United States Patent Office 2,941,999 Patented June 21, 1960

2,941,999

PHENTHIAZINE DERIVATIVES

Robert Michel Jacob, Ablon-sur-Seine, and Jacques Georges Robert, Gentilly, France, assignors to Societe des Usines Chimiques Rhone-Poulenc, Paris, France, a French body corporate

No Drawing. Filed Jan. 10, 1957, Ser. No. 633,395

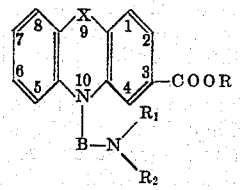
Claims priority, application France Jan. 10, 1956

6 Claims. (Cl. 260—243)

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

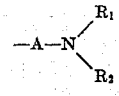
It is known that various 10-aminoalkyl-phenthiazines possess interesting therapeutic properties. Extensive research and experimentation has shown, however, that both the size of the therapeutic index and the nature of the therapeutic effect exhibited by certain compounds of this type can radically be changed (even eliminated) by even small changes in chemical structure. Particularly is this the case with variations in the nature and length of the side chain attached to the 10-position nitrogen atom and with positional substitution in the phenthiazine nucleus.

It has now unexpectedly been discovered that the hitherto unknown phenthiazine derivatives of the general formula:

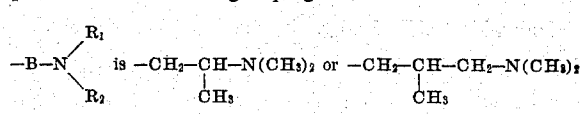


(I)

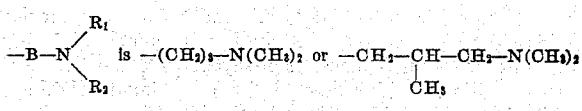
and their salts and their quaternary ammonium derivatives (wherein X represents a sulphur atom or an SO or SO_2 group, R represents an alkyl group containing not more than four carbon atoms, R_1 and R_2 are the same or different and either each represents a lower alkyl group or one of R_1 and R_2 represents a hydrogen atom and the other represents a lower alkyl group or R_1 and R_2 together with the adjacent nitrogen atom collectively represent a heterocyclic group such as pyrrolidino, piperidino, morpholino, piperazino or 4-alkylpiperazino, and B represents a straight or branched chain divalent aliphatic hydrocarbon group containing 2 to 5 carbon atoms unsubstituted or substituted by a group



wherein A represents a single bond or $—CH_2—$ and R_1 and R_2 are as hereinbefore defined) have useful pharmacological properties. Some, in particular, those compounds in which the grouping

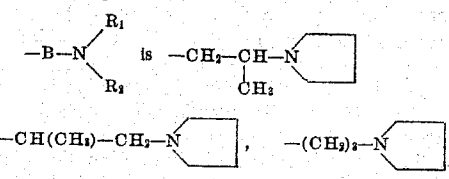


are powerful antihistaminics; others, in particular those compounds in which the grouping

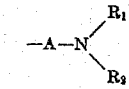


are potentiators of narcosis and very active inhibitors of the vegetative nervous system superior to previously

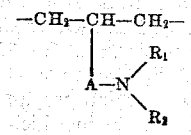
known phenthiazine derivatives, and those compounds in which the grouping



are outstanding hypotensors. Those derivatives in which the chain B carries another amino group



are particularly interesting as spasmolytics and local anaesthetics, and of particular importance are those compounds in which the group B is



