The present invention relates to tertiary amino-lower alkyl-indene. Primarily, it concerns 3-(1-(2-pyridyl)-lower alkyl)-2-(tert-amino-lower alkyl)-indenes, the salts, N-oxides and quaternary ammonium compounds thereof.

A 2-pyridyl residue is preferably unsubstituted or may be substituted by lower alkyl, e.g. methyl, ethyl and the like. Other substituents may be, for example, lower alkoxy, e.g. methoxy, ethoxy and the like, or halogen, e.g. fluorne, chlorine, bromine and the like, or any other suitable functional groups.

The lower alkyl radical of (2-pyridyl)-lower alkyl, which connects the 2-pyridyl portion with the indene nucleus, may be represented by a lower alkylene radical having from one to seven, especially from one to three, carbon atoms, e.g. methylene, 1,1-ethylene, 1,2-ethylen, 1-methyl-1,2-ethylen, 2-methyl-1,2-ethylen, 1-propylene, 1,3-propylene and 2,3-propylene, as well as 1,1-butylene, 2,2-butylene, 2,3-butylene, 1,4-butylen, 1-pentylene and the like.

The lower alkyl portion of the tertiary amino-lower alkyl group attached to the 2-position of the indene nucleus, may be represented by a lower alkylene radical containing from one to seven, preferably from two to three, carbon atoms; such radicals are, for example, 1,2-ethylen, 1-methyl-1,2-ethylen, 2-methyl-1,2-ethylen or 1,3-propylene, as well as methylene, 1,1-ethylen, 1-methyl-1,3-propylene, 1,4-butylen, 1-methyl-1,4-butylen, 1,5-pentylene and the like.

The disubstituted amino groups, which represent tertiary amino group, are, for example, N,N-di-hydrocycrol-amino groups, in which hydrocarbyl represents, for example, lower alkyl, lower alkylen, cycloalkyl, cycloalkyl-lower alkyl, monocylic carboncarbyc aryl-lower alkyl, such as phenyl-lower alkyl. Such radicals contain from one to ten carbon atoms, and may be represented, for example, by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl, pentyl, neopentyl, allyl, methallyl, cyclopentyl, cyclohexyl, cyclopropenylmethyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl and the like. These hydrocarbon radicals may contain further substituents; free hydroxy, lower alkoxly, e.g. methoxy, ethoxy and the like, or any other suitable functional group may be attached to such hydrocarbon radicals. N,N-di-lower hydrocarbyl-alkyl-amino groups are primarily represented by N,N-di-lower alkyl-amino groups in which lower alkyl contains from one to four carbon atoms, e.g. N,N-dimethylamino, N,N-dimethyl-N-ethylamino, N,N-dimethyl-N,N-di-ethylamino, N,N-di-iso-propylamino and the like, by N-cycloalkyl-N-lower alkylamino in which cycloalkyl contains from two to seven ring carbon atoms and lower alkyl contains from one to three carbon atoms; e.g. N-cyclopropyl-N-methylamino, N-ethylhexyl-N-methylamino, N-cyclohexyl-N-methylamino and the like, or N lower alkyl-N-phenyl-lower alkyl-amino, in which lower alkyl contains from one to four carbon atoms, e.g. N-benzyl-N-methylamino, N-benzyl-N-ethylamino, N,N-methyl-N-(1-phenylethyl)-amino, N,N-methyl-N-(2-phenylethyl)-amino and the like, or any other N,N-di-hydrocarbyl-amino group. These hydrocarbyl radicals, particularly lower alkyl, may also contain functional groups, such as hydroxy, lower alkoxly, e.g. methoxy, ethoxy and the like, lower alkymercaptopto, e.g. methylmercapto, ethylmercapto and the like, or any other suitable functional groups.

The disubstituted amino groups may also be represented by 1-N,N-alkylene-imino or by 1-N,N-aza-alkylene-imino groups in which the alkylene portions contain from four to six carbon atoms, as well as by 1-N,N-oxa-alkylene-imino and by 1-N,N-thia-alkylene-imino, in which alkylene contains preferably four carbon atoms. Together with the nitrogen atom such alkylene, aza-alkylene, oxa-alkylene or thia-alkylene radicals represent, for example, 1-N,N-alkylene-imino, in which alkylene contains from four to six carbon atoms, such as 1-pyrolydino radicals, e.g. 1-pyrolyl, 2-methyl-1-pyrolyldino and the like, 1-piperidino radicals, e.g. 1-piperidino, 2-methyl-1-piperidino, 4-methyl-1-piperidino, 3-acetoxy-1-piperidino, 3-hydroxyethyl-1-piperidino and the like, 1-N,N-1,6-hexylene-imino and the like, 1-N,N-(aza-alkylene)-imino, in which alkylene contains from four to six carbon atoms, particularly 1-N,N-(lower alkyl-aza-alkylene)-imino, in which alkylene contains from four to six carbon atoms, such as 1-N,N-(3-aza-1,5-pentylene)-imino, particularly 1,NN-(3-aza-lower alkyl-1,5-pentylene)-imino, e.g. 4-methyl-1-piperazino, 4-ethyl-1-piperazino and the like, as well as 4-hydroxyethyl-1-piperazino, 4-acetoxyethyl-1-piperazino and the like, 1,NN-(3-aza-1,6-hexylene)-imino, particularly 1,N-NN-(3-aza-3-methyl-1,6-hexylene)-imino, e.g. 1-N,N-(3-aza-3-methyl-1,6-hexylene)-imino, and the like, or 1,N,N-(4-aza-1,7-heptamethylene)-imino, particularly 1,N,N-(4-aza-4-lower alkyl-1,7-heptamethylenimino)-imino, e.g. 1,N,N-(4-aza-4-lower alkyl-1,7-heptamethylenimino)-imino and the like, 1,N,N-(3-thia-1,5-pentylene)-imino, e.g. 1-thiaramorpholine and the like.

The tertiary amino-lower alkyl radical may also be represented by a heterocyclic or a heterocyclic-lower alkyl radical, in which the disubstituted amino group is part of the heterocyclic nucleus. Such nucleus may be connected through one of its ring carbon atoms or through a lower alkylene radical, e.g. methylene, 1,2-ethylen and the like, by the 2-position of the indene ring. Such radicals are represented, for example, by 1-methyl-3-pyrolyldinomethyl, 1-methyl-3-piperidinomethyl, 1-methyl-4-piperidino and the like.

The 1-position of the indene nucleus is preferably unsubstituted, or, if substituted, contains preferably a hydrocarbyl radical, particularly lower alkyl, e.g. methyl, ethyl and the like, or monocylic carboncarbyc aryl-lower alkyl, e.g. benzyl and the like.

The six-membered carbocyclic aryl portion of the indene nucleus is preferably unsubstituted or may contain one or more than one substituent, which may be located in any of the four positions available for substitution; whenever at least two substituents are present, these may be of the same or of different nature. Such substituents may be, for example, lower alkyl, e.g. methyl, ethyl and the like, halogen, lower alkoxy, e.g. methoxy, ethoxy and the like or lower alkenoxy, etherified hydroxyl, such as lower alkoxy, e.g. methoxy, ethoxy and the like, or lower alkenedioxy, etherified hydroxy and the like.
e.g. methylenedioxy, esterified hydroxyl, such as lower alkoxy-carbonyloxy, e.g. methoxy-carbonyloxy, ethoxy-carbonyloxy and the like, lower alkanoyloxy, e.g. acetyloxy, propionyloxy and the like, or halogen, e.g. fluoro-, chloro-, bromo- and the like, as well as lower alkylmethoxy, e.g. acetylmethoxy, propionylmethoxy and the like, etherified mercapto, such as lower alkyl-mercapto, e.g. methyl-mercapto, ethylmercapto and the like, nitro, amino, for example, unsubstituted amino, N-mono-substituted amino, such as N-lower alkyl-alkyl-amino, e.g. N-methylamino and the like, or preferably N,N-di-lower alkyl-amino, for example, N,N-di-lower alkyl-amino, e.g. N,N-dimethyl-amino and the like. The six-membered carbocyclic aryl portion of the indene ring may, therefore, be represented, for example, by an unsubstituted, a lower alkyl-substituted, a halogeno-lower alkyl-substituted, a lower alkoxy-substituted, a lower alkenyloxy-substituted, a lower alkylmercapto-substituted, a lower alkoxy-carbonyloxy-substituted, a lower alkanoyloxy-substituted, a halogeno-substituted, a lower alkylamino-substituted, or a lower alkoxy-substituted, a lower alkenylamino-substituted or an N,N-di-lower alkyl-amino-substituted six-membered carbocyclic aryl portion of the like.

Salts of the compounds of this invention are primarily therapeutically acceptable acid addition salts with inorganic or organic acids. Suitable inorganic acids are, for example, mineral acids, such as hydrochloric acid, hydrobromic acid and the like, or sulfuric acid, phosphoric acid and the like. Organic acids are organic carboxylic acids, such as lower aliphatic mono-carboxylic acids, for example, lower alkane monocarboxylic acids, e.g. formic, acetic, propionic, pivalic acid and the like, lower alkeno monocarboxylic acid, e.g. 3-butenic acid and the like, hydroxy-lower alkane monocarboxylic acids, e.g. glycolic, lactic acid and the like, lower alkoxy-lower alkane monocarboxylic acids, e.g. methoxy-actic, ethoxy-actic acid and the like, lower alkanoyl-lower alkane monocarboxylic acids, e.g. pyruvic acid and the like, halogeno-lower alkane monocarboxylic acids, e.g. chloroacetic, dichloroacetic, trichloroacetic, bromoacetic acid and the like, lower aliphatic dicarboxylic acids, for example, lower alkeno dicarboxylic acids, e.g. oxalic, malonic, succinic, methylsuccinic, dimethylsuccinic, glutaric, a-methylglutaric, a,a-dimethylglutaric, p-methylglutaric acid and the like, lower alkeno dicarboxylic acid halides with lower alkanols, e.g. succinic acid monomethyl ester, glutaric acid monoethyl ester and the like, lower alkeno dicarboxylic acids, e.g. itaconic, homitaconic, maleic, citraconic, homocitaconic, pyroxiconic, xeronic, furamic acid and the like, lower alkeno dicarboxylic acid halides with lower alkanols, e.g. maleic acid monomethyl ester and the like, hydroxy-lower alkane dicarboxylic acids, e.g. maleic, tartaric acid and the like, as well as their optically active forms, lower alkoxy-lower alkane dicarboxylic acids, e.g. a,b-di-methoxysuccinic and the like, lower alkoxy-lower alkane dicarboxylic acid, e.g. ethoxymaleic acid and the like, halogeno-lower alkane dicarboxylic acids, e.g. chloro maleic acid and the like, lower aliphatic tricarboxylic acids, for example, lower alkane tricarboxylic acids, e.g. tricarballylic acid and the like, lower alkeno tricarboxylic acids, e.g. aceticid acid and the like, hydroxy-lower alkane tricarboxylic acids, e.g. citric acid and the like, lower alkeno tricarboxylic acids, e.g. cycloalkane monocarboxylic acids, such as cycloalkane monocarboxylic acids, the like, cycloalkane dicarboxylic acids, such as cycloalkane dicarboxylic acids, the like, cycloalkane tricarboxylic acids, such as cycloalkane tricarboxylic acids, the like, cycloalkane tetracarboxylic acids, such as cycloalkane tetracarboxylic acids, the like, cycloalkane pentacarboxylic acids, such as cycloalkane pentacarboxylic acids, the like, cycloalkyl-lower alkane monocarboxylic acids, e.g. cyclopentylpropionic acid and the like, monocyclic or bicyclic monocarboxylic aromatic or aryldicarboxylic acids, e.g. benzoic, dihydroxycinnamic, cinamic, mandelic, salicylic, 4-aminoaacetic, 2-phenoxybenzoic, 2-acetoxymethoxybenzoic acid and the like, or monocyclic or bicyclic monocarboxylic aromatic or aryldicarboxylic acids, e.g. phthalic acid and the like, monocyclic or bicyclic heterocyclic aromatic carboxylic acids, e.g. nicotinic, isoisonicotinic, quinonic, pyridonic, pyridinic or the like, or any other suitable carboxylic acid. In addition, amino carboxylic acids, such as methionine, tryptophane, lysine, arginine, aspartic, glutamic, hydroxyglutamic acid and the like, organic sulfonic acids, such as lower alkane sulfonic acids, e.g. methane sulfonic, ethane sulfonic acid and the like, lower alkeno sulfonic acids, e.g. 2-hydroxyethane sulfonic acid and the like, aromatic sulfo acids, such as monocyclic aromatic sulfo acids, e.g. p-toluene sulfonic acid and the like, or mixtures of acids, such as the mixture known as tannic acid, are suitable for salt formation. Particularly useful are acid addition salts with mineral acids, lower alkeno dicarboxylic acids, e.g. maleic, citraconic acid and the like, lower hydroxy-alkane dicarboxylic acids, e.g. maleic, tartaric acid and the like, hydroxy-lower alkane dicarboxylic acids, e.g. hydroxymaleic, dihydroxymaleic acid and the like, or hydroxy-lower alkane tricarboxylic acid, e.g. citric acid and the like.

Salts, which may be prepared primarily for identification purposes, are, for example, those with acidic organic nitro compounds, e.g. picric, picrolic, flavic acid and the like, or metal complex acids, e.g. phosphotungstic, phosphomolybdic, chloroplatinic, Reinecke acid and the like. Mono- or poly-salts may be formed depending on the number of salt-forming groups and/or the conditions used for the salt formation.

Also included within the scope of the present invention are the N-oxides of the afore-mentioned compounds, as well as acidic or basic hydroxides, salts and the like, e.g. 4-aminosalicylic, 2-phenoxybenzoic acid and the like, or mono- or poly-N-oxides may be formed depending on the reaction conditions and/or number of tertiary amino groups.

Quaternary ammonium compounds of the indene derivatives of this invention may be either mono- or poly-quaternary ammonium compounds depending on the conditions of the quaternization reaction and/or the number of tertiary amino groups present. Quaternary ammonium compounds are particularly those with lower aliphatic hydrocarbon halides, sulfates, or sulfonates, such as halogenoalkanes, halogenoalkyls, halogenoalkyl sulfates, such as methyl, ethyl-, propyl or isopropyl chloride, bromide, iodide and the like, di- and lower alkyl sulfates, e.g. dimethyl sulfate, diethyl sulfate and the like, lower alkyl lower alkane sulfonates, such as methyl or ethyl methane sulfonate, ethane sulfonate, lower alkyl lower hydroxy-alkane sulfonates, such as 2-hydroxy-ethane sulfonate and the like, lower alkyl monocyclic carboxylic aryl sulfonates, such as methyl or ethyl pentaoxy sulfonate and the like. Also included as quaternary ammonium compounds are the corresponding quaternary ammonium hydroxides, and the salts of such hydroxides with acids, particularly with the organic carboxylic acids mentioned hereinabove.

