PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C07d.

COMPLETE SPECIFICATION

New Indene Compounds and Pharmaceutical Preparation containing them

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basel, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

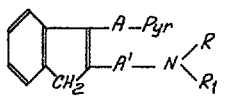
The present invention provides 2 - (tertiary amino - lower alkyl) - 3 - (pyridyl - lower alkyl) - indenes, especially 2 - (tertiary amino - lower alkyl) - 3 - [(2 - pyridyl) - lower alkyl] - indenes, their acid addition salts, N-oxides and quaternary ammonium compounds. In the N-oxides the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group. The term "lower" in this connection and throughout the specification means groups having 1—5 carbon atoms unless otherwise stated. The invention also provides pharmaceutical preparations comprising such compounds in admixture or conjunction with pharmaceutically suitable carriers.

The pyridyl radical is a pyridyl - (2), pyridyl - (3) or pyridyl - (4) radical. It may be substituted by a lower alkyl radical, such as methyl or ethyl, or by a lower alkoxy group, such as methoxy or ethoxy, or by a halogen atom, e.g. chlorine or bromine; it is preferably unsubstituted. The lower alkylene group which links the pyridine ring with the indene nucleus contains 1 to 3 carbon atoms, for example methylene, 1:1-ethylene, 1:2-ethylene, 1-methyl-1:2-ethylene, 2-methyl-1:2-ethylene, 1:1-propylene. The lower alkylene group which connects the tertiary amino group with the indene nucleus contains 1 to 5 carbon atoms; it preferably contains 2 or 3 carbon atoms in a straight chain between the indene nucleus and the amino nitrogen, such as for instance 1:2-ethylene, 1-methyl-1:2-ethylene, 2-methyl-1:2-ethylene, 1:3-propylene. Tertiary amino groups are di-lower alkylamino groups, such as dimethylamino, diethylamino, and N:N-alkyleneimino groups having 5 or 6 ring members whose alkylene chain can be interrupted by nitrogen, oxygen or sulfur, for example piperidino, piperazino, morpholino, thiomorpholino or pyrrolidino groups. The heterocyclic rings may be substituted by methyl groups.

The 1-position of the indene nucleus is preferably unsubstituted, or substituted by a lower alkyl group.

The benzene nucleus of the indene is preferably unsubstituted; it may contain as substituents halogen atoms or lower alkyl or alkoxy groups.

The invention provides more especially indenes of the formula



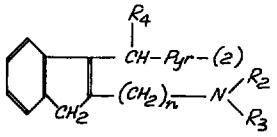
in which A stands for a straight or branched lower alkylene group having 1 to 3 carbon atoms such as methylene, ethylene or methylmethylene, and A^1 for a straight or branched lower alkylene group having 2 or 3 carbon atoms in a straight chain between the indene nucleus and the amino nitrogen, and Pyr for a pyridine residue which may be substituted as mentioned above, and in wh' R and R_1 represent lower alky_ groups, or form together with the amino nitrogen atom a heterocyclic ring as defined above, their acid addition salts,

[*Price 4s. 6d.*]

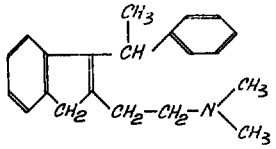
N-oxides and quaternary ammonium compounds.

The new compounds have a very good antihistaminic effect and can accordingly be used as medicaments, for example in the case of allergies caused by an excess of histamine, such as ~~uritcaria~~, hay fever, allergies caused by food, medicaments or plant pollen. In addition, the new compounds have sedative and quieting properties and may be used as sedatives and tranquillizers to counteract states of nervousness, anxiety, stress or shock. The compounds have also local anaesthetic effects so that they can be employed as local anaesthetics, for example in minor surgery.

Outstanding with respect to their antihistaminic activity are more especially the compounds of the formula

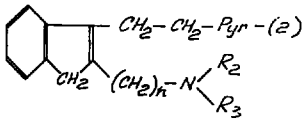


in which n=2 or 3, R_2 and R_3 stand for lower alkyl radicals having 1 to 3 carbon atoms, and R_4 for hydrogen or a lower alkyl radical having 1 to 3 carbon atoms, especially methyl, and particularly 2 - (2 - dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene of the formula



and the acid addition salts thereof, for example with ~~hydrochloric~~ acids, lower alkene dicarboxylic acids, e.g. maleic acid, and hydroxy-lower alkane dicarboxylic acids, e.g. tartaric acid, and corresponding N-oxides.

Pronounced sedative and tranquillizing properties are exhibited, for example, by the compounds of the formula



in which n, R_2 and R_3 have the meaning given above, and their acid addition salts, for example with mineral acids or lower aliphatic di- or tricarboxylic acids.

The new compounds can be prepared in various ways.

1. One process consists, for example, in treating a 1 - pyridyl - lower alkyl - 2 - (Z—A^{11}) - ~~indene~~ in which the pyridine and benzene rings are unsubstituted, or are substituted as described above, and in which Z stands for a tertiary amino group or a radical convertible into or replaceable by such a group and A^{11} for an alkylene group having 1 to 7 carbon atoms, and which is substituted by a hydroxyl group in the 5-ring of the ~~indene~~, with an agent capable of eliminating water and, if the resulting compound contains a radical which is convertible into or replaceable by a tertiary amino group, converting or replacing such a radical into or by a tertiary amino group. The hydroxyl group may be in the 1-, 2- or 3-position of the cyclopentane ring. The elimination of water can, for example, be effected by an acid agent, such as an aqueous mineral acid, for example oxalic acid or *p*-toluene-sulfonic acid, or an acid halide, such as phosphorus oxychloride or acetyl chloride, or an organic carboxylic acid anhydride, such as acetic anhydride, or by a base, such as for example an alkali metal hydroxide, or pyridine, or by merely heating. Groups which can be converted into or replaced by a tertiary amino group are, for example, free, esterified or etherified hydroxyl groups, primary or secondary amino groups, or the diazo group. The conversion into or replacement by the tertiary amino group is carried out in one step, such as for example, when reactive esterified hydroxyl groups, e.g. halogen atoms, are present which are reacted directly with a secondary amine to the tertiary amine, or in several steps, such as for example when Z is a free hydroxyl group which must first be converted into a reactive esterified hydroxyl group.

