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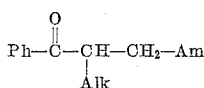
3,151,124

ALPHA OXY-BETA ALKYL-GAMMA TERTIARY AMINO-ALPHA PHENYL PROPANES

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7 Claims. (Cl. 260—326.5)

The present invention concerns ketones, particularly 1-lower alkyl-2-tertiary amino-ethyl monocyclic carbocyclic aryl ketones, salts N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, as well as process for the preparation of these compounds.

More especially, the invention relates to compounds of the formula



in which Ph is a monocyclic carbocyclic aryl radical, Alk stands for lower alkyl having from three to five carbon atoms, and Am is a tertiary amino group, salts, N-oxides, salts of N-oxides or quaternary ammonium derivatives thereof, as well as process for the manufacture of these compounds.

The monocyclic carbocyclic aryl radical Ph is represented by phenyl or phenyl substituted by lower alkyl, hydroxyl, etherified hydroxyl, esterified hydroxyl, nitro, amino, trifluoromethyl or any analogous substituent. Substituted phenyl groups are, for example, (lower alkyl)-phenyl, in which lower alkyl has preferably from one to six carbon atoms, e.g. 2-methyl-phenyl, 4-methyl-phenyl, 3-ethyl-phenyl, 4-isopropyl-phenyl, 4-tertiary butyl-phenyl, 2,4-dimethyl-phenyl, 2,5-dimethyl-phenyl and the like, (hydroxy)-phenyl, e.g. 3-hydroxy-phenyl, 4-hydroxy-phenyl and the like, (etherified hydroxy)-phenyl, such as (lower alkoxy)-phenyl, in which lower alkoxy has preferably from one to six carbon atoms, e.g. 2-methoxy-phenyl, 4-methoxy-phenyl, 4-ethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,4,5-trimethoxy-phenyl, 4-i-propyloxy-phenyl, 4-n-butyloxy-phenyl, 4-isopentyloxy-phenyl and the like, (lower alkenyloxy)-phenyl, in which alkenyl has preferably from two to six carbon atoms, e.g. 2-allyloxy-phenyl, 4-allyloxy-phenyl, 3-(2-butenyloxy)-phenyl and the like, (lower alkylenedioxy)-phenyl, e.g. 3,4-methylenedioxy-phenyl, 3,4-(1,1-ethylenedioxy)-phenyl and the like, or any other (etherified hydroxyl)-phenyl, (esterified hydroxy)-phenyl, such as (lower alkoxy-carbonyloxy)-phenyl, e.g. 3-methoxycarbonyloxy-phenyl, 4-ethoxycarbonyloxy-phenyl and the like, (lower alkanoyloxy)-phenyl, e.g. 3-acetoxy-phenyl, 4-propionyloxy-phenyl and the like, (halogeno)-phenyl (halogeno representing a hydroxyl group esterified with a hydrohalic acid), e.g. 4-fluoro-phenyl, 2-chloro-phenyl, 4-chloro-phenyl, 3-bromophenyl, 3,4-dichloro-phenyl, 2,5-dibromo-phenyl and the like, or any other (esterified hydroxy)-phenyl group, (mercapto)-phenyl, e.g. 4-mercapto-phenyl and the like, (etherified mercapto)-phenyl, such as (lower alkyl-mercapto)-phenyl, e.g. 4-methylmercapto-phenyl, 3-ethylmercapto-phenyl and the like, (nitro)-phenyl, e.g. 4-nitrophenyl and the like, (amino)-phenyl, particularly (tertiary amino)-phenyl, such as (N,N-di-lower alkyl-amino)-phenyl, e.g. 4-N,N-dimethylamino-phenyl, 3-N,N-diethylamino-phenyl and the like, (trifluoromethyl)-phenyl, e.g. 4-trifluoromethyl-phenyl and the like, or any other suitable substituted phenyl radical, which has one or more than one of the same or of different substituents in any of the positions available for substitution.

The group Alk is lower alkyl having from three to five carbon atoms, which may be arranged in a straight or branched carbon chain. It stands primarily for n-

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propyl, as well as isopropyl, n-butyl, secondary butyl, tertiary butyl, n-pentyl, isopentyl, neopentyl and the like.

