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ALKOXY-SUBSTITUTED 2-PHENYL-1-(TERTIARY-AMINOALKOXY)PHENYL-3,4-DIHYDROPHENALENES

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This invention relates to novel 3,4-dihydronaphthalenes and is more particularly concerned with novel alkoxy substituted 2-phenyl-1-(tertiaryaminalkoxy) phenyl-3,4-dihydronaphthalenes and acid addition salts, quaternary ammonium salts, N-oxides and N-oxide acid addition salts thereof, and with processes for their preparation.

This pending application is a division of application Serial No. 135,767, filed September 5, 1961.

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:

\[ \text{alkoxy} \]

wherein \( R_1 \) and \( R_2 \) are selected from the class consisting of lower-alkyl and lower-alkyl 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, \( C_6H_{10} \) represents alkylene from 2 to 6 carbon atoms, inclusive, alkoxy contains from 1 to 8 carbon atoms, inclusive, and \( x \) is an integer from 1 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. Examples of alkoxy containing from 1 to 8 carbon atoms, inclusive, are methoxy, ethoxy, propoxy, butoxy, amylxoxy, hexyloxy, heptyloxy, octyloxy, 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 pyrrolidino, 2-methylpyrrolidino, 2,2-dimethylpyrrolidino, and like alkylpyrrolidino groups, piperazino, 4-methylpiperazino, 2,4-dimethylpiperazino, and like alkylpiperazino groups, morpholinio, piperidino, 2-methylpiperidino, 3-methylpiperidino, and like alkylpiperidino groups, hexamethyleneimino, homopiperazino, homomorpholinio, 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, methane-sulfonic, p-toluene-sulfonic, salicylic, acetic, propionic, maleic, malic, tartaric, citric, cyclohexylsulfamic, sucinonic, 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 arylsulphonates, and the like. The term "lower-alkyl" has the meaning hereinafter 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, ethyl bromide, 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 anti-inflammatory agents, antifertility agents, antientrogenic agents, and as agents for the lowering of cholesterol blood levels in mammals including man and animals of economic value. For purposes of administration to mammals, the novel compounds of the invention can be employed per se, for example, enclosed in a hard capsule for oral administration, or 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 moth-proofing 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 1-keto-1,2,3,4-tetrahydronaphthalene (i.e., an a-tetralone) having the formula:

\[ \text{alkoxy} \]

wherein alkoxy and \( x \) have the significance hereinbefore defined (with the exception noted below), with a Grignard reagent have the formula:

\[ \text{alkoxy} \]

wherein \( R_1, R_2, \) and \( C_6H_{10} \) 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 diisopropyl ether, diisobutyl 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 dihydroxynaphthalene 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 the desired compound (I) contaminated with minor impurities and uncharged starting material which can be removed by simple procedures, for example by isolation of the desired compound (I) as an acid addition salt.

However, in some cases the desired 3,4-dihydroxynaphthalene (I) is contaminated with appreciable quantities of the corresponding 1-hydroxy-1,2,3,4-tetrahydronaphthalene having the formula (IV) below and in certain cases the reaction product obtained is largely this compound containing only a small amount of the desired compound (I).

In the above formula R₁, R₂, C₅H₄Hal, alkoxy and x have the significance hereinbefore defined.

The compound (IV), when obtained as the major reaction product or when present in significant quantities in the above-described reaction product, can be converted to the desired compound (I) by dehydration. The dehydration can be effected in most instances by heating the compound (IV) in a solvent such as benzene, toluene, xylene, and the like which forms an azeotrope with water, in the presence of a trace of a strong acid such as hydrochloric, sulfuric, p-toluene sulfonic acid, 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 compound (I) from which the latter can be isolated by evaporation or other conventional procedures.

In certain cases, the dehydration of the 1-hydroxy-1,2,3,4-tetrahydronaphthalene (IV) requires more drastic conditions such as heating the compound at, or slightly above, its melting point, preferably in the presence of an inert gas, until evaporation of water is complete.

