1,186,973

PATENT SPECIFICATION

NO DRAWINGS

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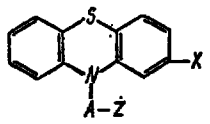
COMPLETE SPECIFICATION

New Phenthiazine Derivatives

We, RHONE-POULENC S.A., a French Body Corporate, of 22, Avenue Montaigne, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

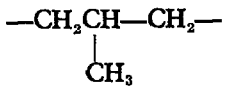
THE INVENTION relates to new therapeutically useful phenthiazine derivatives, to processes for their preparation and pharmaceutical compositions containing them.

In the specification of our Patent No. 904208 there are described and claimed phenthiazine derivatives of the general formula:

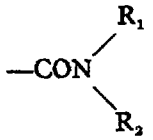


I

(wherein A represents a $-(CH_2)_3-$ or



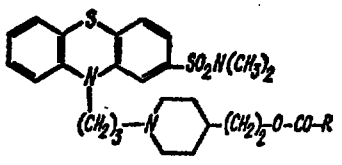
group, X represents a lower alkyl, alkoxy or acyl group or a cyano, methylthio, methanesulphonyl, trifluoromethyl or dimethylsulphamoyl group, and Z represents a pyrrolidino or piperidino group substituted by a group of the formula $-C_nH_{2n}OR$ wherein n represents 0, 1, 2 or 3 and R represents a hydrogen atom or a carboxylic acyl group, or a grouping



wherein R_1 and R_2 are the same or different and each represents a hydrogen atom or a lower alkl group or R_1 and R_2 together with the nitrogen atom to which they are attached collectively represent a mononuclear, saturated heterocyclic ring) which possess pharmacodynamic properties and are, in particular, active as sedatives and antiemetics and some have a useful degree of analgesic activity.

It has now been found after research and experimentation that phenthiazine derivatives of the aforesaid formula wherein A represents $-(CH_2)_3-$, X represents a dimethylsulphamoyl group and Z represents a piperidino group substituted in the *para*-position by an acyloxyethyl group with at least five carbon atoms in the acyl radical, also possess pharmacodynamic properties. These new phenthiazine derivatives are very active as long-acting neuroleptics, anti-emetics and tranquillisers and have the advantage over the compounds within the disclosure of the prior patent, e.g. 3 - dimethylsulphamoyl - 10 - [3 - (4 - hydroxymethyl - piperidino)propyl] - phenthiazine, in having a longer duration of activity, for example, anti-emetic activity.

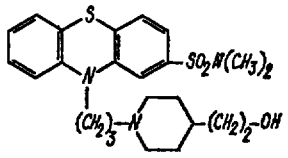
According to the present invention, therefore, there are provided the new phenthiazine derivatives of the general formula:



II

wherein R represents a straight or branched alkyl, alkenyl or alkynyl group containing at least 4 carbon atoms, and preferably not more than 17 carbon atoms, for example, butyl, t-butyl, pentyl, hexyl, 1-ethylpentyl, 1-methylhexyl, heptyl 1,1-dimethyl-hexyl, octyl, nonyl, non-1-enyl, dec-9-enyl, dec-9-ynyl, decyl, undecyl, tridecyl, pentadecyl or heptadecyl, and acid addition salts thereof. When the group R contains a multiple bond between carbon atoms, the multiple bond may be located in any position of the hydrocarbon chain.

According to a feature of the present invention, the phenthiazine derivatives of formula II are prepared by the process which comprises reacting 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino] propyl}phenthiazine of the formula:



III

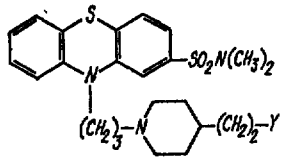
with a compound of the general formula R—CO—X, wherein R is as hereinbefore defined and X represents the acid residue of a reactive ester, for example a halogen atom, the hydroxy group, an alkoxy group containing from 1 to 4 carbon atoms, an imidazolyl group, or an alkanoyloxy, alkenoyloxy or alkynoyloxy group which may have a straight or branched hydrocarbon chain, and may, more particularly, be such that the compound R—CO—X represents the acid anhydride of formula R—CO—O—CO—R, R being as hereinbefore defined.

