1,065,296

PATENT SPECIFICATION

NO DRAWINGS

1,065,296

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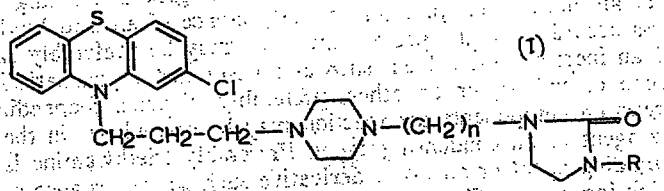
Int. Cl.:— C 07 d 99/10 // A 61 k

COMPLETE SPECIFICATION

Phenthiazine Derivatives

We, ASTA-WERKE AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Brackwede/Westf., 79—91 Bielefelder Strasse, Germany, 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 relates to novel phenthiazine derivatives of the general formula I

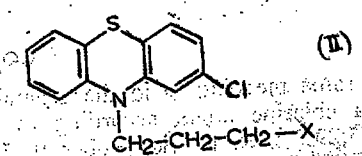


(I)

wherein R is methyl or ethyl and n is the numeral 2 or 3, preferably however 2, and salts thereof with pharmacologically acceptable acids, said products having an improved psychosedative and antiemetic effectiveness. The invention accordingly provides, as new compounds, compounds of the general formula I above which may be in association with a pharmaceutically acceptable carrier.

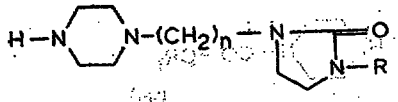
The new compounds according to the present invention may be produced by the following N-alkylation methods:

a) Reacting a phenthiazine derivative of the general formula II



(II)

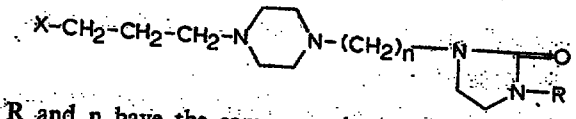
wherein X is the residue of a reactive ester, preferably a halogen atom or the residue of a sulphuric or sulphonic acid ester, with an imidazolidone derivative of the general formula III



(III)

wherein R and n have the same meaning as in the general formula I, at an elevated temperature.

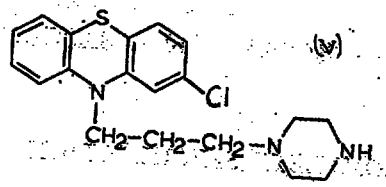
b) Reacting 3-chloro-phenthiazine with an imidazolidone derivative of the general formula IV



(IV)

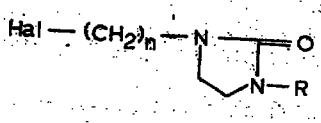
wherein R and n have the same meaning as in the general formula I and X has the same meaning as in the general formula II, at an elevated temperature.

c) Reacting a phenthiazine derivative of the general formula V



(V)

with an imidazolidone derivative of the general formula VI

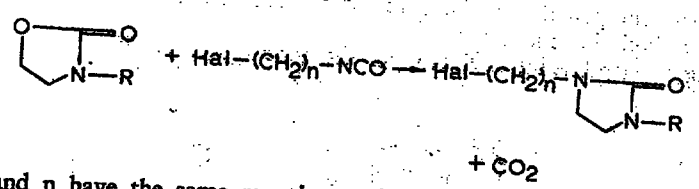


(VI)

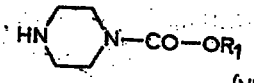
wherein n and R have the same meaning as in the general formula I and Hal is a halogen, at an elevated temperature in the presence of an acid binding agent.

The process according to the present invention may be preferably carried out in the presence of an inert organic solvent such as for instance an aromatic hydrocarbon, preferably toluene or xylene, or an ether, preferably dioxane. Depending upon the nature of the reaction components the reaction may be carried out in the presence of an acid binding agent or an condensing agent. Preferably triethylamine is used as the necessary acid binding agent or an alkali derivative such as for instance sodium amide is used as condensing agent. The reaction is carried out at an elevated temperature such as the boiling point of the applied solvent.

