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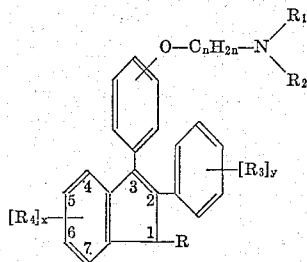
2-PHENYL-3-(TERTIARY AMINO ALKOXY) PHENYL-INDENES

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This invention relates to novel indenenes and is more particularly concerned with novel substituted 2-phenyl-3-(tertiaryaminoalkoxy)phenylindenenes and acid addition salts, quaternary ammonium salts, N-oxides, and N-oxide acid addition salts thereof, and with processes for their preparation.

The novel compounds of the invention are selected from the class consisting of (a) the free bases, (b) the pharmacologically acceptable acid addition salts, (c) the N-oxides, (d) the N-oxide pharmacologically acceptable acid addition salts, and (e) the quaternary ammonium salts of compounds having the formula:



wherein R is selected from the class consisting of hydrogen and lower-alkyl, R_1 and R_2 are selected from the class consisting of lower-alkyl and lower-alkyl groups linked together to form a 5 to 7 ring atom saturated heterocyclic radical, one of the ring atoms of which, in addition to the amino nitrogen atom, is selected from the class consisting of carbon, nitrogen, and oxygen, the other ring atoms being carbon, R_3 and R_4 are selected from the class consisting of trifluoromethyl, lower-alkyl, lower-alkenyl, hydroxy, lower-alkoxy, lower-alkenyloxy, aryloxy from 6 to 12 carbon atoms, inclusive, halogen, lower-alkylmercapto, and arylmercapto from 6 to 12 carbon atoms, inclusive, C_nH_{2n} represents an alkylene group from 2 to 6 carbon atoms, inclusive, and x and y are integers from 0 to 4, inclusive.

The term "lower-alkyl" means an alkyl group containing from 1 to 8 carbon atoms, inclusive, such as methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, and isomeric forms thereof. The term "lower-alkenyl" means an alkenyl group containing from 2 to 8 carbon atoms, inclusive, such as vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, and isomeric forms thereof. The term "lower-alkoxy" means an alkoxy group containing from 1 to 8 carbon atoms, inclusive, such as methoxy, ethoxy, propoxy, butoxy, amyoxy, hexyloxy, heptyloxy, octyloxy, and isomeric forms thereof. The term "lower-alkenyloxy" means an alkenyloxy group containing from 2 to 8 carbon atoms, inclusive, such as vinyloxy, allyloxy, butenyloxy, pentenyloxy, hexenyloxy, heptenyloxy, octenyloxy, and isomeric forms thereof. The term "aryloxy" from 6 to 12 carbon atoms, inclusive" includes phenoxy, tolyloxy, xylyloxy, naphthyloxy, biphenyloxy, and the like. The term "halogen" is inclusive of fluorine, chlorine, bromine, and iodine. The term "lower-alkylmercapto" means an alkylmercapto group containing from 1 to 8 carbon atoms, inclusive, such as methylmercapto, ethylmercapto, propylmercapto, butylmercapto, amylmercapto, hexylmercapto, heptylmercapto, octylmercapto, and isomeric forms thereof. The term "arylmercapto" from 6 to 12 carbon atoms, inclusive" includes phenyl-

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mercapto, tolylmercapto, xylylmercapto, naphthylmercapto, biphenylmercapto, and the like. The term "alkylene group from 2 to 6 carbon atoms, inclusive" includes ethylene, propylene, butylene, amylene, hexylene, and isomeric forms thereof.

The term "lower alkyl groups linked together to form a 5 to 7 ring atom saturated heterocyclic radical, one of the ring atoms of which, in addition to the amino nitrogen atom, is selected from the class consisting of carbon, nitrogen, and oxygen, the other ring atoms being carbon" is inclusive of pyrrolidino, 2-methylpyrrolidino, 2,2-dimethylpyrrolidino, and like alkylpyrrolidino groups, piperazino, 4-methylpiperazino, 2,4-dimethylpiperazino, and like alkylpiperazino groups, morpholino, piperidino, 2-methylpiperidino, 3-methylpiperidino, and like alkylpiperidino groups, hexamethyleneimino, homopiperazino, homomorpholino, and the like.

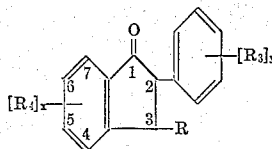
The acid addition salts of the invention comprise the salts of the compounds having the Formula I and of the corresponding N-oxides with pharmacologically acceptable acids such as sulfuric, hydrochloric, nitric, phosphoric, lactic, benzoic, methanesulfonic, p-toluenesulfonic, salicylic, acetic, propionic, maleic, malic, tartaric, citric, cyclohexylsulfamic, succinic, nicotinic, ascorbic acids, and the like.

The quaternary ammonium salts of the invention are the salts obtained by reacting the free bases having the Formula I with quaternating agents, for example, lower-alkyl halides, lower-alkenyl halides, di(lower-alkyl) sulfates, aralkyl halides, lower-alkyl arylsulfonates, and the like. The term "lower-alkyl" has the meaning hereinbefore defined. The term "aralkyl" means an aralkyl group containing from 7 to 13 carbon atoms, inclusive, such as benzyl, phenethyl, phenylpropyl, benzhydryl, and the like. Examples of quaternary salts of the compounds of Formula I are the methobromide, methiodide, ethobromide, propyl chloride, butyl bromide, octyl bromide, methyl methosulfate, ethyl ethosulfate, allyl chloride, allyl bromide, benzyl bromide, benzhydryl chloride, methyl toluenesulfonate and the like.

The novel compounds of the invention, including the free bases of Formula I, the acid addition salts thereof, the quaternary ammonium salts thereof, and the corresponding N-oxides and N-oxide acid addition salts possess pharmacological activity. Illustratively, the compounds of the invention are useful as antifertility agents, anti-estrogenic agents, and as agents for the lowering of cholesterol blood levels in mammals including animals of economic value. For purposes of administration to mammals, the novel compounds of the invention can be combined with solid or liquid pharmaceutical carriers and formulated in the form of tablets, powder packets, or capsules, using starch and like excipients, or dissolved or suspended in suitable solvents or vehicles, for oral or parenteral administration.

In addition to their pharmacological activity, the compounds of the invention are also useful as intermediates. For example, the compounds having the Formula I can be reacted with fluosilicic acid to form the fluosilicate salts which in dilute aqueous solution are effective mothproofing agents as more fully disclosed in U.S. Patents 2,075,359 and 1,915,334.

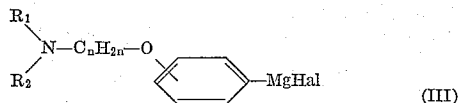
The novel compounds of the invention having the Formula I can be prepared by reaction of an appropriately substituted indanone having the formula:



(II)

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wherein R_3 , R_4 , x , and y have the significance hereinbefore defined (with the exception noted below) with a Grignard reagent having the formula:



wherein R_1 , R_2 , and C_nH_{2n} have the significance hereinbefore defined and Hal represents a halogen atom. The reaction is carried out advantageously in the presence of an inert solvent under anhydrous conditions in accordance with the established procedure for Grignard reactions. Suitable inert solvents include diethyl ether, tetrahydrofuran, and the like. The reaction can be carried out at temperatures within the range of about 0°C . to about the boiling point of the solvent employed and is preferably carried out at elevated temperatures, for example, at or near the boiling point of the reaction mixture.

The reaction time varies within wide limits according to the temperature at which the reaction is conducted. Generally speaking, where the reaction is carried out at elevated temperatures such as the boiling point of the reaction mixture, it is necessary to employ a reaction time of the order of several hours to ensure completion of the reaction.

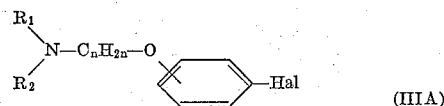
The desired indene having the Formula I can be isolated from the reaction mixture by conventional procedures, for example, by decomposing the reaction mixture with water, ammonium chloride, and the like followed by separation of the organic layer and removal of solvent therefrom. In many cases the product so obtained is largely indene having the Formula I contaminated with minor impurities and unchanged starting material which can be removed by simple procedures, for example, by isolation of the indene (I) as an acid addition salt. However, in some cases the indene (I) so obtained is contaminated with appreciable quantities of the corresponding indanol which is formed as intermediate in the reaction of the indanone (II) and the Grignard (III) and which is dehydrated to yield the desired indene. Where such a mixture of indene (I) and the corresponding indanol is obtained, said mixture can be treated by procedures known to effect the dehydration of a tertiary carbinol whereby the indanol present in the mixture is converted to the desired indene (I). A particularly convenient method of effecting the dehydration is to heat the mixture in a solvent such as benzene, toluene, xylene and the like which forms an azeotrope with water, and in the presence of a trace of a strong acid such as hydrochloric, sulfuric, p-toluenesulfonic acids and the like. The water which is formed in the dehydration is removed from the reaction mixture azeotropically. There is thereby obtained a solution of the desired indene (I) free from indanol. The indene (I) can then be isolated by evaporation of the solvent or by other conventional procedures, for example, extraction with aqueous acid followed by liberation of the free base indene (I) by basification of the acid solution.

