PATENT SPECIFICATION

NO DRAWINGS

833,473

Date of Application and filing Complete Specification: Dec. 18, 1956.

No. 38571/56.

Application made in United States of America on Jan. 3, 1956.

Application made in United States of America on Sept. 18, 1956.

Complete Specification Published: April 27, 1960.

Index at acceptance:—**Classes 2(3),** B4(A1:E:M), C1C(2:9:11F:11G), C1E(3K4:4K4:5K4:5K6:6K4:7K4), C1F1D3, C1G(5A:5B:6A1:6B3:6B4:6B6), C2(A3:A11:S16), C3A7(A4:B:C:E1:L), C3A10A(4G:5F), C3A12(A4A:A4C:B3:C6) C3A13A3(A4:B1:C:L), C3A13C(1C:2C:3C:9:10D:10F:10H), C3A16, C3C10; **and 81(1),** B(1G:1S:2G:2S).

International Classification:—**A61k. C07d.**

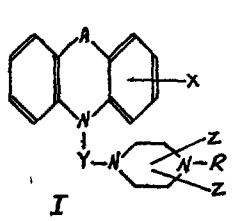
COMPLETE SPECIFICATION

Phenothiazine Derivatives

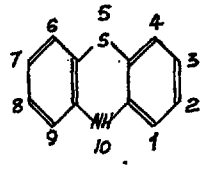
We, SCHERICO LIMITED of Kapellplatz 10, Lucerne 2, Switzerland, a Swiss Company organised and existing under the laws of Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new group of phenothiazyl piperazines, and processes for their manufacture.

The final products of the present invention are represented by formula (I).



I



II



III

wherein A is S, SO or SO_2, X is hydrogen, halogen or lower alkoxy, or lower alkyl, Y^1 is a lower alkylene group; Z is a hydrogen atom or a lower alkyl group, and R is an unsaturated lower alkyl group, or is a lower alkyl group carrying as substituent a hydroxy, acyloxy (other than acetoxy), alkoxy or hydroxyalkoxy group, or is an alicyclic group having less than seven carbon atoms, and their pharmaceutically acceptable acid addition salts. Representative of the group R are allyl, propargyl, butenyl, hydroxy-cyclohexyl, hydroxy-alkyl and esters and ethers of those groups which carry a hydroxy group, e.g. β-hydroxyethyl and its carbamate and carbonate, and ethers such as methyl-, ethyl-, and hydroxyethyl ethers.

The numbering of the atoms in the ring systems present in the compounds of the invention is in conformity with "Chemical Abstracts" and is shown for phenothiazine and piperazine by formulae (II) and (III), respectively.

The compounds of the present invention are characterised by their therapeutically useful effect upon the central nervous system and manifest themselves by exerting a clamping or tranquillizing effect. Thus, in their ability to calm mentally disturbed patients, the restlessness and hyperactivity of the patient are relieved, permitting an improvement in appetite and sleeping habits. Furthermore, along with their general tranquilizing properties, these compounds are useful in allaying anxiety and tension which arise from a myriad of sources, such as gynecologic disorders, dermatologic conditions, environmental pressure, premenstrual tension, dysmenorrhea, and menopause.

In addition to their use in the treatment of nausea and emesis, some of the compounds possess antihistaminic properties whereby they allay allergic disorders of local or systemic nature. Other of the compounds exhibit broad spectrum, antifungal properties.

For the schizophrenic or hyperactive neuropsychiatric patient, it has been found that the preferred compounds of the invention are effective in doses ranging from 150 mg. daily, the average clinical dose being 200 to 250 m.g. daily depending upon the syndrome. For the ambulatory patient showing mild anxiety

[*Price 3s. 6d.*]

or low-grade tension, the preferred compounds of the invention are effective in a dose range of 10 to 100 mg. daily, the average dose being 20 to 60 mg. For the control of emesis, the compounds of this invention exert a depressant effect at doses from 10 to 15 mg. daily.

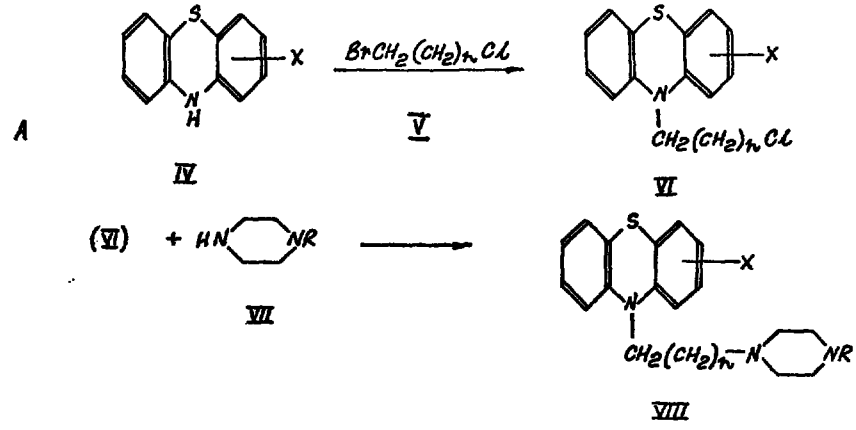
It has been found that, unlike most of the neuropsychiatric drugs in clinical use, the preferred compounds of this invention show few untoward side effects. Among the undesirable side effects which are minimised by the use of the compounds of the present invention are dry mouth, mydriasis, fall in blood pressure, and tachycardia. By virtue of the lowered incidence of these side effects, the compounds of the invention can be used with relative safety in conjunction with barbiturates for preoperative medication for reduction of anxiety.

Although all of the compounds of formula (I) exhibit the aforementioned properties, the strength of such properties quite naturally differs in degree between structures. For chemopsychotherapeutic application we prefer to use compounds of formula (I) in which X is a chlorine atom, A is sulphur, Y is an alkylene group having 3 or 4 carbon atoms, and R is β-hydroxyethyl or an unsaturated alkyl group having 2, 3 or 4 carbon atoms, e.g. allyl, propargyl, or butenyl. Increasing the number of carbon atoms in Y to 5 or 6 produces a decrease in tranquillizing effect and an increase in bactericidal properties.

Since for the most part, compounds of the general formula (I) are insoluble in aqueous media, they are preferably administered in the form of a soluble pharmaceutically acceptable acid addition salt, such as hydrochloride, maleate, tartrate or citrate. The preferred mode of administration is oral by means of tablets or elixirs in conjunction with suitable carriers and other types of pharmaceutical dosage units which lend themselves to such administration. In certain instances where parenteral administration is indicated, the compound in the form of a pharmaceutically acceptable acid addition salt is prepared in sterile solutions or suspensions.

For application as bactericides the compounds are preferably administered in the form of ointments or creams.

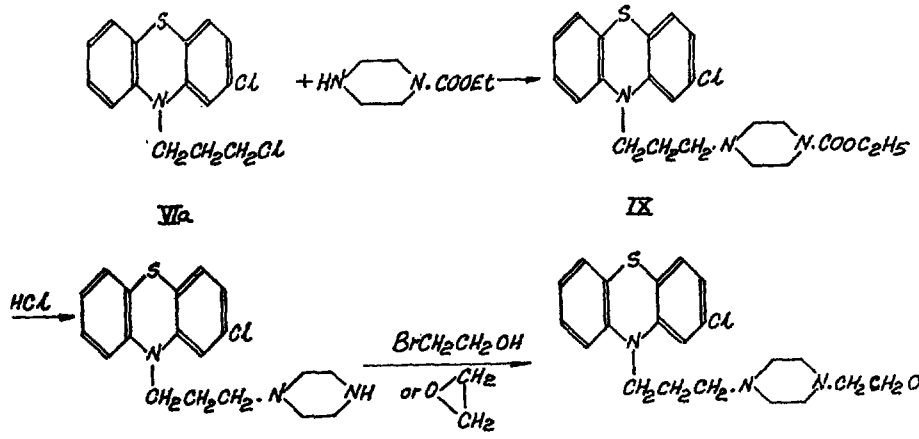
The compounds of the invention are prepared by a number of alternative, but equivalent, alkylation reactions. Equation A sets forth



the preferred reaction sequence wherein a substituted phenothiazine (IV) is alkylated with an α-bromo-ω-chloroalkane (V) whereby a 10-ω-chloroalkylphenothiazine (VI) is produced. Although the intermediate, (VI) may be prepared by heating a mixture of the two reactants in an inert solvent, such as benzene or toluene, it is preferred to employ a basic condensing agent and carry out the reaction in liquid ammonia solvent. Representative of the type of condensing agents which may be used are the amides of sodium, potassium and lithium. The intermediate (VI), is used to alkylate a substituted piperazine (VII), producing the piperazino derivative (VIII) which is a compound falling within the scope of formula (I). Although the alkylation of (VII) by (VI) may be carried out in similar fashion to that described above, i.e. in liquid ammonia and sodamide, the preferred method in this instance is merely to use an excess of the piperazine base to take up the hydrogen chloride formed in the alkylation.