The imidazolidone derivatives of the general formulas III and IV which are used as starting materials in the processes according to the present invention are not known in the prior art. They may be obtained by subjecting an oxazolidone to reaction with an isocyanate according to the following equation



wherein R and n have the same meaning as in the general formula I and Hal is a halogen atom, preferably a chlorine atom, according to copending British patent application 36949/64, 1,065,295, filed on September 9, 1964 and entitled "PROCESS FOR THE PRODUCTION OF IMIDAZOLIDONES" and subjecting the 1-alkyl-3-(ω-halogenoalkyl)-imidazolidones VI thus obtained in manners known per se to reaction with piperazine to yield compounds of the general formula III or, respectively, with mono-substituted piperazines to compounds of the general formula IV. In place of piperazine, a mono-N-carbalkoxy-piperazine of the formula VII



(VII)

wherein R_1 is an alkyl group, preferably a lower alkyl group, may be used as reaction component; in this case, the carbalkoxy group has to be split off before the compound is further reacted. The phenthiazine derivative of the general formula V may be obtained for instance by subjecting 3-chloro-10-(γ-chloropropyl)-phenthiazine to reaction with piperazine. In this case, too, a mono-N-carbalkoxy-piperazine of the

formula VII may be used in place of piperazine whereafter the carbalkoxy group is split off in the resulting product in manners known per se.

The preferred salts are the hydrochlorides.

The process according to the present invention is illustrated to the following examples wherein the compounds are named according to the nomenclature used in Beilstein's Handbuch der Organischen Chemie (Handbook of Organic Chemistry).

In order that the invention may be more fully understood, the following examples are given, by way of illustration only:

Example 1.

a) N-[β-(1-methyl-2-oxo-imidazolidyl)-ethyl]-piperazine

32.5 g. of 1-methyl-3-β-chloroethyl-imidazolidone-(2) are dissolved in 200 cc. of dioxane. After having added thereto 31.6 g. of monocarbethoxypiperazine and 20.2 g. of triethylamine the reaction mixture is heated to boiling under reflux for 8 hours. Thereafter, the precipitated triethylamine hydrochloride is filtered off and the dioxane is distilled off in a vacuo. The residue is distilled in a high vacuo. B.p. $_{0.01\ mm.}$: 203—207° C. Yield: 45 g. (79.11% of the theoretical).

30 g. of the thus obtained N-[1-methyl-imidazolidone-(2)-ethyl-(3)]-N'-(carbethoxy)-piperazine are dissolved in 250 cc. of a 10% alcoholic solution of potassium hydroxide and heated to boiling under reflux for 15 hours. The precipitated potassium carbonate is filtered off and the alcohol is distilled off on a steam bath. The residue is treated with a 40% aqueous solution of sodium hydroxide and the thus separating oil is extracted several times with benzene. The combined benzene extracts are dried over potassium carbonate and are evaporated on a steam bath. The resulting residue is distilled in a high vacuo. 16 g. of N-[β-(1-methyl-2-oxo-imidazolidyl)-ethyl]-piperazine are obtained. Yield: 71.15% of the theoretical (B.p. $_{0.01\ mm.}$: 155—158° C., n_D^{22}: 1.5153).

b) 3 - Chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - ethyl - imidazolidyl) - 4' - piperazino-n-propyl]-phenthiazine

23 g. of 3-chloro-10-(γ-chloropropyl)-phenthiazine are dissolved in 100 cc. of dioxane and 15.36 g. of N-[β-(1-methyl-2-oxo-imidazolidyl)-ethyl]-piperazine obtained according to Example 1 and 7.49 g. of triethylamine are added thereto. The mixture is heated to boiling under reflux for 12 hours. After cooling the precipitated triethylamine hydrochloride is filtered off and the solvent is distilled off in a vacuo. The resulting residue is mixed with ether, the ethereal layer is washed several times with water and finally dried over potassium carbonate. After having distilled off the ether, the resulting residue is fractionated in a high vacuo and the 3-chloro-10-[1'-(1''-methyl-2''-oxo-3''-ethyl-imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine base is obtained. B.p. $_{0.01\ mm.}$: approx. 260° C. Yield: 18.5 g. (51.33% of the theoretical).

For preparing the dihydrochloride the distilled base is dissolved in anhydrous ether and ethereal hydrogen chloride is added to this solution with cooling. The precipitated dihydrochloride is filtered off and preferably recrystallized from dioxane or acetone mixed with a small amount of methanol. M.Pt.: 255° C.

Example 2.

