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2,953,568

DERIVATIVES OF PIPERAZINE

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No Drawing. Filed Mar. 3, 1958, Ser. No. 718,476

13 Claims. (Cl. 260—268)

The present invention concerns new piperazine compounds. More particularly it relates to 1-(di-monocyclic aryl-methoxy-lower alkyl)-4-(acyloxy-lower alkyl)-piperazines, in which the lower alkyl radicals contain from 2 to 3 carbon atoms, salts or quaternary ammonium compounds thereof, as well as process for the preparation of such compounds.

The carbon atoms in the piperazine ring are preferably unsubstituted, but they may contain as substituents lower alkyl groups, e.g. methyl or ethyl.

The monocyclic aryl radicals stand for phenyl radicals which may be unsubstituted or may contain as substituents lower alkyl radicals, e.g. methyl or ethyl; hydroxyl groups; lower alkoxy groups, e.g. methoxy, ethoxy or α,β -methylenedioxy; lower alkoxyloxy, e.g. acetoxy; nitro groups; amino groups, such as primary amino, secondary amino, e.g. methylamino, or tertiary amino, e.g. dimethylamino; or halogen atoms, e.g. chlorine or bromine.

Lower alkyl radicals contain preferably from 2 to 3 carbon atoms and are therefore represented by 1,2-ethylene, 1,2-propylene or 1,3-propylene. These radicals separate the oxy groups from the nitrogen atoms of the piperazine ring by at least 2 carbon atoms.

An acyl radical is derived from an organic carboxylic or thiocarboxylic acid, for example, a lower aliphatic carboxylic acid, such as a lower alkanic acid, e.g. acetic, propionic, pivalic, hydroxyacetic and the like; a lower alkenic acid, e.g. acrylic or methacrylic acid; an aryl carboxylic acid, particularly a monocyclic aryl carboxylic acid, e.g. benzoic, 4-hydroxybenzoic, 3,4,5-trimethoxybenzoic, 3,4-methylenedioxybenzoic, 3-dimethylamino-benzoic, 3,4-dichloro-benzoic or carbethoxy-syringic acid, or a bicyclic aryl carboxylic acid, e.g. naphthalene carboxylic acid; an aralkanoic acid, e.g. phenylacetic acid; an arylalkanoic acid, e.g. cinnamic or 3,4,5-trimethoxy-cinnamic acid; a aryloxyalkanoic acid, e.g. phenoxyacetic acid; a carbonic acid, particularly an amino-carbonic acid, such as an N-unsubstituted, N-monosubstituted or an N,N-disubstituted amino-carbonic acid, for example, an N-lower alkyl-carbamic acid, an N,N-di-lower alkyl-carbamic acid, an N-monocyclic aryl-carbamic acid or an N-bicyclic aryl-carbamic acid, e.g. carbamic, N-methyl-carbamic, N,N-dimethyl-carbamic, an N-phenyl-carbamic or an N-naphthyl-carbamic acid; or a thiocarbonic acid, particularly an amino-

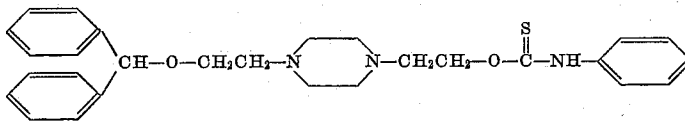
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thiocarbamic, N,N-dimethyl-thiocarbamic, an N-phenyl-thiocarbamic or an N-naphthyl-thiocarbamic acid. Additional substituents may be attached to the aliphatic and aromatic portions of the acyl radicals, for example, lower alkyl radicals, e.g. methyl or ethyl; hydroxyl groups; etherified hydroxyl groups, such as lower alkoxy groups, e.g. methoxy, ethoxy or α,β -methylenedioxy; esterified hydroxyl groups, such as lower alkoxyloxy groups, e.g. acetoxy; nitro groups; amino groups, such as primary amino; secondary amino, e.g. methylamino or ethylamino; or tertiary amino, e.g. dimethylamino or diethyl amino; or halogen atoms, e.g. chlorine or bromine.