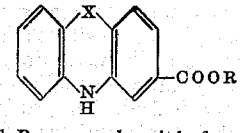
Compounds of outstanding utility and having the aforesaid chain groupings are: 3-methoxycarbonyl-10-(3-dimethylaminopropyl)phenthiazine, 3-methoxycarbonyl-10-(2-methyl-3-dimethylaminopropyl)phenthiazine, 3-methoxycarbonyl - 10 - (3 - pyrrolidinopropyl)phenthiazine, 3-methoxycarbonyl - 10 - (2 - methyl - 3 - pyrrolidinopropyl) phenthiazine, 3 - ethoxycarbonyl - 10 - (3 - dimethylaminopropyl) - phenthiazine, 3 - butoxycarbonyl - 10 - (3 - dimethylaminopropyl)phenthiazine, 3 - methoxycarbonyl-10- (2 - diethylaminoethyl)phenthiazine, 3 - methoxycarbonyl - 10 - (2 - diethylaminopropyl)phenthiazine, 3-methoxycarbonyl - 10 - (2:3 - bis - dimethylaminopropyl)-phenthiazine, 3 - methoxycarbonyl - 9:9 - dioxy - 10 - (3-dimethylaminopropyl)phenthiazine, 3 - methoxycarbonyl-9:9 - dioxy - 10 - (2 -methyl - 3 - dimethylaminopropyl)-phenthiazine.

The term "lower alkyl" as used in this specification and in the appended claims means that the alkyl group contains not more than five carbon atoms.

The new phenthiazine compounds of the present invention may be prepared in a number of different ways.

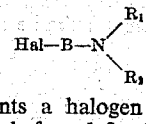
Preferred processes of manufacture are as follows:

(1) Interaction of a 3-alkoxycarbonylphenthiazine of the general formula:



(II)

(wherein X and R are as hereinbefore defined) with a halogenoamine of the formula:



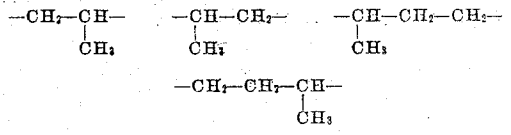
(III)

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

The reaction may be carried out with or without a solvent in the presence or absence 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-

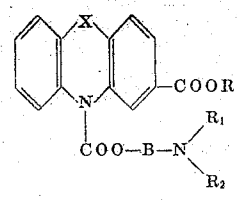
butylate, butyllithium and phenyllithium. The reaction is preferably carried out at the boiling temperature of the solvent. It is advantageous to use the halogenoamine in the form of the free base in solution, for example, with benzene, toluene or xylene, and to add this to the mixture of the other reactants in which the 3-alkoxycarbonylphenthiazine 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.

In the case where the divalent aliphatic hydrocarbon group —B— is an asymmetric branched chain, such for example, as



isomerisation can take place during the course of the reaction. This isomerisation is analogous to that which takes place in the preparation of promethazine by the condensation of phenthiazine with a dimethylaminohalogenopropane [Charpentier, C. R. 225, 306 (1947)], which gives with 2-dimethylamino-1-chloropropane or with 1-dimethylamino-2-chloropropane as starting material the same final mixture in which promethazine predominates.

(2) Decomposition of a phenthiazine-10-carboxylate of an aminoalcohol of the formula:



(IV)

(wherein the various symbols are as hereinbefore defined) by heating the carboxylate to a temperature above 100° C., and preferably between 150 and 220° C. There is no advantage in operating at higher temperatures which, in any event, can cause discoloration of the reaction products.

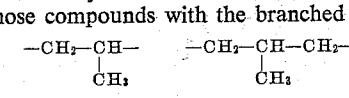
The reaction can be effected with the phenthiazine-10-carboxylate alone, i.e. without a diluent, or in an inert medium such as liquid paraffin, diphenyl or diphenyl oxide, or in the classical diluents for decarboxylation, such, for example, as quinoline or weak bases with a sufficiently high boiling point, or in solution in a chlorinated aromatic compound, such as o-dichlorobenzene.

During the course of the decomposition of the phenthiazine-10-carboxylate an isomerisation, similar to that hereinbefore described in process (1), takes place when the divalent aliphatic hydrocarbon group B is an asymmetric branched chain and a mixture of isomers is obtained. Separation of the isomers may be effected by, for example, fractional crystallisation of salts such as the hydrochlorides from a suitable solvent such as alcohol.

The phenthiazine-10-carboxylates employed as starting materials may be obtained by known methods. For example, they may be prepared by the action of a halide (or an ester) of a 3-alkoxycarbonylphenthiazine-10-carboxylic acid on the appropriate aminoalcohol; or by the action of a halogenoalkyl ester of such an acid on an appropriate amine.