The final piperazine compounds represented by (VIII) are generally obtained as high boiling viscous oils which are readily purified by conversion to one or another acid addition salt, such as the dihydrochloride or di-maleate.

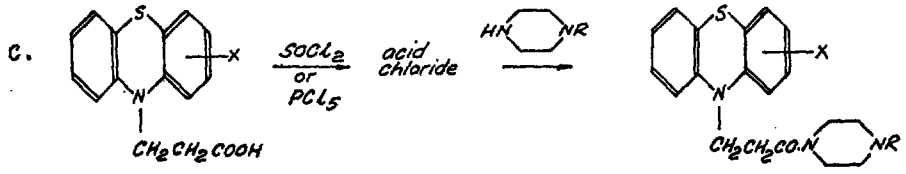
In Equation A, the reactants all contain their respective substituents which appear in the final product equation B

B 

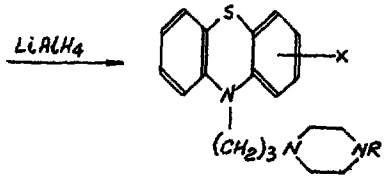
VIa IX

X VIIIa

whereby the substituent R is introduced as the last step, being particularly applicable wherein R represents 2-hydroxyethyl. In this sequence, the chloroalkylphenothiazine is condensed with 1-carbethoxypiperazine and the carbethoxypiperazino compound (IX) so produced is hydrolysed with aqueous acid. The hydrolysis product (X) possessing a secondary amino group is alkylated with bromoethanol or ethylene oxide, yielding (VIIIa). An alternative procedure as shown by Equation C:

C. 

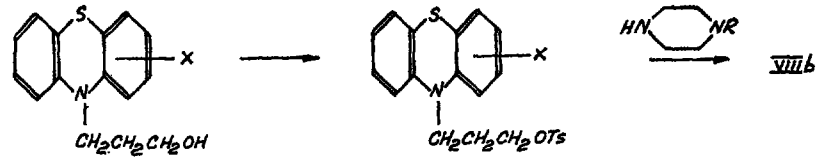
XI XII XIII



VIIIb

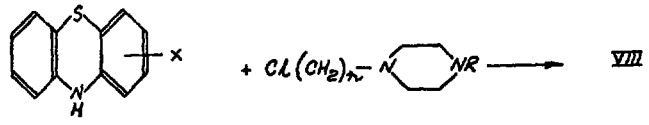
employs a phenothiazylalkanoic acid represented by (XI) as starting material. Conversion of (XI) to its acid chloride, (XII), is effected by means of the usual reagents such as thionyl chloride or phosphorus pentachloride. Condensation of (XII) with a substituted piperazine (VII) forms the intermediate amide (XIII) which is easily reduced to (VIIIb) by means of lithium aluminium hydride in conventional manner.

The compound (VIa) may be condensed with a piperazine in which one NH group is protected by a $COOC_2H_5$ group to give compound (IX) which may then be hydrolysed to give 3-[2-chloro-10-phenothiazyl] - propyl - piperazine (X). This intermediate may then be converted into its 1 - crotanoyl derivative, and the amide carbonyl group may be reduced with lithium - aluminium hydride to yield 1 - (2-butenyl) - 4 - [3 - (2 - chloro - 10 - phenothiazyl) - propyl]piperazine.

D. 

Alternatively as shown in Equation D, a phenothiazyl alkanol represented by (XIV) is converted into its tosylate ester (XV) by means of *p* - toluenesulphonyl chloride. Reaction of (XV) with a substituted piperazine such as (VII) yields (VIIIb).

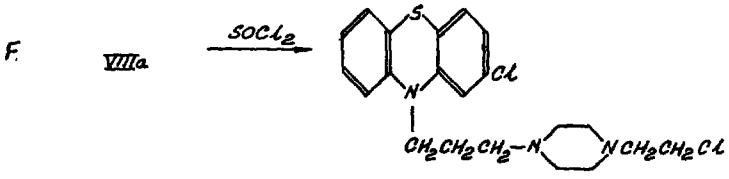
Equations A to D referred to above all relate to the preferred preparation of compounds of formula I wherein a piperazine is alkylated with a phenothiazyl alkyl halide or an equivalent thereof. The converse procedure whereby a phenothiazine is alkylated by a piperazino-alkyl halide or an equivalent thereof also results in the formation of the compounds of formula (I), as exemplified by Equation E.

E. 

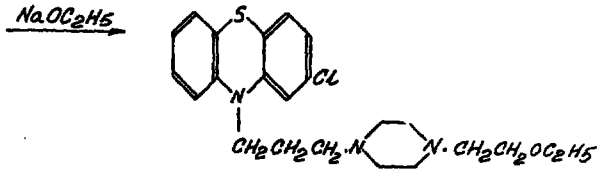
XVI VIII

wherein n is an integer from 1 to 6. In this reaction, a phenothiazine (XVI) is reacted with an ω-halogenated alkyl piperazine (XVII) preferably in liquid ammonia solvent in the presence of a basic condensing agent such as sodamide, yielding the final product (VIII). Although the reaction might proceed without the use of a catalyst, it is preferred to employ the condition set forth in order to obtain a more rapid reaction and higher yield. Specifically, adding a mole of phenothiazine or a substituted phenothiazine to one equivalent of sodamide in liquid ammonia results in the formation of N-sodio-phenothiazine. Alkylation of the sodio derivative in the usual manner with, for example, 1 - allyl - 4 - (3 - chloropropyl) - piperazine, yields 1 - allyl - 4 - [3 - (10 - phenothiazyl) - propyl] piperazine, after work-up according to the above-described procedures. Although other equivalents of the chloride may be employed, such as bromide or tosylate, it is preferred to use the chloride by reason of ease of its preparation and handling.

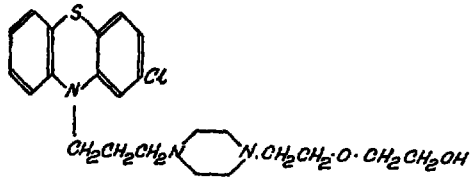
Compounds of formula (I) wherein R represents a lower alkyl group which is further substituted by hydroxy, for example, 2-hydroxyethyl, may be transformed into other members of formula (I) by relatively simple procedures. Equation F:

F 

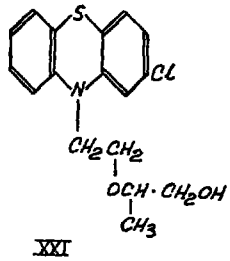
XVIII



XIX



XX

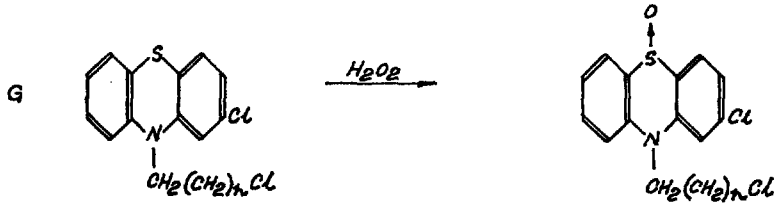


XXI

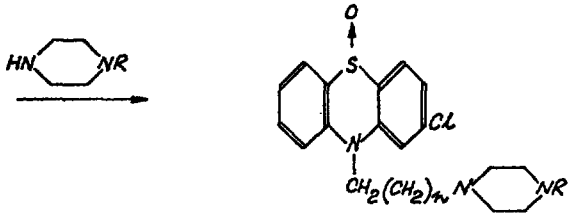
is presented by way of example to show the conversion of (VIIIa) which contains a 2-hydroxyethyl group to an ether derivative, specifically, a compound containing a 2-ethoxyethyl group. The hydroxy group in (VIIIa) is replaced by halogen in the conventional re-

action employing thionyl chloride or phosphorus pentachloride or similar equivalents whereby the 2 - chloroethyl piperazino derivative (XVIII) is formed. Reacting XVIII with a metal alkoxide, in this instance sodium ethoxide, yields 1 - (2 - ethoxyethyl) - 4 - [3-(2 - chloro - 10 - phenothiazyl)-propyl] piperazine (XIX). By substituting in equation F a derivative of a poly-hydroxy alcohol for the sodium alkoxide, for example, the mono-sodio derivative of ethylene glycol or propylene glycol, there are obtained the corresponding derivatives (XX) and (XXI).