When the symbol X represents a halogen atom, in particular chlorine, or an imidazolyl, alkanoyloxy, alkenoyloxy, or alkynoyloxy group, it is advantageous to carry out the process in an inert organic solvent (for example benzene, toluene or chloroform), and preferably at the boiling point of the solvent employed in the absence or presence of an inorganic or organic acid-binding agent.

When the symbol X represents the hydroxy group, the process is generally carried out in an inert organic solvent in the presence of either a strong acid or a Lewis acid or of dicyclohexylcarbodiimide.

When the symbol X represents an alkoxy group, the process is generally caried out in an inert organic solvent such as toluene and the alcohol formed is removed by azeotropic distillation.

According to a further feature of the invention, the phenthiazine derivatives of formula I are prepared by the process which comprises reacting a phenthiazine of the formula:



IV

wherein Y represents the acid residue of a reactive ester such as a halogen atom or a sulphuric or sulphonic ester residue (for example a methanesulphonyloxy or toluene - p - sulphonyloxy residue) with an alkali metal salt of an acid of the formula R—CO—OH (wherein R is as hereinbefore defined), the process being carried out in an inert organic solvent and preferably at the boiling point of the solvent employed.

The alcohol of formula III may be prepared, for example, by application of the processes described in the specification of our British Patent No. 904208.

The phenthiazine compounds of general formula IV may be prepared from the alcohol of formula III by applying any process which is known *per se* for replacing a hydroxy group by a reactive ester residue, such as Y defined above.

The phenthiazine derivatives of formula II obtained according to the foregoing processes may be purified by physical methods such as distillation, crystallisation or chromatography, or by chemical methods such as the formation of salts, crystallisation of the salts and decomposition of them in an alkaline medium. In the said chemical method, the nature of the anion of the salt is immaterial, the only requirement being that the salt must be well-defined and readily crystallisable.

The phenthiazine derivative of formula II may be converted in manner known *per se* into acid addition salts. The acid addition salts may be obtained by the action of acids on the new phenthiazine derivatives in appropriate solvents. As organic solvents there may be used, for example, alcohols, ethers, ketones or chlorinated hydrocarbons. The salt which is formed is precipitated, if necessary after concentration of its solution, and is separated by filtration or decantation.

The phenthiazine derivatives of the present invention have given good results as long-acting neuroleptics, anti-emetics and tranquillisers in physiological experiments with animals at doses of 0.005 to 1.0 mg./kg. of animal weight by subcutaneous or intramuscular administration. Preferred compounds are 3 - dimethylsulphamoyl - 10 - {3 - [4 -(2 - palmitolyloxyethyl)piperidino] - propyl} phenthiazine, 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl)

piperidino]propyl}phenthiazine and 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroloxyethyl)piperidino]propyl}phenthiazine.

The following Examples illustrate the invention.

EXAMPLE I

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl) piperidino]propyl} - phenthiazine (9.5 g.), palmitoyl chloride (5.5 g.) and anhydrous toluene (165 cc.) are heated under reflux for 5 hours. After cooling, the reaction mixture is stirred for 15 minutes in the presence of distilled water (200 cc.) and an aqueous 10% solution of sodium carbonate (50 cc.). The decanted organic solution is washed three times with distilled water (total 600 cc.) until neutral, dried over anhydrous magnesium sulphate and evaporated under reduced pressure (20 mm.Hg.). The residue (14.9 g.), dissolved in acetone (50 cc.) under reflux, is treated with anhydrous oxalic acid (1.9 g.) dissolved in acetone (10 cc.). After 17 hours cooling at 3°C, the crystals which have appeared are filtered off, washed twice with ice-cooled acetone (total 50 cc.) and dried under reduced pressure (20 mm. Hg.). 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - palmitoyloxyethyl)piperidino] - propyl}phenthiazine oxalate (15.2 g.), melting at about 134°C, is obtained.

The palmitoyl chloride (b.p. 157—165°C/0.2 mm.Hg) is prepared according to W. G. Rose, J. Am. Chem. Soc., 69, 1384 (1947).