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 diisopropyl ether, dibutyl ether, tetrahydrofuran, and the like with the appropriately substituted haloarene having the formula:

\[
\begin{array}{c}
\text{R}_1 \\
\text{N}-\text{C}_6\text{H}_{5}-\text{Hal}
\end{array}
\]

wherein R₁, R₂, C₅H₄Hal and Hal have the significance hereinbefore defined, using procedures well-known in the art for the preparation of Grignard reagents.

The haloarenes having the Formula V can be prepared by ethylation of the corresponding haloarenes with the appropriate tertiaryaminoalkyl halide:

\[
\begin{array}{c}
\text{R}_1 \\
\text{N}-\text{C}_6\text{H}_{5}-\text{Hal}
\end{array}
\]

wherein R₁, R₂ and C₅H₄Hal and Hal have the significance hereinbefore defined. The etherification is conducted advantageously in an inert solvent such as a lower alkane, 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

\[
\begin{array}{c}
\text{R}_1 \\
\text{N}-\text{C}_6\text{H}_{5}-\text{Hal}
\end{array}
\]

wherein R₁, R₂, C₅H₄Hal and Hal have the significance hereinbefore defined, employed in the preparation of the haloarenes (V) can themselves be prepared by halogenation of the corresponding tertiaryaminoalkanols, which tertiaryaminoalkanols in turn can be made by interaction of the requisite secondary amine.

and the haloarene Hal—C₅H₄OH, wherein Hal and C₅H₄Hal have the significance hereinbefore defined, in accordance with known methods. The condensation between the secondary amine

\[
\begin{array}{c}
\text{R}_1 \\
\text{N}-\text{C}_6\text{H}_{5}-\text{Hal}
\end{array}
\]

and the haloarene Hal—C₅H₄OH 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

\[
\begin{array}{c}
\text{R}_1 \\
\text{N}-\text{C}_6\text{H}_{5}-\text{Hal}
\end{array}
\]

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.

The a-tetralones (II) which are employed as starting materials in the process of the invention can be prepared...
by the following methods. For example, they can be prepared according to the following reaction scheme:

In the above reaction sequence, alkoxy and x have the significance hereinbefore described with the exceptions noted above.

The chalcone (VIII) so obtained is then converted to the corresponding nitrile (IX) by reaction with hydrogen cyanide, for example, by treatment with an alkali metal cyanide such as potassium cyanide, sodium cyanide, and the like in the presence of acetic acid and an inert solvent such as aqueous methanol, aqueous ethanol and the like, using the procedure described by Newman, J. Am. Chem. Soc. 60, 2947, 1938 for the conversion of benzaldehyde phenone (chalcone) to a-phenyl-ß-benzoylpropionitrile. The desired nitrile (IX) generally separates from the reaction mixture as a solid and can be isolated by filtration and purified by recrystallization.

The nitrile (IX) so obtained is hydrolyzed to the corresponding keto acid (X) by conventional procedures for the hydrolysis of nitriles, for example, by heating under reflux in the presence of aqueous mineral acid such as sulfuric acid until hydrolysis is substantially complete. The desired acid (X) generally separates from the reaction mixture as a solid and is isolated by filtration and purified by recrystallization or by other conventional procedures, for example, by conversion to an alkali metal salt followed by acidification of the latter to regenerate the free acid.

The keto acid (X) so obtained is then subjected to reduction to form the corresponding acid (XI). The reduction can be effected using any of the methods customarily employed for the conversion of a keto group to a methylene group. A particularly suitable reducing agent is amalgamated zinc in the presence of a mineral acid affords the desired acid (XI) in excellent yield. The acid (XI) can be isolated from the reaction mixture by conventional procedures, for example, by decantation of the liquid reaction mixture, followed by solvent extraction of the decanted liquid and evaporation of the solvent. Generally speaking, the acid (XI) is sufficiently pure to be used in the next step of the synthesis without further treatment. If desired, however, the acid (XI) so obtained can be purified by conventional procedures, for example, by distillation in the case of a liquid or recrystallization in the case of a solid or by conversion to an alkali metal salt followed by acidification of the latter to yield the free acid.

