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19 SEP. 1962

PATENT SPECIFICATION

NO DRAWINGS

833,474

Date of Application and filing Complete Specification: Dec. 13, 1957.
No. 38774/57.
Application made in United States of America on Dec. 13, 1956.
(Patent of Addition to No. 833,473, dated Dec. 18, 1956).
Complete Specification Published: April 27, 1960.

Index at acceptance:—Class 2(3), C1C(2:3:4:9:10:11F:11G:11J)

International Classification:—C07d.

COMPLETE SPECIFICATION

Piperazine Derivatives

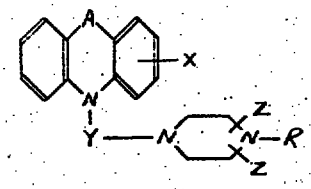
We, SCHERICO LIMITED, of Kapellplatz 10, Lucerne 2, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare this invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the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

This invention relates to a new group of piperazine compounds which have valuable therapeutic properties and to methods for their manufacture. More particularly, this invention relates to 1-(2-hydroxyethyl)- and 1-(3-hydroxypropyl) - 4 - [3 - (2 - trifluoromethyl-10-phenothiazyl)-propyl]-piperazines, their esters, lower alkyl ethers, and non-toxic acid addition salts.

The new compounds of this invention produce an ataraxic or calming effect and are thus useful in allaying apprehensive states by tranquillization. In addition, the new compounds are useful in controlling emesis and nausea.

We have found that in general, ethers such as lower alkyl ethers of the aforementioned alcohols are equivalent in their action and potency to the free alcohol and may be used with equal advantage in place of the free alcohol. We have observed a similar general effect with esters of the free alcohols—with one major exception. Esterifying the alcohol with a lower alkanoyl carboxylic acid such as acetic or propionic acid does not materially alter the pharmacology or therapeutic advantage of the alcohol. Furthermore, esters produced by reaction with ethyl chlorocarbonate, phenyl chlorocarbonate, or a dialkylcarbamyl chloride, for example, are for all intents and purposes similar in action and potency to the free alcohol. The exception to our general observation is that the carbamates are 3 to 6 times as potent as the free alcohol. In view of no apparent increase in toxicity, a very favourable therapeutic ratio is achieved with the carbamic esters. Thus, simple esterification or etherification of the free alcohols, with the exception of the carbamates, merely produces a somewhat equivalent substance whose sole advantage may reside in selective solubility.

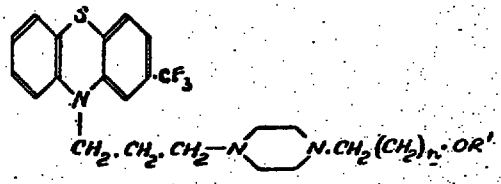
The present invention may be regarded as an improvement in or modification of the invention of our co-pending Application No. 38571/56 (Serial No. 833,473), which describes and claims therapeutically valuable compounds of the general formula (I):



(I)

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 hydrogen or lower alkyl, and R is an unsaturated lower alkenyl or a hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl or acyloxyalkyl group, and their non-toxic acid addition salts.

The compounds of the present invention are characterised, *inter alia*, by the presence of a 2-trifluoromethyl group in the phenothiazine nucleus and have the formula (II):



(II)

wherein *n* is 1 or 2 and R^1 stands for hydrogen or a lower alkyl group or the residue of a lower aliphatic carboxylic acid such as an acetyl, propionyl, carbamyl, N-substituted

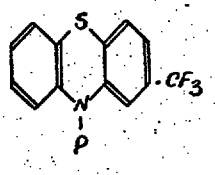
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carbamyl or alkyl- or acyl-carbonato- group; and the pharmaceutically acceptable acid addition salts thereof.

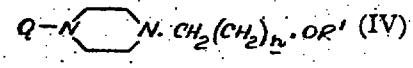
By "lower" alkyl groups and aliphatic carboxylic acids, we mean such groups and acids as contain 1 to 6 carbon atoms.

The preferred compounds are the alcohols (R^1=hydrogen), the carbamic esters (R^1=—$CONH_2$), and their pharmaceutically acceptable acid addition salts.