The 1-, 2- or 3-hydroxy-~~indenes~~ used as starting material can be formed in the course of the reaction and need not necessarily be isolated. The starting materials can be prepared by conventional methods.

a) For instance, 1 - pyridyl - lower alkyl - 2 - tertiary amino - lower alkyl - indan - 1 - ols are obtained by reacting corresponding 2 - tertiary amino - alkyl - indan - 1 - ones with pyridyl - lower alkyl metal compounds of groups I A, II A or II B of the Periodic System. As examples of pyridyl-lower alkyl metal compounds there come into consideration more especially magnesium compounds of the Grignard type, but also other pyridyl-lower alkyl metal halides of the second group of the Periodic System, for example zinc compounds. Furthermore, pyridyl-lower alkyl compounds with an alkali metal, such as sodium, potassium or especially lithium can be used. When the reaction is carried out with pyridyl lower alkyl metal compounds whose lower alkyl group contains more than 1 carbon atom, compounds are obtained in which the pyridyl residue is connected with the indene nucleus through the carbon atom which is vicinal to the pyridine nucleus, that is to say 2 - (tertiary amino - lower alkyl) - 3 - [pyridyl - (R_4) - methyl] - indenes, in which

R_4 represents lower alkyl. Alternatively, a 2-tertiary amino-lower alkyl-indan-1-one can be reacted with an alkali metal salt of an alkali metal pyridine lower alkanoic acid, such as is obtained, for example, by treating sodium pyridine-lower alkanoate with an alkali metal amide, hydride or hydrocarbon, such as lithium or sodium amide or hydride, *n*-butyl-lithium or phenyl-lithium or-sodium. The reactions are carried out in known manner in an inert solvent, such as for example hexane, benzene, toluene, diethyl ether, anisol, diphenyl ether, tetrahydrofurane or dioxane, if necessary in an inert gas atmosphere. When indan - 1 - ones are reacted with alkali metal pyridyl-lower alkanoates, there is added to the reaction product an acid agent, such as for example hydrochloric acid or sulfuric acid, the 3 - pyridyl - lower alkyl - 2 - tertiary aminoalkyl - indenes being obtained directly. Also in the case of the reaction of indan - 1 - ones with pyridyl-lower alkyl metals or metal halides, the 3 - pyridyl - lower alkyl - 2 - tertiary aminoalkyl - indan - 1 - ols need not be isolated but can be converted directly in the reaction medium into the corresponding indene derivatives with an agent capable of eliminating water.

The pyridyl metal compounds are prepared by methods known *per se;* pyridyl lower alkyl metal compounds, e.g. lithium compounds, are obtained for instance by reacting a lower alkyl pyridine with an aryl metal, e.g. phenyl lithium, or for example with an alkyl metal, for instance *n*-butyl-lithium, in an inert solvent (see above), or by treating an ether, formed for example from a lower alkanol and a pyridyl-lower alkanol, with lithium; the reaction solution can be employed directly for the reaction with the indanone.

The 2-substituted indan - 1 - ones are known or can be prepared by methods known *per se,* for example by reacting an α-benzyl-malonic acid ester, for example ethyl or tetrahydropyranyl ester, with a reactive ester of a tertiary amino-lower alkanol, preferably in the presence of an alkali metal alcoholate, and cyclizing the resulting ester to the indan - 1 - one derivative. Ring closure can be carried out before or after hydrolysis of the ester groups, preferably by treatment with a strong Lewis acid, such as a strong mineral acid or boron trifluoride or aluminium chloride.

2 - (Tertiary aminoethyl) - indan - 1 - ones are also obtained by reacting an indan - 1 - one with a secondary amine or a salt thereof, particularly a salt with a mineral acid, in the presence of formaldehyde or a substance yielding formaldehyde according to the Mannich procedure.

In the same manner as the 1-pyridyl-lower alkyl-2-tertiary amino-lower alkyl-indan-1-ols, compounds can be prepared which instead of the tertiary amino group contain a substituent convertible into or replaceable by such a group. Thus, for example, a 1 - (pyridyl - lower alkyl) - indan - 1 -ol which contains in the 2-position a reactive esterified hydroxyl group bound to an alkylene group can be prepared by reacting an α-alkali metal-α-benzyl-malonic acid ester with an etherified hydroxy-lower alkyl halide, e.g. methoxy, ethoxy, phenoxy-alkyl halide, and the resulting ester is subjected to ring closure to form the indan - 1 - one derivative. The pyridyl-lower alkyl radical is introduced in the manner described above, and the resulting 1-pyridyl-lower alkyl-2-(alkoxy- or aryloxy-lower alkyl)-indan-1-ol dehydrated. The ether bond is then hydrolysed and the hydroxyl group esterified, for example by conversion into the corresponding halide, such as chloride or bromide. For this purpose the ether can be treated, for example, with a hydrohalic acid or the alkanol obtained by hydrolysis can be treated with a thionyl halide. Instead of with an etherified hydroxy-alkyl halide, the benzyl-malonic acid ester can be reacted, for example, also with a lower alkylene oxide, such as ethylene oxide, propylene oxide, to form an α - benzyl - α - (hydroxy - lower alkoxy) - malonic acid ester which can be hydrolysed, decarboxylated and subjected to ring closure. The hydroxyl group is esterified in known manner and the pyridyl substituent introduced. The order of the process steps can be varied. The conversion of the ester into the tertiary amine takes place in known manner by reaction with a secondary amine or a salt thereof.

b) 1 - Pyridyl - lower alkyl - 2 - tertiary aminoalkyl - indan - 2 - ols or compounds which contain the group (Z—A^{11}) in which A^{11} and Z have the meaning given above can be prepared, for example, by reacting 1 - pyridyl - lower alkyl - indan - 2 - ones with the corresponding (Z—A^{11}) - Grignard compounds or other metal halides of the second group of the Periodic System. Thus, for example, a 1 - pyridyl - lower alkyl - indan - 2 - one can be reacted with an etherified hydroxyl-lower alkyl-Grignard reagent. 1 - Pyridyl - lower alkyl - indan - 2 - ones are prepared, for example, by condensing indan-2-ones with pyridyl-lower alkyl-aldehydes in the presence of a base and reducing the resulting alkylidene compounds. The replacement of the etherified hydroxyl group by a tertiary amino group takes place as described above.

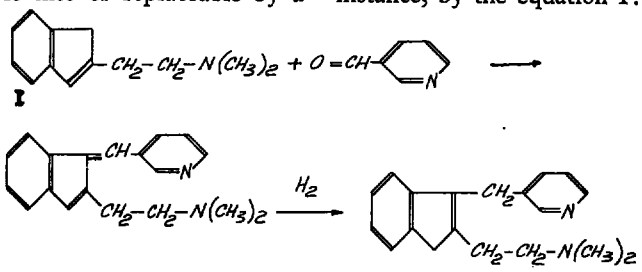
c) 1 - Pyridyl - lower alkyl - 2 - (Z—A^{11}) - indane compounds of the type described which contain in the 3-position a hydroxyl group can be prepared as follows: 2 - (Z—A^{11}) - inden - 1 - ones which are substituted in the 3-position by a lower alkoxy group, for example a methoxy group, are used as starting material; a pyridyl-lower alkyl radical is introduced in the 1-position in the manner described above. The reaction product is de-

hydrated, for example by means of a mineral acid, and the double bond formed is hydrogenated. The enol ether group in the 3-position is then converted into an oxo group, for example by treatment with a strong inorganic acid, and the oxo group reduced by means of catalytically activated hydrogen, nascent hydrogen, alkali metal aluminium hydride or alkali metal boron hydride or aluminium alcoholate to the hydroxyl group.