In the final stage of the synthesis the acid (XI) is cyclized to the required 2-tetralone (XII) in the presence of a Lewis acid, using the general procedure described by Fieser and Fieser, 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 pentfluoride, 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 acid (XI) according to the above procedure comprises adding the acid (XI) to liquid hydrogen fluoride with stirring and then allowing the hydrogen fluoride to evaporate at about 20-30°C. The desired 2-tetralone (XII) is then isolated from the residue by conventional methods, for example, by dissolving the residue in a suitable solvent such as ether, washing the solution 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 2-tetralone (XII) so obtained can be purified, if desired, by conventional procedures, for example, by recrystallization.

Alternatively, the acid (XI) can be cyclized to the 2-tetralone (XII) by conversion of the acid (XI) to the corresponding acid chloride and treatment of the latter with aluminum chloride or stannic chloride according to the procedure described by Fieser et al., J. Am. Chem. Soc. 60, 170, 1938.

The alkyl phenyl ketones (VI) which are employed as starting materials in the above described synthesis of the α-tetralones (II) can be prepared from the corresponding nuclear-substituted benzoic acids by conversion of the latter to the acid chlorides followed by reaction of the latter with the appropriate dialkyl cadmium according to the procedure described in Chemical Reviews 40, 15, 1947. Many of the alkyl phenyl ketones (VI) are known in the literature.

An alternative method for the preparation of the α-tetralones of Formula II is that described by Newman, J. Am. Chem. Soc. 62, 2295, 1940, for the preparation of 2-0-tolyl-3-methyl-α-tetralone. The method comprises reacting the benzylic cyanide with the appropriately substituted phenethyl bromide (alkoxy and x having the significance hereinbefore defined) in the presence of sodamide and hydrolyzing the resulting nitrile to give the corresponding acid (XII) which is then cyclized as hereinbefore described to the α-tetralone (II).

The acid addition salts of the compounds of the invention having the Formula I can be prepared by methods

\[ \text{alkoxy} \text{R} \text{CN} + \text{alkoxy} \text{R} \text{CHO} \rightarrow \text{alkoxy} \text{R} \text{C} = \text{O} + \text{alkoxy} \text{R} \text{H} \]

\[ \text{alkoxy} \text{R} \text{C} = \text{O} + \text{H}_2 \text{O} \rightarrow \text{alkoxy} \text{R} \text{COO}^{-} + \text{H}_3 \text{C} \text{CN} \]

\[ \text{HOOC} \text{R} \text{C} = \text{O} + \text{H}_2 \text{O} \rightarrow \text{HOOC} \text{R} \text{CH}_2 \text{COO}^{-} \]
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 suitable base, such as sodium hydroxide, a pharmaceutically acceptable acid, as hereinbefore defined, in the presence of an inert solvent 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 under 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 alkanolates 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 (1) 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 for at least 15 minutes, such as sodium hydrosulfite, sodium bisulfite, nickel, 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 procedure 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 alkenyl halide such as allyl chloride, alky 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 arylsulfonate such as methyl p-toluene-sulfonate, 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, 1300 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, over a period of 30 minutes, a solution of 213 g. of 2-diethylaminomethyl 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, and the filtrate was evaporated. The residue was distilled under reduced pressure and the fraction having a boiling point of 110-115°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.