3 - Chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - ethyl - imidazolidyl) - 4' - piperazino-n-propyl]-phenthiazine

22 g. (0.071 mols) of 3-chloro-10-(γ-chloropropyl)-phenthiazine are dissolved in 100 cc. of dioxane and 16.05 g. (0.071 mols) of N-[β-(1-ethyl-2-oxo-imidazolidyl)-ethyl]-piperazine (B.p. $_{0.01\ mm.}$: 160—165° C.; n_D^{22}: 1.5111) and 7.17 g. (0.071 mols) triethylamine are added thereto. The mixture is heated to boiling under reflux for 16 hours. The N-[β-(1-ethyl-2-oxo-imidazolidyl)-ethyl]-piperazine has been prepared as described in Example 1 from 1-ethyl-3-β-chloroethyl-imidazolidone-(2) and mono-N-carbethoxy-piperazine. The reaction mixture is worked up as described in Example 2. Thus, 3 - chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - ethyl-imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine base is obtained. B.p. $_{0.01\ mm.}$: 260—265° C. Yield: 19 g. (53.57% of the theoretical).

For preparing the dihydrochloride, the base is dissolved in anhydrous ether and ethereal hydrogen chloride is slowly added to this solution while cooling. The precipitated dihydrochloride is filtered with suction and preferably recrystallized from dioxane or a mixture consisting of acetone and a small amount of methanol. M.Pt.: 215—216° C.

EXAMPLE 3.

3 - Chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl) - 4' - piperazino-n-propyl]-phenthiazine

24.8 g. (0.08 mols) of 3-chloro-10-(γ-chloropropyl)-phenthiazine are dissolved in 100 cc. of dioxane and 18 g. (0.08 mols) of N-[γ-(1-methyl-2-oxo-imidazolidyl)-n-propyl]-piperazine (B.p. $_{0.02}$ mm.: 165—170° C.; n_D^{21}: 1.5140) and 8.1 g. (0.08 mols) of triethylamine are added thereto. The mixture is heated to boiling under reflux for 12 hours. The N-[γ-(1-methyl-2-oxo-imidazolidyl)-n-propyl]-piperazine has been prepared as described in Example 1 from 1-methyl-3-γ-chloro-n-propyl-imidazolidone-(2) and mono-N-carbethoxypiperazine.

The reaction mixture is worked up as described in Example 2. Thus, the 3-chloro-10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl) - 4' - piperazino-n-propyl]-phenthiazine base is obtained. B.p. $_{0.01}$ mm.: 265—270° C. Yield: 19 g. (47.49% of the theoretical).

For preparing the dihydrochloride, the base is treated with ethereal hydrogen chloride as described in Example 1 and recrystallized from a mixture of acetone and methanol. M.Pt.: 233° C.

EXAMPLE 4.

3 - Chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl) - 4' - piperazino-n-propyl]-phenthiazine

24 g. (0.77 mols) of 3-chloro-10-(γ-chloropropyl)-phenthiazine are dissolved in 100 cc. of dioxane and 18.60 g. (0.077 mols) of N-[γ-(1-ethyl-2-oxo-imidazolidyl)-n-propyl]-piperazine (B.p. $_{0.01}$ mm.: 168—170° C.) and 7.82 g. (0.077 mols) of triethylamine are added thereto. The mixture is heated to boiling under reflux for 12 hours. The N-[γ-(1-ethyl-2-oxo-imidazolidyl)-n-propyl]-piperazine has been prepared as described in Example 1 from 1-ethyl-3-γ-chloro-n-propyl-imidazolidone-(2) and mono-N-carbethoxy-piperazine. The separation and purification of the 3-chloro-10-[1' - (1'' - ethyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl) - 4' - piperazino - n-propyl]-phenthiazine base is carried out as described in Example 2. B.p. $_{0.01}$ mm.: approx. 270° C. Yield: 22 g. (55.30% of the theoretical).

For the preparation of the dihydrochloride, the base is treated with ethereal hydrogen chloride as described in Example 2 and is recrystallized from a mixture of acetone and methanol. M.Pt.: 225° C.

The dimaleate is obtained as follows:

7 g. of the base are dissolved in acetone. A solution of 5 g. of maleic acid anhydride (excess) in a small amount of water is added thereto and the mixture is allowed to stand over night. The precipitated crystals may be recrystallized from ethanol. M.Pt.: 166° C. Yield: 6 g. (69.95% of the theoretical).

EXAMPLE 5.

