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SUBSTITUTED ALKYLENEDIPIPERAZINES

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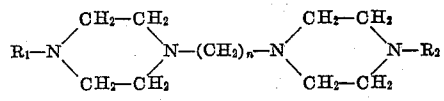
This invention relates to a new series of organic compounds. More particularly, this invention relates to α,ω-[1-(4-substituted)piperazinyl]alkanes, their quaternary and mineral acid salts and methods for their preparation.

Considerable difficulty has been encountered in the past in the synthesis of orally active, non-toxic, adrenergic blocking agents. This is particularly true where such compounds are intended for use in the treatment of hypertensive states. In such cases the prescribed course of therapy usually requires administration of the drug over a prolonged period of time. If the drug is toxic, such prolonged administration may result in the manifestation of undesirable side effects such as headache, nasal congestion, drowsiness, nausea, myosis, diarrhea and tachycardia.

We have now discovered a series of synthetic organic compounds which are extremely effective as hypotensive agents and vasodilators. The present application is a continuation-in-part of our application Serial Number 445,452, filed July 23, 1954. The compounds of the present invention have an effective dose in the range of 0.5 milligram per kilogram of body weight, are relatively non-toxic and may be administered orally. The latter property is most advantageous inasmuch as many of the available hypotensive agents must be administered intravenously in order to produce a maximal physiological response.

Another desirable property of the compounds of the present invention resides in their ability to induce long-term blood pressure depression with one effective dose. Thus, following administration of one average dose, blood pressure may remain reduced for a period longer than 5 hours without the necessity for repeated administration.

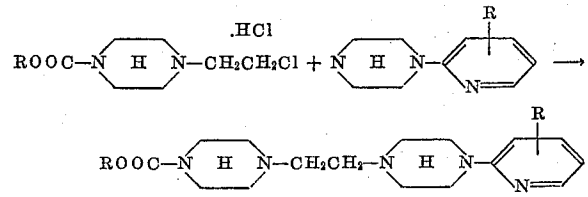
The compounds of the present invention are those having the following general formula:



wherein n is a positive integer from 2 to 10, R_1 is a member selected from the group consisting of aralkyl, heterocyclic, and alkylheterocyclic radicals, and R_2 is a member selected from the group consisting of carbalkoxy, aralkyl, heterocyclic, and alkylheterocyclic radicals. As examples of aralkyl substituents may be naphthylmethyl, benzyl, α-o-chlorotolyl and α-p-chlorotolyl. As examples of heterocyclic or alkyl substituted heterocyclic substituents may be pyrimidyl, pyridyl, methylpyridyl, ethylpyridyl, thiazolyl, pyrazinyl, quinoxalyl, pyrazolyl, thienyl, oxazoyl, and oxazinyl. The quaternary and mineral acid salts of these compounds are intended to be included within the scope of the present invention, as well as the symmetrically and unsymmetrically substituted derivatives.

For therapeutic purposes the preferred compounds of this invention are those wherein R_1 in the above general formula is a carbalkoxy group such as carbethoxy and

R_2 is a heterocyclic group such as a pyridyl or alkylpyridyl group. In preparing these compounds it is preferable first to synthesize a 1-(ω-haloalkyl)-4-substituted piperazine hydrochloride and then to react this derivative with a 1-substituted piperazine. The last step of the reaction may be more readily exemplified by the following equation:



where R is alkyl or hydrogen.

In more particular detail it may be stated that the 1-(ω-haloalkyl)-4-substituted piperazine shown above may first be prepared by reacting a 1-substituted piperazine with a polymethylene halohydrin such as ethylenebromhydrin, propylenechlorhydrin or nonalenechlorohydrin in the presence of a suitable basic carrier, such as, for example, an alkali metal carbonate or bicarbonate. We prefer to use sodium bicarbonate for this purpose. The condensation is preferably carried out at reflux temperature in the presence of alcohols or other suitable organic solvents, such as a lower alkyl alcohol, chloroform, or dioxane.

