The present invention relates to basic ethers, especially to N-(x-lower alkoxy-3-monoacylic carbocyclic aryl-propyl)-N'-monoacylic aryl-dicycloalkanes, in which lower alkyloxy and monocyclic arylcarboxylic aryl substitute the same carbon atom and are separated by two to four carbon atoms from the nitrogen atom of the dicycloalkane portion which has from four to six ring carbon atoms separating the two nitrogen atoms by two to three carbon atoms, and in which monocyclic arylcarboxylic aryl is phenyl, (lower alkoxy)-phenyl, (lower alkoxy)-phenyl or (trifluoromethyl)-phenyl, and monocyclic ary is phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or pyridyl. More particularly, it relates to compounds having the formula

\[ O-R \quad Z' \]

\[ \quad PH-DH-(C_2H_5)-N \quad Na \]

in which the group Ph represents phenyl, (lower alkoxy)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or (trifluoromethyl)-phenyl, R stands for lower alkyloxy, the group of the formula \(-\langle C_2H_5 \rangle -\) is lower alkoxy having from one to six carbon atoms (i.e. the letter \( n \) stands for an integer from 1 to 6), and separating the carbon atom carrying the groups \(-O-R \) and \( Ph \) from the nitrogen atom by one to three carbon atoms, each of the groups \( Z_1 \) and \( Z_2 \) stands for alkyloxy having from two to seven carbon atoms and separating the two nitrogen atoms by two to three carbon atoms, and \( Ar \) stands for phenyl, (lower alkoxy)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or pyridyl, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, as well as process for the preparation of these compounds.

The monocyclic arylcarboxylic aryl radical (i.e. the group Ph in the above formula), represents phenyl or phenol substituted by one or more of the same or different substituents attached to any of the positions available for substitution in the phenyl nucleus. Substituents are lower alkoxy, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like, halogeno, e.g. fluoro, chloro, bromo and the like, or trifluoromethyl. The monocyclic arylcarboxylic aryl group Ph represents primarily phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl, or (trifluoromethyl)-phenyl.

The lower alkoxy group represented by \(-O-R \) in the above formula, has from one to seven, preferably from one to four, carbon atoms, and stands above all for methoxy or ethoxy, as well as for n-propoxy, isopropoxy, n-butoxy, isobutoxy, secondary butoxy, tertiary butoxy, n-pent oxy, isopentoxy, n-hexyloxy and the like.

The lower alkoxy radical separating lower alkoxy and the monocyclic arylcarboxylic aryl group Ph from the nitrogen atom of the dicycloalkane portion by two to four carbon atoms, has from two to seven carbon atoms. Preferably, such radical has from two to four carbon atoms, arranged in an unbranched carbon chain; above all, it is a 1,2-ethylen or a 1,3-propylen radical, and the compounds of this invention not primarily N-(2-lower alkoxy-3-monoacylic carbocyclic aryl-ethyl)-N'-monoacylic aryl-dicycloalkane compounds or N-(3-lower alkoxy-3-monoacylic carbocyclic aryl-propyl)-N'-monoacylic aryl-dicycloalkane compounds. In the above formula, the group of the formula \(-\langle C_2H_5 \rangle -\) stands, therefore, for lower alkyloxy having from one to six carbon atoms (i.e. the letter \( n \) stands for an integer from 1 to 6), particularly for methylene (the letter \( n \) is 1) or 1,2-ethylen (the letter \( n \) is 2).

Each of the groups \( Z_1 \) and \( Z_2 \) in the above formula represents alkyloxy having from two to eleven carbon atoms, and separating the two nitrogen atoms by from two to three carbon atoms. These alkyloxy radicals are above all 1,2-ethylen or 1,2-propylen, as well as 1,3-propylen, but may also stand for 1,2-butylen, 2,3-butylen, 1,2-isobutylen, 1,2-pentyl ene, 2,3-pentyl ene, 1,2-isopentyl ene, 1,2-hexylene, 3,4-hexylene, 3-methyl-1,2-isopentyl ene, 1,2-heptylene and the like.

The monocyclic aryl group represented by Ar in the above formula, stands primarily for phenyl or phenyl substituted by one or more than one of the same or different substituents attached to any of the positions available for substitution. Substituents are lower alkyloxy, e.g. methyl, ethyl, n-propyl, isopropyl, tertiary butyl and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like, halogeno, e.g. fluoro, chloro, bromo and the like. The monocyclic aryl group, such as Ar in the above formula, stands particularly for phenyl, (lower alkoxy)-phenyl, (lower alkoxy)-phenyl, or (halogeno)-phenyl. A monocyclic aryl group, such as Ar in the above formula, stands for pyridyl, e.g. 2-pyridyl, 3-pyridyl or 4-pyridyl.

Salts of the compounds of this invention are acid addition salts, such as pharmaceutically acceptable salts, or pharmaceutically acceptable addition salts with acids, such as inorganic acids, e.g. hydrochloric, hydrobromic, nitric, sulfuric, phosphoric acids and the like, or organic acids, such as organic carboxylic acids, e.g. acetic, propionic, glycolic, malonic, succinic, maleic, hydroxymaleic, fumaric, maleic, tartaric, citric, benzoic, salicylic, 4-amino salicylic, 2-fluorobenzoic, nicotinic, isonicotinic acid and the like, or organic sulfuric acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxy-ethane sulfonic, ethane 1,2-disulfonic, benzene sulfonic, toluene sulfonic, naphthalene 2-sulfonic acid and the like. Other acid addition salts serve as intermediates for the preparation of other acid addition salts, such as pharmaceutically acceptable, non-toxic acid addition salts, or in the purification of the free compounds, as well as for identification and characterization purposes. Acid addition salts primarily used for identification purposes are, for example, those with acidic organic nitro compounds, e.g. picro, picrolonic, flavianic acid and the like, or with metal complex acids, e.g. phosphotungstic, phosphomolybdic, chloroplatinate, Reineck acid and the like. Mono- or poly-salts may be formed depending on the conditions used for the preparation of the salts.

The compounds of this invention may also be in the form of N-oxides thereof, or the acid addition salts, such as the pharmaceutically acceptable, non-toxic acid addition salts, of such N-oxides, particularly the salts thereof with the above mentioned inorganic or organic acids.

Quaternary ammonium derivatives of the compounds of this invention are those with the general formula of quaternary ammonium salts with alcohols and strong acids, particularly those with lower alkyl halides, e.g. methyl, ethyl, n-propyl or isopropyl chloride, bromide or iodide and the like, phenyl-lower alkyl halides, e.g. benzyl chloride, benzyl bromide, 2-phenethyl bromide and the like, di-lower alkyl sulfates, e.g. dimethy sulfate, diethyl sulfate and the like, lower alkyl lower alkane sulfonates, e.g. methyl methanesulfonate or ethanesulfonate and the like, or lower alkyl monocyclic carboxylic aryl sulfonylates, e.g. methyl p-toluene sulfonate and the like.
the like. Also included as quaternary ammonium compounds are the quaternary ammonium hydroxides, and other quaternary ammonium salts having an anion other than a halogeno, sulfate or sulfonate ion. Mono- or poly-quaternary ammonium compounds may be formed, depending on the conditions of the quaternization reaction.

The compounds of this invention have adrenolytic, anti-hypertensive, anti-inflammatory, diuretic, saluretic, analgesic, and antifibrillatory properties and can be used accordingly.

Compounds of the present invention having adrenolytic effects are useful as vasodilators in peripheral vascular diseases, e.g. Reymann's disease, causalgia and the like, or to counteract the pronounced effects on the tissue of pressor substances, such as norepinephrine and the like; they are also useful as diagnostic tools to determine the proper functioning of the adrenal glands, due to their capability of suppressing the release of pressure substances, e.g. epinephrine, norepinephrine and the like, from normal functioning glands.

Compounds of this invention having antihypertensive properties are useful as hypotensive agents to lower the blood pressure in hypertensive conditions; they exert their hypotensive effects without causing tachycardia.

Compounds of this invention having anti-inflammatory properties, as demonstrated in the granuloma pouch test (Selye, Proc. Soc. Exp. Biol. & Med., vol. 82, p. 328 (1955), as modified by Robert et al., Acta Endocrinologica, vol. 25, p. 105 (1957)), the cotton pellet implant test (Meier et al., Exp, Mediterrium, vol. 6, p. 469 (1950)) or the pleural cavity inflammation test (Holtcamp, Fed. Proc., vol. 17, p. 379 (1958)), are useful as anti-inflammatory agents in place of corticoid steroids, e.g. cortisone, hydrocortisone and the like, for example, in the treatment of tissue inflammations, such as arthritic inflammations and the like.

Compounds having diuretic and saluretic properties are useful as diuretic and saluretic agents to relieve conditions of excessive water and salt retention caused, for example, by kidney or heart ailments.

Compounds of this invention having analgesic effects are useful as analgesic agents in raising the threshold of pain, as associated, for example, with arthritic conditions and the like.

Compounds of this invention having antifibrillatory effects are useful as antifibrillatory agents in the treatment of heart fibrillations, such as neurogenic or cardiogenic, auricular or ventricular fibrillation.

Especially useful are the compounds of the formula

```
R₂⁺  CH(CH₃₃–₅)₅ N⁺
R₁⁻  CH₂–CH₂–CH₂–O–R
```

in which R has the previously-given meaning, i.e. stands for lower alkyl having preferably from one to four carbon atoms, the radical R₁ represents hydrogen or methyl, and each of the groups R₂ and R₃ stands for hydrogen, lower alkyl having preferably from one to four carbon atoms, lower alkoxy having preferably from one to four carbon atoms, or halogeno having preferably an atomic weight between 19 and 80, both inclusive, and the acid addition salts, particularly the pharmaceutically acceptable, non-toxic acid addition salts, thereof.