3-Chloro-10-[1'-(1''-methyl-2''-oxo-3''-ethyl-imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine dihydrochloride

46.8 g. of 3-chloro-phenthiazine (0.2 mols) are added gradually with stirring to a suspension of sodium amide in liquid ammonia (prepared from 4.6 g. of sodium (0.2 mols) and 200 cc. of liquid ammonia to which a small amount of $Fe(NO_3)_3 \times 9 H_2O$ is added) in a 1 litre three-neck-flask which is cooled with an ice-sodium chloride-cooling mixture. Thereafter, 200 cc. of toluene are added and the ammonia is allowed to evaporate (solution I).

A solution of 4.8 g. (0.21 mols) of sodium dispersed in 150 cc. of toluene is added to a solution of 56.8 g. (0.21 mols) of N-[β-(1-methyl-2-oxo-imidazolidyl)-ethyl]-N'-(hydroxy-propyl)-piperazine in 50 cc. of toluene. 40 g. of *p*-toluenesulfonyl chloride dissolved in 100 cc. of toluene are added dropwise with stirring to this solution at 0° to 5° C.

The resulting mixture is stirred at this temperature for 2 hours. Thereafter, the precipitated sodium chloride is filtered off, thus yielding a solution of N-[β-(1-methyl - 2 - oxo - imidazolidyl) - ethyl] - N' - [- (*p* - toluenesulfonyloxy) - propyl]-piperazine in toluene. This solution is added dropwise with stirring at 90° C. to the above solution I. The reaction mixture is further stirred for 2 hours at this temperature. After cooling, the precipitated sodium salt of p-toluenesulfonic acid is filtered off and the filtrate is evaporated in a vacuo. The resulting residue is dissolved in benzene and washed several times with water. After drying and separating the benzene by distillation, the resulting residue is dissolved in anhydrous ether and ethereal hydrogen chloride is added thereto in excess while cooling. The precipitated dihydrochloride of the base is filtered off and recrystallized from acetone containing a small amount of methanol. Yield: 34 g.; M.Pt.: 223° C.

EXAMPLE 6.

3-Chloro-10-[1'-(1''-methyl-2''-oxo-3''-ethyl-imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine dihydrochloride

9 g. of 10-(piperazinopropyl)-3-chlorophenthiazine (0.025 mols) are dissolved in 100 cc. of dioxane and 5 g. (0.031 mols) of 1-methyl-3-β-chloroethyl-imidazolidone-(2) and 2.55 g. (0.025 mols) of triethylamine are added thereto. The mixture is heated to boiling under reflux for 15 hours. After cooling, the precipitated triethylamine hydrochloride is filtered off and the filtrate is evaporated on a steam bath. The resulting residue is treated with ether and the ethereal phase is washed several times with water. After drying the phenthiazine base is precipitated from this solution by the addition of an excess of ethereal hydrogen chloride while cooling. After separation by filtration, the hydrochloride is recrystallized from acetone containing a small amount of methanol. Yield: 4 g.; M.Pt.: 223° C.

The phenthiazine derivatives of the general formula I produced according to the present invention are pharmacologically interesting particularly because of their strong psychosedative and antiemetic effectiveness which in comparison to known phenthiazine derivatives with similar constitution is improved to a surprisingly high extent as follows from the following data.

The following compounds have been compared in the following pharmacological tests a—d;

1. 3 - chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - ethyl - imidazolidyl) - 4'-piperazino-n-propyl]-phenthiazine according to Example 2;
2. 3 - chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - ethyl - imidazolidyl) - 4'-piperazino-n-propyl]-phenthiazine according to Example 3;
3. 3 - chloro - 10 - {γ - [4' - (β - hydroxyethyl) - piperazino] - n - propyl}-phenthiazine;
4. 3-chloro-10-(γ-dimethylamino-propyl)-phenthiazine.

The compound No. 3 is traded in Germany under the trade name "PERPHENZIN" and the compound No. 4 is traded in Germany under the trade name "CHLORPROMAZIN". They are regarded as highly effective neuroleptics of the phenthiazine series.

a) The test compounds were administered subcutaneously to rats for testing their sedative effectiveness. The test animals were regarded as sedated if they showed neither spontaneous motility nor were caused to move by weak mechanical stimulus (by pushing) (Table 2).

TABLE 2: Sedative effectiveness on rats; s.c.