Depending on the number of asymmetric carbon atoms the indene compounds of this invention may be obtained as mixtures of racemates, racemates or antipodes, the separation and resolution of which will be discussed and illustrated hereinbelow. This type of compounds of this invention show antihistaminic effects and are intended to be used as antihistaminic agents to relieve allergic disorders, especially those caused by an excess of histamine; such allergic conditions are, for example, hay fever, urticaria, allergies caused by food, plant pollen or medicinal agents, and the like. In addition, compounds of this invention have a central nervous system depressing effect, thus exert sedative and quieting properties; they can, therefore, be used as sedative agents to counteract states of nervousness, anxiety, stress or shock, as well as local anesthetic effects, which render these compounds useful as local.
anesthetics, for example, in connection with minor surgery and the like.

Furthermore, compounds of this invention also exert analgesic properties, which can be utilized to raise the threshold of pain, for example, in connection with surgery, anti-hypertensive effects, which are useful in lowering blood pressure in states of hypertension such as renal or essential hypertension, or, particularly quaternary ammonium derivatives of the compounds of this invention, antispasmodic properties, which make such compounds useful as agents to counteract spastic conditions.

Compounds with particularly outstanding antihistaminic properties are indenes of the formula:

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\begin{align*}
\text{R}_1 & \text{ attached to any of the positions available for substitution, represents hydrogen, lower alkyl containing from one to four carbon atoms, e.g. methyl, ethyl n-propyl, isopropyl, \text{n-butyl and the like, lower alkoxy containing from one to four carbon atoms, e.g. methoxy, ethoxy, \text{n-propoxy, isopropoxy, \text{n-butoxy and the like, or halogen having an atomic weight below 80, e.g. fluoro, chloro or bromo, R}_2 \text{ represents hydrogen or lower alkyl, e.g. methyl, ethyl, \text{n-propyl, isopropyl and the like, R}_3 \text{ stands for alkylene containing from one to three carbon atoms, e.g. methane, 1,1-ethylenne, 1,2-ethylenne, 1,1-propylene, 1,2-propylene, 1,3-propylene or 2,2-propylene, P represents 2-pyridyl or lower alkyl-substituted 2-pyridyl, A}_4 \text{ stands for lower alkylene containing from one to three carbon atoms, particularly for lower alkylene, which contains from two to three carbon atoms and separates the group \text{A} \text{m from the 2-position of the indene nucleus by from two to three carbon atoms, e.g. 1,2-ethylenne, 1-methyl-1,2-ethylenne, 2-methyl-1,2-ethylenne or 1,3-propylene, and \text{A} \text{m represents N,N-di-lower alkyl-amino, in which lower alkyl contains from one to four carbon atoms, e.g. N,N-di-methylamino, N-ethyl-N-methylamino, N,N-diethylamino, N,N-di-a-propylamino, N,N-di-butyramino, N,N-di-isopropylamino, N,N-di-n-butyramino and the like, N-cycloalkyl-N-lower alkyl-amino, in which cycloalkyl contains from five to seven ring carbon atoms and lower alkyl contains from one to four carbon atoms, e.g. N-cyclopentyl-N-methylamino, N-cyclopentyl-N-propylamino, N-cyclohexyl-N-ethylamino, N-cyclohexyl-N-methylamino and the like, lower alkyl-N-phenyl-lower alkyl-amino, in which lower alkyl contains from one to four carbon atoms, e.g. N-benzyl-N-ethylamino, N-benzyl-N-propylamino, N-methyl-N(1-phenylethyl)-amino, N-methyl-N-(2-phenylethyl)-amino, N-methyl-N-(3-phenyl-propyl)-amino and the like, 1-N,N-lower alkylene-imino, in which lower alkylene contains from four to seven carbons atoms, e.g. pyrrolidino, 1-piperidino, 1,N,N-6,6-hexylene-imino and the like, 4-morpholinol, 1,N,N(4-aza-ylalkylene)-imino, in which alkylene contains from four to six carbon atoms, particularly 4-lower alkyl-1-piperazino, e.g. 4-methyl-1-piperazino, 4-ethyl-1-piperazino, and the like, as well as 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, and the therapeutically acceptable acid addition salts thereof, as well as N-oxides, therapeutically acceptable acid addition salts of such compounds, or lower alkyl quaternary ammonium halides, sulfates or sulfonates of such compounds.}
\end{align*}
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Compounds with particularly outstanding antihistaminic properties are indenes of the formula:

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\begin{align*}
\text{either in the form of its racemate or the optically active forms, particularly the levo-rotatory \text{L}-form, and salts of these compounds with therapeutically acceptable acids, such as mineral acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, lower alkane dicarboxylic acids, e.g. isonic, maleic acid and the like, hydroxy-lower alkane dicarboxylic acids, e.g. tartaric acid and the like and the optically active forms of such acids, particularly the d-form of tartaric acid, as well as the N-oxide thereof and acid addition salts of such N-oxide with therapeutically acceptable acids. A more pronounced central nervous system depressing effect is exhibited, for example by 2-(2-N,N-di-methylamino-ethyl)-3-(2-pyridyl)-ethyl-indene and its therapeutically acceptable acid addition salts. Included within the scope of this invention are, furthermore, the 3-(4-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes, in which 4-pyridyl is unsubstituted or contains as substituents those previously described for the corresponding 2-pyridyl nucleus, and lower alkyl of the (4-pyridyl)-lower alkyl portion, as well as tertial amino-lower alkyl having the above given meaning, and in which the six-membered carbocyclic aryl portion of the indene nucleus is unsubstituted or substituted as previously demonstrated, and the salts, the N-oxides, salts of the N-oxides and the quaternary ammonium derivatives of such compounds. They exhibit antihistaminic effects and can be used as antihistaminic agents to relieve allergic disorders, particularly those caused by an excess of histamine, such as hay fever, urticaria, allergies caused by food or plant pollen, etc. An outstanding effect is exhibited by the 2-(N,N-di-lower alkyl-amino-lower alkyl)-3-(4-pyridyl)-lower alkyl-indene, in which lower alkyl contains from one to three carbon atoms, and in which lower alkyl, separating the N,N-di-lower alkyl-amino group from the 2-position of the indene nucleus by from two to three carbon atoms, contains from two to three carbon atoms, and lower alkyl of the (2-pyridyl)-lower alkyl portion contains from one to three, preferably one to two, carbon atoms, and the therapeutically acceptable acid addition salts thereof, as well as the N-oxide thereof and acid addition salts of such N-oxides with therapeutically acceptable acids.}
\end{align*}
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A similar antihistaminic activity is shown by corresponding 3-(3-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes, in which the tertiary amino-lower alkyl portion and lower alkyl of the (3-pyridyl)-lower alkyl radical have the above given meaning, and the aromatic hexacyclic portion of the indene nucleus and the 3-pyridyl nucleus are unsubstituted or substituted as indicated above, the salts, the N-oxides, salts of the N-oxides and the quaternary ammonium derivatives of such compounds; they may be used to relieve allergic conditions, such as those mentioned hereinafter. The 2-(N,N-di-lower alkyl-amino-lower alkyl)-3-(3-pyridyl)-lower alkyl-indenes, in which lower alkyl of (3-pyridyl)-lower alkyl contains from one to three carbon atoms, and in which lower alkyl, separating the N,N-di-lower alkyl-amino group from the 2-position of the indene nucleus...
by from two to three carbon atoms, stands for an alkylene radical having from two to three carbon atoms, their therapeutically acceptable acid addition salts, the N-oxides thereof and acid addition salts of such N-oxides with therapeutically acceptable acids, show a remarkable antimicrobial effect.

The new compounds of this invention may be used as medicaments in the form of pharmaceutical preparations, which contain the new indene derivatives, including racemates, antipodes, N-oxides, salts of N-oxides and particularly the therapeutically acceptable acid addition salts thereof, admixed with a solid or liquid vehicle suitable for internal, oral, or parenteral administration. To relieve allergic skin troubles, the new indene compounds may also be employed topically. For making up the preparations there may be used substances, which do not react with the new compounds, such as water, gelatine, lactose, starches, lactic acid, stearic acid, magnesium stearate, stearyl alcohol, t alc, vegetable oils, ben zyl alcohols, gums, propylene glycol, polyethylene glycols, or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as capsules, tablets or drages, in liquid form, for example, as solutions, suspensions or emulsions, or in the form of ointments, creams or lotions for topical administration. If desired, they may contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, buffering agents, and the like. They may also contain, in combination, other therapeutically useful substances.

The indene compounds of the present invention may also be used as intermediates for the preparation of other useful compounds.

The indene compounds of this invention may be prepared according to several procedures, the selection of which may primarily depend on the nature of the pyridyl-lower alkyl portion attached to the indene nucleus. For example, compounds of this invention may be obtained by introducing a (2-pyridyl)-lower alkyl radical into a 2-(tertiary amino-lower alkyl)-indane compound, and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting a free compound into a salt, an N-oxide, a salt of an N-oxide or a quaternary ammonium compound thereof, and/or, if desired, separating a resulting mixture of homotactic single racemates, and/or, if desired, resolving a resulting racemate into the antipodes.

A specific modification of the general procedure comprises reacting a 2-(tertiary amino-lower alkyl)-indan-1-one with a (2-pyridyl)-lower alkyl metal compound, in which the metal is selected from metal elements of group IA of the periodic system, i.e. from alkali metals, such as sodium, potassium, or preferably lithium. The reaction is carried out in the presence of an inert sal vent, for example, a hydrocarbon, such as an aliphatic hydrocarbon, e.g. pentane, hexane and the like, or an aromatic hydrocarbon, e.g. benzene, toluene, xylene and the like, or an ether, such as a di-lower alkyl ether, e.g. diethyl ether, di-isopropyl ether and the like, or a cyclic ether, e.g. tetrahydrofuran, p-dioxane and the like. If necessary, the reaction mixture may be cooled, or the temperature may be elevated, for example, to the boiling point of the solvent. Furthermore, the reaction may be performed in the atmosphere of an inert gas, e.g. nitrogen.

The above-mentioned (2-pyridyl)-lower alkyl metal compounds, particularly the lithium derivatives, may be formed by reacting a 2-lower alkyl-pyridine with an aryl metal compound, such as a monocyclic carbocyclic aryl metal compound, e.g. phenyl lithium, or with an aliphatic hydrocarbon metal compound, particularly a lower alkyl lithium derivative, e.g. n-butyl lithium and the like. Such reaction is carried out in the presence of an inert solvent, for example, a lower aliphatic hydrocarbon, e.g. pentane, hexane and the like, an aromatic hydrocarbon, e.g. benzene, toluene, xylene and the like, or an ether, such as a di-lower alkyl ether, e.g. diethyl ether, di-isopropyl ether and the like, or a cyclic ether, e.g. tetrahydrofuran, p-dioxane and the like, preferably in the atmosphere of an inert gas, e.g. nitrogen.

The preparation of the chromium(II) metal, particularly lithium, reagent may be modified. A (2-pyridyl)-lower alkyl lithium reagent may also be obtained by treating with lithium an ether formed, for example, by a lower alkanol and a (2-pyridyl)-lower alkyl lower alkanol, in which the hydroxy group is attached to the carbonyl group of the alcohol, advantageously, such reaction occurs by using a diluted solution of the ether reagent in an inert solvent, preferably in tetrahydrofuran. The solution of the resulting lithium reagent is then treated with the 2-(tertiary amino-lower alkyl)-indan-1-one according to the previously described procedure.

Whenever an alkali metal compound of a 2-lower alkyl-pyridine, in which the lower alkyl portion contains more than one carbon atom, is used as the reagent, the (2-pyridyl)-lower alkyl portion will be attached to the carbon atom of the lower alkyl portion through the carbon atom of the lower alkyl portion which is adjacent to the pyridine nucleus. For example, 2-ethyl-pyridine, when reacted in the form of its lithium derivative, furnishes the 1-(2-pyridyl)-ethyl radical. The above procedure is, therefore, particularly suitable for 2-aminobenzyl-o-(tertiary amino-lower alkyl)-2-(tertiary amino-lower alkyl)-indane, in which the radical R represents hydrogen or lower alkyl, such as methyl.

The above reaction of indan-1-one compounds with (2-pyridyl)-lower alkyl metal derivatives may furnish directly the desired 3-(1-(pyridyl)-lower alkyl)-2-(tertiary amino-lower alkyl)-indanes, as intermediate formed 1-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indane-1-ols may dehydrate under the conditions of the reaction and yield directly the desired indene derivatives of this invention. Such direct dehydration takes place, if at any stage of the isolation procedure of the reaction product acidic conditions are prevailing. If necessary, dehydration of a resulting indan-1-ol compound may be achieved and completed, for example, by treatment of the latter with an acidic reagent, for example, with concentrated hydrochloric acid, or with a mixture of concentrated hydrochloric acid and acetic acid.

These acids may be used in the presence of water and/or an organic solvent, such as, for example, glacial acetic acid. Dehydration may also be accomplished by treatment with an organic acid reagent, such as an organic carboxylic acid, e.g. oxalic, p-toluene sulfonic acid and the like, or an organic carboxylic acid anhydride, e.g. acetic acid anhydride and the like, or with an inorganic or organic acid halide, e.g. phosphorus oxychloride, acetyl chloride and the like, if desired, in an organic base, e.g. pyridine and the like, and, if necessary, while heating. The indan-1-one may also lose water at an elevated temperature without the presence of a specific dehydrating agent.