A general method for the preparation of the basic compounds of the invention is by condensing (preferably in the presence of a basic condensing agent, e.g. an alkali metal amide or carbonate or excess piperazine base) 2-trifluoro-methylphenothiazine of formula (III) with a piperazine of formula (IV).



(III)



(IV)

wherein of P and Q one is hydrogen and the other is a group —$CH_2CH_2CH_2X$ or —CH_2CH_2COX, X being a reactive electronegative atom or radical such as a halogen atom or an aryl sulphonic ester (e.g. toluene sulphonic ester) radical, and R^1 and n have the above significance. Where P or Q is —CH_2CH_2COX, reduction of the condensation product to replace CO by CH_2 is necessary. The condensation is equally effected by heating a mixture of the two reactants alone or in the presence of an inert aromatic hydrocarbon solvent.

Thus 2-trifluoromethyl-10-(3-chloropropyl) phenothiazine obtainable from 2 - trifluoromethylphenothiazine and 1 - chloro - 3 - bromopropane, may be reacted with 1-(2-hydroxyethyl)piperazine or 1 -(3 - hydroxypropyl) piperazine to give the basic alcohol, which may then be esterified or etherified by well-known standard methods for the conversion of alcohols into esters or ethers. To obtain the carbamic ester, the basic alcohol may be condensed with phenyl chlorocarbonate to give the phenylcarbonato - compound, which by treatment with liquid ammonia is converted into the carbamate.

The piperazine may carry the completed (i.e. etherified or esterified) N-1 substituent before condensation with the 2 - trifluoromethyl - 10 - (3 - chloropropyl)phenothiazine.

An alternative method of preparing the basic compounds is to condense 2 - trifluoromethylphenothiazine with a 4 - (3 - chloropropyl)piperazine carrying a suitable substituent in position 1, i.e. with a compound of formula (IV) where Q is 3 - chloropropyl.

The basic compounds are preferably isolated in the form of their salts, e.g. the dihydrochlorides. As the basic compounds are relatively insoluble in water, our new piperazine derivatives are preferably converted into soluble, pharmaceutically acceptable salts. The basic compounds readily form salts by well-known standard methods with a variety of inorganic and strong organic acids, such as hydrochloric, maleic, citric, tartaric, phosphoric, and sulphuric acids.

The invention is illustrated but not limited by the following Examples.

EXAMPLE 1.

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

To a mixture of sodium amide (from 2.5 g. of sodium) and 300 ml. of liquid ammonia there is added 26.5 g. of 2 - trifluoromethylphenothiazine. After stirring the reaction mixture for one hour, 17 g. of 1-chloro-3-bromopropane is added dropwise. The ammonia is allowed to evaporate, the residue is decomposed with water and the oil which separates is extracted with ether. The ether extracts are dried and concentrated to a residue. The residue consisting of crude 10-(3-chloropropyl)-2-trifluoromethylphenothiazine is used without further purification.

The crude trifluoromethyl intermediate is heated and stirred with 30 g. of 1-(2-hydroxyethyl) - piperazine on a steam bath for sixteen hours. The reaction mixture is treated with water. The oil which separates is extracted with ether and the ether layer is extracted with dilute hydrochloric acid. The acid extracts are combined, made basic with dilute sodium hydroxide solution. The resultant oil is extracted with ether, and the ether extracts dried and concentrated. The product of the example is obtained as a dark brown viscous oil, b.p. 268—274° C./0.5 mm.

An alcoholic solution of the free base when treated with two equivalents of alcoholic hydrogen chloride yields the crystalline dihydrochloride. Recrystallization of the dihydrochloride from anhydrous ethanol gives the pure salt which is hygroscopic, m.p. 235—237° C.

A solution of the free base in ethyl acetate when treated with two equivalents of maleic acid in ethyl acetate gives the dimaleate which is recrystallized from methanol. By substituting 1 - (3 - hydroxypropyl) - piperazine in the foregoing reaction, the corresponding propyl derivative is obtained.

EXAMPLE 2.