When either or both of the groups R_3 and R_4 in the starting indanone (II) represents free hydroxy, it is necessary, before carrying out the Grignard reaction described above, to protect this group with a radical which can be removed subsequently to yield the corresponding indene (I) with a free hydroxy group or groups. A particularly convenient manner in which a free hydroxy group or groups in the starting indanone can be so protected is by conversion to the corresponding tetrahydropyranyl ether. The latter conversion can be accomplished readily by treating the indanone (II) containing a free hydroxyl group or groups with 2,3-dihydropyran in the presence of a trace of mineral acid such as hydrochloric acid. After the indanone (II) with hydroxy group or groups protected in this manner has been converted to the corresponding indene (I) by the reaction described above, the tetrahydropyranyl ether can

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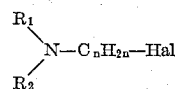
be hydrolyzed, for example, using aqueous mineral acid to liberate the free hydroxy group.

The Grignard reagents having the Formula III which are employed as starting materials in the process of the invention can be prepared by reaction of magnesium in an anhydrous inert organic solvent such as ether, tetrahydrofuran and the like with the appropriately substituted halobenzene having the formula:



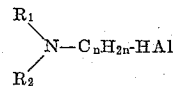
wherein R_1 , R_2 , C_nH_{2n} , and Hal have the significance hereinbefore defined, using procedures well known in the art for the preparation of Grignard reagents.

The halobenzenes having the Formula IIIA can be prepared by etherification of the corresponding halophenol with the appropriate tertiaryaminoalkyl halide



wherein R_1 , R_2 , C_nH_{2n} , and Hal have the significance hereinbefore defined. The etherification is conducted advantageously in an inert solvent such as a lower alkanol, for example, methanol, ethanol, isopropyl alcohol, and the like in the presence of a base such as sodium hydroxide, sodium methoxide, and the like.

The tertiaryaminoalkyl halides having the formula



wherein R_1 , R_2 , C_nH_{2n} , and Hal have the significance hereinbefore defined, employed in the preparation of halobenzenes (IIIA) can themselves be prepared by halogenation of the corresponding tertiaryaminoalkanols, which tertiaryaminoalkanols in turn can be made by interaction of the requisite secondary amine



wherein R_1 and R_2 have the significance hereinbefore defined, with the appropriate haloalkanol, $\text{Hal}-C_nH_{2n}\text{OH}$, wherein Hal and C_nH_{2n} have the significance hereinbefore defined, in accordance with known methods. The condensation between the secondary amine



and the haloalkanol $\text{Hal}-C_nH_{2n}\text{OH}$ can be carried out, for example, using the procedure described by Moffett, J. Org. Chem. 14, 862, 1949. Alternatively, the desired tertiaryaminoalkanols can be prepared by heating the secondary amine



with the appropriate haloalkanoic acid ester, followed by reduction of the thus-produced aminoalkanoic acid ester with lithium aluminum hydride according to the method described by Moffett, supra.

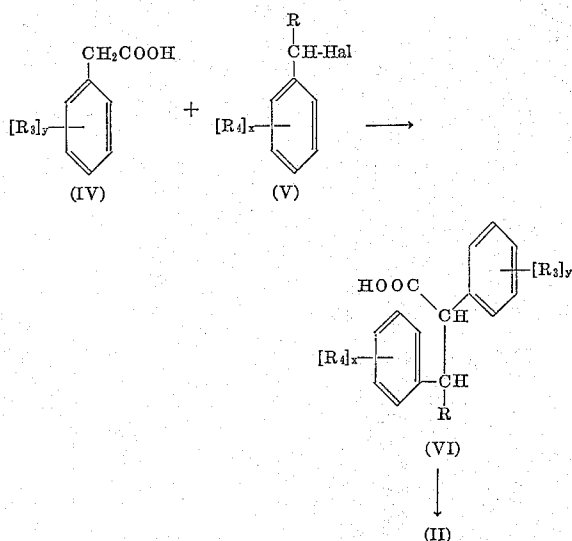
The conversion of the tertiaryaminoalkanols so obtained to the corresponding tertiaryaminoalkyl halides can be carried out by the use of known halogenating agents such as thionyl bromide, thionyl chloride, phosphorus tribromide, phosphorus trichloride, and the like, using, for example, the procedure described by Moffett et al., J. Am. Chem. Soc. 77, 1565, 1955.

A number of the indanones having the Formula II

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which are employed as starting materials in the process of the invention are known. The known compounds include 2-phenyl-1-indanone, 5-methoxy-2-(p-methoxyphenyl)-1-indanone, 7-methoxy-2-(p-methoxyphenyl)-1-indanone, 5-methoxy-2-phenyl-1-indanone, 6-methoxy-2-phenyl-1-indanone, 5-isopropoxy-2-phenyl-1-indanone, and 5,6-dimethoxy-2-phenyl-1-indanone.

The starting indanones of Formula II, except those in which R_3 and R_4 represent hydroxy or alkenyloxy, can be prepared conveniently according to the following reaction scheme:



wherein R , R_3 , R_4 , x , and y have the significance hereinbefore defined, and Hal represents chlorine or bromine. It is to be noted that the benzyl halide (V) must be unsubstituted in at least one of the ortho positions in order that the compound (VI) can be cyclized as described below.

The reaction of the phenylacetic acids (IV) with the benzyl halides (V) to give the corresponding α -phenylhydrocinnamic acids (VI) can be effected, for example, using the procedure described by Hauser and Chambers, J. Am. Chem. Soc. 78, 4942, 1956, for the preparation of α -phenylhydrocinnamic acid from phenylacetic acid and benzyl chloride. The α -phenylhydrocinnamic acids (VI) [$R=H$] can also be prepared by Perkin condensation of a phenylacetic acid (IV) with the appropriately substituted benzaldehyde followed by reduction of the intermediate α -phenylcinnamic acid so obtained. The procedure employed in this alternate synthesis is preferably that described by Solmssen, J. Am. Chem. Soc. 65, 2370, 1943.

The α -phenylhydrocinnamic acids (VI) so obtained are then cyclized to the required indanones (II) in the presence of a Lewis acid, using the general procedure described by Fieser and Hershberg, J. Am. Chem. Soc. 61, 1272, 1939. The term "Lewis acid" is well known in the art and is defined succinctly by Fieser and Fieser, "Organic Chemistry," Third Edition, page 138 (Reinhold, 1956). Examples of such compounds are hydrogen fluoride, boron trifluoride, arsenic trifluoride, phosphorus pentafluoride, titanium tetrafluoride, concentrated sulfuric acid, polyphosphoric acid, and the like. The preferred Lewis acid for use in the above process is hydrogen fluoride.

A particularly convenient method of cyclizing the α -phenylhydrocinnamic acids (VI) according to the above procedure comprises adding the acid (VI) to liquid hydrogen fluoride with stirring and then allowing the hydrogen fluoride to evaporate at room temperature. The desired indanone (II) is then isolated from the residue by conventional methods, for example, by dissolving the residue in a suitable solvent such as ether, washing the solu-

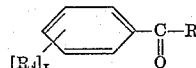
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tion so obtained with an aqueous solution of a base such as sodium carbonate, sodium hydroxide, and the like, and then evaporating the washed solution to dryness. The indanone (II) so obtained can be purified, if desired, by conventional procedures, for example, by distillation. The indanones of Formula II wherein R_3 or R_4 represents hydroxy can be prepared conveniently by dealkylation of the corresponding compounds of Formula II in which R_3 or R_4 represents alkoxy. The dealkylation can be effected using conventional methods, for example, by heating with aluminum chloride or bromide in the presence of an inert solvent such as benzene, xylene, and the like.

The indanones of Formula II wherein R_3 or R_4 represents alkenyloxy can be prepared conveniently by alkenylation of the corresponding compounds wherein R_3 or R_4 represents hydroxy. The alkenylation can be effected using conventional procedures, for example, by reacting the free hydroxy compound with the appropriate alkenyl halide in the presence of a base such as potassium carbonate, sodium methoxide, and the like.

The benzyl halides (V) [$R=H$], which are employed as starting materials in the above-described preparation, and many of which are known in the art, can themselves be prepared from the correspondingly substituted benzoic acids, for example, by reduction of said acids or simple alkyl esters thereof, for example, with lithium aluminum hydride according to the procedure described by Nystrom and Brown, J. Am. Chem. Soc. 69, 2548, 1947. The benzyl alcohols so obtained are then converted to the corresponding benzyl halides (V) using procedures known in the art, for example, that described by Gilman and Kirby, J. Am. Chem. Soc. 51, 475, 1929.

