PATENT SPECIFICATION

NO DRAWINGS

1,043,852

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No. 25969/63.
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Int. Cl.:—C 07 d 99/10

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act, 1949 are:— JANY RENZ, Kirschblütenweg 12, Basle, Switzerland; JEAN-PIERRE BOURQUIN, Starenstrasse 14, Basle, Switzerland; HANS WINKLER, Oberer Batterieweg 10, Basle, Switzerland; CONRAD BRÜSCHWEILER, Rheinparkatrasse 5, Birsfelden/Baselland, Switzerland and GUSTAV SCHWARB, ~~Hewingelstrasse~~ 12, Neu-Allschwil/Baselland, Switzerland, all Swiss citizens.

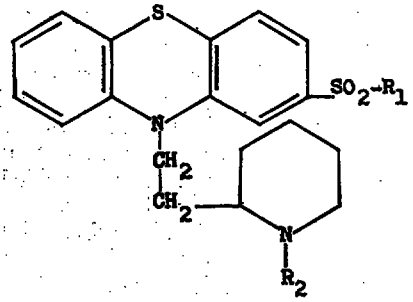
COMPLETE SPECIFICATION

Improvements in or relating to Phenothiazine Compounds

We, SANDOZ PATENTS LIMITED of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, 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 the production of novel heterocyclic compounds and to a process for their manufacture.

The present invention provides phenthiazine compounds of formula I,

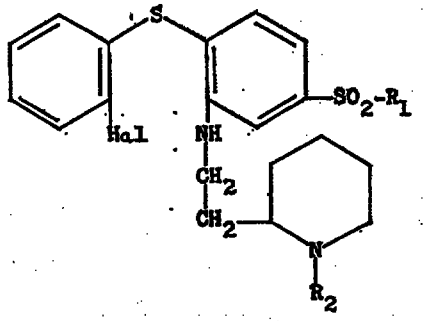


I

in which R_1 and R_2 each denote a lower alkyl radical,

their acid addition salts and pharmaceutical compositions containing, in addition to an inert carrier, a compound I or an acid addition salt thereof.

The present invention also provides a process for the production of the compounds I and their acid addition salts, which process comprises cyclizing a diphenyl sulphide derivative of formula II,



II

in which R_1 and R_2 have the above significance, and
Hal denotes a chlorine, bromine or iodine atom,

and, when it is desired to produce an acid addition salt, salifying with an organic or inorganic acid.

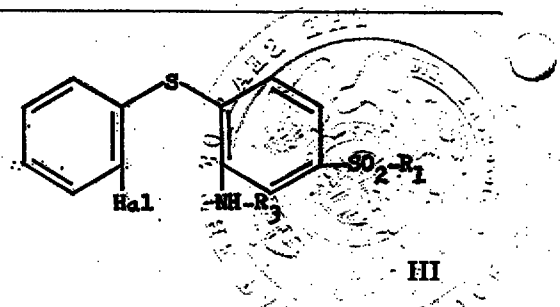
The process is carried out, for example, by heating for a prolonged period a diphenyl sulphide derivative of formula II in a suitable solvent, e.g. dichlorobenzene, decalin or dimethyl formamide, after adding an alkaline condensation agent e.g. an alkali metal carbonate or alkali metal hydroxide, and, if desired, a small amount of copper powder. When reaction is complete, filtration is effected and the filtrate, when the solvent used is immiscible with water, is extracted directly with

a dilute mineral or organic acid. When the solvent used is miscible with water, this latter is first removed by evaporation in a vacuum, the residue is dissolved in a solvent which is immiscible with water and only then extracted with acid. The compounds I are separated from the acid extract by adding a caustic alkali solution or ammonia and if they are precipitated in solid form, they are filtered, otherwise they are taken up in benzene or other solvent which is immiscible with water and then freed from the solvent by evaporation. The bases may be purified by crystallization from a suitable solvent or purified by distillation in a high vacuum and converted into a suitable salt with organic or inorganic acids or with 8-chlorotheophylline.