Salts, especially the bis-salts of the piperazine derivatives of this invention are particularly therapeutically useful acid addition salts, for example, those with inorganic acids, such as, hydrohalic acids, e.g. hydrochloric or hydrobromic acid; thiocyanic acid; sulfuric or phosphoric acids; or those with organic acids, such as, formic, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, ascorbic, hydroxymaleic, dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, mandelic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, methane sulfonic, ethane sulfonic, hydroxyethane sulfonic, benzene sulfonic, p-toluene sulfonic, naphthalene sulfonic or sulfanilic acid or methionine, tryptophane, lysine or arginine.

Quaternary ammonium compounds, especially bis-quaternary ammonium compounds are those with reactive esters formed by hydroxylated hydrocarbons and strong inorganic or organic acids. Particularly mentioned may be the quaternary ammonium compounds formed with lower alkyl halides, e.g. methyl chloride, methyl bromide, methyl iodide, ethyl chloride, ethyl bromide, ethyl iodide or propyl chloride; with di-lower alkyl sulfates, e.g. dimethyl sulfate or diethyl sulfate; or with lower alkyl aryl sulfonates, e.g. methyl p-toluene sulfonate, as well as the corresponding quaternary ammonium hydroxides and the salts formed therefrom with other inorganic or organic acids.

The new piperazine derivatives of this invention have stimulating and/or analgesic properties. They may therefore be used as stimulating agents in states of drowsiness, in cases of barbiturate poisoning or to overcome general fatigue, and/or as analgesic agents to alleviate pain. A particularly pronounced stimulating effect is observed with the 1-(2-di-monocyclic aryl-methoxy-ethyl)-4-(2-acyloxy-ethyl)-piperazines, in which the acyl group is derived from an amino-carbonic acid, such as a carbamic acid or a thiocarbamic acid, and in which the monocyclic aryl radicals have the above-given meaning, and addition salts with hydrohalic acids, e.g. hydrochloric or hydrobromic acid, or with hydroxy-carboxylic acids, e.g. tartaric or citric acid. Representing this group of compounds, is, for example, the 1-(2-diphenyl-methoxy-ethyl)-4-[2-(N-phenyl - thiocarbamyloxy)-ethyl]-piperazine of the formula:

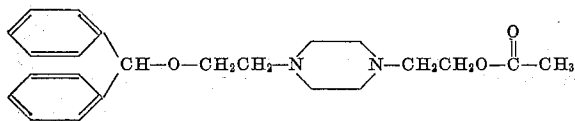


thiocarbonic acid, such as an N-unsubstituted, N-monosubstituted or an N,N-di-substituted amino-thiocarbonic acid, for example an N-lower alkyl-thiocarbamic acid, an N,N-di-lower alkyl - thiocarbamic acid, an N-monocyclic aryl - thiocarbamic acid or an N - bicyclic aryl-thiocarbamic acid, e.g. thiocarbamic, N-methyl-

and the dihydrochloride thereof.

Compounds of this invention, which exhibit analgesic properties, are particularly the 1-(2-di-monocyclic aryl-methoxy-ethyl)-4-(2-acyloxy-ethyl)-piperazines, in which the acyl group is derived from an aromatic and, particularly, from an alkanic acid, and in which the

monocyclic aryl radicals have the above-given meaning, and the addition salts with hydrohalic acids, e.g. hydrochloric or hydrobromic acid, or with organic hydroxycarboxylic acids, e.g. tartaric or citric acid. For example, the 1-(2-diphenylmethoxy-ethyl)-4-(2-acetoxyethyl)-piperazine of the formula:



of the dihydro-chloride thereof, have a marked analgesic effect.

The new compounds may be used as medicaments in the form of pharmaceutical preparations, which contain the new compounds in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral, e.g. oral, or parenteral administration. For making up the preparations there may be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as tablets, dragees or capsules, or in liquid form, for example, as solutions, e.g. isotonic solutions, or as emulsions. If desired, they may contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain, in combination, other therapeutically useful substances.