Compound No.	DE 95 (μmol./kg.)	Relative effectiveness [PERPHENAZIN (No. 3) = 100]
1	2.2	268
2	5.4	109
3	5.9	100
4	17.0	35

If calculating the effectiveness of the various test compounds to compound No. 3 (PERPHENAZIN) as 100, it may be seen that test compound No. 1 according to the present invention has almost three times the effectiveness of PERPHENAZIN. The test compounds according to the present invention are about three times and, respectively, 8.5 times more effective than CHLORPROMAZIN (test compound No. 4).

b) The narcosis prolonging effectiveness has been tested on mice. The test compounds were administered to the test animals intraperitoneally and 30 minutes after the intravenous administration of 68 mg./kg. of hexobarbital-Na. The reappearance of the retrogate reflex was used as the time of termination of the narcosis (Table 3).

TABLE 3: Narcosis prolonging effectiveness on mice; i.p.

Test Compound No.	Dose [1] (μmol/kg.)	Relative effectiveness (PERPHENAZIN = 100)
1	3.4	212
2	3.7	195
3	7.2	100
4	6.8	106

[1] Dose effecting a 100% prolongation of the duration of narcosis.

In this test, compounds No. 1 and 2 according to the present invention produced twice the effectiveness of the known test compounds No. 3 and 4.

c) In order to examine the hypothermic effectiveness of the compounds on rats, the dose which produced an average decrease of the normal body temperature for −1.0° C. after subcutaneous application was determined (Table 4).

TABLE 4: Hypothermic effectiveness on rats; s.c.

Test Compound No.	DE −1.0°C. (μmol./kg.)	Relative effectiveness (PERPHENAZIN = 100)
1	1.1	275
2	1.9	158
3	3.0	100
4	3.7	81

In this test, compounds No. 1 and 2 according to the present invention produced an increase in effectiveness for 1.6 to 2.8 times when compared with compound No. 3 and for 2 to 3.5 times when compared with compound No. 4.

d) The antiemetic effectiveness was tested on dogs after administration of apomorphine. The animals were regarded as protected if 30 minutes after the subcutaneous injection of the test compounds no vomiting was caused by intramuscular administration of 0.05 to 0.07 mg./kg. of apomorphine (Table 5).

TABLE 5: Antiemetic effectiveness on dogs; s.c.

Test Compound No.	DE 95 (μmol./kg.)	Relative effectiveness (PERPHENAZIN = 100)
1	0.143	122
2	0.096	179
3	0.172	100
4	7.3	2.3

With respect to antiemetic effectiveness compound No. 2 was particularly effective (79% increase of effectiveness in comparison to PERPHENAZIN (test compound No. 3). In the same way, test compound No. 1 according to the present invention still was 22% more effective than this highly effective comparitive compound No. 3. Compound No. 4 (CHLORPROMAZIN) in contrast thereto showed only a very low antiemetic effectiveness.

The comparitive toxicity tests on rats (s.c.) showed that all of the test compounds have a rather low toxicity.

TABLE 6: Toxicity

Test Compound No.	DL 50+) (μmol./kg.)	Relative toxicity (PERPHENAZIN = 100)
1	1156	84
2	1188	82
3	973	100
4	1307	74

+) seven days test.

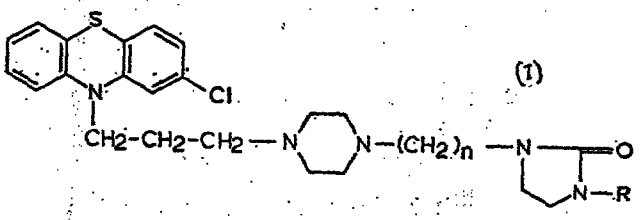
From these toxicity values the therapeutic index regarding the sedative and the antiemetic effectiveness may be calculated as follows:

TABLE 7: Therapeutic index

Test Compound No.	Therapeutic Index (DL 50/DE 95)	
	Sedative Effectiveness on Rats s.c.	Antiemetic Effectiveness on Dogs s.c.
1	525	8080
2	220	12380
3	165	5660
4	77	179

WHAT WE CLAIM IS:—

1. Phenthiazine derivatives of the general formula I



(I)

wherein R is ethyl or methyl and n is 2 or 3, and salts thereof with pharmacologically acceptable acids.