Compounds with outstanding antihypertensive, as well as diuretic and saluretic properties are those of the formula

```
R₂⁺  CH(CH₃₃–₅)₅ N⁺
R₁⁻  CH₂–CH₂–CH₂–O–R
```

in which R has the previously given meaning, and the acid addition salts, particularly the pharmaceutically acceptable, non-toxic acid addition salts, thereof.

Compounds with pronounced adrenolytic effects are those of the formula

```
H₂C–O–R
```

in which R has the previously-given meaning, and R₄ is methyl, methoxy or chloro, or the acid addition salts, particularly the pharmaceutically acceptable, non-toxic acid addition salts thereof.

Strong anti-inflammatory effects are exhibited by the compounds of the formula

```
R₂⁺  CH(CH₃₃–₅)₅ N⁺
R₁⁻  CH₂–CH₂–CH₂–O–R
```

in which R has the previously-given meaning. R₅ is hydrogen, methyl, methoxy or chloro, R₆ is hydrogen or halogeno, especially fluoro or chloro, R₇ is hydrogen or methyl, and the letter m stands for one of the integers 1 and 2, or acid addition salts, such as pharmaceutically acceptable, non-toxic acid addition salts, thereof; compounds of this type show anti-inflammatory effects, when given orally.

The new compounds of this invention are used in the form of compositions for enteral, e.g. oral, or parenteral administration, which contain the new compounds in admixture with a pharmaceutically acceptable, organic or inorganic, solid or liquid carrier. For making up the preparations, there are employed known carrier substances, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, tragacanth, vegetable oils, benzyl alcohols, gums accacia, propylene glycol, polyalkylene glycols or any other carrier material suitable for such preparations. The latter are in solid form, e.g. capsules, tablets, dragees, suppositories and the like, or in liquid form, e.g. solutions, suspensions, emulsions and the like. If necessary, they contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying, coloring, flavoring agents and the like, salts for varying the osmotic pressure, buffers, etc. They may also contain, in combination, other useful substances.

The compounds of this invention are prepared according to known methods, for example, by reacting an N-monocyclic aryl-diazacycloalkane, in which the diazacycloalkane group has from six to eight ring members and its two nitrogen atoms are separated from one another by two to three carbon atoms, and monocyclic aryl has the above-given meaning, especially a compound of the formula

```
Z₁⁻  N⁺  Z₂⁻
```

in which Ar, Z₁ and Z₂ have the previously-given meaning, or a salt thereof, with a reactive ester of an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkanoic acid, in which lower alkoxy and monocyclic carbocyclic aryl substitute the same carbon atom and are separated from the esterified hydroxyl group by two to four carbon atoms, and monocyclic carbocyclic aryl has the previously-given meaning, particularly with a compound of the formula

```
O–R
```

in which R, Ph and the group of the formula —(CH₂)₇— have the previously-given meaning, and R₈ is a reactive esterified hydroxyl group, and, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting compound into an N-oxide or a quaternary ammonium compound, and/or, if desired, converting a resulting compound or an N-oxide into a salt thereof, and/or, if desired, con-
verifying a quaternary ammonium compound into another quaternary ammonium compound, and/or, if desired, separating a resulting mixture of isomers into the single isomers.

A salt of an N-monocyclic aryl-diazacycloalkane starting material is primarily a metal compound, such as an alkali metal, e.g. lithium, sodium, potassium and the like, compound thereof. Such compound is prepared according to known methods; for example, a solution of the N-monocyclic aryl-diazacycloalkane compound in a suitable solvent (the selection of which depends on the solubility of the starting material and/or the reactivity of the salt-forming reagent) or solvent mixture, is treated with an alkali metal, e.g. sodium and the like, with an alkali metal hydride or amide, e.g. lithium, sodium or potassium hydride or amide and the like, with an alkali metal carbonate, e.g. sodium carbonate, potassium carbonate and the like, or any other suitable salt-forming reagent, such as, for example, an alkali metal lower alkanolate and the like, if necessary, while cooling or heating, and/or in the atmosphere of an inert gas, e.g. nitrogen.

A reactive ester of an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl is primarily an ester thereof with a strong inorganic acid, particularly a hydrochloric acid, e.g. hydrochloric, hydrobromic and the like, as well as sulfuric acid, or any other equivalent acid, or a strong organic sulfonic acid, e.g. methanesulfonic, p-toluene sulfonic acid and the like. R₇ in the above formula is primarily halogeno, particularly chloro, or bromo, as well as a sulfonilxoy group, e.g. methyl-sulfonilxoy, 4-methyl-phenyl-sulfonilxoy and the like. The preferred starting materials are represented by the x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl halides, in which lower alkyl separates lower alkoxy from the monocyclic carbocyclic aryl group from halogeno by two to four carbon atoms, such as the compounds of the formula

\[ \text{O} - \text{R} \]

in which Ph, R and the group of the formula \(-\text{(C₆H₅O)}\) have the previously-given meaning, and Hal stands for halogeno, particularly halogeno having an atomic weight between 35 and 80, both inclusive, especially chloro, or bromo, as well as bromo.

The reaction is carried out according to known methods. Thus, whenever the free N-monocyclic aryl-diazacycloalkane is used, the acid generated thereby with the reactive ester of an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl is neutralized by adding an excess of the N-monocyclic aryl-diazacycloalkane, or another base, e.g. sodium acetate, sodium carbonate, potassium carbonate and the like. The two starting materials may also be mixed together and the basic condensing reagent may then be added to bring about the reaction. The latter is preferably performed in the presence of a diluent (such as, for example, one of those used for the preparation of the metal compound), if necessary, while cooling or heating, in the atmosphere of an inert gas, e.g. nitrogen, and/or in a closed vessel.

The starting materials used in the above reaction are known or may be prepared according to known methods. The compounds of this invention may also be prepared by reacting an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl-amine, in which lower alkoxy and monocyclic carbocyclic aryl substitute the same carbon atom and are separated from the amino group by two to four carbon atoms, and monocyclic carbocyclic aryl has the above given meaning, particularly a compound of the formula

\[ \text{O} - \text{R} \]

in which Ph, R and the group of the formula \(-\text{(C₆H₅O)}\) have the previously-given meaning, with an N,N-bis-(reactive esterified hydroxy-alkyl)-N-monocyclic aryl-amine, in which the nitrogen is separated from the reactive esterified hydroxy groups by two to three carbon atoms, and monocyclic aryl has the above given meaning, particularly a compound of the formula

\[ \text{R}_1 \text{Z}_1 - \text{R}_2 \text{N} - \text{Ar} \]

in which Ar, Z₁ and Z₂ have the previously-given meaning, and each of the groups R₁ R₂ and R₂' stand for an esterified hydroxyl group, or a salt thereof, and, if desired, carrying out the optional steps.

In the above starting material, the reactive esterified hydroxyl groups R₂' and R₂" have the same meaning as R₁ and represent primarily halogeno, having preferably an atomic weight between 35 and 80, both inclusive, i.e. chloro or bromo, as well as reactive organic sulfonilxoy groups. The reaction is carried out according to known methods, if necessary, at an increased temperature, in a closed vessel, in the atmosphere of an inert gas, e.g. nitrogen, and/or in the presence of an acid neutralizing base.

The starting materials are known or may be prepared according to the known methods. For example, a reactive ester of an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl, when reacted with ammonia or an equivalent reagent, such as an N-alkali metal-thalliumamide and then hydrazine, may be converted into the desired x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkylamidine.

A further process for the preparation of the compounds of this invention comprises reacting an N,N-di-(reactive esterified hydroxy-alkyl)-N-(x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl)-amine, in which alkyl separates the nitrogen atom from the reactive esterified hydroxyl groups by two to three carbon atoms, and lower alkoxy and monocyclic carbocyclic aryl substitute the same carbon atom and are separated from the nitrogen atom by two to four carbon atoms, and in which monocyclic carbocyclic aryl has the above given meaning, particularly a compound of the formula

\[ \text{O} - \text{R} \]

in which Ph, R, Z₁, Z₂, R₁, R₂, R₂' and the group of the formula \(-\text{(C₆H₅O)}\) have the previously-given meaning, or a salt thereof, with an N-monocyclic aryl-amine, in which monocyclic aryl has the previously-given meaning, particularly a compound of the formula Ar-NH₂, in which Ar has the previously-given meaning, and, if desired, carrying out the optional steps.

The above reaction is carried out according to known methods, such as those mentioned hereinbefore. The starting material, i.e. an N,N-bis-(reactive esterified hydroxy-alkyl)-N-(x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl)-amine, may be obtained, for example, by treating a reactive ester of an x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl-amine, in which lower alkoxy and monocyclic carbocyclic aryl radical substitute the same carbon atom and are separated from the esterified hydroxyl group by two to four carbon atoms, and monocyclic carbocyclic aryl has the previously-given meaning, with an N,N-bis-(hydroxy-alkyl)-amine, in which alkyl has two to seven carbon atoms separating nitrogen from the hydroxyl groups by two to three carbon atoms, and converting in a resulting N,N-bis-(hydroxy-alkyl)-N-(x-lower alkoxy-x-monocyclic carbocyclic aryl-lower alkyl)-amine, in which alkyl has two to seven carbon atoms separating the nitrogen atom from the hydroxyl group by two to three carbon atoms, and lower alkyl and monocyclic carbocyclic aryl substitute the same carbon atom and are separated from the nitro-
The starting materials used in the above procedure are prepared according to known methods, for example, by reducing in an N-(x-monocyclic carboxylic aroyl-x-oxylower alkyl)-N'-mono-cyclic aroyl-diazo-cycloalkane the exo into a hydroxyl group by reduction, for example, by treatment with sodium borohydride and the like.