The 2 - (Z—A^{11}) - inden - 1 - ones used as starting materials and which contain a lower alkoxy group in the 3-position can be prepared, for example, by reacting a lower alkyl phthalate with a (Z—A^{11})-nitrile in the presence of a base, such as for example an alkali metal alcoholate. The resulting (Z—A^{11}) - indane - 1:3 - dione is then converted into the desired enol ether by treatment with an alcohol in the presence of an acid, for example hydrochloric acid or sulfuric acid, or with a diazoalkane, for example diazomethane.

2. Another procedure for the preparation of the new compounds consists in treating a 1 - (pyridyl - lower alkyl) - Δ^2 - indene whose benzene and pyridine nuclei may be substituted and which is substituted in the 2-position by the group Z—A^{11} in which A^{11} and Z have the meanings given above, with a strong acid or base and/or heating it for the purpose of shifting the double bond into the 1:2-position, and, if the resulting compound contains a radical convertible into or replaceable by a tertiary amino group, this group is so converted or replaced. As an agent for the rearrangement there are suitable, for example, mineral acids, such as hydrochloric acid, sulfuric acid, or a strong organic acid, such as aryl-sulfonic acid, or an alkali metal hydroxide in aqueous or alcoholic solution, also alkali metal alcoholates. The conversion or replacement of a radical convertible into or replaceable by a tertiary amino group takes place, as mentioned under 1), for example, by reacting an esterified hydroxyl group with a secondary amine. The 1 - pyridyl - lower alkyl - 2 - (Z—A^{11}) - Δ^2 - indenes used as starting material can be prepared in known manner. Thus, a 1 - methyl - 2 - (Z—A^{11}) - indene can be reacted with a pyridine-lower alkyl-aldehyde in the presence of a basic agent and the resulting pyridine-alkylidene compound reduced. The compounds may also be obtained by the procedures described under 1.c)

3. The new compounds can also be obtained by treating a 1 - (pyridyl - lower alkylidene) - Δ^2 - indene whose benzene and pyridine nuclei may also be substituted and which is substituted in the 2-position by the group Z—A^{11} in which A^{11} and Z have the meanings given above, with a reducing agent, and if the resulting compound contains a radical convertible into or replaceable by a tertiary amino group, this radical is so converted or replaced. The reaction is represented, for instance, by the equation I:



The compounds used as starting materials are obtained by condensing a 2-(Z—A^{11})-indene in which Z and A^{11} have the meanings given above, with a pyridyl-lower alkanal e.g. pyridyl formaldehyde, pyridyl-acetaldehyde. Thus, for example, a 2 - (tertiary amino - lower alkyl) - indene can be reacted with pyridyl - (2) - formaldehyde. The reduction takes place preferably with catalytically activated hydrogen. The condensation of the aldehyde with the indene compound is carried out in known manner according to Claisen in the presence of a condensing agent, such as for example an alcoholate.

4. A modification of the last mentioned procedure comprises condensing a 2 - (Z—A^{11}) - indene with a lower alkenyl-pyridine instead of with a pyridylaldehyde, for example with 2-vinyl-pyridine or 2-allyl-pyridine. The condensation is carried out under the conditions of the Claisen condensation, for example in the presence of an alkali metal alcoholate, amide or hydride.

Depending on the procedure used, the new compounds are obtained in the form of the free bases or their salts. From the salts the free bases can be obtained by reacting the salts with alkali: From the bases the salts can be obtained by reaction with acids which are suitable for the formation of therapeutically useful salts, such as hydrohalic acids, for example hydrochloric acid or hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, phosphoric acid; or with an organic acid, such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, ascorbic acid, hydroxymaleic acid, dihydroxymaleic acid, benzoic acid, phenylacetic acid, 4-aminobenzoic acid, 4-hydroxybenzoic acid, anthranilic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicyclic acid, 2-phenoxy-benzoic

acid, 2-acetoxybenzoic acid, methane-sulfonic acid, ethane-sulfonic acid, hydroxyethane-sulfonic acid, benzene or *p*-toluene-sulfonic acid, ~~napthalene~~-sulfonic acid, sulfamylic acid, methionine, ~~tryptophane~~, lysine, arginine or a therapeutically active acid.

The N-oxides are prepared by reacting the tertiary base with hydrogen peroxide in alcoholic solution, for example methanol or absolute ethanol.

The quaternary ammonium compounds of the indene derivatives of the present invention are prepared by reacting the tertiary base with an ester from an alkanol and a strong inorganic or organic acid. Such acids are, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid or *p*-toluene-sulfonic acid. Alkanols are primarily lower alkanols with 1 to 6 carbon atoms. Quaternization can take place in the presence or absence of a solvent. Suitable solvents are more especially lower alkanols, for example methanol, ethanol, propanol, isopropanol, butanol or pentanol, or a lower alkanone, for example acetone or methylethylketone, or an organic acid amide, for example formamide or dimethylformamide.

The new compounds can be used as medicaments, for example in the form of pharmaceutical preparations which contain them or their salts in admixture or conjunction with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral, parenteral or topical administration. As carriers there are used substances which do not react with the new ~~compounds~~, such as for example water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol or other known carriers for medicaments. The pharmaceutical preparations can be made up for example as tablets, dragees, salves, creams or in liquid form as solutions, suspensions or emulsions. They may be sterilized and/or contain auxiliary substances, such as preserving, stabilizing, wetting or emulsifying agents, salts for modifying the osmotic pressure or buffers. They may also contain other therapeutically useful substances.

The following ~~Exmaples~~ illustrate the invention. The 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 - 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 hydrochloric acid in 100 ml of water.

The acidic extract, containing 2 - (2 - 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 - dimethylaminoethyl) - 3 - [(2 - pyridyl) - methyl] - indene, b.p. 168—170°/0.7 mm.

The free base is converted to the dihydrochloride by treatment of an ethanol solution of the former with ethanolic hydrogen chloride and precipitation of the salt with ether. The hydroscopic 2 - (2 - dimethylaminoethyl) - 3 - [(2 - pyridyl) - methyl] - indene dihydrochloride is recrystallized from a mixture of ethanol and ether, m.p 175—177°C. The corresponding maleate, prepared by treating an ethanol solution of the base with maleic acid, melts at 140° after recrystallization from ethanol.

By treating an acetone solution of the 2 - (2 - dimethylaminoethyl) - 3 - [(2 - pyridyl) - methyl] - indene with methyliodide the dimethiodide of 2 - (2 - dimethylaminoethyl) - 3 - [(2 - pyridyl) - methyl] - indene may be obtained.