**PREPARATION 2**

**3'-methoxychalcone**

A solution of 45 g. of m-methoxyacetophenone in 75 ml. of 95% ethanol was added to a cooled solution of 16 g. of sodium hydroxide in 140 ml. of water. The mixture was then placed in an ice bath and 31.8 g. of benzaldehyde was added at such a rate as to keep the temperature below 20°C. The mixture was stirred for an additional 30 minutes in the cold and was then stirred for 27 hours at room temperature. The resulting solution was extracted with ether and the extract was washed with saturated brine solution before being percolated through anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was distilled under reduced pressure. There was thus obtained 50.9 g. of 3'-methoxychalcone in the form of an oil having a boiling point of 180 to 185°C at a pressure of 4 mm. of mercury.

**PREPARATION 3**

**2-phenyl-4-(3-methoxyphenyl)-4-ketobutyronitrile**

A solution of 27.8 g. of potassium cyanide in 50 ml. of water was added to a mixture of 20.9 g. of 3'-methoxychalcone, 13.0 g. of acetic acid, and 100 ml. of 95% ethanol over a period of 10 minutes. The temperature was maintained at 45°C. The turbid mixture was then stirred for 6 hours and allowed to stand overnight in the cold. The crystalline solid which had separated was isolated by filtration, washed with ice-cold aqueous ethanol and with water, and recrystallized from ethanol. There was thus obtained 49.22 g. of 2-phenyl-4-(3-methoxy-phenyl)-4-ketobutyronitrile in the form of a crystalline solid having a melting point of 96 to 101°C. The infrared spectrum of the compound (mineral oil mull) exhibited maxima at 2200, 1660, and 1580 reciprocal centimeters.
PREPARATION 4

2-phenyl-4-(3-methoxyphenyl)-4-ketobutyric acid

A suspension of 49.22 g. of 2-phenyl-4-(3-methoxyphenyl)-4-ketobutyronitrile in a mixture of 140 ml of concentrated sulfuric acid and 125 ml of water was heated on a steam bath with vigorous stirring for 4 hours. The resulting mixture was cooled and diluted with ice water. The solid which separated was isolated by filtration and recrystallized from aqueous ethanol and then from benzene. There was thus obtained 29.5 g. of 2-phenyl-4-(3-methoxyphenyl)-4-ketobutyric acid in the form of a crystalline solid having a melting point of 140 to 145°C. An analytical sample having a melting point of 143 to 145°C was obtained by recrystallization from benzene.

Analysis.—Calcd. for C_17H_16O_2: C, 80.92; H, 6.39. Found: C, 81.08; H, 6.35.

PREPARATION 5

2-phenyl-4-(3-methoxyphenyl)butyric acid

A total of 300 g. of mossy zinc was washed briefly with 2.5 N hydrochloric acid and then with water. The metal was covered with a solution of 6.7 g. of mercuric chloride in 500 ml of water, and this mixture was allowed to stand for 30 minutes with occasional shaking. The liquid phase was decanted and the amalgamated metal was washed well with water. To the amalgamated zinc so produced was added a mixture of 29.3 g. of 2-phenyl-4-(3-methoxyphenyl)-3-ketobutyric acid and 400 ml of hydrochloric acid. The mixture was heated cautiously to reflux temperature and then heated under reflux for a total of 20 hours. Additional portions of hydrochloric acid being added after 5 hours and 10 hours of heating. The resulting mixture was cooled and the liquid was decanted from the solid. The solid residue was washed well with ether and the decanted liquid was extracted with water. The ether extract and washings were combined and washed with water and then with saturated brine solution before being percolated through anhydrous magnesium sulfate. The percolate was evaporated to dryness. There was thus obtained 26.2 g. of 2-phenyl-4-(3-methoxyphenyl)butyric acid in the form of a viscous oil which was employed without further purification in the process of Preparation 6. The infrared spectrum of the compound (mineral oil null) exhibited a maximum at 1705 reciprocal centimeters.