The new piperazine derivatives of this invention may be prepared by esterifying in a 1-(di-monocyclic aryl-methoxy-lower alkyl)-4-(hydroxy-lower alkyl)-piperazine or a salt thereof the free hydroxyl group with the acyl radical of an organic carboxylic acid, and, if desired, converting a resulting salt into the free base, and/or, if desired, converting a resulting base into a salt or a quaternary ammonium compound thereof.

The esterification of the free hydroxyl group is carried out according to known esterification procedures. The esterifying acid is particularly used in the form of a reactive derivative thereof, for example, as an acid halide, e.g. chloride, or an acid anhydride. These derivatives are used either in the absence or preferably in the presence of a basic condensing agent, for example, an organic base, e.g. pyridine, collidine or benzyl trimethyl ammonium hydroxide; or an alkali metal or alkaline earth metal carbonate, e.g. sodium carbonate or potassium hydrogen carbonate. The reaction is carried out either in an excess of the liquid organic base, e.g. pyridine, or in the presence of a non-hydroxylated solvent, such as a hydrocarbon, e.g. hexane, benzene, toluene or xylene. The reaction occurs under cooling, at room temperature or may be performed at an elevated temperature, for example, the boiling temperature of the solvent; it may be carried out in an open vessel under normal pressure or in a closed vessel under an elevated pressure, and, if desired, in the presence of an inert gas, e.g. nitrogen.

The reaction may also be performed by preparing the metal salt, such as an alkali metal, e.g. lithium, sodium or potassium, salt of a 1-(di-monocyclic aryl-methoxy-lower alkyl)-4-(2-hydroxy-lower alkyl)-piperazine, by reacting the latter with an alkali metal amide or hydride, e.g. lithium, sodium or potassium amide or hydride, or an alkali metal lower alkylate, e.g. sodium or potassium methylate or ethylate, in a suitable solvent such as a hydrocarbon, e.g. hexane, benzene, toluene or xylene; an ether, e.g. 1,4-dioxane or diethyleneglycol dimethylether; or a lower alkanol, e.g. methanol or ethanol. Such salt is then reacted with the acyl halide, e.g. chloride or bromide. This process is

particularly suited for the esterification with the halide, e.g. chloride, of a carbamic or thiocarbamic acid. If necessary, the reaction may be carried out at an elevated temperature and/or the reaction may be performed in a closed vessel under increased pressure, and, if desired, in the atmosphere of an inert gas, e.g. nitrogen.

The acyl radical of a carbamic or thiocarbamic acid may also be introduced by reacting a 1-(di-monocyclic aryl-methoxy-lower alkyl)-4-(hydroxy-lower alkyl)-piperazine or a salt thereof with an isocyanate or isothiocyanate, for example, an alkali metal, e.g. sodium or potassium, or an ammonium isocyanate or isothiocyanate; or an N-monosubstituted isocyanate and isothiocyanate, for example, an N-lower alkyl isocyanate, e.g. methylisocyanate, or an N-monocyclic or N-bicyclic aryl-isocyanate, e.g. a phenyl isocyanate or a naphthyl isocyanate, or the corresponding isothiocyanate derivatives. Such reaction may be carried out in the absence or preferably in the presence of a solvent, such as a hydrocarbon, e.g. hexane, benzene, toluene, or xylene; under cooling, at room temperature or at an elevated temperature; at atmospheric pressure or in a closed vessel under increased pressure, and, if desired, in the presence of an inert gas, e.g. nitrogen.

The starting materials used in the above process are known or may be prepared according to methods used for the preparation of the known intermediates. For example, by reacting a metal salt of a 1,4-bis-(2-hydroxyethyl)-piperazine, prepared by treatment with a metal salt forming reagent, such as an alkali metal amide or hydride, e.g. lithium, sodium or potassium amide or hydride; or an alkali metal lower alkanolate, e.g. sodium or potassium methylate or ethylate, with a di-monocyclic arylmethyl halide, such as a diphenylmethyl halide, e.g. chloride or bromide, in a non-hydroxylated solvent, such as a hydrocarbon, e.g. hexane, benzene, toluene or xylene, or in an ether, e.g. p-dioxane or diethylene glycol dimethylether.