The resulting substituted piperazinyl alkanol is then halogenated in the presence of an inert solvent at a temperature varying from about 0° C. to about 10° C. Although the preferred halogenating agent for this reaction is thionyl chloride, others may be used, as for example phosphorus tribromide, phosphorus pentachloride, phosphorus oxychloride. The solvents we prefer to use in this reaction are those of the non-hydroxylic type, such as, for example, ether, chloroform, carbon tetrachloride, benzene, and toluene.

The object of the halogenation reaction is, of course, to replace the available hydroxy group with a halogen. Once this is done, the substituted piperazine may be further condensed with another piperazine, the latter being employed in the form of its salt or free base.

The α,ω-bis[1-(4-substituted)piperazinyl]alkanes of the present invention which are symmetrically substituted may be synthesized by reacting a di-haloalkane with a 1-substituted piperazine in the presence of a suitable organic or inorganic base. For example, the compound 1,3-bis{1-[4-(2-pyridyl)]piperazinyl}propane may be conveniently prepared by reacting 1,3-dibromopropane with 1-(2-pyridyl)piperazine in the presence of sodium bicarbonate.

It is preferred that an inert organic solvent also be present in the reaction mixture. Among the solvents which may be used are the lower alkyl alcohols, such as methanol, ethanol and propanol; benzene, toluene, chlorobenzene, dioxane, chloroform and aqueous-alcoholic mixtures. In addition, organic bases such as pyridine, quinoline, and the like may be used. These latter compounds have the advantage of serving both as solvents and acid acceptors for neutralizing the excess acid formed during the course of the reaction.

Although our preferred mode of carrying out the reaction is one in which an organic solvent is employed, it is possible to carry out the condensation in the absence of such solvent. An excess of the piperazine starting material is used in such cases. The piperazine being basic in character acts as the acid acceptor in lieu of the organic solvent.

Any alkali metal carbonate, bicarbonate, or hydroxide may be used as the base in lieu of the sodium bicarbonate

in the above reaction, as for example potassium or sodium hydroxide, potassium or sodium carbonate and the like. In addition, the alkali metal amides may be used, as, for example, sodamide or potassium amide.

It is preferred to carry out the reaction at reflux temperatures in order to minimize the time required for the reaction to reach completion. Although lower temperatures, such as room temperature, are suitable, a longer period of time may be required when this is done. A period of about 1–30 hours is sufficient when the reaction is carried out at reflux temperature, whereas a week or more may be required at room temperature. If the reaction is carried out at reflux in the absence of a solvent, the solids are fused before being subjected to refluxing.

The quaternary or mineral acid salts of the compounds of the present invention may be readily prepared by known methods. For example, the basic compounds may be treated with methyl iodide in the presence of an inert organic solvent in which the base is soluble, as, for example, benzene, ether, chloroform and the like. Upon standing at room temperature for a period of about 1 hour to 3 days, depending upon the nature of the base used, the quaternary salt is deposited from solution. In a similar manner, treatment of the same basic material with a hydrohalogen gas, such as hydrogen chloride or hydrogen bromide, or a mineral acid, such as sulfuric or phosphoric acid, results in the formation of the corresponding salt. It is preferred to carry out the reaction in the presence of an inert non-hydroxylic organic solvent, such as benzene, chloroform, or toluene.

In order to obtain maximum yields, where n in the above general formula is equal to 4 or 5, a slight modification of the above procedure is necessary for the purpose of minimizing the formation of spiro compounds. Accordingly, when it is intended to prepare a compound of this type, the di-haloalkane is added dropwise to a refluxing mixture of the piperazine starting material in the presence of the base. Since the amine is present initially in large excess, the formation of a spiro piperazinium compound is minimized. In the event any spiro compound is formed, however, it may be readily removed by washing the cooled reaction mixture with water. The spiro quaternary compound dissolves in water, whereas the basic α,ω-bis[1-(4-substituted)piperazinyl]alkane does not.

The following examples illustrate our invention in more particular detail, but they are not intended to limit the scope thereof. All parts are by weight unless otherwise indicated.

