtained, the hydrochloride of which melts at 217—218°C. (Kofler) after crystallisation from acetone and whose acid maleate melts at 187—188°C. (Kofler) after crystallisation from ethanol.

The amide starting material is the crude product obtained by condensing with dimethylamine the product obtained by the action of thionyl chloride upon 2-methyl-3-(10-phenthiazinyl)propionic acid, m.p. 148°C. (Kofler).

EXAMPLE VI

10 - (3 - Dimethylamino - 2 - methylpropyl)phenthiazine (5.96 g.) and ethyl iodide (2.5 c.c.) are dissolved in acetone (5 c.c.). The mixture is left to stand for 24 hours at room temperature and, on seeding, the mass crystallises. The product is filtered off, washed with acetone and ether and dried *in vacuo* over sulphuric acid. [2-Methyl-3-(10-phenthiazinyl)-

propyl]-dimethylethylammonium iodide (7.9 g.) is thus obtained, m.p. 180—190° C. (Kofler) (not sharp).

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PROVISIONAL SPECIFICATION
No. 22854 A.D. 1957.

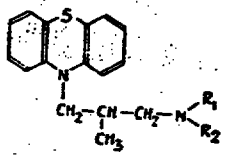
New Phenthiazine Derivatives and Processes for their Preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate of 21 rue Jean-Goujon, Paris 8e, France, do hereby declare this invention to be described in the following statement:—

This invention provides new phenthiazine derivatives and their salts, quaternary ammonium derivatives and addition compounds (for example with 8-chlorotheophylline) and processes for their preparation.

In Application No. 34589/54 there are described new phenthiazine derivatives as aforesaid.

These new phenthiazine derivatives are of the general planar formula:—



I

and include the optically active isomers, mixtures thereof and the corresponding racemates.

In the foregoing formula either R_1 represents an alkyl group containing not more than 4 carbon atoms and R_2 represents an alkyl group containing not more than 4 carbon atoms or R_1 and R_2 together with the adjacent nitrogen atom collectively represent a heterocyclic group such as pyrrolidino, piperidino or morpholino.

According to the present invention there are provided new phenthiazine derivatives of the foregoing formula in which R_1 represents, instead of an alkyl group, a hydrogen atom.

The said compounds may be made by processes strictly analogous to those set out in Application No. 34589/54.

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