The tertiary amino group is represented, for example, by N,N-di-substituted amino, particularly by N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino, N-ethyl-N-methylamino, N,N-diethylamino, N,N-di-n-propylamino and the like, as well as by N-cycloalkyl-N-lower alkyl-amino, e.g. N-cyclopentyl-N-methyl-amino, N-cyclohexyl-N-ethyl-amino and the like, N-lower alkyl-N-phenyl-lower alkyl-amino, e.g. N-benzyl-N-methyl-amino, N-methyl-N-(2-phenyl-ethyl)-amino and the like, or any other N,N-di-substituted amino group, such as (for example, N-hydroxy-lower alkyl-N-lower alkyl-amino, e.g. N-ethyl-N-(2-hydroxyethyl)-amino and the like, N,N-di-hydroxy-lower alkyl-amino, e.g. N,N-di-(2-hydroxyethyl)-amino and the like. The tertiary amino group Am may also stand for N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms, e.g. 1-pyrrolidino, 1-piperidino, 2-methyl-1-piperidino, 1-N,N-(1,6-hexylene)-imino, 1-N,N-(1,7-heptylene)-imino and the like. Other tertiary amino groups are, for example, N,N-oxa alkylene-imino, in which alkylene has preferably four carbon atoms, e.g. 4-morpholino and the like, N,N-thia-alkylene-imino, in which alkylene has primarily four carbon atoms, e.g. 4-thiamorpholino and the like, or N,N-aza-alkylene-imino, in which alkylene has from four to six carbon atoms, and in which the aza-nitrogen atom may be substituted, for example, by lower alkyl, hydroxy-lower alkyl, esterified hydroxy-lower alkyl, acyl, such as lower alkanoyl or carbo-lower alkoxy and the like; N,N-aza-alkylene-imino groups are, for example, piperazino, 4-lower alkyl-piperazino, e.g. 4-methyl-1-piperazino, 4-ethyl-1-piperazino and the like, 4-hydroxy-lower alkyl-piperazino, e.g. 4-(2-hydroxy-ethyl)-1-piperazino and the like, 4-(2-lower alkanoyloxy-ethyl)-1-piperazino, e.g. 4-(2-acetyloxyethyl)-1-piperazino and the like, 4-lower alkanoyl-1-piperazino, e.g. 4-acetyl-1-piperazino and the like, 4-carbo-lower alkoxy-1-piperazino, e.g. 4-carbethoxy-1-piperazino and the like, as well as other 1-N,N-(N-lower alkyl-aza-alkylene)-imino groups, such as, for example, 1-N,N-(3-aza-3-methyl-1,6-hexylene)-imino, 1-N,N-(4-aza-4-methyl-1,7-heptylene)-imino and the like.

Salts of the compounds of this invention are particularly pharmaceutically acceptable, non-toxic acid addition salts with inorganic acids, e.g. hydrochloric, hydrobromic, nitric, sulfuric, phosphoric acid and the like, with organic carboxylic acids, e.g. acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, hydroxymaleic, dihydroxymaleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, salicylic, 4-amino-salicylic, 2-phenoxybenzoic, 2-acetoxybenzoic acid and the like, or with organic sulfonic acids, e.g. methane sulfonic ethane sulfonic, 2-hydroxyethane sulfonic, benzene sulfonic, p-toluene sulfonic acid and the like.

The compounds of this invention may also be in the form of their N-oxides or the salts of such N-oxides.

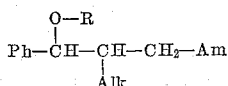
Quaternary ammonium derivatives of the compounds of this invention are particularly those with reactive esters formed by hydroxylated compounds with strong acids, especially those with lower alkyl halides, e.g. methyl, ethyl, propyl or isopropyl chloride, bromide or iodide and the like, di-lower alkyl sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, lower alkyl lower alkane sulfonates, e.g. methyl or ethyl methane or ethane sulfonate and the like, lower alkyl hydroxy-lower alkane sulfonates, e.g. methyl 2-hydroxy-ethane sulfonate and the like, lower alkyl aryl sulfonates, e.g. methyl p-toluene sulfonate and the like, phenyl-lower alkyl halides, e.g. benzyl, 1-phenylethyl or 2-phenylethyl chloride, bromide or iodide and the like, or any other suitable reactive esterified hydroxyl compounds. Also included as quaternary ammonium compounds are the quaternary am-

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monium hydroxides, and the salts obtained by reacting such quaternary ammonium hydroxides with inorganic or organic acids, such as those used hereinabove for the preparation of the acid addition salts.

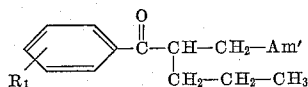
The compounds of this invention produce an increase in coordinated motor activity in the unanesthetized dog, which effect is of considerable duration. They also antagonize sedation induced by administering tranquilizer-type sedatives; the antagonism becomes evident a short period after administration and is noticeable over an appreciable period. In view of these stimulating effects the compounds of this invention can be used as stimulating agents to counteract excessive fatigue, lack of concentration, depressive states and the like, as well as in the treatment of barbiturate poisoning, or for the shortening of the recovery time after anesthesia.