PREPARATION 6

2-phenyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthalene

A total of 150 ml of liquid hydrogen fluoride was added to 26.2 g. of 2-phenyl-4-(3-methoxyphenyl)butyric acid with cooling and swirling. The resulting mixture was allowed to stand at room temperature for 3 days. The residue was dissolved in methylene chloride and the solution was poured into excess concentrated aqueous potassium carbonate solution. The organic layer was separated, washed with water and saturated brine solution, and then evaporated to dryness. The residue was dissolved in 2 l of mixed hexanes (Skellysolve B) containing 7.5% by volume of acetone and the solution was passed through a column of magnesium silicate (Florisil), prewashed with the same solvent mixture. The eluate was evaporated to dryness and the residue (17.0 g.) was recrystallized twice from cyclohexane. There was thus obtained 13.38 g. of 2-phenyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthalene in the form of a crystalline compound having a melting point of 113 to 116°C.

Analysis.—Calcd. for C_17H_14O_2: C, 80.92; H, 6.39. Found: C, 81.08; H, 6.35.

PREPARATION 7

2-phenyl-4-methyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthalene

A solution of 5 g. of 2-phenyl-4-(3-methoxyphenyl)-3-ketobutyric acid in 100 ml of ether is cooled to 0°C, and treated dropwise with stirring with 29 ml of 3 M ethereal methyl magnesium bromide solution. When the addition is complete the mixture is stirred for several hours at room temperature and then heated under reflux for 1 hour. The reaction mixture is decomposed by the addition of ice water and dilute hydrochloric acid solution. The etheral layer is separated, washed with aqueous ammonium chloride solution and with water, and then dried over anhydrous sodium sulfate. The dried solution is filtered, and the filtrate is evaporated to dryness and the residue is recrystallized from aqueous ethanol. There is thus obtained 2-phenyl-4-(3-methoxyphenyl)-4-hydroxyvaleric acid.

A mixture of 1 g. of 2-phenyl-4-(3-methoxyphenyl)-4-hydroxyvaleric acid, 100 mg. of p-toluenesulfonic acid and 100 ml of benzene is heated under reflux with removal of evolved water until no further water is eliminated from the reaction mixture. The residual solution is extracted with an excess of aqueous sodium hydroxide solution and the latter is acidified with hydrochloric acid. The solid which separates is isolated by filtration, washed with water, and dried. The residue (2-phenyl-4-(3-methoxyphenyl)-3-pentenoic acid) is dissolved in ethanol and hydrogenated in the presence of palladium-on-charcoal catalyst until the uptake of hydrogen is complete. The resulting solution is filtered and the filtrate is evaporated to dryness. There is thus obtained 2-phenyl-4-(3-methoxyphenyl)valeric acid. The latter acid is then cyclized using the procedure described in Preparation 6 to give 2-phenyl-4-methyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthalene.

Examples 1 through 19 below illustrate the preparation of representative 2-phenyl-1-[p-(tertaryaminooalkoxy)phenyl]-3,4-dihydronaphthalene free bases and acid addition salts, quaternary ammonium salts, N-oxides, and N-oxide acid addition salts thereof. The corresponding 2-phenyl-1-[o- and m-(tertiaryaminooalkoxy)phenyl]-3,4-dihydronaphthalene free bases and acid addition salts, quaternary ammonium salts, N-oxides, and N-oxide acid addition salts thereof are prepared as follows. The appropriate o- and m-(tertiaryaminooalkoxy) bromobenzenes are substituted for the corresponding p-(tertiaryaminooalkoxy) bromobenzenes in Examples 1 through 17 to obtain the corresponding 2-phenyl-1-[o- and m-(tertiaryaminooalkoxy)phenyl]-3,4-dihydronaphthalene free bases and addition salts thereof. The acid addition salts thus obtained are substituted for the corresponding 2-phenyl-1-[p-(tertiaryaminooalkoxy)phenyl]-3,4-dihydronaphthalene acid addition salts in Examples 18 and 19 to obtain the corresponding quaternary ammonium salts, N-oxides, and N-oxide acid addition salts.