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino]propyl} - phenthiazine employed as starting material is prepared by the procedure described in the specification of British Patent No. 904208 by reacting 4 - (2 - hydroxyethyl)piperidine with 3 - dimethylsulphamoyl - 10 - (3 - hydroxy - propyl)phenthiazine methanesulphonate.

EXAMPLE II

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino] - propyl}phenthiazine (9.5 g.) undec - 10 - enoyl chloride (4.05 g.) and toluene (165 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxy - ethyl)piperidino]propyl}phenthiazine oxalate (12.8 g.), melting at about 126°C, is obtained.

Undec-10-enoyl chloride employed as starting material (b.p. 74—75°C/0.2 mm.Hg) is prepared according to J. English *et coll,* J. Am. Chem. Soc., 67, 1413, (1945).

EXAMPLE III

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino] - propyl}phenthiazine (9.5 g., lauroyl chloride (4.40 g.) and toluene 165 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroyloxyethyl)piperidino] - propyl} phenthiazine oxalate (13.1 g.), melting at about 130°C, is obtained.

Lauroyl chloride employed as starting material (b.p. 110°C/2 mm.Hg) is prepared according to H. Richet, Bull. Soc. Chim. Fr., (1946), 52.

EXAMPLE IV

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino] - propyl}phenthiazine (4.75 g.), decanoyl chloride (2.11 g.) and toluene (110 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - decanoyloxyethyl) - piperidino]propyl}phenthiazine oxalate (6.20 g.) melting at about 134°C, is obtained.

Decanoyl chloride employed as starting material (b.p. 100—102°C/10 mm.Hg) is prepared according to J. Cason *et coll,* J. Org, Chem. 26, 1768, (1961).

EXAMPLE V

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl) - piperidino]propyl}phenthiazine (6.8 g.), heptanoyl chloride (2.4 g.) and toluene (130 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - heptanoyloxyethyl)piperidino]propyl}phenthiazine oxalate (2.12 g.), melting at about 140°C, is obtained.

Heptanoyl chloride employed as starting material (b.p. 87—88°C/25 mm.Hg) is prepared according to M. Sulzbacher *et coll,* J. Org. Chem., 13, 303, (1948).

EXAMPLE VI

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino]propyl} - phenthiazine 4.75 g.), 2 - methylheptanoyl chloride (1.8 g.) and toluene (110 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - 2′ - methylheptanoyloxy - ethyl)piperidino]propyl}phenthiazine oxalate (6.1 g.), melting at about 156°C, is obtained.

2 - Methylheptanoyl chloride employed as starting material (b.p. 60—62°C/12 mm. Hg) is prepared according to P. Karrer *et coll.,* Helv. Chim. Acta, 13, 1292, (1930).

EXAMPLE VII

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino]propyl} - phenthiazine (9.5 g.), 2,2 - dimethylheptanoyl chloride (3.53 g.) and toluene (165 cc.) 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - 2′, 2′ - dimethylheptanoyloxyethyl)piperidino]propyl}phenthiazine oxalate (13.1 g.), melting at about 160°C, is obtained.

2.2 - Dimethylheptanoyl chloride employed as starting material (b.p. 71.5°C/10 mm.Hg) is prepared according to M. Nuraya, Chem. Pharm. Bull. (Tokyo), 6, 186, (1958).

EXAMPLE VIII

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl) - piperidino]propyl}phenthiazine (4.75 g.), 2-ethylhexanoyl chloride (1.8 g.) and toluene (100 cc.), 3 - dimethylsulhpamoyl - 10 - {3 - [4 - (2 - 2' - ethylhexanoyloxy - ethyl)piperidino]propyl}phenthiazine oxalate (6.1 g.), melting at about 166°C., is obtained.

2 - Ethylhexanoyl chloride employed as starting material (b.p. 71—72°C/20 mm.Hg) is prepared according to E. H. Man *et coll*, J. Am. Chem. Soc., 73, 901 (1951).