In order to prepare the compounds of formula I which contain one or more oxygen atoms attached to the sulphur of the phenothiazine group, it is preferred to introduce the oxygen function at an early stage of the synthesis rather than attempt an oxidation of the final product. For example, in equation G, an appropriate intermediate such as (VI) upon treatment with hydrogen peroxide in ethanol yields the corresponding sulphoxy analogue (XXII):



VI XXII



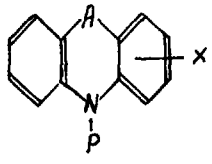
XXIII

Condensation of (XXII) with an appropriately substituted piperazine yields (XXIII) the sulphoxy analogue of (VII).

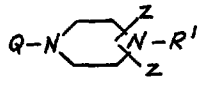
Where a sulphone derivative is desired the intermediate sulphoxy phenothiazine (XXII) is further oxidized by means of agents such as chromic oxide in acetic acid whereupon the sulphone is formed. The sulphone is subject to the same type of transformations as the sulphoxy and other phenothiazines giving rise to analogous compounds possessing the 5,5-dioxido function.

The foregoing, taken with the equations represents methods of synthesis of the compounds of this invention, specific examples being illustrated in certain instances. It is understood, however, that by reacting appropriately substituted materials according to the equations, the analogously substituted products will be obtained. For example, it has been shown that 1 - chloro - 3 - bromopropane can be used in reaction with a phenothiazine to produce a phenothiazyl propyl halide. There may also be employed the dihaloalkanes or cycloalkanes such as 1 - bromo - 4 - chlorobutane, chloro and bromo cyclohexanols. Thus by appropriate substitutions in the equations referred to, the various compounds embraced by formula I can be prepared by methods illustrated in the annexed examples.

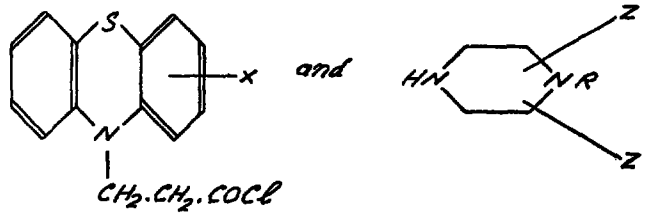
It is evident that reactions A to E fall within the broad class of alkylation. They can be generalised as the interaction of a phenothiazine



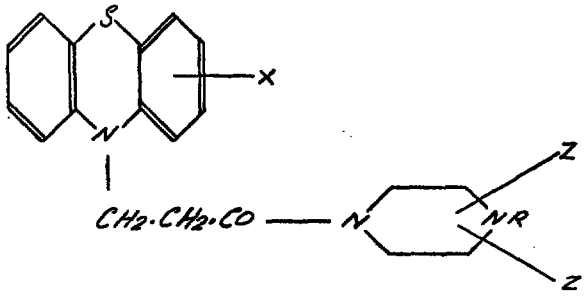
with a piperazine compound



wherein of P and Q one is attached directly to the relevant nitrogen and the other is connected to the relevant nitrogen atom through a divalent group Y^1, R^1 and Y^1 standing for R and Y, respectively, or for groups convertible into R and Y, respectively, P and Q are atoms or groups of opposite polarity capable of being eliminated as the compound PQ in the course of the reaction, preferably in the presence of an acceptor for PQ. For example, P may be Cl and Q may be H, the two reactants being



The reaction product has the formula



and the CO group is reduced to CH_2, e.g. by treatment with lithium aluminium hydride.

The equations B show the production of compound (VIIIa) from 10 - [γ - chloropropyl] - 2 - chlorophenothiazine (VIa) by condensation with 1 - carbethoxypiperazine to give compound (IX) which is hydrolysed to the 1 - piperazinyl - 2 - chlorophenothiazine (X) and then condensed with β - bromoethanol or with ethylene oxide to yield compound VIIIa.

In equations C a β - phenothiazylpropionic acid (XI) is converted into the acid chloride (XII), which is condensed with a 1 - R - piperazine to give a β - phenothiazinylpropionylpiperazine (XIII) which can be reduced with lithium aluminium hydride to compound (VIIIb).

Equation D illustrates the condensation of the p-toluene sulphuric ester (XV) of 10-[γ-hydroxypropyl] - phenothiazine (XIV) with a piperazine to give compound (VIIIb).

In equation E a phenothiazine (XVI) is condensed with 4 - 10 - chloropropylpiperazine (XVII) to give compound (VIII).

Equation F shows the conversion of compound (VIIIa) into the 2 - chloro - 10 - [1-10 - chloropropyl - 4 - piperazinyl - propyl]-phenothiazine (XVIII) and thence into the 1 - β - ethoxyethyl compound (XIX). Compounds (XX) and (XXI) may be obtained in a similar manner.

Throughout the description and claims the word "lower" means "containing less than seven carbon atoms in the molecule".

Example 1

1 - (2 - Hydroxyethyl) - 4 - [3 - (2 - chloro-10 - phenothiazyl)propyl] - piperazine

To a suspension of sodamide (from 3 g. of sodium) in 300 ml. of liquid ammonia, there is added 30 g. of 2 - chlorophenothiazine. After stirring for one hour, 19 g. of 1 - bromo-3 - chloropropane is added. The ammonia is allowed to evaporate and to the residue there is then added 200 ml. of water. The oily layer which separates is extracted with ether. The ether extracts are dried over anhydrous sodium sulfate, filtered and concentrated. 10 - (3-Chloropropyl) - 2 - chlorophenothiazine is obtained in the form of a crude oil.

A mixture of 25 g. of 1 - (2 - hydroxyethyl)-piperazine and 15 g. of the crude 10 - (3-chloropropyl) - 2 - chlorophenothiazine obtained above is heated for 18 hours on a steam bath. The mixture is decomposed by the addition of 200 ml. of water and the aqueous mixture is extracted several times with ether. The ether layer is then extracted with dilute hydrochloric acid. The acid layer is made alkaline with sodium hydroxide solution and the resulting oil is extracted with ether. The ether extracts are dried, concentrated and the residue distilled, yielding the product of this example as an oil having a b.p. of 278—281° C/1.0 mm. The distillate oil crystallizes in the receiver and upon recrystallization from ethyl acetate melts at 100—101°C.

According to the above procedure and using 3 - chlorophenothiazine or 4 - chlorophenothiazine as the starting material, the corresponding isomers are obtained and isolated as the dihydrochlorides according to the procedure of Example 2. Each of the salts crystallizes from alcohol with 1/2 mole of water of crystallization. The dihydrochloride of the 3 - chloro isomer melts at 189—191°C. and the salt of the 4-chloro isomer melts at 180°C.

Example 2

1 - (2 - Hydroxyethyl) - 4[3 - (2 - chloro-10 - phenothiazyl)propyl] - piperazine dihydrochloride

A solution of 10 g. of the free base obtained in Example 1 in 100 ml. of absolute ethanol is treated with a saturated solution of hydrogen

chloride in anhydrous ethanol. Upon the addition of 100 ml. of anhydrous ether, the hydrochloride of this example is obtained, purified by recrystallization from ethanol, and recovered in the form of white crystals, m.p. 222—223° C.

The dimaleate salt is prepared by adding an excess of maleic acid in isopropyl acetate to a solution of 1 - (2 - hydroxyethyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl]piperazine in isopropyl acetate, m.p. 179—180°C.

EXAMPLE 3

1-(2-Hydroxyethyl)-4-[3-(10-phenothiazyl)-propyl]piperazine

The product of this example is prepared from the condensation of 8 g. of 10 - (3-chloropropyl) phenothiazine with 9 g. of 1-(2 - hydroxyethyl) piperazine according to the procedure described in Example 1. A yield of 8 g. of the product in the form of a white solid is obtained m.p. 98—99°C. following recrystallization from hexane.

The dihydrochloride of the compound of this example is prepared by the procedure described in Example 2; m.p. 223—225°C. following recrystallization from ethanol. The salt contains 1 mole of water of crystallization.

EXAMPLE 4

1-(2-Hydroxyethoxyethyl)-4-[3-(10-phenothiazyl)propyl]piperazine 1-(2-chloroethyl)-4-[3-(10-phenothiazyl) propyl]piperazine:

To a solution of 19 g. of 1 - (2 - hydroxylethyl) - 4 - [3-(10-phenothiazyl) propyl]piperazine in 250 ml. of anhydrous benzene there is added 9 g. of purified thionyl chloride in 25 ml. of benzene while cooling in an ice bath. The mixture is stirred at room temperature for three hours and made basic with dilute sodium hydroxide solution, keeping the temperature below 5°C. The benzene layer is separated, the aqueous layer extracted with ether, the benzene and ether layers then combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The material is sufficiently pure for use in the following reaction.