The starting material may be prepared as follows: 33.2 g of dihydropyran 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 diethylether kept at 30° during the addition of the dihydropyran. The mixture is stirred for an additional 15 minutes, then poured on ice, and the ether phase is extracted with aqueous potassium carbonate. After washing with water and drying over magnesium sulfate, the ether is evaporated under reduced pressure by keeping the temperature below 30° to yield the di-tetrahydropyranyl α-benzyl-malonate. A toluene solution of this ester is gradually added to a toluene solution of a 50% suspension of 4.86 g of sodium hydride mineral oil while heating and stirring for six hours. A solution of 10.8 g of 2-dimethylaminoethyl 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 di-tetrahydropyranyl α - benzyl - α - (2 - dimethylaminoethyl) - malonate; yield: 32.2 g of crude material.

A mixture of the resulting ester in 180 g of polyphosphoric acid is stirred at 110—120° during thirty minutes, and then at 150° 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% aqueous hydro-

chloric acid, the aqueous layer is neutralized with potassium carbonate and again extracted with ether. After washing the ether layer with water and drying over magnesium sulfate, the solvent is evaporated to yield the 2 - (2 - dimethylaminoethyl) - indan - 1 - one, yield: 8 g of crude material. The hydrochloride of the base melts at 165° after recrystallization from a mixture of ethanol and ether.

EXAMPLE 2

26 g of 2-ethyl-pyridine is added dropwise with cooling to 20° and in an atmosphere of nitrogen to a stirred solution of 650 ml of an 0.37 molar solution of phenyl lithium in benzene. After two hours a solution of 10 g of 2 - (2 - 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 - (2 - dimethylaminoethyl) - 1 - [1 - (2 - pyridyl) - ethyl] - indan - 1 - ol, is heated on the steam bath for thirty minutes to effect dehydration of 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 sulphate, filtered, evaporated and the residue distilled. At 15 mm pressure the excess of 2-ethyl-pyridine is removed, at 120°/0.5 mm some unreacted 2 - (2 - dimethylaminoethyl) - indan - 1 - one distills and at 165/175°/0.5 mm the 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is collected. It may be converted to an aqueous solution of the dihydrochloride by dissolving it in the appropriate amount of dilute hydrochloric acid.

A solution of 2.0 g of 2 - (2 -N,N - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene in 5 ml of ethyl acetate is treated at room temperature with 0.65 ml of methyl iodide. The crystalline precipitate is filtered off after 15 minutes to yield the 2 - (2 - N,N - dimethyl - aminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene methiodide which melts at 225—226°.

EXAMPLE 3

To a solution of 1.0 g of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene in 10 ml of ethanol is added while stirring and heating 0.4 g of maleic acid. On cooling the 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl - indene maleate crystallizes, is filtered off, washed with a small amount of ethanol and recrystallized from ethanol, m.p. 158°.

1.75 g of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - 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 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene base. This is dissolved in 2 ml of ethanol and treated with 0.5 ml of 30% hydrogen peroxide. After standing 24 hours at room temperature, the excess hydrogen peroxide is destroyed by adding a catalytic amount of platinum oxide. This is removed by filtration and the filtrate evaporated to dryness. 0.5 g of maleic acid in 3 ml of ethanol is added and the solution evaporated to dryness leaving 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene N-oxide maleate in which the N-oxide oxygen is attached to the nitrogen atom of the dimethylamino group as a non-crystalline powder. The picrate melts at 160°C.

EXAMPLE 4

To 1.0 g of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene in about 10 ml of ethanol is added a solution of 0.52 g of 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 L-tartrate of one of the optically active forms of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene melts at 135—137°; $[\alpha]_D^{25°}$—106° (in ethanol). By treating an aqueous suspension of this salt with ammonia and ether an optically active form of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is obtained, which is converted to the corresponding maleate according to the procedure of Example 3, $[\alpha]_D^{25°}$—166.8° (in ethanol).

EXAMPLE 5

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

EXAMPLE 6

To a solution of 3 g of potassium hydroxide in 100 ml of methanol is added 7 g of 2 - (2 - dimethylaminoethyl) - indene hydrochloride and then 7 ml of 3-pyridine carboxaldehyde, while stirring and cooling to room temperature. After standing at that temperature over night, the greater part of the solvent is removed by distillation under reduced pressure, water is added and the crude 2 - (2 - dimethylaminoethyl) - 1 - [β - pyridyl) - methylidene] - 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 (10%) until one mole of hydrogen is absorbed in about one hour. The reaction mixture is filtered, the solvent removed under reduced pressure and the residue dissolved in 10 ml of benzene. The benzene solution is chromatographed in 100 g of aluminium oxide (basic, activity I). Cyclohexane elutes the desired 2 - (2 - dimethylaminoethyl) - 3 - [(3 - pyridyl) - methyl] - indene, which is distilled at 160—170°/0.5 mm. It may be converted into its maleate according to the procedure of Example 3. The reaction is represented by equation I.

The starting material used in the above procedure may be prepared as follows: To a solution of 35 g of 2 - (2 - dimethylamino - ethyl) - 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, then the greater part of the ethanol is removed by distillation and the residue diluted with water. The 2 - (2 - dimethylaminoethyl) - indan - 1 - ol is extracted with ether and the crude base obtained after removal of the solvent; its picrate melts at 169—170°.

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, and most of the solvent then distilled under reduced pressure. The residue is diluted with water, made basic with ammonia and extracted with ether. On addition of 6N ethanolic hydrogen chloride to the ether solution the 2 - (2 - dimethylaminoethyl) - indene hydrochloride precipitates and is recrystallized from ethanol, m.p. 202—205°.

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 bromo-benzene in 200 ml of dry ether. The reaction is carried out in the atmosphere of nitrogen. The additional bromobenzene solution is given to the reaction in such a rate as to maintain the latter.

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 - dimethylaminoethyl) - 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 - dimethylaminoethyl) - 1 - [(2 - pyridyl) - ethyl] - indan - 1 -ol, is heated on the steam bath for one-half hour. After cooling the solution is basified with aqueous ammonia and extracted with ether. The 2 - (2 - dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is 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 - dimethylaminoethyl) - 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 separated and the organic phase is extracted with 60 ml of 6N aqueous hydrochloric acid.

The acid extract, containing the 2 - (2 - dimethylaminoethyl) - 1 - [1 - (2 - pyridyl) - propyl] - indan - 1 - ol, 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 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - propyl] - indene is distilled, b.p 165—175°/0.5 mm.

The monomethiodide of 2 - (2 - dimethylaminoethyl) - 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 under an atmosphere of dry nitrogen. After standing an additional two hours, a solution of 15 g of 2 - (2 - dimethylaminoethyl) - indan - 1 - one in 50 ml of ether is added; the reaction mixture is allowed to stand for one day at room temperature and then worked up as described in Example 8. The dehydration product of any intermediarily formed 2 - (2 - dimethylaminoethyl) - 1 - [dimethyl - (2 - pyridyl) - methyl] - indan - 1 - ol, is distilled to yield the desired 2 - (2 - dimethylaminoethyl) - 3 - [dimethyl - (2 - pyridyl) - methyl] - indene, b.p 155—160°/0.4 mm.