EXAMPLE IX

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino] - propyl}phen - thiazine (8.45 g.) is reacted with hexanoyl chloride (2.55 g.) in toluene (150 cc.) by the procedure described in Example I. After washing and evaporating the solvent, the resulting base is recrystallised from ethanol. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - hexanoyloxyethyl) piperidino] propyl} phen - azine (6.2 g.), melting at about 73°C, is obtained.

Hexanoyl chloride employed as starting material (b.p. 38—40°C/12 mm.Hg) is prepared according to F. L. Jackson *et coll*, J. Am. Chem. Soc., 73, 4280, (1951).

EXAMPLE X

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino]propyl}phenthiazine (4.75 g.), octanoyl chloride (1.76 g.) and toluene (110 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - octanoyloxyethyl) - piperidino]propyl} phenthiazine oxalate (5.95 g.), melting at about 148°C, is obtained.

Octanoyl chloride employed as starting material (b.p. 96—97°C/25 mm.Hg) is prepared according to J. Cason, J. Org, Chem., 23, 1492, (1958).

EXAMPLE XI

By following the procedure described in Example I but starting with 3 - dimethylsul - phamoyl - 10 - {3 - [4 - (2 - hydroxyethyl) piperidino]propyl}phenthiazine (4.75 g.) and valeryl chloride (1.35 g.) in toluene (110 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - valeryloxyethyl)piperidino]propyl}phenthiazine oxalate (4.2 g.), melting at about 136°C, is obtained.

Valeryl chloride employed as starting material is prepared according to H. C. Brown *et coll*, J. Am. Chem. Soc., 60, 1325, (1938).

EXAMPLE XII

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino]propyl}phenthiazine 4.75 g.) and pivaolyl chloride (1.33 g.) in toluene (110 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - pivaloyloxyethyl)piperidino] - propyl} - phenthiazine oxalate (4.7 g.), melting at about 156°C, is obtained.

Pivaloyl chloride employed as starting material is prepared according to J. G. Traynham *et coll*, J. Org. Chem., 22, 1551, (1957).

EXAMPLE XIII

By following the procedure described in Example I but starting with 3 - dimethylsul - phamoyl - 10 - {3 - [4 - (2 - hydroxyethyl) - piperidino] - propyl}phenthiazine 4.75 g.) and undecanoyl chloride (2.3 g.) in toluene (100 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - undecanoyloxy - ethyl)piperidino] propyl}phenthiazine oxalate (6.2 g.) melting at about 130°C, is obtained.

Undecanoyl chloride employed as starting material is prepared according to H. E. Fierz-David and W. Kuster, Helv. Chim. Acta., 22, 89 (1939).

EXAMPLE XIV

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino] - propyl}phenthiazine (4.7 g.) and nonanoyl chloride (1.95 g.) in toluene (100 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - nonanoyloxyethyl)piperidino]propyl} - phenthiazine oxalate (2.95 g.), melting at about 140°C., is obtained.

Nonanoyl chloride employed as starting material is prepared according to H. E. Fierz-David and W. Kuster, Helv. Chim. Acta, 22, 89 (1939).

EXAMPLE XV

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)-piperidino]propyl}phenthiazine (4.75 g.) and undec - 10 - ynoyl chloride (2.2 g.) in toluene (100 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10' - ynoyloxyethyl)piperidino]propyl}phenthiazine oxalate (5 g.), melting at about 133°C., is obtained.

Undec - 10 - ynoyl chloride is prepared according to L. D. Bergel'son *et coll*, Zh. obshch, Khim., 32, 58 (1962); Chem. Abstr., 57, 14930 b (1962).

EXAMPLE XVI

By following the procedure described in Example I but starting with 3 - dimethylsul - phamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)-piperidino]propyl}phenthiazine (4.75 g.) and myristoyl chloride (3.7 g.) in toluene (100

cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - myristoyloxy - ethyl)piperidino]propyl} - phenthiazine oxalate (6.3 g.), melting at about 134°C., is obtained.

Myristoyl chloride employed as starting material is prepared according to H. E. Fierz-David and W. Kuster, Helv. Chim. Acta., 22, 89 (1939).

