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2,794,804

SUBSTITUTED PIPERAZINES AND METHOD OF PREPARING THE SAME

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This invention relates to N,N-disubstituted piperazines, their salts and methods of preparation thereof.

There are chemical compounds commercially available which possess adrenergic blocking activity, that is, they have the ability to diminish or inhibit the vasoconstrictor activity of epinephrine or norepinephrine and reflexly induced increased activity of the adrenergic division of the autonomic nervous system. Many of these drugs have certain limitations, however, which restrict their use. In particular, they are not effective when administered orally. The compounds which constitute this invention are disubstituted aminoethylpiperazines and have the advantages of being orally-active vasodilators and adrenergic blocking agents.

In the past, 1-[β -(N-phenylamino)ethyl]-4-phenylpiperazine has been described by Van Alphen, Rec. Trav. Chim., 56, 1007 (1937). However, it has been demonstrated that the pharmacological activity of this compound is much less than the activities shown by the compounds of the present invention. It is evident that when compounds of this type are prepared, where the β -aminoethyl nitrogen is tertiary and at least one of the substituents is a phenyl or aralkyl radical, a very marked increase in vasodilator activity is exhibited. When a further substituent is present on the tertiary amino group, such as an alkyl radical having from 2 to 8 carbon atoms, greatly increased activity is obtained, as shown in Table I.

Table I—Vasodilator activity

Group	1 [β -(N-phenylamino)ethyl]-4-phenyl piperazine		1 [β -(N-phenyl-N-ethylamino)ethyl]-4-phenyl piperazine	
	5 micrograms dose	10 micrograms dose	5 micrograms dose	10 micrograms dose
	(A)	(B)	(A)	(B)
1.....	110	142	146	226
2.....	100	134	121	192
3.....	104	118	169	192
4.....	85	102	123	140
5.....	111	151	150	135
6.....	95	137	111	148
7.....	71	106	100	127

When these vasodilators are tested for their duration of adrenergic blocking activity, Compound (B) is greatly superior to Compound (A), as shown in Table II below.

Table II—Duration of epinephrine reversal¹

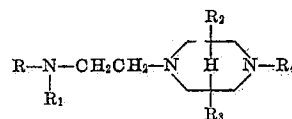
Experiment No.	Compound (A), Duration in Hours	Compound (B), Duration in Hours
1.....	2½	5½
2.....	2	4½
3.....	2	8

¹ Compounds tested at dose level of 5 mgm./kgm. intravenously.

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We have now found that disubstituted aminoethylpiperazines generally have greatly superior activity as vasodilators to the imidazolines and β -(secondary amino)-ethylpiperazines. The present compounds are characterized by being relatively non-toxic and long-acting vasodilators. This application is a continuation-in-part of our copending application Serial No. 423,216, filed April 14, 1954, now abandoned.

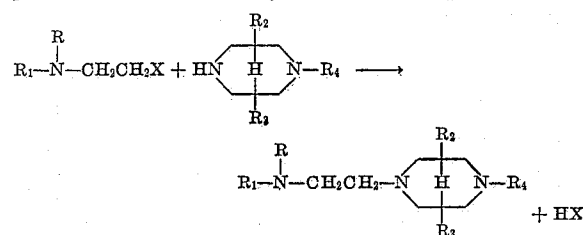
The compounds of the present invention may be illustrated by the following structural formula:



in which R is a member of the group consisting of phenyl and lower aralkyl, R₁ is a member of the group consisting of alkyl radicals having 2 to 8 carbon atoms, lower aralkyl, lower haloaralkyl, lower alkanoyl radicals, R₂ and R₃ are members of the group consisting of hydrogen, lower alkyl and hydroxy lower alkyl, R₄ is a member of the group consisting of lower alkyl, halophenyl, phenyl, loweralkylaminoloweralkyl, phenyl, carbloweralkoxy, lower alkanoyl, pyridyl, lower alkylpyridyl, thiazolyl, pyrimidyl, lower alkoxyphenyl and acid addition salts.

The disubstituted aminoethylpiperazines of the present invention are, in general, solids or heavy oils at room temperature. In the form of their acid addition salts, they are usually crystalline solids having a definite melting point and being soluble in water.

