



PATENT SPECIFICATION

NO DRAWINGS

1.047.935

Date of Application and filing Complete Specification: Aug. 6, 1963.

No. 30926/63.

Three Applications made in United States of America (Nos. 270,534 270,536 and 270,537) on April 4, 1963.

Complete Specification Published: Nov. 9, 1966.

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Index at acceptance:—C2 C(1F2C6, 1F2D3, 1H1A3, 1H1B, 1H1C3, 2A3, 2A5, 2A7, 2A9, 2A12, 2A14, 2B2A4, 2B2C, 2B2G1B, 2G2G4, 2G2G8, 2B2J, 2B3A4, 2B3B, 2B3C, 2B3G1, 2B3G4, 2B4A4, 2B4C, 2B4F, 2B4G1, 2B4G8, 2B5, 2B9, 2B18, 2B45D1, 2B45G1, 2R15, 2R17, 2R18, 2R19, 2R20)

Int. Cl.:—C 07 d 51/64

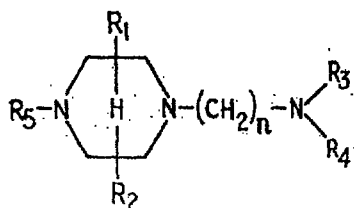
COMPLETE SPECIFICATION

Substituted Piperazines and preparation thereof

We, AMERICAN CYANAMID COMPANY, a corporation organized under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, 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 new 1-substituted-4-substituted aminoalkylene piperazines and methods of preparing the same.

The substituted piperazines of this invention have the formula



... I

wherein n is 3 or 4; R₁ and R₂ are each hydrogen atoms or lower alkyl groups; R₃ and R₄ are each hydrogen atoms, lower alkyl or aralkyl groups; and R₅ is a substituted aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; and the pharmaceutically acceptable salts of the above.

When R₅ is a heterocyclic radical, the heterocycle contains not more than four hetero atoms and the remainder are carbon atoms.

When R₅ is an aryl radical, the radical may be, for example, a chlorophenyl, nitrophenyl, aminophenyl, acetamidophenyl, trinitrophenyl, chloronaphthyl radical.

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When R₅ is an acyl radical it is preferably a benzoyl, trimethoxybenzoyl, dichlorobenzoyl, phenyltriazoloyl, benzyloxycarbonyl, furoyl, alkoxycarbonyl or trihaloacetyl group.

The heterocyclic compounds found useful in preparing the products of the present invention are, for example, 2-halopyridines, 4-halopyridines, 5-nitro-2-halopyridines, 2,5-dihalopyrimidines, 2-halothiazoles, 5-nitro-2-halothiazoles, 2-halobenzothiazoles, 2-halo-6-alkoxybenzothiazoles, 2-halobenzoxazoles, 2-halo-5-nitro-1,3,4-thiadiazoles, 4,7-dihaloquinolines, 2-haloquinolines, 4-halo-6-methoxyquinolines, 6-halopurines, 2-halopyrazines, 4-haloquinazolines, and 2-halo-6-phenylimidazo[2,1-b]-1,3,4-thiadiazoles.

The new compounds of this invention may be, for example, 1-benzoyl-4-(3-dimethylaminopropyl)piperazine; 1-(p-chlorophenyl)-4-(3-dimethylaminopropyl)piperazine; 1-(4-acetamidophenyl)-4-(3-dimethylaminopropyl)piperazine; 1-(3-dimethylaminopropyl)-4-(4-pyridyl)piperazine; 1-(7-chloro-4-quinoliny)-4-(3-dimethylaminopropyl)piperazine; 1-(3-dimethylaminopropyl)-4-(3,4,5-trimethoxybenzoyl)piperazine; and 1-(2-benzothiazolyl)-4-(3-dimethylaminopropyl)piperazine.

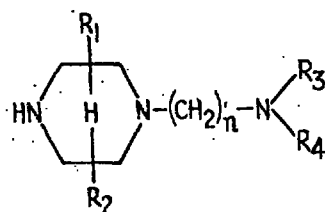
The invention also relates to the acid addition salts of the compound of formula I such as the hydrochlorides, sulfates, maleates, and 1,1'-methylene-bis-(2-naphthol-3-carboxylates) and quaternary ammonium salts.

The free bases of the above compounds of formula I are, in general, oils or lower melting solids, somewhat soluble in water and easily soluble in lower alkanols, benzene, toluene, acetone and chloroform. The salts of the above compounds of formula I are characteristically soluble in water and other hydroxy-

lated solvents and are usually insoluble in non-polar solvents.

As used herein, the term "lower alkyl" refers to alkyl radicals having from 1 to 6 carbon atoms.

In accordance with this invention there is provided a process for preparing the substituted piperazines of formula I, and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula



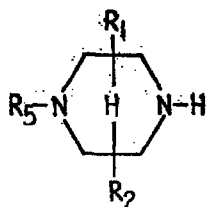
in which n , R_1 , R_2 , R_3 and R_4 are as defined for formula I above, with a compound of the formula



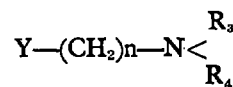
wherein Z is halogen, OH , O -Alkyl, S -Alkyl, SO -Alkyl, SO_2 -Alkyl, sulfonato, nitro, or an anhydride residue, and R_5 is as defined for formula I above, to form the product of formula I, and, if desired, forming pharmaceutically acceptable salts.

The above reaction is usually carried out according to standard procedures. For example, when Z is halogen the reaction may be carried out in a solvent such as, for example, a β -alkoxy alkanol, a lower alkanol, tetrahydrofuran or phenol, and the reaction is then usually carried out by heating the reaction mixture in the presence of an acid acceptor such as a bicarbonate or triethylamine.

Also, in accordance with the present invention there is provided a process for preparing the substituted piperazines of formula I, and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula

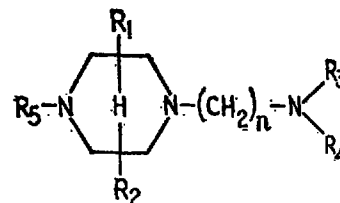


in which R_1 , R_2 and R_3 are as defined for formula I above, with a compound of the formula



wherein Y is halogen, OH , OSO_2 Alkyl, or OSO_2 Aryl, and n , R_3 and R_4 are as defined for formula I above, to form the product of formula I, and, if desired, forming pharmaceutically acceptable salts. The reaction is carried out by procedures which are standard in the art. For example, when Y is halogen the reaction may be carried out in a solvent such as a lower alkanol by heating the reaction mixture in the presence of an acid acceptor such as a lower alkoxide or a carbonate or bicarbonate.

Furthermore, there is provided in accordance with this invention a composition comprising a pharmaceutically acceptable carrier and a substituted piperazine of the formula



... IA

wherein n is 3 or 4; R_1 and R_2 are each hydrogen atoms or lower alkyl groups; R_3 and R_4 are each hydrogen atoms, lower alkyl or aralkyl groups; and R_5 is an aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; or a pharmaceutically acceptable salt of such a compound.

There is also provided in accordance with this invention a process for preparing a pharmaceutically active composition, which comprises admixing with a pharmaceutical carrier.