The compounds of this invention may also be used as intermediates for the preparation of over pharmacologically active compounds. Upon reduction of the carbonyl group and, if desired, conversion of a resulting hydroxyl group into an esterified hydroxyl group according to methods described hereinbelow, they may be converted into compounds having the following formula:

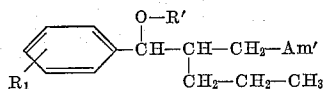


in which Ph, Alk and Am have the previously-given meaning, and R is hydrogen of the acyl radical of an organic carboxylic acid, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof. The group R in the above formula, which also stands for hydrogen, may be the acyl radical of a lower aliphatic carboxylic acid, such as, for example, a lower alkyl carbonic acid, e.g. methyl carbonic, ethyl carbonic acid and the like, carbamic acid an N-lower alkyl-carbamic acid, e.g. N-methyl-carbamic, N-ethyl-carbamic acid and the like, or, above all, a lower alkanolic acid, e.g. acetic, propionic, butyric, pivalic acid and the like, as well as any other suitable organic carboxylic acid, e.g. cyclohexane carboxylic, β -cyclopentyl propionic, benzoic, 3,4,5-trimethoxybenzoic, phenylacetic, nicotinic, isonicotinic acid and the like. These compounds also have stimulating properties, and, in addition, show analgesic effects; they can, therefore, be used as stimulants and/or as analgesics for the relief of pain.

Particularly useful as central nervous system stimulants are the compounds of the formula



in which R₁ is hydrogen, lower alkyl having from one to four carbon atoms, lower alkoxy having from one to four carbon atoms, halogeno having an atomic weight between 18 and 80, or trifluoromethyl, and Am' stands for N,N-di-lower alkyl-Amino, in which lower alkyl has from one to four carbon atoms, or N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms or pharmaceutically acceptable, non-toxic acid addition salts thereof. When used as intermediates, these compounds furnished the preferred group of compounds having the formula

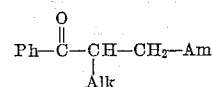


in which R₁ and Am' have the previously-given meaning, and R' is hydrogen or lower alkanoyl, and the pharmaceutically acceptable, non-toxic acid addition salts thereof, which shows CNS-stimulating, as well as analgesic properties.

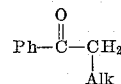
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The new compounds of this invention may be used in the form of pharmaceutical preparations, which contain the new compounds or the derivatives thereof, in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral or parenteral administration. For making up the preparations there can be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols or any other inert carrier used in pharmaceutical preparations. These may be in solid form, for example, as capsules, tablets, dragees and the like, or in liquid form, for example, as solutions, suspensions, emulsions and the like. If necessary, they may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying 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 having the formula



in which Ph, Alk and Am have the previously-given meaning, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, may be prepared according to per se conventional methods. For example, they are formed by reacting a ketone of the formula



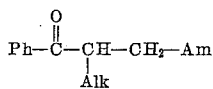
in which Ph and Alk have the previously-given meaning, with an amine of the formula H—Am, in which Am has the previously-given meaning, or a salt thereof, in the presence of formaldehyde or a reactive derivative thereof, and, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting compound into a salt, an N-oxide or a quaternary ammonium compound thereof, and/or, if desired, converting an N-oxide into a salt thereof, and/or, if desired, converting a resulting quaternary ammonium compound into another quaternary ammonium compound, and/or, if desired, separating a mixture of isomers into the single isomers.

The above reaction of the starting material with the amine in the presence of formaldehyde or a reactive derivative thereof is carried out according to the procedure known as the Mannich Reaction, which is described, for example, in detail by F. F. Blicke in Organic Reactions, volume 1, page 303 (Wiley, 1942). The salt of an amine of the formula H—Am is an acid addition salt, particularly the salt with a mineral acid, e.g. hydrochloric, hydrobromic, sulfuric acid and the like. Reactive derivatives of formaldehyde are those furnishing formaldehyde under the conditions of the reaction; such derivatives are, for example, polymeric derivatives of formaldehyde, e.g. paraformaldehyde, trioxane and the like, acetals of formaldehyde with lower alkanols, e.g. dimethoxymethane, diethoxymethane and the like, hexamethylenetetramine or any other suitable formaldehyde-furnishing reagent. The reaction is preferably carried out in the presence of an inert solvent, for example, a lower alkanol, e.g. ethanol and the like, preferably at an elevated temperature, and, if necessary, in the presence of a small amount of an acid, such as a mineral acid, e.g. hydrochloric, sulfuric acid and the like, and/or, in a closed vessel, and/or, in the atmosphere of an inert gas, e.g. nitrogen.