The crude 1 - (2 - chloroethyl) - 4 - [3-(10-phenothiazyl) propyl]piperazine in 50 ml. of anhydrous benzene is added to a stirred solution of 1.15 g. of sodium in 80 g. of ethylene glycol. The reaction mixture is heated on a steam bath for two hours, allowing the benzene to distill, and then stirred for 18 hours at room temperature. The reaction mixture is treated with 100 ml. of water, extracted with benzene and the benzene layer extracted with dilute hydrochloric acid. The acid layer is made basic with dilute sodium hydroxide, the resulting oil extracted with ether and benzene, and the combined ether and benzene layers dried and concentrated. The crude oil is dissolved in ethyl acetate, and to it is added an excess of maleic acid in ethyl acetate. The dimaleate crystallizes as a white solid, melting point 152—154°C. after a recrystallization from ethanol-ether.

EXAMPLE 5

1-(2-Hydroxypropyl)-4-[3-(10-phenothiazyl) propyl]piperazine

The product of this example is prepared from the condensation of 25 g. of 10-(3-chloropropyl) phenothiazine and 27.5 g. of 1 - (2-hydroxypropyl) piperazine according to the procedure described in Example 1. There is obtained 28 g. of the above-entitled base as a colorless solid, m.p. 92—93° after recrystallization from hexane.

The dihydrochloride of the compound of this example is prepared by the procedure described in Example 2; m.p. 254—255°C. after several recrystallizations from ethanol.

In the foregoing procedure, substituting 2-chloro - 10 - (3 - chloropropyl)phenothiazine yields the corresponding 2 - chloro analog, b.p. 270—275°C./1.0 mm., m.p. 90—92°C. from ethyl acetate, dihydrochloride m.p. 253—254°C. from ethanol.

EXAMPLE 6

1-[2-(2-hydroxyethoxy)-propyl]-4-[3-(10-phenothiazyl)propyl]-piperazine

The requisite intermediate, 1 - (2 - chloropropyl) - 4 - [3 - (10 - phenothiazyl) propyl]-piperazine is prepared from 15 g. of 1 - (2-hydroxypropyl) - 4 - [3 - (10 - phenothiazyl)-propyl]piperazine and 8 g. of thionyl chloride according to the procedure described in Example 4. The condensation of this crude intermediate with a solution of 0.92 g. of sodium in 75 g. of ethylene glycol was carried out in the same manner as in Example 4. The compound of this example is isolated as the dihydrochloride employing the procedure described in Example 2, m.p. 242—243°C. after recrystallization from ethanol-ether.

EXAMPLE 7

1 - (2 - Hydroxyethyl) - 4 - [3 - (2 - methyl-10 - phenothiazyl)propyl]piperazine

The requisite intermediate, 10 - (3 - chloropropyl) - 2 - methyl phenothiazine is prepared by the alkylation of 21.3 g. of 2 - methyl phenothiazine with sodamide (from 2.5 g. of sodium) and 16 g. of 1 - chloro - 3 - bromopropane according to the procedure of Example 1. The crude oil thus obtained is condensed with 26 g. of 1 - (2 - hydroxyethyl) piperazine in the manner described in Example 1 yielding the compound of this example, b.p. 268—274°C./1.5 mm.

The dihydrochloride prepared as in preceding examples is recrystallized from ethanol, m.p. 246—248°C.

Alternatively, the compound of this example is prepared as follows: A suspension of 115 g. of 2-methylphenothiazine in 200 ml. of acrylonitrile is cooled to −50°C. in an acetone-dry ice bath. To the mixture is added 5 ml. of a 40% alcoholic solution of choline and the mixture is allowed to come to room temperature. The mixture is heated on a steam bath for one hour and poured into 5 l. of acetone whereupon the nitrile crystallizes. Hydrolysis of the nitrile

is effected by refluxing with 10% aqueous alcoholic sodium hydroxide followed by acidification yielding β - (2 - methyl - 10 - phenothiazyl) propionic acid. The acid so obtained is converted in ether solution to the acid chloride by treatment with thionyl chloride and pyridine. The acid chloride is purified by recrystallization from petroleum ether.

A mixture of 10 g. of β - (2 - methyl - 10-phenothiazyl)-propionyl chloride and 30 g. of 1 - (2 - hydroxyethyl)piperazine is stirred and heated on a steam bath for 16 hours. The mixture is treated with water, the oil extracted with chloroform and the chloroform layer extracted with dilute hydrochloric acid. The acid extracts are made basic with dilute sodium hydroxide and the oil extracted with chloroform. Concentration of the chloroform layer gives a viscous oil which solidifies upon trituration with petroleum ether, yielding 1 - (2-hydroxyethyl) - 4 - [β - (2 - methyl - 10-phenothiazyl) - propionyl]piperazine.

Reduction of the above obtained intermediate is carried out as follows:

To a solution of 2 g. of lithium aluminum hydride in 100 ml. of anhydrous ether there is added over one hour a solution of 12 g. of 1 - (2 - hydroxyethyl) - 4 - [β - (2 - methyl-10 - phenothiazyl) - propionyl] - piperazine in 65 ml. of anhydrous tetrahydrofuran. The reaction mixture is refluxed for eight hours and decomposed with a minimum of water containing a small amount of sodium hydroxide. The mixture is filtered, the filtrate dried over sodium sulfate and concentrated *in vacuo* and crystallized.

EXAMPLE 8

1 - (2 - Ethoxyethyl) - 4 - [3 - (2 - chloro - 10 - phenothiazyl)propyl] - piperazine.

The requisite intermediate, 1 - (2 - chloroethyl) - 4 - [3 - (2 - chloro - 10 - phenothiazyl)propyl] piperazine is prepared as in Example 4, and reacted with sodium ethoxide solution (from 1.15 g. of sodium and 100 ml. of absolute ethanol). The compound of this example is obtained as a yellow viscous oil, b.p. 265—270°C./1.0 mm., dihydrochloride m.p. 221—223°C. from ethanol.

By substituting sodium methoxide solution for sodium ethoxide in the foregoing procedure there is obtained 1 - (2 - methoxyethyl)-4-[3-(2 - chloro - 10 - phenothiazyl) - propyl]-piperazine; b.p. 260—265°C./1.0 mm., dihydrochloride m.p. 239—240°C. from ethanol.

An alternative procedure for preparing the compound of this example is as follows:

The requisite intermediate, 1 - (2 - ethoxyethyl) - 4 - (3 - hydroxypropyl) piperazine is prepared by heating a mixture of 33 g. of 1-(2 - ethoxyethyl) piperazine and 10 g. of 3-chloropropanol on a steam bath for eight hours with stirring. The reaction mixture is treated with water, saturated with potassium carbonate and extracted with ether. The ether extracts are dried, concentrated and the residue fractionated, b.p. 132—136°C./4.0 mm.

To a solution of 21.6 g. of the piperazine compound prepared above in 200 ml. of anhydrous benzene there is added 15 g. of thionyl chloride, keeping the temperature at 10°C. during the addition. The reaction mixture is refluxed for four hours, cooled and the hygroscopic hydrochloride filtered rapidly and washed with benzene. The crude salt is suspended in 150 ml. of dry toluene and ammonia gas is bubbled through the mixture with cooling. The inorganic salts are filtered and the toluene solution of 1 - (3 - chloropropyl) - 4-(2 - ethoxyethyl)piperazine is used in the following step.

To a suspension of sodamide (from 2.5 g. of sodium) in 200 ml. of dry toluene there is added 21 g. of 2 - chlorophenothiazine. After refluxing for one hour, the mixture is cooled and the toluene solution of 1 - (3 - chloropropyl) - 4 - (2 - ethoxyethyl) - piperazine is added dropwise. After the addition is complete, the reaction mixture is refluxed and stirred for eight hours, decomposed with water and the organic layer extracted with 200 ml. of 48% hydrobromic acid.

The acid layer is separated, cooled and made basic with dilute sodium hydroxide solution. The oil is extracted with ether, dried, concentrated and the residual oil distilled.

EXAMPLE 9

1-(2-Hydroxyethyl)-4-[3-(2-chloro-10-phenothiazyl)propyl]2,5-dimethyl piperazine

The requisite intermediate 1 - (2 - hydroxyethyl) - 2,5 - dimethyl piperazine, (prepared from 2,5 - dimethylpiperazine and ethylene oxide; b.p. 132—136°C./10 mm.), is condensed in the amount of 30 g. with 15 g. of crude 10 - (3 - chloropropyl) - 2 - chlorophenothiazine as in Example 1. There is obtained a glassy oil, b.p. 275—279°C./0.5 mm.