EXAMPLE XVII

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino]propyl}phen - thiazine (4.75 g.) is reacted with stearoyl chloride (3.34 g.) in toluene (100 cc.) according to the procedure described in Example I. After washing and evaporating the solvent, the resulting base is recrystallised from ethanol to give 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - stearoyloxyethyl)piperidino] - propyl}phenthiazine (5.9 g.), melting at about 62°C.

Stearoyl chloride employed as starting material is prepared according to H. E. Fierz-David and W. Kuster, Helv. Chim. Acta, 22, 89 (1939).

EXAMPLE XVIII

By following the procedure described in Example I but starting with 3 - dimethyl - sulphamoyl - 10 - {3 - [4 - (2 - hydroxy - ethyl)piperidino] - propyl}phenthiazine (9.5 g.) and dec - 2 - enoyl chloride (4.14 g.) in toluene (200 cc.), 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - dec - 2′ - enoyl - oxyethyl)-piperidino]propyl}phenthiazine oxalate (6.8 g.), melting at about 138°C., is obtained.

Dec-2-enoyl chloride employed as starting material is prepared according to P. Van Romburgh, Rec. Trav. Chim. Pays-Bas, 57, 494 (1938).

EXAMPLE XIX

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl)piperidino]-propyl}phenthiazine oxalate (308 g.), prepared as described in Example II, is suspended in distilled water (2 litres) and methylene chloride (1 litre). A 10% aqueous solution of sodium bicarbonate (1.250 litres) is added and the mixture is stirred for 5 minutes. After decantation of the organic phase, the aqueous phase is extracted twice with methylene chloride (total 1 litre). The organic phases are combined, washed three times with distilled water (total 1.5 litres) and dried over anhydrous sodium sulphate. After filtration, the solvent is removed by heating initially at 60°C. under ordinary pressure and then at 100°C. under reduced pressure (20 mm. Hg.). The crude oily base obtained (274 g.) is purified by chromatography through a column of neutral alumina (1 kg.) and elution with benzene (total 5.5 litres).

The benzene is then evaporated under reduced pressure (20 mm. Hg) to yield the purified base (240 g.), which is dissolved at 60°C. in cyclohexane (650 cc.). After cooling to 40°C., petroluem ether (b.p. 40—65°C., 1,350 cc.) is added. The mixture is cooled to 20°C., crystallisation of the product initiated, and then it is left for 2 hours at 20°C. and overnight at 3°C. The crystals which form are filtered off, washed twice with iced petroluem ether (300 cc. total) and dried under reduced pressure (20 mm. Hg.) to yield 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl)piperidino]pro - pyl}phenthiazine (222 g.) melting at 58—59°C.

The present invention includes within its scope pharmaceutical compositions containing, as active ingredient, at least one of the phenthiazine derivatives of formula I in association with a pharmaceutical carrier or coating. The invention includes especially such preparations made up for parenteral, in particular intramuscular or subcutaneous, administration.

Preparations for parenteral administration include sterile non-aqueous solutions. Examples of suitable non-aqueous solvents are injectable vegetable oils, such as sesame oil or olive oil, and injectable organic esters such as ethyl oleate. The preparations may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage depends on the desired therapeutic effect and on the duration of the treatment. In human therapy the compositions should generally be administered so as to give to an adult between 5 mg. and 100 mg. of active substance at the rate of one intramusicular injection every two to four weeks.

The following Examples illustrate the preparation of pharmaceutical compositions according to the invention.

EXAMPLE XX

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroyloxyethyl)piperidino]propyl}phen - thiazine oxalate (170 mg.) is treated at ambient temperature with a mixture of a 1% aqueous solution of sodium bicarbonate (110 cc.) and diethyl ether (50 cc.). After dissolution, the ethereal phase is decanted, washed with distilled water (2×50 cc.) until neutral, and then dried over anhydrous magnesium sulphate. After concentration under reduced pressure (20 mm.Hg), the residue (150 mg.) is dissolved in sesame oil (15 cc.) at 40°C. After cooling to ambient temperature, a clear yellow solution containing 1% of 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroyloxy - ethyl)piperidino]propyl}phenthiazine is obtained.