Example 1

1-[p-(2-diethylaminooethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof

To 0.73 g. of dry magnesium chips maintained in an atmosphere of nitrogen was added 3 ml of tetrahydrofuran and 4 drops of methyl iodide and the mixture was stirred until reaction started. To the resulting mixture was added a solution of 8.15 g. of p-(2-diethylaminoethoxy) bromobenzene in 85 ml of tetrahydrofuran. The resulting mixture was heated under reflux until substantial decomposition of the magnesium had occurred and to the residual solution was added with stirring a solution of 7.55 g of 2-phenyl-6-methoxy-1,2,3,4-tetrahydro-1-naphthalene in 90 ml of tetrahydrofuran. The mixture so obtained was heated under reflux for 16 hours before being cooled. The cooled solution was treated with ether and a small quantity of water. The gel which
formed was removed by filtration and washed well with ether. The ether filtrate and washings were combined and washed with water before being dried over anhydrous sodium sulfate and evaporated to dryness. The residual oil was dissolved in a mixture of ether and benzene and the solution so obtained was extracted with excess 0.5 N hydrochloric acid. The acid extract was extracted with methylene chloride and the methylene chloride extract was evaporated to dryness. The residue (6.48 g.) was recrystallized from a mixture of chloroform and ethyl acetate. There was thus obtained 3.42 g. of 1-[p-(2-diethylaminooethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene hydrochloride in the form of a crystalline solid having a melting point of 171 to 173° C. after partially melting and resolidifying at 126° C. An analytical sample was obtained by drying for 96 hours at 110° C. in vacuo.

**Analysis.**—Calcd. for C_{37}H_{36}ClNO_3: C, 75.06; H, 7.39; N, 3.02. Found: C, 74.74; H, 7.40; N, 3.03.

A solution of 1 g. of the above hydrochloride in water was made basic by the addition of aqueous sodium hydroxide solution. The basic solution was extracted with ether, washed with water and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from aqueous ethanol to obtain 1-[p-(2-diethylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene in the form of a crystalline solid.

**Example 2**

1-[p-(2-diethylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminooxyethoxy) bromobenzene by p-(2-diethylaminooxyethoxy) bromobenzene, there is obtained 1-[p-(2-diethylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

**Example 3**

1-[p-(2-diethylaminopropoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminooxyethoxy) bromobenzene by p-(2-diethylaminopropoxy) bromobenzene, there is obtained 1-[p-(2-diethylaminopropoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

**Example 4**

1-[p-(2-dibutylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminooxyethoxy) bromobenzene by p-(2-dibutylaminooxyethoxy) bromobenzene, there is obtained 1-[p-(2-dibutylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

**Example 5**

1-[p-(2-N-methyl-N-ethylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminooxyethoxy) bromobenzene by p-(2-N-methyl-N-ethylaminooxyethoxy) bromobenzene, there is obtained 1-[p-(2-N-methyl-N-ethylaminooxyethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.
Example 13
1-(p-(2-morpholinoethoxy)phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminoethoxy) bromobenzene by p-(2-morpholinoethoxy) bromobenzene, there is obtained 1-(p-(2-morpholinoethoxy)phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof, which latter has a melting point of 200 to 204°C.

Example 14
1-(p-[2-(l'-methyl-4'-piperazino)ethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

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

Example 15
1-(p-[2-(hexamethyleniminoethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminoethoxy) bromobenzene by p-[2-hexamethyleniminoethoxy] bromobenzene, there is obtained 1-(p-[2-hexamethyleniminoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Example 16
1-(p-[2-homopiperazinoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminoethoxy) bromobenzene by p-[2-homopiperazinoethoxy] bromobenzene, there is obtained 1-(p-[2-homopiperazinoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Example 17
1-(p-[2-homomorpholinoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Using the procedure described in Example 1, but replacing p-(2-diethylaminoethoxy) bromobenzene by p-[2-homomorpholinoethoxy] bromobenzene, there is obtained 1-(p-[2-homomorpholinoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene and the hydrochloride thereof.