Example 1

A solution consisting of 8.2 grams (0.05 mole) of 1-(2-pyridyl)piperazine, 4.7 grams (0.025 mole) of 1,2-dibromoethane and 5.04 grams (0.06 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for a period of 15 hours. At the end of this period, the volatile materials were removed at steam cone temperature and reduced pressure. The solid residue was taken up in chloroform, treated with activated charcoal and concentrated to one-fifth the original volume. On cooling, this solution deposited a white crystalline mass of 1,2-bis{1-[4-(2-pyridyl)]piperazinyl}ethane, which was collected and recrystallized from ethanol. The product melted at 156–158° C.

Example 2

The compound 1,3-bis{1-[4-(2-pyridyl)]piperazinyl}propane was prepared in accordance with the process set forth in Example 1 using 8.2 grams (0.05 mole) of 1-(2-pyridyl) piperazine, 5.1 grams (0.025 mole) of 1,3-dibromopropane, and 5.04 grams (0.06 mole) of sodium bicarbonate in 100 ml. of ethanol. The mixture was refluxed overnight and the crude product was recrystallized from ethanol. The recrystallized product melted at 73–75° C.

Example 3

Dry hydrogen chloride was passed through a solution of 5.0 grams of 1,3-bis{1-[4-(2-pyridyl)]piperazinyl}propane in 75 ml. of toluene. A gelatinous precipitate formed immediately and this material was collected and dried at the temperature of the steam cone. The granular product, 1,3-bis{1-[4-(2-pyridyl)]piperazinyl}propane dihydrochloride, was recrystallized from hot water and found to melt at 240–243° C. with effervescence.

Example 4

The compound 1,10-bis{1-[4-(2-pyridyl)]piperazinyl}-decane was prepared in accordance with the method set forth in Example 1 using 7.5 grams (0.025 mole) of 1-(2-pyridyl)piperazine, 3.6 grams (0.012 mole) of 1,10-dibromodecane and 4.2 grams (0.05 mole) of sodium bicarbonate in 100 ml. of ethanol. The crude product was recrystallized from ethanol and found to melt at 94–96° C.

Example 5

3.5 grams (0.01 mole) of 1,2-bis{1-[4-(2-pyridyl)]-piperazinyl}ethane was treated with 6.7 ml. of 2.98 N hydrochloric acid. The solution was evaporated to dryness at steam cone temperature and reduced pressure to yield 1,2-bis{1-[4-(2-pyridyl)]piperazinyl}-ethane dihydrochloride which melted at a temperature exceeding 290° C. After two recrystallizations from ethanol, the pure material melted in the same range.

Example 6

3.5 grams (0.001 mole) of 1,3-bis{1-[4-(2-pyridyl)]-piperazinyl} propane was dissolved in 40 ml. of dry benzene and treated with 2.8 grams (0.002 moles) of methyl iodide. After 3 hours, the solution deposited 2.0 grams of a white, crystalline, quaternary salt of 1,3-bis{1-[4-(2-pyridyl)]piperazinyl}propane. The material was recrystallized from an ethanol-ether solution and melted at 144–147° C.

Example 7

A solution consisting of 6.1 grams (0.025 mole) of 1,6-dibromohexane, 8.2 grams (0.05 mole) of 1-(2-pyridyl)piperazine and 5.0 grams (0.06 mole) of sodium bicarbonate in 150 ml. of ethanol was refluxed for 15 hours. At the end of this period the volatile materials were removed at steam-cone temperature and reduced pressure. The solid residue was taken up in chloroform, decolorized with activated charcoal and concentrated to one-fifth of the original volume. On cooling, this solution deposited white crystals of crude 1,6-bis{1-[4-(2-pyridyl)]piperazinyl}hexane, which were collected and recrystallized twice from ethanol. The sample melted at 98–100° C.

Example 8

1,6-bis{1 - [4 - (2-pyridyl)]piperazinyl}hexane (4.08 grams; 0.01 mole) was treated with 6.7 mls. of 2.98 N hydrochloric acid and the resulting mixture was concentrated to a white granular material. The dihydrochloride of 1,6-bis{1 - [4 - (2-pyridyl)]-piperazinyl}hexane melted at 260–262° C. after two recrystallizations from ethanol.