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

EXAMPLE 10

To a stirred soultion 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 - dimethylaminoethyl) - 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 - dimethylaminoethyl) - 3 - [(6 - methyl - 2 - pyridyl) - methyl] - indene, b.p. 150—155°/0.4 mm is obtained after dehydration of any intermediarily formed 2 - (2 - dimethylaminoethyl) - 1 - [(6 - methyl - 2 - pyridyl) - methyl] - indan - 1 - ol with hydrochloric acid.

The substitution of 2,6-lutidine by 5-chloro-2-methyl-pyridine in the above procedure yields the desired 3 - [(5 - chloro - 2 - pyridyl) - methyl] - 2 - (2 - dimethylaminoethyl) - 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 added 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 - diethylaminoethyl) - indan - 1 - one in ether is slowly added while stirring. The reaction mixture is allowed to stand at room temperature over night and is then decomposed by carefully adding water. The organic material is extracted with ether, and the ether solution is washed with 15 per cent aqueous hydrochloric acid to separate the basic material. The acidic layer, containing 2 - (2 - diethylaminoethyl) - 1 - [1 - (2 - pyridyl) - ethyl] - indan - 1 - ol, 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 - diethylaminoethyl) - 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 recrystallisation from ethanol.

A solution of 0.8 g of 2 - (2 - N,N - diethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is treated with 0.5 ml of methyl iodide at room temperature. After fifteen minutes 15 ml of ethyl acetate, saturated with water, is added. A gummy precipitate which slowly crystallizes is filtered off, and the desired 2 - (2 - N,N - diethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene methiodide melts at 152—154° after recrystallization from ethanol.

The starting material used in the above reaction may be prepared as follows: To a warm suspension of 22 g of sodium hydride in 1,000 ml of toluene is added dropwise while stirring 100 g of diethyl α-benzyl-malonate. The reaction mixture is refluxed for one hour after completion of the addition, then a solution of 70 g of 2-diethylaminoethyl chloride in toluene is added and the reaction mixture is refluxed overnight. The toluene 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 α - benzyl - α - (2 - diethylaminoethyl) - malonate, the oxalate of which melts at 117—119°C.

A mixture of 136 g of diethyl α - benzyl - α - (2 - diethylaminoethyl) - 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 α - benzyl - α - (2 - diethylaminoethyl) - malonic acid is filtered off and washed with ice water and ethanol. After drying under reduced pressure, it melts at 128°; yield 103 g.

103 g of α - benzyl - α - (2 - diethylaminoethyl) - malonic acid is heated to 180° with occasional stirring until foaming ceases; the decarboxylation is complete after approximately 15 minutes. The resulting melt is cooled and diluted with about 15 ml of ethanol, ether is added and 2 - benzyl - 4 - diethylamino - butyric acid crystallizes, m.p. 102—104°; yield 83 g.

83 g of 2 - benzyl - 4 - diethylamino - butyric acid is added to 415 g of polyphosphoric acid kept at 100—120°. The temperature is then raised to 140—145° 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 - diethylaminoethyl) - 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°; yield: 12.3 g.

EXAMPLE 12

The 5 - chloro - 2 - (2 - dimethylaminoethyl) - 3 - [(2 - pyridyl) - methyl] - indene, purified by distillation, may be obtained by treatment of 6 - chloro - 2 - (2 - dimethylaminoethyl) - indan - 1 - one with the lithium compound of α-picoline according to the procedure outlined in Example 1, whereby any intermediarily formed 6 - chloro - 2 - (2 -

dimethylaminoethyl) - 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) - malonate, b.p. 150—151°/0.5 mm, obtained by reacting 4-chlorobenzyl chloride with sodium diethyl malonate, is added to a stirred suspension of 8 g of sodium hydride in 500 ml of refluxing toluene. After 2 hours, 34 g of 2-dimethylaminoethyl 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 - dimethylaminoethyl) - malonate is separated in a separatory funnel. It is characterized as the crystalline oxalate which melts at 175—178° after recrystallization from a mixture of ethanol and ether.

The diethyl α - (4 - chlorobenzyl) - α - (2 - dimethylaminoethyl) - malonate is hydrolyzed with potassium hydroxide as described in Example 4; the resulting α - (4 - chlorobenzyl) - α - (2 - dimethylaminoethyl) - malonic acid melts at 180—181° after recrystallization from water. The 2 - (4 - chlorobenzyl) - 4 - dimethylamino - butyric acid is obtained by decarboxylating the malonic acid derivative at a temperature of 185° 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 - dimethylaminoethyl) - indan - 1 - one which is converted to its hydrochloride, 175—176°.

EXAMPLE 13

On heating an aqueous hydrochloric acid solution of 1 - [(2 - pyridyl) - methyl] - 2 - [2 - pyrrolidino - (N) - ethyl] - indan - 1 - ol, formed by reacting the lithium compound of α-picoline with 2 - [2 - pyrrolidino - (N) - ethyl] - indan - 1 - one according to the procedure of Example 1, for one hour the 3 - [(2 - pyridyl) - methyl] - 2 - [2 - pyrrolidino - (N) - ethyl] - indene is obtained and purified by distillation.

The starting material may be prepared as follows: To a cooled solution of the sodium diethyl α-benzyl-malonate, prepared from 75 g of diethyl α-benzyl-malonate and 16 g of a 1:1-mixture of sodium hydride and mineral oil, in 150 ml of toluene is added a toluene solution of 2 - pyrrolidino - (N) - ethyl chloride. This solution is prepared by shaking 61 g of 2 - pyrrolidino - (N) - ethyl chloride hydrochloride in 200 ml of toluene with 50 ml of water containing 23 g of sodium hydroxide, drying the organic solution over potassium hydroxide pellets and using it without further purification. The reaction mixture is heated at 120° for 6 hours while stirring. The organic solvent is then evaporated under reduced pressure and the residue is refluxed for 7 hours with a solution of 40 g of sodium hydroxide in 200 ml of water and 300 ml of ethanol. The mixture is acidified with concentrated aqueous hydrochloric acid and evaporated to dryness under reduced pressure. The remaining residue is heated in an oil bath with the temperature slowly raising to 180° over about one hour; the decarboxylation is complete after 30 minutes heating at this temperature. The mixture is digested with 250 ml of hot ethanol, the hot solution is filtered and the solvent is evaporated to dryness to give the crystalline 2 - benzyl - 4 - pyrrolidino - (N) - butyric acid hydrochloride, m.p. 178—182°.