(3) In the case where X represents an SO or SO_2 group, oxidation by known methods of the corresponding phenthiazine compounds (X=S) of general Formula I.

Certain of the compounds conforming to general Formula I have an asymmetric carbon atom in the chain B, such as those compounds with the branched chains



and consequently can exist in optically active forms. The invention includes within its scope the racemates as well as the corresponding optically active isomers of such compounds. The optically active isomers may be obtained by methods (1) and (3) described above by commencing with starting materials which are themselves optically active. They may also be prepared by resolution of the corresponding racemates.

For therapeutic purposes, the bases of general Formula I are preferably employed in the form of acid addition salts containing pharmaceutically acceptable anions (such as hydrochlorides and other hydrohalides, 8-chlorotheophyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, oxalates, methanesulphonates and ethanedisulphonates) or of quaternary ammonium salts obtained by reaction with organic halides (e.g. methyl or ethyl iodide, chloride or bromide or allyl or benzyl chloride or bromide) or other reactive esters.

The following examples show how the invention may be put into practice. The melting points are those determined on the Kofler bench.

Example I

Sodamide (95%, 2.25 g.) is added to a boiling solution of 3-methoxycarbonylphenthiazine (12.85 g.) (Baltzly R., Harfenist M., Webb, F. J.—J. Am. Chem. Soc. 68, 2673 (1946)) in anhydrous xylene (200 cc.) and the mixture is heated under reflux for 1 hour. A xylene solution (186 cc.) containing 3-dimethylamino-1-chloropropane (6.68 g.) is then run in over 20 minutes and heating under reflux is continued for a further 16 hours. After cooling, the mixture is agitated with 2 N hydrochloric acid (200 cc.) and ether (100 cc.). The ethereal layer is separated and the aqueous layer is extracted with ether (200, 100 and 100 cc. successively). The aqueous layer is separated, treated with 4 N sodium hydroxide (120 cc.) and extracted with ether (200, 100 and 100 cc. successively). The ethereal extracts are combined and dried over potassium carbonate and ether is removed on the water-bath. There remains a brown oil (13 g.) which is purified by chromatography over alumina (200 g.) after dissolving in a mixture (650 cc.) of equal parts of benzene and cyclohexane. Elution is effected with the following solvents:

(*a*) 500 cc. of a mixture of 1 part benzene and 1 part cyclohexane,
(*b*) 500 cc. of a mixture of 3 parts benzene and 1 part cyclohexane, and
(*c*) 500 cc. of pure benzene

The solutions are combined and the solvents are evaporated on the water-bath. There remains a product (4.68 g.) which is treated with maleic acid in ethyl acetate. There is thus obtained the maleate of 3-methoxycarbonyl-10-(3-dimethylaminopropyl)phenthiazine (4.94 g.), M.P. 145° C. after recrystallisation from ethyl acetate.

Example II

Sodamide (95%, 3.06 g.) is added to a boiling solution of 3-methoxycarbonylphenthiazine (20.0 g.) in anhydrous xylene (250 cc.) and the mixture is heated under reflux for 1 hour. A solution of 1-chloro-2-methyl-3-dimethylaminopropane (10.2 g.) in anhydrous xylene (30 cc.) is then run in over 15 minutes and heating under reflux is continued for 20 hours. After cooling, the mixture is agitated with water (100 cc.) and 4 N hydrochloric acid (40 cc.). The xylene phase is decanted and the aqueous phase, in which the hydrochloride has crystallised, is diluted with water (1 litre) and made alkaline while hot with 4 N sodium hydroxide (60 cc.). The base which precipitates is extracted with ether, the com-

bined ethereal extracts are dried over anhydrous potassium carbonate and the ether is removed on the water-bath. A brown oil (20 g.) remains which is purified by chromatography over alumina (400 g.) after being dissolved in a mixture (1 litre) of benzene and cyclohexane (3:7). After elution as in Example I and evaporation of the solutions there is obtained a product (6.1 g.) which is dissolved in ethyl acetate and treated with ethereal hydrogen chloride. There is thus obtained 3-methoxycarbonyl-10-(2 - methyl-3-dimethylaminopropyl) phenthiazine hydrochloride (5.3 g.), M.P. 198° C. after recrystallisation from a mixture of chloroform and ethyl acetate.