The 2-(tertiary amino-lower alkyl)-indan-1-one compounds used as the starting materials in the above reaction are known, or, if new, may be prepared according to methods used for the manufacture of known analogs. For example, the 1-(2-pyridyl)-lower alkyl compounds, e.g. a lower alkyl, e.g. methyl, ethyl and the like, ester, as well as a heterocyclic, e.g. 2-tetra-hydropryanyl, ester, in which the benzyl portion may be unsubstituted or substituted as outlined hereinafter, is treated with a reactive ester formed by a tertiary amino-lower alkanol, in which the lithium amide and the like may be separated from the hydroxyl group by at least two carbon atoms, and a strong inorganic or organic acid, such as, for example, a mineral acid, e.g. hydrochloric, hydrobromic, hydriodic, sulfurous acid and the like. The reaction produces an 2-(tertiary amino-lower alkyl)-malonic acid ester, in which
the tertiary amino group is separated from the α-carbon atom by at least two carbon atoms. This condensation may preferably be carried out in the presence of a base, such as an alkali metal lower alkanolate, e.g. lithium, sodium or potassium methanolate, ethanolate, propanolate, isopropanolate, tertiary butanolate and the like. The resulting malonic acid ester may then be cyclized to the 2-(tertiary amino-lower alkyl)-indan-1-one, in which the tertiary amino group is separated from the indane nucleus by at least two carbon atoms. The cyclization may be performed prior or after hydrolysis of the ester groups, which may occur, for example, under alkaline conditions, such as in the presence of an aqueous alkali metal hydroxide, e.g. sodium hydroxide, potassium hydroxide and the like, and, if necessary, subsequent de-carboxylation of one carbonyl group, for example, by heating, if desired, in the presence of a mineral acid, e.g. hydrochloric, sulfuric acid and the like. The cyclization may be carried out, for example, by treatment with a strong Lewis acid, such as a strong mineral acid, e.g. anhydrous hydrochloric, sulfuric, phosphoric acid (preferably in the form of polyphosphoric acid), boron trifluoride (primarily in the form of its etherate), aluminum chloride and the like.

The 2-(tertiary amino-methyl)-indan-1-ones may be prepared, for example, by reacting an indan-1-one with a secondary amine or a salt thereof in the presence of formaldehyde according to the Mannich procedure. Secondary amines are those which furnish the N,N-disubstituted amino groups described hereinbefore; salts of such amines are particularly inorganic acid addition salts, for example, salts with mineral acids, e.g. hydrochloric, hydrobromic, sulfuric acid and the like. The formaldehyde may be used in the form of a solution, e.g. aqueous formaldehyde, as a polymer, e.g. trioxymethylene, paraformaldehyde and the like, or as an acetal with a lower alkanol, e.g. dimethoxymethane, diethoxyethane and the like. The reaction is advantageously performed in the presence of a solvent, for example, a lower alkanol, e.g. methanol, ethanol and the like, or an aqueous mixture thereof, and/or in the presence of an acid, for example, a mineral acid, e.g. hydrochloric, sulfuric acid and the like, especially when the formaldehyde is employed in the form of an amine or an acetal thereof. The reaction may be completed by heating, and the resulting 2-(tertiary amino-methyl)-indan-1-one may be isolated as the free base or as an acid addition salt thereof.

The above described procedure for the manufacture of indane compounds is also applicable for the preparation of 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes, mentioned hereinbefore to have anthistaminic properties. Thus, when a 2-(tertiary amino-lower alkyl)-indan-1-one is reacted with a 2-(pyridyl)-lower alkyl alkanol compound, particularly the lithium compound, according to the aforementioned procedure, the resulting 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indene is formed directly or after dehyration of any intermediately formed 1-(2-pyridyl)lower alkyl-2-(tertiary amino-lower alkyl)-indan-1-ol, which dehyration may be carried out as outlined hereinbefore.

A modification of the general method for the preparation of the compounds of this invention, i.e. introduction of the (2-pyridyl)-lower alkyl radical into a 2-(tertiary amino-lower alkyl)-indan compound, comprises reacting a 2-(tertiary amino-lower alkyl)-indan-1-one with a 2-(pyridyl)-lower alkyl Grignard reagent. The desired 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indene may be obtained directly or after dehyration of an intermediately formed indan-1-ol compound. A (2-pyridyl)-lower alkyl Grignard reagent is, for example, a (2-pyridyl)-lower alkyl metal halide compound, in which the metal is selected from metal elements of the groups IA and IB of the periodic system capable of forming organo-metallic compounds. Such metal is primarily magnesium, and the halogen atom in a Grignard reagent may be chlorine, bromine or iodine; (2-pyridyl)-lower alkyl magnesium halides, e.g. chlorides, bromides and the like, are the preferred reagents. The rection of the indan-1-one derivative with the (2-pyridyl)-lower alkyl Grignard reagent may be carried out in the presence of the solvent used during the preparation of the organo-metallic compound, which is preferably diethyl ether, or in the presence of another suitable inert solvent, for example, another ether, such as a carbo cyclic aryl lower alkyl ether, e.g. anisole and the like, a dimonocyclic carboxylic aryl ether, e.g. diphenyl ether and the like, or a cyclic ether, e.g. tetrahydrofuran, p-dioxane and the like, or an organic base, e.g. N-ethylmorpholine, pyridine and the like. Other solvents, which may also be added after the formation of the Grignard reagent and, if desired, after the removal of the solvent used for the formation of the Grignard reagent, are hydrocarbons, such as monocyclic carboxylic hydrocarbons, e.g. benzene, toluene, xylene and the like, or aliphatic hydrocarbons, e.g. pentane, hexane and the like. The reaction may be carried out under cooling or at room temperature, and may be completed by heating, for example, to the boiling point of the solvent. An inert gas, such as dry nitrogen, may be used to avoid any contact with atmospheric oxygen.

An intermediately formed indan-1-ol compound may be dehydrated directly to the desired indene compound under the conditions of the reaction or dehyration may occur by treatment with a dehydration agent, particularly an acidic reagent, as previously shown.

The above-described method, using a 2-(pyridyl)-lower alkyl Grignard reactant, is especially suited for the preparation of those 3-(2-pyridyl)-lower alkyl-indene derivatives, in which the lower alkyl portion, connecting the 2-pyridyl radical to the indene ring, is not branched at the methylene group attached to the pyridyl radical.

This modification of the first procedure may also be used for the preparation of 3-(4-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes, for example, by reacting a 2-(tertiary amino-lower alkyl)-indan-1-one with a 4-(pyridyl)-lower alkyl-Grignard compound according to the above-given procedure. Furthermore, this modification may also be applied for the manufacture of 1-(3- or -2 - (tertiary amino-lower alkyl)-indenes by substituting a 3-(pyridyl)-lower alkyl-Grignard reagent for the corresponding (4-pyridyl)-lower alkyl derivative.

A second generally applicable method for the manufacture of 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes comprises reacting a 2-(tertiary amino-lower alkyl)-indene, containing an unsubstituted methylene group as a ring member of the five-membered portion of the indene nucleus, with a 2-pyridyl-alkanen, dehydrating, if necessary, an intermediately formed 1-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indan-1-ol, which dehyration may be carried out as outlined hereinbefore.

(2-pyridyl)-lower alkannals are, for example, aldehydes containing a 2-pyridyl radical, e.g. 2-pyridine carboxaldehyde, and the like. These aldehydes may also be used in the form of reactive derivatives thereof, such as, for example, the bisulfite addition compounds.

The reaction of the (2-pyridyl)-lower alkanal with the 2-(tertiary amino-lower alkyl)-indene compound may be carried out according to conditions used in Claisen condensations, for example, in the presence of a salt-forming condensing reagent, and, preferably of a solvent. A condensing reagent is particularly an alkali metal salt-forming reagent, such as, for example, an alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, po-
Potassium hydroxide and the like, used in the presence of a solvent, such as a lower alkanol, e.g. methanol, ethanol, n-propanol and the like. Further alkali metal salt-forming reagents are, for example, alkali metal lower alkanoate, e.g. lithium, sodium or potassium propionate, propanoate, isopropanoate, tertiary butanoate and the like; these reagents are employed in the presence of a solvent, such as, for example, the corresponding lower alkanol, e.g. methanol, ethanol, propanol, isopropanol and the like. Similar salt-forming reagents are, for example, alkali metals, e.g. lithium, sodium or potassium hydroxide or amide, e.g. lithium, sodium or potassium hydroxide or amide, which reagents are employed in the presence of an inert, preferably non-hydroxylic solvent, such as, for example, an ether, e.g. tetrahydrofuran, p-dioxane, diethylenglycol dimethyl-ether and the like, or an aromatic hydrocarbon, e.g. benzene, toluene, xylene and the like, if necessary while heating. Other, non-metallic condensing reagents may be, for example, quaternary ammonium hydroxides, e.g. benzyl-trimethylammonium hydroxide and the like. The reaction may be carried out under cooling, at room temperature or at an elevated temperature and, if necessary, in the atmosphere of an inert gas, e.g. nitrogen.

Whereas the reaction of the aldehyde with the indene compound in the presence of an alkali metal hydroxide or an alkali metal lower alkanoate in a lower alkanol solvent may yield directly the 1-(2-pyridyl)-lower alkylidene)-2-(tertiary amino-lower alkyl)-indene compound, the condensation in the presence of an alkali metal or the corresponding hydrides and amides in a non-hydroxylic solvent furnishes predominantly the 1-(2-pyridyl)-hydroxy-lower alkyl-2-(tertiary amino-lower alkyl)-indene; the latter have to be dehydrated as will be shown hereinbelow.

Other salt-forming compounds may be Grignard reagents, such as, for example, carboxylic aryl magnesium halides, particularly monocyclic carboxylic aryl magnesium halides, e.g. phenyl magnesium chloride, phenyl magnesium bromide and the like, or lower hydrocarbon magnesium halides, such as lower alkyl magnesium halides, e.g. methyl, ethyl, n-propyl or n-buty1 magnesium chloride, bromide or iodide and the like. Upon treatment with a 2-(tertiary amino-lower alkyl)-indene, these reagents yield an organo-metallic derivative of the indene compound, which may be reacted with the above-described (2-pyridyl)-lower alkanoate to form a 1-(2-pyridyl)-hydroxy-lower alkyl-2-(tertiary amino-lower alkyl)-indene; the latter may be converted into the desired indene compound as shown hereinbelow. Treatment of a 2-(tertiary amino-lower alkyl)-indene with the Grignard reagent is preferably carried out in the presence of a solvent, such as, for example, an ether, e.g. tetrahydrofuran and the like.

If necessary, intermediarily formed 1-(2-pyridyl)-hydroxy-lower alkyl-2-(tertiary amino-lower alkyl)-indenes may be dehydrated. Dehydration may be accomplished according to previously given methods, for example, by treatment with an acid, such as a mineral acid, e.g. hydrochloric, sulfuric acid and the like. A resulting 1-(2-pyridyl)-lower alkylidene)-2-(tertiary amino-lower alkyl)-indene compound is converted into the desired 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indene by reduction. A preferred procedure is represented by treatment with hydrogen in the presence of a catalyst, such as a palladium catalyst, e.g. palladium on charcoal and the like, whereby care has to be taken that only one mol of hydrogen is taken up and that the pyridine nucleus is not hydrogenated simultaneously. The reduction may be carried out in a solvent, preferably in a non-acidic medium, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like. It may also be performed with nascent hydrogen, as furnished by the reaction of a metal or a metal amalagam with a hydrogen donor, for example, by aluminum amalgam with wet ether, an alkali metal or an alkali metal amalgam, e.g. sodium or sodium amalgam and the like, with a lower alkanol, e.g. methanol, ethanol, butanol and the like, as well as any other suitable combination.

The desired 3-(2-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indene compound, or the latter may be obtained after rearranging a double bond in the reduction product. Treatment with a mineral acid, e.g. hydrochloric, sulfuric acid and the like, or with a base, such as, for example, lower alkanoic acid, e.g. sodium hydroxide, potassium hydroxide and the like, or an alkali metal lower alkanoate, e.g. sodium or potassium methanoate, ethanoate and the like, may bring about the rearrangement of a double bond. These rearrangement reagents are preferably used in the presence of a solvent, such as, for example, water or a lower alkanol or aqueous mixture thereof, depending on the solubility and/or reactivity of the reagent or the reactant.

The starting materials used in this procedure are known or may be prepared according to known methods. For example, a 2-(tertiary amino-lower alkyl)-indene-1-one may be converted to the corresponding indone by reduction, for example, by treatment with catalytically activated hydrogen, such as hydrogen in the presence of a nickel catalyst, e.g. Raney nickel and the like, or a palladium catalyst, e.g. palladium on charcoal and the like, with nascent hydrogen, as furnished by the reaction of an alkali metal or a metal amalgam with a hydrogen donor, with an alkali metal borohydride, e.g. sodium borohydride and the like, with an alkali metal aluminum hydride, e.g. lithium aluminum hydride and the like, or with an aluminum lower alkoxide in the presence of a lower alkanol according to Meerwein-Ponndorf-Verley method, for example, with aluminum isopropanoxide in isopropanol. A resulting 2-(tertiary amino-lower alkyl)-indan-1-ol is then dehydrated, for example, in the presence of an acid, such as a mineral acid, e.g. hydrochloric, sulfuric acid and the like, as previously shown.

The above-described modification of the general procedure may also be used for the manufacture of 3-(4-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes by substituting in the above method the (2-pyridyl)-lower alkanoate by a (4-pyridyl)-lower alkanoate. The corresponding 3-(3-pyridyl)-lower alkyl-2-(tertiary amino-lower alkyl)-indenes may be prepared by treating a 2-(tertiary amino-lower alkyl)-indene, which contains a methylene group as a ring member of the five-membered portion of the indene nucleus, with a 3-(3-pyridyl)-lower alkanoate, and reducing the resulting (tertiary amino-lower alkyl)-1-(3-pyridyl)-lower alkylidene)-indene compound the (3-pyridyl)-lower alkylidene portion to a (3-pyridyl)-lower alkyl group, if necessary, after dehydrating an intermediarily formed 1-(3-(pyridyl)-hydroxy-lower alkyl)-2-(tertiary amino-lower alkyl)-indene. These reactions are carried out as previously shown.

A more specific procedure, which is particularly useful for the introduction of a 2-(2-pyridyl)-ethoxy group, comprises converting a 2-(tertiary amino-lower alkyl)-indene, which contains an unsubstituted methylene group as a member of the five-membered portion of the indene nucleus, into a salt thereof and reacting the latter with a 2-vinylpyridine, and, if desired, carrying out the optional steps.