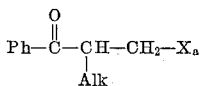
The starting materials are known and can be prepared according to per se conventional methods.

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The compounds of this invention having the formula



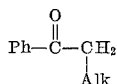
in which Ph, Alk and Am have the previously-given meaning, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, may also be prepared by reacting a compound of the formula



in which Ph and Alk have the previously-given meaning, and X_a is a reactive esterified hydroxyl group, with an amine of the formula $\text{H}-\text{Am}$ in which Am has the above-given meaning, and, if desired, carrying out the optional steps.

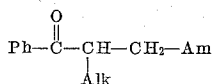
The reactive esterified hydroxyl group X_a stands primarily for halogeno (representing a hydroxyl group esterified with a hydrochloric acid), e.g. chloro, bromo and the like, as well as an organic sulfonyloxy group, e.g. p-toluene sulfonyloxy and the like. The above reaction between the reactive ester and the amine is carried out according to per se conventional methods, preferably by maintaining an excess of the amine, which may simultaneously serve as a base to bind the generated acid. The latter may also be neutralized by adding another alkaline reagent, e.g. sodium carbonate, potassium carbonate and the like. The reaction is preferably completed at an elevated temperature, if desired, in the presence of an inert solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like, or any other suitable diluent, and/or, in a closed vessel, and/or in the atmosphere of an inert gas, e.g. nitrogen.

The starting materials may be prepared according to methods known per se, for example, by introducing into the α -position of a compound of the formula



in which Ph and Alk have the previously-given meaning, a carbo-lower alkoxy group, e.g. carbethoxy and the like (for example, by treatment of an alkali metal compound of the ketone with a lower alkyl orthoformate, e.g. ethyl orthoformate and the like) or a hydroxy-methylene group (for example, by treating an alkali metal compound of the ketone with a lower alkyl formate, e.g. ethyl formate and the like). In a resulting compound, the carbo-lower alkoxy (if necessary, after hydrolysis to the free carboxyl group) or the hydroxy-methylene group is then converted into a hydroxy-methyl group by reduction, for example, by treatment with a hydride reagent, e.g. lithium aluminum hydride and the like, or any other suitable reduction procedure, such as catalytic hydrogenation, electrolytic reduction and the like. The free hydroxyl group of the hydroxy-methyl group is then replaced by the desired reactive esterified hydroxyl group, for example, by halogeno (e.g. by treatment with a thionyl halide, e.g. thionyl chloride and the like), or by an organic sulfonyloxy group (e.g. by esterification with an organic sulfonic acid halide, e.g. p-toluene sulfonic acid chloride and the like, preferably in the presence of a base, e.g. pyridine and the like).

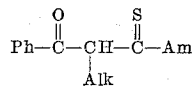
The compounds of the formula



in which Ph, Alk and Am have the previously-given meaning, salts, N-oxides, salts of N-oxides or quaternary

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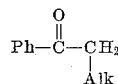
ammonium compounds thereof, may also be prepared by converting in a compound of the formula



in which Ph, Alk and Am have the previously-given meaning, the thiocarbonyl group into methylene, and, if desired, carrying out the optional steps.

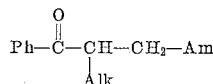
The replacement of the thiono group by two hydrogen atoms is carried out according to known methods, for example, by treatment with freshly prepared Raney nickel or any other hydrogenation catalyst, in the presence of a suitable solvent, such as a lower alkanol, e.g. methanol, ethanol and the like.

The starting materials used in the above reaction may be prepared, for example, by introducing into the α -position of a compound of the formula

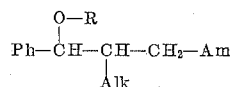


in which Ph and Alk have the previously-given meaning, a carbo-lower alkoxy group, e.g. carbethoxy and the like (according to the previously-described procedure), reacting the resulting compound having a carbo-lower alkoxy group, e.g. carbethoxy and the like, in the α -position, with an amine of the formula $\text{H}-\text{Am}$, in which Am has the above-given meaning, and converting in a resulting compound the carbamyl group in the α -position into a thiocarbamyl group (for example, by treatment with phosphorus pentasulfide and the like).