The resulting acid hydrochloride is added in small quantities while stirring to 400 g of polyphosphoric acid kept at 100°. The temperature is then raised to 120° and held for 30 minutes; the mixture is then poured onto ice, made alkaline and extracted with ether. After the removal of the organic solvent, the 2 - [2 - pyrrolidino - (N) - ethyl] - indan - 1 - one is distilled at 148—152°/0.4 mm.

EXAMPLE 14

The reaction of the lithium compound of 2-ethyl-pyridine with 2 - [2 - (4 - methyl - 1 - piperazino) - ethyl] - indan - 1 - one according to the procedure of Example 7 furnishes 2 - [2 - (4 - methyl - 1 - piperazino) - ethyl] - 1 - [1 - (2 - pyridyl) - ethyl] - indan - 1 - ol, which is dehydrated by heating with aqueous hydrochloric acid to the desired 2 - [2 - (4 - methyl - 1 - piperazino) - ethyl] - 3 - [1 - (2 - pyridyl) - ethyl] - indene, purified by distillation.

The starting material may be prepared according to the procedure given in Example 13 by using the same quantities of starting material, and replacing 2 - pyrrolidino - (N) - ethyl chloride by 2 - (4 - methyl - 1 - piperazino) - ethyl chloride. The intermediate 2 - benzyl - 4 - (4 - methyl - 1 - piperazino) - butyric acid hydrochloride melts at 195—200° and is cyclized to the 2 - [2 - (4 - methyl - 1 - piperazino) - ethyl] - indan - 1 -one, b.p. 168—170°/0.4 mm.

EXAMPLE 15

A solution of 2 - (2 - dimethylaminoethyl) - 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 - dimethylaminoethyl) - 6 - methoxy - 1 - [(2 - pyridyl) - methyl] - indan - 1 - ol, is dehydrated by heating with aqueous hydrochloric acid to yield the 2 - (2 - dimethylaminoethyl) - 5 - methoxy - 3 - [(2 - pyridyl) - methyl] - indene, which is purified by distilla-

tion 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 113.5 g of diethyl malonate at 50°. The clear reaction solution is treated dropwise with 110.7 g of 4-methoxybenzyl 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 washed and dried, and the solvent evaporated. The diethyl α-(4-methoxybenzyl)-malonate is distilled, b.p. 155—165°/0.75 mm; yield: 66.7 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)-malonate and the reaction mixture is refluxed for one hour. A solution of 31 g of 2-dimethylamino-ethyl chloride in toluene is added, the reaction mixture heated overnight and the toluene solution 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 evaporated. 77 g of diethyl α - (4 - methoxybenzyl) - α - (2 - dimethylaminoethyl) - malonate is obtained and characterized as the hydrochloride salt, 145—147°.

A mixture of 73.4 g of diethyl α - (4 - methoxybenzyl) - α - (2 - dimethylaminoethyl) - malonate, 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 - (4 - methoxy - benzyl) - α - (2 - dimethylaminoethyl) - malonic acid 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 - (4 - methoxybenzyl) - α - (2 - dimethylaminoethyl) - malonic acid is heated to 180° 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 2 - (4 - methoxybenzyl) - 4 - dimethylamino - butyric acid crystallizes, m.p. 87°; yield: 33.7 g. 33.7 g of 2 - (4 - methoxybenzyl) - 4 - dimethylamino - butyric acid is gradually added to 168 g of polyphosphoric acid kept at 90—120°, and the reaction mixture is heated to 140—150° 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 - dimethylaminoethyl) - 6 - methoxy - indan - 1 - one is converted to the hydrochloride, m.p. 225—227°; yield: 14.5 g.

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 and under an atmosphere of dry nitrogen 15 g of 2 - (2 - dimethylaminoethyl) - indene. After the addition is completed, 17 g of freshly distilled 2-vinylpyridine 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 - dimethylaminoethyl) - 3 - [2 - (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 - dimethylaminoethyl) - 3 - [2 - (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 dimethiodide of 2 - (2 - dimethylaminoethyl) - 3 - [2 - (2 - pyridyl) - ethyl] - indene is recrystallized from a mixture of ethanol and water, m.p. 235—237° (with decomposition).

The starting material may be prepared as described in Example 6. The resulting hydrochloride is converted 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 sodium sulfate, the solvent is evaporated and the 2 - (2 - dimethylaminoethyl) - indene is distilled at 108—115°/1 mm.

The 2 - (2 - dimethylaminoethyl) - indene, used as the starting material in the above reaction, may be replaced by 2 - (3 - dimethylaminopropyl) - indene, prepared according to the procedure given in Example 6, i.e. reducing an ethanol solution of the 2 - (3 - dimethylaminopropyl) - indan - 1 - one (example 19) with sodium borohydride, dehydrating the resulting 2 - (3 - dimethylamino - propyl) - 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 - dimethylaminoethyl) - indene into the free base. The latter, when converted into the potassium salt 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 - dimethylaminopropyl) - 3 - [2 - (2 - pyridyl) - ethyl] - indene.

EXAMPLE 17

The reaction of 2 - (2 - dimethylaminoethyl) - 3 - methyl - indan - 1 - one with the lithium compound of 2-ethyl pyridine according to the procedure of Example 7 furnishes 2 - (2 - dimethylaminoethyl) - 3 - methyl - 1 - [1 - (2 - pyridyl) - ethyl] - indan - 1 - ol, which is dehydrated to the desired 2 - (2 - dimethylaminoethyl) - 1 - methyl - 3 - [1 - (2 - 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 12.3 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-phenyl-ethyl bromide. The reaction mixture is refluxed for about one hour, the resulting sodium chloride is filtered off and the solvent is evaporated. The residue is distilled to give 83 g of diethyl α-(1-phenylethyl)-malonate, b.p. 165—170°/18 mm.

The diethyl α-(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 and a toluene solution of 55 g of 2-dimethylaminoethyl chloride is added. The reaction mixture is refluxed overnight and then extracted with 15% aqueous hydrochloric acid; the acid solution is made basic with ammonia and extracted with ether. The ether is removed to yield 93 g of the desired diethyl α - (2 - dimethylaminoethyl) - α - (1 - phenylethyl) - malonate, the oxalate of which melts at 136—138°.

This ester is hydrolyzed by refluxing with 27.7 g of sodium hydroxide 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 hydrochloric 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 fuller's 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 neutralized with potassium carbonate. The desired 2 - (2 - dimethylaminoethyl) - 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) under cooling to 25° and in an atmosphere of dry nitrogen. After three hours 12 g of 2 - (2 - dimethylamino - 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 4N-aqueous hydrochloric acid.

The acidic solution, containing 2 - (2 - dimethylamino - 2 - methyl - ethyl) - 1 - [1 - (2 - pyridyl) - ethyl] - indan - 1 - ol, 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 separated, dried over sodium sulfate 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 - dimethylamino - 2 - methyl - ethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene.