The compounds of this invention, in which the α-group of the lower alkyl portion is a methylene group of the formula \(-\text{CH}_2-\), may also be prepared by converting in an N-(x-lower alkoxy-x-monocyclic carboxylic aroyl-lower alkoxyalkyl)-N'-monocyclic aroyl-diazo-cycloalkane or in an N-(x-lower alkoxy-x-monocyclic carboxylic aroyl-lower thioalkanoyl)-N'-monocyclic carboxylic aroyl-diazo-cycloalkane, in which lower alkoy and monocyclic carboxylic aroyl group substitute the same carbon atoms and are separated from the carbonyl or thio carbonyl group by one to three carbon atoms, and in which the diazo-cycloalkane portion has from six to eight ring members, and its two nitrogen atoms are separated from one another by two to three carbon atoms, and monocyclic carboxylic aroyl and monocyclic aroyl have the previously given meaning, particularly in a compound of the formula

\[
\text{O} - \text{R} \quad \text{X} \quad \text{N} - \text{Ar}
\]

in which Ph, R, Z₁, Z₂ and Ar and the group of the formula \(-(\text{C}_4\text{H}_6)_{n}\)- have the previously given meaning, or a salt thereof, the hydroxyl group into lower alkoxy, and, if desired, carrying out the optional steps.

The conversion of hydroxyl into lower alkoxy is carried out, for example, by treatment with a lower diaza-alkane, preferably in the presence of a suitable Lewis acid, such as fluoboric acid, aluminum chloride, boron trifluoride etherate, an aluminum lower alkylolate, e.g. aluminum isopropionate and the like, or any other suitable reagent. The conversion of hydroxyl into the desired lower alkoxy group is also carried out indirectly, for example, by converting the starting material into a metal compound, particularly into an alkali metal, e.g. sodium, potassium and the like, compound (for example, according to the previously described process) and reacting the latter with a reactive ester of a lower alkanol, for example, a lower alkyl halide, e.g. chloride, bromide, iodide and the like. Furthermore, the free hydroxyl group of the starting material may be converted into a reactive esterified hydroxyl group, such as halogeno, e.g. chloro, bromo and the like, or an organic sulfonofxyl group, e.g. methanesulfonofxy, p-toluenesulfonyl, p-bromo-phenylbenzenesulfonyl, p-nitro-phenylbenzenesulfonyl, m-nitro-phenylsulfonyl and the like, according to the previously described method. A resulting N-(x-reactive esterified hydroxy-x-monocyclic carboxylic aroyl-lower alkyl)-N'-monocyclic aroyl-diazo-cycloalkane is then reacted with a suitable reagent capable of replacing the reactive esterified hydroxyl group by the desired lower alkoxy group; halogeno in an N-(x-halogeno-x-monocyclic carboxylic aroyl-lower alkyl)-N'-mono-cyclic aroyl-diazo-cycloalkane may be replaced by lower alkoxy by treating the intermediate with an alkali metal lower alkoxy, e.g. sodium or potassium methoxide, ethoxide, n-propoxide, isopropoxide, n-butoxide and the like, whereas the organic sulfonofxy group in an N-(x-monocyclic carboxylic aroyl-x-organic sulfonofxy-lower alkyl)-N'-monocyclic aroyl-diazo-cycloalkane may be exchanged for lower alkoxy by treatment of the intermediate compound with a lower alkanol, e.g. methanol, ethanol, n-propanol, isopropanol, n-butanol and the like, preferably in the presence of a suitable base, e.g. N,N-diethylamine, N,N,N-triethylamine, pyridine and the like, and, if necessary, at an elevated temperature, in a closed vessel and/or in the atmosphere of an inert gas.
by reacting it with an acid, such as one of the inorganic or organic acids mentioned before, for example, by treating a solution of the base in a suitable solvent or solvent mixture with the acid or a solution thereof, or with a suitable anion exchange preparation, and isolating the desired salt. The mono- or poly-salts may also be obtained in the form of hydrates thereof or may contain solvent of crystallization.

The compounds of the present invention form N-oxides, which are prepared according to known methods, for example, by reacting a resulting compound, preferably a solution thereof in an inert solvent, with an N-oxiding reagent, such as, for example, hydrogen peroxide, ozone, persulfuric acid, or an organic peracid, such as an organic percarboxylic acid, e.g. peracetic, perbenzoic, monoperphthalic acid and the like, or an organic persulfonic acid, e.g. p-toluene persulfonic acid and the like. A resulting N-oxide may be converted into its acid addition salts according to the above methods.

Quaternary ammonium derivatives of the compounds of this invention are obtained, for example, by reacting the free compound with an ester formed by an alcohol and a strong inorganic or organic acid, such as one of those previously mentioned. The quaternizing reaction may be performed in the presence or absence of a suitable solvent, if necessary, while cooling or at an elevated temperature, at atmospheric pressure or in a closed vessel under increased pressure, and/or in the atmosphere of an inert gas, e.g. nitrogen.

Resulting quaternary ammonium compounds may be converted into other quaternary ammonium compounds, such as the corresponding quaternary ammonium hydroxides, for example, by reacting a quaternary ammonium halide with silver oxide, or a quaternary ammonium sulfate with barium hydroxide, by treating a quaternary ammonium salt with an anion exchange preparation, by electrodialysis and the like. From a resulting quaternary ammonium hydroxide, there may be prepared a quaternary ammonium salt by reaction with an acid or with a lower alkyl sulfate, e.g. methyl sulfate, ethyl sulfate and the like. A quaternary ammonium salt may also be converted directly into another quaternary ammonium salt without the formation of an intermediary quaternary ammonium hydroxide; for example, a quaternary ammonium iodide may be reacted with freshly prepared silver chloride or with hydrogen chloride in anhydrous methanol to yield the quaternary ammonium chloride, or a quaternary ammonium salt may be treated with a suitable anion exchange preparation and converted into another quaternary ammonium salt. Quaternary ammonium compounds may be isolated in the form of hydrates or may contain solvent of crystallization.

A resulting mixture of isomers may be separated into single isomers. For example, a mixture of diastereoisomeric compounds may be separated into the individual racemic compounds on the basis of physico-chemical differences, such as solubility, for example, by fractional crystallization and the like. Racemates may be resolved into the optically active d- and l-forms according to known resolution procedures, for example, reacting the free racemic compound, preferably in the presence of a suitable solvent, with one of the optically active forms of an acid having an asymmetric carbon atom or a solution thereof. Especially useful as optically active forms of the above isomers having an asymmetric carbon atom are D-tartaric and L-tartaric, and d- and l-tartaric acid, as well as the optically active forms of malic, mandelic, camphor 10-sulfonic, quinic acid and the like. The resulting salts of the antipodes with the optically active acid are separated on the basis of physico-chemical differences, particularly different solubilities, and, if desired, converted into the free acid accordingly to the above procedure. An optically active base may be converted into another acid addition salt, an N-oxide, an acid addition salt of an N-oxide or a quaternary ammonium compound according to the above-described methods.

The invention also comprises any modification of the 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.

This is a continuation-in-part application of our application Serial No. 253,247, filed January 23, 1963 (now abandoned), which in turn is a continuation-in-part application of our application Serial No. 238,027, filed November 15, 1962 (now abandoned), which in turn is a continuation-in-part application of our application Serial No. 168,544, filed January 24, 1962 (now abandoned), which in turn is a continuation-in-part application of our application Serial No. 96,691, filed March 20, 1961 (now abandoned).

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

Example 1

To a solution of 8.8 g. of 2-methyl-1-phenyl-piperazine in 50 ml. of toluene is added 2.4 g. of a mineral oil suspension of sodium hydride (of 53 percent strength); the mixture is refluxed for two hours, and is then treated with 11.6 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride. Refluxing is continued overnight; the inorganic material is filtered off, the filtrate is evaporated under reduced pressure, and the residue is distilled to yield 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]1-3-methyl-4-phenyl-piperazine of the formula

\[
\text{H}_3\text{C} \quad \begin{array}{c}
\text{O} \quad \text{NH} \\
\text{CH}_2-\text{CH} = \text{CH}-
\end{array}
\]

which boils at 182–184°C/0.2 mm.