2. 3 - Chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - ethyl - imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

3. 3 - Chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - ethyl - imidazolidyl) - 4'-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

4. 3 - Chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

5. 3 - Chloro - 10 - [1' - (1'' - ethyl - 2'' - oxo - 3'' - n - propyl - imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

6. 3 Chloro - 10 - [1' - (1'' - methyl - 2'' - oxo - 3'' - ethyl - imidazolidyl)-4'-piperazino-n-propyl]-phenthiazine dihydrochloride.

TABLE 6: Toxicity

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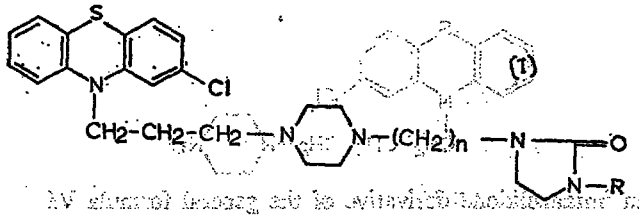
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1. Phenthiazine derivatives of the general formula I



(I)

wherein R is ethyl or methyl and n is 2 or 3, and salts thereof with pharmacologically acceptable acids.

2. 3 - Chloro - 10 - [1′ - (1″ - methyl - 2″ - oxo - 3″ - ethyl - imidazolidyl)-4′-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

3. 3 - Chloro - 10 - [1′ - (1″ - ethyl - 2″ - oxo - 3″ - ethyl - imidazolidyl) - 4′-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

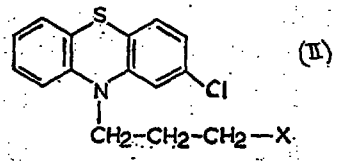
4. 3 - Chloro - 10 - [1′ - (1″ - methyl - 2″ - oxo - 3″ - n - propyl - imidazolidyl)-4′-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

5. 3 - Chloro - 10 - [1′ - (1″ - ethyl - 2″ - oxo - 3″ - n - propyl - imidazolidyl)-4′-piperazino-n-propyl]-phenthiazine and pharmaceutically acceptable acid addition salts thereof.

6. 3 Chloro - 10 - [1′ - (1″ - methyl - 2″ - oxo - 3″ - ethyl - imidazolidyl)-4′-piperazino-n-propyl]-phenthiazine dihydrochloride.

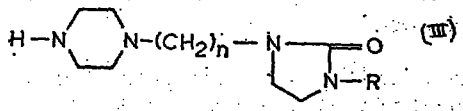
* C L M S *

7. A process for the preparation of phenthiazine derivatives as claimed in claim 1 in which a phenthiazine derivative of the general formula II



(II)

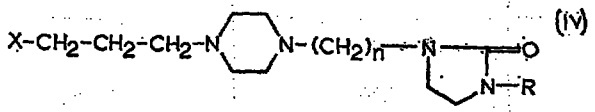
wherein X is the residue of a reactive ester, is reacted with an imidazolidone derivative of the general formula III



(III)

wherein R and n have the meaning specified in claim 1, at an elevated temperature, the resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

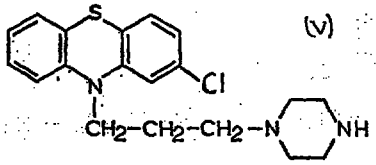
8. A process for the preparation of phenthiazine derivatives as claimed in claim 1 in which 3-chloro-phenthiazine is reacted with an imidazolidone derivative of the general formula IV



(IV)

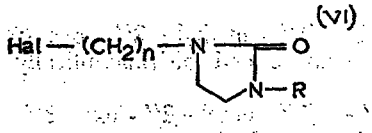
wherein R and n have the meaning specified in claim 1 and X has the same meaning as in formula II, at an elevated temperature, the resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

9. A process for the preparation of phenthiazine derivatives as claimed in claim 1 in which the phenthiazine derivative of the general formula V



(V)

is reacted with an imidazolidone derivative of the general formula VI



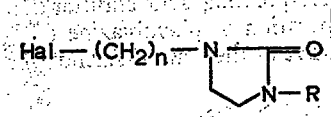
(VI)

wherein n and R have the meaning specified in claim 1 and Hal is a halogen atom, at an elevated temperature and in the presence of an acid binding agent, the resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

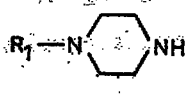
10. A process as claimed in claim 7 or claim 8 in which X is a halogen atom and the reaction is carried out in the presence of an acid binding agent.