The compounds I are oily or crystalline at room temperature and form relatively stable salts with acids and with 8-chlorotheophylline. They have therapeutically valuable pharmacodynamic properties, *e.g.* they potentiate the effect of narcotically, ~~hapnotically~~ or analgesically active drugs. As a consequence of this, they have a neuroplegic and sedative action in psychic diseases and may also be used for narcosis preparation. The compounds I also have cateleptic properties, for which reason they can be used in psychiatry for the treatment of motor excitation conditions. The compound 3-methylsulphonyl-10-[2′-(1″-methylpiperidyl-2″)-ethyl-1′]-phenthiazine has been found to exhibit an especially strong motor-inhibitory effect and an anti-emotional effect.

The compounds I may be worked up in the form of pharmaceutical preparations. These contain the compound of the invention in admixture with an organic or inorganic carrier which is suitable for enteral, parenteral or logical application and which does not react with the compounds I, *e.g.* gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gum arabic, polyalkylene glycols, petroleum jelly, cholesterol or other known pharmaceutical carriers. The pharmaceutical preparations may, for example, be in the form of tablets, dragées, powders, creams, suppositories or in liquid form as solutions, suspensions or emulsions; they may, if desired, be sterilized and/or contain adjuvants such as preserving agents, stabilizers, wetting agents or emulsifiers, or other therapeutically active substances.

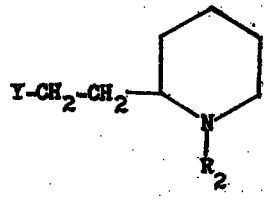
The starting Materials II are described and claimed in ~~British Specification~~ Serial No. 1,043,853 (54125/65). They may be produced by condensation of a compound of formula III,



III

in which R_3 denotes hydrogen or a lower acyl radical, and
R_1 and Hal have the above significance,

with a piperidine derivative of the formula IV,



IV

in which R_2 has the above significance and
Y denotes chlorine or bromine,
and splitting off hydrolytically any acyl radical present.

This condensation may, if desired, be effected by heating in a suitable organic solvent in the presence of an alkaline condensation agent. On completing the reaction, the reaction mixture is shaken out with water and the organic solution extracted with a dilute mineral or organic acid. The base is separated from the aqueous phase by adding a caustic alkali solution or ammonia. After taking up the precipitated base in a solvent which is immiscible with water, e.g. benzene, and evaporating the solvent under reduced pressure, the base is purified by crystallization or by distillation in a high vacuum and converted, if desired, into a salt with a suitable inorganic or organic acid, e.g. hydrochloric, hydrobromic, sulphuric, citric, tartaric, succinic, maleic, malic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic acid. When a substance III is used, in which R_3 is a lower acyl radical, the condensation product must be deacylated before further reaction, if deacylation has not already taken place during condensation; this may be effected by boiling with an aqueous mineral acid or with an alkali metal hydroxide in

a higher alcohol. The diphenyl sulphides II also possess a good spasmolytic action; some compounds II have a spasmolytic action which is several times stronger than papaverine on the isolated guinea-pig intestine.

It should be noted that the specific acids mentioned in the immediately preceding paragraph are suitable also for converting the free bases I above into their acid addition salts.

As used herein to qualify "alkyl" and "acyl" the word "lower" indicates alkyl or acyl radicals containing from 1 to 4 carbon atoms inclusive.

In the following non-limitative Examples, all temperatures are indicated in degrees Centigrade. Melting points are corrected.

EXAMPLE 1:

3 - methylsulphonyl - 10 - [2' - (1'' - methylpiperidyl - 2'') - ethyl - 1'] - phenthiazine

a) 2 - bromo - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - methylsulphonyl - diphenylsulphide

50.0 g of 2 - bromo - 2' - acetamino - 4' - methylsulphonyl - diphenylsulphide (m.p. 151—153°, produced by acetylation of 2 - bromo - 2' - amino - 4' - methylsulphonyl - diphenylsulphide, m.p. 125—127°) and 5.85 g of finely powdered sodamide in 200 cc of absolute xylene are heated to boiling under reflux while stirring for one hour at an oil bath temperature of 180°. Without interrupting heating, a solution of 22.1 g of 2 - (1' - methyl - piperidyl - 2') - 1 - chloroethane in 25 cc of absolute xylene is added dropwise. After heating for a further 5 hours, the reaction mixture is cooled and shaken out three times with 25 cc of water, after adding 10 g of ammonium chloride. The xylene solution is extracted with 450 cc of 15% aqueous tartaric acid, the tartaric acid extract washed with 150 cc of benzene and rendered alkaline to phenolphalein with 110 cc of concentrated sodium hydroxide solution. The oily base which separates is taken up in a total of 300 cc of benzene, the benzene extract washed out with 75 cc of water, dried over potassium carbonate, filtered and reduced in volume by evaporation under reduced pressure. 12.6 g of the residue after evaporation are dissolved in 65 cc of absolute alcohol and ethanolic hydrogen chloride added until a congo-acid reaction is obtained. After twice recrystallizing from absolute ethanol, the pure 2 -bromo - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - acetamino - 4' - methylsulphonyl - diphenylsulphide hydrochloride showing a constant melting point at 188—190° is obtained.