As previously mentioned, the compounds of the formula



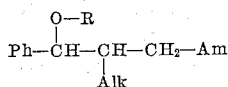
in which Ph, Alk and Am have the previously-given meaning, may serve as intermediates for the preparation of the compounds having the formula



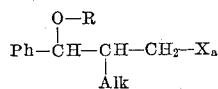
in which Ph, Alk, Am and R have the previously-given meaning; the latter compounds, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, may be obtained by reducing in the starting material having the above formula the carbonyl group into a carbinol group, and, if desired, converting in a resulting compound the free carbinol group into an esterified carbinol group, and/or, if desired, carrying out the optional steps.

Reduction of the carbonyl group is carried out according to conventional methods, for example, with a hydride reagent, such as lithium aluminum hydride, sodium borohydride and the like, which reagents may be used in the presence of an activator, such as aluminum chloride and the like. Other methods suitable for the conversion of the carbonyl group into a carbinol group are, for example, treatment with certain metal lower alkanolates, e.g. aluminum isopropanolate and the like, which are used according to the Meerwein-Ponndorf-Verley method (A. L. Wilds, Organic Reactions, volume 2, page 178, Wiley, 1944), reaction with certain metals in the presence of an acid or a base, for example, iron in the presence of aqueous acetic acid, zinc in the presence of sodium hydroxide in ethanol and the like, catalytic hydrogenation using Raney nickel, palladium preparations and the like, as the catalysts, electrolytic reduction or any other suitable reagent.

The compounds of the formula

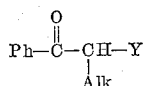


in which Ph, Alk, Am and R have the previously-given meaning, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, may also be prepared by reacting a compound of the formula



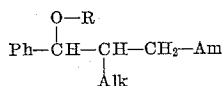
in which Ph, Alk, R and X_a have the previously-given meaning, with an amine of the formula $\text{H}-\text{Am}$, in which Am has the previously-given meaning, and, if desired carrying out the optional steps.

The above reaction is carried out according to the previously-described method. The starting materials used in the reaction may be obtained, for example, by converting in a compound having the formula

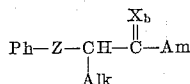


in which Ph and Alk have the above-given meaning, and Y stands for a group of the formula $-\text{CH}-\text{X}_a$, in which X_a is a reactive esterified hydroxyl group, or a carbinol group or a group capable of being converted into a carbinol group (such as a carbo-lower alkoxy group, e.g. carbethoxy and the like, a hydroxymethylene group and the like), the carbonyl group into a carbinol group (for example, according to one of the reduction methods previously described), and, if necessary, converting in a resulting compound, in which Y stands for a group capable of being converted into a carbinol group, such group into a carbinol group (for example, by one of the reduction methods previously described), and/or, if necessary, converting in a resulting compound, in which the group Y is a carbinol group, such carbinol group into the group of the formula $-\text{CH}_2-\text{X}_a$, in which X_a is a reactive esterified group (for example, by treatment with a thionyl halide, e.g. thionyl chloride and the like, or with an organic sulfonyl halide, e.g. chloride and the like, according to the previously-shown procedure), and, if desired converting in a resulting compound the secondary carbinol group adjacent to the monocyclic carbocyclic aryl group into an esterified carbinol group (according to the procedure described below).

The compounds of the formula



in which Ph, Alk, Am and R have the previously-given meaning, salts, N-oxides, salts of N-oxides and quaternary ammonium compounds thereof, may also be prepared by converting in a compound having the formula



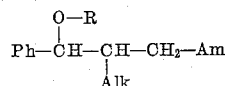
in which Ph, Alk and Am have the previously-given meaning, Z stands for a carbinol group, an esterified carbinol group or a carbonyl group, and X_b is oxygen or sulfur, the group of the formula $>\text{C}=\text{X}_b$ into methylene, and, if necessary, converting in a resulting compound having a carbonyl group, such carbonyl group into a carbinol group, and, if desired, carrying out the optional steps.

A group of the formula $>\text{C}=\text{X}_b$, in which X_b stands for oxygen, represents the carbonyl portion of the amide grouping, which is converted into a methylene group according to known methods, for example, by treatment with a suitable hydride reagent, e.g. lithium aluminum

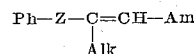
hydride and the like. In starting materials having a carbonyl group Z, such carbonyl group may be reduced simultaneously to the desired carbinol group. A group of the formula $>\text{C}=\text{X}_b$, in which X_b is sulfur, is the thio-carbonyl portion of a thioamide grouping, which is converted into methylene according to the previously-mentioned method, involving, for example, desulfurization with Raney nickel or any other suitable hydrogenation catalyst. Desulfurization may also be achieved by electrolytic hydrogenation according to per se known methods. If necessary, the carbonyl group Z may have to be converted into the desired carbinol group according to one of the previously described methods.