The dihydrochloride of 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]1-3-methyl-4-phenyl-piperazine, M.P. 190–192°C, is prepared by treating a solution of the free base in ethanol with a saturated solution of hydrogen chloride in ethanol and recrystallizing the resulting salt from ethanol. Other compounds prepared according to the above procedure are, for example:

1. [3-ethoxy-3-(phenyl-propyl)]1-3-methyl-4-phenyl-piperazine, B.P. 168–170°C/0.075 mm., the dihydrochloride of which melts at 194°C;
2. [3-isopropoxy-3-(4-methyl-phenyl)-propyl]1-3-methyl-4-phenyl-piperazine, B.P. 146–154°C/0.04 mm., the dihydrochloride of which melts at 169°C;
3. [3-methoxy-3-(4-methyl-phenyl)-propyl]1-4-phenyl-piperazine, B.P. 170–172°C/0.05 mm., the dihydrochloride of which melts at 200°C;
4. [3-ethoxy-3-(4-methyl-phenyl)-propyl]1-4-phenyl-piperazine, B.P. 196–198°C/0.04 mm., the dihydrochloride of which melts at 194°C (after recrystallization from ethanol);
5. [3-ethoxy-3-(4-methyl-phenyl)-propyl]1-4-(3-methylphenyl)-piperazine, B.P. 172–174°C/0.04 mm., the dihydrochloride of which melts at 165°C (after recrystallization from acetone);
6. [3-methoxy-3-(4-methyl-phenyl)-propyl]1-3-methyl-4-phenyl-piperazine, B.P. 176–178°C/0.1 mm., the dihydrochloride of which melts at 197–198°C (after recrystallization from acetone);
7. [3-methoxy-3-(4-methyl-phenyl)-propyl]1-4-(2-methylphenyl)-piperazine, B.P. 180–182°C/0.12 mm., the dihydrochloride of which melts at 162°C (after recrystallization from acetone);
- (2-chloro-phenyl)-1-(3-methoxy-3-(4-methyl-phenyl)-propyl)piperazine, B.P. 152–184°/0.05 mm, the hydrochloride of which melts at 153–155° (after recrystallization from acetone);

1 - [3-methoxy-3-(4-methyl-phenyl)-propyl]-4-(3-methyl-phenyl)-piperazine, B.P. 174–178°/0.07 mm, the dihydrochloride of which melts at 153° (after recrystallization from acetone);

1 - [3-isopropoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methyl-phenyl)-piperazine, B.P. 176–180°/0.04 mm, the dihydrochloride of which melts at 171–173° (after recrystallization from isopropanol);

4 - (2-chloro-phenyl)-1-(3-isopropoxy-3-(4-methyl-phenyl)-propyl)piperazine, B.P. 194–200°/0.04 mm, the hydrochloride of which melts at 159° (after recrystallization from acetone);

1 - [3-isopropoxy-3-(4-methyl-phenyl)-propyl]-4-(4-methyl-phenyl)-piperazine, B.P. 190–192°/0.09 mm, the dihydrochloride of which melts at 172° (after recrystallization from acetone);

2 - (2-chloro-phenyl)-1-(3-ethoxy-3-phenyl-propyl)-piperazine, B.P. 176–178°/0.03 mm, the dihydrochloride of which melts at 141–143° (after recrystallization from a mixture of acetone and diethyl ether);

1 - [3-methoxy-3-(4-methyl-phenyl)-propyl]-4-(4-methyl-phenyl)-piperazine, B.P. 208–212°/0.09 mm, the dihydrochloride of which melts at 192° (after recrystallization from isopropanol);

2 - (2-chloro-phenyl)-1-(3-ethoxy-3-phenyl-propyl)piperazine, B.P. 238–240°/0.08 mm, the dihydrochloride of which melts at 155° (after recrystallization from isopropanol);

4 - (2-methyl-phenyl)-1-(3-ethoxy-3-phenyl-propyl)-piperazine, B.P. 180–182°/0.2 mm, the dihydrochloride of which melts at 150–154° (after recrystallization from ethanol);

4 - (4-methyl-phenyl)-1-(3-ethoxy-3-phenyl-propyl)-piperazine, B.P. 180–183°/0.2 mm, the dihydrochloride of which melts at 200° (after recrystallization from ethanol);

4 - (4-methoxy-phenyl)-1-(3-ethoxy-3-phenyl-propyl)piperazine, the dihydrochloride of which melts at 210–211° (after recrystallization from ethanol);

as well as 1-[3-(4-methoxy-phenyl)-3-n-propoxy-propyl]-3-methyl-4-phenyl-piperazine, 1-[3-ethoxy-3-(4-trifluoromethylbenzyl)-propyl]-3-methyl-4-phenyl-piperazine and the like.

Example 2

To a solution of 8.1 g. of 1-phenyl-piperazine in 50 ml. of toluene is added 2.4 g. of a sodium hydride suspension in mineral oil (53 percent strength); the reaction mixture is refluxed for 2½ hours and is then treated with 9.9 g. of 3-ethoxy-3-phenyl-propyl chloride. After refluxing for an additional four hours, the desired 1-(3-ethoxy-3-phenyl-propyl)-4-phenyl-piperazine of the formula

\[
\begin{align*}
\text{O}_2\text{CH}_3 & \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 & \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 & \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 & \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}\text{CH}_2-\text{CH}_2-\text{N}
\end{align*}
\]

is isolated according to the procedure shown in Example 1, B.P. 160°/0.15 mm.

The dihydrochloride of 1-(3-ethoxy-3-phenyl-propyl)-4-phenyl-piperazine is prepared by treating a solution of the free base in ethanol with a concentrated solution of hydrogen chloride in ethanol, adding diethyl ether while stirring and recrystallizing the salt from ethanol and diethyl ether, M.P. 202–203°.

Example 3

A mixture of 4.89 g. of 1-(2-pyridyl)piperazine and 2.0 g. of a mineral oil suspension of sodium hydride (53 percent strength) in 50 ml. of toluene is refluxed for six hours and then treated with 8.0 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride; the reaction mixture is worked up as described in Example 1 to yield the 1-(3-ethoxy-3-(4-methyl-phenyl)-propyl)-4-(2-pyridyl)-piperazine of the formula

\[
\text{H}_2 \text{C} \quad \text{O}_2\text{CH}_3 \\
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}
\]

which boils at 162–163°/0.25 mm, and is converted into its trihydrochloride, M.P. 194–195°.

Example 4

To a solution of 7.0 g. of 1-phenyl-piperazine in 100 ml. of toluene is added 2.3 g. of a 53 percent suspension of sodium hydride in mineral oil. The reaction mixture is refluxed for 2½ hours, then cooled to room temperature, treated with 9.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride, and refluxed for an additional 36 hours. After standing overnight, the inorganic material is filtered off, the filtrate is evaporated to dryness under reduced pressure and the residue is distilled to yield the 1-(3-(4-chloro-phenyl)-3-ethoxy-propyl)-4-phenyl-piperazine of the formula

\[
\text{O}_2\text{CH}_3 \\
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}
\]

which is collected at 168°/0.1 mm and dissolved in 10 ml. of ethanol. The solution is treated with 10 ml. of ethanol saturated with hydrogen chloride and the desired 1-(3-(4-chloro-phenyl)-3-ethoxy-propyl)-4-phenyl-piperazine dihydrochloride precipitates and is recrystallized from ethanol, M.P. 208°.

Example 5

A mixture of 7.0 g. of 1-phenyl-piperazine and 4.56 g. of sodium carbonate in 100 ml. of ethanol is refluxed for four hours, then cooled to room temperature and treated with 9.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride. The reaction mixture is refluxed for an additional 18 hours and worked up as described in Example 4 to yield the 1-(3-(4-chloro-phenyl)-3-ethoxy-propyl)-4-phenyl-piperazine, collected at 196–212°/0.07–0.09 mm, which is converted into its dihydrochloride M.P. 199°, and is identical with the product obtained according to the procedure described in Example 4.

Example 6

To a solution of 24.0 g. of 2-methyl-1-phenyl-piperazine in 250 ml. of toluene is added 7.5 g. of a 53 percent suspension of sodium hydride in mineral oil; the reactive mixture is refluxed for four hours, cooled to room temperature and treated with 32.6 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride. After refluxing for an additional 18 hours and stirring at room temperature for 2½ days, the solid material is filtered off, the filtrate is concentrated under reduced pressure and the residue is distilled to yield the 1-(3-(4-chloro-phenyl)-3-ethoxy-propyl)-3-methyl-4-phenyl-piperazine of the formula

\[
\text{O}_2\text{CH}_3 \\
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} \\
\text{CH}_3 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}
\]

which is collected at 206–208°/0.07 mm, and converted into its dihydrochloride, M.P. 192° (after three recrystallizations from acetone).

Example 7

A mixture of 6.7 g. of 1-(2-methyl-phenyl)-piperazine and 4.0 g. of sodium carbonate in 150 ml. of ethanol is refluxed for four hours, then cooled to room temperature and treated with 8.0 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride; the reaction mixture is heated to reflux for 18½ hours, filtered, and the filtrate is evapo-
is dissolved in ethanol, and the solution is heated with ethanol saturated with hydrogen chloride and diluted with diethyl ether. The precipitate is filtered off and recrystallized from acetone to yield the 4-(2-methoxy-phenyl) - 1 - [3 - methoxy - 3 - (4 - methyl - phenyl)-propyl]-piperazine dihydrochloride of the formula

which melts at 175-177°.

A mixture of 11.8 g. of 1-(4-chloro-phenyl)-piperazine and 6.3 g. of sodium carbonate in 250 ml. of ethanol is refluxed for four hours and then cooled to room temperature; 14.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride is added and refluxing is continued for an additional 18 hours. The reaction mixture is worked up as described in Example 4; the desired 4-(4-chloro-phenyl) - 1 - [3 - (4 - chloro - phenyl) - 3 - ethoxy-propyl]-piperazine of the formula

which is collected at 214-216°/0.11 mm. and converted into its hydrochloride, M.P. 188° (after recrystallization from acetone).