The salt of the indene compound is preferably an alkali metal salt thereof, and can be obtained by known procedures. For example, the indene compound may be reacted with an alkali metal lower alkanoate in a lower alkanol, such as, for example, lithium, sodium or potassium methanoate, ethanoate, n-propanoate, isopropanoate, n-butoxanolate, isobutanolate, tertiary butanoate and the like in the corresponding lower alkanoate, e.g. methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tertiary butanol and the like: a reagent of choice is potassium tert-butoxide in tertiary butanol.
Other reagents, which may be useful for the preparation of alkali metal salts are, for example, alkali metal amides, hydrides or hydroxides, e.g. lithium, sodium or potassium amide, hydride or hydroxide, in appropriate solvents, particularly inert organic solvents with a high dielectric constant. For example, ethers, e.g. p-dioxane, diethylene glycol dimethyl ether and the like, or formamides, e.g. formamidine, N,N-dimethylformamide and the like, may be used with alkali metal amides or hydrides; organic tertiary bases, e.g. pyridine and the like, or lower alkanols, e.g. butanol and the like, may be employed with alkali metal hydroxides. The alkali metal salt may also be obtained by treatment of the indene compound with an alkali metal 3-liquid ammonia. If necessary, the alkali metal salt formation may be carried out under cooling or at an elevated temperature, and/or in a closed vessel or in the atmosphere of an inert gas, e.g. nitrogen. Other useful salts of indene compounds are Grignard salts, particularly magnesium halide derivatives of the indene compounds. Such salts may be prepared as previously shown.

Reaction of the salt, particularly the alkali metal salt of the indene compound with a 2-vinyl-pyridine may be carried out by adding the latter to the solution of the salt. The solvent employed in the salt formation may also be used during the addition reaction, or it may be replaced by one of the above-mentioned solvents; an excess of the 2-vinyl-pyridine compound may also serve as a solvent. The addition reaction may be carried out at an elevated temperature, and, if desired, under an increased pressure or in the atmosphere of an inert gas, e.g. nitrogen.

2-vinyl-pyridine is the reagent of choice; other reagents, such as, for example, 2-ethyl-6-vinyl-pyridine, which furnishes 3-(2-(2-ethyl-6-pyridyl)-ethynyl)-2-(tertiary amino) lower alkyl) indenes, may also be used. Condensation 3-(2-(2-ethyl-6-pyridyl)-ethynyl)-2-(tertiary amino) lower alkyl indenes may be obtained, by using in the above reaction 4-vinylpyridine instead of the 2-vinyl-pyridine reagents.

Compounds of the present invention which contain more than one asymmetric atom, may be obtained in the form of mixtures of racemates. Such mixtures of racemates may be separated into individual racemic compounds, salts or the quaternary ammonium compounds thereof, using known methods, which may be, for example, based on physico-chemical differences, such as solubility. Thus, mixtures of racemates may be separated by fractional distillation, if necessary, by using a derivative, e.g. a salt or a quaternary ammonium compound, of a mixture of racemates, by fractional distillation and the like.

Separated racemates or racemates of compounds which contain one asymmetric carbon atom only may be resolved into the optically active forms, the levo-rotatory 1-form and the dextro-rotatory d-form. Such resolution procedure may be carried out according to methods which are suitable for the separation of a racemate. For example, to a solution of the free base of a racemate (a d,l-compound) in a solvent, such as a lower alkanol, e.g. methanol, ethanol, 2-propanol and the like, a lower alkanoic acid, e.g. acetic acid, ethyl methyl ketone and the like, or a mixture of such solvents or any other suitable solvent, is added one of the optically active forms of an acid, containing an asymmetric carbon atom, or a solution thereof, for example, in the same lower alkanol, lower alkanone or solvent hereinafter referred to. Salts, which are formed by the optically active forms of the base with the optically active form of the acid may then be isolated, primarily on the basis of their different solubilities. Especially useful as optically active forms of salt-forming acids, having an asymmetric carbon atom are the d-tartaric acid (L-tartaric acid and the D-tartaric acid; the optically active forms of dibenzoyl tartaric, di-p-toluyl tartaric, malaic, mandelic, 10-carboxyl sulfonic acid, quinic acid and the like, may also be used. The free and optically active base may be obtained from a resulting salt according to methods known for the conversion of a salt into a base, for example, as is outlined hereinafter. An optically active base may be converted into a therapeutically useful acid addition salt with one of the acids mentioned hereinafter, or may be converted into a quaternary ammonium compound as will be described hereinafter. The optically active forms may also be isolated by biochemical methods.

If desired, optically active forms of compounds of this invention, or of salts thereof, may be recovered into racemates. Racemization may be achieved according to certain racemization procedures, for example, by heating of the optically active free base or a salt thereof, such as, for example, a salt of the free base with one of the optically active forms of tartaric acid or with any other suitable acid, if desired, in the presence of a solvent. The conversion of an isomer into a racemate may also occur upon treatment with other energy sources, such as, for example, ultrasonic waves and the like, or by allowing a solution of the isomer to stand over a period of time. Racemization may also be possible by treatment of the free base or of a salt thereof either with an alkaline reagent, such as, for example, aqueous alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, or an alkali carbonate, sodium carbonate and the like, or an alkali metal amide, e.g. sodium amide, potassium amide and the like, in liquid ammonia, or any other suitable alkaline reagent, or with an acidic reagent, such as an inorganic acid, for example, a mineral acid, e.g. hydrochloric, sulfuric acid and the like, or a strong organic acid, for example, a strong sulfonic acid, e.g. p-toluene sulfonic acid and the like. Racemization of one of the optically active forms may be advantageously employed to enhance the yield in the formation of the other optically active form which has the opposite rotation; a racemate resulting from such a racemization procedure can then be recycled into the resolution procedure.

The indene compounds of this invention may be obtained in the form of the free bases or as the salts thereof. A salt may be converted into the free base, for example, by reaction with an alkaline reagent, such as aqueous alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, aqueous alkali metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, ammonia, such as aqueous ammonia, in a lower alkatan, e.g. methanol, ethanol, and the like, or any other suitable alkaline reagent, such as, for example, anion-exchanging resin. A free base may be converted into its therapeutically useful acid addition salts by reacting the former with one of the acids mentioned hereinafter. The salt-forming reaction may be carried out, for example, by treating a solution of the free base in a solvent, such as a lower alkatan, e.g. methanol, ethanol, 2-propanol and the like, an ether, e.g. diethyl ether, diisopropylether and the like, a lower alkanone lower alkanolate, e.g. methyl acetate, ethyl acetate and the like, a lower alkanoate, e.g. acetone, ethyl methyl ketone and the like, an aliphatic hydrocarbon, e.g. pentane, hexane and the like, a halogenated aliphatic hydrocarbon, e.g. chloroform, ethylene chlorohydrate and the like, a monosyclic carbocyclic aryl hydrocarbon, e.g. benzene, toluene, xylene and the like, or any other suitable solvent or solvent mixture, with the acid or a solution thereof and isolating the desired salt. The salts may also be obtained as the hemihydrates, mono-, sesquihydrates or polyhydrates depending on the conditions used in the formation of the addition of the salts. Metho- or poly-salts may be formed according to the conditions used in the procedure for the preparation of the salts and/or the number of salt-forming groups present.

N-oxides of the compounds of the present invention
may be prepared, for example, by treating a solution of the resulting compound containing a tertiary nitrogen atom or a salt thereof in an inert solvent with an N-oxidizing reagent. Such reagents are, for example, ozone, hydrogen peroxide, inorganic peroxides, e.g., peracetic acid, e.g., p-toluene sulfonic acid and the like, organic peroxycarboxylic acids, e.g., p-toluene sulfonic acid and the like, or primarily organic percarboxylic acids, e.g., peracetic acid, perbenzoic acid, monoperoxphthalic acid and the like. Inert solvents are, for example, halogenated lower aliphatic hydrocarbons, e.g., methylene dichloride, ethylene chloride and the like, monocyclic carbocyclic aryl hydrocarbons, e.g., benzene, toluene and the like, or any other suitable, inert solvent employed in N-oxidation reactions. The N-oxides may be obtained in the form of the free bases or as the acid addition salts thereof; N-oxide free bases may be converted into their therapeutically acceptable acid addition salts or the salts may be converted into the free N-oxide bases according to the previously described procedures. Mono- or poly-N-oxides and acid addition salts thereof may be obtained.

The quaternary ammonium compounds of the indene derivatives of this invention may be obtained, for example, by reacting the tertiary base with an ester formed by a hydroxylated lower aliphatic hydrocarbon and a strong inorganic or organic acid. Hydroxylated lower aliphatic hydrocarbon compounds may contain from two to seven carbon atoms and the esters thereof are more especially those with mineral acids, e.g., hydrochloric, hydrobromic, hydriodic, sulfuric acid and the like, or with strong organic acids, such as lower alkane sulfonic acids, e.g., methane sulfonic, ethane sulfonic acid and the like, or with aromatic acids, e.g., hydroxy-lower alkane sulfonic acids, e.g., 2-hydroxy-ethane sulfonic acid and the like, or monocyclic carbocyclic aryl sulfonic acids, e.g., p-toluene sulfonic acid and the like. Such esters are specifically lower alkyl halides, e.g., methyl, ethyl, n-propyl or isopropyl chloride, bromide, iodide and the like, or lower alkyl lower alkane sulfonates, e.g., methyl or ethyl methane sulfonate, methyl ethane sulfonate, ethyl methane sulfonate, ethyl ethane sulfonate and the like, lower alkane hydroxy-lower alkane sulfonate, e.g., methyl 2-hydroxy-ethane sulfonate, ethyl 2-hydroxy-ethane sulfonate and the like, or lower alkyl carbocyclic aryl sulfonate, e.g., methyl-p-toluene sulfonate and the like.

The quaternizing reactions may be performed in the absence or presence of a 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. Suitable solvents are more especially lower alcohols, e.g., methanol, ethanol, propanol, isopropanol, tertiary butanol, n-pentanol and the like, lower alkanones, e.g., acetone, ethyl methyl ketone and the like, organic acid amides, e.g., formamide, N,N-dimethylformamide and the like, aliphatic hydrocarbons, e.g., pentane, hexane and the like, halogenated hydrocarbons, e.g., chloroform, ethylene chlorides, monocylic carbocyclic aryl hydrocarbon, e.g., benzene, toluene and the like, or any other suitable solvent.

Resulting quaternary ammonium compounds may be converted into the corresponding quaternary ammonium hydroxides, for example, by treating a quaternary ammonium halide with silver oxide or a quaternary ammonium salt with barium hydroxide, by treating a quaternary ammonium salt with an anion exchanger, or by electrodialysis. From a resulting quaternary ammonium hydroxide there may be obtained quaternary ammonium salts by reacting the base with acids, for example, those used for the preparation of acid addition salts. A quaternary ammonium compound may also be converted directly into another quaternary ammonium salt without the formation of an intermediate 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. Quaternary ammonium compounds may also be isolated as hydrates; depending on the conditions for their formation and/or the stage of the process used as starting material and the remaining steps of the process carried out. It also includes any new intermediates, which may be formed in one of the procedures outlined hereinbefore.

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 my application Serial No. 852,208 filed November 12, 1959 (now abandoned), which in turn is a continuation-in-part application of my application Serial No. 825,886, filed July 9, 1959, which in turn is a continuation-in-part application of my application Serial No. 810,998, filed May 5, 1959, (now U.S. Patent No. 2,947,756, issued August 2, 1960) which in turn is a continuation-in-part application of my application Serial No. 792,263, filed February 10, 1959, which in turn is a continuation-in-part application of my application Serial No. 771,225, filed November 3, 1958, now Patent No. 2,970,149, which in turn is a continuation-in-part application of my application Serial No. 754,526, filed August 12, 1958 (now abandoned).

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

To 650 ml. of a 0.37 molar solution of phenyl lithium in benzene is added dropwise 24 ml. of dry α-picoline under an atmosphere of nitrogen. After one hour, a solution of 10 g. of 2-(2-N,N-dimethylaminoethyl)-indan-1-one in 20 ml. of benzene is added while stirring, and the reaction mixture is allowed to stand at room temperature for several days. 50 ml. of water is added while cooling and stirring. The water layer is discarded and the benzene solution extracted with a solution of 20 ml. of concentrated aqueous hydrochloric acid in 100 ml. of water.

The acidic extract, containing 2-(2-N,N-dimethylaminoethyl)-1-(2-pyridyl)-methyl-indan-1-ol, is heated on the steam bath for one hour, the solution is then cooled, made basic with aqueous ammonia and then extracted with ether. The ether solution is dried over sodium sulfate, the solvent is removed, and the residue is distilled to yield the 2-(2-N,N-dimethylaminoethyl)-3-(2-pyridyl)-methyl-indene, B.P. 168-170°/0.7 mm.

The free base is converted to the dibydrochloride by treating an ethanolic solution of the former with ethanolic hydrogen chloride and precipitating the salt with ether. The hydroscopic 2-(2-N,N-dimethylaminoethyl)-3-(2-pyridyl)-methyl-indene dibydrochloride is recrystallized from a mixture of ethanol and ether, M.P. 175-177°. The corresponding maleate, prepared by treating an ethanolic solution of the base with maleic acid, melts at 140° after recrystallization from ethanol.

By treating an acetone solution of the 2-(2-N,N-dimethylaminoethyl)-3-(2-pyridyl) -methyl -indene with methyl iodide the diiodoethide of 2-(2-N,N-dimethylaminoethyl)-3-(2-pyridyl)-methyl -indene may be obtained.

The starting material may be prepared as follows: 33.2 g. of dihydropropyran is slowly added to a stirred mixture of 50 g. of α-benzyl-malonic acid and 0.1 g. of p-toluene sulfonic acid in 130 ml. of diethyl ether kept at 30° during
the addition of the dihydropyran. The mixture is stirred for an additional 15 minutes and then poured onto ice. The ether phase is washed with aqueous potassium carbonate, then with water and is dried over magnesium sulfate; the ether is evaporated under reduced pressure by keeping the temperature below 30°C to yield the dihydroxypropyl-3-benzyl-1-malonate. A toluene solution of this ester is gradually added to a solution of 4.86 g. of a 50% suspension of sodium hydride in mineral oil while heating and stirring for six hours. A solution of 10.8 g. of 2-N,N-dimethy laminoethanol chloride in toluene is added dropwise, and the reaction mixture is refluxed for an additional 48 hours. The toluene layer is washed with water, dried over magnesium sulfate and evaporated to yield the dihydroxypropyl-3-benzyl-1-(2-N,N-dimethylaminoethyl)-malonate; yield: 32.2 g. of crude material.

A mixture of the resulting dihydroxypropyl-3-benzyl-1-(2-N,N-dimethylaminoethyl)-malonate in 180 g. of polyphosphoric acid is stirred at 110–120°C during thirty minutes, and then at 150°C during an additional twenty minutes. The reaction mixture is cooled, poured into ice- water, the acidic phase is neutralized with potassium carbonate and extracted with ether. The ether solution is washed with 15 percent aqueous hydrochloric acid solution, the aqueous layer is neutralized with potassium carbonate and again extracted with ether. After washing the ether layer with water and drying it over magnesium sulfate, the solvent is evaporated to yield the 2-(N,N-dimethylaminoethyl)-indan-1-one, yield: 8 g. of crude material. The hydrochloride of the base melts at 165°C after recrystallization from a mixture of ethanol and ether.

