This invention relates to 4-imidoalkyl-3-methyl-2-phenylmorpholines and processes for the manufacture thereof. More particularly, this invention relates to compounds of the formula

\[
\text{RCH}_2\text{NAll-R}
\]

wherein Alk is an alkylene, and R an imido radical.

Among the alkylene radical comprehended by Alk in the foregoing formula, lower alkylene radicals are preferred, such radicals being bivalent, saturated, acyclic, straight- or branched-chain, hydrocarbon radicals of empirical formula

\[
\text{C}_n\text{H}_m
\]

wherein \(n\) is a positive integer generally amounting to less than nine. Examples of the lower alkylene radicals contemplated are:

- Methylene (-CH\(_2\)-)
- 1,2-ethylene (-CH\(_2\)CH\(_2\)-)
- Trimethylene (-CH\(_2\)CH\(_2\)CH\(_2\)-)
- 1,2-propylene (CH\(_2\)CH\(_3\))
- Tetramethylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-)
- 2-methyl-1,2-propylene (-CH\(_2\)CH\(_3\))
- 2,4-pentylene (CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\))
- 2,3-dimethyl-1,2-propylene (-CH\(_3\)CH\(_2\)CH\(_2\)CH\(_3\))
- 3-methyl-1-butenylene (-CH\(_2\)CH\(_3\)CH\(_2\)CH\(_3\))
- Hexamethylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-)
- Octamethylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-)

and \(X\) is one equivalent of an anion for example, chloride, bromide, iodide, nitrate, phosphate, sulfate, sulfinate, methyl sulfate, ethyl sulfate, benzensulfonate, toluenesulfonate, acetate, lactate, succinate, malate, maleate, tartrate, citrate, gluconate, ascorbate, benzoate, cinnamate, or the like—which, in combination with the cationic portion of a salt aforesaid, is neither pharmaceutically nor otherwise undesirable in pharmaceutical dosage.

This application is a continuation-in-part of applicants' application Serial No. 659,224, filed May 15, 1957 and now abandoned.

The compounds of this invention are useful because of their valuable pharmacological properties. Especially, they are anorectic agents, being capable of a substantial and sustained inhibition of the appetite. Additionally, the subject compounds have been found to affect water balance; they can be mildly diuretic, and adapted to relieve the swelling associated with edematous inflammatory processes.

Those skilled in the art will recognize that the compounds to which this invention relates are characterized by the presence of two asymmetric carbon atoms in each molecular unit. There are, then four optically active and two racemic forms of such units; and the relative pharmacological potency of the various forms can vary appreciably. Thus, for example, the dextrorotatory 3-methyl-2-phenyl-4-succinimidomethylmorpholine herein after exemplified appears to produce an anorectic response somewhat more than twice as great, at selected doses, as that of the racemic material set forth.

Non-stereospecific manufacture of the imidomethylamines of this invention proceeds by heating 3-methyl-2-phenylmorpholine with an imide, RH, in the presence of formalin, using an alcoholic reaction medium. Synthesis is ordinarily complete in from 2 to 8 hours when boiling ethanol is the medium of choice. Imidethylamines can be prepared by interaction of 3-methyl-2-phenylmorpholine with ethylene oxide in alcoholic medium to give the N-hydroxyethyl derivative, which is converted to the N-chloroethyl compound with thionyl chloride. This, in turn, is reacted with a selected imide salt, RK, by heating in an alcoholic medium, to yield the imidomethylmorpholine. However, a preferred procedure—suitable not only for imidethyllamines hereof but also for other imidalkylamines of the invention wherein the alkylene bridge contains more than 1 carbon atom—comprises heating 3-methyl-2-phenylmorpholine with a haloalkylamide, Hnl—Alk—R, in the presence of anhydrous base. Hal can be either chlorine or bromine, and the base employed can be an amine, such as triethylamine, or it can be a carbonate, as for example potash, or it can even be a caustic, such as caustic soda. When a solid base is used, the reaction mixture is desirably diluted with a solvent, for example, a ketonic substance such as butanone. An alternative procedure for the manufacture of imidoalkylamines containing more than 1 carbon in the alkylene bridge comprises condensing 3-methyl-2-phenylmorpholine with an appropriate haloalkylhalide, Br—Alk—Cl, in the presence of anhydrous base; and then reacting the N-chloroalkylmorpholine which results with a selected imide salt as in the case of the imidoethylamine preparations referred to previously. This procedure, however, has the disadvantage that particularly those chloroalkylmorpholines wherein the alkyl constituent comprises 4 or 5 carbon atoms are characterized by a tendency to cyclize with the formation of spiroquaternary compounds.
A variety of means exist for obtaining optically active forms of the products of this invention. Where the product occurs in crystals with apparently differing arrangements of the faces, manual separation of the isomers is possible. Alternatively, such of the products as are rendered by bacteria or molds will be found to undergo this fermentation at varying rates, and appropriate selections of the microorganisms involved will enable preparation of one or either enantiomorph by destruction of the other. Yet another widely-recognized method of resolving racemic products of the type represented by the basic amines herein disclosed consists in preparing salts thereof with optically active acids, and taking advantage of the differential solubilities of these salts to effect their separation, followed by freeing of the constituent stereospecific amine with caustic. Finally, one can proceed from optically active starting materials to optically active final products as illustrated by the disclosure of Example 6 hereinafter.