The reaction products are isolated according to standard procedures, such as, for example, extraction, distillation, adsorption or crystallization and are purified, for example, by distillation, recrystallization, which may include the use of adsorption reagents, or by salt formation.

Depending on the conditions used the new piperazine compounds are obtained in the form of the free bases or the salts thereof. A salt may be converted into the free base in the customary way, for example, by reaction with an aqueous alkaline reagent, such as an alkali metal hydroxide, e.g. sodium or potassium hydroxide, an alkali metal carbonate, e.g. sodium carbonate or potassium hydrogen carbonate, or ammonia. A free base may be transformed into its therapeutically useful acid addition salts by reaction with appropriate inorganic or organic acids, such as those mentioned hereinabove, for example, in an alcohol, e.g. methanol, ethanol, propanol or isopropanol, solution or an ether, e.g. diethylether, solution or in a mixture of such solvents.

The compounds of this invention may be converted into the quaternary ammonium compounds by reacting the tertiary bases with a reactive ester formed by a hydroxylated lower hydrocarbon compound and a strong inorganic or organic acid. Hydroxylated lower hydrocarbon compounds contain from 1 to 7 carbon atoms and the esters thereof are more especially those with strong inorganic acids, such as mineral acids, e.g. hydrochloric, hydrobromic, hydriodic or sulfuric acid, or with a strong organic acid such as aryl sulfonic acids e.g. p-toluene sulfonic acid. Such reactive esters are particularly lower alkyl halides, e.g. methyl iodide, methyl bromide, methyl chloride, ethyl iodide, ethyl bromide, ethyl chloride or propyl chloride; di-lower alkyl sulfates, e.g. dimethyl sulfate or diethyl sulfate; or lower alkyl aryl sulfonates, e.g. methyl p-toluene sulfonate. The quaternizing reactions are performed in the presence or absence of a sol-

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vent, such as a lower alkanol, e.g. methanol, ethanol, propanol, isopropanol, butanol or pentanol; or an organic acid amide, e.g. formamide or dimethylformamide; under cooling, at room temperature or at an elevated temperature; at atmospheric pressure or in a closed vessel under increased pressure, and, if desired, in the atmosphere of an inert gas, e.g. nitrogen.

Resulting quaternary ammonium compounds may be converted into the corresponding quaternary ammonium hydroxides, for example, by reaction of a resulting quaternary ammonium halide with silver oxide, or by reaction of a quaternary ammonium sulfate with barium hydroxide or by treatment of a quaternary ammonium salt with an anion exchanger or by electro dialysis. From the resulting quaternary ammonium base there may be formed thereapeutically suitable quaternary ammonium salts by reaction with acids, for example, those outlined hereinbefore for the preparation of the salts. A quaternary ammonium salt may be directly converted into another quaternary salt without preparation of the quaternary ammonium hydroxide; for example, a quaternary ammonium iodide may be reacted with freshly prepared silver chloride to yield the quaternary ammonium chloride, or the quaternary ammonium iodide may be converted into the corresponding chloride by treatment with hydrochloric acid in anhydrous methanol.

The following examples illustrate the invention; they are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

Example 1

A mixture of 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 0.7 g. of phenylisocyanate is heated for thirty minutes. The reaction product is dissolved in 30 ml. of ethyl acetate and on addition of a solution of hydrogen chloride in ethyl acetate the 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-phenyl-carbamyl-oxo)-ethyl]-piperazine dihydrochloride precipitates, which after recrystallization melts at 239-241°; yield: 2.2 g.