The benzyl halides (V) [$R=\text{alkyl}$] can be prepared by reduction of the appropriate alkanophenone



wherein R is alkyl, and R_4 and x have the significance hereinbefore defined, using, for example, sodium in alcohol, followed by halogenation of the phenylalkylcarbinol so obtained, using, for example, a hydrogen halide as described by Kharasch and Kleiman, J. Am. Chem. Soc. 65, 11, 1943, or using, for example, a phosphorus oxyhalide as described by Gerrard, J. Chem. Soc. 1945, 106.

The phenylacetic acids (IV), which are employed as starting materials in the above-described preparation, and many of which are known in the art (see, for example, Corse et al., J. Am. Chem. Soc. 70, 2837, 1948) can themselves be prepared from the corresponding benzyl halides (V) [$R=H$] by procedures well known in the art. For example, the benzyl halides (V) can be reacted with an alkali metal cyanide, such as sodium cyanide, to form the corresponding benzyl cyanide which latter is then hydrolyzed, for example, using an aqueous mineral acid or aqueous alkali, to yield the desired phenylacetic acid (IV). A suitable procedure for carrying out the conversion of the benzyl halide (V) [$R=H$] to the phenylacetic acid (IV) is that described by Silverman and Bogert, J. Org. Chem. 11, 34, 1946.

The acid addition salts of the compounds of the invention having the Formula I can be prepared by methods well known in the art. For example, the acid addition salts of the invention can be prepared by reacting a free base having the Formula I with a pharmacologically acceptable acid, as hereinbefore defined, in the presence of an inert solvent such as water, ether, and lower alkanols such as methanol, ethanol, and the like.

The N-oxide compounds of the invention can be prepared by methods well known in the art, for example, by reacting the free base of the Formula I with an oxidizing agent such as hydrogen peroxide, peracetic acid, Caro's acid, and the like. Advantageously, the reaction is carried out at ordinary temperatures (e.g., of the order of 20 to 30° C.) in the presence of an inert solvent such as

benzene, chloroform, lower-alkyl alkanoates such as ethyl acetate, and lower alkanols such as methanol, ethanol, isopropyl alcohol, and the like. Suitably the oxidizing agent is employed in at least stoichiometric proportion with respect to the free base (I) and preferably the oxidizing agent is present in a slight excess. When the reaction has been completed, any excess of oxidizing agent can be removed by treating the reaction mixture with an agent such as platinum oxide, palladium, Raney nickel, and inorganic hydrosulfites, such as sodium hydrosulfite, and the like.

The N-oxide acid addition salts of the invention can be prepared from the corresponding N-oxide and a pharmacologically acceptable acid using the procedures hereinbefore described for the preparation of the acid addition salts of the compounds (I).

The quaternary ammonium salts of the invention can be prepared by reacting a free base of the Formula I with a quaternating agent, for example, an alkyl halide such as methyl iodide, ethyl chloride, isopropyl bromide, and the like, an alkyl halide such as allyl chloride, allyl bromide, and the like, a dialkyl sulfate such as dimethyl sulfate, diethyl sulfate, and the like, an aralkyl halide such as benzhydryl chloride, phenethyl bromide, and the like, or an alkyl arylsulfonate such as methyl p-toluenesulfonate, and the like. Preferably the reaction is effected by heating the reactants together in the presence of an inert solvent such as acetonitrile, acetone, methanol, ethanol, and the like. Generally speaking, the desired quaternary salt separates from solution upon cooling the reaction mixture and can be isolated by filtration. Purification of the quaternary salt can be effected by conventional methods, for example, by recrystallization.

The following preparations and examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

PREPARATION 1

p-(2-Diethylaminoethoxy)Bromobenzene

A mixture of 272 g. (1.57 moles) of *p*-bromophenol, 1500 ml. of ethanol, and 340 g. (equivalent to 1.57 moles of sodium methoxide) of a 25% solution of sodium methoxide in methanol was stirred and heated under reflux and to the refluxing solution was added dropwise, with stirring, over a period of 30 minutes, a solution of 213 g. of 2-diethylaminoethyl chloride in 200 ml. of ethanol. After the addition was complete the mixture was stirred and heated under reflux for a further 3 hours. At the end of this time the reaction mixture was cooled and filtered, and the filtrate was evaporated under reduced pressure. The residual oil was dissolved in 1500 ml. of ether and the ether solution was washed with two 200-ml. portions of dilute aqueous sodium hydroxide solution and then with four 200-ml. portions of water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated. The residue was distilled under reduced pressure and that fraction having a boiling point of 110 to 115° C. at a pressure of 0.3 mm. of mercury was collected. There was thus obtained 310 g. of *p*-(2-diethylaminoethoxy)bromobenzene in the form of an oil. The free base so obtained was converted to the hydrochloride having a melting point of 139 to 140° C.

Anal.—Calcd. for $C_{12}H_{19}BrClNO$: C, 46.69; H, 6.20; N, 4.54. Found: C, 47.04; H, 6.47; N, 4.49.

Using the above procedure, but replacing 2-diethylaminoethyl chloride by 3-dimethylaminopropyl chloride, 2-diethylaminopropyl chloride, 2-dibutylaminoethyl bromide, 2-methylethylaminoethyl bromide, 3-diethylaminobutyl chloride, 5-dimethylaminopentyl bromide, 2-diethylaminopentyl bromide, 6-dimethylaminohexyl chloride, 2-pyrrolidinoethyl chloride, 3-(2,2-dimethylpyrrolidino)propyl bromide, 2-piperidinoethyl chloride, 2-piperidinopropyl bromide, 2-morpholinoethyl chloride, 2-morpholinobutyl bromide, 1-methyl-4-(2'-chloroethyl)piperazine,

2-hexamethyleneiminoethyl chloride, 2-homopiperazinoethyl chloride, and 2-homomorpholinoethyl chloride, there are obtained *p*-(3-dimethylaminopropoxy)bromobenzene, *p*-(2-diethylaminopropoxy)bromobenzene, *p*-(2-dibutylaminoethoxy)bromobenzene, *p*-(2-N-methyl-N-ethylaminoethoxy)bromobenzene, *p*-(3-diethylaminobutoxy)bromobenzene, *p*-(5-dimethylaminopentoxy)bromobenzene, *p*-(2-diethylaminopentoxy)bromobenzene, *p*-(6-dimethylaminohexyloxy)bromobenzene, *p*-(2-pyrrolidinoethoxy)bromobenzene, *p*-[3-(2,2-dimethylpyrrolidino)propoxy]bromobenzene, *p*-(2-piperidinoethoxy)bromobenzene, *p*-(2-piperidinopropoxy)bromobenzene, *p*-(2-morpholinoethoxy)bromobenzene, *p*-(2-morpholinobutoxy)bromobenzene, *p*-[2-(1'-methyl-4'-piperazino)ethoxy]bromobenzene, *p*-(2-hexamethyleneiminoethoxy)bromobenzene, *p*-(2-homopiperazinoethoxy)bromobenzene, and *p*-(2-homomorpholinoethoxy)bromobenzene, respectively.

Using the above procedure, but replacing *p*-bromophenol by *o*-bromophenol and *m*-bromophenol, the corresponding *o*- and *m*-(tertiaryaminoalkoxy)bromobenzenes are obtained.

Examples 1 through 43 below illustrate the preparation of representative 2-phenyl-3-[*p*-(tertiaryaminoalkoxy)phenyl]indene free bases and acid addition salts, quaternary ammonium salts, N-oxides, and N-oxide acid addition salts thereof. The corresponding 2-phenyl-3-[*o*- and *m*-(tertiaryaminoalkoxy)phenyl]indene free bases and acid addition salts, quaternary ammonium salts, N-oxides, and N-oxide acid addition salts thereof are prepared as follows. The *o*- and *m*-(tertiaryaminoalkoxy)bromobenzenes obtained above are substituted for the corresponding *p*-(tertiaryaminoalkoxy)bromobenzenes in Examples 1 through 40, to obtain the corresponding 2-phenyl-3-[*o*- and *m*-(tertiaryaminoalkoxy)phenyl]indene free bases and acid addition salts thereof. The acid addition salts thus obtained are substituted for the corresponding 2-phenyl-3-[*p*-(tertiaryaminoalkoxy)phenyl]indene acid addition salts in Examples 41 through 43, to obtain the corresponding 2-phenyl-3-[*o*- and *m*-(tertiaryaminoalkoxy)phenyl]indene quaternary ammonium salts, N-oxides, and N-oxide acid addition salts.