Example III

A solution of 3-methoxycarbonyl phenthiazine (15 g.) in anhydrous xylene (200 cc.) is heated to 115° C.; 95% sodamide (2.45 g.) is added and the mixture is heated under reflux for 10 minutes. A solution of 1-chloro-3-pyrrolidinopropane (9.3 g.) in anhydrous xylene (75 cc.) is then added and refluxing is continued for 5 hours. After cooling, the reaction liquors are washed with water (2 x 300 cc.) and the xylene layer is separated, dried over anhydrous potassium carbonate and concentrated to dryness at 100° C. under a pressure of 20 mm. Hg. The residual oil is dissolved in boiling n-heptane (500 cc.) and the solution is cooled to 10° C. and separated from the resin which has precipitated.

The heptane solution is passed over a column of alumina (200 g.) for chromatography and is eluted with 10 fractions of n-heptane (250 cc.). The filtrates from the elution are combined and the solvent is evaporated.

The purified base (6.4 g.) is converted into an acid oxalate in acetone and, after recrystallisation from methanol, there is obtained 3-methoxycarbonyl-10-(3-pyrrolidinopropyl)phenthiazine acid oxalate (5 g.) as a pale yellow crystalline powder, M.P. 176° C.

Example IV

Proceeding as in Example III but replacing the 1-chloro-3-pyrrolidinopropane by 1-chloro-2-methyl-3-pyrrolidinopropane (10.2 g.), the residual oil (20 g.) remaining from the evaporation of the xylene is dissolved in a boiling mixture (500 cc.) of equal parts of cyclohexane and petroleum ether (B.P. 35° C. to 50° C.). The solution is cooled to 5° C. and the solid resins which have precipitated are filtered off.

The clear solution obtained is passed over a column of alumina (250 g.) for chromatography and is eluted with 16 fractions of a mixture (250 cc.) of equal parts of cyclohexane and petroleum ether. The filtrates from the elution are combined, the solvent is evaporated and the purified base is recrystallised from n-heptane. There is thus obtained 3-methoxycarbonyl-10-(2-methyl-3-pyrrolidinopropyl)phenthiazine as a yellow crystalline powder, M.P. 95° C.

Example V

A solution of 3-ethoxycarbonylphenthiazine (13.6 g.) in anhydrous xylene (200 cc.) is heated to 100° C.; 95% sodamide (2.25 g.) is added and the mixture is heated under reflux for 5 minutes. A solution of 1-chloro-3-dimethylaminopropane (6.7 g.) in anhydrous xylene (180 cc.) is then poured in over 15 minutes, and refluxing is continued for 2 hours. After cooling, the reaction mixture is diluted with ether (100 cc.) and shaken with hydrochloric acid (about 0.8 N, 125 cc.). The aqueous acid phase is separated, washed with ether (3 x 400 cc.) and made alkaline with 4 N sodium hydroxide solution (30 cc.) and the liberated base is extracted with ether (400 cc.). The ethereal phase is dried over anhydrous carbonate and the solvent is removed at ordinary pressure and then under a pressure of 20 mm. Hg with heating on the water-bath.

The residual oil (8.5 g.) is dissolved in a mixture (425 cc.) of cyclohexane and benzene (3:7); the solution is passed over a column of alumina (160 g.) for chromatography and the adsorbed product is eluted successively with benzene (1400 cc.) and a mixture (900 cc.) of benzene and ethyl acetate (9:1). The filtrates from the elution are combined, the solvent is evaporated and the purified base obtained is converted into the acid maleate in ethyl acetate. After recrystallisation from ethanol there is obtained 3-ethoxycarbonyl-10-(3-dimethylaminopropyl)-phenthiazine acid maleate (1.2 g.) as a yellow crystalline powder, M.P. 48° C.

The initial 3-ethoxycarbonylphenthiazine, M.P. 152° C., is prepared by the esterification of phenthiazine-3-carboxylic acid with ethanol in the presence of sulphuric acid.

