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PHENOTHIAZINE COMPOUNDS

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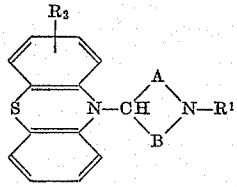
6 Claims. (Cl. 260—243)

The invention relates to phenothiazine derivatives which are of pharmaceutical value.

This application is a continuation-in-part of my copending application Serial Number 418,477 filed March 24, 1954, now U.S. Pat. No. 2,784,185.

The compounds of this invention may be represented by the following structural formula:

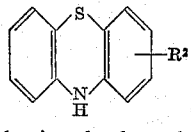


I

wherein R^1 denotes lower alkyl, R^2 denotes hydrogen, halogen, lower alkyl or lower alkoxy. A denotes methylene or ethylene, B denotes ethylene or propylene, the sum of the number of carbon atoms contained in the radicals A and B being four. Also included in this invention are the nontoxic acid addition salts of the compounds having the above structural formula.

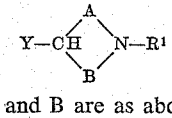
It is an object of this invention to provide compounds which generally depress the vital body functions such as the blood pressure and the pulse and breathing rates. Further, these compounds potentiate the physiological action of narcotics—a property which renders them extremely valuable in surgery.

The compounds of this invention may readily be prepared by reacting a compound having the formula



II

with a compound having the formula



III

wherein R^1, R^2, A and B are as above defined, and Y is halogen.

The reaction is carried out in the presence of a basic condensing agent such as sodamide, lithium amide, sodium, sodium alcoholate, sodium hydride, and the like, and in the presence of an inert solvent such as benzene, toluene, xylene, cyclohexane, tetralin, decalin, and the like. The free bases obtained by the reaction described above, are converted to nontoxic acid addition salts thereof with inorganic acids or organic acids, in the usual manner.

The following example will serve to illustrate this invention:

EXAMPLE 1

10-(1-ethyl-3-piperidyl)phenothiazine hydrochloride

A mixture of 0.25 mole of phenothiazine and 0.31 mole of lithium amide in 250 ml. of tetralin is heated at 150–175° C. for about two hours, then 0.25 mole of 1-ethyl-3-bromopiperidine in 150 ml. of tetralin is added over a period of two hours at 170–175° C. After the addition has been completed, heating is continued at 170–175° C. for three to four hours. After cooling, the product is extracted with aqueous acetic acid and the organic layer is removed. The aqueous layer is made strongly alkaline with sodium hydroxide and the organic base is extracted with ether. The ether is removed, yielding 10-(1-ethyl-3-piperidyl)phenothiazine which distills at 220–225° C./2–3 mm. The hydrochloride is prepared by heating the free base in aqueous hydrochloric acid and allowing the resulting liquid to cool, whereupon the desired substance is obtained, M.P. 230–231° C.

In a corresponding manner, the following compounds were prepared:

10-(1-methyl-4-piperidyl)phenothiazine: Boiling point 196° C./2–3 mm.; melting point of hydrochloride 244–246° C.

10-(1-methyl-3-piperidyl)-2-chlorophenothiazine: Boiling point 191°/0.1 mm.; melting point of hydrochloride 203–206° C.

10-(1-methyl-3-piperidyl)-4-chlorophenothiazine: Boiling point 187–189° C./0.18 mm.; melting point of picrate 181–183° C. (dec); melting point of hydrochloride 227–230° C. (dec).

10-(1-n-propyl-3-piperidyl)-2-methylphenothiazine: Boiling point 175–178° C./0.075 mm.; melting point of picrate 169–171° C.; melting point of oxalate 178–180° C.

10-(1-n-propyl-3-piperidyl)-3-methylphenothiazine: Boiling point 178–179° C./0.10 mm.; melting point of picrate 153–154° C.; melting point of oxalate 164–166° C.

10-(1-n-propyl-3-piperidyl)-4-methylphenothiazine: Boiling point 174–175° C./0.1 mm.; melting point of picrate 141–143° C. (dec); melting point of oxalate 180–182° C. (dec).

10-(1-propyl-3-piperidyl)-2-methoxyphenothiazine: Boiling point 208–210° C./0.4 mm.; melting point of picrate 168–171° C.

10-(1-methyl-3-piperidyl)-3-methoxyphenothiazine: Boiling point 185–186° C./0.06 mm.; melting point of picrate 194–196° C. (dec).

10-(1-methyl-4-piperidyl)-2-chlorophenothiazine: Boiling point 198–200° C./2–3 mm.; hydrochloride is hygroscopic, and the melting point thereof could not be determined.

10-(1-methyl-4-piperidyl)-4-chlorophenothiazine: Boiling point 194–198° C./0.3 mm.; melting point of picrate 180–182° C. (dec); melting point of oxalate 217–220° C. (dec).

10-(1-methyl-3-piperidyl)phenothiazine: Melting point of hydrochloride 236–238° C.

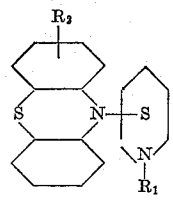
10-(1-n-butyl-3-piperidyl)phenothiazine: Boiling point 235–240° C./2–3 mm.; the hydrochloride is hygroscopic, and the melting point thereof cannot be determined.

Since certain changes may be made in the compounds above described without departing from the scope of this invention, it is intended that all matter contained in the

above description shall be interpreted as illustrative, and not in a limiting sense.

I claim:

1. A piperidyl substituted phenothiazine compound selected from the group consisting of compounds of the formula



wherein R_1 is lower alkyl and R_2 is selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkoxy, and the non-toxic acid addition salts thereof.

2. 10-(1-methyl-4-piperidyl)phenothiazine.
3. 10-(1-n-propyl-3-piperidyl)-2-methylphenothiazine.
4. 10-(1-methyl-3-piperidyl)-3-methoxyphenothiazine.
5. 10-(1-ethyl-3-piperidyl)phenothiazine.
6. 10(1-n-butyl-3-piperidyl)phenothiazine.

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