Carbamate of 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazyl)-propyl]-piperazine.

To a stirred solution of 22 g. of 1 - (2-hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl-10 - phenothiazyl) - propyl] - piperazine in 50 ml. of anhydrous pyridine is added 10 g. of

phenyl chlorocarbonate keeping the temperature between 25—30° After stirring at room temperature for 12—16 hours, 50 ml. of water is added and the mixture is extracted with chloroform. The chloroform extracts are washed with water, dried over sodium sulfate and concentrated to a viscous residue consisting of the phenylcarbonate of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl-10 - phenothiazyl) - propyl] - piperazine.

The ester thus obtained is dissolved in 100 ml. of anhydrous ether and added dropwise to 500 ml. of liquid ammonia in an insulated flask with stirring. The reaction mixture is allowed to stir for ten hours at which time all of the ammonia has evaporated. The residue is treated with water, the mixture extracted with ether, the ether extracts washed with dilute sodium carbonate solution, dried over sodium sulfate, and concentrated. The residue consisting of the compound of the example is purified by forming a dihydrochloride with ethanolic hydrogen chloride as in Example 1.

EXAMPLE 3.

Dimethyl carbamate of 1-(2-hydroxyethyl)-4-[3 - (2 - trifluoromethyl - 10 - phenothiazyl) - propyl] - piperazine.

A mixture of 22 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, 1.3 g. of powdered sodium and 250 ml. toluene is stirred and refluxed for three hours. To the cooled mixture there is added with stirring 13 g. of dimethylcarbamyl chloride. After refluxing for three hours, the mixture is cooled, decomposed with water, the toluene layer is separated, dried, and concentrated *in vacuo*.

The crude free base so obtained is dissolved in ethyl acetate and treated with an excess of maleic acid in ethyl acetate. The dimaleate is purified by recrystallization from methanol.

EXAMPLE 4.

Ethyl carbonate of 1 - (2 - hydroxyethyl) - 4-[3 - (2 - trifluoromethyl - 10 - phenothiazyl) - propyl] - piperazine.

A mixture of 22 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, sodium amide (from 1.3 g. of sodium) and 150 ml. of toluene is stirred and refluxed for two hours. The reaction mixture is cooled and 7 g. of ethyl chlorocarbonate is added dropwise. The mixture is refluxed with stirring for six hours, cooled, decomposed with water, and the toluene layer separated and concentrated *in vacuo*.

The crude free base is dissolved in 200 ml. of ethyl acetate, treated wth a solution of 12 g. of maleic acid in 200 ml. of ethyl acetate and the dimaleate filtered.

The salt is purified by several recrystallizations from ethanol. Substituting the hydroxypropyl compounds of Example 1 in the foregoing procedure yields the corresponding 1-(hydroxypropyl) - piperazine derivative.

EXAMPLE 5.

Acetate of 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazyl)-propyl]-piperazine.

A mixture of 10 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, 50 ml. of acetic anhydride and 5 g. of anhydrous sodium acetate is stirred and heated on a steam bath for sixteen hours. The reaction mixture is poured onto ice and water, made basic with a saturated solution of sodium bicarbonate and extracted with ether. The ether extracts are dried, concentrated, the glassy residue converted to its dihydrochloride with ethanolic hydrogen chloride and the salt recrystallized from ethanol. Substituting propionic anhydride and sodium propionate in the foregoing procedure yields the corresponding propionate in place of the acetate.

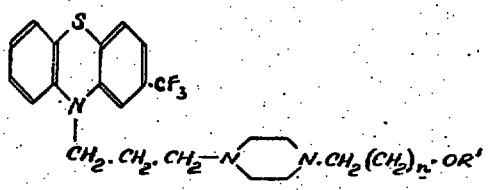
EXAMPLE 6.

1 - (2 - ethoxy) - 4 - [3 - (2 - trifluoromethyl-10 - phenothiazyl) - propyl] - piperazine.