The starting materials used in the above reaction are prepared as previously shown. If desired, a carbonyl group Z is converted into the carbinol group using one of the previously-described reduction methods, which do not attack the carbonyl or thiocarbonyl portion of an amide and a thioamide grouping, respectively, and, if desired, a resulting carbinol group may be converted into an esterified group as will be shown hereinbelow.

The compounds of the formula



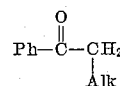
in which Ph, Alk, Am and R have the previously-given meaning, salts, N-oxides, salts of N-oxides or quaternary ammonium compounds thereof, may also be prepared, for example, by reducing the double bond in a compound of the formula



in which Ph, Alk, Am and Z have the previously-given meaning, into a single bond, and, if desired, carrying out the optional steps.

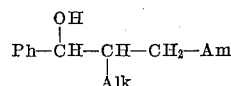
Reduction of the double bond is carried out as previously-described (for example, by treatment with a suitable hydride, catalytically activated hydrogen and the like). In a starting material having a carbonyl group Z, such carbonyl group is simultaneously converted into a carbinol group.

The starting materials are prepared, for example, by introducing into a compound of the formula

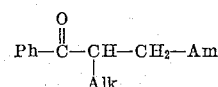


in which Ph and Alk have the previously-given meaning, a hydroxy-methylene group according to the previously-described method (for example, by reacting an alkali metal compound of the ketone with a lower alkyl formate), and reacting the resulting compound having a hydroxy-methylene group in α -position to the carbonyl group, with an amine of the formula $\text{H}-\text{Am}$, in which Am has the previously-given meaning, and, if desired, converting the carbonyl group adjacent to the monocyclic carbocyclic aryl portion Ph, into a carbinol group (for example, by reduction according to the Meerwein-Ponndorf-Verley method), and the latter into an esterified carbinol group by esterification (for example, as shown hereinbelow).

In view of the fact that the compounds of the formula



in which Ph, Alk and Am have the above-given meaning, may be prepared independently from the compounds having the formula



in which Ph, Alk and Am have the previously-given meaning, they may also serve as starting materials; they can be converted into the latter by oxidizing the carbinol group into a carbonyl group, and, if desired, carrying out the optional steps.

Oxidation of the carbinol into the carbonyl group is carried out according to known methods, for example, by treatment with an oxidation reagent containing hexavalent chromium, e.g. potassium dichromate and the like, with aluminum tertiary butanolate according to the Oppenauer oxidation reaction as described, for example, by C. Djerassi, *Organic Reactions*, volume 6, page 207 (Wiley, 1951), or any other oxidation method suitable for the conversion of a carbinol into a carbonyl group.

In a resulting compound having a free carbinol group adjacent to the monocyclic carbocyclic aryl group pH, such carbinol group may be converted into an esterified carbinol group according to known methods. Esterification may be achieved, for example, by treatment with a suitable functional derivative of an acid, such as an organic carboxylic acid halide, particularly an organic carboxylic acid chloride (which may be used in the presence of an inert solvent, such as, for example, benzene, toluene, hexane and the like, and, if necessary, in the presence of a suitable base, e.g. pyridine, N,N,N-triethylamine and the like), an organic carboxylic acid anhydride (which is preferably used in the presence of a suitable base or acid and, if necessary, of an inert diluent), a ketene (which is used in the presence of an inert solvent) or any other esterification reagent.

Depending on the conditions used, the compounds of this invention are obtained in the form of the free bases or the salts thereof. A salt may be converted into the free base, for example, by reaction with a hydroxy ion exchange resin or an alkaline reagent, such as an alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, an alkali metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, ammonia or any other suitable basic reagent.

A resulting salt may be converted directly into other salts, for example, by reacting it with a metal, particularly an alkali metal, salt of an acid or a suitable anion exchange resin. For example, a resulting hydrobromide may be converted into the hydrochloride or the maleate by treatment with sodium chloride and the monosodium salt of maleic acid, respectively.

A free base may be converted into an acid addition salt by reaction with one of the inorganic or organic acids described hereinbefore, for example, by treating a solution of the base in a suitable solvent with the acid or a solution thereof. The salts may also be obtained as the hemihydrates, monohydrates, sesquihydrates or polyhydrates depending on the conditions used in the formation of the salts.

N-oxides of the compounds of this invention may be prepared by treatment of the free base in an inert solvent with an N-oxidizing reagent, such as hydrogen peroxide, an inorganic peracid, such as persulfuric acid, or, more particularly, an organic peracid, e.g. peracetic, perbenzoic, monoperothalic acid and the like. Resulting N-oxides may be converted into their acid addition salts according to the above-described procedure.