The di-hydrochloride prepared as in Example 2 is a white crystalline solid, m.p. 270—271°C. from methanol.

EXAMPLE 10.

1-(2-Hydroxyethyl)-4-[3-(2-methoxy-10-phenothiazyl)propyl]piperazine

The requisite intermediate, 10 - (3 - chloropropyl)-2-methoxy - phenothiazine, is prepared as in Example 1 by the alkylation of 22.9 g. of 2-methoxyphenothiazine with 16 g. of 1-chloro-3-bromopropane and sodamide (from 2.5 g. of sodium) in liquid ammonia. The crude oil thus obtained is condensed with 26 g. of 1 - (2 - hydroxyethyl)piperazine according to Example 1. The compound of this example is a glassy oil, b.p. 280—282°C./0.5 mm.

EXAMPLE 11

1-(4-Hydroxybutyl)-4-[3-(2-chloro-10-phenothiazyl)propyl]-piperazine

This compound is prepared by the condensation of 15.5 g. of crude 10 - (3 - chloropropyl)-2 - chlorophenothiazine and 20 g. of 1 - (4-

hydroxybutyl)piperazine, according to Example 1. The crude product of this example is isolated as the dihydrochloride by treatment with ethanolic hydrogen chloride as in Example 2, m.p. 217—218°C. from ethanol.

EXAMPLE 12

1-[2-(5-Hydroxypentyloxy)-ethyl]-4-[3-(10-phenothiazyl)propyl]-piperazine

A mixture of 27.5 g. of 10-(3-chloropropyl)-phenothiazine and 22 g. of 1-[2-(5-hydroxypentoxy)ethyl]piperazine is heated on a steam bath for 18 hours and treated as in Example 1. The compound of this example is obtained as a glassy oil, b.p. 265—270°C./1.0 mm.

EXAMPLE 13

1-(2-Hydroxyethyl)-4-[2-(10-phenothiazyl)-ethyl]piperazine

A mixture of 27 g. of 10 - (2 - chloroethyl) phenothiazine and 26 g. of 1 - (2-hydroxyethyl)piperazine is reacted according to the procedure described as in Example 1. The compound of this example is obtained as a pale yellow, viscous oil, b.p. 240—244°C./2.0 mm.

In similar fashion by employing 10 - (2-chloroethyl) - 2 - chlorophenothiazine, the corresponding chloro analog is obtained, m.p. dihydrochloride 201°C. from ethanol.

EXAMPLE 14

1-(2-Hydroxycyclohexyl)-4-[3-(2-chloro-10-phenothiazyl)propyl]piperazine

A mixture of 15.5 g. of crude 10-(3-chloropropyl)-2-chlorophenothiazine and 20 g. of 1-(2-hydroxycyclohexyl)piperazine is reacted as in Example 1. The compound of this example is obtained in the form of a glassy oil, which crystallizes on cooling, m.p. 135—136°C. from ethyl acetate, dihydrochloride m.p. 265—266°C.

EXAMPLE 15

1-(2-Hydroxyethyl)-4-[3-(5,5-dioxido-10-phenothiazyl)propyl]piperazine

The requisite intermediate 10-(3-chloropropyl)phenothiazine dioxide is prepared by the alkylation of 23 g. of phenothiazine 5-dioxide with sodamide (from 2.5 g. of sodium) and 16 g. of 1 - chloro - 3 - bromopropane according to the procedure described in Example 1.

The crude chloride thus obtained is condensed with 26 g. of 1 - (2 - hydroxyethyl)-piperazine as in Example 1. The product of this example forms a crystalline dimaleate when treated in ethyl acetate according to the method described for forming the dimaleate salt in Example 4.

EXAMPLE 16

1-(2-Hydroxyethyl)-4-[3-(2-chloro-5-oxido-10-phenothiazyl)propyl]piperazine

The requisite intermediate, 2-chloro-10-(3-chloropropyl)-phenothiazine-5-oxide is prepared in the following manner: A solution of 34 g. of 2 - chloro - 10 - (3 - chloropropyl)-phenothiazine in 1300 ml. of alcohol is stirred and warmed while 125 ml. of 25% aqueous hydrogen peroxide is added dropwise. The reaction mixture is allowed to stand two days and the alcohol is removed *in vacuo*. The residue is recrystallized from ethanol yielding 2 - chloro - 10 - (3 - chloropropyl) - phenothiazine - 5 - oxide, m.p. 106—107°C.

A mixture of 9.5 g. of the oxide so obtained above is heated with 25 g. of 1 - (2 - hydroxyethyl)piperazine and treated according to Example 1.

Instead of distilling the base it is obtained as a crystalline mass which is purified by recrystallization from ethyl acetate, m.p. 144—145°C.

The base upon conversion to its dimaleate salt melts at 174—175°C. after recrystallization from ethanol.

EXAMPLE 17

1 - Allyl - 4 - [3 - (2 - chloro - 10 - phenothiazyl) - propyl]piperazine

A mixture of 20 g. of 10 - (3 - chloropropyl) - 2 - chlorophenothiazine and 18 g. of 1 - allylpiperazine is stirred and heated on a steam for 18 hours. The reaction mixture is diluted with water, and the oil which separates is extracted with ether. The ether extracts are extracted with dilute hydrochloric acid. The aqueous acid solution is made alkaline with sodium hydroxide solution and the resultant mixture extracted with ether. The ether extracts are dried and concentrated to a residue yielding the compound of this example.

The free base obtained above is converted into its dihydrochloride salt according to the procedure of Example 2. The dihydrochloride separates as white crystals and after filtration is purified by recrystallization from ethanol; m.p. 248—248.5°C.

EXAMPLE 18

1-Propargyl-4-[3-(2-chloro-10-phenothiazyl)-propyl]piperazine

The requisite intermediate 1 - (2-propynyl) - piperazine is prepared as follows: A solution of 86 g. of anhydrous piperazine, 60 g. of propargyl bromide and 60 ml. of absolute ethanol is refluxed for 20 hours. The solvent is removed *in vacuo* and the residue is dissolved in 200 ml. of water and the solution so formed is saturated with solid potassium carbonate. The resultant mixture is extracted with ether, the extracts are dried and distilled collecting the fraction; b.p. at 82—90°C./7.0 mm. The substituted piperazine so obtained crystallizes in the receiver; m.p. 53—54°C.

A mixture of 17.5 g. of 1 - propargyl-piperazine, 33 g. of 10 - (3 - chloropropyl) - 2-chlorophenothiazine and 14 g. of anhydrous sodium carbonate is stirred and heated on a steam bath for 20 hours. The mixture is diluted with water and the oil which separates is extracted with ether. The combined ether extracts are extracted with dilute hydrochloric acid. The acid solution is made alkaline with sodium hydroxide solution and the resultant mixture is extracted with ether. The ether ex-

tracts are dried and concentrated and a residue is converted to the dihydrochloride salt as described in Example 2; m.p. 211—212°C. Analysis indicates that the salt crystallizes with 0.5 mole of water of crystallization.

By condensing 1 - propargyl - piperazine with 10 - (4 - chlorobutyl) - 2 - methoxyphenothiazine in similar manner to that described there is obtained the dihydrochloride of 1 - propargyl - 4 - [4 - (2 - methoxy - 10-phenothiazyl) - butyl]piperazine.

EXAMPLE 19

1-(2-Butenyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

The requisite intermediate 1 - crotonoyl-4-[3 - (2 - chloro - 10 - phenothiazyl) - propyl]-piperazine is prepared as follows:

To a solution of 36 g. of 4 - [3 - (2 - chloro-10 - phenothiazyl) - propyl]piperazine, b.p. 262—264°C./1 mm., prepared in a conventional manner from 2 - chloro - 10 - (3-chloropropyl) - phenothiazine and excess anhydrous piperazine and 300 ml. of anhydrous benzene is added 11 g. of crotonoyl chloride. The reaction mixture is stirred and refluxed for 18 hours and extracted with dilute sodium carbonate solution. The benzene layer is dried and concentrated *in vacuo* and the residue is distilled yielding the crotonoyl derivative; b.p. 280—285°C./1.0 mm.

A solution of 40 g. of the crotonoyl derivative obtained above in 200 ml. of anhydrous ether is added to a suspension of 8 g. of lithium aluminum hydride in 600 ml. of anhydrous ether. The reaction mixture is stirred and refluxed for 10 hours and the excess hydride is destroyed by adding a minimum quantity of water. The lithium and aluminum hydroxides so formed are removed by filtration and the ether solution is concentrated to a residue which is purified by distillation; b.p. 272—276°C./1.5 mm.