EXAMPLE XXI

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl) - piperidino]propyl}phenthiazine (2.5 g.) is dissolved at 40°C. in neutralised sesame oil (100 cc.) with agitation. After cooling, the yellow solution obtained is filtered through a bacteriological filter under a nitrogen pressure of 2 kg./cm². The filtered solution is then aseptically distributed into 5 cc. ampoules giving 4.1 cc. of solution per ampoule. The filled ampoules are sealed under nitrogen.

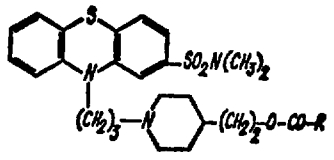
The resulting ampoules each contain 100 mg. of active product ready for intramuscular administration.

EXAMPLE XXII

By proceeding as described in Example XXI but using 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - palmitoyloxyethyl)piperidino] - propyl}phenthiazine, m.p. 61—62°C., ampoules are obtained each containing 100 mg. of active product.

WHAT WE CLAIM IS:—

1. Phenthiazine derivatives of the general formula:



wherein R represents a straight or branched alkyl, alkenyl, or alkynyl group containing at least 4 carbon atoms.

2. Phenthiazine derivatives according to claim 1 wherein R represents an alkyl, alkenyl or alkynyl group containing from 4 to 17 carbon atoms.

3. Phenthiazine derivatives according to claim 2 wherein R represents butyl, t-butyl, pentyl, hexyl, 1-ethylpentyl, 1-methylhexyl, heptyl, 1,1-dimethylhexyl, octyl, nonyl, non-1-enyl, dec-9-enyl, dec-9-ynyl, decyl, undecyl, tridecyl, pentadecyl or heptadecyl.

4. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - palmitoyloxyethyl) - piperidino]propyl}-phenthiazine.

5. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl)piperidino]-propyl}phenthiazine.

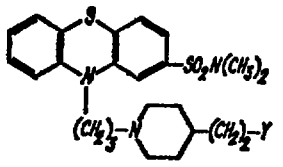
6. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroyloxyethyl)piperidino]propyl}phenthiazine.

7. Acid addition salts of a phenthiazine derivative as claimed in any one of claims 1 to 6.

8. Process for the preparation of phenthiazine derivatives as claimed in claim 1 which comprises reacting 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino]-propyl}phenthiazine with a compound of the general formula R—CO—X, wherein R is as defined in claim 1, and X represents the acid residue of a reactive ester, the hydroxy group, and alkoxy group containing from 1 to 4 carbon atoms, an imidazolyl group, or an alkanoyloxy, alkenoyloxy or alkynoyloxy group.

9. Process according to claim 8 in which X represents a halogen atom.

10. Process for the preparation of phenthiazine derivatives as claimed in claim 1 which comprises reacting a phenthiazine of the formula:



wherein Y represents the acid residue of a reactive ester, with an alkali metal salt of an acid of the formula R—CO—OH, wherein R is as defined in claim 1, in an inert organic solvent.

11. Process according to claim 8, 9 or 10 followed by the step of converting in manner known *per se* the phenthiazine base obtained into an acid addition salt.

12. Process for the preparation of phenthiazine derivatives of the formula specified in claim 1, or acid addition salt thereof, substantially as hereinbefore described with especial reference to any one of Examples I to XVIII.

13. Process for the preparation of phenthiazine derivatives of the formula specified in claim 1 substantially as hereinbefore described with especial reference to Example XIX.

14. Phenthiazine derivatives of the formula specified in claim 1 and acid addition salts thereof when prepared by the process claimed in any one of claims 8 to 13.

15. Pharmaceutical compositions which comprise, as active ingredient, at least one phenthiazine derivative as claimed in any one of claims 1 to 6 and 14 in association with a pharmaceutical carrier.

16. Pharmaceutical compositions according to claim 15 substantially as hereinbefore described with especial reference to Example XX, XXI or XXII.