**Example 2**

26 g. of 2-ethyl-pyridine is added dropwise to a stirred solution of 650 ml. of an 0.37 molar solution of phenyl lithium in benzene. The addition is carried out in an atmosphere of nitrogen and while cooling to 20°C. After two hours, a solution of 10 g. of 2-(N,N-dimethylaminoethyl)-indan-1-one in 50 ml. of dry ether is added over a period of five minutes while stirring and cooling to room temperature. After standing for twenty-four hours the organo-lithium compounds are decomposed by the addition of 50 ml. of water with external cooling. After separating the water phase from the organic solution, the latter is washed several times with 50 ml. of water, and then extracted with a mixture of 40 ml. of concentrated hydrochloric acid and 100 ml. of water.

The acidic solution, containing 2-(N,N-dimethylaminoethyl)-1-[(2-ethylpyridyl)-ethyl]indan-1-ol, is heated on the steam bath for thirty minutes to effect complete dehydration to the desired indene derivative. The solution is cooled, made strongly basic with an aqueous solution of ammonia and then extracted with ether. The ether phase is dried over sodium sulfate, filtered, evaporated, and the residue is distilled. At 155°C pressure, the excess of 2-ethyl-pyridine is removed, at 120°C/0.5 mm. some unreacted 2-(N,N-dimethylaminoethyl)-indan-1-one distills at 165/175°C/0.5 mm. The 2-(N,N-dimethylaminoethyl)-1-[(2-ethylpyridyl)-ethyl]indene is collected. It may be converted to an aqueous solution of the diethylboride by dissolving it in the appropriate amount of dilute hydrochloric acid.

**Example 3**

To a solution of 1.0 g. of 2-(N,N-dimethylaminoethyl)-1-[(2-ethylpyridyl)-ethyl]indene in 10 ml. of ethanol is added while stirring and heating 0.4 g. of hydrochloric acid. On cooling the 2-(N,N-dimethylaminoethyl)-1-[(2-ethylpyridyl)-ethyl]indene maleate crystallizes, is filtered off, washed with a small amount of ethanol and recrystallized from ethanol, M.P. 158°C.

**Example 4**

To 1.0 g. of 2-(N,N-dimethylaminomethyl)-3-[(2-ethylpyridyl)-(ethyl]-indene in about 10 ml. of ethanol is added a solution of 0.52 g. of d-tartaric acid (also designated as L-tartaric acid) in 5 ml. of ethanol. After cooling during a few days in the ice box, a crystalline precipitate is formed, which is filtered off and recrystallized three times from ethanol to obtain complete resolution. The d-tartarate (L-tartarate) of one of the optically active forms of 2-[(2-N,N-dimethylaminomethyl)-3-[(2-ethylpyridyl)-(ethyl]indene melts at 135–137°C; [α]D25° = -106° (in ethanol).

**Example 5**

By reacting the lithium compound formed from 22 g. of α-picoline and phenyl lithium with 10 g. of 2-(N,N-dimethylaminomethyl)-indan-1-one according to the procedure given in Example 2, the 2-(N,N-dimethylaminomethyl)-1-[(4-pyridyl)-methyl]-indene, B.P. 165–170°C/0.7 mm., is obtained after dehydration of intermediates formed 2-[(2-N,N-dimethylaminomethyl)-1-[(4-pyridyl)-methyl]-indan-1-ol. It can be converted into its maleate according to the procedure described in Example 3.

The following compounds can be prepared according to the above procedure using the appropriate starting materials: 2-[(2-N,N-dimethylaminomethyl)-1-[(4-pyridyl)-methyl]-indene, 2-(N,N-dimethylaminomethyl)-1-[(4-pyridyl)-ethyl]-indene, 2-(N,N-dimethylaminomethylpropylyl)-3-[(4-pyridyl)-ethyl]-indene and the like, and therapeutically acceptable acid addition salts thereof.

**Example 6**

To a solution of 3 g. of potassium hydroxide in 100 ml. of methanol is added 7 g. of 2-(N,N-dimethylaminomethyl)-indene hydrochloride and then 7 ml. of 3-pyridine carboxaldehyde, while stirring and cooling to room temperature. After standing at that temperature overnight, the greater part of the solvent is removed by distillation under reduced pressure, water is added to the crude 2-[(2-N,N-dimethylaminomethyl)-1-[(3-pyridyl)-methyl]-indene is extracted with ether. The solvent is removed by distillation and the residue is dissolved in 50 ml. of ethanol and hydrogenated over 0.5 g. of palladium on charcoal (of 10 percent strength) until one mol of hydrogen is absorbed during about one hour. The reaction mixture is filtered, the solvent is removed under reduced pressure, and the residue is dissolved in 10 ml. of benzene. The benzene solution is chromatographed on 100 g. of aluminum oxide (basic, activity I). Cyclohexane eluates the desired 2-(2-N,N-dimethylaminomethyl)-3-[(3-pyridyl)-methyl]-indene, which is distilled at 160–170°C/0.5 mm. It may be converted into its maleate according to the procedure of Example 3.

The starting material used in the above procedure may be prepared as follows: To a solution of 35 g. of 2-(N,N-dimethylaminomethyl)-indan-1-one in 100 ml. of ethanol is gradually added 10 g. of sodium borohydride while stirring. The reaction mixture is refluxed for two hours, the greater part of the solvent is then removed by distillation and the residue is diluted with water. The 2-(2-N,N-dimethylaminomethyl)-indan-1-ol is extracted with ether and the crude base is obtained after removal of the solvent; its piperate melts at 160–170°C. A solution of the crude base in 350 ml. of glacial acetic acid and 125 ml. of concentrated hydrochloric acid is refluxed for one-half hour; most of the solvent is then removed by distillation under reduced pressure. The residue is diluted with water, made basic with ammonia and extracted with ether. On addition of 60 ml. of ethanolic hydrogen chloride to the ether solution, the 2-(2-N,N-dimethylaminoethyl)-hydrochloride precipitates and is recrystallized from ethanol, M.P. 202–205°C.

The 2-(3-N,N-dimethylaminopropyl)-3-[(3-pyridyl)-methyl]-indene, 2-(2-N,N-dimethylaminomethyl)-3-[(2-ethylpyridyl)-(ethyl)]indene and the like as well as their therapeutically acceptable acid addition salts thereof, can...
be prepared according to the above procedure by using the appropriate starting materials.

Example 7
To a stirred suspension of 14 g. of lithium in 400 ml. of dry ether is added about 10 ml. of a mixture of 159 g. of bromobenzene in 200 ml. of dry ether, in the atmosphere of dry nitrogen. The additional bromobenzene solution is given to the mixture at such a rate as to maintain the exothermic reaction. A total of 80 g. of 2-ethyl-pyridine, dried over calcium hydride, is then added dropwise at 20° while stirring. After standing at room temperature for four hours an ether solution of 50 g. of 2-(2,2,2-trimethylacryloyl)indan-1-one is added while stirring and cooling to room temperature, at which temperature the reaction is allowed to stand for three days. After filtration and dilution with ether, the organic solution is washed three times with water and then extracted with 15% aqueous hydrochloric acid.

The acidic solution, containing 2-(2,2,2-trimethylacryloyl)indan-1-one, is neutralized with aqueous ammonia and extracted with ether. The 2-(2,2,2-trimethylacryloyl)-3-[1-(2-pyridyl)-ethyl]-indene obtained after washing, drying and evaporating the solvent and distillation; yield: 23 g.

Example 8
A solution of 17 g. of 2-propyl-pyridine in 50 ml. of ether is added over a period of 15 minutes to a stirred solution of 8 g. of butyl lithium in 50 ml. of hexane in an atmosphere of dry nitrogen. After three hours a solution of 13 g. of 2-(2,2,2-trimethylacryloyl)-indan-1-one in 50 ml. of ether is added over a period of fifteen minutes while stirring. The reaction mixture is allowed to stand for two days at room temperature; 50 ml. of water is then added dropwise, the aqueous layer is removed and the organic phase is extracted with 60 ml. of 6N aqueous hydrochloric acid.

The acidic extract, containing 2-(2,2,2-trimethylacryloyl)-1-[1-(2-pyridyl)-propyl]-indan-1-one, is heated on the steam bath for one hour, cooled, basified with aqueous ammonia and extracted with ether. The ether is removed by distillation and the 2-(2,2,2-trimethylacryloyl)-3-[1-(2-pyridyl)-propyl]-indene is distilled, B.P. 165-175°/0.5 mm.

The monomethiodide of 2-(2,2,2-trimethylaminoethy1)-3-[1-(2-pyridyl)-propyl]-indene, M.P. 255° (decomposition) after recrystallization from water, is prepared by reacting the free base in ethanol with methyl iodide.

Example 9
50 ml. of an ether solution of phenyl lithium, prepared from 1.75 g. of lithium and 20 g. of bromobenzene according to the procedure described in Example 7, is added dropwise and very slowly over a period of three hours to a stirred solution of 12 g. of 2-isopropyl-pyridine in 25 ml. of ether in an atmosphere of dry nitrogen. After standing for an additional two hours, a solution of 15 g. of 2-(2,2,2-trimethylacryloyl)-indan-1-one in 50 ml. of ether is added; the reaction mixture is allowed to stand for one day at room temperature and is then worked up as described in Example 8. The dehydration product of any intermediately formed 2-(2,2,2-trimethylacryloyl)-1-[1-(2-pyridyl)-2-propyl]-indan-1-one, is distilled to yield the desired 2-(2,2,2-trimethylacryloyl)indan-1-one, B.P. 155-160°/0.4 mm.

The methodide of 2-(2,2,2-trimethylacryloyl)-3-[2-(2-pyridyl)-2-propyl]-indene, prepared according to the previously given procedure, melts at 234° (with decomposition) after recrystallization from ethanol.

Example 10
To a stirred solution of 10.7 g. of 2,6-lutidine in 25 ml. of ether in an atmosphere of dry nitrogen is added dropwise and over a period of three hours 50 ml. of an ether solution of phenyl lithium, prepared from 1.75 g. of lithium and 20 g. of bromobenzene according to the procedure described in Example 7. After standing for an additional two hours at room temperature, 15 g. of 2-(2,2,2-trimethylacryloyl)-indan-1-one in 50 ml. of ether is added and the reaction mixture is allowed to stand at room temperature. It is worked up as described in Example 8; the 2-(2,2,2-trimethylacryloyl)-3-[1-(2-pyridyl)-ethyl]-indene, B.P. 150-157/0.4 mm., is obtained after dehydration of an intermediately formed 2-(2,2,2-trimethylacryloyl)-1-[1-(2-pyridyl)-propyl]-indan-1-one with hydrochloric acid.

Substituting 2,6-lutidine by 5-chloro-2-methyl-pyridine in the above procedure yields the desired 3-[1-(5-chloro-2-pyridyl)-methyl]-2-(2,2,2-trimethylacryloyl)-indene.

Example 11
To an ether solution of 0.125 mol of phenyl lithium (prepared from 1.75 g. of lithium and 20 g. of bromobenzene) is given while stirring in an atmosphere of nitrogen and at room temperature an ether solution of 13.3 g. of 2-ethyl-pyridine.

After standing for two hours, the reaction mixture is cooled to –5° with an ice-salt mixture, and a solution of 12.5 g. of 2-(2,2,2-trimethylacryloyl)-indan-1-one in ether is slowly added while stirring. The reaction mixture is allowed to stand at room temperature overnight and is then decomposed by carefully adding water. The organic material is extracted with ether and the ether solution is washed with 15 percent aqueous hydrochloric acid to separate the basic material. The acidic layer, containing 2-(2,2,2-trimethylacryloyl)-1-[1-(2-pyridyl)-ethyl]-indan-1-one, is heated on the steam bath for thirty minutes and, after cooling, is made basic with aqueous ammonia. The organic material is extracted with ether, the ether layer is washed with water and dried over sodium sulfate. The solvent is evaporated and the 2-(2,2,2-trimethylacryloyl)-3-[1-(2-pyridyl)-ethyl]-indene is distilled, B.P. 178-180°/0.55 mm.; yield: 10 g.

The maleate is prepared according to the procedure of Example 3 and melts at 120° after recrystallization from ethanol.

The starting material used in the above reaction may be prepared as follows: To a warm suspension of 25 g. of sodium hydride in 1,000 ml. of toluene is given dropwise while stirring 100 g. of diethyl a-benzyl malonate. The reaction mixture is refluxed for one hour after completion of the addition, then a solution of 70 g. of 2,2,2-trimethylacryloyl chloride in toluene is added and the reaction mixture is refluxed overnight. The tolulene solution is extracted with aqueous hydrochloric acid, the acidic layer is made basic with aqueous ammonia and the organic material is extracted with ether. The ether solution is washed, dried and evaporated under reduced pressure to yield 136 g. of diethyl a- (a)-benzyl-2-(2,2,2-trimethylacryloyl) malonate, the oxalate of which melts at 117-119°.

A mixture of 136 g. of diethyl a-benzyl-α-(2,2,2-trimethylacryloyl) malonate, 65.5 g. of potassium hydroxide, 85 ml. of water and 340 ml. of ethanol is refluxed for 4 hours, then concentrated under reduced pressure. The solid residue is dissolved in a minimum amount of water, the aqueous solution is neutralized with acetic acid while externally cooling and the resulting a-benzyl-α-(2,2,2-dimethylacryloyl) malonic acid is filtered off and washed with ice water and ethanol. After being reduced under pressure, it melts at 128°; yield: 103 g. 103 g. of a-benzyl-α-(2,2,2-dimethylacryloyl) malonic acid is heated to 180° with occasional stirring until foaming ceases; the decarbonylation is complete after approximately 15 minutes. The resulting melt is cooled.
and diluted with about 15 ml. of ethanol, ether is added and the 2-benzyl-4-N,N-diethylamino-butyric acid is added to 15 g. of polyphosphoric acid, kept at 100-120°C. The temperature is then raised to 140-145°C for about 20 minutes and the acid is decomposed by pouring the reaction mixture into ice water and neutralizing the aqueous solution with potassium carbonate. The 2-(2-N,N-diethyiaminoethyl)-indan-1-one is extracted with ether, the ether solution is washed and dried, and the ether is evaporated. The hydrochloride salt, prepared according to the previously given procedure, melts at 164-166°C; yield: 12.3 g.