The present compounds are preferably prepared by reacting an N-substituted piperazine with an N-(β -haloethyl)disubstituted amine. The reaction which takes place can be illustrated by the following equation:



in which R, R₁, R₂, R₃, and R₄ are as defined hereinbefore and X is halogen.

The N-(β -haloethyl)disubstituted amines used as starting material are preferably used in the form of acid salts, for example, β -(N-phenyl-N-ethylamino)ethylchloride hydrochloride; β -(N-phenyl-N-ethylamino)ethylbromide hydrobromide; β -(N-phenyl-N-n-hexylamino)ethylchloride hydrochloride; β -(N,N-dibenzylamino)ethylchloride hydrochloride, etc.

The N-substituted piperazines used as starting materials can be compounds such as, for example, 1-phenylpiperazine; 1-acetylpiperazine; 1-propionylpiperazine; 1-butyrylpiperazine; 1-carbethoxypiperazine; 1-carbomethoxypiperazine; 1-carbopropoxypiperazine; 1-carbobutoxypiperazine; 1-methylpiperazine; 1-ethylpiperazine; 1-propylpiperazine; 1-butylpiperazine; 1-(4-methoxyphenyl)piperazine; 1-(2'-thiazolyl)piperazine; 1-(2'-pyridyl)piperazine; 1-[2-(6-methyl)pyridyl]piperazine; 1-(2'-pyrimidyl)piperazine; and ring-substituted piperazines such as 2-hydroxymethylpiperazine and the like.

The reaction to prepare the compounds of the present invention can be carried out at a temperature of from 25° C. to 175° C., depending upon the solvent used. We prefer to use an alcohol, such as methanol, ethanol, propanol, butanol, etc., as a solvent. However, the reactions can be carried out in water-alcohol solutions. Other solvents can be used, for example, mixtures of water and

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dioxane or 2-ethoxyethanol. Organic solvents such as, for example, toluene, xylene or benzene can also be used. The reaction is easily carried out by heating the reactants in the solvent at the refluxing temperatures of the solvent for a period which may vary from a few minutes to several hours.

When the reaction is complete, the product may be recovered by concentrating the reaction mixture and extracting the free base by means of an organic solvent, for example, ether, benzene, or chloroform. The solvent can be removed by distillation and the desired compound then distilled, preferably under reduced pressure. The base compound can be treated with an acid to form the acid addition salt or with an alkyl halide to form quaternary salts thereof, which are generally crystalline and can be purified by crystallization.

The following examples describe in greater detail the preparation of N,N-disubstituted piperazines and salts thereof.

EXAMPLE 1

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-phenylpiperazine

A solution consisting of 20.0 grams (0.11 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride and 35.2 grams (0.22 mole) of 1-phenylpiperazine in 85 ml. of ethanol and 50 ml. of water was refluxed overnight. The resulting solution was concentrated to a semi-crystalline mass, which was taken up in 75 ml. of warm water, treated with activated charcoal and filtered. The aqueous filtrate was made alkaline with 35 ml. of 50% aqueous potassium hydroxide solution and the insoluble organic layer was extracted with three 100 ml. portions of ether. The etheral extracts were combined and then concentrated to a brownish oil, which was fractionally distilled. The portion boiling at 208°–210° C./0–1 mm. was collected and weighed. The yield was 11.0 grams.

EXAMPLE 2

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-phenylpiperazine monohydrochloride

A solution consisting of 309 grams of 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-phenylpiperazine in 2000 cc. dry ether was cooled to 10°–20° C. and treated with 190 cc. of 5.2 N ethanolic hydrogen chloride. An immediate precipitation of the monohydrochloride was obtained. The monohydrochloride salt was recrystallized from warm ethanol and found to melt with decomposition at 223°–224° C. The trihydrochloride salt can be obtained by using an excess of hydrogen chloride gas.