The compounds of the present invention are active in inhibiting the growth of protozoa. They are particularly active in inhibiting protozoa of the genus *Trypanosoma*, different species of which are known to be the causative agent of serious parasitic diseases in man and animals (e.g., Trypanosomiasis or "sleeping sickness"). For example, the compound 1 - (7 - chloro - 4 - quinolinyl) - 4 - (3 - dimethylaminopropyl) piperazine has been found to be active against experimental infections with *Trypanosoma cruzi* in mice. *Trypanosoma cruzi* is the causative agent of Chagas' disease in South America, an American Trypanosomiasis.

The substituted piperazines described above may be dispensed as the active ingredient in compositions of the compound and an edible carrier. While the amount of drug to be given

- daily will depend on many factors such as size, weight, age, etc. of the warm blooded animal, it has been found that a daily intake of from 1 mg. to 500 mg./kg. of body weight will produce good results. The dosage unit may be in a form for a single unit per day, or smaller forms for use as multiple units per day. In the case of tablets, they may be of larger size, scored for use as fractional units one or more times per day.
- The compositions can be dispensed in the form of soft- or hard-shell gelatin capsules. Also present in the capsules may be diluents such as lactose, starch, magnesium oxide and magnesium stearate. The capsules may be large enough to provide the desirable daily dosage or smaller to be used in multiple doses per day.
- The compositions may be dispensed as parenteral solutions or suspensions. If larger doses in small amounts are desirable it may in some cases be necessary to use parenteral suspensions.
- The compositions of the present invention may take the form of syrups or pediatric drops. Such formulations usually contain one or more of the following suspending agents, buffer salts, stabilizers, and preservatives.
- The following exemplifies the process of this invention.
- EXAMPLE 1
- Preparation of 1 - (7 - Chloro - 4 - quinolinyl) - 4 - (3 - dimethylaminopropyl)piperazine trihydrochloride hydrate
- To a mixture of 8.6 g. (0.05 mole) of 1-(3-dimethylaminopropyl)piperazine and 4.2 g. (0.05 mole) of solid sodium bicarbonate in 200 ml. of methyl "Cellosolve" is added 10.5 g. (0.053 mole) of 4,7 - dichloroquinoline. The word "Cellosolve" is a registered Trade Mark. The mixture is refluxed for 16.5 hours, cooled, filtered and the filtrate stripped of solvent at the water pump. The residual oil in 100 ml. of methanol is treated with 37.5 ml. of 8N methanolic hydrogen chloride. After adding enough ether to precipitate all of the product, the mixture is filtered. The crude product is treated with activated charcoal and recrystallized from methanol to give the analytically pure hygroscopic product, 7.3 g. (32.3%) melting point 263° (dec.).
- EXAMPLE 2
- Preparation of 1 - (7 - Chloro - 4 - quinolinyl) - 4 - (3 - dimethylaminopropyl)piperazine trihydrochloride
- A mixture of 19.8 g. (0.1 mole) of 4,7-dichloroquinoline, 17.1 g. (0.1 mole) of 1-(3-dimethylaminopropyl)piperazine and 88 ml. (ca 1 mole) of phenol is stirred at 150—160° for 2½ hours in a 1 liter 3-necked flask equipped with a "Teflon" paddle stirrer, and an immersion thermometer. The word "Teflon" is a registered Trade Mark. The reaction mixture is cooled to about 70°C. and poured into 300 ml. of 2N hydrochloric acid and cracked ice. The resulting two-liquid phased mixture is extracted with three 200 ml. portions of ether. The aqueous layer is treated with a solution of 40 g. of potassium hydroxide in 100 ml. of water followed by the addition of enough potassium hydroxide pellets to bring the pH to 13.5. The resulting mixture containing an insoluble oil is extracted with three 200 ml. portions and two 100 ml. portions of chloroform. The extracts are combined, washed with three 100 ml. portions of water, dried over anhydrous magnesium sulfate, and stripped of solvent at the water pump to give 25.9 g. of a residual brown oil. The oil in 200 ml. of ethanol is treated with activated charcoal, filtered, and the filtrate is treated with 68.5 ml. of 7.13N hydrogen chloride in isopropanol. The mixture is cooled and filtered to give 32.2 g. of crude product, melting point 264°C. (dec.). The solid is recrystallized from 100 ml. of methanol and then from a mixture of 150 ml. of isopropanol and 220 ml. of methanol to give 21.6 g. (48.9%) of pale yellow product, melting point 277°C. (dec.).
- The trimaleate salt of the free base can be prepared from the base and maleic acid in methanolic solution melting point 159°—161°C. with decomposition.
- EXAMPLE 3
- Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (5 - nitro - 2 - pyridyl)piperazine dihydrochloride
- This compound is prepared by the method of Example 1, an equimolar quantity of 2-chloro - 5 - nitropyridine replacing the 4,7-dichloroquinoline. The compound is pure yellow, hygroscopic, product melting at 260°C. with decomposition.
- EXAMPLE 4
- Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (5 - nitro - 2 - thiazolyl)piperazine dihydrochloride
- This compound is prepared by the method of Example 1, an equimolar quantity of 2-bromo - 5 - nitrothiazole replacing the 4,7-dichloroquinoline. The compound is a pure yellow solid, decomposing at 260—270°C.
- EXAMPLE 5
- Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (6 - purinyl)piperazine
- This compound is prepared by the method of Example 1, an equimolar quantity of 6-chloropurine replacing the 4,7-dichloroquinoline. The compound is a white crystalline solid melting at 218—220°C.
- EXAMPLE 6
- Preparation of 1 - (3 - Dimethylaminopropyl) - 4-(2-pyridyl)piperazine trihydrochloride
- This compound is prepared by the method of Example 1, an equimolar quantity of 2-bromopyridine replacing the 4,7-dichloroquinoline. The compound is a white crystalline solid melting at 258—265°C. with decomposition.

EXAMPLE 7

Preparation of 1 - (2 - Benzothiazolyl) - 4 - (3 - dimethylaminopropyl)piperazine

- 5 This compound is prepared by the method of Example 1, an equimolar quantity of 2-chlorobenzothiazole replacing the 4,7-dichloroquinoline. The compound is a white crystalline solid melting at 92—94°C.

EXAMPLE 8

- 10 Preparation of 1 - (7 - Chloro - 4 - quinolinyl) - 4 - (3 - benzylmethylaminopropyl)piperazine trimaleate

- 15 This compound is prepared by the general method of Example 1, an equimolar quantity of 1 - (3 - benzylmethylaminopropyl)piperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The compound is isolated as the trimaleate, melting at 133—135°C. with decomposition.

EXAMPLE 9

- 20 Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (5 - nitro - 1,3,4 - thiadiazol - 2 - yl)piperazine dimaleate

- 25 The subject compound is prepared essentially by the procedure of Example 1, an equimolar quantity of 2 - bromo - 5 - nitro - 1,3,4 - thiadiazole replacing the 4,7 - dichloroquinoline. In this case, ethanol replaces methyl cellosolve as the solvent. The compound is a yellow solid melting at 159—162°C. with decomposition.

EXAMPLE 10

- 35 Preparation of 1 - (5 - Bromo - 2 - pyrimidinyl) - 4 - (3 - dimethylaminopropyl)piperazine dihydrochloride

- 40 The subject compound is prepared essentially by the procedure of Example 1, an equimolar quantity of 5 - bromo - 2 - chloropyrimidine replacing the 4,7 - dichloroquinoline. In this case, ethanol replaces methyl cellosolve as the solvent. The compound is a white solid melting above 290°C. with decomposition.

EXAMPLE 11

- 45 Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (2-quinolinyl)piperazine trihydrochloride

- 50 The subject compound is prepared essentially by the procedure of Example 1, an equimolar quantity of 2-chloroquinoline replacing the 4,7-dichloroquinoline. The product is a white solid melting at 274—280°C. with decomposition.

EXAMPLE 12

- 55 Preparation of 1 - (2 - Benzoxazolyl) - 4 - (3 - dimethylaminopropyl)piperazine dihydrochloride

- 60 The subject compound is prepared essentially by the method of Example 1, an equimolar quantity of 2-chlorobenzoxazole replacing the 4,7-dichloroquinoline. The compound is a white solid melting at 275—295°C. with decomposition.

EXAMPLE 13

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (4 - pyridyl)piperazine trimaleate

This compound is prepared essentially by the procedure of Example 1, an equimolar quantity of 4-chloropyridine replacing the 4,7-dichloroquinoline. The compound is a white crystalline solid melting at 177—179°C.

EXAMPLE 14

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (6 - methoxy - 4 - quinolinyl)piperazine trimaleate

A mixture of 0.97 g. (0.005 mole) of 4-chloro-6-methoxyquinoline and 1.8 g. (0.010 mole) of 1-(3-dimethylaminopropyl)piperazine is heated in an oil bath slowly, being heated from room temperature to 195°C. during ninety minutes. An exothermic reaction occurred at about 155°. The cooled reaction mixture is triturated with acetone and filtered. The acetone filtrate is taken down under reduced pressure to an oil, which is dissolved in 125 ml. of benzene. The benzene solution is washed with a little water, dried over magnesium sulfate and the benzene removed under reduced pressure. The residual pale yellow oil is dissolved in acetone and added to a solution of 5.0 g. (0.043 mole) of maleic acid in 100 ml. of acetone. The resultant precipitate is collected and recrystallized from ethanol to give the pure compound, melting at 177—180°C.

EXAMPLE 15

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (2 - pyrazinyl)piperazine dimaleate

This compound is prepared by the method described in Example 14 except that an equimolar quantity of 2-chloropyrazine instead of the 4 - chloro - 6 - methoxyquinoline is used. The compound is a white crystalline solid melting at 182—184°C.

EXAMPLE 16

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (quinazoliny)piperazine trimaleate

This compound is prepared by the method of Example 1, an equimolar quantity of 4-chloroquinazoline replacing the 4,7-dichloroquinoline. The compound is a white solid melting at 152°C. with decomposition.

EXAMPLE 17

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (2 - thiazolyl)piperazine dimaleate

This compound is prepared by the method of Example 14, an equimolar quantity of 2-bromothiazole replacing the 4 - chloro - 6 - methoxyquinoline. The compound is a white solid melting at 164—165°C.

EXAMPLE 18

Preparation of 1 - (3 - Dimethylaminopropyl) - 4 - (6 - phenylimidazo[2,1 - b] - 1,3,4 - thiadiazol - 2 - yl)piperazine dimaleate

This compound is prepared by the method of Example 1, an equimolar quantity of 2-bromo - 6 - phenylimidazo[2,1 - b] - 1,3,4 - thiadiazole replacing the 4,7-dichloroquinoline.

This compound is a white solid melting at 175—178°C. with decomposition.

EXAMPLE 19

Preparation of 1 - (3 - Dimethylaminopropyl)-
4 - (6 - ethoxy - 2 - benzothiazolyl)piperazine

This compound is prepared by the procedure of Example 14, an equimolar quantity of 2 - chloro - 6 - ethoxybenzothiazole replacing the 4 - chloro - 6 - methoxyquinoline. The compound is a white solid melting at 90—92°C.

EXAMPLE 20

Preparation of 1 - (2 - Benzothiazolyl) - trans
2,5 - dimethyl - 4 - (3 - dimethylaminopropyl)piperazine

This compound is prepared by the method of Example 7, an equimolar quantity of *trans* 2,5 - dimethyl - 1 - (3 - dimethylaminopropyl)piperazine replacing the 1 - (3 - dimethylaminopropyl) - piperazine of Example 7. The product of the example is recovered.

EXAMPLE 21

Preparation of 1 - (2 - Benzothiazolyl) - 4 -
(3 - dimethylaminopropyl)piperazine dimetho-
sulfate

Ten milliliters of dimethylsulfate are added to a solution of 6.1 g. of 1 - (2 - benzothiazolyl) - 4 - (3 - dimethylaminopropyl)piperazine (Example 7) in 500 ml. of dry acetone. A precipitate commenced forming at once. After standing at room temperature for six days, the pure white product is filtered off and dried; weight, 8.22 g., melting point 169—173°C. with decomposition.

EXAMPLE 22

Preparation of 1 - (2 - Benzothiazolyl) - 4 -
(4 - dimethylaminobutyl)piperazine

This compound is prepared by the method of Example 7, an equimolar quantity of 1 - (4 - dimethylaminobutyl)piperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The product of the invention is recovered as described in Example 1.

EXAMPLE 23

Preparation of 1 - (7 - Chloro - 4 - quino-
linyl)piperazine

A mixture of 99.0 g. (0.50 mole) of 4,7-dichloroquinoline, 172.0 g. (2.0 moles) of anhydrous piperazine and 440 ml. (5.0 moles) of phenol (100%) is heated with stirring at 150—160°C. for 2½ hours in an oil bath at 195—200°C. The mixture is cooled to about 60°C. and poured into 2 liters of 2*N* hydrochloric acid. The resulting two liquid layered mixture is extracted with ether, 2 × 250 ml. portions. The aqueous layer is again extracted with ether, 2 × 500 ml. portions. The resulting aqueous layer is combined with the aqueous layer obtained from the lower liquid layer which separated after combining all ether extracts, is added to 1 liter of water containing 20 ml. of concentrated hydrochloric acid and is filtered. The combined aqueous layer (3260 ml.) is treated with a solution of 326 g. (5.8

moles) of potassium hydroxide in 1800 ml. of aqueous solution. An oil separated out of the alkaline (pH 10) solution. After adjusting the pH to 13.5 by the addition of potassium hydroxide pellets, the oil that separated out is extracted from the mixture with benzene, 4 × 500 ml. portions. The benzene extract is washed with water, dried over anhydrous potassium carbonate and magnesium sulfate and stripped of solvent at the water pump to give the solid, pale yellow product, 85.0 g. (69%), melting point 111—113°. Analytically pure product (pale yellow) melting at 113.5—114.5°C. is obtained by recrystallization from cyclohexane.

The salts of the product that are prepared are: dihydrobromide, melting point 266°C. (dec.) yellow solid; dihydrochloride . ½ H₂O, melting point 280° (dec.) yellow solid; mono-maleic acid salt, melting point 167°C. (dec.) yellow solid.

The following Examples 24 to 27 illustrate the preparation of compounds used as starting materials in the process of this invention.

EXAMPLE 24

Preparation of 1 - (3 - Dimethylaminopropyl)-
piperazine

A mixture of 500 g. (5.8 moles) of piperazine, 460 g. (2.9 moles) of 3-dimethylaminopropyl chloride hydrochloride, 550 g. (6.55 moles) of sodium bicarbonate, and 2.5 liters of ethanol are stirred at reflux for seven hours. After cooling to room temperature, the inorganic salts are filtered off and washed with 500 ml. of ethanol. The combined filtrates and wash are concentrated to constant volume on the steam bath. The residual oil is mixed with 500 ml. of methyl "Cellosolve" and taken down to constant volume *in vacuo* (water pump) on the steam bath. The residual oil is then distilled at 6 mm pressure. After a slight forerun, the bulk of the pure product comes over at 96—101°C., yield 207 g., n_D^{26} 1.4750.

The subject compound may also be prepared by the acid hydrolysis of ethyl 4 - (3 - dimethylaminopropyl)piperazine 1 - carboxylate followed by neutralization with an alkali. The properties of the material prepared by this procedure are identical with those described above.

EXAMPLE 25

Preparation of *trans* 2,5 - Dimethyl - 1 -
(3 - dimethylaminopropyl)piperazine trihydro-
chloride

This compound is prepared by the method of Example 24, *trans* 2,5-dimethylpiperazine replacing the piperazine. The compound is a white solid melting at 230—235°C. with decomposition.

EXAMPLE 26

Preparation of 1 - (4 - Dimethylaminobutyl)-
piperazine

A solution of 48 g. of 1 - benzyl - 4 - (3 - cyanopropyl)piperazine in 250 ml. of dry di-

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- ethyl ether is added slowly to a stirred suspension of 10 grams of lithium aluminum hydride in 500 ml. of dry diethyl ether. After addition is complete, the excess hydride is destroyed by the careful addition of water. The ether layer is removed and concentrated under reduced pressure to yield the 1 - (4 - amino-butyl) - 4 - benzylpiperazine. This compound is dissolved in 200 ml. of 90% formic acid, an excess of 37% formaldehyde solution added and the mixture then refluxed for several hours. The reaction mixture is then cooled, made alkaline, and extracted with diethyl ether. The ether is removed under reduced pressure, leaving the 1 - benzyl - 4 - (4 - dimethylaminobutyl)piperazine. This compound is dissolved in ethanol, 500 mg. of platinum oxide added, and the mixture subjected to hydrogenation under pressure until the benzyl group is completely removed. Removal of the catalyst by filtration and the solvent under reduced pressure leaves the 1 - (4 - dimethylaminobutyl)piperazine as a viscous oil.
- EXAMPLE 27**
 Preparation of 1 - (4 - Dimethylaminobutyl) - trans 2,5 - dimethylpiperazine
 This compound is prepared according to the general method of Example 26, an equimolar quantity of 1 - benzyl - 4 - (3 - cyanopropyl) - trans 2,5 - dimethylpiperazine replacing the 1 - benzyl - 4 - (3 - cyanopropyl)piperazine. The subject compound is recovered.
- EXAMPLE 28**
 Preparation of 1 - (7 - Chloro - 4 - quinolinyl) - 4 - (4 - dimethylaminobutyl) - trans 2,5 - dimethylpiperazine trimaleate
 This compound is prepared by the general method of Example 1, an equimolar quantity of 1 - (4 - dimethylaminobutyl) - trans 2,5 - dimethylpiperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The compound is isolated as the trimaleate.
- EXAMPLE 29**
 Preparation of 1 - (9 - Acridinyl) - 4 - (3 - dimethylaminopropyl)piperazine
 This compound is prepared by the method of Example 14, an equimolar quantity of 9-chloroacridine replacing the 4 - chloro - 6 - methoxyquinoline. The product of the example is a greenish-yellowish solid melting at 100°—102°.
- EXAMPLE 30**
 Preparation of 1 - (4,6 - Diamino - 1,3,5 - triazin - 2 - yl) - 4 - (3 - dimethylaminopropyl)piperazine
 The subject compound is prepared essentially by the procedure of Example 14, an equimolar quantity of 2 - chloro - 4,6 - diamino - 1,3,5 - triazine replacing the 4-chloro - 6 - methoxyquinoline. The product of the example is a white solid melting at 99°.
- EXAMPLE 31**
 Preparation of 1 - (3 - Dimethylaminopropyl)-4-(6-phenanthridinyl)piperazine trimaleate
 The subject compound is prepared essentially by the procedure of Example 14, an equimolar quantity of 6-chlorophenanthridine replacing the 4 - chloro - 6 - methoxyquinoline. The compound is a white crystalline solid melting at 155—157°C.
- EXAMPLE 32**
 Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (1,3,4 - thiadiazol - 2 - yl)piperazine dimaleate
 The subject compound is prepared essentially by the procedure of Example 14, an equimolar quantity of 2 - bromo - 1,3,4 - thiadiazole replacing the 4 - chloro - 6 - methoxyquinoline. The subject compound is recovered and melts at 157°—160°.
- EXAMPLE 33**
 Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (4 - quinolinyl - 1 - oxide)piperazine
 This compound is prepared by the general method of Example 1, an equimolar quantity of 4 - chloroquinoline - 1 - oxide replacing the 4,7 - dichloroquinoline. The compound is isolated as the trimaleate melting at 118°—120°.
- EXAMPLE 34**
 Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (4 - quinolinyl)piperazine trimaleate
 This compound is prepared by the general method of Example 1, an equimolar quantity of 4 - chloroquinoline replacing the 4,7-dichloroquinoline. The isolated compound melts at 158°—9°.
- EXAMPLE 35**
 Preparation of 1 - (6 - Chloro - 2 - pyrazinyl)-4 - (3 - dimethylaminopropyl)piperazine dimaleate
 This compound is prepared by the method described in Example 1 except that an equimolar quantity of 2,6-dichloropyrazine is used instead of the 4,7-dichloroquinoline. It melts at 168°—170°.
- EXAMPLE 36**
 Preparation of 1 - (3 - Dimethylaminopropyl)-4 - phenylpiperazine trihydrochloride
 A mixture of 32.4 g. (0.2 mole) of 1-phenylpiperazine, 40 g. (0.25 mole) of 3-dimethylaminopropyl chloride hydrochloride, 50 g. (0.6 mole) of sodium bicarbonate and 250 ml. of ethanol is stirred at reflux for sixteen hours. The inorganic salts are removed by filtration. Removal of the ethanol *in vacuo* gives a viscous oil, which is subjected to vacuum distillation at 3 mm of pressure. The 1 - (3 - dimethylaminopropyl) - 4 - phenylpiperazine is collected at 180°—182°C.
 A sample of the free base dissolved in dry ether and treated with dry hydrogen chloride in isopropanol gives the trihydrochloride salt, melting at 235°—240°C. with decomposition.

EXAMPLE 37

Preparation of 1 - (3 - Chlorophenyl) - 4 - (3 - dimethylaminopropyl)piperazine dimaleate

5 The subject compound is prepared essentially by the procedure of Example 36, an equimolar quantity of 1 - (3 - chlorophenyl)-piperazine dihydrochloride replacing the 1-phenylpiperazine. The compound is obtained
10 as a white solid, melting at 172°—173°C. with decomposition.

EXAMPLE 38

Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (4 - nitrophenyl)piperazine dihydrochloride

15 A mixture of 17.1 g. (0.1 mole) of 1-(3-dimethylaminopropyl)piperazine and 15.75 g. (0.1 mole) of *p*-nitrochlorobenzene is heated in an oil bath (150°—160°C.) for one hour.
20 The reaction mixture is then cooled and dissolved in 200 ml. of methanol. Addition of 15 ml. of 8*N* methanolic hydrogen chloride precipitates a hygroscopic yellow solid, which after recrystallization from ethanol, melts at
25 263°C. with decomposition.

EXAMPLE 39

Preparation of 1 - (4 - Acetamidophenyl)-4 - (3 - dimethylaminopropyl)piperazine dimaleate

30 Fifty-three grams (0.18 mole) of 1-(3-dimethylaminopropyl) - 4 - (4 - nitrophenyl)-piperazine (Example 37) is suspended in 750 ml. of ethanol and reduced to the 4-aminophenyl derivative by hydrogenation in the presence of platinum oxide. The free amine is
35 converted to the tetrahydrochloride by the addition of hydrochloric acid.

A mixture of 12.3 g. (0.03 mole) of 1-(4-aminophenyl) - 4 - (3 - dimethylaminopropyl)-piperazine tetrahydrochloride, 10.0 g. (0.12 mole) of sodium acetate, 6 ml. (excess) of acetic anhydride and 150 ml. of glacial acetic acid is refluxed for 6 hours. The inorganic salts are filtered off and the filtrate is taken
40 to dryness. The crude 1 - (4 - acetamidophenyl) - 4 - (3 - dimethylaminopropyl)piperazine is dissolved in ethanol and heated with an ethanol solution of 12.0 g. (0.1 mole) of maleic acid. The precipitated dimaleate is
50 recrystallized from methanol. It then melts at 147°—149°C., with decomposition.

EXAMPLE 40

Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (2,3,6 - trinitrophenyl)piperazine hydrochloride

55 A solution of 5 g. of 1-(3-dimethylaminopropyl)piperazine in 50 ml. of diethyl ether is mixed with a solution of 7½ g. of picryl chloride in 300 ml. of diethyl ether. A precipitate forms at once. After standing at room temperature for 30 minutes, the precipitate is collected, dried and recrystallized from
60 methanol. Cooling gives the pure compound, melting point 218°—220°C., decomposition.

EXAMPLE 41

Preparation of trans 2,5 - Dimethyl - 1 - (3 - dimethylaminopropyl) 4 - (4 - nitrophenyl)piperazine dihydrochloride

This compound is prepared by the method of Example 38, an equimolar quantity of *trans* 2,5 - dimethyl - 1 - (3 - dimethylaminopropyl)piperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The product is recovered as shown in Example 38.

EXAMPLE 42

Preparation of 1 - (3 - Benzylmethylaminopropyl) - 4 - (4 - nitrophenyl)piperazine dihydrochloride

This compound is prepared by the method of Example 38, an equimolar quantity of 1-(3-benzylmethylaminopropyl)piperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The product as the dihydrochloride salt is recovered as described in Example 38.

EXAMPLE 43

Preparation of 1 - (4 - Dimethylaminobutyl)-4 - (4 - nitrophenyl)piperazine dihydrochloride

This compound is prepared by the method of Example 38, an equimolar quantity of 1 - (4 - dimethylaminobutyl)piperazine replacing the 1 - (3 - dimethylaminopropyl)-piperazine. Following completion of the reaction, the compound is recovered as the dihydrochloride salt.

EXAMPLE 44

Preparation of 1 - (3 - Dimethylaminopropyl)-4 - phenylpiperazine trimethosulfate

A solution of 8 grams of 1 - (3 - dimethylaminopropyl) - 4 - phenylpiperazine in 400 ml. of dry acetone is stirred as 12 ml. of dimethyl sulfate is slowly added. After a few hours, a heavy oil separated out. The acetone is decanted, and the oil dissolved in 50 ml. of ethanol. Addition of 200 ml. of diethyl
105 ether precipitates a white oil that slowly crystallizes on prolonged storage at -10°C. The product is separated by filtration from the ether.

EXAMPLE 45

Preparation of trans 2,5 - Dimethyl - 1 - (4 - dimethylaminobutyl) - 4 - (4 - nitrophenyl)piperazine dihydrochloride

This compound is prepared by the method of Example 38, an equimolar quantity of *trans* 2,5 - dimethyl - 1 - (4 - dimethylaminobutyl)-piperazine replacing the 1 - (3 - dimethylaminopropyl)piperazine. The product is recovered as shown in Example 38, and melts
120 at 225°—233° with decomposition.

EXAMPLE 46

Preparation of 1 - (4 - Methoxyphenyl) - 4 - (3 - dimethylaminopropyl)piperazine dimaleate

A mixture of 25.0 g. (0.094 mole) of 1 - (4 - methoxyphenyl)piperazine dihydrochloride, 18.6 g. (0.118 mole) of 3-dimethylaminopropyl chloride hydrochloride, 33.6 g.

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- (0.4 mole) of sodium bicarbonate and 200 ml. of methyl cellosolve is stirred at reflux for 24 hours. The inorganic salts are removed by filtration and the filtrate stripped of solvent at the water pump. The residual oil is taken up in 100 ml. of benzene and the solution is washed twice with 25 ml. of water. The benzene extract is dried over anhydrous potassium carbonate and magnesium sulfate and is stripped of solvent at the water pump. The residual oil in 50 ml. of acetone is added to a solution of 31.3 g. (0.27 mole) of maleic acid in 250 ml. of acetone to give the product, melting at 162°—3°.
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- EXAMPLE 47**
Preparation of 1 - Benzoyl - 4 - (3 - dimethylaminopropyl)piperazine dihydrochloride
- To a stirred mixture of 20.7 g. (50 mmol.) of 1 - (3 - dimethylaminopropyl)-piperazine . 3HBr and 150 ml. of 1N sodium hydroxide is added dropwise and at 0—5°C., 11.6 ml. (0.1 mole) of benzoyl chloride and 270 ml. of 1N sodium hydroxide (20% excess) simultaneously during 30 minutes. Stirring with ice bath cooling is continued for one hour after which time 110 g. of solid sodium chloride is added, followed by extraction with three 250 ml. portions of chloroform. The residual oil (15.3 g.), obtained by stripping the extract of solvent at the water pump, is dissolved in 150 ml. of ethanol. The resulting solution is cooled and treated with an excess of ethanolic hydrogen chloride (ice bath cooling) to give a white solid which is recrystallized from methanol to give analytically pure product, 11.6 g. (66.6%) melting point 274—278°C. (dec.).
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- EXAMPLE 48**
Preparation of Isobutyl 4 - (3 - dimethylaminopropyl) - 1 - piperazine carboxylate dihydrochloride
- This compound is prepared by the method of Example 47, an equimolar quantity of carboisobutyloxy chloride replacing the benzoyl chloride. The compound is a white solid melting at 266°C. with decomposition.
- 40
- EXAMPLE 49**
Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (3,4,5 - trimethoxybenzoyl)piperazine dihydrochloride
- The subject compound is prepared essentially by the procedure of Example 47, an equimolar quantity of 3,4,5-trimethoxybenzoyl chloride replacing the benzoyl chloride. In this case pyridine is employed as the acid binder and as solvent. The compound is a white solid, melting at 263°—265°C., with decomposition.
- 45
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- EXAMPLE 50**
Preparation of Benzyl 4 - (3 - dimethylaminopropyl) - 1 - piperazine carboxylate dihydrochloride
- A mixture of 55 g. of benzyl 1 - piperazine-carboxylate, 79 g. of 3-dimethylaminopropyl chloride hydrochloride, 60 g. of sodium bi-
- carbonate and 500 ml. of methyl "Cellosolve" is stirred at reflux for 3 hours. The methyl "Cellosolve" is then removed by distillation under reduced pressure. The residue is dissolved in 250 ml. of water and the water solution is then saturated with solid potassium carbonate. Extraction with 700 ml. of chloroform, followed by removal of the chloroform by distillation gives a thick residual oil. This is dissolved in 250 ml. of isopropanol and a solution of 26 g. of hydrogen chloride in 100 ml. of isopropanol is added. The resultant precipitate is collected, washed with ether, dried and recrystallized from ethanol. The pure compound is obtained as a white crystalline solid, melting point 218—219°C. with decomposition.
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- EXAMPLE 51**
Preparation of 1 - (2,4 - Dichlorobenzoyl) - 4 - (3 - dimethylaminopropyl)piperazine dihydrochloride
- A solution of 7.5 g. (0.036 mole) of 2,4-dichlorobenzoyl chloride in 100 ml. of diethyl ether is added to a stirred solution of 5.4 g. (0.032 mole) of 1 - (3 - dimethylaminopropyl)-piperazine in 400 ml. of diethyl ether. An immediate precipitate forms. The mixture is stirred at room temperature for an hour and then allowed to stand overnight. A solution of 2.6 g. of dry hydrogen chloride in 10 ml. of isopropanol is then added. The white crystalline solid is collected and recrystallized from methanol to give 9.5 g. of pure compound, decomposing at 265—270°C.
- 85
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- EXAMPLE 52**
Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (2 - furoyl)piperazine hydrochloride
- The subject compound is prepared essentially by the method of Example 51, an equimolar quantity of 2-furoyl chloride replacing the 2,4-dichlorobenzoyl chloride. The compound is a white solid melting at 268°C. with decomposition.
- 100
105
- EXAMPLE 53**
Preparation of 1 - (3 - Dimethylaminopropyl)-4 - (2 - phenyl - 2H - 1,2,3 - triazol - 4 - oyl)piperazine dimaleate
- The subject compound is prepared essentially by the procedure of Example 51, an equimolar quantity of 2 - phenyl - 2H - 1,2,3-triazol - 4 - oyl chloride replacing the 2,4-dichlorobenzoyl chloride. The compound is a white solid melting at 176°—177°C.
- 110
115
- EXAMPLE 54**
Preparation of n - Octyl - 4 - (3 - dimethylaminopropyl)piperazine - 1 - carboxylate dihydrochloride
- The compound is prepared essentially by the method of Example 51, an equimolar quantity of n-octyl chloroformate replacing the 2,4-dichlorobenzoyl chloride. The compound is a white crystalline solid, melting at 258°—259°C. with decomposition.
- 120
125

EXAMPLE 55

Preparation of 1 - (3 - Dimethylaminopropyl)-4-trichloroacetyl piperazine dihydrochloride

The subject compound is prepared essentially by the method of Example 51, an equimolar quantity of trichloroacetyl chloride replacing the 2,4-dichlorobenzoyl chloride. The compound is a white solid, decomposing at 240°—245°C.

EXAMPLE 56

Preparation of 1 - Benzoyl - trans 2,5 - dimethyl - 4 - (3 - dimethylaminopropyl) piperazine dimaleate

This compound is prepared by the method of Example 47, an equimolar quantity of trans 2,5 - dimethyl - 1 - (3 - dimethylaminopropyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The product is recovered as described in Example 47, and melts at 243°—4° with decomposition.

EXAMPLE 57

Preparation of 1 - Benzoyl - 4 - (3 - benzylmethylaminopropyl) piperazine dihydrochloride

This compound is prepared by the method of Example 47, an equimolar quantity of 1 - (3 - benzylmethylaminopropyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The compound is recovered as described in Example 47.

EXAMPLE 58

Preparation of 1 - Benzoyl - 4 - (4 - dimethylaminobutyl) piperazine dihydrochloride

This compound is prepared by the method of Example 47, an equimolar quantity of 1 - (4 - dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. It melts at 270°—1° with decomposition.

EXAMPLE 59

Preparation of 1 - Benzoyl - 4 - (3 - dimethylaminopropyl) piperazine dimethosulfate

A solution of 8.5 g. of 1 - benzoyl - 4 - (3 - dimethylaminopropyl) piperazine in 400 ml. of dry acetone is treated with 12 ml. of dimethyl sulfate. After some hours an oil is present. The reaction mixture is then stored at -10°C., the oil slowly crystallizing to a white solid which is separated by filtration.

EXAMPLE 60

Preparation of 1 - Benzoyl - trans 2,5 - dimethyl - 4 - (4 - dimethylaminobutyl) piperazine dihydrochloride

This compound is prepared by the method of Example 51, an equimolar quantity of trans 2,5 - dimethyl - 1 - (4 - dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine and an equimolar quantity of benzoyl chloride replacing the 2,4-dichlorobenzoyl chloride. The product is recovered as described in Example 51, and melts at 233°—240° with decomposition.

EXAMPLE 61

Preparation of 1 - (4 - Dimethylaminobutyl)-4 - (7 - chloro - 4 - quinolinyl) piperazine trimaleate 65

This compound is prepared by the method of Example 1, an equimolar quantity of 1-(4-dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The compound is a pale yellow solid melting at 118°—120°. 70

EXAMPLE 62

Preparation of 1 - (9,10 - Anthraquinone - 2 - carbonyl) - 4 - (3 - dimethylaminopropyl) piperazine dihydrochloride 75

This compound is prepared by the method of Example 3, an equimolar quantity of 9,10-anthraquinone - 2 - carbonyl chloride replacing the 3,4,5 - trimethoxybenzoyl chloride. The compound is a white solid melting at 296° with decomposition. 80

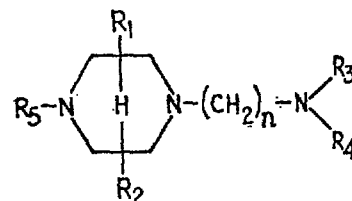
EXAMPLE 63

Preparation of 4' - [4 - (3 - Dimethylaminopropyl) - 1 - piperazinyl] - acetanilide dimaleate 85

A mixture of 29.2 parts of 4' - (1 - piperazinyl) - acetanilide dihydrochloride, 18 parts of 3-dimethylaminopropyl chloride hydrochloride, 35 parts of sodium bicarbonate, and 200 parts of methyl cellosolve were stirred at reflux for twelve hours. The reaction mixture was cooled, the inorganic salts filtered off, and the filtrate concentrated *in vacuo*. The residue was extracted with 300 parts of acetone at the boil, clarified, and added to a solution of 25 parts of maleic acid in 200 parts of hot acetone. The mixture was cooled to 4°, and the precipitate of crude 4' - [4 - (3-dimethylaminopropyl) - 1 - piperazinyl] acetanilide dimaleate collected. Recrystallization from boiling ethanol gave the pure compound, m.p. 145°—7°. 95

WHAT WE CLAIM IS:—

1. A process for preparing substituted piperazines of the formula 105



wherein n is 3 or 4; R₁ and R₂ are each hydrogen atoms or lower alkyl groups; R₃ and R₄ are each hydrogen atoms, lower alkyl or aralkyl groups; and R₅ is a substituted aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula 115

EXAMPLE 55

Preparation of 1 - (3 - Dimethylaminopropyl)-4-trichloroacetyl piperazine dihydrochloride

- 5 The subject compound is prepared essentially by the method of Example 51, an equimolar quantity of trichloroacetyl chloride replacing the 2,4-dichlorobenzoyl chloride. The compound is a white solid, decomposing at 240°—245°C.

EXAMPLE 56

Preparation of 1 - Benzoyl - trans 2,5 - dimethyl - 4 - (3 - dimethylaminopropyl) piperazine dimaleate

- 10 This compound is prepared by the method of Example 47, an equimolar quantity of trans 2,5 - dimethyl - 1 - (3 - dimethylaminopropyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The product is recovered as described in Example 47, and
20 melts at 243°—4° with decomposition.