The following compounds can be obtained according to the above-described procedure by selecting the appropriate starting materials prepared according to the previously outlined method:

- 2 - (2 - (N - cyclopentyl - N - methylamino) - ethyl) - 3 - (1 - (2 - pyridyl)-ethyl)-indene
- 2 - (2 - (N - cyclohexyl - N - ethyl - amino) - ethyl) - 2 - (1 - (2 - pyridyl)-ethyl)-indene
- 2 - (2 - (N - benzyl - N - methyl - amino) - ethyl) - 3 - (1 - (2 - pyridyl)-ethyl)-indene
- 2 - (2 - (N - ethyl - N - (1 - phenylethyl) - amino) - ethyl)-3-(1-(2-pyridyl)-ethyl)-indene
- 2 - (2 - (N - methyl - N - (2 - phenylethyl) - amino)-ethyl)-3-(1-(2-pyridyl)-ethyl)-indene and the like.

**Example 12**

The 5-chloro-2-(2-N,N-dimethylaminomethyl)-3-(1-(2-pyridyl)-methyl)-indene, purified by distillation, is obtained by treatment of 6-chloro-2-(2-N,N-dimethylaminomethyl)-indan-1-one with the lithium compound of α-picoline according to the procedure outlined in Example 1, where, by any intermediately formed 6-chloro-2-(2-N,N-dimethylaminomethyl)-1-(1-(2-pyridyl)-methyl)-indan-1-ol is dehydrated by heating the acidic extract of the reaction product.

The starting material used in the above reaction may be prepared as follows: 70 g. of diethyl α-(4-chlorobenzyl)-methylmalonate, B.P. 150-151°C/0.5 mm., is added to a stirred suspension of 8 g. of sodium hydride in 50 ml. of refluxing toluene. After 2 hours, 34 g. of 2-N,N-dimethylaminomethyl chloride is added dropwise and the mixture is refluxed for an additional 12 hours, then cooled and extracted with an excess of hydrochloric acid. The acidic extract is treated with aqueous ammonia and diethyl α-(4-chlorobenzyl)-α-(2-N,N-dimethylaminomethyl)-malonate is separated in a separatory funnel. It is characterized as the crystalline oxalate, which melts at 172-178°C after recrystallization from a mixture of ethanol and ether.

The diethyl α-(4-chlorobenzyl)-α-(2-N,N-dimethylaminomethyl)-malonate is hydrolyzed with potassium hydroxide as described in Example 4; the resulting α-(4-chlorobenzyl)-α-(2-N,N-dimethylaminomethyl)-malonic acid is melted at 180-181°C after recrystallizing from water. The 2-(4-chlorobenzyl)-4-N,N-dimethylamino-butyric acid is obtained by decarboxylating the malonic acid derivative at a temperature of 185°C for 5 minutes, and is obtained in crystalline form from ether. It is cyclized as described in Example 11 by treatment with polyphosphoric acid to yield the desired 6-chloro-2-(2-N,N-dimethylaminomethyl)-indan-1-one which is converted to its hydrochloride. 175-176°C.

The above procedure can also be used for the preparation of 2-(2-N,N-dimethylaminomethyl)-5-methyl-3-(1-(2-pyridyl)-methyl)-indene by using 2-(2-N,N-dimethylaminomethyl)-6-methyl-indan-1-one, prepared according to the aforementioned procedure, as the starting material.

**Example 13**

By reacting the lithium compound of α-picoline with...
the above procedure by using 2-(2-(4-ethyl-1-piperazino)-ethyl)-indan-1-one as the starting material.

**Example 15**

A solution of 2-(2-N,N-dimethylaminomethyl)-6-methoxy-indan-1-one in ether is added slowly to an ether solution of the lithium compound of α-picoline under an atmosphere of nitrogen. The reaction mixture is decomposed by the addition of water, the organic material is extracted with ether and the residue of the ether extract, containing 2-(2-N,N-dimethylaminomethyl)-6-methoxy-1-(2-pyridyl)-ethyl-indan-1-ol, is dehydrated by heating with aqueous hydrochloric acid to yield the 2-(2-N,N-dimethylaminomethyl)-5-methoxy-3-(2-(2-pyridyl)-ethyl)-methyl-2-indanone, which is purified by distillation and may be converted into the maleate according to the procedure of Example 3.

The starting material used in the above reaction may be prepared as follows: To a solution of 16.25 g. of sodium in 288 ml of ethanol is slowly added 115.3 g. of diethyl maleate at 50°C. The clear reaction solution is treated dropwise with 110.7 g. of 4-methoxy-benzyl chloride and the reaction mixture is refluxed for one hour. After filtration and evaporation of the solvent, the residue is diluted with water and the oily product is extracted with ether, the ether solution is washed and dried, and the solvent is evaporated. The diethyl α-(4-methoxybenzyl)-maleate is distilled, B.P. 155-165°/0.75 mm.; yield: 66.67 g.

To a refluxing suspension of 6.1 g. of sodium hydride in 550 ml of toluene is added dropwise while stirring 66.7 g. of diethyl α-(4-methoxybenzyl)-maleate and the reaction mixture is refluxed for one hour. A solution of 31 g. of 2-N,N-dimethylaminomethyl chloride in toluene is added, the reaction mixture is heated overnight and the toluene solution is then extracted with aqueous hydrochloric acid. The acidic layer is made basic with aqueous ammonia, the organic material is extracted with ether, the ether solution is washed and dried and the solvent is evaporated. 77.0 g. of diethyl α-(2-N,N-dimethylaminomethyl)-α-(4-methoxybenzyl)-maleate is obtained and characterized as the hydrochloride salt, 145-147°C.

A mixture of 73.4 g. of diethyl α-(2-N,N-dimethylaminoethyl)-α-(4-methoxybenzyl)-maleate, 26.8 g. of potassium hydroxide, 30 ml of water and 148 ml of ethanol is refluxed for 4 hours and then concentrated under reduced pressure. The solid residue is dissolved in a minimum amount of water and neutralized with acetic acid under external cooling. The resulting α-(2-N,N-dimethylaminomethyl)-α-(4-methoxybenzyl)-maleic anhydride is filtered off, washed with ice water and ethanol and dried under reduced pressure, M.P. 163-165°; yield: 45.5 g.

45.5 g. of α-(2-N,N-dimethylaminomethyl)-α-(4-methoxybenzyl)-maleic anhydride is heated to 180°C with occasional stirring until foaming ceases after completion of decarboxylation. The resulting melt is diluted with about 10 ml of ethanol, ether is added, and the 4-N,N-dimethylamino-2-α-(4-methoxybenzyl)-butyric acid crystallizes, M.P. 87°C; yield: 33.7 g.

33.7 g. of 4-N,N-dimethylaminomethyl-2-(4-methoxybenzyl)-butyric acid is gradually added to 168 g. of polyphosphoric acid kept at 90-120°C, and the reaction mixture is heated to 140-150°C for 20 minutes. It is then poured into ice water, neutralized with potassium carbonate, and, because no crystalline product is formed, is made strongly basic with 3N aqueous sodium hydroxide. The organic material is extracted with ether, the ether solution is washed with water and dried over sodium sulfate, and the solvent is then evaporated. The resulting 2-(2-N,N-dimethylaminomethyl)-6-methoxy-indan-1-one is converted to the hydrochloride, M.P. 225-227°C; yield: 14.5 g.

The 2-(2-N,N-dimethylaminomethyl)-6-methoxy-indan-1-one, used as the starting material in the above reaction, may be replaced by 2-(2-N,N-dimethylaminomethyl)-6-methyl-indan-1-one or 2-(2-N,N-dimethylaminomethyl)-6-trifluoromethyl-indan-1-one and reacted with the lithium compound of α-picoline to yield the desired 2-(2-N,N-dimethylaminomethyl)-5-methyl-3-(2-pyridyl)-methyl-2-indanone, respectively; the latter may be obtained after dehydration of any intermediate formed 2-(2-N,N-dimethylaminomethyl)-6-methyl-1-(2-pyridyl)-methyl-1-indan-1-ol or 2-(2-N,N-dimethylaminomethyl)-1-(2-pyridyl)-methyl-1-indan-1-ol, respectively, in the presence of an acid. The starting materials used for the manufacture of the above compounds may be prepared according to the procedure described in detail hereinabove by substituting 4-methylbenzyl-bromide or 4-trifluoromethyl-benzyl chloride for the 4-methoxybenzyl chloride.

**Example 16**

To a solution of potassium tertiary butoxide, prepared by dissolving 4 g. of potassium in 300 ml of anhydrous tertiary butanol, is added dropwise under an atmosphere of dry nitrogen 15 g. of 2-(2-N,N-dimethylaminomethyl)-indene. After the addition is completed, 17 g. of freshly distilled 2-vinyl-pyridine is given to the solution of the potassium salt; the reaction mixture is then refluxed overnight. The major part of the solvent is removed under reduced pressure, water is added to the concentrated solution, and the separating oil is extracted into ether. The ether solution is dried over sodium sulfate, the solvent is evaporated and the residue is distilled under reduced pressure. The excess 2-vinyl-pyridine is removed first at 15 mm. and the desired 2-(2-N,N-dimethylaminomethyl)-3-(2-pyridyl)-ethyl-indene distills at 175-180/0.7 mm.

1 ml of methyl iodide is added to a solution of 1 g. of 2-(2-N,N-dimethylaminomethyl)-3-(2-pyridyl)-ethyl-indene in 5 ml of ethanol at room temperature; the reaction mixture is allowed to stand for one hour and the crystalline material is then filtered off. The diethylidio 2-(2-N,N-dimethylaminomethyl)-3-(2-pyridyl)-ethyl-indene is recrystallized from a mixture of ethanol and water, M.P. 235-237°C (with decomposition). The starting material may be prepared as described in Example 6. The resulting hydrochloride is added to the free base by dissolving the salt in a minimum amount of water, adding aqueous ammonia and extracting the free base with ether; the ether solution is dried over soda lime under reduced pressure, the solvent is evaporated and the 2-(2-N,N-dimethylaminomethyl)-indene is distilled at 108-115°C/1 mm.

The 2-(2-N,N-dimethylaminomethyl)-indene, used as the starting material in the above reaction, may be replaced by 2-(3-N,N-dimethylaminopropanyl)-indan-1-one (Example 19) with sodium borohydride, dehydrating the resulting 2-(3-N,N-dimethylaminopropanyl)-indan-1-ol by heating a solution of the latter in a mixture of glacial acetic acid and concentrated hydrochloric acid and converting the resulting hydrochloride of the 2-(3-N,N-dimethylaminomethyl)-indene into the free base. The potassium salt of the latter, obtained by treatment with potassium tertiary butoxide in tertiary butanol, may be reacted with 2-vinyl-pyridine as shown hereinabove to yield the desired 2-(3-N,N-dimethylaminopropanyl)-3-(2-pyridyl)-ethyl-indene.

**Example 17**

The reaction of 2-(2-N,N-dimethylaminomethyl)-3-methyl-indan-1-one with the lithium compound of 2-(2-pyridyl)-pyridine according to the procedure of Example 7 furnishes 2-(2-N,N-dimethylaminomethyl)-3-methyl-1-(2-pyridyl)-ethyl-indan-1-ol, which is dehydrated to the desired 2-(2-N,N-dimethylaminomethyl)-1-methyl-3-(2-(2-N,N-dimethylaminomethyl)-6-methoxy-ethyl)-6-trifluoromethyl-indan-1-one and reacted with the lithium compound of α-picoline to yield the desired...
pyridyl)-ethyl)-indene by treatment with warm aqueous hydrochloric acid.

The starting material used in the above reaction may be prepared as follows: To a solution of 12.5 g. of sodium in 200 ml. of ethanol, kept at 50°, is slowly added 81 ml. of diethyl malonate, followed by dropwise addition of 100 g. of 1-phenylethyl bromide. The reaction mixture is refluxed for about one hour, the resulting sodium bromide is filtered off and the solvent is evaporated. The residue is distilled to give 83 g. of diethyl a-(1-phenylethyl)-malonate, B.P. 165-170°/18 mm.

The diethyl a-(1-phenylethyl)-malonate is slowly added to a heated suspension of 17.5 g. of sodium hydride (1:1 mixture in mineral oil) in 750 ml. of toluene. The reaction mixture is refluxed for one hour, a tolune solution of 55 g. of 2-N,N-dimethylaminomethyl chloride is added, and refluxing is continued overnight. The basic material is extracted with 15% aqueous hydrochloric acid; the acid solution is then made basic with ammonia and extracted with ether. The ether is evaporated to yield 93 g. of the desired diethyl a-(2-N,N-dimethylaminoethyl)-a-(1-phenylethyl)-malonate, the oxalate of which melts at 156-158°.

This ester is hydrolyzed by refluxing with 27.7 g. of sodium hydride in 45.5 ml. of water and 186 ml. of ethanol for 8 hours. After evaporation of the organic solvent, a minimum amount of water is added to complete solution, whereupon the hydrochloride is formed by the addition of concentrated aqueous hydrochloric acid. The water is evaporated under reduced pressure and the residue is treated with boiling ethanol to extract the hydrochloride salt. The separated organic solution is evaporated and the residue is decarboxylated by heating at 150° for 15 minutes and then raising the temperature to 180-190° until foaming ceases. The non-crystalline residue is dissolved in a minimum amount of hot ethanol and poured onto a suspension of a diatomaceous earth in ethanol. The mixture is filtered and added to 600 g. of polyphosphoric acid at a temperature of 85° while vigorously stirring. The reaction temperature is kept at 90-95° during the addition and then raised to 95-100° for 20 minutes. After cooling, it is poured onto ice, the solution is filtered and the filtrate is neutralized with potassium carbonate. The desired 2-(2-N,N-dimethylaminomethyl)-3-methyl-indan-1-one is extracted with ether and distilled after the evaporation of the organic solvent, B.P. 135°/1 mm.; yield: 31.5 g.

Example 18
A solution of 15 g. of dry 2-ethyl-pyridine in 25 ml. of dry benzene is added to a solution of 60 ml. of butyl lithium in hexane (equivalent to 9 g. of butyl lithium) while cooling to 25° and in an atmosphere of dry nitrogen. After three hours, 12 g. of 2-(2-N,N-dimethylaminoethyl)-2-methyl-ethyl)-(indan-1-one in 25 ml. of benzene is added at 25°. The reaction mixture is allowed to stand for seven days at room temperature, 100 ml. of water is added dropwise to decompose the organic lithium salts and the water layer is separated. The remaining organic phase is extracted with 75 ml. of 4 N aqueous hydrochloric acid.