Conversion of the amine bases of this invention to corresponding acid addition salts is accomplished by simple admixture of these compounds with one equivalent of any of various inorganic and strong organic acids, the anionic portion of which conforms to X as hereinafter defined.

The following examples describe in detail certain of the compounds illustrative of the present invention and methods which have been devised for their manufacture. However, the invention is not to be construed as limited thereby, either in spirit or in scope, since it will be apparent to those skilled in the art of organic synthesis that many modifications, both of materials and of methods, may be practiced without departing from the purpose and intent of this disclosure. In the examples hereinafter-detailed, temperatures are given in degrees centigrade (°C.), pressures in millimeters (mm.) of mercury, and relative amounts of materials in parts by weight, except as otherwise noted. Specific rotations refer to the D line of sodium and were determined in methyl alcohol solution at room temperature.

**EXAMPLE 1**

3-methyl-2-phenyl-4-succinimidomethylmorpholine.—To a solution of 9 parts of succinimide in 80 parts of absolute ethanol is added 8 parts of 3-methyl-2-phenylmorpholine and 18 parts of 36% formalin. The mixture is heated at approximately 90° C. for 1 hour, whereupon sufficient water is introduced to produce turbidity. Crystallization occurs on cooling and standing. The product thrown down is filtered off and recrystallized from cyclohexane to give 3-methyl-2-phenyl-4-succinimidomethylmorpholine, which melts at 127°-130° C. (corr.). The product has the formula

![Chemical structure](image)

**EXAMPLE 2**

3-methyl-2-phenyl-4-phthalimidomethylmorpholine.—To 5 parts of phthalimide dissolved in 80 parts of warm absolute ethanol is added 3 parts of 3-methyl-2-phenylmorpholine and 7 parts of 36% formalin. The reactants are heated at temperatures in the neighborhood of 90° C. for approximately 45 minutes, following which they are chilled and left to stand until crystallization. The solid precipitate which forms is filtered off and extracted with hot cyclohexane. Unchanged phthalimide remains insoluble and is removed by filtration. From the filtrate, on cooling, 3-methyl-2-phenyl-4-phthalimidomethylmorpholine precipitates as a crystalline solid, which melts at 142°-144° C. (corr.). The product has the formula

![Chemical structure](image)

**EXAMPLE 3**

(A) 3-methyl-2-phenyl-4-(2-succinimidomethyl)-morpholine.—To a solution of 8 parts of 3-methyl-2-phenylmorpholine and 9 parts of N-(2-bromoethyl)succinimide in 40 parts of butanone is added 3 parts of powdered anhydrous potash. The mixture is heated, with agitation, at the boiling point of the solvent under reflux for 46 hours, whereupon it is freed of insoluble matter by filtration and stripped of solvent by distillation. The oily residue is taken up in dilute muriatic acid. The acid solution is washed with ether, then saturated with an excess of potash. The material thus salted out is extracted into a mixture of chloroform and ether, following which solvent is removed by distillation, leaving a residue which is extracted with ethanol. Evaporation of alcohol from the ethanol extract leaves pure 3-methyl-2-phenyl-4-(2-succinimidomethyl)morpholine, the formula of which is

![Chemical structure](image)

(B) 3-methyl-2-phenyl-4-(2-succinimidomethyl)-morpholine hydrochloride.—Addition of a very slight excess of 2-propanolic hydrogen chloride to the base of the foregoing Part A of this example converts it to the hydrochloride, which is induced to crystallize by addition of ether. The 3-methyl-2-phenyl-4-(2-succinimidomethyl)morpholine hydrochloride thus obtained melts at 287°-289° C. (corr.).

**EXAMPLE 4**

(A) 3-methyl-2-phenyl-4-(2-phthalimidoethyl)-morpholine.—A solution of 13 parts of N-(2-bromomethyl)phthalimide and 9 parts of 3-methyl-2-phenylmorpholine in 5 parts of triethylamine is heated, with agitation, at the boiling point under reflux for 11 hours. The reactants are then filtered and stripped of solvent by distillation. The residue is extracted with dilute muriatic acid and the acid solution washed with ether. The solution is then basified with potash, and the resultant mixture extracted with ether. The ether extract is dried over anhydrous potash, following which solvent is evaporated. The residue is 3-methyl-2-phenyl-4-(2-phthalimidoethyl)morpholine, of the formula

![Chemical structure](image)

(B) 3-methyl-2-phenyl-4-(2-phthalimidoethyl)morpholine hydrochloride.—3-methyl-2-phenyl-4-(2-phthalimidoethyl)morpholine is converted to the hydrochloric acid addition salt by dissolution in absolute ethanol followed by addition of a very slight excess of 2-propanolic hydrogen chloride. Addition of anhydrous ether induces
crystallization. Recrystallization from a mixture of ethanol and ether affords 3-methyl-2-phenyl-4-(2-phthalimidoethyl)morpholine hydrochloride melting at 247-251°C. (corr.)