EXAMPLE 1

2-Phenyl-3-[*p*-(2-Diethylaminoethoxy)Phenyl]Indene and Acid Addition Salts Thereof

A solution of 4.16 g. (0.02 mole) of 2-phenyl-1-indanone (v. Miller and Rohde, Ber. 25, 2095, 1892) in 50 ml. of tetrahydrofuran was added to a solution of *p*-(2-diethylaminoethoxy)phenyl magnesium bromide prepared from 5.44 g. (0.02 mole) of *p*-(2-diethylaminoethoxy)bromobenzene and 0.66 g. of magnesium in 50 ml. of tetrahydrofuran. The resulting mixture was heated for 16 hr. under reflux and allowed to cool. Water and ether were added to the cooled mixture and the resulting mixture was filtered through diatomaceous earth (Celite). The organic layer of the filtrate was separated, washed with water, and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether and the solution was washed with 400 ml. of 0.5 N hydrochloric acid. The acid extract was extracted with 400 ml. of methylene chloride and the methylene chloride extract was evaporated to dryness. The residue was heated under reflux with a mixture of 100 ml. of benzene and 0.15 g. of *p*-toluenesulfonic acid for 2 hrs., the evolved water being collected in a water trap. The benzene solution was cooled and aqueous sodium bicarbonate solution and ether were added. The organic layer was separated and extracted with 0.5 N hydrochloric acid. The acid extract was extracted with methylene chloride and the methylene chloride extract was evaporated to dryness. The residual gum was dissolved in a small quantity of benzene and the benzene solution was washed with aqueous sodium bicarbonate solution before being chromato-

graphed on a magnesium silicate (Florisil) column. The column was eluted with Skellysolve B (a mixture of hexanes) containing a small proportion of acetone and the eluate containing the desired amine was evaporated to dryness. There was thus obtained 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]indene in the form of an oily gum. The latter gum was dissolved in ether and extracted with 90 ml. of aqueous 24% perchloric acid solution. The acid extract was extracted with methylene chloride and the methylene chloride extract was evaporated to dryness. The residual foam was triturated with ethyl acetate and the crystals which separated were isolated by filtration and recrystallized from ethyl acetate. There was thus obtained 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]indene perchlorate in the form of a crystalline solid having a melting point of 156 to 157.5° C. The ultraviolet absorption spectrum of the compound (in solution in ethanol) exhibited maxima at 232, 248, 305, and 313 millimicrons.

Anal.—Calcd. for $C_{27}H_{30}ClNO_5$: C, 67.00; H, 6.25; N, 2.89. Found: C, 67.05; H, 6.36; N, 3.10.

Another run was made in which the starting materials were 5.0 g. of 2-phenyl-1-indanone, 6.55 g. of p-(2-diethylaminoethoxy)bromobenzene, and 0.8 g. of magnesium. The procedure was the same as described above through the step of heating the benzene solution of the 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrochloride in the presence of p-toluenesulfonic acid. The benzene solution, after being washed with saturated aqueous sodium bicarbonate solution, was shaken with aqueous 10% hydriodic acid. Three phases separated, an aqueous phase, a benzene phase, and an oil. The oil was separated and extracted with methylene chloride and the extract was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The solid residue was recrystallized three times from methylene chloride-ethyl acetate mixture. There was thus obtained 4.29 g. of 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]indene hydroiodide having a melting point of 175.5 to 177.5° C.

EXAMPLE 2

2 - (p - Methoxyphenyl) - 3 - [p-(2 - Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(p-METHOXYPHENYL)-1-INDANONE

A solution of 39.0 g. (0.235 mole) of p-methoxyphenylacetic acid in 500 ml. of ether was added to a solution of potassium amide prepared from 20.4 g. (0.52 mole) of potassium in 750 ml. of liquid ammonia. To the resulting mixture was added slowly, with stirring, over a period of 10 minutes, a solution of 33.0 g. (0.26 mole) of benzyl chloride in 60 ml. of ether. The mixture was stirred for a further 30 minutes, at the end of which time an additional 3 ml. (0.003 mole) of benzyl chloride was added and the liquid ammonia was then allowed to evaporate. The residue was dissolved in water and the aqueous solution so obtained was extracted with ether and then filtered through diatomaceous earth (Celite). The filtrate was acidified by the addition of concentrated hydrochloric acid and the solid which separated was isolated by filtration and recrystallized from a mixture of chloroform and hexane. There was thus obtained 53.85 g. of α -benzyl-p-methoxyphenylacetic acid in the form of a crystalline solid having a melting point of 105 to 108° C.

The acid (53.85 g.) so obtained was added portionwise to 300 ml. of well stirred liquid hydrogen fluoride. The hydrogen fluoride was then allowed to evaporate at room temperature and the residue was dissolved in ether. The ethereal solution was washed successively with water, aqueous sodium bicarbonate solution, aqueous 0.5 N sodium hydroxide solution, and finally with brine. The washed ethereal solution was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated to dryness.

The residual oily solid was dissolved in benzene and chromatographed over a column of magnesium silicate (Florisil). The column was eluted with Skellysolve B containing 5% by volume of acetone. The major crystalline fraction was recrystallized from aqueous methanol. There was thus obtained 29.73 g. of 2-(p-methoxyphenyl)-1-indanone in the form of a crystalline solid having a melting point of 74 to 79° C. An analytical sample having a melting point of 79 to 81° C. was obtained by further recrystallization from aqueous methanol.

Anal.—Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.55; H, 5.99.

B. 2-(p-METHOXYPHENYL)-3-[p-(2-DIETHYLAMINO-ETHOXY)PHENYL]INDENE HYDROCHLORIDE

A solution of 4.88 g. (0.0205 mole) of 2-(p-methoxyphenyl)-1-indanone in 75 ml. of tetrahydrofuran was added with stirring to a Grignard reagent prepared from 5.60 g. (0.0205 mole) of p-(diethylaminoethoxy)bromobenzene and 0.51 g. of magnesium in 75 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for 16 hr. before being cooled to room temperature. To the cooled solution were added ether and water. The organic layer was separated, washed with water and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and the ether solution was extracted with 0.5 N hydrochloric acid. The acid extract was extracted with methylene chloride and the methylene chloride solution was evaporated to dryness. The residual foam (6.55 g.) was heated under reflux for 2 hr. with 150 ml. of benzene containing 0.25 g. of p-toluenesulfonic acid. The evolved water was collected in a water trap. The residue was cooled and ether and saturated aqueous sodium bicarbonate solution were added. The organic layer was separated and extracted with 0.5 N hydrochloric acid. The acid extract was extracted with methylene chloride and the methylene chloride solution was evaporated. The residue was recrystallized twice from a mixture of methylene chloride and ethyl acetate to yield 3.67 g. of 2-(p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrochloride in the form of a crystalline solid having a melting point of 168 to 171° C. An analytical sample having a melting point of 170 to 172° C. was obtained by further recrystallization from the above solvent mixture. The ultraviolet absorption spectrum of the compound (in solution in ethanol) exhibited maxima at 236, 244, 310, and 320 millimicrons.

Anal.—Calcd. for $C_{28}H_{32}ClNO_2$: C, 74.73; H, 7.17; N, 3.11. Found: C, 74.36; H, 7.32; N, 3.31.

EXAMPLE 3

2-(p-Tolyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrobromide Thereof

A. 2-(p-TOLYL)-1-INDANONE

A solution of 15.0 g. (0.10 mole) of p-tolylacetic acid in 50 ml. of ether was added to a solution of 0.20 mole of potassium amide (prepared from 8.82 g. of potassium) in 250 ml. of liquid ammonia. The mixture was stirred for 5 minutes and then a solution of 13.9 g. (0.11 mole) of benzyl chloride in 50 ml. of ether was added slowly with stirring. After the addition was complete the resulting mixture was stirred for a period of 30 minutes, at the end of which time a further 2 g. of benzyl chloride was added. The mixture was again stirred for a further 30 minutes before the liquid ammonia was allowed to evaporate. The residue was dissolved in 200 ml. of water and the aqueous solution was filtered through diatomaceous earth. The filtrate was acidified with concentrated hydrochloric acid and the solid which separated was isolated by filtration and recrystallized three times from hexane. There was thus obtained 12.6 g. of α -benzyl-p-tolylacetic acid in the form of a crystalline solid having a melting point

of 104 to 107° C. The acid so obtained was dissolved portionwise in 100 ml. of liquid hydrogen fluoride and, when the addition was complete, the hydrogen fluoride was allowed to evaporate. The residue was dissolved in ether and the ethereal solution was washed successively with water, aqueous sodium bicarbonate solution, aqueous 0.5 N sodium hydroxide solution, and brine, and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residual oil was distilled under reduced pressure and that fraction having a boiling point of 155 to 160° C. at a pressure of 1.5 to 2 mm. of mercury was collected. There was thus obtained 6.32 g. of 2-(p-tolyl)-1-indanone in the form of an oil.

Anal.—Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.52; H, 6.58.