A solution of 51.3 g of 2 - bromo - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - acetamino - 4' - methylsulphonyl - diphenylsulphide hydrochloride in 480 cc of 18% aqueous hydrochloric acid is boiled under reflux for 6 hours at an oil-bath temperature of 160°. After cooling, approximately 250 cc of concentrated sodium hydroxide solution are added until a phenolphthalein alkaline reaction is obtained and the base which separates is extracted with 300 cc of benzene. The benzene solution is washed with 100 cc of water, dried over potash, filtered and reduced in volume by evaporation. After twice recrystallizing the residue from acetone, pure 2 - bromo - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - methylsulphonyl - diphenylsulphide is obtained, having a constant melting point of 123—125°.

b) 3 - methylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine

A mixture of 20.0 g of 2 - bromo - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - methylsulphonyl - diphenylsulphide (m.p. 123—125°), 11.4 g of finely powdered potassium carbonate, 0.75 g of copper powder and 200 cc of dimethylformamide is heated to boiling under reflux of 48 hours, while stirring, at an oil bath temperature of 210°. After cooling, filtration is carried out and the filtrate is freed of solvent in a vacuum. The residue left after evaporation is dissolved in 200 cc of benzene and shaken out with 100 cc of 15% aqueous tartaric acid. After washing out the tartaric acid extract with 75 cc of benzene, 25 cc of concentrated sodium hydroxide solution are added until a phenolphthalein alkaline reaction is obtained, the base which separates is taken up in 150 cc of benzene, the benzene extract washed with 75 cc of water, dried over potassium carbonate, filtered and reduced in volume by evaporation. After crystallizing the residue three times from acetone and adding petroleum ether, the pure 3 - methyl - sulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine is obtained, having a melting point of 121—123°.

EXAMPLE 2:

3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine

a) 2 - chloro - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - ethylsulphonyl - diphenylsulphide

A solution of 328 g of 2 - chloro - 2' - amino - 4' - ethylsulphonyl - diphenylsulphide and 186 g of 2 - (1' - methyl - piperidyl - 2') - 1 - chloroethane in 2000 cc of toluene is heated to boiling under reflux, while stirring, with water separator, at an oil bath temperature of 150° and 168 g of finely powdered potassium hydroxide added in portions to the boiling solution during the course of 1½ hours. After a further 5 hours boiling, the reaction mixture is cooled, washed

with 750 cc of water and the basic substances extracted with 1400 cc of 15% aqueous tartaric acid. After washing out the tartaric acid extract with 500 cc of benzene, this is rendered alkaline to phenolphthalein with approximately 350 cc of concentrated sodium hydroxide solution and the precipitated base taken up in 1500 cc of benzene, the benzene phase washed with 500 cc of water and reduced in volume by evaporation and the residue crystallized from 750 cc of acetone. After crystallizing once more from acetone, analytically pure 2 - chloro - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - ethylsulphonyl - diphenylsulphide is obtained, having a constant melting point of 110—112°.