Example 9

4.62 grams (0.01 mole) of 1,10-bis{1-[4-(2-pyridyl)]-piperazinyl}decane was treated with 6.7 mls. (0.02 mole) of 2.98 N hydrochloric acid and the resulting mixture concentrated to a white, granular material. The 1,10-bis{1-[4-(2-pyridyl)]piperazinyl}decane dihydrochloride melted at 220–223° C. (with sintering at 215° C.) after recrystallization from hot water.

Example 10

A mixture consisting of 8.2 grams (0.05 mole) of 1-(2-pyrimidyl)piperazine, 5.1 grams (0.025 mole) of 1,3-dibromopropane and 16.8 grams (0.2 mole) of sodium bicarbonate in 150 ml. of ethanol was refluxed 15 hours.

At the end of this time the volatile materials were removed at steam-cone temperature under reduced pressure and the crystalline residue was washed with warm water and then dissolved in chloroform. The chloroformic solution was treated with activated charcoal, dried over anhydrous magnesium sulfate and concentrated to a brown oil which solidified on standing. The crude material was recrystallized from ethanol, yielding 1,3-bis {1-[4-(2-pyrimidyl)]-piperazinyl}propane which melted at 68–70° C.

Example 11

To 150 ml. of ethanol was added 11.7 g. (0.072 mole) of 1-(2-pyridyl)piperazine, 19.4 g. (0.072 mole) of 1-carbethoxy-4-(γ-chloropropyl)piperazine monohydrochloride and 24.9 g. (0.287 mole) of sodium bicarbonate. The mixture was refluxed for about 16 hours. At the end of this time the ethanol was removed and the semi-crystalline residue was extracted with two 100 ml. portions of chloroform. The chloroform extracts were combined, decolorized with activated charcoal, filtered and concentrated to a heavy, brown oil. This residual oil was treated with distilled water, made alkaline in the cold with 50% potassium hydroxide solution and extracted with three 100 ml. portions of ether. The ether extracts were combined, concentrated, and the desired 1-[1-(4-carbethoxy)piperazinyl] - 3 - {1-[4-(2-pyridyl)]-piperazinyl}propane was deposited as a crystalline mass. The compound is a white solid having a melting point of 76–78° C.

Example 12

To 15.2 g. (0.042 mole) of the product of Example 11 was added two molar equivalents of hydrochloric acid. The dihydrochloride salt was recrystallized from ethanol and the product, 1-[1-(4-carbethoxy)piperazinyl]-3-{1-[4-(2-pyridyl)]piperazinyl} propane dihydrochloride had a melting point of 246–248° C.

Example 13

A suspension consisting of 11.0 g. (0.062 mole) of 1-[2-(6-methyl)pyridyl]piperazine, 15.4 g. (0.062 mole) of 1-carbethoxy-4-(β-chloroethyl)piperazine hydrochloride and 15.2 g. (0.188 mole) of sodium bicarbonate was refluxed in 150 ml. of ethanol for 16 hours. The reaction mixture was filtered and the filtrate concentrated to a heavy oil. This residual material was made strongly alkaline with 50% potassium hydroxide and extracted with two 100 ml. portions of chloroform. These extracts were combined, treated with activated charcoal and concentrated to an oily, basic material. The desired product was obtained by distilling this oil under reduced pressure and collecting the portion boiling at 210–215° C./0.3–0.4 mm. (53%).

Example 14

Reacting 1-[3-(6-chloro)pyridazyl]piperazine with 1-carbethoxy-4-(β-chloroethyl)piperazine hydrochloride in the presence of sodium bicarbonate gave 1-[1-(4-carbethoxy)piperazinyl] - 2 - [1-{4-[3-(6-chloro)pyridazyl]}piperazinyl]ethane having a melting point of 121–123° C.