Other compounds, which may be prepared according to the above procedure are, for example:

1. [3 - 4 - chloro - phenyl] - 3 - ethoxy - propyl] - 4 - (3-methoxy-phenyl)-piperazine, B.P. 204-205°/0.12 mm., the dihydrochloride of which melts at 165° (after recrystallization from ethanol);

2. [3 - (4 - chloro - phenyl)] - 3 - methoxy - propyl] - 3 - methyl - 4 - phenyl - piperazine, B.P. 170-178°/0.05 mm., the dihydrochloride of which melts at 184°;

3. [3 - (4 - chloro - phenyl)] - 3 - ethoxy - propyl] - 4 - (4-methyl - phenyl) - piperazine, B.P. 196-200°/0.04 mm., the dihydrochloride of which melts at 197° (after recrystallization from isopropanol);

4. [3 - (4 - chloro - phenyl) - 3 - isopropoxy - propyl] - 4 - phenyl - piperazine, B.P. 198-200°/0.09 mm., the dihydrochloride of which melts at 200° (after recrystallization from ethanol);

5. [3 - (4 - chloro - phenyl) - 3 - methoxy - propyl] - 4 - (4-methyl - phenyl) - piperazine, B.P. 192-194°/0.08 mm., the dihydrochloride of which melts at 215° (after recrystallization from acetone);

6. [3 - (4 - chloro - phenyl) - 3 - methoxy - propyl] - 4 - (2-methyl - phenyl) - piperazine, B.P. 208-210°/0.17 mm., the dihydrochloride of which melts at 165° (after recrystallization from acetone);

7. [3 - (4 - chloro - phenyl) - 3 - ethoxy - propyl] - 4 - (3-methyl - phenyl) - piperazine, B.P. 180-182°/0.04 mm., the dihydrochloride of which melts at 175° (after recrystallization from ethanol);

8. as well as 1 - [3-ethoxy - 3 - (4-fluoro-phenyl)-propyl] - 3-methyl-4-phenyl-piperazine, 1-3(3-bromo-phenyl)-3-ethoxy-propyl] - 3-methyl-4-phenyl-piperazine, 4 - (2-chloro-phenyl) - 1 - [3-ethoxy-3-(4-fluoro-phenyl)-propyl]-piperazine and the like.

To a solution of 10.6 g. of 1-(4-methyl-phenyl)-piperazine in 250 ml. of ethanol is added 6.4 g. of sodium carbonate; the mixture is then refluxed for four hours, cooled to room temperature, treated with 6.4 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride and again heat-
15
cod to reflux for 18 hours. The solid material is filtered off, the filtrate is evaporated to dryness and the residue is extracted with diethyl ether. The organic solution is evaporated to dryness, and the residue is distilled to yield the 1 - 13 - ethoxy - 3 - (4 - methyl - phenyl) - propyl - 4-(4-methyl-phenyl)-piperazine of the formula

which is collected at 192-196°C/0.011 mm., and converted into its dihydrochloride, M.P. 194-195° (after recrystallization from acetone).

The 1 - [3 - isopropoxy - 3 - (4 - methyl - phenyl) - propyl]-4-(4-methoxy-phenyl)-piperazine is prepared according to the above procedure, collected at 215°/0.26 mm., and converted into its dihydrochloride, M.P. 179° (after recrystallization from isopropanol).

Example 14

A mixture of 3.6 g. of 1-(4-chloro-phenyl)-piperazine and 1.65 g. of sodium carbonate in 150 ml. of ethanol is refluxed for 4 hours, cooled and treated with 3.32 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride. The reaction mixture is refluxed for 18 hours, filtered and evaporated to dryness; the residue is dissolved in 10 percent aqueous hydrochloric acid, and, upon adding diethyl ether, an oil precipitates. The liquids are decanted, and the residue is triturated with diethyl ether. The desired 4 - (4-chloro-phenyl) - 1 - [3 - ethoxy - 3 - (4-methyl-phenyl) - propyl] - piperazine hydrochloride of the formula

solidifies and is recrystallized from acetone, M.P. 174-176°.

Example 15

To a solution of 10.6 g. of 1-(2-methyl-phenyl)-piperazine in 250 ml. of ethanol is added 6.4 g. of sodium carbonate; the reaction mixture is refluxed for four hours, cooled and treated with 14.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride and then refluxed for 18 hours. After cooling and filtering, the filtrate is evaporated under reduced pressure; the residue is extracted with diethyl ether, the organic solution is dried and evaporated, and the oily residue is distilled to yield the 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-(2-methyl-phenyl)-piperazine of the formula

which is collected at 198-202°/0.16 mm., and converted into the dihydrochloride, M.P. 184° (after recrystallization from acetone).

Example 16

To a solution of 11.8 g. of 1-(2-chloro-phenyl)-piperazine in 250 ml. of ethanol is added 6.4 g. of sodium carbonate; the reaction mixture is refluxed for four hours, then cooled to room temperature and treated with 14.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride. After refluxing for 18 hours and filtering, the solution is taken to dryness under reduced pressure and the residue is distilled. The desired 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-piperazine of the formula

is collected as a yellow oil, B.P. 210-212°/0.07 mm., and converted into its dihydrochloride by dissolving the free base in ethanol, adding ethanolic hydrogen chloride and precipitating the salt, which melts at 120° after recrystallization from acetone.

The 4-(3-chloro-phenyl) - 1 - [3-(4-chloro-phenyl)-3-ethoxy-propyl]-piperazine, which is prepared according to the above procedure, is collected at 206-208°/0.06 mm., and converted into its dihydrochloride, M.P. 169° (after recrystallization from isopropanol).

Example 17

A mixture of 3.0 g. of 1-phenyl-piperazine and 2.0 g. of sodium carbonate in ethanol is refluxed for four hours; after cooling, it is treated with 4.3 g. of 3-(2-chloro-phenyl)-3-ethoxy-propyl chloride and refluxing is continued for 18 hours. The reaction mixture is worked up as described in Example 16 and yields the 1-[3-(2-chloro-phenyl)-3-ethoxy-propyl]-4-phenyl-piperazine of the formula

which is collected at 182-184°/0.08 mm., and converted into the dihydrochloride hemihydrate, M.P. 170° after recrystallization from isopropanol.

Example 18

A mixture of 21.0 g. of 1-phenyl-piperazine, 13.7 g. of sodium carbonate and 29.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride in 200 ml. of ethanol is refluxed for 19 hours and then cooled to room temperature. After filtering, the filtrate is evaporated under reduced pressure and the residue is distilled to yield the 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-phenyl-piperazine, which is collected at 196-208°/0.06 mm., and converted into its dihydrochloride, M.P. 201-203° (after recrystallization from ethanol). The compound is identical with the one obtained according to the procedure of Example 5.

The 1 - [3-ethoxy - 3-(4-methyl-phenyl)-propyl]-4-phenyl-1,4-diazacycloheptane, 1-[3-isopropoxy-3-phenyl-propyl]-3-phenyl-1,5-diazacyclo-octane, 1-[3-ethoxy-3-(2,4-dimethyl-phenyl)-propyl]-4-(4-chloro-phenyl)-piperazine, 2,6 - dimethyl-4-(3-methoxy-3-phenyl-propyl)-1-phenyl-piperazine and the like, may be prepared according to one of the above-described procedures, for example, by reacting the sodium salt of 1-phenyl-1,4-diazacyclo-

1,4-(4-chloro-phenyl)-piperazine, 2,6-dimethyl-1-phenyl-piperazine and the like, with 3-ethoxy-3-(4-methyl-phenyl)-propyl chloride, 3-isopropoxy-3-phenyl-propyl chloride, 3-ethoxy-3-(2,4-dimethyl-phenyl)-propyl chloride, 3-methoxy-3-phenyl-propyl chloride, respectively.

Example 19

A mixture of 21.3 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl-amine and 25.2 g. of N,N-di-(2-chloroethyl)-N-(2-chloro-phenyl)-amine in 100 ml. of methanol is refluxed in the presence of an excess of potassium carbonate for fifteen hours while stirring. The solid material is filtered off, the filtrate is concentrated under reduced pressure, and the residue is distilled to yield the 4-(2-chloro-phenyl) - 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-piperazine, which is collected at 210-212°/0.07 mm., and converted into its dihydrochloride, M.P. 120°.

The starting material used in the above procedure is prepared as follows: A mixture of 50.0 g. of 3-(4-chloro-phenyl)-3-ethoxy-propyl chloride and 44.0 g. of potassium phthalimide in 80 ml. of N,N-dimethyformamide is refluxed for two hours in the presence of a few crystals of potassium iodide as a catalyst. The hot solution is poured onto 200 g. of crushed ice; the organic material is extracted with chloroform, and the extract is washed with 1 N aqueous solution of potassium hydroxide, 0.5 N
aqueous hydrochloric acid and water. After drying over sodium sulfate, the organic solution is concentrated to dryness under reduced pressure. The residue is treated with 200 ml of methanol containing 20 ml of hydrazine hydrate (99–100%) and refluxed for two hours. The solution is cooled, acidified with concentrated hydrochloric acid and again refluxed thirty minutes. After filtration, it is taken to dryness under reduced pressure, and the residue is dissolved in a minimum amount of water. The aqueous solution is made strongly alkaline with a 50 percent solution of potassium hydroxide, salted with potassium carbonate and extracted with diethyl ether. The organic extract is dried and concentrated under reduced pressure to yield the 3-(4-chlorophenyl)-3-ethoxy-propyl-amine, which is used in the subsequent step without further purification.

The N,N-di-(2-chloroethyl)-N-(2-chloro-phenyl-amine used in the above procedure is prepared by heating a mixture of 2-chloro-ethylamine and ethylene oxide in a sealed tube and converting in a resulting N-(2-chlorophenyl)-N,N-di-(2-hydroxyethyl)-amine, the hydroxyl groups into chloro by treatment with thionyl chloride.

**Example 20**

A mixture of 33.8 g. of N,N-di-(2-chloroethyl)-N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-amine and 12.8 g. of 4-chloro-aniline in 100 ml of methanol is refluxed in the presence of an excess of sodium carbonate for fifteen hours while stirring. The solid material is filtered off, the filtrate is evaporated to dryness, and the residue is distilled to yield the 3-(4-chlorophenyl)-1-[3-(4-chlorophenyl)-3-ethoxy-propyl]-piperazine, which is collected at 214–216°/0.11 mm. and converted into its hydrochloride, M.P. 188°.

The starting material used in the above procedure is prepared as follows: A mixture of 21.3 g of 3-(4-chlorophenyl)-3-ethoxy-propyl-amine and 9.0 g. of ethylene oxide is heated in a sealed tube at 90–150° for sixteen hours. The content of the tube is extracted with ethanol, and the organic solution is carefully concentrated under reduced pressure to yield the N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-N,N-di-(2-hydroxyethyl)-amine.