11. A process as claimed in claim 7 or claim 8 in which X is the residue of a sulfonic acid ester.

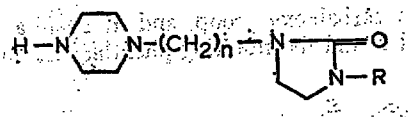
12. Process for the preparation of phenthiazine derivatives as claimed in claim 1 in which an imidazolidone derivative of the general formula VI



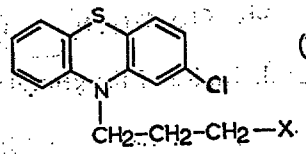
wherein Hal is a halogen atom, is reacted with a piperazine of the general formula VIII



wherein R_1 is hydrogen or a carbalkoxy group, and, if R_1 is a carbalkoxy group, this group is split off hydrolytically, and the resulting imidazolidone derivative of the general formula III

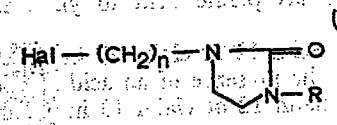


wherein R and n have the meaning specified in claim 1, is reacted with a phenthiazine derivative of the general formula II

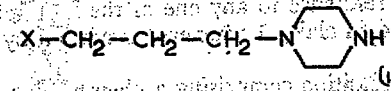


wherein X is the residue of a reactive ester, at an elevated temperature, the resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

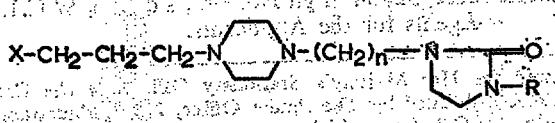
13. A process for the preparation of phenthiazine derivatives as claimed in claim 1 in which an imidazolidone derivative of the general formula VI



wherein Hal is a halogen atom, is reacted with a piperazine of the general formula IX



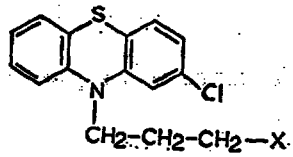
wherein X has the same meaning as in formula II, and the thus obtained imidazolidone derivative of the general formula IV



wherein R and n have the meaning specified in claim 1 and X has the same meaning as in formula II, is reacted with 3-chloro-phenthiazine at an elevated temperature, the

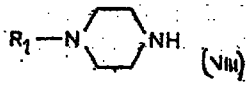
resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

14. A process for the preparation of phenthiazine derivatives as claimed in claim 1 in which a phenthiazine derivative of the general formula II



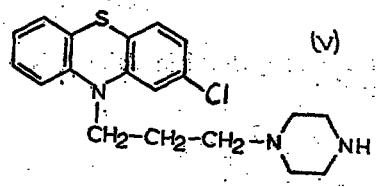
(II)

wherein X is the residue of a reactive ester, is reacted with a piperazine of the general formula VIII



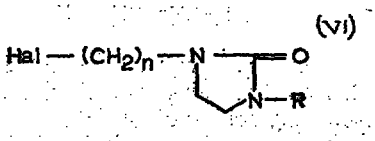
(VIII)

wherein R_1 is hydrogen or a carbalkoxy group, and, if R_1 is a carbalkoxy group this group is split off hydrolytically, and the resulting phenthiazine derivative of the general formula V



(V)

is reacted with an imidazolidone derivative of the general formula VI



(VI)

wherein n and R have the meaning specified in claim 1 and Hal is a halogen atom, at an elevated temperature, the resulting phenthiazine derivatives if desired then being reacted with a pharmacologically acceptable acid to yield the corresponding acid addition salt.

15. A process as claimed in claim 12 or claim 13 in which X is a halogen atom and the last step is carried out in the presence of an acid binding agent.

16. A process as claimed in claim 12 or claim 13 in which X is the residue of a sulfonic acid ester.

17. A process as claimed in any of claims 7 to 16 in which hydrochloric acid is used as pharmacologically acceptable acid.

18. A process for the preparation of compounds as claimed in claim 1 substantially as herein described with reference to any one of the Examples.

19. Compounds as claimed in claim 1 whenever produced by a process as claimed in any of claims 7 to 16.

20. A pharmaceutical composition comprising a phenthiazine derivative as claimed in any of claims 1 to 6 and 19 in association with a pharmaceutically acceptable carrier.

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