Salts of this mixture can be 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 - dimethylamino - 2 - methyl - ethyl) - 3 - [1 - (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 collected by evaporating the solvent. The distillation of the separated methiodides at 170°/0.2 mm yields the single racemates of 2 - (2 - dimethylamino - 2 - methyl - ethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene.

The starting material used in the above reaction may be prepared as follows: 300 g of diethyl α-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 - dimethylamino - 2 - methyl - ethyl chloride in toluene (prepared by dissolving 310 g of 2 - dimethylamino - 2 - methyl - ethyl chloride hydrochloride in 600 ml of water, basifying the aqueous solution and ex-

tracting 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 oil is extracted with ether. After drying, the ether is evaporated, leaving 396 g of diethyl α - benzyl - α - (2 - dimethylamino - 2 - methyl - ethyl) - malonate as a residue.

120 g of diethyl α - benzyl - α - (2 - 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 - dimethylamino - 2 - methyl - ethyl) - 2 - carbethoxy - indan - 1 - one. 75 g of this residue is refluxed with 650 ml of 2N-aqueuos 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 pure 2 - (2 - dimethylamino - 2 - methyl - ethyl) - indan - 1 - one by treatment with ammonia.

EXAMPLE 19

A solution of 3.4 g of 2-ethyl-pyridine in 50 ml ether is added while stirring, at room temperature and under 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 - dimethylaminopropyl) - indan - 1 - one in 10 ml of ether is added. The reaction mixture is allowed to stand overnight, is decomposed by adding water and then extracted with 30 ml of 3N aqueous hydrochloric acid. The acidic extract is heated for one hour on the steam bath, then made basic with aqueous ammonia and extracted with ether. The ether extract is dried over sodium sulfate and the ether, and 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 aluminium oxide. The eluate with benzene is evaporated to dryness and the resulting 2 - (3 - dimethylaminopropyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is converted to the maleate. The salt is recrystallized from ethanol, m.p. 154—155°C.

The 2 - (3 - 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 Example 11. The intermediate α - benzyl - α - (3 - dimethylaminopropyl) - malonic acid melts at 204—205° (after recrystallization from water) and the α - benzyl - α - (3 - dimethyl - aminopropyl) - acetic acid at 110° (after recrystallization from a mixture of ethanol and ether).

EXAMPLE 20

3 g of 4 - chloro - 2 - (2 - dimethylaminoethyl) - 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-ethylpyridine in 50 ml of ether. After standing overnight, water is added dropwise to decompose the organometallic compounds. The organic layer is extracted with 85 ml of 3N 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-ethylpyridine is removed at 15 mm pressure and the desired 7 - chloro - 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene is collected at 200—205°/0.5 mm.

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

The starting material may be prepared as follows: To a solution of 36 g of sodium in 800 ml of absolute ethanol is added 290 ml of diethyl malonate. A total of 257 g of 2 - chloro-benzyl chloride is given 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 diluted with an equal amount of water, 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 α-(2-chloro-benzyl)-malonate.

To a hot suspension of 39 g of sodium hydride (of fifty per cent strength) in 1500 ml of toluene is added dropwise while stirring 200 g of diethyl α-(2-chloro-benzyl)-malonate. After refluxing for one hour a toluene solution of 98.5 ml of 2-dimethylaminoethyl chloride is added. The reaction mixture is refluxed overnight; the toluene solution is extracted with 15 per cent 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 α - (2 - chloro - benzyl) - α - (2 - dimethylaminoethyl) - malonate.

A mixture of 235 g of diethyl α - (2 - chloro - benzyl) - α - (2 - dimethylaminoethyl) - malonate, 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 α - (2 - chloro - benzyl) - α - (2 - dimethylaminoethyl) - malonic acid, m.p. 123—125° (with decarboxylation).

The α - (2 - chloro - benzyl) - α - (2 - dimethylaminoethyl) - malonic acid is decarboxylated by heating at 170—180° until the evolution of carbon dioxide ceases. The resulting melt is cooled and recrystallized from ether; the desired 2 - (2 - chloro - benzyl) - 4 - dimethylamino - butyric acid melts at 83°; yield: 75 g.

50 g of the 2 - (2 - chlorobenzyl) - 4 - 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 - dimethylaminoethyl) - indan - 1 - one, b.p. 135—138°/1 mm. Its hydrochloride salt melts at 220—221°.

EXAMPLE 21

The 3 - [(2 - pyridyl) - lower alkyl] - 2 - (tertiary amino - lower alkyl) - indene compounds may be made up into pharmaceutical preparations. Thus, the 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene maleate may be formulated into tablets, containing 0.002 g of the active ingredients, as follows (for 100,000 tablets):

Ingredients:

2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate	200.000 g
Lactose (spray dried)	13546.000 g
Magnesium stearate	87.500 g
Talc	875.000 g
Corn starch	875.000 g
Polyoxyethylene stearate	79.000 g
Carbowax 6000 (micropulverized)	875.000 g
Confectioners Sugar	875.000 g
Colloidal silica	87.500 g

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 weighing 0.175 g by employing 10/32".

Tablets having a core, suitable for sustained and prolonged action and containing as the active ingredient 0.0001 g of 2 - (2 -dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene maleate, and a coating designed for immediate release and containing 0.0001 g of the same active ingredient, may be prepared as follows (for 1000 tablets):

Ingredients for core:

2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate	1.000 g
Lactose, spray dried	29.000 g
Castorwax	19.750 g
Stearic acid	19.750 g
Polyethylene glycol 4000 monostearate	3.000 g
Talc	1.500 g
Magnesium stearate	1.000 g

A mixture of the castorwax, stearic acid and polyethylene glycol 4000 monostearate is melted in a steam kettle. A triturate of 2 - (2 - 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 8/32" punches.

Ingredients for coating:

2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate	1.000 g
Tragacanth	3.300 g
Polyethylene glycol 6000	6.800 g
Lactose, spray dried	157.080 g
Talc	5.100 g
Magnesium stearate	1.700 g
FDC Blue No. 1	0.020 g
50 per cent 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 mixture is mixed with this liquid until proper granules are formed, which are dried at 80° to a moisture content of 3 per cent. The granulate is passed through a No. 20 screen, the 2 - (2 - 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 11/32" punches for a total tablet weight of 0.250 g.