A mixture of 17 g. of crude 10-(3-chloropropyl) - 2 - trifluoromethyl - phenothiazine prepared as described in Example 1 and 20 g. of 1 - (2 - ethoxy - ethyl) - piperazine is heated on a steam bath for sixteen hours. The reaction is treated with water and processed as described in Example 1. The compound of this example is obtained as a viscous oil, b.p. 275—279° C./1.5 mm.

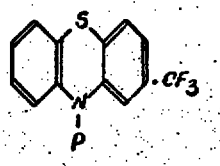
WHAT WE CLAIM IS:

1. Process for the manufacture of trifluoromethylphenothiazylpropylpiperazines of formula (II):

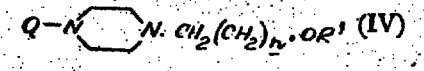


(II)

wherein n is 1 or 2 and R^1 stands for hydrogen or a lower alkyl group or the residue of a lower aliphatic carboxylic acid such as an acetyl, propionyl, carbamyl, N-substituted carbamyl or alkyl- or acyl-carbonato group, the said process comprising condensing a 2-trifluoromethylphenothiazine of formula (III) with a piperazine of formula (IV):



(III)



(IV)

phenyl chlorocarbonate keeping the temperature between 25—30°. After stirring at room temperature for 12—16 hours, 50 ml. of water is added and the mixture is extracted with chloroform. The chloroform extracts are washed with water, dried over sodium sulfate and concentrated to a viscous residue consisting of the phenylcarbonate of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl-10 - phenothiazyl) - propyl] - piperazine.

The ester thus obtained is dissolved in 100 ml. of anhydrous ether and added dropwise to 500 ml. of liquid ammonia in an insulated flask with stirring. The reaction mixture is allowed to stir for ten hours at which time all of the ammonia has evaporated. The residue is treated with water, the mixture extracted with ether, the ether extracts washed with dilute sodium carbonate solution, dried over sodium sulfate, and concentrated. The residue consisting of the compound of the example is purified by forming a dihydrochloride with ethanolic hydrogen chloride as in Example 1.

EXAMPLE 3.

Dimethyl carbamate of 1-(2-hydroxyethyl)-4-[3 - (2 - trifluoromethyl - 10 - phenothiazyl) - propyl] - piperazine.

A mixture of 22 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, 1.3 g. of powdered sodium and 250 ml. toluene is stirred and refluxed for three hours. To the cooled mixture there is added with stirring 13 g. of dimethylcarbamyl chloride. After refluxing for three hours, the mixture is cooled, decomposed with water, the toluene layer is separated, dried, and concentrated *in vacuo*.

The crude free base so obtained is dissolved in ethyl acetate and treated with an excess of maleic acid in ethyl acetate. The dimaleate is purified by recrystallization from methanol.

EXAMPLE 4.

Ethyl carbonate of 1 - (2 - hydroxyethyl) - 4-[3 - (2 - trifluoromethyl - 10 - phenothiazyl) - propyl] - piperazine.

A mixture of 22 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, sodium amide (from 1.3 g. of sodium) and 150 ml. of toluene is stirred and refluxed for two hours. The reaction mixture is cooled and 7 g. of ethyl chlorocarbonate is added dropwise. The mixture is refluxed with stirring for six hours, cooled, decomposed with water, and the toluene layer separated and concentrated *in vacuo*.

The crude free base is dissolved in 200 ml. of ethyl acetate, treated wth a solution of 12 g. of maleic acid in 200 ml. of ethyl acetate and the dimaleate filtered.

The salt is purified by several recrystallizations from ethanol. Substituting the hydroxypropyl compounds of Example 1 in the foregoing procedure yields the corresponding 1-(hydroxypropyl) - piperazine derivative.

EXAMPLE 5.

Acetate of 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazyl)-propyl]-piperazine.

A mixture of 10 g. of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl) - propyl] - piperazine, 50 ml. of acetic anhydride and 5 g. of anhydrous sodium acetate is stirred and heated on a steam bath for sixteen hours. The reaction mixture is poured onto ice and water, made basic with a saturated solution of sodium bicarbonate and extracted with ether. The ether extracts are dried, concentrated, the glassy residue converted to its dihydrochloride with ethanolic hydrogen chloride and the salt recrystallized from ethanol. Substituting propionic anhydride and sodium propionate in the foregoing procedure yields the corresponding propionate in place of the acetate.