Example VI

A solution of 3-butoxycarbonylphenthiazine (12 g.) in anhydrous xylene (200 cc.) is heated to 100° C.; 95% sodamide (1.78 g.) is added and the mixture is heated under reflux for 1 hour. A solution of 1-chloro-3-dimethylaminopropane (5.34 g.) in anhydrous xylene (50 cc.) is then run in over 15 minutes and refluxing is continued for 3 hours. After cooling, the reaction mixture is diluted with ether (200 cc.) and agitated with methanesulphonic acid (about 0.4 N, 170 cc.). The aqueous acid phase is separated and made alkaline with 4 N sodium hydroxide solution (30 cc.) and the liberated base is extracted with ether (200 cc.). The ethereal phase is dried over anhydrous potassium carbonate and the solvent is removed at ordinary pressure and finally at 80° C. under a pressure of 20 mm. Hg.

The residual oil (12 g.) is dissolved in a mixture (600 cc.) of equal parts of cyclohexane and benzene, the solution is passed over a column of alumina (240 g.) for chromatography and the adsorbed product is eluted successively with benzene (1000 cc.), 2% ethyl acetate in benzene (1500 cc.), 5% ethyl acetate in benzene (750 cc.) and 10% ethyl acetate in benzene (500 cc.). The filtrates from the elution are combined and concentrated to dryness and the purified base obtained (3.8 g.) is converted into the acid oxalate in acetone. After recrystallisation from ethanol there is obtained 3-butoxycarbonyl-10-(3 - dimethylaminopropyl)phenthiazine acid oxalate (3.3 g.) as a pale yellow crystalline powder, M.P. 138–140° C.

The initial 3-butoxycarbonylphenthiazine, M.P. 149° C., is prepared by the esterification of phenthiazine-3-carboxylic acid with n-butanol in the presence of sulphuric acid.

Example VII

A solution of 3-methoxycarbonylphenthiazine-10-carbonyl chloride (32 g.) in anhydrous toluene (150 cc.) is heated to 90° C. and diethylaminoethanol (23.4 g.) is added over 20 minutes. The mixture is then heated under reflux for 5 hours and, after cooling, is diluted with ether (150 cc.) and agitated with water (150 cc., 100 cc., and 100 cc. successively). The organic phase is then agitated with 1.5 N hydrochloric acid (130 cc.), the aqueous acid phase is separated, washed with ether (200 cc.) in three lots and then made alkaline with sodium hydroxide solution (d=1.33, 30 cc.) and the precipitated base is extracted with ether (500 cc.). The ethereal solution is dried over anhydrous potassium carbonate and the solvent is removed on the water-bath.

The brown residual oil comprising crude 2-diethylaminoethyl-3-methoxycarbonylphenthiazine - 10 - carboxylate is dissolved in o-dichlorobenzene (220 cc.) and the solution is heated between 140–170° C. until the evolution of carbon dioxide has ceased, that is for about 1½ hours. After cooling, the mass is treated with ether (530 cc.) and agitated with 3 successive amounts of 0.35 N (approx.) hydrochloric acid (total 450 cc.). The aqueous acid phases are combined, washed with ether (200 cc.) and made alkaline with 4 N sodium hydoxide solution (45 cc.) and the liberated base is extracted with ether (400 cc.) in four lots. The ethereal phase is dried over

anhydrous potassium carbonate and the solvent is removed on the water-bath.

The residual oil (22 g.) is dissolved in petroleum ether (250 cc., B.P. 35–50° C.), the solution is passed over a column of alumina (250 g.) for chromatography and the adsorbed product is eluted successively with petroleum ether, cyclohexane and benzene. The filtrates from the elution are combined and concentrated to dryness and the base thus purified (15.7 g.) is converted into the hydrochloride in acetone by the addition of ethereal hydrogen chloride. After recrystallisation from ethanol there is obtained 3-methoxycarbonyl-10-(2-diethylaminoethyl)phenthiazine hydrochloride (14.8 g.) as a creamy white crystalline powder, M.P. 200–201° C.