Example 15

The product of Example 14 reacted with two molar equivalents of hydrochloric acid produced 1-[1-(4-carbethoxy)piperazinyl] - 2 - [1-{4-[3-(6-chloro)pyridazyl]} piperazinyl]ethane dihydrochloride having a melting point of 296–297° C.

Example 16

The compound 1-[1-(4-carbethoxy)piperazinyl]-2-{1-[4-(2-pyridyl)]piperazinyl} ethane was prepared by reacting 1-[2-pyridyl]-piperazine with 1-carbethoxy-4-(β-chloroethyl)piperazine hydrochloride. This basic material melted at 87–88° C.

Example 17

The compound of Example 16 reacted with two molar equivalents of hydrochloric acid produced 1-[1-(4-carbethoxy)piperazinyl] - 2 - {1-[4-(2-pyridyl)]piperazinyl} ethane dihydrochloride having a melting point of 258–260° C.

Example 18

The compound 1-[1-(4-carbethoxy)piperazinyl]-3-[1-{4-[2-(6-methyl)pyridyl]}piperazinyl]propane was prepared by reacting 1-[2-(6-methyl)pyridyl]-piperazine with 1-(γ-chloropropyl)-4-carbethoxy-piperazine hydrochloride in the presence of sodium bicarbonate using ethanol as a solvent. The basic material obtained in this manner was purified by high vacuum distillation and the desired product boiled at 225–235° C./1.0 mm.

Example 19

The compound described in Example 8 was reacted with two molar equivalents of hydrochloric acid and the dihydrochloride was isolated as a white, grandular solid, which crystallized as a monohydrate; melting point 260–262° C. (slight decomposition).

Example 20

A solution consisting of 15.0 g. (0.095 mole) of 1-carbethoxy-piperazine and 114.0 g. (0.38 mole) of 1,10-dibromodecane in 200 ml. of ethanol was refluxed for at least 24 hours. After this period of reflux the solvent was removed under reduced pressure and the waxy residue was triturated with three-100 ml. portions of warm, high-boiling petroleum ether, treated with dry hydrdogen chloride gas and collected on a sintered glass funnel. The filter cake was taken up in 200 ml. of chloroform, washed with two-100 ml. portions of water, clarified with activated carbon and dried over magnesium sulfate for twenty minutes. After removing the chloroform under reduced pressure at steam-cone temperature, the 1-(ω-bromodecyl) - 4 - carbethoxy-piperazine hydrobromide was collected, dried over solid potassium hryroxide under reduced pressure and used in the next step without further purification.

1 - [2 - (6-methyl)pyridyl]-piperazine (2.69 g.; 0.015 mole) and 2.29 g. (0.005 mole) of 1-(ω-bromodecyl)-4-carbethoxy-piperazine hydrobromide were mixed without solvent and heated at 90–100° C. for approximately thirty minutes. The reaction mass was cooled, triturated with 50 ml. of warm water and the insoluble material was separated and dissolved in 3.5 N hydrochloric acid (25 ml.). Activated carbon was used to decolorize this acidic solution which yielded a low-melting solid when made basic with 20% sodium hydroxide solution. This solid, basic material was recrystallized twice from an ether-petroleum ether (boiling point 90–100° C.) solution to give 0.90 g. of the pure 1-[1-(4-carbethoxy)-piperazinyl]-10-[1-{4-[2 - (6-methyl)pyridyl]} - piperazinyl] - decane; melting point 73–75° C.

Example 21

The compound 1-[1-(4-carbethoxy)piperazinyl]-10-{1-[4-(2-pyridyl)]-piperazinyl}-decane was prepared in accordance with the procedure set forth in Example 20 using 7.15 g. (0.0167 mole) of 1-(ω-bromodecyl-4-carbethoxy-piperazine hydrobromide and 8.15 g. (0.050 mole) of 1-(2-pyridyl)piperazine. The crude product was recrystallized twice from an ether-petroleum ether (boiling point 90–100° C.) solution to yield a pure product when melted at 65–67.5° C.