B. 2-(p-TOLYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROBROMIDE THEREOF

A solution of 6.32 g. (0.0285 mole) of 2-(p-tolyl)-1-indanone in 65 ml. of tetrahydrofuran was added slowly with stirring to a solution of 0.0285 mole of p-(2-diethylaminoethoxy)phenyl magnesium bromide in 80 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for 16 hr. before being cooled to room temperature and treated with a small amount of water. The mixture so obtained was filtered and the filtrate was diluted with ether. The organic layer was separated and washed with water and then with brine before being dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and the ether solution was extracted with 0.5 N hydrochloric acid. The acid extract was extracted with five 50-ml. portions of methylene chloride and the combined methylene chloride extracts were evaporated to dryness. The residual foam was heated under reflux for 2 hr. with 200 ml. of benzene containing 0.2 g. of p-toluenesulfonic acid and the evolved water was collected in a water trap. The residual benzene solution was washed with aqueous sodium bicarbonate solution and then with brine before being evaporated to dryness. There was thus obtained 2-(p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene as an oil. The oil was dissolved in ether and the ether solution was extracted with aqueous 10% hydrobromic acid. The acid extract was extracted with methylene chloride and the methylene chloride extract was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized twice from a mixture of methylene chloride and ethyl acetate. There was thus obtained 5.6 g. of 2-(p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrobromide in the form of a crystalline solid having a melting point of 188 to 190° C.

Anal.—Calcd. for $C_{28}H_{32}BrNO$: C, 70.28; H, 6.74; N, 2.93. Found: C, 70.12; H, 7.02; N, 2.95.

EXAMPLE 4

2-Phenyl-3-[p-(2-Diethylaminoethoxy)Phenyl]-5-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-phenyl-6-methoxy-1-indanone (Jocelyn, J. Chem. Soc. 1954, 1640), there was obtained 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-5-methoxyindene and the hydrochloride thereof. The hydrochloride was recrystallized from ethyl acetate to give an ethyl acetate solvate of 2-phenyl-3-[p-(2-diethylaminoethoxy)-phenyl]-5-methoxyindene hydrochloride in the form of a crystalline solid having a melting point of 104 to 110° C.

Anal.—Calcd. for $C_{28}H_{32}ClNO_2 \cdot \frac{1}{4}CH_3CO_2C_2H_5$: C, 73.79; H, 7.26; N, 2.97. Found: C, 73.42; H, 6.62; N, 3.05.

The unsolvated hydrochloride was obtained by heating the solvated salt at 80° C. in vacuo for a prolonged period.

EXAMPLE 5

2-Phenyl-3-[p-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

A solution of 5.40 g. (0.0237 mole) of 2-phenyl-5-methoxy-1-indanone (Jocelyn, supra) in 75 ml. of tetrahydrofuran was added slowly with stirring to the Grignard reagent prepared from 6.30 g. (0.023 mole) of p-(2-diethylaminoethoxy)bromobenzene and 0.59 g. of magnesium in 65 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for 16 hr. before being cooled and treated with a small amount of water. The mixture so obtained was filtered and the filtrate was washed with water. The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and the ether solution was extracted with 0.5 N hydrochloric acid. The aqueous layer formed a gel which was separated and extracted with 800 ml. of chloroform. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness. The residue was heated under reflux for 1.5 hr. with 200 ml. of benzene containing 0.2 g. of p-toluenesulfonic acid, the evolved water being collected in a water trap. The residual benzene solution containing 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene salts was washed with aqueous sodium bicarbonate solution and then with brine and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was saturated with hydrogen chloride before being evaporated to dryness. The residue was recrystallized twice from a mixture of methylene chloride and ethyl acetate. There was thus obtained 4.24 g. of an ethyl acetate solvate of 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride in the form of a crystalline solid having a melting point of 174.5 to 177° C. An analytical sample having a melting point of 174 to 176° C. was obtained by further recrystallization from the same solvent mixture. The ultraviolet absorption spectrum of the compound (in solution in ethanol) exhibited maxima at 224, 234, 251, 313, and 332 millimicrons.

Anal.—Calcd. for $C_{28}H_{32}ClNO_2 \cdot \frac{1}{4}CH_3CO_2C_2H_5$: C, 73.79; H, 7.26; N, 2.97. Found: C, 74.18; H, 6.98; N, 3.01.

The unsolvated hydrochloride was obtained by heating the solvated salt at 80° C. in vacuo for a prolonged period.

EXAMPLE 6

2-(p-Methoxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydroiodide Thereof

A solution of 4.0 g. (0.015 mole) of 2-(p-methoxyphenyl)-5-methoxy-1-indanone (Solmssen, J. Am. Chem. Soc. 65, 2370, 1943) in 100 ml. of tetrahydrofuran was added slowly with stirring to the Grignard reagent prepared from 4.80 g. (0.075 mole) of p-(2-diethylaminoethoxy)bromobenzene and 0.35 g. of magnesium in 40 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for 16 hr. and then cooled to room temperature. The cooled mixture was treated with a small quantity of water and then filtered. The filtrate was diluted with ether and the organic layer was washed with water and brine before being evaporated to dryness. The residue was dissolved in ether and the ether solution was extracted with 0.5 N hydrochloric acid. The acid extract was extracted with six 50-ml. portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate and the dried solution was filtered. The filtrate was evaporated to dryness and the residue was heated under reflux for 1.5 hr. with 150 ml. of benzene

containing 0.15 g. of p-toluenesulfonic acid, the evolved water being collected in a water trap. The residual benzene solution was washed with aqueous sodium bicarbonate solution and water and then evaporated to dryness. There was thus obtained 2-(p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)-phenyl]-6-methoxyindene in the form of a foam. The latter was dissolved in ether and the ether solution was extracted with aqueous 10% hydriodic acid. The acid extract was extracted with methylene chloride and the methylene chloride extract was dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness. The residue was recrystallized from benzene. There was thus obtained a benzene solvate of 2-(p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydroiodide in the form of a crystalline solid having a melting point of 156 to 160° C. after softening and resolidifying at approximately 90° C.

Anal.—Calcd. for $C_{29}H_{34}INO_3 \cdot \frac{1}{2}C_6H_6$: C, 62.94; H, 6.11; N, 2.29. Found: C, 63.09; H, 5.98; N, 2.45.

The unsolvated hydroiodide was obtained by heating the solvated salt at 70° C. for several hours.

EXAMPLE 7

2-Phenyl-3-[p-(2-Diethylaminoethoxy)Phenyl]-5,6-Dimethoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-phenyl-5,6-dimethoxy-1-indanone (Jocelyn, supra), there was obtained 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-5,6-dimethoxyindene and the hydrochloride thereof. The hydrochloride was obtained as its hemihydrate in the form of a crystalline solid having a melting point of 210 to 212° C.

Anal.—Calcd. for $C_{29}H_{34}ClNO_3 \cdot \frac{1}{2}H_2O$: C, 71.22; H, 7.21; N, 2.86. Found: C, 71.01; H, 7.06; N, 2.77.

The anhydrous hydrochloride was obtained by heating the hydrated salt at 100° C. in vacuo for a prolonged period.

EXAMPLE 8

2-(p-Tolyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

A. 2-(p-TOLYL)-5-METHOXY-1-INDANONE

Using the procedure described in Example 3, Part A, but replacing benzyl chloride by m-methoxybenzyl chloride, there was obtained 2-(p-tolyl)-5-methoxy-1-indanone in the form of a crystalline solid having a melting point of 99 to 103° C.

Anal.—Calcd. for $C_{17}H_{18}O_2$: C, 80.92; H, 6.39. Found: C, 80.99; H, 6.52.

B. 2-(p-TOLYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]-6-METHOXYINDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-tolyl)-5-methoxy-1-indanone, there was obtained 2-(p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof. The hydrochloride was obtained in the form of an ethyl acetate solvate having a melting point of 212 to 215° C.

Anal.—Calcd. for $C_{29}H_{34}ClNO_2 \cdot \frac{1}{4}CH_3CO_2C_2H_5$: C, 74.13; H, 7.47; N, 2.88. Found: C, 74.25; H, 7.20; N, 3.08.

EXAMPLE 9

2-(p-Chlorophenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(p-CHLOROPHENYL)-1-INDANONE

A solution of potassium amide, prepared from 10.6 g. of potassium in 400 ml. of liquid ammonia, was added to a solution of 23.1 g. (0.136 mole) of p-chlorophenylacetic acid in 100 ml. of ether. The mixture was stirred

for 5 minutes before adding slowly a solution of 19.0 g. of benzyl chloride in 100 ml. of ether. The mixture was then stirred at room temperature and, at intervals of 30 minutes, two further 5-g. portions of benzyl chloride were added. After the second addition had been made, the liquid ammonia was allowed to evaporate. The residue was dissolved in water and the aqueous solution so obtained was extracted with ether and then filtered through diatomaceous earth (Celite). The filtrate was acidified by the addition of concentrated hydrochloric acid and the solid which separated was isolated by filtration and recrystallized twice from a mixture of acetone and hexane. There was thus obtained 20 g. of α -benzyl-p-chlorophenylacetic acid in the form of a crystalline solid having a melting point of 112 to 116.5° C. An analytical sample having a melting point of 115 to 116.5° C. was obtained by further recrystallization from the above solvent mixture.