The starting material may be prepared as follows: A solution of 26.1 g. of bis-1,4-(2-hydroxyethyl)-piperazine in 240 ml. of diethyleneglycol dimethylether is heated for three hours to 140-145° with 7.3 g. of a 50 percent suspension of sodium hydride in mineral oil. 40.5 g. of diphenylmethylbromide is then added and the reaction mixture is stirred for an additional 5 hours at 140°. After cooling the reaction mixture is filtered and a solution of hydrogen chloride in ethyl acetate is added. The supernatant solution is decanted from the precipitate and the resulting 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine dihydrochloride is dissolved in water. An aqueous solution of sodium carbonate is added, the aqueous solution extracted with ether, and the resulting base is distilled under reduced pressure, B.P., 213-217°/0.5 mm. It crystallizes upon standing, M.P. 67-68°; yield: 13 g.

Example 2

A mixture of 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 0.78 g. of 2-methylphenylisocyanate in 4 ml. of benzene is heated to 70-80° for thirty minutes. The benzene is evaporated under reduced pressure and the residue worked up as described in Example 1 to yield 2.5 g. of the 1-(2-diphenylmethoxy-ethyl)-4-[2-[N-(2-methyl-phenyl)-carbamyloxy]-ethyl]-piperazine dihydrochloride, M.P. 212-215°.

By using naphthyl-2-isocyanate instead of the 2-methylphenylisocyanate the 1-(2-diphenylmethyl-ethyl)-4-[2-[N-naphthyl-(1)-carbamyloxy]-ethyl]-piperazine, is produced, which may be identified as the dihydrochloride or the dioxalate.

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Example 3

The 1-(2-diphenylmethoxy-ethyl)-4-[2-[N-(2-methoxyphenyl)-carbamyloxy]-ethyl]-piperazine dihydrochloride, M.P. 231-233°, is prepared by reacting 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine with 0.89 g. of 2-methoxyphenylisocyanate; yield: 2.3 g.

Example 4

A mixture of 3.4 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 1.83 g. of 2-chlorophenylisocyanate in 8 ml. of benzene is treated according to the procedure given in Example 2 to yield 5.0 g. of the 1-(2-diphenylmethoxy-ethyl)-4-[2-[N-(2-chlorophenyl)-carbamyloxy]-ethyl]-piperazine dihydrochloride, melting at 220-223° after recrystallization from methanol.

Example 5

A mixture of 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 0.81 g. of phenylisothiocyanate in 4 ml. of benzene is heated to 80-85° for two hours. The solvent is removed under reduced pressure, the residue dissolved in ether and then worked up as described in Example 1 to yield the 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-phenyl-thiocarbamyloxy)-ethyl]-piperazine dihydrochloride, which melts at 214-215° after recrystallization from isopropanol; yield: 2.7 g.

The dihydrochloride may be converted into the free base by treatment with aqueous ammonia and extract with ether. On addition of methyl iodide to the ether solution the mono- or dimethiodide of 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-phenyl-thiocarbamyloxy)-ethyl]-piperazine may precipitate.

Example 6

The 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-n-butylcarbamyloxy)-ethyl]-piperazine dihydrochloride, M.P. 207-209° after recrystallization from isopropanol, is prepared by reacting 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine with 0.6 g. of n-butylisocyanate according to the procedure given in Example 2; yield: 2.0 g.

Example 7

A mixture of 3.4 g. of 1-(diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 0.71 g. of a 55 percent toluene suspension of sodium amide in 20 ml. of toluene is refluxed for three hours. 1.11 g. of N,N-dimethylcarbonyl chloride is added, and the reaction mixture is refluxed for an additional four hours. After cooling, filtration and removal of the solvent, the residue is dissolved in 50 ml. of ether and on addition of a solution of hydrogen chloride in ethyl acetate the 1-(2-diphenylmethoxy-ethyl)-4-[2-(N,N-dimethylcarbamyloxy)-ethyl]-piperazine dihydrochloride precipitates and melts at 202-204° after recrystallization from isopropanol; yield: 3.8 g.