The latter compound may also be prepared as follows: A mixture of 53.0 g. of 3-(4-chlorophenyl)-3-ethoxy-propyl-amine and 100.0 g. of ethylene chlorohydrin in 250 ml of water containing 35.0 g. of calcium carbonate is refluxed overnight while stirring. The hot mixture is filtered, and with sodium chloride, cooled and extracted with diethyl ether. The organic solution is concentrated under reduced pressure to yield the N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-N,N-di-(2-hydroxyethyl)-amine.

To a suspension of 25.0 g. of powdered phosphorus pentachloride in 100 ml. of dry chloroform is added 30.2 g. of N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-N,N-di-(2-hydroxyethyl)-amine while cooling. After refluxing for one hour, the resulting solution is poured onto ice, the chloroform layer is separated, dried and concentrated under reduced pressure to yield the N,N-di-(2-chloroethyl)-N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-amine. The latter may also be prepared by reacting the N-[3-(4-chlorophenyl)-3-ethoxy-propyl]-N,N-di-(2-hydroxyethyl)-amine with about 1.2 moles of phosphorus oxychloride in benzene or about 1.4 moles of thionyl chloride in benzene at 0°.

**Example 21**

A mixture of 9.65 g. of 3-ethoxy-3-(4-methyl-phenyl)-propyl-amine and 11.6 g. of N,N-di-(2-chloroethyl)-N-(2-methyl-phenyl)-amine in 50 ml of methanol is refluxed in the presence of an excess of potassium carbonate while stirring. The precipitate is filtered off, the filtrate is concentrated under reduced pressure, and the residue is distilled to yield the [3-ethoxy-3-(4-methyl-phenyl)-propyl] + 4 - (2-methyl-phenyl)-piperazine, which is collected at 186°/0.05 mm., and is converted into its dihydrochloride. M.P. 164–166°.

**Example 22**

A mixture of 15.9 g of N,N-di-(2-chloroethyl)-N-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-amine and 12.3 g. of 2-methoxyaniline in 50 ml of methanol is refluxed in the presence of an excess of sodium carbonate for fifteen hours while stirring. The solid material is filtered off, the filtrate is evaporated to dryness, and the residue is distilled to yield the 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methoxy-phenyl)-piperazine, which is collected at 222–224°/0.14 mm. and converted into its hydrochloride, M.P. 186°.

The starting material used in the above procedure is prepared as follows: A mixture of 19.4 g of 3-ethoxy-3-(4-methyl-phenyl)-propyl-amine and 9.0 g. of ethylene oxide is heated in a sealed tube at about 120° for sixteen hours. The reaction mixture is extracted with ethanol, and the ethanol solution is carefully concentrated under reduced pressure to yield the N,N-di-(2-hydroxyethyl)-N-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-amine.

To a suspension of 25.0 g. of powdered phosphorus pentachloride in 100 ml of dry chloroform is added 29.8 g. of N,N-di-(2-hydroxyethyl)-N-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-amine while cooling. After refluxing for one hour, the resulting solution is poured onto ice, the chloroform layer is separated, dried and concentrated under reduced pressure to yield the N,N-di-(2-chloroethyl)-N-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-amine.

**Example 23**

A mixture of 10.05 g of 1-(2-methoxy-phenyl)-piperazine and 11.5 g of 2-(4-chlorophenyl)-2-ethoxy-ethylchloride in 200 ml of butanol is refluxed for 24 hours in the presence of 40.0 g. of sodium carbonate while stirring. The inorganic material is filtered off, the filtrate is concentrated to dryness and the residue is di-
ethyl-4-phenyl-piperazine, B.P. 128-140°/0.35 mm., the dihydrochloride of which melts at 182-185°;
4 - (2-chloro-phenyl) - 1 - (2-ethoxy-2-phenyl-ethyl)-piperazine, B.P. 200-205°/0.55 mm., the hydrochloride of which melts at 200-203° (after recrystallization from ethyl acetate);
1 - (2-ethoxy-2-phenyl-ethyl) - 3 - methyl - 4 - phenyl-piperazine, collected at 165-180°/0.5 mm., the dihydrochloride of which melts at 230-235° (after recrystallization from ethanol);
1 - (2-(3,4-dichloro-phenyl)-2-ethoxy-ethyl)-4-(2-methoxy-phenyl)-piperazine, collected at 210-220°/0.7 mm., the dihydrochloride of which melts at 221-225° (after recrystallization from ethanol and diethyl ether);
4 - (2-chloro-phenyl) - 1 - (2-(4-chloro-phenyl)-2-ethoxy-ethyl)-piperazine, collected at 185-190°/0.2 mm., the dihydrochloride of which melts at 240-244° (after recrystallization from ethanol);
1 - (2-(3-chloro-phenyl)-2-ethoxy-ethyl)-4-(3-methyl-phenyl)-piperazine, collected at 180-200°/0.7 mm., the dihydrochloride of which melts at 192-193° (after recrystallization from ethanol and diethyl ether);
4 - (3-methyl-phenyl) - 1 - (2-ethoxy-2-phenyl-ethyl)-piperazine, collected at 185-190°/0.2 mm., the dihydrochloride of which melts at 197-199° (after recrystallization from ethanol);
1 - (2-ethoxy-2-phenyl-ethyl)-4-(2-pyridyl)-piperazine, collected at 185-190°/0.5 mm., the dihydrochloride of which melts at 125-130° (after recrystallization from ethanol and diethyl ether);
as well as 4 - (2-chloro-phenyl) - 1 - (2-(4-chloro-phenyl)-2-ethoxy-ethyl)-piperazine, 1 - (2-ethoxy-2-(4-methyl-phenyl)-ethyl)-4-(2-methyl-phenyl)-piperazine, 1 - (2-ethoxy-2-phenyl-ethyl)-4-(3-methyl-phenyl)-piperazine, 1 - (2-ethoxy-2-phenyl-ethyl)-4-(4-pyridyl)-piperazine, 1 - (2-(2-methyl-2-phenyl-ethyl))-4-phenyl-1,4-di-azia-cyclohepane, 1 - (2-isoproxy-2-phenyl-ethyl)-5-(3-methyl-phenyl)-1,5-di-azia-cyclo-ocetane, 1 - (4-ethoxy-4-phenyl-butil)-4-phenyl-piperazine, 1 - (4-chloro-phenyl)-4-ethyl-butil) - 4 - (2-methoxy-phenyl-piperazine and the like.

Example 26
A mixture of 10.6 g. of 1-(3-methyl-phenyl)-piperazine, 11.9 mg. of 3-ethoxy-3-phenyl-propion chloride and 6.4 g. of sodium carbonate in 250 ml. of ethanol is refluxed for 18 hours while stirring, then cooled and filtered. The filtrate is evaporated under reduced pressure and the residue is distilled to yield the 1-(3-ethoxy-3-phenyl-propion)-4-(3-methyl-phenyl)-piperazine of the formula

which is collected at 172-174°/0.05 mm. The dihydrochloride, which is prepared by treating an ethanol solution of the free base with a saturated solution of hydrogen chloride in ethanol, melts at 166° after recrystallization from ethanol; yield: 3.6 g.
A mixture of 10.9 g of 1-(2-methoxy-phenyl)-piperazine and 6.0 g of sodium carbonate in 250 ml of ethanol is refluxed while stirring for four hours, then cooled and treated with 13.3 g of 3-(4-chloro-phenyl)-3-ethoxypropyl chloride. The reaction mixture is refluxed for 18½ hours, filtered and evaporated to dryness under reduced pressure. The residue is distilled to yield the 1-(3-(4-chloro-phenyl)-3-ethoxypropyl)-4-(2-methoxy-phenyl)-piperazine of the formula

which is collected at 206-210°/0.13 mm and converted into its dihydrochloride, which melts at 200° after recrystallization from isopropanol.

A solution of 2,530 g of 1-(3-hydroxy-3-(4-methyl-phenyl)-propyl)-4-(2-methyl-phenyl)-piperazine in 19,000 ml of benzene is gassed with hydrogen chloride until the pH is 2. The hydrochloride salt precipitates, and the residue is treated with a solution of 2,750 g of thionyl chloride in 12,000 ml of benzene, while maintaining the temperature below 30°. After refluxing and stirring for two hours, the benzene and the excess of thionyl chloride are evaporated; the residue is diluted with 8,000 ml of benzene and again evaporated to remove the remaining thionyl chloride. The residue is taken up into 12,000 ml of anhydrous ethanol.

A solution of 718 g of sodium in 23,400 ml of anhydrous ethanol is cooled to 10° and added to the above solution while cooling and keeping the temperature below 15°. After completion of the addition, the reaction mixture is refluxed for one hour, and is then allowed to stand overnight. The solution is evaporated to dryness, the residue is dissolved in 80,000 ml of water while cooling, and the oily product is extracted with one portion of 40,000 ml and two portions of 20,000 ml, each of chloroform. The combined organic extracts are dried over sodium sulfate, treated with 150 g of a charcoal preparation, and evaporated to dryness to yield 2,700 g of 1-(3-ethoxy-3-(4-methyl-phenyl)-propyl)-4-(2-methyl-phenyl)-piperazine, which is dissolved in 12,200 ml of methanol. The organic solution is passed with hydrogen chloride gas until the pH is 2. After maintaining the temperature below 40°, after stirring at room temperature for three hours, the precipitate is filtered off, washed three times with three portions of 1,000 ml each of cold methanol and dried at 60° under reduced pressure. The resulting 1-(3-ethoxy-3-(4-methyl-phenyl)-propyl)-4-(2-methyl-phenyl)-piperazine dihydrochloride melts at 165-168°.