The 2 - chloro - 2' - amino - 4' - ethylsulphonyl - diphenylsulphide used as starting material may be produced as follows: *p,p'* - dichloro - diphenyl - disulphide is split with sodium sulphide and the resulting *p* - chlorothiophenol converted into *p* - ethylmercapto - chlorobenzene (b.p. 109—112°/12 mm Hg) by alkylation with diethyl sulphate. The *p* - ethylmercapto - chlorobenzene is oxidised with hydrogen peroxide in glacial acetic acid to give *p* - ethylsulphonyl - chlorobenzene (m.p. 37—39°) and then nitrified. The resulting 2 - chloro - 5 - ethylsulphonyl - nitrobenzene (m.p 98—100°) is condensed with the sodium salt of *o* - chlorothiophenol to give 2 - chloro - 2' - nitro - 4' - ethylsulphonyl - diphenylsulphide (m.p. 144—146°) and this compound reduced with iron and hydrochloric acid to 2 - chloro - 2' - amino - 4' - ethylsulphonyl - diphenylsulphide.

b) 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine

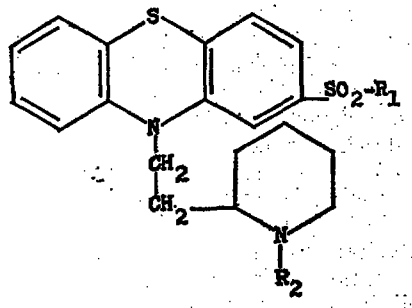
A mixture of 100 g of 2 - chloro - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - ethylsulphonyl - diphenylsulphide (m.p. 110—112°), 30.5 g of finely powdered potassium carbonate, 4 g of copper powder and 1000 cc of dimethylformamide is heated to boiling under reflux while stirring for 15 hours at an oil bath temperature of 210°. After cooling, filtration is effected and the filtrate freed of solvent in a vacuum. The residue left after evaporation is dissolved in 400 cc of benzene and shaken out with 400 cc of 15% aqueous tartaric acid. After washing the tartaric acid extract with 200 cc of benzene, 100 cc of concentrated sodium hydroxide solution are added to this until a phenolphthalein-alkaline reaction is obtained, the precipitated base is taken up in 500 cc of benzene, the benzene extract washed with 200 cc of water, dried over potassium carbonate, filtered and reduced in volume. After crystallizing the residue three times from acetone, pure 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine of m.p. 105—107° is obtained.

Benzenesulphonate

14.0 g of the base and 5.85 g of benzenesulphonic acid are dissolved in 60 cc of absolute ethanol, while boiling and the solution is then cooled. The salt which crystallizes out is crystallized from 60 cc of absolute ethanol, whereupon the pure 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine - benzene sulphonate is obtained, having a melting point of 147—149°.

WHAT WE CLAIM IS:—

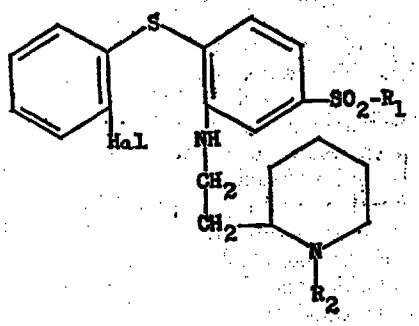
1. A process for the production of phenthiazine compounds of formula I,



I

in which R_1 and R_2 each denote a lower alkyl radical,

and their acid addition salts which comprises cyclizing a diphenyl sulphide derivative of formula II,



II

in which R_1 and R_2 have the above significance, and

Hal denotes a chlorine, bromine or iodine atom,

and, when it is desired to produce an acid addition salt, salifying with an organic or inorganic acid.

with 750 cc of water and the basic substances extracted with 1400 cc of 15% aqueous tartaric acid. After washing out the tartaric acid extract with 500 cc of benzene, this is rendered alkaline to phenolphthalein with approximately 350 cc of concentrated sodium hydroxide solution and the precipitated base taken up in 1500 cc of benzene, the benzene phase washed with 500 cc of water and reduced in volume by evaporation and the residue crystallized from 750 cc of acetone. After crystallizing once more from acetone, analytically pure 2 - chloro - 2' - [2'' - (1''' - methyl - piperidyl - 2''') - ethyl - 1''] - amino - 4' - ethylsulphonyl - diphenylsulphide is obtained, having a constant melting point of 110—112°.