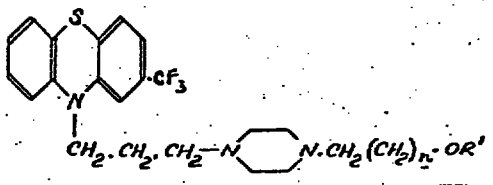
EXAMPLE 6.

1 - (2 - ethoxy) - 4 - [3 - (2 - trifluoromethyl-10 - phenothiazyl) - propyl] - piperazine.

A mixture of 17 g. of crude 10-(3-chloropropyl) - 2 - trifluoromethyl - phenothiazine prepared as described in Example 1 and 20 g. of 1 - (2 - ethoxy - ethyl) - piperazine is heated on a steam bath for sixteen hours. The reaction is treated with water and processed as described in Example 1. The compound of this example is obtained as a viscous oil, b.p. 275—279° C./1.5 mm.

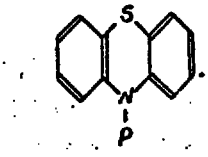
WHAT WE CLAIM IS:

1. Process for the manufacture of trifluoromethylphenothiazylpropylpiperazines of formula (II):

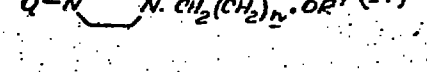


(II)

wherein n is 1 or 2 and R^1 stands for hydrogen or a lower alkyl group or the residue of a lower aliphatic carboxylic acid such as an acetyl, propionyl, carbamyl, N-substituted carbamyl or alkyl- or acyl-carbonato group, the said process comprising condensing a 2-trifluoromethylphenothiazine of formula (III) with a piperazine of formula (IV):



(III)



(IV)

* C L M S *

wherein of P and Q one is hydrogen and the other is a group $.CH_2CH_2CH_2X$, or $.CH_2CH_2COX$, X being a reactive electronegative atom or radical such as a halogen atom or an aryl sulphonic ester radical (e.g. $O.SO_2C_7H_7$), and R^1 and n have the above significance, and if necessary reducing the chain $.CH_2CH_2.CO.$ to propylene.

2. Process as claimed in Claim 1 wherein R^1 stands for carbamyl.

3. Process as claimed in Claim 1 or 2 wherein P stands for 3-chloropropyl and Q for hydrogen.

4. Process as claimed in Claim 1 or 2 wherein P stands for the group $.CH_2CH_2.CH_2.OSO_2C_7H_7$.

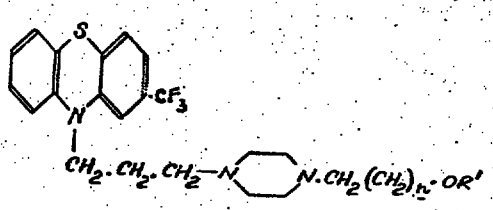
5. Process as claimed in any of the preceding claims wherein the condensation is effected in the presence of a basic condensing agent.

6. Process as claimed in Claim 5 wherein condensation is effected in an inert aromatic hydrocarbon solvent in the presence of an alkali metal amide or an alkali metal carbonate.

7. Process as claimed in any of the preceding claims wherein R^1 is hydrogen and the product is converted into the carbamic ester by esterification.

8. Process as claimed in Claim 1 substantially as described with reference to each of the foregoing Examples.

9. A compound having the formula (II):



(II)

wherein n and R^1 are as defined in Claim 1, and the pharmaceutically acceptable acid addition salts thereof.

10. 1 - (2 - Hydroxyethyl) - 4 - [3 - (2-trifluoromethyl - 10 - phenothiazyl)propyl] piperazine and its pharmaceutically acceptable acid addition salts.

11. The carbamic ester of 1 - (2 - hydroxyethyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazyl)propyl] piperazine and its pharmaceutically acceptable acid addition salts.

12. The 2 - trifluoromethyl - 10 - phenothiazylpropylpiperazines obtainable by the process of 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.

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