In the foregoing illustration, by starting with an equivalent quantity of 2 - methyl piperazine or 2,5 - dimethyl - piperazine, there is ultimately obtained 1 - (2 - butenyl) - 4 - [3-(2 - chloro - 10 - phenothiazyl) - propyl] - 2 (or 3) methyl piperazine, b.p. 275—280°C./1 mm. or 1 - (2 - butenyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl] - 2,5-dimethyl piperazine, b.p. 285—290°C./1 mm. The position of the methyl group in the mono methyl derivative has not been determined.

The free base so obtained is converted into its dihydrochloride according to the procedure described in Example 2.

EXAMPLE 20

1-(2-methylallyl)-3-[3-(2-chloro-10-phenothiazyl)-propyl] piperazine

The requisite intermediate 1 - (2 - methylallyl) - piperazine is prepared as follows: To a mixture of 1 mole of 1 - carbethoxy - piperazine, 3 moles of sodium bicarbonate and 300 ml. of 95% ethanol to all of which is added 1.2 moles of 3 - chloro - 2 - methyl - propene and the resultant mixture stirred and heated at 40—50°C. for 5 hours. The alcohol is removed by distillation and one liter of water is added. The mixture is saturated with potassium carbonate and extracted with ether, the ether extracts being dried and concentrated. The residue obtained from the ether solution is refluxed with 500 ml. of concentrated hydrochloric acid for 40 hours. The resultant solution is concentrated to a dryness, the residue dissolved in water, the aqueous solution saturated with potassium carbonate and thoroughly extracted with ether. The ether extracts are dried and concentrated and the residue obtained therefrom is distilled, yielding 1 - (2-methyl - allyl) - piperazine; b.p. 115—118°C./6.5 mm.

A mixture of 31 g. of 10 - (3 - chloropropyl) - 2 - chloro - phenothiazine and 28 g. of 1 - (2 - methylallyl) - piperazine are stirred and heated on a steam bath for 18 hours. The reaction mixture is processed according to the analogous procedure of Example 1, yielding the free base of this example; b.p. 261—264 C./0.5 mm. The free base so obtained is converted to its dihydrochloride with ethanolic hydrogen chloride as heretofore described, m.p. 234—235°C., from ethanol.

EXAMPLE 21

1-(3-methyl-2-butenyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

The requisite intermediate 1 - (3 - methyl-2 - butenyl) - piperazine is prepared according to the analogous procedure of Example 20 whereupon 1 - carbethoxypiperazine is alkylated with 1 - chloro - 3 - methylbutene - 2 in the presence of sodium bicarbonate with hydrolysis of the carbethoxy group occurring in the presence of hydrochloric acid; b.p. 110—112°C./5 mm.

By reacting 31 g. of 10 - (3 - chloropropyl)-2 - chlorophenothiazine and 31 g. of 1 - (3-methyl - 2 - butenyl)piperazine according to the procedure of Example 1, the free base of this example is obtained as a viscous oil; b.p. 267—270°C./1.0 mm.

EXAMPLE 22

1 - Allyl - 4 - [2 - (2 - chloro - 10 - phenothiazyl) - ethyl] - piperazine

From the reaction of 20 grams of 10-(2-chloroethyl) - 2 - chlorophenothiazine and 18 grams of 1 - allylpiperazine according to the procedure described in Example 1, there is obtained the free base of this example as a viscous oil. Purification and derivatization is effected by dissolving the oily free base in isopropropyl acetate and adding two equivalents of maleic acid whereby the crystalline dimaleate salt is obtained and is purified by recrystallization from isopropyl acetate.

EXAMPLE 23

1 - Propargyl - 4 - [5 - (2 - methyl - 10-phenothiazyl)-pentyl]-piperazine

The requisite intermediate 2 - methyl - 10-(5 - chloropentyl) - phenothiazine is prepared

from the reaction of 2 - methylphenothiazine and 1 - bromo - 5 - chloropentane according to the analogous procedure described in Example 1.

From the reaction of 17.5 grams of 1-propargyl - piperazine and 35 grams of 10-(5 - chloropentyl) - 2 - methylphenothiazine according to the procedure described in Example 1, the free base of this example is obtained and is purified by conversion to its dihydrochloride salt.

EXAMPLE 24

1-(2-butenyl)-4-[3-(2-methoxy-10-phenothiazyl)-propyl] piperazine

The requisite intermediate 2-methoxy-10-(3-chloro-propyl)-phenothiazine is prepared by substituting an equivalent quantity of 2-methoxyphenothiazine for the 2-chlorophenothiazine in Example 1. Reaction of the intermediate so obtained with 1 - crotonoyl - piperazine followed by reduction with lithium aluminum hydride as described in Example 19 yields the compound of this example. Purification is preferably effected by conversion to the dihydrochloride salt followed by recrystallization.

EXAMPLE 25

1-Allyl-4-[3-(2-bromo-10-phenothiazyl)-propyl]-piperazine

By substituting an equivalent quantity of 2 - bromo phenothiazine in Example 1 and following the process of Example 17.

EXAMPLE 26

1-Allyl-4-[3-(2-chloro-5,5-dioxido-10-phenothiazyl)-propyl]-piperazine

2 - Chloro - 10 - (3 - chloropropyl) - phenothiazine - 5 - dioxide prepared by alkylating 25 g. of 2 - chlorophenothiazine - 5 - dioxide with sodamide and 16 g. of 1 - chloro - 3-bromopropane is condensed with 1 - allylpiperazine.

EXAMPLE 27

1-Allyl-4-[3-(2-chloro-5-oxido-10-phenothiazyl)-propyl]piperazine

20 g. of 2 - chloro - 10 - (3 - chloropropyl)-5 - oxido - phenothiazine (Example 16) is heated with 17 g. of 1 - allylpiperazine yielding the free base of this example.

EXAMPLE 28

1-(2-hydroxyethyl)-[3-(2-fluoro-10-phenothiazyl)-propyl]piperazine

By substituting 2 - fluorophenothiazine in the procedure of Example 1, the above fluoro compound is obtained, b.p. 272-275°C./1 mm; m.p. 52—55°C. from ethyl acetate-hexane; dihydrochloride, m.p. 237—238°C. from methanol.

EXAMPLE 29

1-(2-hydroxyethyl)-4-[3-(2-bromo-10-phenothiazyl)propyl]-piperazine

By substituting an equivalent quantity of 2-bromophenothiazine in the procedure of Example 1, the compound of this example is obtained, b.p. 282—284°C./1.0 mm., dihydrochloride m.p. 224—225.5°C. from ethanol.

EXAMPLE 30

1-(2-propoxyethyl)-4-[3-(2-chloro-10-phenothiazyl)propyl]piperazine

A mixture of 10 g. of the base of Example 1, 50 ml. of propionate anhydride and 5 g. of powdered sodium propionate is heated with stirring for 16 hours on a steam bath. The mixture is poured into 500 ml. of ice water, made alkaline with sodium bicarbonate and the oil which separates is extracted with ether. The ether extracts are dried, concentrated and the residue consisting of the free base of this example is converted to its dihydrochloride as in Example 2, m.p. 223—225°C.

Similarly, butyric anhydride and sodium butyrate afford the butyryl ester, m.p. of dihydrochloride, 221—222°C. from ethanol.

EXAMPLE 31

1-(2-ethyl carbonate ester of hydroxyethyl)-4-[3-(2-chloro-10-phenothiazyl)propyl]-piperazine

A mixture of 1.3 g. of powdered sodium, 20 g. of the base of Example 1 and 150 ml. of toluene is refluxed for two hours. The reaction mixture is cooled in an ice bath and 7 g. of ethyl chlorocarbonate is added dropwise. The mixture is refluxed and stirred for 6 hours, cooled and diluted with water. The toluene layer is separated, dried and concentrated. The crude viscous oil consisting of the basic ester of this example is converted to its dimaleate in ethyl acetate, m.p. 168—169°C. from ethanol.

EXAMPLE 32

1-(2-dimethylcarbamoylethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

By substituting dimethylcarbamoyl chloride for ethyl chlorocarbonate in Example 31, the free base of this example is obtained, m.p. dihydrochloride 227—228°C. from ethanol.