The 2 - chloro - 2' - amino - 4' - ethylsulphonyl - diphenylsulphide used as starting material may be produced as follows: *p,p'* - dichloro - diphenyl - disulphide is split with sodium sulphide and the resulting *p* - chlorothiophenol converted into *p* - ethylmercapto - chlorobenzene (b.p. 109—112°/12 mm Hg) by alkylation with diethyl sulphate. The *p* - ethylmercapto - chlorobenzene is oxidised with hydrogen peroxide in glacial acetic acid to give *p* - ethylsulphonyl - chlorobenzene (m.p. 37—39°) and then nitrified. The resulting 2 - chloro - 5 - ethylsulphonyl - nitrobenzene (m.p 98—100°) is condensed with the sodium salt of *o* - chlorothiophenol to give 2 - chloro - 2' - nitro - 4' - ethylsulphonyl - diphenylsulphide (m.p. 144—146°) and this compound reduced with iron and hydrochloric acid to 2 - chloro - 2' - amino - 4' - ethylsulphonyl - diphenylsulphide.

b) 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine

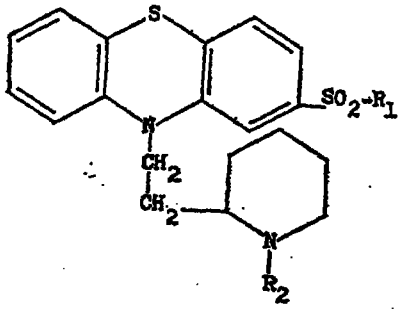
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Benzenesulphonate

14.0 g of the base and 5.85 g of benzenesulphonic acid are dissolved in 60 cc of absolute ethanol, while boiling and the solution is then cooled. The salt which crystallizes out is crystallized from 60 cc of absolute ethanol, whereupon the pure 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine - benzene sulphonate is obtained, having a melting point of 147—149°.

WHAT WE CLAIM IS:—

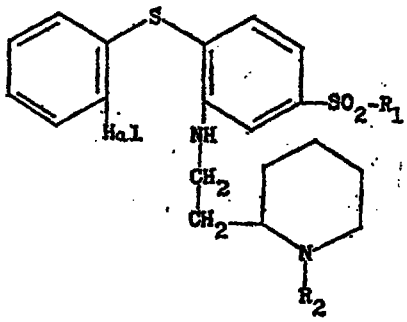
1. A process for the production of phenthiazine compounds of formula I,



I

in which R_1 and R_2 each denote a lower alkyl radical,

and their acid addition salts which comprises cyclizing a diphenyl sulphide derivative of formula II,



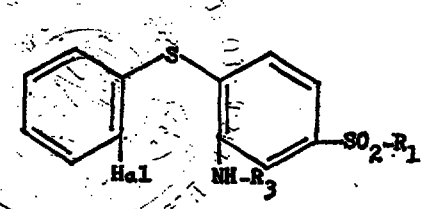
II

in which R_1 and R_2 have the above significance, and

Hal denotes a chlorine, bromine or iodine atom,

and, when it is desired to produce an acid addition salt, salifying with an organic or inorganic acid.

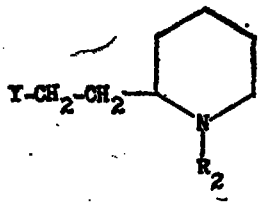
2. A process according to Claim 1, in which the compound II is produced by condensing a compound of formula III,



III

in which Hal and R_1 have the significance stated in Claim 1, and
R_3 denotes hydrogen or a lower acyl radical,

with a compound of formula IV,



IV

in which R_2 has the significance stated in Claim 1, and
Y denotes chlorine or bromine,

and hydrolytically splitting off any acyl radical present.

3. A process for the production of compounds I stated in Claim 1 and their acid addition salts, substantially as herein described with reference to any one of the Examples.

4. The compounds I stated in Claim 1 and their acid addition salts, whenever produced by the process claimed in any one of the preceding Claims.

5. The compounds I stated in Claim 1 and their acid addition salts.

6. 3 - methylsulphonyl - 10 - [2' - (1'' - methylpiperidyl - 2'') - ethyl - 1'] - phenthiazine.

7. 3 - ethylsulphonyl - 10 - [2' - (1'' - methyl - piperidyl - 2'') - ethyl - 1'] - phenthiazine.

8. The acid addition salts of the compounds claimed in either one of Claim 6 and 7.

9. Pharmaceutical compositions containing, in addition to an inert carrier, a compound claimed in any one of Claims 4—8.

For the Applicants:—
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* C L M S *