The acidic solution, containing 2 - (2-N,N-dimethy lamino - 2 - methyl-ethyl)-1-[(2-pyridyl)-ethyl]-indan-1-o1, is heated on the steam bath for thirty minutes and is then made basic with aqueous ammonia. After extraction with ether the organic layer is washed over sodium carbonate and then evaporated. The remaining residue is distilled under reduced pressure and the fraction, boiling at 165-170°/0.2 mm., is collected. This fraction is a mixture of approximately equal amounts of the two racemates of 2-(2-N,N-dimethylamino-2-methyl-ethyl)-2-[(2-pyridyl)-ethyl]-indene.

The above mixture is prepared according to the procedure given in Example 3.

The two racemates of the above mixture of racemates may be separated as follows: 5 g. of the mixture is dissolved in 20 ml. of ethanol and 3 ml. of methyl iodide is added. Within ten minutes one of the racemates of 2-(2-N,N-dimethylamino - 2 - methyl-ethyl)-3-[(2-pyridyl)-ethyl]-indene methiodide crystallizes and is separated by filtration, M.P. 215° (decomposition). The second racemate methiodide, which is non-crystalline, can be separated by evaporating the solvent. The distillation of the separated methiodides at 170°/0.2 mm. yields the single racemates of 2-(2-N,N-dimethylamino-2-methyl-ethyl)-3-[(2-pyridyl)-ethyl]-indene.

The starting material used in the above reaction may be prepared as follows: 300 g. of diethyl a-benzyl malonate is added over a period of thirty minutes to a refluxing suspension of 66 g. of sodium hydride in mineral oil (50% sodium hydride) in 2000 ml. of toluene. After refluxing for one hour a solution of 2-N,N-dimethylamino-2-methyl-ethyl chloride in toluene (prepared by dissolving 310 g. of 2-N,N-dimethylamino-2-methyl-ethyl chloro hydrochloride in 600 ml. of water, basifying the aqueous solution and extracting it with 1000 ml. of toluene, which solution is dried over sodium sulfate) is added over a period of one hour. After refluxing overnight, the reaction mixture is cooled and extracted with aqueous hydrochloric acid. The acidic extract is basified with ammonia and the separating solvent is extracted with ether. After drying, the ether is evaporated, leaving 396 g. of diethyl a-benzyl-a-(2-N,N-dimethylamino-2-methyl-ethyl)-malonate as a residue.

120 g. of diethyl a-benzyl-a-(2-N,N-dimethylamino-2 methyl-ethyl)-malonate is added to 840 g. of polyphosphoric acid at 100° while stirring. The temperature is raised slowly to 150-160° and held for thirty minutes. After treatment with ice water, the reaction mixture is made basic with potassium carbonate and extracted with ether. The ether is evaporated to yield a residue containing as the main constituent the 2-(2-N,N-dimethylamino-2-methyl-ethyl)-2-carbethoxy-indan-1-one. 75 g. of this residue is re-extracted with 650 ml. of 2 N aqueous hydrochloric acid for four hours. The acidic solution is made basic with ammonia, the organic material is extracted with ether, the ether evaporated and the residue distilled at 112-114°/0.23 mm. This fraction is converted to the hydrochloride with ethanolic hydrogen chloride and the crystalline material is recrystallized from ethanol, M.P. 194-196°. This hydrochloride yields the free 2-(2-N,N-dimethylamino-2-methyl-ethyl)-indan-1-one by treatment with ammonia.

Example 19
A solution of 3.4 of 2-ethyl-pyridine in 50 ml. ether is added, while stirring, at room temperature and in an atmosphere of dry nitrogen, to 14 ml. of a 2.4 molar butyl lithium solution in hexane. After standing for one hour, a solution of 2 g. of 2-(3-N,N-dimethylaminopropyl)-indan-1-one in 10 ml. of ether is added. The reaction mixture is allowed to stand overnight, water is added and the basic material is then extracted with 30 ml. of 3 N aqueous hydrochloric acid. The acidic extract is treated for one hour on the steam bath, the aqueous hydrogen chloride and the aqueous ammonia and extracted with ether. The ether extract is dried over sodium sulfate and the ether, as well as any excess of 2-ethyl-pyridine is removed by distillation at 15 mm. by gradually raising the bath temperature to 120°. The residue is dissolved in a small amount of benzene and chromatographed on 30 g. of alumina oxide. The eluate with benzene is evaporated to dryness and the resulting 2-(3-N,N-dimethylaminopropyl)-3-[(2-pyridyl)-ethyl]-indene is converted to the maleate. The salt is recrystallized from ethanol, M.P. 154-155°.

The (2-N,N-dimethylaminopropyl)-indan-1-one, of which the hydrochloride melts at 118-120°, and which is used as the starting material in the above reaction, may be prepared according to the procedure used for other starting materials, as, for example, outlined in Ex-
ample 11. The intermediate \( \alpha \)-benzyl-\( \omega \)-(3-N,N-dimethylamino)propyl)-malonic acid melts at 204-205° (after recrystallization from water) and the \( \alpha \)-benzyl-\( \omega \)-(3-N,N-dimethylamino)propyl)-succinic acid at 110° (after recrystallization from a mixture of ethanol and ether).

**Example 20**

3 g. of 4-chloro-2-(2-N,N-dimethyaminomethyl)-indan-1-one in 25 ml. of ether is added at room temperature to a solution of the lithium compound of 2-ethyl-pyridine, prepared by adding 28 ml. of a 2.5 molar solution of butyl lithium in hexane to 7.5 g. of 2-ethyl-pyridine in 50 ml. of ether. After standing overnight, water is added dropwise to decompose the organometallic compound. The organic layer is extracted with 85 ml. of 3 N aqueous hydrochloric acid and the extract is heated for one hour on the steam bath. The solution is made basic with aqueous ammonia, then extracted with ether, the ether layer is dried, and the solvent is evaporated. The residue is distilled; any excess of 2-ethyl pyridine is removed at 15 mm. pressure and the desired 7-chloro-2-(2-N,N-dimethyaminomethyl)-3-[1-(2-pyridyl)]-ethyl-1-indene is collected at 200-205°/0.5 mm.

2.8 g. of the free base is treated with an ethanol solution of 5 g. of maleic acid; the solution is evaporated to dryness to yield the desired 7-chloro-2-(2-N,N-dimethyaminomethyl)-3-[1-(2-pyridyl)]-ethyl-1-indene maleate.

The starting material may be prepared as follows: To a solution of 56 g. of sodium in 800 ml. of absolute ethanol is added 230 ml. of diethyl malonate. A total of 257 g. of 2-chlorobenzyl chloride is added to the solution while maintaining refluxing conditions. After boiling for an additional two hours, the solution is filtered and the solvent is evaporated. The residue is distilled with an azeotrope of water and alcohol. After washing the organic material is extracted with chloroform and the chloroform layer is dried over magnesium sulfate and evaporated. The residue is distilled at 195-205°/20 mm. to yield the desired diethyl \( \alpha \)-(2-chloro-benzoyl)-malonate.

To a hot suspension of 39 g. of sodium hydride (of fifty percent strength) in 1500 ml. of toluene, the desired diethyl \( \alpha \)-(2-chloro-benzoyl)-malonate is added dropwise while stirring 200 g. of diethyl \( \alpha \)-(2-chloro-benzoyl)-malonate. After refluxing for one hour a toluene solution of 98.5 ml. of 2-N,N-dimethylaminomethyl chloroide is added. The reaction mixture is refluxed overnight; the toluene solution is extracted with 15 percent aqueous hydrochloric acid and the acid layer is made basic with aqueous ammonia. The organic material is extracted with ether, the ether solution is washed with water, dried over magnesium sulfate and evaporated. The residue represents 259 g. of crude diethyl \( \alpha \)-(2-chloro-benzoyl)-malonate.

A mixture of 253 g. of diethyl \( \alpha \)-(2-chloro-benzoyl)2-(2-N,N-dimethylamino)acetic acid, 147 g. of potassium hydroxide, 470 ml. of ethanol and 128 ml. of water is refluxed for four hours, then concentrated under reduced pressure. The residue is dissolved in a minimum amount of water and cautiously neutralized with acetic acid. The crystalline material is filtered off, washed with ice water and ethanol to yield 160 g. of the \( \alpha \)-(2-chloro-benzoyl)-\( \alpha \)-(2-N,N-dimethylaminomethyl) malonic acid, M.P. 123-125° (with decarboxylation).

The \( \alpha \)-(2-chloro-benzoyl)-\( \alpha \)-(2-N,N-dimethylaminomethyl) malonic acid is decarboxylated by heating at 170-180° until the evolution of carbon dioxide cesses. The resulting melt is cooled and recrystallized from ether; the desired 2-(2-chloro-benzoyl)-4-N,N-dimethylamino-butyric acid melts at 83°; yield: 75 g.

50 g. of the \( \alpha \)-(2-chloro-benzoyl)-4-N,N-dimethylamino-butyric acid is added gradually and at a temperature of 95-100° to 250 g. of polyphosphoric acid; the reaction mixture is then heated at 115-120° for one hour and poured into ice water. After neutralizing with solid potassium carbonate, the organic material is extracted with ether, the ether layer is washed with water, dried over magnesium sulfate and evaporated. The residue is distilled to yield the desired 4-chloro-2-(2-N,N-dimethylaminomethyl)-indan-1-one, B.P. 135-138°/mm. Its hydrochloride salt melts at 220-221°.

**Example 21**

To a solution of 29.3 g. of 2-(2-N,N-dimethylamino)ethyl)-3-[1-(2-pyridyl)-ethyl]-indene in 50 ml. of acetone is added 15 g. of d-tartaric acid (also designated as L-tartaric acid) in 50 ml. of ethanol. The solution is concentrated to 75 ml. under atmospheric pressure and diluted with 50 ml. of acetone. The solution is cooled to −5° and allowed to stand for 48 hours; the crystalline precipitate is filtered off, washed with 25 ml. of acetone, dried at 50° under reduced pressure and then dissolved in 60 ml. of anhydrous ethanol. The mixture is filtered, the filtrate is diluted with 60 ml. of acetone, the solution is cooled to −5° and allowed to stand overnight. The crystalline material is filtered off, washed with 10 ml. of acetone and dried at 50° under reduced pressure. The resulting d-tartarate (or L-tartarate) of 1,2-(2-N,N-dimethylamino)ethy1)-3-[1-(2-pyridyl)-ethyl]-indene melts at 134-136°, [\( \alpha \)]\text{D} = −110° (in ethanol).

It is repeatedly recrystallized from a 1:1 mixture of ethanol and acetone until a compound of constant melting point and constant rotation is obtained. The pure d-tartarate (or L-tartarate) of 1,2-(2-N,N-dimethylamino)ethyl)-3-[1-(2-pyridyl)-ethyl]-indene melts at 142-143°, [\( \alpha \)]\text{D} = −116.2° (in ethanol) and [\( \alpha \)]\text{D} = −77.8° (in water).

A solution of 6.0 g. of the d-tartarate (or L-tartarate) of 1,2-(2-N,N-dimethylamino)ethyl)-3-[1-(2-pyridyl)-ethyl]-indene in 20 ml. of water, containing 10 g. of crushed ice, is treated with 5 ml. of aqueous ammonia; the liberated 1,2-(2-N,N-dimethylamino)ethyl)-3-[1-(2-pyridyl)-ethyl]-indene is extracted with two 25 ml. portions of ethyl acetate. The organic phase is separated, washed neutral with water, dried over 5 g. of magnesium sulfate and clarified by filtration. The filtrate is neutralized by adding 1.7 g. of maleic acid in 10 ml. of acetone, the solvent is evaporated at 40° to 50° and the crystalline residue is dissolved in 20 ml. of acetone. By cooling to −5°, a crystalline precipitate is formed, which is removed by filtration and washed with 5 ml. of acetone. The resulting 1,2-(2-N,N-dimethylamino)ethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate is recrystallized from 15 ml. of acetone, M.P. 128-130°, [\( \alpha \)]\text{D} = −66.8° (in ethanol, [\( \alpha \)]\text{D} = −123.4° (in water); yield: 3.1 g.

Generally, the maleate of 1,2-(2-N,N-dimethylaminomethyl)-3-[1-(2-pyridyl)-ethyl]-indene may be prepared according to procedures known for the preparation of a salt, for example, by reacting 1,2-(2-N,N-dimethylaminomethyl)-3-[1-(2-pyridyl)-ethyl]-indene with maleic acid in the presence of a diluent. Appropriate solvents are, for example, lower alkanols, e.g. methanol, ethanol, isopropanol and the like, lower alkanones, e.g. acetone, ethyl methyl ketone and the like, lower alkyl lower alkanones, e.g. methyl acetate, ethyl acetate and the like, ethers, e.g. diethyl ether, tetrahydrofuran and the like, or mixtures of such solvents. Preferably, a solution of the free base in one of the above solvents, for example, ethyl acetate and the like, is treated with the maleic acid, which may be used in the form of a solution with one of the above alcohols, ketones and ethers, preferably isopropanol and the like. The desired maleate is isolated according to known methods; it may precipitate from the reaction mixture, if necessary, after concentrating or diluting the latter, or the solution may be concentrated to dryness and the desired salt may be obtained as the residue. The maleate of 1,2-(2-N,N-dimethylaminomethyl)-3-[1-(2-pyridyl)-ethyl]-indene may be purified by recrystallization, using, for example, one of the above-mentioned solvents or mixtures thereof; if desired, a solution of the salt may be clarified with an adsorbent, such as char-
3,060,186

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coc, a diatomaceous earth and the like, prior to the re-
crystallization step. Other therapeutically acceptable
acid addition salts of 1-2-(2-N,N-dimethylaminoethyl)-
3-[1-(2-pyridyl)-ethyl]-indene are, for example, those
with previously described acids; they may be prepared
according to known methods, for example, by treating
the free base with an acid, preferably in the presence of a
diluent.
The d-2-(2-N,N-dimethylaminoethyl) - 3 - [1 - (2 - pyri-
dyl)-ethyl]-indene maleate may be prepared as follows: All
the mother liquor from the crystallization and re-
crystallization of the d-tartate (D-tartate) of the 2-2
(2-N,N-dimethylaminoethyl) - 3 - [1 - (2 - pyridyl)ethyl-
indene (as described hereinbefore) are combined and
made alkaline with 15 ml. of concentrated aqueous am-
monia while cooling to 0°. The free base is extracted
with ethyl acetate, the solution is dried over magnesium
sulfate and then filtered and the solvent is evaporated.
The residue is dissolved in acetone, 10 g. of D-tartaric
acid (D-tartaric acid) in about 50 ml. of ethanol is ad-
ded; the solution is concentrated to a volume of about
75 ml., 100 ml. of aceton is added and the solution is
chilled to -5°. The resulting precipitate is filtered off
and is recrystallized three times from ethanol to yield the
desired tartarate (also designated as the D-tartrate) of
D-2-(2-N,N-dimethylaminoethyl) - 3 - [1 - (2 - pyridyl)eth-
yl]indene, M.P. 142-145°, [α]D25 = +113.9° (in eth-
anol), [α]D25 = +78.6° (in water).
The free base of d-2-(2-N,N-dimethylaminoethyl)-3-
[1-(2-pyridyl)-ethyl]-indene is obtained by treatment of the
above-described tartarate (D-tartarate) with aqueous am-
monia and can be converted to its maleate by reac-
ting a solution of the free base in ethyl acetate with maleic
acid as shown herebefore for the preparation of the
maleate of the L-isomer. The pure maleate of d-
2-(2-N,N-dimethylaminoethyl)-3 - [1 - (2 - pyridyl)eth-
yl]indene melts at 130-132°, [α]D25 = +125.7° (in
water).