EXAMPLE 3

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-acetyl-piperazine

A mixture consisting of 18.6 g. (0.15 mole) of 1-acetyl-piperazine, 12.0 g. (0.07 mole) of β-(N-phenyl-N-ethylamino)-ethyl chloride monohydrochloride, 50 ml. of water and 70 ml. of ethanol was refluxed for fifteen hours at steam-cone temperature. A semi-crystalline mass resulted when the solvents were distilled off under reduced pressure. The residual material was treated with 2–100 ml. portions of chloroform and these combined extracts were treated with activated charcoal and filtered. A crude, brown oil was obtained when the solvent was removed and this crude yield was fractionated under reduced pressure. The portion boiling at 192°–197° C./0–1 mm. was collected and amounted to a 25% yield.

EXAMPLE 4

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-acetyl-piperazine monohydrochloride

The basic 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-acetyl-piperazine (4.6 g.; 0.017 mole) was dissolved in 75 ml. of ether and treated with an excess of dry hydrogen chloride gas. A white, granular material precipitated

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immediately and this salt was collected and washed with 2–25 ml. portions of ether. The monohydrochloride melted at 183°–188° C. with decomposition and effervescence.

EXAMPLE 5

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-carbethoxy-piperazine

1-carbethoxypiperazine (43.3 g.; 0.28 mole) and 25.4 g. (0.14 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride were dissolved in 100 ml. of water and 175 ml. of ethanol. This solution was refluxed for fifteen hours and then concentrated to a brown, semi-crystalline mass. The crude material was taken up in chloroform, filtered and the chloroform distilled off under reduced pressure, leaving a brown oil. The oil was fractionated and the portion boiling at 186°–189° C./0–1 mm. was collected and amounted to a 48% yield.

EXAMPLE 6

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-carbethoxy-piperazine monohydrochloride

Eleven grams (0.04 mole) of 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-carbethoxypiperazine was dissolved in 100 ml. of ether and then treated with an excess of dry hydrogen chloride. The white granular precipitate obtained by this process was collected and washed with 2–25 ml. portions of ether. The hydrochloride was recrystallized from a chloroform-ether solution and melted at 200°–202° C. with effervescence.

EXAMPLE 7

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-methylpiperazine

A solution consisting of 34.1 g. (0.34 mole) of 1-methylpiperazine and 31.4 g. (0.17 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride in 225 ml. of ethanol and 125 ml. of water was refluxed for fifteen hours. The solvents were then removed under reduced pressure and the oily residue was made basic with 3 mls. of concentrated potassium hydroxide solution. The organic material was extracted with ether and the combined extracts were treated with activated carbon, filtered and concentrated to a yellow-brown oil. This crude material was fractionated under reduced pressure and the portion boiling at 138°–142° C./0–1 mm. was collected.

EXAMPLE 8

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-p-chlorophenyl-piperazine

A mixture consisting of 11.2 g. (0.06 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride, 24.0 g. (0.12 mole) of 1-(p-chlorophenyl)piperazine and 10.0 g. (0.12 mole) of sodium bicarbonate in 100 ml. of ethanol and 50 ml. of water was refluxed approximately fifteen hours at water-bath temperature. A brown oil resulted when the solvents were distilled off under reduced pressure. The residual material was treated with 3–100 ml. portions of chloroform and these combined extracts were treated with activated carbon and filtered. The yellow, oily residue obtained from the concentrated extracts was fractionally distilled at a pressure of 0–1 mm. The portion boiling at 220°–222° C./0–1 mm. was collected and amounted to a 14.8% yield.

EXAMPLE 9

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-p-chlorophenyl-piperazine monohydrochloride

Five grams of 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-p-chlorophenylpiperazine were dissolved in 20 ml. of dry ether and treated with an excess of dry hydrogen chloride gas. The gelatinous precipitate obtained in this manner was collected and dried over the steam-cone. The gelati-

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nous material changed to a granular precipitate under these conditions. The hydrochloride melted at 180°–183° C.

EXAMPLE 10

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-(2-pyridyl)-piperazine

To a solution of 13.9 g. (0.09 mole) of 1-(2-pyridyl)-piperazine in 50 ml. of ethanol and 50 ml. of water was added 16.8 g. (0.09 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride and 7.6 g. (0.09 mole) of sodium bicarbonate. This mixture was refluxed fifteen hours and then concentrated to a yellow, viscous oil. The oily residue was taken up in 150 ml. of chloroform, filtered and concentrated to yellowish oil which was fractionated under reduced pressure. The material distilling at 210°–215° C./0–1 mm. was collected.