The starting material used in the above procedure is prepared as follows: A mixture of 2,490 g of 1-(2-methyl-phenyl)-piperazine dihydrochloride, 285 g of paraformaldehyde and 1,735 g of 4-methyl-acetophenone in 7,500 ml of anhydrous ethanol is refluxed for twenty-two hours while stirring. After cooling to 10°, the precipitate is filtered off and washed three times with 1000 ml of cold acetone. The resulting 1-(3-(4-methylphenyl)-3-oxo-propyl)-4-(2-methyl-phenyl) piperazine hydrochloride is dried overnight at 50° under reduced pressure.

The pH of a solution of 2,660 g of 1-(3-(4-methylphenyl)-3-oxo-propyl)-4-(2-methyl-phenyl) piperazine hydrochloride in 10,800 ml of methanol is adjusted to 10 by adding a 50 percent aqueous solution of sodium hydroxide. After cooling to 6°, a total of 407 g of sodium borohydride is added over a period of one hour, maintaining the temperature between 6° and 20°. After warming to 25° and stirring for three hours, the reaction mixture is acidified to pH 2 with concentrated hydrochloric acid, and is again stirred for twenty minutes. The reaction mixture is diluted with 18,000 ml of water and 11,000 ml of chloroform, and while stirring and cooling to 25°, the pH is again adjusted to 10 with a 50 percent solution of sodium hydroxide in water. The organic layer is separated, the aqueous phase is extracted with two additional portions of 7,000 ml each of chloroform. The combined organic extracts are dried over sodium sulfate, filtered and evaporated. The oily residue crystallizes to yield the 1-(3-hydroxy-3-(4-methyl-phenyl)-propyl)-4-(2-methyl-phenyl)-piperazine, which melts at 80-83°; yield: 2,530 g.

A mixture of 8.9 g of 3-ethoxy-3-phenyl-propyl-amine and 11.6 g of N,N-di-(2-chloroethyl)-N-(3-methyl-phenyl)-amine in 50 ml of methanol containing an excess of potassium carbonate is refluxed for fifteen hours while stirring. The solid material is filtered off, the filtrate is concentrated under reduced pressure and the residue is distilled to yield the 1-(3-ethoxy-3-phenyl-propyl)-4-(3-methyl-phenyl)-piperazine, which is collected at 172-174°/0.05 mm, and is converted into its dihydrochloride, M.P. 166°.

The starting material used in the above procedure is prepared as follows: A mixture of 21.3 g of 3-ethoxy-3-phenylpropyl chloride and 22.0 g of potassium pthalimide in 40 ml of N,N-dimethylformamide is refluxed for two hours in the presence of a few crystals of potassium iodide as a catalyst. The hot solution is poured onto 150 g of crushed ice; the organic material is extracted with chloroform, and the extract is washed with a 1 N aqueous solution of potassium hydroxide, 0.5 N aqueous hydrochloric acid and water. After drying over sodium sulfate, the organic solution is concentrated to dryness under reduced pressure. The residue is treated with 100 ml of methanol containing 10 ml of hydroxyde hydrate (99-100%) and refluxed for two hours. The solution is cooled, acidified with concentrated hydrochloric acid and again refluxed thirty minutes. After filtration, it is taken to dryness under reduced pressure; the residue is dissolved in a minimum amount of water and the aqueous solution is made strongly alkaline with a 50 percent solution of potassium hydroxide, salted with potassium carbonate and extracted with diethyl ether. The organic extract is dried and concentrated under reduced pressure to yield the 3-ethoxy-3-phenyl-propylamines, which is used in the subsequent step without further purification.

The N,N-di-(2-chloroethyl)-N-(3-methyl-phenyl)amine used in the above procedure is prepared by heating a mixture of 3-methyl-aniline and ethylene oxide in a sealed tube and converting the hydroxyl groups in a resulting N,N-di-(2-hydroxyethyl)-N-(3-methyl-phenyl)amine into chloro by treatment with thionyl chloride.

A mixture of 15.2 g of N,N-di-(2-chloroethyl)-N-(3-ethoxy-3-phenyl-propyl)-amine and 5.4 g of m-toluidine in 100 ml of methanol is refluxed in the presence of an excess of sodium carbonate for fifteen hours while stirring. The solid material is filtered off, the filtrate is evaporated to dryness and the residue is distilled to yield the 1-(3-ethoxy-3-phenyl-propyl)-4-(3-methyl-phenyl)-piperazine, which is collected at 172-174°/0.5 mm. and converted into its dihydrochloride, M.P. 166°.

The starting material used in the above procedure is prepared as follows: A mixture of 8.9 g of 3-ethoxy-3-phenyl-propyl-amine and 4.5 g of ethylene oxide is heated in a sealed tube at 150° for sixteen hours. The content of the tube is extracted with ethanol, and the organic solution is carefully concentrated under reduced pressure to yield the N-(3-ethoxy-3-phenyl-propyl)-N,N-di-(2-hydroxyethyl)-amine.

To a suspension of 13.0 g of powdered phosphorus pentachloride in 100 ml of dry chloroform is added.
13.4 g. of N-(3-ethoxy-3-phenyl-propyl)-2,N-di-(2-hydroxyethyl)-amine while cooling. After refluxing for one hour, the resulting solution is poured onto ice, the chloroform layer is separated, dried and concentrated under reduced pressure to yield the N,N-di-(2-chloroethyl)-N-(3-ethoxy-3-phenyl-propyl)-amine.

**Example 31**

A solution of 14.12 g. of 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)3-hydroxy-propyl]-piperazine in 100 ml. of benzene is gassed with hydrogen chloride until the pH is 2. The hydrochloride salt precipitates, and the reaction mixture is then treated with a solution of 13.8 g. of thionyl chloride in 60 ml. of benzene, while maintaining the temperature below 30°C. After refluxing and stirring for two hours, the solvent and the excess of thionyl chloride are evaporated; the residue is diluted with 40 ml. of benzene and again evaporated to remove the remaining thionyl chloride. The residue is taken up into 60 ml. of anhydrous ethanol, and a cold solution of 3.59 g. of sodium in 120 ml. of anhydrous ethanol is added while keeping the temperature below 15°C. After completion of the addition, the reaction mixture is refluxed for one hour, and is then allowed to stand overnight. The solution is then evaporated to dryness, the residue is dissolved in 400 ml. of water while cooling, and the organic material is extracted with three portions of chloroform. The combined organic extracts are dried over sodium sulfate, treated with a charcoal preparation, and the resulting mixture is filtered off to dryness to yield the 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-piperazine. A methanol solution of the latter is treated with hydrogen chloride until the pH is 2, while cooling to below 40°C. After stirring for three hours, the precipitate is filtered off, washed three times with cold methanol and dried at 60°C under reduced pressure. The resulting 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-piperazine dihydrochloride melts at 120°C after recrystallization from acetone.

The starting material used in the above procedure is prepared as follows: A mixture of 27.8 g. of 1-(2-chloro-phenyl)-piperazine dihydrochloride, 3.85 g. of paraformaldehyde and 20.0 g. of 4-chloroacetophenone in 75 ml. of anhydrous ethanol is refluxed for twenty-two hours while stirring. After cooling to −10°C, the precipitate is filtered off and washed three times with cold acetone. The resulting 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-oxy-propyl]-piperazine hydrochloride is dried overnight at 50°C under reduced pressure, and is used without further purification.

A solution of 30.0 g. of 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-oxy-propyl]-piperazine hydrochloride in 120 ml. of methanol is made basic with a 50 percent aqueous solution of sodium hydroxide, is cooled to 6°C, and is then treated with a total of 4.07 g. of sodium borohydride which is added over a period of one hour, while maintaining the temperature below 20°C. After stirring for three hours at room temperature, the reaction mixture is acidified with concentrated hydrochloric acid, and is again stirred for twenty minutes. The reaction mixture is then diluted with 200 ml. of water and 120 ml. of chloroform, and while stirring and cooling to 25°C, the reaction mixture is again made basic by adding a 50 percent solution of sodium hydroxide in water. The organic layer is separated, the aqueous phase is extracted with two additional portions of chloroform. The combined chloroform extracts are dried over sodium sulfate, filtered and evaporated. The residue, representing the 4-(2-chloro-phenyl)-1-[3-(4-chloro-phenyl)-3-hydroxy-propyl]-piperazine, is used without further purification.

**Example 32**

A mixture of 10 g. of 2-ethoxy-2-(4-fluoro-phenyl)-ethyl chloride and 8.7 g. of 2-methyl-1-phenyl-piperazine in 200 ml. of butanol containing a few drops of water together with 10.0 g. of sodium carbonate is refluxed for 72 hours while stirring. The reaction mixture is filtered, the filtrate is concentrated under reduced pressure, and the residue is taken up into diethyl ether. The insoluble material is filtered off, and the filtrate is washed with water, dried and concentrated under reduced pressure. The desired 4-(2-ethoxy-2-(4-fluoro-phenyl)-ethyl)-3-methyl-4-phenyl-piperazine of the formula is distilled, collected at 170°-175°/0.6 mm., and converted into its dihydrochloride by treatment with an ethanol solution in hydrogen chloride; the salt melts at 228°-232° after recrystallization of ethanol and diethyl ether.