The quaternary ammonium derivatives of the compounds of this invention may be obtained, for example, by reacting the tertiary base with an ester formed by a hydroxylated compound and a strong inorganic or organic acid. Suitable quaternizing reagents are, for example, 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, 1-phenylethyl or 2-phenylethyl chloride or bromide and the like, di-lower alkyl sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, or lower alkyl monocyclic carbocyclic aryl sulfonates, e.g. methyl p-toluene sulfonate and the like. The qua-

ternizing reaction may be performed in the absence or presence of an inert solvent, under cooling, at room temperature or at an elevated temperature, at atmospheric pressure or in a closed vessel under pressure, and, if desired, in the atmosphere of an inert gas, e.g. nitrogen.

Quaternary ammonium compounds obtained may be converted into 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 exchanger, by electrodialysis or any other suitable procedure. From any resulting quaternary ammonium base there may be prepared quaternary ammonium salts by reacting the former with an acid, for example, with one of those used for the preparation of the acid addition salts, or with a mono-lower alkyl sulfate, e.g. methyl sulfate, ethyl sulfate and the like. A quaternary ammonium compound may also be converted directly into another quaternary ammonium salt without the formation of the quaternary ammonium hydroxide; for example, a quaternary ammonium iodide may be reacted with freshly prepared silver chloride to yield the quaternary ammonium chloride, or a quaternary ammonium iodide may be converted into the corresponding chloride by treatment with hydrochloric acid in anhydrous methanol, or upon treatment with an anion exchange resin, the anion in a quaternary ammonium salt may be exchanged by another anion. Quaternary ammonium compounds may also crystallize as the hydrates.

Compounds of this invention may be obtained as mixtures of diastereoisomeric forms, which may be separated into the individual racemic compounds on the basis of physico-chemical differences, such as solubility, for example, by fractionated crystallization.

Racemates of compounds of this invention may be resolved into the optically active d- and l-forms according to procedures used for the resolution of racemic compounds. For example, the free base of a racemic d,l-compound in an inert solvent may be treated with one of the optically active forms of an acid having at least one asymmetric carbon atom. Especially useful as optically active forms of salt-forming acids having an asymmetric carbon atom are D-tartaric (l-tartaric) and L-tartaric (d-tartaric) acid, as well as the optically active forms of di-o-toluytl-tartaric, malic, mandelic, camphor-10-sulfonic, quinic acid and the like. A salt may then be isolated, which is formed by the optically active acid with one of the optically active forms of the base, and may be converted into the optically active base according to known methods, such as those mentioned hereinabove.

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.

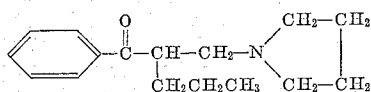
In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

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

Example 1

A mixture of 78 g. of valerophenone, 5.38 g. of pyrrolidine hydrochloride, and 19.5 g. of paraformaldehyde in 100 ml. of ethanol containing 1 ml. of concentrated hydrochloric acid is refluxed for twelve hours. The solvent is then evaporated, the residue is taken up in water, and the aqueous solution, after being extracted with diethyl ether, is made basic with aqueous ammonia. The organic material is extracted with diethyl ether, and the organic solution is dried over magnesium sulfate and evaporated. The residue is distilled to yield the α -n-

propyl- β -(1-pyrrolidino)-propiophenone of the formula

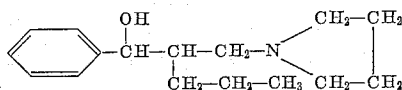


which is collected at B.P. 132–136/0.7 mm.; yield: 49 g.