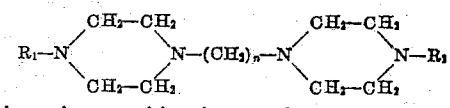
Example 22

To 2.295 g. (0.005 mole) of the product of Example 21 was added two molar equivalents of hydrochloric acid. The dihydrochloride salt obtained in this manner was recrystallized from ethanol and the pure product, 1-[1-(4-carbethoxy)piperazinyl]-10-{1-[4 - (2 - pyridyl)] piperazinyl} - decane dihydrochloride, melted at 208–210° C.

Other compounds of this invention include 1-[1-(4-carbopropoxy)piperazinyl]-3-{1-[4-(2-pyridyl)]piperazinyl}propane, prepared by reacting 1-(γ-chloropropyl)-4-carbopropoxy-piperazine hydrochloride with 1-(2-pyridyl)piperazine; 1-[1-(4-carbobutoxy)piperazinyl]-3-{1-[4-(2-pyrimidyl)]piperazinyl}propane prepared by reacting 1-(γ-chloropropyl)-4-carbobutoxy-piperazine hydrochloride with 1-(2-pyrimidyl)piperazine; 1-[1-(4-carbethoxy)piperazinyl]-5-[1-{4-[2-(4-ethyl)pyridyl]}piperazinyl]pentane prepared by reacting 1-(ω-chloropentyl)-4-carbethoxy-piperazine hydrochloride with 1-[2-(4-ethyl)pyridyl]piperazine; 1-[1-(4-carbethoxy)piperazinyl]-7-{1-[4-(2-pyridyl)]piperazinyl}heptane prepared by condensing 1-(ω-chloroheptyl)-4-carbethoxy-piperazine hydrochloride with 1-(2-pyridyl)-piperazine; 1-[1-(4-carbopropoxy)piperazinyl]-8-[1-{4-[3-(6-chloro)-pyridazyl]}piperazinyl]octane, prepared by reacting 1-(ω-chlorooctyl)-4-carbopropoxy-piperazine hydrochloride with 1-[3-(6-chloro)pyridazyl]-piperazine; 1-[1-(4-carbopropoxy)piperazinyl]-9-[1-{4-[2-(6-methyl)-pyridyl]}piperazinyl]nonane prepared by reacting 1-(ω-chlorononyl)-4-carbopropoxy-piperazine hydrochloride with 1-[2-(6-methyl)pyridyl]piperazine; 1-[1-(4-carbobutoxy)piperazinyl]-10-{1-[4-(2-pyridyl)]-piperazinyl}decane prepared by reacting 1-(ω-chlorodecyl)-4-carbobutoxy-piperazine hydrochloride with 1-(2-pyridyl)piperazine; the dihydrochlorides and quatenary salts of these compounds, prepared in accordance with the methods of Examples 5 and 6, respectively.

We claim:

1. Compounds selected from the group having the general formula:



wherein n is a positive integer from 2 to 10, R_1 is a member selected from the group consisting of carbloweralkoxy, pyridyl, and pyrimidyl radicals. R_2 is a member selected from the group consisting of pyridyl, lower alkylpyridyl, chloropyridazyl, and pyrimidyl radicals, and the non-toxic quaternary and mineral acid salts thereof.

2. The α-[1-(4-carbloweralkoxy)piperazinyl]-ω-{1-[4-(2-pyridyl)]piperazinyl}lower alkanes.

3. 1-[1-(4-carbethoxy)piperazinyl]-3-{1-[4-(2-pyridyl)]-piperazinyl}propane.

4. 1-[1-(4-carbethoxy)piperazinyl]-2-{1-[4-(2-pyridyl)]-piperazinyl}ethane.

5. 1-[1-(4-carbethoxy)piperazinyl]-3-[1-{4-[2-(6-methyl)pyridyl]}piperazinyl]-propane.

6. 1-[1-(4-carbethoxy)piperazinyl]-10-{1-[4-(2-pyridyl)]piperazinyl}decane.

7. 1-[1-(4-carbethoxy)piperazinyl]-3-{1-[4-(2-pyridyl)]piperazinyl}propane dihydrochloride.

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