Example 8

A mixture of 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxyethyl)-piperazine and 0.81 g. of n-butylisothiocyanate in 4 ml. of benzene is reacted according to the procedure described in Example 5 to yield 2.0 g. of the 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-n-butyl-thiocarbamyloxy)-ethyl]-piperazine dihydrochloride, which melts at 177-179° after recrystallization from isopropanol.

Example 9

The 1-(2-[4-chlorophenyl]-phenyl-methoxy)-ethyl]-piperazine dihydrochloride may be obtained by reacting 1-(2-[4-chlorophenyl]-phenyl-methoxy)-ethyl)-4-(2-hydroxy-ethyl)-piperazine with phenylthioisocyanate according to the procedure described in Example 5.

The starting material may be prepared by treating the sodium salt of bis-1,4-(2-hydroxyethyl)-piperazine with (4-chlorophenyl)-phenyl-methylbromide according to the procedure given in Example 1.

Example 10

A mixture of 1.7 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxy-ethyl) piperazine, 4 ml. of pyridine and 1 ml. acetic anhydride is allowed to stand at room temperature for 16 hours. After concentrating under reduced pressure, 20 ml. of water are added, and the reaction product is extracted into ether. The ether solution is dried and the ether removed. The base is taken up in 100 ml. of ether and the 1-(2-diphenylmethoxy-ethyl)-4-(2-acetoxy-ethyl)-piperazine dihydrochloride precipitates on addition of a solution of hydrogen chloride in ethyl acetate and melts at 211-213° after recrystallization from isopropanol; yield: 1.8 g.

By treating an ethanolic solution of the above described free base with an excess of methyl iodide and removing the solvent the 1-(2-diphenylmethoxy-ethyl)-4-acetoxy-ethyl-piperazine dimethiodide may be obtained.

Example 11

A mixture of 3.4 g. of 1-(2-diphenylmethoxy-ethyl)-4-(2-hydroxy-ethyl)-piperazine, 40 ml. of toluene and 0.4 g. of sodium amide is refluxed with stirring for 3 hours. A solution of 2.53 g. of 3,4,5-trimethoxybenzoyl chloride in toluene is added and refluxing is continued for four hours. The reaction mixture is then cooled, filtered and concentrated. The residue is dissolved in 150 ml. of ether. On addition of a solution of hydrogen chloride in ethyl acetate the 1-(2-diphenylmethoxy-ethyl)-4-[2-(3,4,5-trimethoxybenzoyloxy)-ethyl]-piperazine dihydrochloride precipitates. After recrystallization from a mixture of methyl ethyl ketone and ether it melts at 177-179° C.; yield: 3.4 g.

A modification of the above process for the preparation of piperazine derivatives of this invention comprises treating a metal salt, such as an alkali metal, e.g. lithium, sodium or potassium, salt of a 1-hydroxy-lower alkyl-4-acyloxy-lower alkyl-piperazine with a reactive ester of a di-monocyclic aryl-methanol and, if desired, carrying out the optional steps. A metal salt of a hydroxy-lower alkyl-piperazine derivative may be prepared according to the procedure outlined hereinbefore, for example, by reaction with an alkali metal hydride, e.g. sodium hydride. A reactive ester of a di-monocyclic aryl-methanol is particularly one with a strong inorganic or organic acid, for example, with a mineral acid, e.g. hydrochloric, hydrobromic, or hydriodic acid. The reaction may be carried out in solution, for example, in an ether, e.g. 1,4-dioxane or diethyleneglycol dimethylether, or in a hydrocarbon, e.g. hexane, benzene, toluene or xylene; and at room temperature or preferably at an elevated temperature, for example, at the boiling temperature of the solvent.

Furthermore, the compounds of the present invention may also be obtained by using any of the methods known for the preparation of piperazine derivatives, for example by reacting an appropriately substituted primary amine with a reactive diester, formed by an N,N-bis-(2-hydroxyethyl)-N-substituted amine and a strong acid, such as a mineral acid, e.g. hydrochloric, hydrobromic, hydriodic or sulfuric acid. Or, piperazine derivatives may be prepared by reducing in a piperazine-one derivative the carbonyl group, for example, by treatment with a di-lignt metal hydride capable of converting the carbonyl of an amide grouping in a methylene radical, such as an alkaline metal aluminum hydride e.g. lithium aluminium hydride, preferably used in an ether solution, e.g. diethylether, tetrahydrofuran or 1,4-dioxane.