Example 18
1-(p-[2-diethylaminoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene methiodide.

A solution of 1 g. of 1-(p-[2-diethylaminoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene in 12 ml. of acetonitrile is cooled in ice. To the cooled solution is added 1.5 ml. of methyl iodide and the mixture is allowed to stand overnight before being poured into 100 ml. of ether. The solid which separates is isolated by filtration and recrystallized from a mixture of ethyl acetate and ether, there is thus obtained 1-(p-[2-diethylaminoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene methiodide in the form of a crystalline solid.

Similarly, using the above procedure, but replacing methyl iodide by ethyl bromide, propyl bromide, allyl bromide, and benzyl bromide, there are obtained the ethylbromide, propyl bromide, allyl bromide, and benzyl bromide, respectively, of 1-(p-[2-diethylaminoethoxy]phenyl)-2-phenyl-6-methoxy-3,4-dihydronaphthalene.
wherein $R_1$ and $R_2$ are selected from the class consisting of lower-alkyl from 1 to 8 carbon atoms, inclusive, and together with the nitrogen atom, a member 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, $C_{n}H_{2n}$ represents alkylene from 2 to 6 carbon atoms, inclusive, alkoxy has from 1 to 8 carbon atoms, inclusive, and $x$ is an integer from 1 to 4, inclusive;

(b) the nontoxic pharmacologically acceptable acid addition salts of compounds of the above formula;

(c) the N-oxides of compounds of the above formula;

(d) the nontoxic pharmacologically acceptable acid addition salts of N-oxides of compounds of the above formula; and

(e) quaternary ammonium salts of compounds of the above formula, selected from the class consisting of 20 lower-alkyl quaternary ammonium halides, lower-alkenyl quaternary ammonium halides, lower-alkyl quaternary ammonium sulfates, aralkyl quaternary ammonium halides, and lower-alkyl quaternary aroylsulfonates.

2. 1. \( [\text{p}-(2\text{-diethylaminoethoxy})\text{phenyl}]\text{-2-phenyl-6-methoxy-3,4-dihydronaphthalene} \)

3. 1. \( [\text{p}-(2\text{-diethylaminoethoxy})\text{phenyl}]\text{-2-phenyl-6-methoxy-3,4-dihydronaphthalene} \)

4. 1. \( [\text{p}-(2\text{-pyrrolidinoethoxy})\text{phenyl}]\text{-2-phenyl-6-methoxy-3,4-dihydronaphthalene} \)

5. 1. \( [\text{p}-(2\text{-pyrrolidinoethoxy})\text{phenyl}]\text{-2-phenyl-6-methoxy-3,4-dihydronaphthalene} \)

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

\[ R_1 \quad \text{O-\text{C-N}} \quad R_2 \]

wherein $R_1$ and $R_2$ are selected from the class consisting of lower-alkyl from 1 to 8 carbon atoms, inclusive, and together with the nitrogen atom, a member 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, $C_{n}H_{2n}$ represents alkylene from 2 to 6 carbon atoms, inclusive, and alkoxy has from 1 to 8 carbon atoms, inclusive;

(b) the nontoxic pharmacologically acceptable acid addition salts of compounds of the above formula;

(c) the N-oxides of compounds of the above formula;

(d) the nontoxic pharmacologically acceptable acid addition salts of N-oxides of compounds of the above formula; and

(e) quaternary ammonium salts of compounds of the above formula, selected from the class consisting of lower-alkyl quaternary ammonium halides, lower-alkenyl quaternary ammonium halides, lower-alkyl quaternary ammonium sulfates, aralkyl quaternary ammonium halides, and lower-alkyl quaternary aroylsulfonates.

7. A nontoxic pharmacologically acceptable acid addition salt of 1-[p-(2-diethylaminoethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene.

8. A nontoxic pharmacologically acceptable acid addition salt of 1-[p-(2-pyrrolidinoethoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene.

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