Other compounds prepared according to the above procedure are, for example, α -isopropyl- β -(1-pyrrolidino)-propiophenone, B.P. 125–130°/0.6 mm.; β -N,N-diethyl-amino- α -n-propyl-propiophenone, B.P. 100–200°/0.15 mm.; p-bromo- α -n-propyl- β -(1-pyrrolidino)-propiophenone, B.P. 155–158°/0.15 mm.; p-methoxy- α -n-propyl- β -(1-pyrrolidino)-propiophenone, B.P. 158–160°/0.2 mm.; β -N,N-dimethylamino- α -n-propyl-propiophenone, which is converted into its hydrochloride, M.P. 157–158° after recrystallization from a mixture of ethanol and diethyl ether; α -n-propyl- β -(1-piperidino)-propiophenone, B.P. 123–125°/0.3; p-fluoro- α -n-propyl- β -(1-pyrrolidino)-propiophenone, which is converted into its hydrochloride, M.P. 161–163° after recrystallization from a mixture of ethanol and diethyl ether; p-chloro- α -n-propyl- β -(1-pyrrolidino)-propiophenone, which is converted into its hydrochloride, M.P. 160–163° after recrystallization from a mixture of ethanol and diethyl ether; β -[1-N,N-(1,6-hexylene)-imino]- α -n-propyl-propiophenone, B.P. 132–133°/0.15 mm.; β -[1-N,N-(1,7-heptylene)-imino]- α -n-propyl-propiophenone, B.P. 147–149°/0.25 mm.; p-methyl- α -n-propyl- β -(1-pyrrolidino)-propiophenone, B.P. 133–135°/0.25 mm., the hydrochloride of which melts at 152–154° after recrystallization from a mixture of ethanol and diethyl ether, and the like. Upon treatment of the above compounds, such as of α -n-propyl- β -(1-pyrrolidino)-propiophenone, with methyl iodide, the methiodides of these compounds, such as the α -n-propyl- β -(1-pyrrolidino)-propiophenone methiodide, are formed.

Example 2

To a solution of 11.0 g. of α -n-propyl- β -(1-pyrrolidino)-propiophenone in 100 ml. of ethanol is added in small portions 4.75 g. of sodium borohydride. The reaction mixture is refluxed for four hours; the solvent is evaporated and the residue is treated with water. The organic material is extracted with diethyl ether, the organic solution is dried over magnesium sulfate and evaporated. The residue is distilled to give the 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol of the formula



which boils at 128–130°/0.5 mm.; yield: 6.0 g.

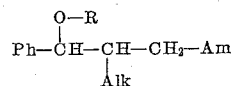
Other compounds, which may be prepared according to the above method are, for example 1-(4-methyl-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, B.P. 131–133°/0.1 mm.; 1-(4-chloro-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, B.P. 150–153°/0.25 mm.; 1-(4-methoxy-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, B.P. 155–157°/0.15 mm., which solidifies upon standing, as well as 3-methyl-1-phenyl-2-(1-pyrrolidino)-methyl-1-butanol, 2-(N,N-diethylaminomethyl)-1-phenyl-1-pentanol, 1-(4-bromo-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, 1-(4-chloro-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, 1-(4-chloro-phenyl)-2-(1-pyrrolidino)-methyl-1-pen-

tanol, 2-N,N-dimethylaminomethyl-1-phenyl-1-pentanol, 2-(1-piperidino)-methyl-1-phenyl-1-pentanol, 1-(4-fluoro-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol, 2-[1-N,N-(1,6-hexylene)-imino]-1-phenyl-1-pentanol, 2-[1-N,N-(1,7-heptylene)-imino]-1-phenyl-1-pentanol and the like. Upon treatment of the above compounds, particularly of 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol, with a saturated solution of hydrogen chloride in ethyl acetate, the hydrochlorides of these compounds, particularly the 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol hydrochloride, are formed. The methiodides of the above compounds, for example, the 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol methiodide, are formed by reacting the tertiary bases with methyl iodide.

Upon treatment of 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol with propionic acid anhydride in the presence of pyridine, the 1-phenyl-2-(1-pyrrolidino)-methyl-1-propionyloxy-pentane can be obtained.

What is claimed is:

1. A member selected from the group consisting of a compound of the formula



in which Ph is a member selected from the group consisting of phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl and (halogeno)-phenyl, Alk is lower alkyl having from three to five carbon atoms, Am is a member selected from the group consisting of N,N-di-lower alkyl-amino and N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms, and R represents a member selected from the group consisting of hydrogen and lower alkanoyl, a pharmaceutically acceptable acid addition salt thereof, and a lower alkyl quaternary ammonium compound thereof.

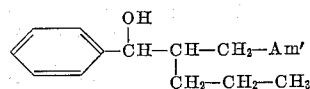
2. 1-phenyl-2-(1-pyrrolidino)-methyl-1-pentanol.

3. 1-(4-methyl-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol.

4. 1-(4-chloro-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol.

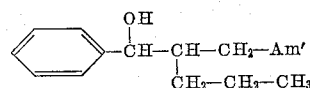
5. 1-(4-methoxy-phenyl)-2-(1-pyrrolidino)-methyl-1-pentanol.

6. A compound of the formula



in which Am' is N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms.

7. A pharmaceutically acceptable acid addition salt of a compound of the formula



in which Am' is N,N-alkylene-imino, in which alkylene has from four to eight carbon atoms.

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