EXAMPLE 33

1-(2-carbamoyl ethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

To a stirred solution of 40 g. of the base of Example 1 in 50 ml. of dry pyridine, there is added dropwise 17.2 g. of phenyl chlorocarbonate keeping the temperature at 25—30°C. The reaction mixture is stirred for sixteen hours, diluted with water and the oil extracted with chloroform. The chloroform extracts are washed with water, dried over sodium sulfate and concentrated. The crude basic ester (dihydrochloride, m.p. 209—210°C. (95% ethanol)) is dissolved in 100 ml. of anhydrous ether and added dropwise to 600 ml. of liquid ammonia in an insulated flask. The reaction mixture is stirred for twenty hours, the ammonia allowed to evaporate and water added. The oil is extracted with ether, the ether extracts washed with dilute sodium carbonate solution, dried and concentrated. The carbamate ester is recrystallized from benzene-petroleum ether, m.p. 88—89°C., dihydro-

chloride m.p. 227—228°C. from alcohol.

EXAMPLE 34

1-(3-Hydroxypropyl)-4-[3-(10-phenothiazyl)-propyl]-piperazine

The *p*-toluenesulfonic acid ester of 3-(10-phenothiazyl)-propanol is first prepared by treating 26 g. of the substituted propanol in 200 ml. of chloroform and 8 g. of pyridine with 20 g. of *p*-toluene sulfonyl chloride, keeping the temperature below 20°C. The pyridine hydrochloride is removed by filtration and the filtrate concentrated to a residue *in vacuo*. The crude *p*-toluene sulfonic acid ester is used in the next step.

A mixture of 41 g. of the crude ester and 30 g. of 1-(3-hydroxypropyl) piperazine is stirred and heated on the steam bath for sixteen hours. The reaction mixture is decomposed with water, the oil extracted with chloroform and the chloroform layer extracted with dilute hydrochloric acid. The acid layer is separated, made basic with dilute sodium hydroxide solution and the oil extracted with chloroform.

The chloroform extracts are dried, concentrated and the residual oil distilled, yielding the base of this example, b.p. 241—246°C./0.5 mm.

EXAMPLE 35

1-(2-Hydroxypropyl)-4-[3-(2-methoxy-10-phenothiazyl)-propyl]-piperazine

To a suspension of sodamide (from 2.5 g. of sodium) in 300 ml. of liquid ammonia there is added 22.9 g. of 2-methoxy-phenothiazine. After stirring for ten minutes, 18 g. of 1-bromo - 3 - chloropropane is added dropwise and the ammonia is allowed to evaporate. The reaction mixture is decomposed with water, the oil extracted with ether, dried and concentrated. The crude 10 - (3 - chloropropyl)-2-methoxyphenothiazine is heated with 35 g. of 1 - carbethoxypiperazine on a steam bath for sixteen hours. The mixture is decomposed with water, the oil extracted with ether, dried and concentrated. The crude 1 - carbethoxy - 4-[3 - (2 - methoxy - 10 - phenothiazyl) propyl] piperazine so obtained is dissolved in 600 ml. of absolute ethanol containing 30 g. of potassium hydroxide and refluxed for 16 hours. The ethanol is removed *in vacuo*, the residue treated with water and the oil extracted with ether; the ether solution is dried and concentrated and the residue distilled, b.p. 264—268°C./1.0 mm. A solution of 35.5 g. of 4-[3 - (2 - methoxy - 10 - phenothiazyl) propyl] piperazine, thus obtained, in 200 ml. of methanol is treated with 20 g. of propylene oxide with cooling. After refluxing for six hours, the methanol is removed *in vacuo*, the residue treated with water and the oil extracted with ether and dried. Concentration of the ethereal extracts give the compound of this example, b.p. 278—282°C./0.5 mm.

EXAMPLE 36

1-(2-Hydroxyethoxyethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

By substituting 1 - (2 - hydroxyethyl)-4-[3 - (2 - chloro - 10 - phenothiazyl) propyl] piperazine from example 1 in the procedure of Example 4, the compound of this example is obtained; dihydrochloride, m.p. 206—207°C. from ethanol.

By employing procedures set forth in the preceding examples, the following compounds are prepared:

1, 1 - (2-(2 - hydroxypropoxy)ethyl - 4[3-(10 - phenothiazyl) propyl] piperazine; dihydrochloride, m.p. 202—203°C. from ethanol.

2. 1 - (3 - hydroxypropyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl] piperazine m.p. 104—105°C. from ethyl acetate; dihydrochloride, m.p. 233—234°C. from ethanol.

3. 1 - (2 - hydroxyethyl) - 2(or 3)-methyl-4 - [3 - (2 - chloro - 10 - phenothiazyl)-propyl] - piperazine; dihydrochloride m.p. 227—228°C. from ethanol.

4. 1 - (2 - hydroxyethyl) - 4 - [2 - (2-chloro - 10 - phenothiazyl) - propyl] - piperazine; dimaleate . 1/2 H_2O, m.p. 139—140° C. from ethanol.

5. 1 - (2,3 - dihydroxypropyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl] - piperazine; dihydrochloride, m.p. 225—226°C. from methanol.

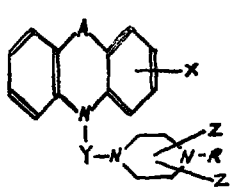
6. 1 - (2 - hydroxy - 3 - isopropoxypropyl)-4 - [3 - (2 - chloro - 10 - phenothiazyl)-propyl] - piperazine, dihydrochloride - 1/2 H_2O, m.p. 222—223°C. from ethanol.

7. 1 - (2 - hydroxyethyl) - 4 - [4 - (2-chloro - 10 - phenothiazyl) - butyl] - piperazine, b.p. 280—290°C./1 mm.; dihydrochloride, m.p. 227—228°C. from methanol.

8. 1 - (2 - hydroxyethyl) - 4 - [5 - (2-chloro - 10 - phenothiazyl) - pentyl] - piperazine; dihydrochloride, m.p. 212—213°C. from ethanol.

WHAT WE CLAIM IS:—

1. A process for the manufacture of basic compounds having the formula



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wherein A is S, SO or SO_2; X is hydrogen, halogen, lower alkoxy or lower alkyl; Y is a lower alkylene group; Z is H or lower alkyl; and R is an unsaturated lower alkyl or a hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl or acyloxyalkyl group, or is an alicyclic group having less than seven carbon atoms and their

chloride m.p. 227—228°C. from alcohol.

EXAMPLE 34

1-(3-Hydroxypropyl)-4-[3-(10-phenothiazyl)-propyl]-piperazine

The *p*-toluenesulfonic acid ester of 3-(10-phenothiazyl)-propanol is first prepared by treating 26 g. of the substituted propanol in 200 ml. of chloroform and 8 g. of pyridine with 20 g. of *p*-toluene sulfonyl chloride, keeping the temperature below 20°C. The pyridine hydrochloride is removed by filtration and the filtrate concentrated to a residue *in vacuo*. The crude *p*-toluene sulfonic acid ester is used in the next step.

A mixture of 41 g. of the crude ester and 30 g. of 1-(3-hydroxypropyl) piperazine is stirred and heated on the steam bath for sixteen hours. The reaction mixture is decomposed with water, the oil extracted with chloroform and the chloroform layer extracted with dilute hydrochloric acid. The acid layer is separated, made basic with dilute sodium hydroxide solution and the oil extracted with chloroform.

The chloroform extracts are dried, concentrated and the residual oil distilled, yielding the base of this example, b.p. 241—246°C./0.5 mm.

EXAMPLE 35

1-(2-Hydroxypropyl)-4-[3-(2-methoxy-10-phenothiazyl)-propyl]-piperazine

To a suspension of sodamide (from 2.5 g. of sodium) in 300 ml. of liquid ammonia there is added 22.9 g. of 2-methoxy-phenothiazine. After stirring for ten minutes, 18 g. of 1-bromo - 3 - chloropropane is added dropwise and the ammonia is allowed to evaporate. The reaction mixture is decomposed with water, the oil extracted with ether, dried and concentrated. The crude 10 - (3 - chloropropyl)-2-methoxyphenothiazine is heated with 35 g. of 1 - carbethoxypiperazine on a steam bath for sixteen hours. The mixture is decomposed with water, the oil extracted with ether, dried and concentrated. The crude 1 - carbethoxy - 4-[3 - (2 - methoxy - 10 - phenothiazyl) propyl] piperazine so obtained is dissolved in 600 ml. of absolute ethanol containing 30 g. of potassium hydroxide and refluxed for 16 hours. The ethanol is removed *in vacuo*, the residue treated with water and the oil extracted with ether; the ether solution is dried and concentrated and the residue distilled, b.p. 264—268°C./1.0 mm. A solution of 35.5 g. of 4-[3 - (2 - methoxy - 10 - phenothiazyl) propyl] piperazine, thus obtained, in 200 ml. of methanol is treated with 20 g. of propylene oxide with cooling. After refluxing for six hours, the methanol is removed *in vacuo*, the residue treated with water and the oil extracted with ether and dried. Concentration of the ethereal extracts give the compound of this example, b.p. 278—282°C./0.5 mm.