The starting material used in the above example is prepared as follows: A mixture of 8.16 g. of magnesium turnings in 275 ml. of diethyl ether is treated with 70 g. of 4-bromo-fluoro-benzene to form the Grignard reagent, which is stirred for another hour while cooling and is then treated dropwise with 48 g. of 2-ethoxy-2-(4-fluoro-phenyl)-ethyl ether. After completion of the addition, the reaction mixture is stirred for thirty minutes at room temperature, then refluxed for one hour and allowed to stand at room temperature overnight. It is then poured onto ice; the aqueous mixture is acidified with concentrated hydrochloric acid and is extracted with diethyl ether. The organic solution is dried and evaporated and the residue is distilled to yield the 2-ethoxy-2-(4-fluoro-phenyl)-ethyl chloride, which is collected at 110°-115°/12 mm.

**Example 33**

A mixture of 11.9 g. of 1-(3-methoxy-phenyl)-piperazine, 7.5 g. of sodium carbonate and 11.2 g. of 3-ethoxy-3-phenyl-propyl chloride in 100 ml. of ethanol is refluxed for forty-eight hours. After cooling, the inorganic material is filtered off, the filtrate is evaporated under reduced pressure and the viscous residue is treated with a small amount of diethyl ether, the solid material is filtered off, washed with water and extracted with diethyl ether. After drying over magnesium sulfate, the solvent is evaporated and the resulting 1-(3-methoxy-3-phenyl-propyl)-4-(3-methoxy-phenyl)-piperazine of the formula is purified by distillation and converted into its dihydrochloride which melts at 163°C after recrystallization from ethanol.

**Example 34**

A solution of 24.4 g. of 1-(2-hydroxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine in benzene is treated with hydrogen chloride gas until the pH is about 2. The hydrochloride salt precipitates, and the reaction mixture is treated with a solution of 27.5 g. of thionyl chloride in 120 ml. of benzene, while maintaining the temperature below 30°C. After refluxing and stirring for two hours, the benzene and the excess of thionyl chloride are evaporated; the residue is diluted with 100 ml. of benzene and again evaporated to remove the remaining thionyl chloride. The residue is taken up into 120 ml. of anhydrous ethanol, and treated with a solution of 7.2 g. of sodium in 250 ml. of anhydrous ethanol while cooling and keeping the temperature below 15°C. After completion of the addition, the reaction mixture is refluxed for one hour, and is then allowed to stand overnight. The solution is evaporated to dryness, the residue is dissolved in 800 ml. of water while cooling, and the oily product is extracted with chloroform. The organic extract is dried over sodium sulfate, treated with a charcoal preparation, and...
evaporated to dryness to yield the 1-(2-ethoxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine, which is purified by distillation and collected at 179–180 °C/0.9 mm. The 1-(2-ethoxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine dihydrochloride is obtained by reacting the 1-(2-ethoxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine with hydrogen chloride as described above and melts at 215–217 °C after recrystallization from ethanol and acetonitrile.

The starting material used in the above procedure is prepared by reacting 1-(2-ethoxy-2-phenyl-ethyl)-piperazine with N-chlorosuccinimide in the presence of sodium carbonate, and recrystallizing the crude product from the resulting 4-(2-methoxy-phenyl)-1-(2-oxo-2-phenyl-ethyl)-piperazine by treating a methanol solution of the latter with sodium borohydride at a pH of about 10, brought about by adding sodium hydrosulfite.

**Example 35**

A mixture of 8.9 g. of 2-ethoxy-2-phenyl-ethyl-amine and 12.4 g. of N,N-di-(2-chloroethy)-N-(2-methoxy-phenyl)-amine in 50 ml. of methanol is refluxed for fifteen hours while stirring in the presence of an excess of potassium carbonate. The solid material is filtered off, the filtrate is concentrated under reduced pressure, and the residue is distilled to yield the 1-(2-ethoxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine, which is collected at 179–180 °C/0.9 mm, and is converted into its dihydrochloride, M.P. 215–217 °C, after recrystallization from ethanol and acetonitrile.

The starting material used in the above procedure is prepared by refluxing a mixture of 2-ethoxy-2-phenyl-ethyl chloride and potassium phthalimide in N,N-di-methylformamide, and converting the resulting N-(2-ethoxy-2-phenyl-ethyl)-phthalimide into the desired 2-ethoxy-2-phenyl-ethyl-amine by refluxing a methanol solution of the former with hydrazine hydrate.

The N,N-di-(2-chloroeth)-N-(2-methoxy-phenyl)-amine used in the above procedure is prepared by heating a mixture of 2-methoxy-aniline and ethylene oxide in a sealed tube and converting the hydroxy groups in a resulting N,N-di-(2-hydroxyethyl)-N-(2-methoxy-phenyl)-amine into chloro by treatment with thionyl chloride.

**Example 36**

A mixture of 7.6 g. of N,N-di-(2-chloroethyl)-N-(2-ethoxy-2-phenyl-ethyl)-amine and 6.2 g. of 2-methoxy-aniline in 50 ml. of methanol is refluxed in the presence of an excess of sodium carbonate for fifteen hours while stirring. The solid material is filtered off, the filtrate is evaporated to dryness, and the residue is distilled to yield the 1-(2-ethoxy-2-phenyl-ethyl)-4-(2-methoxy-phenyl)-piperazine, which is collected at 179–180 °C/0.9 mm, and converted into its dihydrochloride, M.P. 215–217 °C, after recrystallization from ethanol and acetonitrile.

The starting material used in the above procedure is prepared by heating a mixture of 2-ethoxy-2-phenyl-ethylamine and ethylene oxide in a sealed tube at 130 °C for sixteen hours, and reacting the resulting N-(2-ethoxy-2-phenyl-ethyl)-N,N-di-(2-hydroxyethyl)-amine with a suspension of powdered phosphorus pentachloride in dry chloroform at an elevated temperature.

What is claimed is:

1. A member selected from the group consisting of an N-(x-lower alkoxy-x-monocyclic carboxyclic aryl-lower alkoxy)N-monocyclic aryl-diaza-cycloalkane, in which lower alkoxy and monocyclic carboxyclic aryl substituting the same carbon atom and are separated from the nitrogen atom of the diaza-cycloalkane portion by two to four carbon atoms, and in which the diaza-cycloalkane portion has from six to eight ring members, and its two nitrogen atoms are separated from one another by from two to three carbon atoms of alkyne radicals, having from two to seven carbon atoms, and in which monocyclic carboxyclic aryl is a member selected from the group consisting of phenyl, (lower alkoxy)-phenyl, (lower alkoxy)phenyl, (halogeno)-phenyl and (trifluoromethyl)-phenyl, and monocyclic aryl is a member selected from the group consisting of phenyl, (lower alkoxy)-phenyl, (lower alkoxy)phenyl, (halogeno)-phenyl and pyridyl, acid addition salts thereof, N-oxides thereof, acid addition salts of N-oxides thereof, and lower alkyl quaternary ammonium compounds thereof.

2. A compound of the formula

![Formula 1](image1.png)

in which R is lower alkyl, the letter m is the integer 2, the radical R1 stands for hydrogen, and each of the groups R4 and R5 stands for lower alkyl.

3. A compound of the formula

![Formula 2](image2.png)

in which R is lower alkyl, the letter m is the integer 2, the radical R1 stands for hydrogen, the group R8 is halogeno, and the group R9 stands for hydrogen.

4. A compound of the formula

![Formula 3](image3.png)

in which R is lower alkyl.

5. An acid addition salt of a compound of the formula

![Formula 4](image4.png)

in which R is lower alkyl.

6. A compound of the formula

![Formula 5](image5.png)

in which R is lower alkyl, and R5’ is methoxy.

7. A compound of the formula

![Formula 6](image6.png)

in which R is lower alkyl, and R5 is chloro.

8. A compound of the formula

![Formula 7](image7.png)

in which R is lower alkyl, and R5’ is methoxy.

9. A compound of the formula

![Formula 8](image8.png)

in which R is lower alkyl, the letter m is the integer 1, R4 is hydrogen, R6’ is hydrogen, and R6” is methoxy.

10. 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-phenylpiperazine.

11. An acid addition of 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-phenylpiperazine.

12. 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-3-methyl-4-phenylpiperazine.
13. 1-[3-(4-chloro-phenyl)-3-methoxy-propyl]-3-methyl-4-phenyl-piperazine.
14. 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methyl-phenyl)-piperazine.
15. An acid addition salt of 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methyl-phenyl)-piperazine.
16. 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methyl-phenyl)-piperazine dihydrochloride.
17. 1-[3-ethoxy-3-(4-methyl-phenyl)-propyl]-4-(2-methoxy-phenyl)-piperazine.
18. 1-[3-isopropyl-3-(4-methyl-phenyl)-propyl]-4-(2-methyl-phenyl)-piperazine.
19. 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-(3-methyl-phenyl)-piperazine.
20. 1-(3-ethoxy-3-phenyl-propyl)-4-(3-methyl-phenyl)-piperazine.
21. An acid addition salt of 1-(3-ethoxy-3-phenyl-propyl)-4-(3-methyl-phenyl)-piperazine.
22. 1-(3-ethoxy-3-phenyl-propyl)-4-(3-methylphenyl)-piperazine dihydrochloride.
23. 1-[3-(4-chloro-phenyl)-3-ethoxy-propyl]-4-(2-methoxy-phenyl)-piperazine.

References Cited in the file of this patent

FOREIGN PATENTS

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OTHER REFERENCES

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,168,522

George de Stevens et al.

February 2, 1965

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 26, lines 34 to 38, for the right-hand portion of the formula reading

\[ \text{read} \]

column 26, lines 55 to 59, for that portion of the formula reading

\[ \text{read} \]

same column 26, line 70, for "-ethoxy propyl" read --ethoxy-propyl --; line 72, for "addition" read -- addition salt --; column 27, line 12, for "2-" read -- (2- --; line 20, for "-methylphenyl" read --methyl-phenyl --; column 28, line 11, for "2(4-" read -- 2-(4- --.

Signed and sealed this 26th day of October 1965.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents