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PATENT SPECIFICATION

NO DRAWINGS

904,209

Date of Application and filing Complete Specification: Oct. 16, 1958.
No. 9510/61.
Application made in France (No. 749,847) on Oct. 21, 1957.
(Divided out of No. 904,208).
Complete Specification Published: Aug. 22, 1962.

Index at acceptance:—Class 2(3), C2B20.
International Classification:—C07d.

COMPLETE SPECIFICATION

New Phenthiazine Compounds

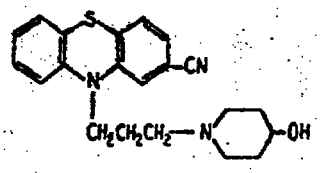
We, RHONE-POULENC S.A. (formerly known as Societe Des Usines Chimiques Rhone-Poulenc), a French body corporate, of 21, rue Jean-Goujon, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to therapeutically useful phenthiazine compounds, to processes for the production of new such phenthiazine compounds, and to pharmaceutical compositions containing the same. This application is divided from Application No. 33066/58 (Serial No. 904,208).

It is known that various 10-aminoalkylphenthiazines possess interesting therapeutic properties. Extensive research and experimentation have shown, however, that both the size of the therapeutic index and the nature of the therapeutic effect exhibited by certain compounds of this type can radically be changed by even small changes in chemical structure. In this connection it is well known that 3-chloro - 10 - (3 - dimethylaminopropyl)phenthiazine (Beilstein nomenclature) has very great importance in clinical medicine particularly in psychiatry, important characteristics of the compound being the calming and sedation effects it produces without any significant hypnosis and without loss of response to stimuli.

It is the object of the present invention to provide new phenthiazine derivatives exhibiting at least some of the valuable characteristics of 3 - chloro - 10 - (3 - dimethylaminopropyl)phenthiazine but with the added advantage of efficacy at a lower dosage rate.

The new phenthiazine compounds of the present invention are 3 - cyano - 10 - [3 - (4-hydroxy - 1 - piperidyl)propyl]phenthiazine of the conventional formula:



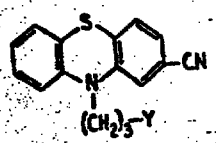
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and its pharmacologically acceptable acid addition and quaternary ammonium salts.

Pharmacological studies of the new compounds show that they have the same indications as 3 - chloro - 10 - (3 - dimethylaminopropyl)phenthiazine in the treatment of mental illness, that is in the treatment, which is essentially symptomatic, of mental states having as characteristic symptoms, anxiety, tension, over-activity and agitation but that they are effective at a lower dosage rate. Also since their activity upon the cardiovascular and vegetative nervous systems is of the same order as that of 3 - chloro - 10 - (3 - dimethylaminopropyl)phenthiazine, side effects upon these systems are reduced by virtue of the lower dosage rate. Clinical results have been obtained with some sixty cases of serious psychotic states and it has been confirmed that the compound of the above structural formula in the form of its hydrochloride is some ten times as active as 3 - chloro - 10 - (3-dimethylaminopropyl)phenthiazine hydrochloride in the directions mentioned above and that, at the effective dosage rate, side effects normally observed with 10-aminoalkylphenthiazines (disturbances of equilibrium, cardiovascular disturbance, somnolence and excitomotor symptoms) are substantially avoided. It can thus be concluded that, as an aid in psychiatric therapy, the compounds of the present invention provide valuable alternatives to 3 - chloro - 10 - (3 - dimethylaminopropyl)-phenthiazine and its pharmacologically accept-

able salts with the added advantage of producing fewer side effects when administered at an effective dosage rate.

According to a feature of the present invention, 3 - cyano - 10 - [3 - (4 - hydroxy - 1-piperidyl)propyl]phenthiazine is prepared by reacting a phenthiazine derivative of the formula:



II

wherein Y represents an acid residue or a reactive ester, such as a halogen atom or a sulphuric or sulphonic ester residue, with 4-piperidinol.

The reaction is carried out with or without a solvent in the presence or absence of an alkaline condensing agent, and optionally at an elevated temperature. The preferred condensing agents are alkali metals and their amides or hydrides. The hydroxy group of the 4-piperidinol may be protected during the reaction by employing the corresponding tetrahydropyranyl derivative with subsequent hydrolysis of the reaction product.

For therapeutic purposes, 3-cyano-10-[3-(4-hydroxy-1-piperidyl)propyl]phenthiazine is employed as such or in the form of a non-toxic acid addition salt, i.e. a salt containing an anion which is relatively innocuous to the animal organism in therapeutic doses of the salt (such as hydrochloride and other hydrohalides, phosphate, nitrate, sulphate, maleate, fumarate, citrate, tartrate, methanesulphonate and ethanedisulphonate) so that the beneficial physiological properties inherent in the base are not vitiated by side-effects ascribable to the anion. However, it may also be employed in the form of a non-toxic quaternary ammonium salt obtained by reaction with an organic halide (e.g. methyl or ethyl iodide, chloride or bromide or allyl or benzyl chloride or bromide) or other reactive ester, e.g. a toluene-*p*-sulphonate.

The following Example illustrates the invention.

EXAMPLE I.

A solution of 3 - cyano - 10 - (3 - toluene-*p*-sulphonyloxypropyl)phenthiazine (10.9 g.) and 4-piperidinol (5 g.) in toluene (80 cc.) is heated under reflux for 4 hours. After cooling, the basic products are extracted by agitation with water (50 cc.) and 4N hydrochloric acid (10 cc.). The aqueous acid phase is made alkaline with 4N sodium hydroxide (20 cc.) and the liberated base is extracted with ethyl acetate (125 cc.). The organic phase is dried over anhydrous potassium carbonate and concentrated to dryness. After recrystallisation of the solid residue from ethyl acetate there is obtained 3 - cyano - 10 - [3 - (4 - hydroxy-1 - piperidyl)propyl]phenthiazine (6.8 g.) as a yellow crystalline powder, m.p. 116—117° C.

The initial 4-piperidinol is prepared according to the method of Emmert *et al.*, Ber., *48*, 688 (1915).

The present invention includes within its scope pharmaceutical compositions comprising 3 - cyano - 10 - [3 - (4 - hydroxy - 1-piperidyl)propyl]phenthiazine, or a pharmacologically acceptable acid addition or quaternary ammonium salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. In clinical practice the compounds of the present invention will normally be administered orally, in consequence of which the preferred formulations are those of the kind suitable for oral administration.

Preparations for oral ingestion can be liquids or solids or any combination of these forms, such as solutions, suspensions, syrups, elixirs, emulsions, powders or tablets. Pharmaceutical preparations for administration of the active therapeutic agents in unit dose form can take the form of compressed powders (or tablets) or of a powder enclosed in a suitable capsule of absorbable material such as gelatin. These compressed powders (or tablets can take the form of the active materials admixed with suitable excipients and/or diluents such as starch, lactose, stearic acid, magnesium stearate or dextrin.

In yet a further embodiment, the active material may, as such or in the form of a diluted composition be put up in powder packets and employed as such.

Preparations for parenteral administration may be sterile solutions or suspensions in water or other liquids, with or without the addition of soluble or insoluble diluents and/or solid or liquid excipients.

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. Obviously several unit dosage forms may be administered at about the same time.

The following Example illustrates pharmaceutical preparations according to the invention.

EXAMPLE II.

There are prepared tablets weighing approximately 140 mg. and having the following composition:

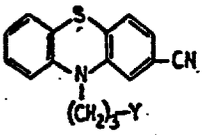
3 - cyano - 10 - [3 - (4 - hydroxy-1 - piperidyl)propyl]phenthiazine	5 mg.
starch	100 mg.
colloidal silica	32 mg.
magnesium stearate	3 mg.

These tablets can be administered to patients, the usual daily dose being from 5 to 20 mg.

WHAT WE CLAIM IS:—

1. 3 - Cyano - 10 - [3 - (4 - hydroxy - 1-piperidyl)propyl]phenthiazine and its pharmacologically acceptable acid addition and quaternary ammonium salts.

2. Process for the preparation of the phenthiazine base claimed in claim 1 which comprises reacting 4-piperidinol with a phenthiazine derivative of the formula:



wherein Y represents the acid residue of a reactive ester.

3. Process according to claim 2 in which the reaction is carried out in a solvent at an elevated temperature.

4. Process according to claim 2 or 3 substantially as described in Example I.

5. 3 - Cyano - 10 - [3 - (4 - hydroxy - 1-piperidyl)propyl]phenthiazine when prepared by the process claimed in any one of claims 2 to 4.

6. A pharmaceutical preparation comprising 3 - cyano - 10 - [3 - (4 - hydroxy - 1-piperidyl)propyl]phenthiazine, or a pharmacologically acceptable acid addition or quaternary ammonium salt thereof, in association with a significant amount of a pharmaceutical carrier.

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London, W. C.1.

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ERRATA

SPECIFICATION NO. 904,209

Page 2, line 25, *after* "hydroxy" *insert* "-1"

Page 2, line 90, *for* "excipitents" *read* "excipients"

THE PATENT OFFICE,
8th October, 1962

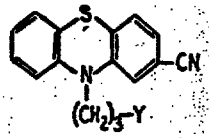
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