Example 22

1.75 g. of 2-(2-N,N-dimethylaminoethyl)-3-[1-(2-pyri-
dyl)-ethyl]-indene maleate is suspended in 5 ml. of water,
made strongly basic with ammonia and extracted with
ether. The ether is evaporated to dryness leaving free
base, which is dissolved in 2 ml. of ethanol and treated
with 0.5 ml. of 30% hydrogen peroxide. After stand-
ing 24 hours at room temperature, the excess hydrogen
peroxide is destroyed by adding a catalytic amount of
platinum oxide. The latter is removed by filtration and
the filtrate evaporated to dryness. 0.5 g. of maleic acid
in 3 ml. of ethanol is added to the residue, containing the
2-(2-N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl-
indene N-oxide, and the solution evaporated to dry-
ness leaving the 2-(2-N,N-dimethylaminoethyl)-3-[1-(2-
pyridyl)-ethyl]-indene N-oxide maleate as a noncrystal-
line powder. The corresponding pircate melts at 160°.

Other N-oxides, such as the 1-2-(2-N,N-dimeth-
laminooethyl)-3-[1-(2-pyridyl)-ethyl]indene N-oxide,
2-(2-N,N-dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl]-
indene N-oxide, 2-(2-N,N-dimethylamino-2-methyl-ethyl)-
3-[1-(2-pyridyl)-ethyl]indene, 2-(2-N,N-dimethylamino-
ethyl)-3-[{(4-pyridyl)-methyl]-indene, 2 - (2-N,N-dimeth-
laminooethyl)-3 - [3 - (pyridyl)-methyl]-indene and the like,
may be prepared according to the above procedure using
the appropriate starting materials.

Example 23

The 3-(2-pyridyl)-lower alkyl)-2-(tertiary aminoo-
lower alkyl)-indene compounds of this invention may be
made up into pharmaceutical preparations. Thus, the
2-(2-N,N-dimethylaminoethyl) - 3 - [1 - (2 - pyridyl)-ethyl-
indene maleate and the D-tartarate (D-tartarate) of this
maleate from about 0.0001 g. to about 0.01 g., for ex-
ample, 0.002 g., of the active ingredient, as follows (for 100,000 tablets):

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(2-N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate</td>
<td>200,000</td>
</tr>
<tr>
<td>Lactose (spray dried)</td>
<td>13,546,000</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>87,500</td>
</tr>
<tr>
<td>Talc</td>
<td>87,500</td>
</tr>
<tr>
<td>Corn starch</td>
<td>875,000</td>
</tr>
<tr>
<td>Polyoxyethylene stearate</td>
<td>79,000</td>
</tr>
<tr>
<td>Carbowax 6000 (micropulverized)</td>
<td>875,000</td>
</tr>
<tr>
<td>Confectioners' sugar</td>
<td>875,000</td>
</tr>
<tr>
<td>Colloidal silica</td>
<td>87,500</td>
</tr>
</tbody>
</table>

All ingredients are screened through a No. 40 mesh stainless steel screen into a mixer and mixed for thirty
minutes. The granulate is compressed into tablets weigh-
ing 0.175 g. by employing 1/46" standard concave punches
and dies.

Tablets having a core, suitable for sustained and pro-
longed action and containing as the active ingredient from
about 0.001 g. to about 0.005 g., for example 0.001 g., of 2-(2-N,N-dimethylaminoethyl)-3-(1-(2-pyridyl)-ethyl)
indene maleate, and a coating, designed for immediate
release and containing from about 0.0001 g. to about
0.005 g., for example, 0.001 g. of the same active in-
gredient, may be prepared as follows (for 1000 tablets):

<table>
<thead>
<tr>
<th>Ingredients for core</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(2-N,N-dimethylaminoethyl) - 3-[1-(2-pyridyl)-ethyl]-indene maleate</td>
<td>1.000</td>
</tr>
<tr>
<td>Lactose, spray dried</td>
<td>29,000</td>
</tr>
<tr>
<td>Castor wax</td>
<td>19.750</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>19.750</td>
</tr>
<tr>
<td>Polyoxyethylene glycol 4000 monostearate</td>
<td>3.000</td>
</tr>
<tr>
<td>Talc</td>
<td>1.500</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.000</td>
</tr>
</tbody>
</table>

A mixture of castor wax, stearic acid and polyethylene glycol 4000 monostearate is melted in a steam kettle.
A triturate of 2-(2-N,N-dimethylaminoethyl)-3-[1-(2-
pyridyl)-ethyl]-indene maleate in lactose is suspended in the melt, which is then flaked and placed into a freezer.
The flakes are screened through a No. 20 screen on the
oscillator, lubricated with the talc and the magnesium stearate and compressed to cores weighing 0.075 g. using
1/46" punches.

<table>
<thead>
<tr>
<th>Ingredients for coating</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(2-N,N-dimethylaminoethyl) - 3 - [1-(2-pyridyl)-ethyl]-indene maleate</td>
<td>1.000</td>
</tr>
<tr>
<td>Tragacanth</td>
<td>3.500</td>
</tr>
<tr>
<td>Polyoxyethylene glycol 6000</td>
<td>6.800</td>
</tr>
<tr>
<td>Lactose, spray dried</td>
<td>157,080</td>
</tr>
<tr>
<td>Talc</td>
<td>5.100</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.700</td>
</tr>
<tr>
<td>FDC Blue No. 1</td>
<td>0.020</td>
</tr>
</tbody>
</table>

50 percent 3A alcohol | q.s.

The tragacanth, lactose, talc and magnesium stearate are
thoroughly mixed after having been passed through a No.
20 screen. The Carbowax is dissolved in approximately
500 ml. of the alcohol, and a solution of the color in
50 ml. of water is added. The previous mixture is treated
with this liquid until proper granules are formed, which
are then dried at 80° to a moisture content of 3 percent.
The granulate is passed through a No. 20 screen, the
2-(2-N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]
indene maleate is triturated with a small part of the
granulate and then added. A coating of 0.175 g. is
compressed around the previously described core using
1/46" punches for a total tablet weight of 0.250 g.

Injection solutions, containing from about 0.0001 g./ml.
to about 0.01 g./ml., for example, 0.001 g./ml.
of 2-(2-N,N-dimethylaminoethyl) - 3 - [1 - (2-pyridyl)-

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ethyl-indene maleate, may be prepared as follows (for 1000 ml.):

Ingredients—

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(2-N,N-dimethylaminoethyl) - 3 - [1-(2-pyridyl)-ethyl]-indene maleate</td>
<td>1.000g</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>18.000g</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>4.140g</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1.520g</td>
</tr>
<tr>
<td>Sodium sulfate</td>
<td>1.000g</td>
</tr>
<tr>
<td>Bis-sodium salt of ethylenediaminetetraacetic acid</td>
<td>0.100g</td>
</tr>
</tbody>
</table>

Water for injection, q.s., up to 1000.000 ml.

The lactic acid and the sodium hydroxide are given to 40 ml. of water for injection, and the bis-sodium salt of ethylenediaminetetraacetic acid, the 2-(2-N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate, the sodium chloride and the sodium sulfate are added in this order. Nitrogen gas is passed during thirty minutes through the solution, which is then filtered through a medium porosity sintered glass filter. The solution is filled into ampules, which are sterilized in an autoclave at 10 pounds per square inch pressure and at 115° C. for thirty minutes.

What is claimed is:

1. A member of the group consisting of a compound of the formula:

```
    R1 -- Ar -- Py
```

in which R1 is a member of the group consisting of hydrogen, lower alkyl, lower alkoxy and halogen, R2 stands for a member of the group consisting of hydrogen and lower alkyl, A1 stands for alkylene having from one to three carbon atoms, Py stands for a member of a group consisting of pyridyl and lower alkyl-pyridyl, A2 stands for lower alkylene, and Am stands for a member of the group consisting of N,N-di-lower alkyl-amino, N-cycloalkyl-N-lower alkyl-amino, in which cycloalkyl has from five to seven carbon atoms, N-lower alkyl-N-phenyl-lower alkyl-amino, 1-N,N-alkylene-imino, in which alkylene has from four to seven carbon atoms, 4-morpholinol, 4-lower alkyl-1-piperazinol, 1,N,N-(3-aza-3-lower alkyl-1,6-hexylene)-imino and 1,N,N-(4-aza-4-lower alkyl-1,7-heptylene)-imino, and therapeutically acceptable acid addition salts thereof.

2. 2-(N,N-di-lower alkyl - amino - lower alkyl)-3-([2-pyridyl]-lower alkyl)-indene, in which lower alkyl, separating the N,N-di-lower alkyl-amino group from the 2-position of the indene nucleus by from two to three carbon atoms, has from two to three carbon atoms, and lower alkyl of the (2-pyridyl)-lower alkyl portion has from one to three carbon atoms.

3. Therapeutically acceptable acid addition salts of 2-(N,N-di-lower alkyl-amino-lower alkyl)-3-([2-pyridyl]-lower alkyl)-indene, in which lower alkyl separating the N,N-di-lower alkyl-amino group from the 2-position of the indene nucleus by from two to three carbon atoms, and lower alkyl of the (2-pyridyl)-lower alkyl portion has from one to three carbon atoms.

4. 2-(N,N-dimethylaminoethyl)-3-1([2-pyridyl]-ethyl)-indene.

5. Therapeutically acceptable acid addition salts of 2-(N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene.

6. The maleate of 2-(N,N-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene.

7. 1-(2-N,N-dimethylaminoethyl) - 3 - [1-(2-pyridyl)-ethyl]-indene.

8. Therapeutically acceptable acid addition salts of 1-2-(N,N-dimethylaminoethyl)-3-[1 - (2-pyridyl)-ethyl]-indene.


11. 2 - (2-N,N-dimethylaminoethyl)-3-[2-(pyridyl)-methyl]-indene.

12. A member of the group consisting of 2-(N,N-di-lower alkyl-amino-lower alkyl) - 3 - ([4-pyridyl]-lower alkyl)-indene, in which lower alkyl of the (4-pyridyl)-lower alkyl portion consists of from one to three carbon atoms, and lower alkyl, separating N,N-di-lower alkyl-amino from the 2-position of the indene nucleus by from two to three carbon atoms, consists of from two to three carbon atoms, and therapeutically acceptable acid addition salts thereof.

13. A member of the group consisting of 2-(N,N-di-lower alkyl-amino-lower alkyl) - 3 - ([3-pyridyl]-lower alkyl)-indene, in which lower alkyl of the (3-pyridyl)-lower alkyl portion consists of from one to three carbon atoms, and lower alkyl, separating N,N-di-lower alkyl-amino from the 2-position of the indene nucleus by from two to three carbon atoms, consists of from two to three carbon atoms, and therapeutically acceptable acid addition salts thereof.

14. Therapeutically acceptable acid addition salts of 2-(N,N-di-lower alkyl-amino-lower alkyl)-3-([4-pyridyl]-lower alkyl)-indene, in which lower alkyl of the (4-pyridyl)-lower alkyl portion has from one to three carbon atoms, and lower alkyl, separating N,N-di-lower alkyl-amino from the 2-position of the indene nucleus by from two to three carbon atoms, has from two to three carbon atoms.

15. Therapeutically acceptable acid addition salts of 2-(N,N-di-lower alkyl-amino-lower alkyl)-3-([3-pyridyl]-lower alkyl)-indene, in which lower alkyl of the (3-pyridyl)-lower alkyl portion has from one to three carbon atoms, and lower alkyl, separating N,N-di-lower alkyl-amino from the 2-position of the indene nucleus by from two to three carbon atoms, has from two to three carbon atoms.

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UNITED STATES PATENTS

2,798,888 Ueberwasser ........................... July 9, 1957
2,947,756 Huebner ............................... Aug. 2, 1960
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 2, lines 40, 41 and 45, for "azo", each occurrence, read -- aza --; column 10, line 1, for "organ-metallic" read -- organo-metallic --; column 12, line 70, for "potassium" read -- potassium --; column 14, lines 33 and 34, for "strong sulfonic" read -- strong organic sulfonic --; column 17, line 58, for "165/175" read -- 165-175° --; line 59, for "ether" read -- ethyl --; column 21, line 23, for "3-1-l" read -- 3-[1- --; column 26, line 51, for "3.4" read -- 3.4 g. --; line 65, for "Thes" read -- The --; column 28, line 3, for "chloro-(2)" read -- chloro-2-(2 --; lines 33 and 34, for "(2-pyridyl)-ethyl]lindene" read -- (2-pyridyl)-ethyl]lindene --; lines 48 and 49, for \([\alpha]_D^{26}=166.8^\circ\ (in\ ethanol)\," read -- \([\alpha]_D^{26}=-166.8^\circ\ (in\ ethanol)\, --; column 30, line 21, for "dimethylamino)" read -- dimethylaminoethyl) --; column 31, lines 28 to 35, the formula should appear as shown below in stead of as in the patent:

\[
\begin{array}{c}
\text{A} & \text{Py} \\
\text{R}_1 \\
\end{array}
\]

\[
\begin{array}{c}
\text{C} & \text{A}_2 & \text{Am} \\
\text{R}_2 \\
\end{array}
\]

column 32, lines 24 and 33, strike out "A member of the group consisting of"; same column, lines 31 and 32, and lines 40 and 41, strike out "and therapeutically acceptable acid addition salts thereof".

Signed and sealed this 4th day of February 1964.

(SEAL)
Attest:
ERNEST W. SWIDER

Attesting Officer

EDWIN L. REYNOLDS
Acting Commissioner of Patents