EXAMPLE 5

(A) N-(5-bromopentyl)succinimide. —To a solution of 20 parts of succinimide in 160 parts of absolute ethanol is added a solution of 5 parts of sodium in 110 parts of absolute ethanol. Solvent is removed by distillation at reduced pressures, and to the solid residue is added 159 parts of 1,5-dibromopentane. The resultant mixture is heated at 135-145°C under reflux overnight, then cooled to room temperature and filtered. The filtrate is distilled in vacuo to remove excess dibromopentane. The residue, a viscous oil, is extracted with a mixture of heptanes boiling in the range 77-115°C. Removal of solvent by distillation leaves as a residue the desired N-(5-bromopentyl)succinimide.

(B) 3-methyl-2-phenyl-4-(5-succinimidopentyl)morpholine. —A mixture of 14 parts of 3-methyl-2-phenyl-4-(5-succinimidopentyl)morpholine, 11 parts of anhydrous powdered potash, and 80 parts of butanone is heated at the boiling point of the solvent under reflux with agitation for 24 hours. Insoluble matter is then removed by filtration, following which solvent is evaporated at 90-100°C, leaving a brown oil. The oil is taken up in dilute aqueous amyl alcohol, whereupon the acid solution is washed with ether to remove neutral material. Alkalization with aqueous 25% caustic soda and ether extraction of the resulting mixture affords, on evaporation of solvent, pure 3-methyl-2-phenyl-4-(5-succinimidopentyl)morpholine, the formula of which is

![Formula](CSP -CH3 O &HCHCHCHCH-N Y O (C) 3 - methyl-2-phenyl-4-(5-succinimidopentyl)morpholine hydrochloride)

The succinimidopentylmorpholine of the preceding Part B of this example is converted to the corresponding hydrochloride with an excess of 2-propanolic hydrogen chloride. Recrystallization from a mixture of ethanol and ether gives 3-methyl-2-phenyl-4-(5-succinimidopentyl)morpholine hydrochloride melting in the range 167.5-173°C. (corr.)

EXAMPLE 6

(A) Levo-2-(2-hydroxyethylamino)-1-phenylpropanol.—To 49 parts of levo-1-hydroxy-1-phenylpropanone (specific rotation, -248°) in 160 parts of absolute ethanol is added 20 parts of 2-aminoethanol and 1 part of platinum oxide catalyst. The resultant mixture is subjected to low pressure hydrogenation, which is terminated when 1 equivalent of hydrogen is absorbed. Catalyst is then removed by filtration and solvent thereupon distilled, leaving as an oily residue the desired levo-2-(2-hydroxyethylamino)-1-phenylpropanol.

(B) Dextro-3-methyl-2-phenylmorpholine. —To the levo-2-(2-hydroxyethylamino)-1-phenylpropanol obtained in the foregoing Part A of this example is cautiously added, with agitation and external cooling, 118 parts of concentrated sulfuric acid. The resultant solution is heated at 90-95°C for 2 hours and then neutralized with aqueous 25% caustic soda, internal temperature being maintained below 40°C during the neutralizing operation. The product is extracted with ether and the ether extract dried over anhydrous potash. Solvent is removed by distillation, leaving as a residue dextro-3-methyl-2-phenylmorpholine boiling at 89°C under 1.0 mm. pressure. The product has a specific rotation of +22.2°.

The corresponding hydrochloride, obtainable upon treatment with a slight excess of 2-propanolic hydrogen chloride, melts at 193.5-196°C. (corr.)

(C) Dextro-3-methyl-2-phenyl-4-(5-succinimidomethyl)morpholine. —To 8 parts of succinimide dissolved in 20 parts of absolute ethanol is added 12 parts of dextro-3-methyl-2-phenylmorpholine (specific rotation, +22.2°) and approximately 11 parts of 36% formalin. The mixture is heated at the boiling point of the solvent under reflux for 1 hour, then filtered hot and set aside to crystallize. The product thrown down is dextro-3-methyl-2-phenyl-4-(5-succinimidomethyl)morpholine melting at 125-134°C (corr.) and having a specific rotation of +8.79°.

What is claimed is:

1. A compound of the formula

   ![Chemical Structure](lower alkylamine-Z)

   wherein Z is a member of the group consisting of radicals of the formulas

   ![Chemical Structures](2. 3-methyl-2-phenyl-4-succinimidomethylmorpholine. 3. 3-methyl-2-phenyl-4-phthalimidomethylmorpholine. 4. 3-methyl-2-phenyl-4-(2-succinimidodithiophenyl)morpholine. 5. 3-methyl-2-phenyl-4-(2-phthalimidodithiophenyl)morpholine. 6. Dextro-3-methyl-2-phenyl-4-succinimidomethylmorpholine.

References Cited in the file of this patent