EXAMPLE 11

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-(2-pyridyl)-piperazine hydrochloride

The hydrochloride of 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-(2-pyridyl)piperazine was formed in 95% yield when 5.0 g. of the basic material was dissolved in 30 ml. of dry ether and treated with an excess of dry hydrogen chloride gas. The salt precipitated immediately and was isolated in its hydrated form (melting point 68°–72° C.). When the hydrate of 1-[β-(N-phenyl-N-ethylamino)ethyl]-4-(2-pyridyl)piperazine hydrochloride was dried over phosphorous pentoxide at 100° C. and 20 mm. pressure for fifteen hours, the anhydrous salt was obtained. This hydrochloride melted at 194°–197° C.

EXAMPLE 12

1,4-bis-[β-(N-phenyl-N-ethylamino)ethyl]-piperazine

Anhydrous piperazine (4.3 g.; 0.05 mole) was dissolved in 100 ml. of ethanol and treated with 4.2 g. (0.05 mole) of sodium bicarbonate and 21.9 g. (0.10 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride. This mixture was refluxed 14–15 hours at steam-cone temperature and then concentrated to a quasi-crystalline mass. The organic material present was extracted with two 100 ml. portions of chloroform and the combined extracts treated with activated carbon and concentrated to a brown mass. This material was taken up in ethanol which on standing deposited a white, granular material. This material was recrystallized from ethanol twice and melted over a constant range of 76°–78° C.

EXAMPLE 13

1,4-bis-[β-(N-phenyl-N-ethylamino)ethyl]-piperazine tetrahydrochloride

Four grams of the basic material was taken up in 50 mls. of chloroform and treated with an excess of dry hydrogen chloride. The chloroform was evaporated off under reduced pressure at steam-cone temperature and the granular material remaining was triturated with dry acetone. The salt obtained in this manner melted at 192°–195° C.

EXAMPLE 14

1-[β-(N-phenyl-N-n-heptylamino)ethyl]-4-phenyl-piperazine

A solution consisting of 2.0 g. (0.01 mole) of 1-bromoheptane, 3.7 g. (0.01 mole) of 1-[β-(N-phenylamino)ethyl]-4-phenylpiperazine, 2.8 g. (0.03 mole) of sodium bicarbonate and 100 ml. of ethanol were refluxed for fifteen hours. At the end of this time the volatile materials were removed at steam-cone temperature under reduced pressure. The residue was taken up in chloroform, treated with activated charcoal and concentrated to a viscous, brown oil. This material was fractionated and the portion boiling at 175°–185° C. was collected.

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EXAMPLE 15

1-[β-(N-phenyl-N-methylamino)ethyl]-4-(2'-thiazolyl)-piperazine

A solution of 1-(2'-thiazolyl)piperazine (6.2 g.; 0.04 mole) in 25 ml. of distilled water and 25 ml. of ethanol was treated with 6.2 g. (0.04 mole) of β-(N-phenyl-N-methylamino)ethylchloride monohydrochloride and 6.1 g. (0.07 mole) of sodium bicarbonate. This mixture was refluxed for approximately fifteen hours and then subjected to a distillation under reduced pressure at water-bath temperature. The residue was taken up in chloroform, treated with activated charcoal, filtered and concentrated in a distilling flask to a brown viscous oil. This material was fractionated and the portion boiling at 216°–218° C./0–1 mm. was collected. This material solidified on standing (melting point 58°–61° C.).

EXAMPLE 16

1-[β-(N-phenyl-N-benzylamino)ethyl]-4-phenyl-piperazine dihydrochloride

A solution consisting of 3.6 g. (0.01 mole) of 1-[β-(N-phenylamino)ethyl]-4-phenylpiperazine, 1.6 g. (0.01 mole) of benzyl chloride, 1.1 g. (0.01 mole) of sodium bicarbonate in 50 ml. of ethanol was refluxed fifteen hours and then concentrated to a yellow-brown oil at water pump pressure and steam-cone temperature. The semi-crystalline residue was treated with chloroform as described above and the crude product obtained in this manner was fractionated. A yellow oil distilled at 230°–240° C./0–1 mm. and this material was collected, taken up in 50 ml. of dry benzene and treated with 210 mls. of 2.7 N ethanolic-hydrogen chloride. On cooling the dihydrochloride precipitated as a yellow, granular, hygroscopic material.

EXAMPLE 17

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-(2'-pyrimidyl)-piperazine

An ethanolic solution of 1-(2'-pyrimidyl)piperazine (6.5 g. in 25 ml. of ethanol) was treated with 25 mls. of water, 7.2 g. (0.04 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride and 6.6 g. (0.08 mole) of sodium bicarbonate. The mixture was refluxed fifteen hours and the crude reaction product was isolated using the method described above. The crude product was fractionated and the portion boiling at 200°–204° C./0–1 mm. was collected.

EXAMPLE 18

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-p-methoxyphenyl-piperazine

Fifteen grams (0.055 mole) of 1-p-methoxyphenylpiperazine hydrobromide, 14.0 g. (0.076 mole) of β-(N-phenyl-N-ethylamino)ethylchloride hydrochloride and 19.7 g. (0.234 mole) of sodium bicarbonate were refluxed with 100 ml. of ethanol for fifteen hours. The ethanol was distilled off and the quasi-crystalline residue was made basic with 5 ml. of concentrated, aqueous potassium hydroxide solution and then extracted with three 100 ml. portions of chloroform. The chloroform extracts were combined, decolorized with activated charcoal and concentrated to a heavy, brown oil. This material was fractionated and the distillate boiling at 235°–240° C./0.1 mm. was collected.

EXAMPLE 19

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-p-methoxyphenyl-piperazine·HCl

The monohydrochloride was formed by treating 4.18 g. (0.012 mole) of the compound of Example 18 with 4.14 ml. of 2.98 N hydrochloric acid. The salt was recrystallized twice from ethanol and melted at 215°–217° C.

EXAMPLE 20

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-[2-(6-methyl-pyridyl)]-piperazine

This material was prepared in a manner similar to that described in Example 18 using 15.0 g. (0.085 mole) of 1-[2-(6-methylpyridyl)]piperazine, 18.7 g. (0.085 mole) of β-(N-phenyl-N-ethylamino)ethylchloride hydrochloride and 21.4 g. (0.255 mole) of sodium bicarbonate in 100 ml. of ethanol. The basic material was isolated as an oil boiling at 205–210° C./0.1 mm.

EXAMPLE 21

1-[β-(N-phenyl-N-ethylamino)ethyl]-4-[2-(6-methyl-pyridyl)]-piperazine·HCl

The monohydrochloride was formed by treating 12.7 g. of the base described in Example 20 with a calculated amount of 2.98 N hydrochloric acid. A pure sample of this salt recrystallized from ethanol melted at 211–213° C.

EXAMPLE 22

1-[β-(N-phenyl-N-acetyl-amino)ethyl]-4-phenylpiperazine

When acetyl chloride (6.75 g.; 0.086 mole) was slowly added to 8.0 g. (0.029 mole) of 1-[β-(anilino)ethyl]-4-phenylpiperazine, an exothermic reaction occurred with the formation of a gummy solid. This material was triturated with dry ether and the resulting brown, granular precipitate was collected and dried. The crude salt (7.5 g.) was dissolved in 25 ml. of water, decolorized and then neutralized in the cold using 25% aqueous, potassium hydroxide solution. Solid, anhydrous, potassium carbonate (10.0 g.) was added to the chilled solution and the oil which separated was taken up in 100 ml. of chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and then fractionated. A high-boiling cut, which distilled at a temperature greater than 200° C./0.1 mm., was the desired product.

EXAMPLE 23

1-[β-(N-phenyl-N-acetyl-amino)ethyl]-4-phenylpiperazine

Equal volumes of acetic anhydride (16.2 g.; 0.159 mole) and 1-[β-(anilino)ethyl]-4-phenylpiperazine (16.9 g.; 0.06 mole) were added together and the mixture distilled under reduced pressure. The product was a yellow, viscous oil, collected at 245–252° C./0.1 mm.