Anal.—Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02. Found: C, 69.32; H, 5.24.

A solution of 20 g. of the α -benzyl-p-chlorophenylacetic acid so obtained in 40 ml. of methylene chloride was added to 120 ml. of liquid hydrogen fluoride. The two-phase mixture was stirred at 5 to 10° C. for 18 hr. and then the hydrogen fluoride was allowed to evaporate at room temperature. The residue was dissolved in ether and the ether solution was washed successively with water, aqueous sodium bicarbonate solution, aqueous 0.5 N sodium hydroxide solution, and with brine. The washed ethereal solution was dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness. The residue was recrystallized from aqueous methanol. There was thus obtained 2-(p-chlorophenyl)-1-indanone in the form of a crystalline solid having a melting point of 78 to 81° C. An analytical sample having a melting point of 79.5 to 81° C. was obtained by further recrystallization from aqueous methanol.

Anal.—Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57. Found: C, 74.15; H, 4.39.

B. 2-(p-CHLOROPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-chlorophenyl)-1-indanone, there was obtained 2-(p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrochloride thereof. The hydrochloride, after two recrystallizations from a mixture of methylene chloride and ethyl acetate, was obtained in the form of an ethyl acetate solvate having a melting point of 206 to 208° C.

Anal.—Calcd. for $C_{27}H_{29}Cl_2NO \cdot \frac{1}{4}CH_3CO_2C_2H_5$: C, 70.55; H, 6.53; N, 2.94. Found: C, 70.19; H, 6.87; N, 2.94.

EXAMPLE 10

2-(p-Fluorophenyl)-3-[p-(Diethylaminoethoxy)Phenyl]Indene and the Hydroiodide Thereof

A. 2-(p-FLUOROPHENYL)-1-INDANONE

Using the procedure described in Example 3, Part A, but replacing p-tolylacetic acid by p-fluorophenylacetic acid, there was obtained α -benzyl-p-fluorophenylacetic acid in the form of a crystalline solid having a melting point of 91 to 94° C. An analytical sample having a melting point of 93.5 to 95° C. was obtained by further recrystallization from a mixture of methylene chloride and hexane.

Anal.—Calcd. for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36; F, 7.79. Found: C, 73.44; H, 5.78; F, 7.73.

The α -benzyl-p-fluorophenylacetic acid so obtained was then cyclized by treatment with liquid hydrogen fluoride using the procedure described in Example 3, Part A, to

obtain 2-(p-fluorophenyl)-1-indanone in the form of a crystalline solid having a melting point of 55.5 to 58° C. after two recrystallizations from hexane.

Anal.—Calcd. for $C_{15}H_{11}FO$: C, 79.62; H, 4.90; F, 8.40. Found: C, 79.45; H, 5.01; F, 8.70.

B. 2-(p-FLUOROPHENYL)-3-[p-(DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROIODIDE THEREOF

Using the procedure described in Example 6, but replacing 2-(p-methoxyphenyl)-5-methoxy-1-indanone by 2-(p-fluorophenyl)-1-indanone, there was obtained 2-(p-fluorophenyl)-3-[p-(diethylaminoethoxy)phenyl]indene and the hydroiodide thereof. The hydroiodide was obtained in the form of a crystalline solid having a melting point of 181 to 183° C. after two recrystallizations from methylene chloride and benzene.

Anal.—Calcd. for $C_{27}H_{29}FINO$: C, 61.27; H, 5.52; F, 3.59; N, 2.65. Found: C, 61.22; H, 5.68; F, 3.61; N, 2.73.

EXAMPLE 11

2-(p-Chlorophenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

A. 2-(p-CHLOROPHENYL)-5-METHOXY-1-INDANONE

Using the procedure described in Example 3, Part A, but replacing p-tolylacetic acid by p-chlorophenylacetic acid and benzyl chloride by m-methoxybenzyl chloride, there was obtained α -(m-methoxybenzyl)-(p-chlorophenyl)acetic acid in the form of a crystalline solid having a melting point of 93 to 95° C. after the recrystallization from a mixture of hexane and acetone.

Anal.—Calcd. for $C_{16}H_{15}ClO_2$: C, 66.09; H, 5.20. Found: C, 66.24; H, 4.88.

The α -(m-methoxybenzyl)-p-chlorophenylacetic acid so obtained was then cyclized by treatment with liquid hydrogen fluoride using the procedure described in Example 3, Part A, to obtain 2-(p-chlorophenyl)-5-methoxy-1-indanone in the form of a crystalline solid having a melting point of 116.5 to 119° C. after recrystallization from ethanol.

Anal.—Calcd. for $C_{16}H_{13}ClO_2$: C, 70.45; H, 4.80; Cl, 13.00. Found: C, 70.12; H, 4.55; Cl, 12.84.

B. 2-(p-CHLOROPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]-6-METHOXYINDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-chlorophenyl)-5-methoxy-1-indanone, there was obtained 2-(p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof. The hydrochloride was obtained as a crystalline solid having a melting point of 199 to 201° C. after recrystallization from a mixture of methylene chloride and ethyl acetate.

Anal.—Calcd. for $C_{28}H_{31}Cl_2NO_2$: C, 69.41; H, 6.45; N, 2.91. Found: C, 69.43; H, 6.48; N, 2.89.

EXAMPLE 12

2-Phenyl-3-[p-(3-Dimethylaminopropoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(3-dimethylaminopropoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(3-dimethylaminopropoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 13

2-Phenyl-3-[p-(2-Diethylaminopropoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-diethylaminopropoxy)bromobenzene, there is obtained 2-

phenyl-3-[p-(2-diethylaminopropoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 14

2-Phenyl-3-[p-(2-Dibutylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-dibutylaminoethoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(2-dibutylaminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 15

2-Phenyl-3-[p-(2-N-Methyl-N-Ethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-N-methyl-N-ethylaminoethoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(2-N-methyl-N-ethylaminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 16

2-Phenyl-3-[p-(3-Diethylaminobutoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(3-diethylaminobutoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(3-diethylaminobutoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 17

2-Phenyl-3-[p-(5-Dimethylaminopentoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(5-dimethylaminopentoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(5-dimethylaminopentoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 18

2-Phenyl-3-[p-(2-Diethylaminopentoxy)phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-diethylaminopentoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(2-diethylaminopentoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 19

2-Phenyl-3-[p-(6-Dimethylaminohexyloxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(6-dimethylaminohexyloxy)bromobenzene, there is obtained 2-phenyl-3-[p-(6-dimethylaminohexyloxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 20

2-Phenyl-3-[p-(2-Pyrrolidinoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-pyrrolidinoethoxy)bromobenzene, there is obtained 2-phenyl-3-[p-(2-pyrrolidinoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 21

2-Phenyl-3-P{p-[3-(2,2-Dimethylpyrrolidino)Propoxy]Phenyl}-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-

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[3 - (2,2 - dimethylpyrrolidino)propoxy]bromobenzene, there is obtained 2-phenyl-3-[p-[3-(2,2-dimethylpyrrolidino)propoxy]phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 22

2-Phenyl-3-[p-(2-Piperidinoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-piperidinoethoxy)bromobenzene, there is obtained 2-phenyl - 3-[p - (2-piperidinoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 23

2-Phenyl-3-[p-(2-Morpholinoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-morpholinoethoxy)bromobenzene, there is obtained 2-phenyl - 3 - [p-(2-morpholinoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 24

2 - Phenyl - 3 - {p - [2-(1'-Methyl-4'-Piperazino)Ethoxy]Phenyl} - 6 - Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-[2-(1'-methyl-4'-piperazino)ethoxy]bromobenzene, there is obtained 2 - phenyl-3-{p-[2-(1'-methyl-4'-piperazino)ethoxy]phenyl} - 6 - methoxyindene and the hydrochloride thereof.

EXAMPLE 25

2-Phenyl-3-[p-(2-Hexamethyleneiminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-hexamethyleneiminoethoxy)bromobenzene, there is obtained 2 - phenyl-3-[p-(2-hexamethyleneiminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 26

2-Phenyl-3-[p-(2-Homopiperazinoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-homopiperazinoethoxy)bromobenzene, there is obtained 2 - phenyl - 3 - [p-(2-homopiperazinoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 27

2-Phenyl-3-[p-(2-Homomorpholinoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 5, but replacing p-(2-diethylaminoethoxy)bromobenzene by p-(2-homomorpholinoethoxy)bromobenzene, there is obtained 2-phenyl - [3 - p - (2-homomorpholinoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof.

EXAMPLE 28

2-Phenyl-3-[p-(2-Diethylaminoethoxy)Phenyl]-6-Isopropoxyindene and the Hydrochloride Thereof

Using the procedure described in Example 2, part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 5-isopropoxy-2-phenyl-1-indanone (Morris, J. Chem. Soc. 1950, 1913), there is obtained 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-isopropoxyindene and the hydrochloride thereof.