EXAMPLE 57

Preparation of 1 - Benzoyl - 4 - (3 - benzylmethylaminopropyl) piperazine dihydrochloride

- 25 This compound is prepared by the method of Example 47, an equimolar quantity of 1 - (3 - benzylmethylaminopropyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The compound is recovered as described in Example 47.

EXAMPLE 58

Preparation of 1 - Benzoyl - 4 - (4 - dimethylaminobutyl) piperazine dihydrochloride

- 35 This compound is prepared by the method of Example 47, an equimolar quantity of 1 - (4 - dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. It melts at 270°—1° with decomposition.

EXAMPLE 59

Preparation of 1 - Benzoyl - 4 - (3 - dimethylaminopropyl) piperazine dimethosulfate

- 40 A solution of 8.5 g. of 1 - benzoyl - 4 - (3 - dimethylaminopropyl) piperazine in 400 ml. of dry acetone is treated with 12 ml. of dimethyl sulfate. After some hours an oil is present. The reaction mixture is then stored at -10°C., the oil slowly crystallizing to a white solid which is separated by filtration.

EXAMPLE 60

Preparation of 1 - Benzoyl - trans 2,5 - dimethyl - 4 - (4 - dimethylaminobutyl) piperazine dihydrochloride

- 50 This compound is prepared by the method of Example 51, an equimolar quantity of trans 2,5 - dimethyl - 1 - (4 - dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine and an equimolar quantity of benzoyl chloride replacing the 2,4-dichlorobenzoyl chloride. The product is recovered as described in Example 51, and
60 melts at 233°—240° with decomposition.

EXAMPLE 61

Preparation of 1 - (4 - Dimethylaminobutyl)-4 - (7 - chloro - 4 - quinolinyl) piperazine tri-maleate 65

This compound is prepared by the method of Example 1, an equimolar quantity of 1-(4-dimethylaminobutyl) piperazine replacing the 1 - (3 - dimethylaminopropyl) piperazine. The compound is a pale yellow solid melting at 118°—120°. 70

EXAMPLE 62

Preparation of 1 - (9,10 - Anthraquinone - 2 - carbonyl) - 4 - (3 - dimethylaminopropyl) piperazine dihydrochloride 75

This compound is prepared by the method of Example 3, an equimolar quantity of 9,10-anthraquinone - 2 - carbonyl chloride replacing the 3,4,5 - trimethoxybenzoyl chloride. The compound is a white solid melting at 296° with decomposition. 80

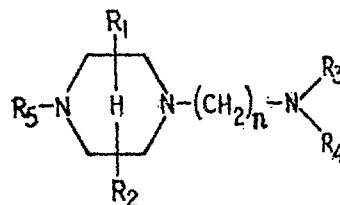
EXAMPLE 63

Preparation of 4' - [4 - (3 - Dimethylaminopropyl) - 1 - piperazinyl] - acetanilide dimaleate 85

A mixture of 29.2 parts of 4' - (1 - piperazinyl) - acetanilide dihydrochloride, 18 parts of 3-dimethylaminopropyl chloride hydrochloride, 35 parts of sodium bicarbonate, and 200 parts of methyl cellosolve were stirred at reflux for twelve hours. The reaction mixture was cooled, the inorganic salts filtered off, and the filtrate concentrated *in vacuo*. The residue was extracted with 300 parts of acetone at the boil, clarified, and added to a solution of 25 parts of maleic acid in 200 parts of hot acetone. The mixture was cooled to 4°, and the precipitate of crude 4' - [4 - (3-dimethylaminopropyl) - 1 - piperazinyl] acetanilide dimaleate collected. Recrystallization from boiling ethanol gave the pure compound, m.p. 145°—7°. 95

WHAT WE CLAIM IS:—

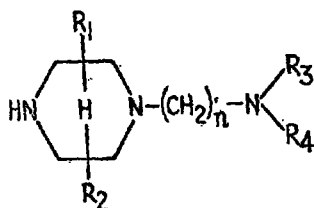
1. A process for preparing substituted piperazines of the formula 105



I

wherein n is 3 or 4; R₁ and R₂ are each hydrogen atoms or lower alkyl groups; R₃ and R₄ are each hydrogen atoms, lower alkyl or aralkyl groups; and R₅ is a substituted aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula 115



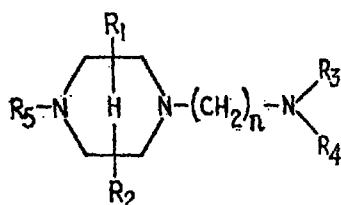


in which n , R_1 , R_2 , R_3 and R_4 are as defined for formula I above, with a compound of the formula



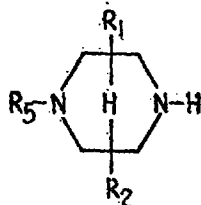
wherein Z is halogen, OH, O-Alkyl, S-Alkyl, SO-Alkyl, SO₂-Alkyl, sulfonato, nitro, or an anhydride residue, and R_5 is as defined for formula I above, to form the product of formula I, and, if desired, forming pharmaceutically acceptable salts.

10 2. A process for preparing substituted piperazines of the formula

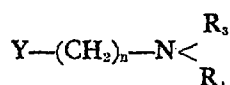


I

15 wherein n is 3 or 4; R_1 and R_2 are each hydrogen atoms or lower alkyl groups; R_3 and R_4 are each hydrogen atoms, lower alkyl or aralkyl groups; and R_5 is a substituted aryl radical of the benzene type series of an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; and the pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula



25 in which R_1 , R_2 and R_3 are as defined for formula I above, with a compound of the formula



30 wherein Y is halogen, OH, OSO₂Alkyl, or OSO₂Aryl, and n , R_3 and R_4 are as defined for formula I above, to form the product of

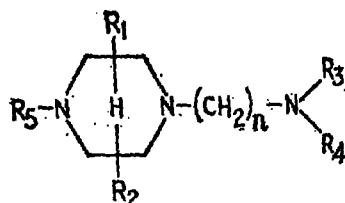
formula I, and, if desired, forming pharmaceutically acceptable salts.

3. A process according to claim 1 or 2, wherein when R_5 is an acyl radical, it is a benzoyl, trimethoxybenzoyl, dichlorobenzoyl, phenyltriazoloyl, benzyloxycarbonyl, furoyl, alkoxy carbonyl, trihaloacetyl or 9,10-anthraquinone-carbonyl group.

4. A process for preparing substituted piperazines of formula I substantially as hereinbefore described.

5. Substituted piperazines of formula I whenever prepared by a process substantially as hereinbefore described.

6. Substituted piperazines of the formula



I

wherein n is 3 or 4; R_1 and R_2 are each hydrogen atoms or lower alkyl groups; R_3 and R_4 are each hydrogen atoms, lower alkyl or aralkyl groups; and R_5 is a substituted aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; and the pharmaceutically acceptable salts of the above.

7. 1 - (3 - Dimethylaminopropyl) - 4 - (5-nitro - 2 - pyridyl) - piperazine.

8. 1 - (3 - Dimethylaminopropyl) - 4 - (5-nitro - 2 - thiazolyl) - piperazine.

9. 1 - (3 - Dimethylaminopropyl) - 4 - (6-purinyl)piperazine.

10. 1 - (3 - Dimethylaminopropyl) - 4 - (2-pyridyl)piperazine.