EXAMPLE 36

1-(2-Hydroxyethoxyethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine

By substituting 1 - (2 - hydroxyethyl)-4-[3 - (2 - chloro - 10 - phenothiazyl) propyl] piperazine from example 1 in the procedure of Example 4, the compound of this example is obtained; dihydrochloride, m.p. 206—207°C. from ethanol.

By employing procedures set forth in the preceding examples, the following compounds are prepared:

1, 1 - (2-(2 - hydroxypropoxy)ethyl - 4[3-(10 - phenothiazyl) propyl] piperazine; dihydrochloride, m.p. 202—203°C. from ethanol.

2. 1 - (3 - hydroxypropyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl]piperazine m.p. 104—105°C. from ethyl acetate; dihydrochloride, m.p. 233—234°C. from ethanol.

3. 1 - (2 - hydroxyethyl) - 2(or 3)-methyl-4 - [3 - (2 - chloro - 10 - phenothiazyl)-propyl] - piperazine; dihydrochloride m.p. 227—228°C. from ethanol.

4. 1 - (2 - hydroxyethyl) - 4 - [2 - (2-chloro - 10 - phenothiazyl) - propyl] - piperazine; dimaleate . 1/2 H_2O, m.p. 139—140° C. from ethanol.

5. 1 - (2,3 - dihydroxypropyl) - 4 - [3 - (2-chloro - 10 - phenothiazyl) - propyl] - piperazine; dihydrochloride, m.p. 225—226°C. from methanol.

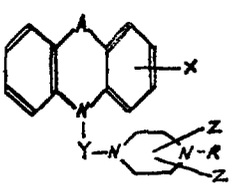
6. 1 - (2 - hydroxy - 3 - isopropoxypropyl)-4 - [3 - (2 - chloro - 10 - phenothiazyl)-propyl] - piperazine, dihydrochloride — 1/2 H_2O, m.p. 222—223°C. from ethanol.

7. 1 - (2 - hydroxyethyl) - 4 - [4 - (2-chloro - 10 - phenothiazyl) - butyl] - piperazine, b.p. 280—290°C./1 mm.; dihydrochloride, m.p. 227—228°C. from methanol.

8. 1 - (2 - hydroxyethyl) - 4 - [5 - (2-chloro - 10 - phenothiazyl) - pentyl] - piperazine; dihydrochloride, m.p. 212—213°C. from ethanol.

WHAT WE CLAIM IS:—

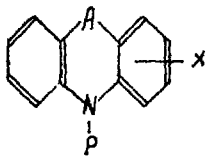
1. A process for the manufacture of basic compounds having the formula



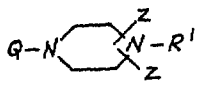
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wherein A is S, SO or SO_2; X is hydrogen, halogen, lower alkoxy or lower alkyl; Y is a lower alkylene group; Z is H or lower alkyl; and R is an unsaturated lower alkyl or a hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl or acyloxyalkyl group, or is an alicyclic group having less than seven carbon atoms and their

pharmaceutically acceptable acid addition salts, the said process comprising interacting a compound of formula



with a compound of formula



wherein of P and Q one is attached directly to the relevant nitrogen atom and the other is connected to the relevant nitrogen atom through a divalent group Y^1, R^1 and Y^1 standing for R and Y, respectively, or for groups convertible into R and Y, respectively and P and Q being atoms or groups of opposite polarity capable of being eliminated as the compound PQ in the course of the reaction, preferably in the presence of an acceptor for PQ.

2. A process as claimed in Claim 1 wherein P is hydrogen and is attached directly to the relevant nitrogent atom, and Q is an inorganic or organic ester group, such as a halide or a sulphonate, connected to the relevant nitrogen atom through Y^1.

3. A process as claimed in Claim 1 wherein Q is hydrogen and is attached directly to the relevant nitrogen atom, and P is an inorganic or organic ester group, such as a halide or a sulphonate, connected to the relevant nitrogen atom through Y^1.

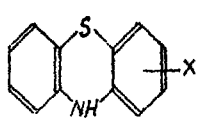
4. A process as claimed in Claim 2 wherein the grouping QY^1— is a monohalogenated, preferably a monochlorinated, lower alkyl group, e.g. 3 - chloropropyl.

5. A process as claimed in Claim 3 wherein the grouping PY^1— is a monohalogenated, preferably a monochlorinated, lower alkyl group, e.g. 3 - chloropropyl.

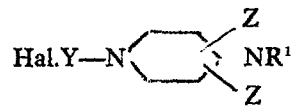
6. A process as claimed in Claim 2 wherein the grouping QY^1 is a *p* - toluenesulphoxy lower alkyl, e.g. 3 - *p* - toluenesulphoxypropyl.

7. A process as claimed in Claim 3 wherein the grouping PY^1 is a *p*-toluenesulphoxy lower alkyl, e.g. 3 - *p* - toluenesulphoxypropyl.

8. A process as claimed in Claim 1 wherein a phenothiazine of formula



is interacted with a piperazine of formula



Hal. standing for halogen, preferably chlorine, reaction being preferably effected in liquid ammonia in the presence of an alkali metal amide or in an aromatic hydrocarbon solvent in the presence of an alkali metal salt of carbonic acid.

9. A process as claimed in any of the preceding claims wherein R^1 is a hydroxyalkyl group, which includes the step of converting the hydroxy group into a lower alkoxy group.

10. A process as claimed in any of Claims 1—8 wherein R^1 is a hydroxyalkyl group, which includes the steps of replacing the hydroxy-group by halogen, preferably chlorine, and then reacting the halogen compound with an alkali metal lower alkoxide to form the alkoxy-compound.

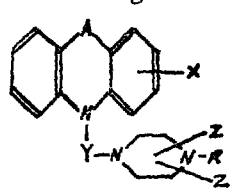
11. A process as claimed in Claim 9 or 10 wherein the alkoxy-compound contains a further hydroxy group.

12. A process as claimed in any of the preceding claims followed by conversion of the basic product into its salt with a pharmaceutically acceptable acid.

13. A process for the manufacture of 1-(2-hydroxyethyl) - 4 - [3 - (2 - chloro - 10-phenothiazyl)propyl]-piperazine and its salts with pharmaceutically acceptable acids, which comprises heating together 3 - (2 - chloro-10 - phenothiazyl)propyl chloride with 1 - (2-hydroxyethyl)-piperazine, and if desired converting the resulting base into the appropriate salt.

14. A process for the manufacture of phenothiazylalkylpiperazines and their salts substantially as described with reference to each of the foregoing Examples.

15. Compounds having the formula (I)



I

wherein A, X, Y, Z and R have the same significance as in Claim 1, and their salts with pharmaceutically acceptable acids.

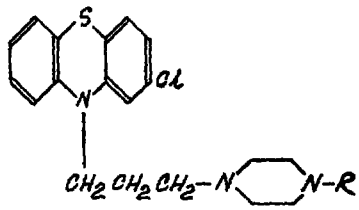
16. Compounds as claimed in Claim 15 wherein R is a lower hydroxyalkyl or acyloxyalkyl or alkoxyalkyl, and the substituent X is in position 2.

17. Compounds as claimed in Claim 15 wherein R is a lower alkenyl or alkynyl group, e.g. allyl, butenyl or propargyl.

18. Compounds as claimed in Claim 15 wherein R is a hydroxyalkoxyalkyl, e.g. hydroxyethoxyethyl or hydroxypropoxyethyl.

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19. Compounds having the formula



wherein R stands for a lower hydroxyalkyl, e.g. 2 - hydroxyethyl or 3-hydroxypropyl, or a lower alkenyl or alkynyl e.g. allyl or propargyl, and their salts with pharmaceutically acceptable acids.

20. Compounds having the formula given in Claim 19 wherein R stands for an ester or lower alkyl ether of a lower hydroxyalkyl, e.g. 2 - ethoxyethyl, 2 - acetoxyethyl, 2 - ethylcarbonatoethyl, 2 - dimethylcarbamyloxyethyl, or 2 - carbamyloxyethyl, and their salts with pharmaceutically acceptable acids.

21. 1 - (2 - Hydroxyethyl) - 4 - [3 - (2-chloro - 10 - phenthiazyl)propyl] - piperazine, and its salts with pharmeceutically acceptable acids.

22. The phenothiazylpropylpiperazines and their salts obtainable as described with reference to each of the foregoing Examples.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1960.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

* C L M S *