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EXAMPLE 29

2-(m-Trifluoromethylphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]indene and the Hydrochloride Thereof

A. 2-(m-TRIFLUOROMETHYLPHENYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing p-methoxyphenylacetic acid by m-trifluoromethylphenylacetic acid (Corse et al., J. Am. Chem. Soc. 70, 2837, 1948), there is obtained 2-(m-trifluoromethylphenyl)-1-indanone.

B. 2-(m-TRIFLUOROMETHYLPHENYL)-3-[p-(2 - DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(m-trifluoromethylphenyl)-1-indanone, there is obtained 2-(m - trifluoromethylphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrochloride thereof.

EXAMPLE 30

2-(p-Methoxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]-5-Trifluoromethylindene and the Hydrochloride Thereof

A. 2-(p-METHOXYPHENYL)-6-TRIFLUOROMETHYL-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing benzyl chloride by p-trifluoromethylbenzyl chloride, there is obtained 2-(p-methoxyphenyl)-6-trifluoromethyl-1-indanone.

B. 2-(p-METHOXYPHENYL)-3-[p - (2 - DIETHYLAMINOETHOXY)PHENYL] - 5 - TRIFLUOROMETHYLINDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-methoxyphenyl)-6-trifluoromethyl-1-indanone, there is obtained 2-(p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-5-trifluoromethylindene and the hydrochloride thereof.

EXAMPLE 31

2-(p-Methoxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]-5-(1,3-Dimethylbutyl)Indene and the Hydrochloride Thereof

A. 2-(p-METHOXYPHENYL)-6-(1,3-DIMETHYLBUTYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing benzyl chloride by p-(1,3-dimethylbutyl)benzyl chloride (U.S. Patent 2,569,408), there is obtained 2-(p-methoxyphenyl)-6-(1,3-dimethylbutyl)-1-indanone.

B. 2-(p-METHOXYPHENYL)-3-[p - (2 - DIETHYLAMINOETHOXY)PHENYL]-5-(1,3 - DIMETHYLBUTYL)INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-methoxyphenyl)-6-(1,3-dimethylbutyl)-1-indanone, there is obtained 2-(p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-5-(1,3-dimethylbutyl)indene and the hydrochloride thereof.

EXAMPLE 32

2-(p-Methylmercaptophenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(p-METHYLMERCAPTOPHENYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing p-methoxyphenylacetic acid by p-methylmercaptophenylacetic acid (Corse et al., supra), there is obtained 2 (p-methylmercaptophenyl)-1-indanone.

B. 2-(p-METHYLMERCAPTOPHENYL)-3-[p - (2 - DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-

methylmercaptophenyl)-1-indanone, there is obtained 2-(p-methylmercaptophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrochloride thereof.

EXAMPLE 33

2-(p-Phenoxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(p-PHENOXYPHENYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing p-methoxyphenylacetic acid by p-phenoxyphenylacetic acid (Corse et al., supra), there is obtained 2-(p-phenoxyphenyl)-1-indanone.

B. 2-(p-PHENOXYPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-phenoxyphenyl)-1-indanone, there is obtained 2-(p-phenoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrochloride thereof.

EXAMPLE 34

2-(Phenylmercaptophenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(p-PHENYLMERCAPTOPHENYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing p-methoxyphenylacetic acid by p-phenylmercaptophenylacetic acid (Corse et al., supra), there is obtained 2-(p-phenylmercaptophenyl)-1-indanone.

B. 2-(p-PHENYLMERCAPTOPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-phenylmercaptophenyl)-1-indanone, there is obtained 2-(p-phenylmercaptophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrochloride thereof.

EXAMPLE 35

2-(p-Hydroxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene Hydrochloride

A. 2-(p-HYDROXYPHENYL)-1-INDANONE

Heating a mixture of 2-(p-methoxyphenyl)-1-indanone (Example 2, Part A) with aluminum bromide in benzene according to the procedure described by Sam, J. Am. Chem. Soc. 82, 5205, 1960, yields 2-(p-hydroxyphenyl)-1-indanone in the form of a crystalline compound.

B. 2-(p-2-TETRAHYDROPYRANYLOXYPHENYL)-1-INDANONE

A solution of 2-(p-hydroxyphenyl)-1-indanone in ether is treated with an equimolar quantity of 2,3-dihydropyran and one drop of concentrated hydrochloric acid. The mixture so obtained is allowed to stand for several hours, washed with very dilute aqueous sodium hydroxide solution, then with water, and taken to dryness. There is thus obtained 2-(p-2-tetrahydropyranyloxyphenyl)-1-indanone.

C. 2-(p-HYDROXYPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE HYDROCHLORIDE

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-2-tetrahydropyranyloxyphenyl)-1-indanone and allowing the 0.5 N hydrochloric acid extract obtained in the working up to stand for several hours to enable the hydrolysis of the tetrahydropyranyl ether to proceed to completion before finally extracting with methylene chloride, there is obtained 2-(p-hydroxyphenyl)-3-[p-2-diethylaminoethoxy]phenyl]indene hydrochloride.

EXAMPLE 36

2-(p-Allyloxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene Hydrochloride

A. 2-(p-ALLYLOXYPHENYL)-1-INDANONE

A solution of 2-(p-hydroxyphenyl)-1-indanone (Example 35, Part B) in methanol containing a slight excess of sodium methoxide is treated slowly with stirring with an excess of allyl chloride. When the addition is complete the mixture is heated under reflux for several hours before being cooled and poured into water. The resulting mixture is extracted with ether and the ethereal extract is washed with aqueous sodium hydroxide solution and with water before being evaporated to dryness to yield 2-(p-allyloxyphenyl)-1-indanone.

B. 2-(p-ALLYLOXYPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE HYDROCHLORIDE

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(p-allyloxyphenyl)-1-indanone, there is obtained 2-(p-allyloxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrochloride.

EXAMPLE 37

A. 3-METHYL-2-PHENYL-1-INDANONE

2,3-diphenylbutyric acid (Hauser et al., J. Am. Chem. Soc. 80, 4345, 1958) is cyclized with liquid hydrogen fluoride using the procedure of Example 3, Part A, to obtain 3-methyl-2-phenyl-1-indanone.

B. 1-METHYL-2-PHENYL-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROBROMIDE THEREOF

Using the procedure described in Example 3, Part B, but replacing 2-(p-tolyl)-1-indanone by 3-methyl-2-phenyl-1-indanone, there is obtained 1-methyl-2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrobromide thereof.

EXAMPLE 38

1-Propyl-2-(p-Tolyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrobromide Thereof

A. 3-PROPYL-2-(p-TOLYL)-1-INDANONE

Using the procedure described in Example 3, Part A, but replacing benzyl chloride by α -propylbenzyl chloride (Engler and Bethge, Ber. 7, 1125, 1874), there is obtained 3-propyl-2-(p-tolyl)-1-indanone.

B. 1-PROPYL-2-(p-TOLYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROBROMIDE THEREOF

Using the procedure described in Example 3, Part B, but replacing 2-(p-tolyl)-1-indanone by 3-propyl-2-(p-tolyl)-1-indanone, there is obtained 1-propyl-2-(p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene and the hydrobromide thereof.

EXAMPLE 39

2-(3-Allyl-4-Methoxyphenyl)-3-[p-(2-Diethylaminoethoxy)Phenyl]Indene and the Hydrochloride Thereof

A. 2-(3-ALLYL-4-METHOXYPHENYL)-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing p-methoxyphenylacetic acid by 3-allyl-4-methoxyphenylacetic acid (van der Zanden and de Vries, Rec. Trav. Chim. 71, 879, 1952), there is obtained 2-(3-allyl-4-methoxyphenyl)-1-indanone.

B. 2-(3-ALLYL-4-METHOXYPHENYL)-3-[p-(2-DIETHYLAMINOETHOXY)PHENYL]INDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(p-methoxyphenyl)-1-indanone by 2-(3-allyl-4-methoxyphenyl)-1-indanone, there is obtained 2-(3-allyl-4-methoxyphenyl)-3-[p-2-diethylaminoethoxy]phenyl]indene and the hydrochloride thereof.

EXAMPLE 40

2-(*m*-Methoxyphenyl)-3-[*p*-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene and the Hydrochloride ThereofA. 2-(*m*-METHOXYPHENYL)-5-METHOXY-1-INDANONE

Using the procedure described in Example 2, Part A, but replacing *p*-methoxyphenylacetic acid by *m*-methoxyphenylacetic acid and benzyl chloride by *m*-methoxybenzyl chloride, there was obtained α -(*m*-methoxybenzyl)-*m*-methoxyphenylacetic acid having a melting point of 90.5 to 93° C. after recrystallization from cyclohexane.

Anal.—Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.61; H, 6.26.

The α -(*m*-methoxybenzyl)-*m*-methoxyphenylacetic acid so obtained was then cyclized with liquid hydrogen fluoride using the procedure described in Example 2, Part A, to obtain 2-(*m*-methoxyphenyl)-5-methoxy-1-indanone having a melting point of 93 to 96° C. after recrystallization from methanol.