The initial 3 - methoxycarbonylphenthiazine - 10 - carbonyl chloride, M.P. 145–147° C., is obtained by the action of phosgene on 3-methoxycarbonylphenthiazine in toluene in the presence of pyridine at room temperature.

Example VIII

A solution of 3-methoxycarbonylphenthiazine-10-carbonyl chloride (32 g.) in anhydrous toluene (150 cc.) is heated to 90° C.; 1-diethylamino-2-propanol (26.2 g.) is run in over 35 minutes and the mixture is then heated for 5 hours under reflux. Proceeding as in Example VII, there is isolated a brown oil (31.3 g.) comprising crude 3-diethylamino-2-propyl 3-methoxycarbonylphenthiazine-10-carboxylate, the hydrochloride of which prepared in acetone by the addition of ethereal hydrogen chloride melts at 187–190° C.

A solution of the above oil (26.5 g.) in o-dichlorobenzene (140 cc.) is heated between 165–180° C. until the evolution of carbon dioxide ceases, that is for about 1½ hours. Proceeding as in Example VII there is obtained a crude base (21.4 g.) which is dissolved in petroleum ether (250 cc., B.P. 35–50° C.). The solution is passed over a column of alumina (250 g.) for chromatography and the adsorbed product is eluted successively with petroleum ether, cyclohexane and mixtures of cyclohexane and benzene. The residue of the evaporation of the filtrates from the elution (14.6 g.) is purified through the hydrochloride prepared in acetone by the addition of ethereal hydrogen chloride. The hydrochloride, which melts at about 200–210° C., is reconverted into the base by the standard procedure and the base, which readily solidifies, is recrystallised from n-heptane. There is thus obtained 3-methoxycarbonyl-10-(2-diethylaminopropyl)-phenthiazine (2.2 g.) as a yellow crystalline powder, M.P. 90–92° C.

Example IX

A solution of 3-methoxycarbonylphenthiazine-10-carbonyl chloride (15 g.) in anhydrous toluene (150 cc.) is heated to 90° C.; a solution of 3-(4-methylpiperazinyl)propanol (14.4 g.) in anhydrous toluene (50 cc.) is run in over 15 minutes and the mixture is then heated under reflux for 4 hours. Proceeding as in Example VII, there is isolated a brown oil (20 g.) comprising crude 3 - (4 - methylpiperazino)propyl 3 - methoxycaronylphenthiazine-10-carboxylate, the dihydrochloride of which, prepared in ethanol by the addition of ethereal hydrogen chloride, melts at about 235–240° C.

The brown oil (14 g.) is heated between 170–210° C. until the evolution of carbon dioxide ceases, that is for about 45 minutes. On cooling and proceeding as in Example VII, there is obtained a thick oil (7 g.) which is dissolved in a mixture (350 cc.) of cyclohexane and benzene (7:3). The solution is passed over a column of alumina (140 g.) for chromatography and the adsorbed product is eluted with benzene (10 x 250 cc.) and then twice with a mixture of benzene and ethyl acetate (9:1). The filtrates from the elution are combined and evaporated to dryness and the purified base thus obtained (1.3 g.) is converted in methanol into the dihydrochloride by the addition of ethereal hydrogen chloride. After recrystallisation from methanol, there is obtained 3-methoxycarbonyl - 10 - (3 - 4′ - methylpiperazinopropyl)-phenthiazine dihydrochloride (0.8 g.) as a yellow crystalline powder, M.P. about 215° C.

Example X

A solution of 3 - methoxycarbonylphenthiazine - 10 - carbonyl chloride (32 g.) in anhydrous toluene (50 cc.) is heated to 90° C.; 1:3-bis-dimethylamino-2-propanol (14.6 g.) is run in over 15 minutes and the mixture is then heated under reflux for 4 hours. Proceeding as in Example VII there is isolated a brown oil (27.6 g.) comprising crude 1:3-bis-dimethylamino-2-propyl 3-methoxycarbonylphenthiazine-10-carboxylate. After purification through the ditartrate prepared in ethanol, there is obtained the purified base (21.7 g.) which crystallises slowly and melts at 102–106° C.