EXAMPLE 24

1-[β-(N-phenyl-N-acetyl-amino)ethyl]-4-phenyl-piperazine·HCl

One molar equivalent of hydrochloric acid was added to 3.27 g. (0.01 mole) of the basic material of Example 23. The solution was evaporated to dryness at steam-cone temperature and reduced pressure and the residue was taken up in ethanol, treated with activated charcoal and filtered. A pure sample of the monohydrochloride was obtained from an ethanol-petroleum ether solution.

EXAMPLE 25

1-[β-(N-phenyl-N-o-iodobenzoylamino)ethyl]-4-phenyl-piperazine monohydrochloride

Eight grams (0.0285 mole) of 1-[β-(anilino)ethyl]-4-phenylpiperazine and 7.6 g. (0.0285 mole) of o-iodobenzoyl chloride were refluxed for two hours in 100 ml. of toluene. When the solution cooled to room temperature, the crystalline material deposited was collected and dried over solid potassium hydroxide under reduced pressure. The salt weighed 12.5 g. (80%) and after two recrystallizations from hot ethanol, it melted at 209–211° C.

EXAMPLE 26

1,4-di-[β-(N-phenyl-N-ethylamino)ethyl]-2-hydroxy-methylpiperazine

A mixture consisting of 11.12 g. (0.04 mole) of the

dihydrobromide of 2-hydroxymethylpiperazine, 7.0 g. (0.038 mole) of β-(N-phenyl-N-ethylamino)ethylchloride hydrochloride and 16.8 g. (0.20 mole) of sodium bicarbonate was refluxed in 150 ml. of ethanol for approximately fifteen hours. The reaction mixture was concentrated to an oily residue, made basic with concentrated, aqueous potassium hydroxide and extracted with two 100 ml. portions of chloroform. The chloroform extracts were combined, decolorized with activated charcoal and then fractionated under reduced pressure. The material boiling at 245–250° C./1.5–1.7 mm. was collected.

EXAMPLE 27

1-[β-(N-phenyl-N-ethylamino)ethyl]-2,6-dimethyl-4-phenylpiperazine

This product was obtained using the procedure described in Example 18 above. 9.0 g. (0.047 mole) of 2,6-dimethyl-4-phenylpiperazine, 8.7 g. (0.047 mole) of β-(N-phenyl-N-ethylamino)ethylchloride monohydrochloride, and 10.9 g. (0.13 mole) of sodium bicarbonate were refluxed together in 100 ml. of ethanol. The basic material boiled at 205–210° C./0.1 mm.

EXAMPLE 28

1-[β-(N,N-dibenzylamino)ethyl]-4-phenylpiperazine

β-Dibenzylaminoethylchloride monohydrochloride (32.3 g.; 0.109 mole) was condensed with 17.6 g. (0.109 mole) of 1-phenylpiperazine in 100 ml. of a water-ethanol solution (50 ml. of water and 50 ml. of ethanol). Sodium bicarbonate (18.4 g.; 0.218 mole) was added at the beginning of the reaction and the mixture was refluxed for 15 hours. After this time, the volatile material was removed and the heavy, brown oil taken up in chloroform, filtered, decolorized with activated charcoal and then concentrated to a dark-yellow oil which solidified on standing. This waxy material was triturated with water until the release of a white, crystalline material was complete. The crude yield weighed 38.5 g. (91.8%) and after two recrystallizations from warm ethanol, this material melted at 88–91° C.

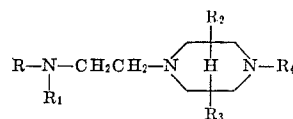
EXAMPLE 29

1-[β-(N,N-dibenzylamino)ethyl]-4-phenylpiperazine dihydrochloride

Four and one half grams (0.012 mole) of the basic material were dissolved in 30 ml. of warm ethanol containing 2.0 ml. of 11.7 N hydrochloric acid (0.024 mole). This solution on standing deposited a white, crystalline material, which melted at 210–212° C.