Anal.—Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.65; H, 6.32.

B. 2-(*m*-METHOXYPHENYL)-3-[*p*-(2-DIETHYLAMINOETHOXY)PHENYL]-6-METHOXYINDENE AND THE HYDROCHLORIDE THEREOF

Using the procedure described in Example 2, Part B, but replacing 2-(*p*-methoxyphenyl)-1-indanone by 2-(*m*-methoxyphenyl)-5-methoxy-1-indanone, there was obtained 2-(*m*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene and the hydrochloride thereof. The hydrochloride was obtained as a crystalline solid having a melting point of 181 to 182° C. after recrystallization from a mixture of chloroform and ethyl acetate.

Anal.—Calcd. for $C_{29}H_{34}ClNO_3$: C, 72.56; H, 7.14; N, 2.92. Found: C, 72.56; H, 6.97; N, 3.15.

EXAMPLE 41

2-(*p*-Methoxyphenyl)-3-[*p*-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene Methiodide

A mixture of 1 g. of 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydroiodide (Example 6), 100 ml. of ether and 50 ml. of saturated aqueous sodium carbonate solution was shaken until all the solid dissolved. The organic layer was separated, washed with brine and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 12 ml. of acetonitrile and the solution so obtained was cooled in ice. To the cooled solution was added 1.5 ml. of methyl iodide and the mixture was allowed to stand overnight before being poured into 100 ml. of ether. The solid which separated was isolated by filtration and recrystallized twice from acetonitrile-ethyl acetate mixture. There was thus obtained 0.7 g. of 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene methiodide in the form of a crystalline solid having a melting point of 183 to 185° C.

Anal.—Calcd. for $C_{30}H_{36}INO_3$: C, 61.54; H, 6.20; N, 2.39. Found: C, 61.76; H, 6.26; N, 2.36.

Similarly using the above procedure, but replacing methyl iodide by ethyl bromide, propyl bromide, allyl bromide, and benzyl bromide, there are obtained the ethobromide, propyl bromide, allyl bromide, and benzyl bromide, respectively, of 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.

EXAMPLE 42

2-Phenyl-3-[*p*-(2-Diethylaminoethoxy)Phenyl]-6-Methoxyindene Methiodide

Using the procedure described in Example 41, but re-

placing 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydroiodide by 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride (Example 5), there is obtained 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene methiodide.

Using the above procedure, but replacing 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride by the appropriately substituted indene acid addition salt, there are obtained the methiodides of 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]indene, 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene, 2-(*p*-tolyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene, 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-5-methoxyindene, 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-5,6-dimethoxyindene, 2-(*p*-tolyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene, 2-(*p*-chlorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene, 2-(*p*-fluorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene, and 2-(*p*-chlorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.

EXAMPLE 43

2-Phenyl-3-[*p*-(2-Diethylaminoethoxy)phenyl]-6-Methoxyindene N-Oxide and the Hydrochloride Thereof

A mixture of 1 g. of 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride (Example 5), 100 ml. of ether, and 50 ml. of saturated aqueous sodium carbonate solution is shaken until all the solid dissolves. The ether solution is separated, washed with brine and dried over anhydrous sodium sulfate. The dried solution is filtered and the filtrate is evaporated to dryness. The residue is dissolved in 50 ml. of absolute ethanol and to the solution is added an equimolar quantity of 30% hydrogen peroxide. The mixture is allowed to stand for 4 days at room temperature, at the end of which time the mixture is shaken with 0.5 g. of platinum oxide until a test for peroxide is negative. The mixture is then filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is recrystallized from chloroform-ethyl acetate mixture. There is thus obtained 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene N-oxide.

The N-oxide so obtained is converted to the corresponding hydrochloride by dissolving the N-oxide in ether and treating the ether solution with an excess of a saturated solution of hydrogen chloride in ether. The solid which separates is isolated by filtration. There is thus obtained 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene N-oxide hydrochloride.

Using the above procedure, but replacing 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride by the appropriately substituted indene acid addition salt, there is obtained 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]indene N-oxide, 2-(*p*-methoxyphenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene N-oxide, 2-(*p*-tolyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene N-oxide, 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-5-methoxyindene N-oxide, 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-5,6-dimethoxyindene N-oxide, 2-(*p*-tolyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene N-oxide, 2-(*p*-chlorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene N-oxide, 2-(*p*-fluorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]indene N-oxide, and 2-(*p*-chlorophenyl)-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene N-oxide and the hydrochlorides thereof.

EXAMPLE 44

Ten thousand (10,000) tablets, each containing 125 mg. of 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-

methoxyindene hydrochloride and suitable for oral administration, are prepared from the following materials:

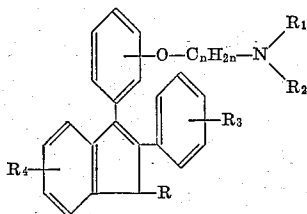
	G.	
2 - phenyl - 3 - [p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride	1250	5
Dicalcium phosphate	2500	
Methylcellulose U.S.P. (15 cps.)	65	
Talc, bolted	450	
Calcium stearate, fine powder	35	10

The powdered 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride and dicalcium phosphate are mixed well and granulated with a 7.5% aqueous solution of the methylcellulose. The granules are passed through a No. 8 screen and dried carefully at 120° F. The dried granules are passed through a No. 12 screen, mixed thoroughly with the talc and calcium stearate, and compressed into tablets.

To produce tablets containing 250 mg. of active ingredient the amount of 2-phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride employed in the above formulation is increased to 2500 g.

I claim:

1. A compound selected from the class consisting of (a) compounds having the formula:



wherein R is selected from the class consisting of hydrogen and lower-alkyl, R₁ and R₂ taken individually represent lower-alkyl and R₁ and R₂ taken together with the attached nitrogen atom represent a heterocyclic radical selected from the class consisting of pyrrolidino, 2-methylpyrrolidino, 2,2-dimethylpyrrolidino, piperazino, 4-methylpiperazino, 2,4-dimethylpiperazino, morpholino, piperidino, 2-methylpiperidino, 3-methylpiperidino, hexamethyleneimino, homopiperazino, and homomorpholino, R₃ and R₄ each represent at least one substituent selected from the class consisting of hydrogen, trifluoromethyl, lower-alkyl, lower mono-olefinic alkenyl from 2 to 8 carbon atoms, inclusive, hydroxy, lower-alkoxy from 1 to 8 carbon atoms, inclusive, lower mono-olefinic alkenyloxy from 2 to 8 carbon atoms, inclusive, unsubstituted aryloxy from 6 to 12 carbon atoms, inclusive, halogen, lower-alkylmercapto from 1 to 8 carbon atoms, inclusive, and unsubstituted arylmercapto from 6 to 12 carbon atoms, inclusive, and C_nH_{2n} represents an alkylene group from 2 to 6 carbon atoms, inclusive;

- (b) the addition salts of the compounds of the above formula with pharmacologically acceptable acids;
- (c) the N-oxides of compounds of the above formula;
- (d) the addition salts of the N-oxides of compounds of the above formula with pharmacologically acceptable acids; and

(e) the quaternary ammonium salts obtained by reacting the free bases of the above formula with a member selected from the group consisting of lower-alkyl halides, allyl halides, di(lower-alkyl)sulfates, phenylalkyl halides, benzhydryl halides and methyl toluenesulfonate.

2. 2 - phenyl - 3 - [p-(2-pyrrolidinoethoxy)-phenyl]-6-methoxyindene.
3. 2 - phenyl - 3 - [p-(2-diethylaminoethoxy)phenyl]indene.
4. 2 - phenyl - 3 - [p-(2-diethylaminoethoxy)phenyl]indene hydroiodide.
5. 2 - (p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene.
6. 2 - (p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrochloride.
7. 2 - (p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene.
8. 2 - (p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrobromide.
9. 2 - phenyl - 3-[p-(2-diethylaminoethoxy)phenyl]-5-methoxyindene.
10. 2 - phenyl - 3-[p-(2-diethylaminoethoxy)phenyl]-5-methoxyindene hydrochloride.
11. 2 - phenyl 3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.
12. 2 - phenyl - 3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride.
13. 2 - (p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.
14. 2 - (p-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydroiodide.
15. 2 - phenyl - 3-[p-(2-diethylaminoethoxy)phenyl]-5,6-dimethoxyindene.
16. 2 - phenyl - 3-[p-(2-diethylaminoethoxy)phenyl]-5,6-dimethoxyindene hydrochloride.
17. 2 - (p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.
18. 2 - (p-tolyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride.
19. 2 - (p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene.
20. 2 - (p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydrochloride.
21. 2 - (p-fluorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene.
22. 2 - (p-fluorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]indene hydroiodide.
23. 2 - (m-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.
24. 2 - (m-methoxyphenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride.
25. 2 - (p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene.
26. 2 - (p-chlorophenyl)-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride.

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