11. 1 - (3 - Dimethylaminopropyl) - 4 - (5-nitro - 1,3,4 - thiadiazol - 2 - yl)piperazine.

12. 1 - (5 - Bromo - 2 - pyrimidinyl) - 4 - (3 - dimethylaminopropyl) - piperazine.

13. 1 - (3 - Dimethylaminopropyl) - 4 - (2-quinolinyl)piperazine.

14. 1 - (2 - Benzoxazolyl) - 4 - (3 - dimethylaminopropyl)piperazine.

15. 1 - (2 - Benzothiazolyl) - 4 - (3 - dimethylaminopropyl) - piperazine.

16. 1 - (7 - Chloro - 4 - quinolinyl) - 4 - (3 - benzylmethylaminopropyl)piperazine.

17. 1 - (3 - Dimethylaminopropyl) - 4 - (4-pyridyl)piperazine.

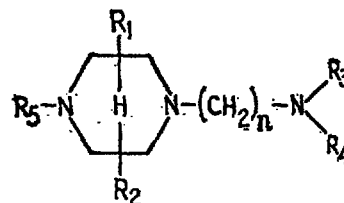
18. 1 - (3 - Dimethylaminopropyl) - 4 - (6-methoxy - 4 - quinolinyl) - piperazine.

19. 1 - (3 - Dimethylaminopropyl) - 4 - (2-pyrazinyl)piperazine.

20. 1 - (3 - Dimethylaminopropyl) - 4 - (4-quinazolinyl)piperazine.



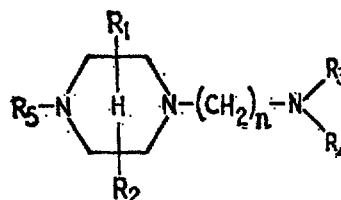
21. 1 - (3 - Dimethylaminopropyl) - 4 - (2-thiazolyl)piperazine. 65
22. 1 - (3 - Dimethylaminopropyl) - 4 - (6-phenylimidazo - [2,1 - b] - 1,3,4 - thiadiazol-2 - yl)piperazine. 70
23. 1 - (3 - Dimethylaminopropyl) - 4 - (6-ethoxy - 2 - benzothiazolyl)piperazine.
24. 1 - (2 - Benzothiazolyl) - trans - 2,5 - dimethyl - 4 - (3 - dimethylaminopropyl)-piperazine. 75
25. 1 - (2 - Benzothiazolyl) - 4 - (4 - dimethylaminobutyl)piperazine.
26. 1 - (7 - Chloro - 4 - quinoliny) - 4 - (4-dimethylaminobutyl) - trans - 2,5 - dimethyl-piperazine. 80
27. 1 - (9 - Acridiny) - 4 - (3 - dimethylaminopropyl)piperazine.
28. 1 - (4,6 - Diamino - 1,3,5 - triazin - 2 - yl) - 4 - (3 - dimethylaminopropyl)piperazine.
29. 1 - (3 - Dimethylaminopropyl) - 4 - (6-phenanthridiny)piperazine. 85
30. 1 - (3 - Dimethylaminopropyl) - 4 - (1,3,4 - thiadiazol - 2 - yl)piperazine.
31. 1 - (3 - Dimethylaminopropyl) - 4 - (4-quinoliny - 1 - oxide)piperazine.
32. 1 - (3 - Dimethylaminopropyl) - 4 - (4-quinoliny)piperazine.
33. 1 - (6 - Chloro - 2 - pyraziny) - 4 - (3-dimethylaminopropyl)piperazine.
34. 1 - (3 - Chlorophenyl) - 4 - (3 - dimethylaminopropyl)piperazine.
35. 1 - (3 - Dimethylaminopropyl) - 4 - (4-nitrophenyl)piperazine.
36. 1 - (4 - Aminophenyl) - 4 - (3 - dimethylaminopropyl)piperazine.
37. 1 - (4 - Acetamidophenyl) - 4 - (3 - dimethylaminopropyl)piperazine.
38. 1 - (3 - Dimethylaminopropyl) - 4 - (2,4,6 - trinitrophenyl)piperazine.
39. Trans - 2,5 - dimethyl - 1 - (3 - dimethylaminopropyl) - 4 - (4 - nitrophenyl)-piperazine.
40. 1 - (3 - Benzylmethylpropyl) - 4 - (4-nitrophenyl)piperazine.
41. 1 - (4 - Dimethylaminobutyl) - 4 - (4-nitrophenyl)piperazine.
42. Trans - 2,5 - dimethyl - 1 - (4 - dimethylaminobutyl) - 4 - (4 - nitrophenyl)-piperazine.
43. 1 - (4 - Methoxyphenyl) - 4 - (3 - dimethylaminopropyl)piperazine.
44. 1 - Benzoyl - 4 - (3 - dimethylaminopropyl)piperazine.
45. Isobutyl 4 - (3 - dimethylaminopropyl)-1 - piperazine carboxylate.
46. 1 - (3 - Dimethylaminopropyl) - 4 - (3,4,5 - trimethoxybenzoyl)piperazine.
47. Benzyl 4 - (3 - dimethylaminopropyl)-1 - piperazine carboxylate.
48. 1 - (2,4 - Dichlorobenzoyl) - 4 - (3 - dimethylaminopropyl)piperazine.
49. 1 - (3 - Dimethylaminopropyl) - 4 - (2-furoyl)piperazine.
50. 1 - (3 - Dimethylaminopropyl) - 4 - (2-phenyl - 2H - 1,2,3 - triazol - 4 - oyl)piperazine.
51. n - Octyl 4 - (3 - dimethylaminopropyl)-piperazine - 1 - carboxylate.
52. 1 - (3 - Dimethylaminopropyl) - 4 - trichloroacetyl piperazine.
53. 1 - Benzoyl - trans - 2,5 - dimethyl - 4 - (3 - dimethylaminopropyl)piperazine.
54. 1 - Benzoyl - 4 - (3 - benzylmethylaminopropyl)piperazine.
55. 1 - Benzoyl - 4 - (4 - dimethylaminobutyl)piperazine.
56. 1 - Benzoyl - trans - 2,5 - dimethyl - 4 - (4 - dimethylaminobutyl)piperazine.
57. 1 - (7 - Chloro - 4 - quinoliny) - 4 - (3-dimethylaminopropyl)piperazine.
58. 1 - (9,10 - Anthraquinone - 2 - carbonyl) - 4 - (3 - dimethylaminopropyl)piperazine dihydrochloride.
59. A composition comprising a pharmaceutically acceptable carrier and a substituted piperazine of the formula



IA

wherein n is 3 or 4; R₁ and R₂ are each hydrogen atoms or lower alkyl groups; R₃ and R₄ are each hydrogen atoms, lower alkyl or aralkyl groups; and R₅ is an aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; or a pharmaceutically acceptable salt of such a compound.

60. A process for preparing a pharmaceutically active composition, which comprises admixing a substituted piperazine of the formula



IA

wherein n is 3 or 4; R₁ and R₂ are each hydrogen atoms or lower alkyl groups; R₃ and R₄ are each hydrogen atoms, lower alkyl or aralkyl groups; and R₅ is an aryl radical of the benzene type series or an aromatic heterocyclic radical of at least 5 ring atoms or an acyl radical; or a pharmaceutically acceptable salt of such a compound, with a pharmaceutical carrier.



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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press
(Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings,
London, W.C.2, from which copies may be obtained.