We claim:

1. A compound selected from the group having the general formula:



in which R is a member of the group consisting of phenyl and benzyl, R₁ is a member of the group consisting of alkyl radicals having 2 to 8 carbon atoms, benzyl, para-chlorophenyl, lower alkanoyl radicals, R₂ and R₃ are members of the group consisting of hydrogen, lower alkyl and hydroxy lower alkyl, R₄ is a member of the group consisting of lower alkyl, halophenyl, phenyl, loweralkylaminoloweralkyl, phenyl, carbloweralkoxy, lower alkanoyl, pyridyl, lower alkylpyridyl, thiazolyl, pyrimidyl, lower alkoxyphenyl and the therapeutically-useful acid addition salts.

2. An unsubstituted 1-[β-(N,N-di(lower alkanoylamino)ethyl)-4-phenylpiperazine.

3. An unsubstituted 1-[β-N-phenyl-N-lower alkanoylamino)ethyl]-4-phenylpiperazine.

4. 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-phenylpiperazine.

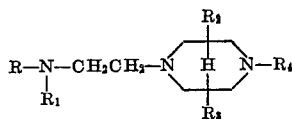
5. 1-[β -(N-phenyl-N-acetylamino)ethyl]-4-phenylpiperazine.

6. 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-p-chlorophenylpiperazine.

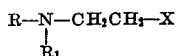
7. 1-[β -(N,N-dibenzylamino)ethyl]-4-phenylpiperazine.

8. 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-(2'-pyridyl)piperazine.

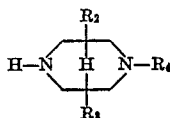
9. A method of preparing compounds having the formula



in which R is a member of the group consisting of phenyl and benzyl, R₁ is a member of the group consisting of alkyl radicals having 2 to 8 carbon atoms, benzyl, parachlorophenyl, lower alkanoyl radicals, R₂ and R₃ are members of the group consisting of hydrogen, lower alkyl and hydroxy lower alkyl, R₄ is a member of the group consisting of lower alkyl, halophenyl, phenyl, loweralkylaminoloweralkyl, phenyl, carbloweralkoxy, lower alkanoyl, pyridyl, lower alkylpyridyl, thiazolyl, pyrimidyl, and lower alkoxyphenyl radicals which comprises heating a compound having the formula



in which R and R₁ are as defined above and X is halogen with a compound having the formula



in which R₂, R₃, and R₄ are as defined above in the presence of an inert organic solvent.

10. A method of preparing a 1-[β -(N,N-di(lower aralkylamino)ethyl)-4-phenylpiperazine which comprises heating a β -(N,N-di(lower aralkylamino)ethyl halide acid salt with a 1-phenyl piperazine in the presence of an inert organic solvent.

11. A method of preparing 1-[β -(N-phenyl-N-lower alkanoylamino)ethyl]-4-phenylpiperazine which comprises heating β -(N-phenyl-N-lower alkanoylamino)ethyl halide acid salts with a 1-phenylpiperazine in the presence of an inert organic solvent.

12. A method of preparing 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-phenylpiperazine which comprises heating β -(N-phenyl-N-ethylamino)ethylchloride monohydrochloride and 1-phenylpiperazine in an aqueous-alcoholic solvent.

13. A method of preparing 1-[β -(N-phenyl-N-acetylamino)ethyl]-4-phenylpiperazine which comprises heating β -N-phenyl-N-acetylaminoethylchloride monochloride and 1-phenylpiperazine in an inert organic solvent.

14. A method of preparing 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-p-chlorophenylpiperazine which comprises heating β -N-phenyl-N-ethylamino)ethylchloride monohydrochloride with 1-(p-chlorophenyl)piperazine in an aqueous alcoholic solvent.

15. A method of preparing 1-[β -(N,N-dibenzylamino)ethyl]-4-phenylpiperazine which comprises heating β -(N,N-dibenzylamino)ethylchloride monohydrochloride with 1-phenylpiperazine in an inert organic solvent.

16. A method of preparing 1-[β -(N-phenyl-N-ethylamino)ethyl]-4-(2'-pyridyl)piperazine which comprises heating β -(N-phenyl-N-ethylamino)ethylchloride monohydrochloride and 1-(2'-pyridyl)piperazine in an aqueous alcoholic solvent.

References Cited in the file of this patent

Van Alphen: Rec. Trav. Chim. 56, 1007-12 (1937).