In addition any alterable functional group attached to

the piperazine derivative, may be converted into another group according to standard procedures, for example, a hydroxyl group may be converted into a lower alkoxy group, e.g. methoxy or ethoxy, or into a acyloxy group, e.g. acetoxy; a nitro group may be reduced to an amino group, if desired, by reductive alkylation, etc.

The invention also comprises any modification of the general process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is (are) carried out, as well as any new intermediates.

In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

What is claimed is:

1. A member of the group consisting of 1-(di-monocyclic carbocyclic aryl-methoxy-lower alkyl)-4-(acyloxy-lower alkyl)-piperazine, in which monocyclic carbocyclic aryl represents a member of the group consisting of phenyl and phenyl substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, nitro, di-lower alkyl-amino and halogen, the lower alkyl radicals contain from 2 to 3 carbon atoms and acyl stands for the acyl radical of an acid selected from the group consisting of benzoic acid, naphthalene carboxylic acid, phenylacetic acid, cinnamic acid, phenoxyacetic acid, N-phenyl-carbamic acid, N-naphthyl-carbamic acid, N-phenylthiocarbamic acid, N-naphthyl-thiocarbamic acid and these acids substituted in the aromatic portion by lower alkyl, hydroxyl, lower alkoxy, lower alkanoyloxy, nitro, amino, lower alkyl-amino, di-lower alkylamino and halogen, and lower aliphatic carboxylic acid, carbamic acid, N-lower alkyl-carbamic acid, N,N-di-lower alkyl-carbamic acid, thio-carbamic acid, N-lower alkyl-thiocarbamic acid and N,N-di-lower alkyl-thiocarbamic acid, therapeutically acceptable acid addition salts and lower alkyl quaternary ammonium halides, sulfates and sulfonates thereof.

2. 1-(2-diphenylmethoxy-ethyl) - 4 - (2-acyloxyethyl)-piperazine, in which acyl stands for the acyl radical of carbamic acid.

3. 1-(2-diphenylmethoxy-ethyl) - 4 - (2-acyloxyethyl)-piperazine, in which acyl stands for the acyl radical of N-lower alkyl-carbamic acid.

4. 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-n-butylcarbamyloxy)-ethyl]-piperazine.

5. 1-(2-diphenylmethoxy-ethyl) - 4 - [2-(N-phenyl-carbamyloxy)-ethyl]-piperazine.

6. 1-(2-diphenylmethoxy-ethyl) - 4 - {2-[N-(2-methylphenyl)-carbamyloxy]-ethyl}-piperazine.

7. 1-(2-diphenylmethoxy - ethyl)-4-{2-[N-(2-methoxyphenyl)-carbamyloxy]-ethyl}-piperazine.

8. 1-(2-diphenylmethoxy-ethyl) - 4 - {2-[N-(2-chlorophenyl)-carbamyloxy]-ethyl}-piperazine.

9. 1-(2-diphenylmethoxy-ethyl) - 4 - (2-acyloxyethyl)-piperazine in which acyl stands for the acyl radical of N-lower alkyl-thiocarbamic acid.

10. 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-n-butyl-thiocarbamyloxy)-ethyl]-piperazine.

11. 1-(2-diphenylmethoxy-ethyl)-4-[2-(N-phenyl-thiocarbamyloxy)-ethyl]-piperazine.

12. 1-(2-diphenylmethoxy - ethyl)-4-(2-acyloxyethyl)-piperazine in which acyl stands for the acyl radical of lower aliphatic carboxylic acid.

13. 1-(2-diphenylmethoxy - ethyl) - 4 - (2 - acetyloxy-ethyl)-piperazine.

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