The crystallised base (18.4 g.) dissolved in o-dichlorobenzene (120 cc.) is heated between 160° and 180° C. until the evolution of carbon dioxide ceases, that is for about 1½ hours. Proceeding as in Example VII there is obtained a thick brown oil (16.3 g.) which is dissolved in cyclohexane (320 cc.). The solution is passed over a column of alumina (160 g.) for chromatography and the adsorbed product is eluted with cyclohexane (1800 cc.), a mixture (1800 cc.) of cyclohexane and benzene (2:1) and benzene (900 cc.). The filtrates from the elution are combined and concentrated to dryness and the purified base thus obtained (12.5 g.) is converted into the monomaleate in ethyl acetate. After recrystallisation from ethanol there is obtained 3-methoxycarbonyl - 10 - (2:3 - bis - dimethylamino - propyl)phenthiazine monomaleate (11.4 g.) as a creamy white crystalline powder, M.P. 180–181° C.

Example XI

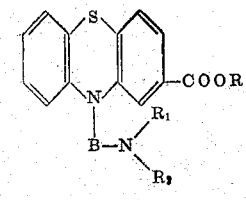
Into a solution of 3-methoxycarbonyl-10-(3-dimethylaminopropyl)-phenthiazine (5.13 g.) in glacial acetic acid (25 cc.) at 30° C. there is run in over ¼ hour a solution of pure sulphuric acid (2.1 g.) in acetic acid (25 cc.) followed by a solution of 32.6% hydrogen peroxide (3.95 cc.) in acetic acid (6 cc.). The mixture is then heated for 15 hours at 60° C. After cooling, the reaction mixture is poured into iced water (300 cc.) and made alkaline with sodium hydroxide solution (d=1.33, 115 cc.). The precipitated base is extracted with ethyl acetate (3 x 100 cc.) and the combined organic extracts are dried over anhydrous potassium carbonate and evaporated to dryness on the water-bath. The crude base obtained is recrystallised from isopropanol. There is thus obtained 3 - methoxycarbonyl-9:9-dioxy-10-(3-dimethylaminopropyl)phenthiazine (2.6 g.) as creamy white crystals, M.P. 116–118° C.

Example XII

Preceeding as described in Example XI but commencing with 3 - methoxycarbonyl - 10 - (2 - methyl - 3 - dimethylaminopropyl)phenthiazine (4.98 g.), there is obtained a crude oily base (4.3 g.). This base is dissolved in ethanol (35 cc.) and a 5 N ethereal solution (2.2 cc.) of dry hydrogen chloride is added. There is thus obtained 3 - methoxycarbonyl - 9:9 - dioxy - 10 - (2 - methyl - 3 - dimethylaminopropyl)phenthiazine hydrochloride (3.9 g.) as white crystals, M.P. about 150° C. with decomposition.

We claim:

1. A phenthiazine compound selected from the class consisting of compounds of the general formula:



wherein R represents an alkyl group containing up to four carbon atoms, R_1 and R_2 are selected from the class consisting of methyl and ethyl groups and groups which with the adjacent nitrogen atom collectively represent pyrrolidino, piperidino, morpholino, piperazino and 4-methyl piperazino groups, and B is a member of the class consisting of straight and branched chain divalent saturated aliphatic hydrocarbon groups containing 2 to 5 carbon atoms and acid addition salts thereof formed with pharmaceutically acceptable anions.

2. 3 - methoxycarbonyl - 10 - (3 - dimethylaminopropyl)phenthiazine.

3. 3 - methoxycarbonyl - 10 - (2 - methyl - 3 - dimethylaminopropyl)phenthiazine.

4. 3 - methoxycarbonyl - 10 - (3 - pyrrolidinopropyl) phenthiazine.

5. 3 - methoxycarbonyl - 10 - (2 - methyl - 3 - pyrrolidinopropyl)phenthiazine.

6. 3 - ethoxycarbonyl - 10 - (3 - dimethylaminopropyl) phenthiazine.

References Cited in the file of this patent

UNITED STATES PATENTS

2,789,978 Rath ---------- Apr. 23, 1957