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EXAMPLE XXI

3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl) - piperi - dino]propyl}phenthiazine (2.5 g.) is dissolved at 40°C. in neutralised sesame oil (100 cc.) with agitation. After cooling, the yellow solution obtained is filtered through a bacteriological filter under a nitrogen pressure of 2 kg./cm². The filtered solution is then aseptically distributed into 5 cc. ampoules giving 4.1 cc. of solution per ampoule. The filled ampoules are sealed under nitrogen.

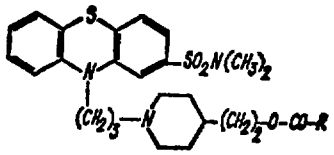
The resulting ampoules each contain 100 mg. of active product ready for intramuscular administration.

EXAMPLE XXII

By proceeding as described in Example XXI but using 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - palmitoyloxyethyl)piperidino] - propyl}phenthiazine, m.p. 61—62°C., ampoules are obtained each containing 100 mg. of active product.

WHAT WE CLAIM IS:—

1. Phenthiazine derivatives of the general formula:



wherein R represents a straight or branched alkyl, alkenyl, or alkynyl group containing at least 4 carbon atoms.

2. Phenthiazine derivatives according to claim 1 wherein R represents an alkyl, alkenyl or alkynyl group containing from 4 to 17 carbon atoms.

3. Phenthiazine derivatives according to claim 2 wherein R represents butyl, t-butyl, pentyl, hexyl, 1-ethylpentyl, 1-methylhexyl, heptyl, 1,1-dimethylhexyl, octyl, nonyl, non-1-enyl, dec-9-enyl, dec-9-ynyl, decyl, undecyl, tridecyl, pentadecyl or heptadecyl.

4. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - palmitoyloxyethyl) - piperidino]propyl}-phenthiazine.

5. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - undec - 10′ - enoyloxyethyl)piperidino]-propyl}phenthiazine.

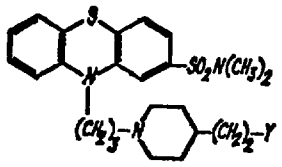
6. 3 - Dimethylsulphamoyl - 10 - {3 - [4 - (2 - lauroyloxyethyl)piperidino]propyl}phenthiazine.

7. Acid addition salts of a phenthiazine derivative as claimed in any one of claims 1 to 6.

8. Process for the preparation of phenthiazine derivatives as claimed in claim 1 which comprises reacting 3 - dimethylsulphamoyl - 10 - {3 - [4 - (2 - hydroxyethyl)piperidino]-propyl}phenthiazine with a compound of the general formula R—CO—X, wherein R is as defined in claim 1, and X represents the acid residue of a reactive ester, the hydroxy group, and alkoxy group containing from 1 to 4 carbon atoms, an imidazolyl group, or an alkanoyloxy, alkenoyloxy or alkynoyloxy group.

9. Process according to claim 8 in which X represents a halogen atom.

10. Process for the preparation of phenthiazine derivatives as claimed in claim 1 which comprises reacting a phenthiazine of the formula:



wherein Y represents the acid residue of a reactive ester, with an alkali metal salt of an acid of the formula R—CO—OH, wherein R is as defined in claim 1, in an inert organic solvent.

11. Process according to claim 8, 9 or 10 followed by the step of converting in manner known *per se* the phenthiazine base obtained into an acid addition salt.

12. Process for the preparation of phenthiazine derivatives of the formula specified in claim 1, or acid addition salt thereof, substantially as hereinbefore described with especial reference to any one of Examples I to XVIII.

13. Process for the preparation of phenthiazine derivatives of the formula specified in claim 1 substantially as hereinbefore described with especial reference to Example XIX.

14. Phenthiazine derivatives of the formula specified in claim 1 and acid addition salts thereof when prepared by the process claimed in any one of claims 8 to 13.

15. Pharmaceutical compositions which comprise, as active ingredient, at least one phenthiazine derivative as claimed in any one of claims 1 to 6 and 14 in association with a pharmaceutical carrier.

16. Pharmaceutical compositions according to claim 15 substantially as hereinbefore described with especial reference to Example XX, XXI or XXII.

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