Injectionable solutions, containing 1 mg/ml of 2 - (2 - dimethylaminoethyl) - 3 - [1 - (2 - pyridyl) - ethyl] - indene, may be prepared as follows (for 1000 ml):

Ingredients:

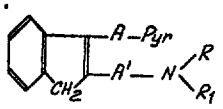
2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate	1.000 g
Lactic acid	18.000 g
Sodium hydroxide	4.140 g
Sodium chloride	1.520 g
Sodium sulfite	1.000 g
Disodium salt of ethylenediamine-tetracetic acid	0.100 g
Water for injection, q.s.	1000.000 ml

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

WHAT WE CLAIM IS:—

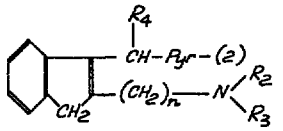
1. 2 - (Tertiary amino-lower alkyl) - 3 - (pyridyl-lower alkyl) - indenes as hereinbefore defined, their acid addition salts, and quaternary ammonium compounds and N-oxides in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

2. Indenes of the formula



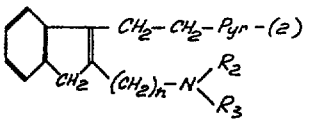
in which A represents a straight or branched lower alkylene group, A^1 represents a straight or branched lower alkylene group having 2 or 3 carbon atoms in a straight chain between the indene nucleus and the amino nitrogen, and Pyr represents a pyridine residue which may be substituted by lower alkyl or alkoxy groups or halogen atoms and in which R and R_1 each represent a lower alkyl group or R and R_1 together with the amino nitrogen atom form an N:N-alkyleneimino group having 5 to 6 ring members, whose alkylene chain may be interrupted by nitrogen, oxygen or sulfur and which may have as substituents methyl groups, and acid addition salts of these compounds, and quaternary ammonium compounds thereof, and N-oxides thereof in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

3. Indenes of the formula



in which n is the whole number 2 or 3, R_2 and R_3 each represent a lower alkyl radical having 1 to 3 carbon atoms, and R_4 represents a hydrogen atom or a lower alkyl radical having 1 to 3 carbon atoms, especially methyl, and acid addition salts, quaternary ammonium compounds or N-oxides of these compounds in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

4. Indenes of the formula



in which n is the whole number 2 or 3, R_2 and R_3 each represent a lower alkyl radical having 1 to 3 carbon atoms, acid addition salts, quaternary ammonium compounds or N-oxides of these compounds in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

5. 2 - (2 - Dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl - ethyl)] - indene and its acid addition salts.

6. 2 - (2 - Dimethylamino - ethyl) - 3 - [2 - (2 - pyridyl - ethyl)] - indene and its acid addition salts.

7. N-oxide of 2 - (2 - dimethylamino - ethyl) - 3 - [1 -(2 - pyridyl - ethyl)] - indene in which the N-oxide oxygen is attached to the nitrogen atom of the dimethylamino group.

8. A compound as claimed in claim 1 and specified in any one of the Examples herein, other than a compound claimed in claims 5 to 7.

Ingredients:

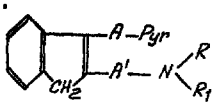
2-(2-dimethylaminoethyl)-3-[1-(2-pyridyl)-ethyl]-indene maleate	1.000 g
Lactic acid	18.000 g
Sodium hydroxide	4.140 g
Sodium chloride	1.520 g
Sodium sulfite	1.000 g
Disodium salt of ethylenediamine-tetracetic acid	0.100 g
Water for injection, q.s.	1000.000 ml

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

WHAT WE CLAIM IS:—

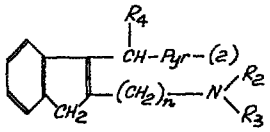
1. 2 - (Tertiary amino-lower alkyl) - 3 - (pyridyl-lower alkyl) - indenes as hereinbefore defined, their acid addition salts, and quaternary ammonium compounds and N-oxides in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

2. Indenes of the formula



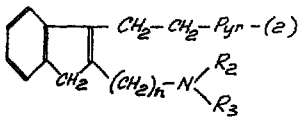
in which A represents a straight or branched lower alkylene group, A^1 represents a straight or branched lower alkylene group having 2 or 3 carbon atoms in a straight chain between the indene nucleus and the amino nitrogen, and Pyr represents a pyridine residue which may be substituted by lower alkyl or alkoxy groups or halogen atoms and in which R and R_1 each represent a lower alkyl group or R and R_1 together with the amino nitrogen atom form an N:N-alkyleneimino group having 5 to 6 ring members, whose alkylene chain may be interrupted by nitrogen, oxygen or sulfur and which may have as substituents methyl groups, and acid addition salts of these compounds, and quaternary ammonium compounds thereof, and N-oxides thereof in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

3. Indenes of the formula



in which n is the whole number 2 or 3, R_2 and R_3 each represent a lower alkyl radical having 1 to 3 carbon atoms, and R_4 represents a hydrogen atom or a lower alkyl radical having 1 to 3 carbon atoms, especially methyl, and acid addition salts, quaternary ammonium compounds or N-oxides of these compounds in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

4. Indenes of the formula



in which n is the whole number 2 or 3, R_2 and R_3 each represent a lower alkyl radical having 1 to 3 carbon atoms, acid addition salts, quaternary ammonium compounds or N-oxides of these compounds in which the N-oxide oxygen is attached to the nitrogen atom of the tertiary amino group.

5. 2 - (2 - Dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl - ethyl)] - indene and its acid addition salts.

6. 2 - (2 - Dimethylamino - ethyl) - 3 - [2 - (2 - pyridyl - ethyl)] - indene and its acid addition salts.

7. N-oxide of 2 - (2 - dimethylamino - ethyl) - 3 - [1 -(2 - pyridyl - ethyl)] - indene in which the N-oxide oxygen is attached to the nitrogen atom of the dimethylamino group.

8. A compound as claimed in claim 1 and specified in any one of the Examples herein, other than a compound claimed in claims 5 to 7.

9. A pharmaceutical preparation which comprises a 2 - (tertiary-amino-lower alkyl) - 3 - (pyridyl-lower alkyl) - indene as hereinbefore defined, or an acid addition salt, quaternary ammonium compound or N-oxide thereof in which the N-oxide oxygen in attached to the nitrogen atom of the tertiary amino group, in admixture or conjunction with a pharmaceutically suitable carrier.

10. A pharmaceutical preparation as claimed in claim 9, which comprises 2 - (2 - dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl - ethyl)] - indene, or an acid addition salt thereof.

11. A pharmaceutical preparation as claimed in claim 10, which comprises an N-oxide of 2 - (2 - dimethylamino - ethyl) - 3 - [1 - (2 - pyridyl - ethyl)] - indene in which the N-oxide oxygen is attached to the nitrogen atom of the dimethylamino group.

12. A pharmaceutical preparation as claimed in claim 9, which comprises 2 - (2 - dimethyl - amino - ethyl) - 3 - [2 - (2 - pyridyl - ethyl)] - indene or an acid addition salt thereof.

13. A pharmaceutical preparation as claimed in any one of claims 9 to 13, which is in the form of a tablet, dragée, ampoule, salve, cream, powder, suppository, solution, suspension or emulsion.

14. A process for the manufacture of a compound claimed in any one of claims 1 to 8, conducted substantially as hereinbefore described.

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