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3,200,132 AMINOMETHYL-BENZOFURANS

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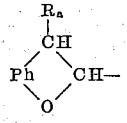
This is a continuation-in-part of application Serial No. 144,061, filed October 10, 1961, and now abandoned.

The present invention relates to 2,3-dihydro-benzofuran derivatives. More particularly, it concerns 2-aminomethyl-2,3-dihydro-benzofurans of the formula:

$$R_1—CH_2—NH—(C_nH_{2n})—R_2$$

in which R_1 represents a 2-(2,3-dihydro-benzofuranyl) radical, n stands for a whole number from one to seven, and R_2 represents a cyclo-aliphatic, a carbocyclic aryl or a heterocyclic aryl radical, or salts of such compounds, as well as process for the preparation thereof.

A 2-(2,3-dihydro-benzofuranyl) group R_1 is particularly a group of the formula:



in which R_a stands primarily for hydrogen, but may also represent an organic radical, for example, an aliphatic radical, such as lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secondary butyl and the like, and Ph represents a 1,2-phenylene (o-phenylene) radical, such as 1,2-phenylene or 1,2-phenylene substituted by one or more than one substituent, which may be attached to any of the four positions available for substitution in a 1,2-phenylene radical. Substituents attached to the 1,2-phenylene radical are, for example, an aliphatic hydrocarbon radical, such as lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl and the like, hydroxyl, etherified hydroxyl, particularly lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, as well as lower alkenyloxy, e.g. allyloxy, 2-methyl-allyloxy and the like, lower alkylene-dioxy, e.g. methylenedioxy, 1,1-ethylenedioxy and the like, cycloalkyloxy, in which cycloalkyl has from five to eight, preferably from five to six, carbon atoms, e.g. cyclopentyloxy, cyclohexyloxy and the like, carbocyclic aryloxy, such as monocyclic carbocyclic aryloxy, e.g. phenoxy and the like, carbocyclic aryl-aliphatic etherified hydroxyl, such as monocyclic carbocyclic aryl-lower alkoxy, for example, phenyl-lower alkoxy, e.g. benzyloxy, 1-phenylethoxy, 2-phenylethoxy and the like, esterified hydroxyl, especially halogeno (representing hydroxyl esterified by a hydrohalic acid), e.g. fluoro, chloro, bromo and the like, trifluoromethyl, mercapto, etherified mercapto, such as lower alkyl-mercapto, e.g. methylmercapto, ethyl-mercapto and the like, nitro, amino, such as N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino, N-ethyl-N-methyl-amino, N,N-diethylamino and the like, or N-acylamino, such as N-lower alkanoyl-amino, e.g. N-acetylamino, N-propionylamino and the like, or N-carbocyclic aroyl-amino, e.g. N-benzoylamino and the like, acyl, such as, for example, lower alkanoyl, e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl and the like, as well as carbocyclic aroyl, such as monocyclic carbocyclic aroyl, e.g. benzoyl and the like, carbocyclic aryl-lower alkanoyl, suh as monocyclic carbocyclic aryl-lower alkanoyl, for example, phenyl-lower alkanoyl, e.g. phenylacetyl and the like, or any other analogous, suitable substituent.

Substituted 1,2-phenylene groups are, for example, aliphatic substituted-1,2-phenylene, such as lower alkyl-1,2-phenylene, e.g. methyl-1,2-phenylene (such as 3-methyl-1,2-phenylene, 4-methyl-1,2-phenylene, 4,5-dimethyl-1,2-phenylene and the like), ethyl-1,2-phenylene (such as 4-ethyl-1,2-phenylene and the like, n-propyl-1,2-phenylene (such as 4-n-propyl-1,2-phenylene and the like), isopropyl-1,2-phenylene (such as 3-isopropyl-1,2-phenylene and the like), or any other analogous lower alkyl-1,2-phenylene radical, hydroxy-1,2-phenylene (such as 3-hydroxy-1,2-phenylene, 4-hydroxy-1,2-phenylene and the like), etherified hydroxy-1,2-phenylene (such as 3-methoxy-1,2-phenylene, 4-methoxy-1,2-phenylene, 3,4-dimethoxy-1,2-phenylene and the like), ethoxy-1,2-phenylene (such as 3-ethoxy-1,2-phenylene, 4-ethoxy-1,2-phenylene, 3,6-diethoxy-1,2-phenylene and the like), n-propyloxy-1,2-phenylene (such as 4-n-propyloxy-1,2-phenylene and the like), isopropyloxy-1,2-phenylene (such as 3-isopropyloxy-1,2-phenylene and the like), n-butyloxy-1,2-phenylene (such as 4-n-butyloxy-1,2-phenylene and the like), or any other analogous lower alkoxy-1,2-phenylene radical, lower alkenyloxy-1,2-phenylene, e.g. allyloxy-1,2-phenylene (such as 3-allyloxy-1,2-phenylene, 4-allyloxy-1,2-phenylene and the like), or any other analogous lower alkenyloxy-1,2-phenylene radical, lower alkylenedioxy-1,2-phenylene e.g. methylenedioxy-1,2-phenylene (such as 3,4-methylenedioxy-1,2-phenylene and the like), or any other analogous lower alkylenedioxy-1,2-phenylene radical, cycloalkyloxy-1,2-phenylene, in which cycloalkyl has from three to eight, preferably from five to six, carbon atoms, e.g. cyclopentyloxy-1,2-phenylene (such as 3-cyclopentyloxyl-1,2-phenylene and the like), cyclohexyloxy-1,2-phenylene (such as 4-cyclohexyloxy-1,2-phenylene and the like) or any other analogous cycloalkyloxy-1,2-phenylene radical, monocyclic carbocyclic aryloxy-1,2-phenylene, e.g. phenyloxy-1,2-phenylene (such as 3-phenyloxy-1,2-phenylene and the like) or any other analogous monocyclic carbocyclic aryloxy-1,2-phenylene radical, monocyclic carbocyclic aryl-lower alkoxy-1,2-phenylene, such as phenyl-lower alkoxy-1,2-phenylene, e.g. benzyloxy-1,2-phenylene (such as 3-benzyloxy-1,2-phenylene, 4-benzyloxy-1,2-phenylene and the like), 2-phenylethoxy-1,2-phenylene [such as 3-(2-phenylethoxy)-1,2-phenylene and the like] or any other analogous monocyclic carbocyclic aryl-lower alkoxy-1,2-phenylene radical, esterified hydroxy-1,2-phenylene, particularly halogeno-1,2-phenylene, e.g. fluoro-1,2-phenylene (such as 3-fluoro-1,2-phenylene, 4-fluoro-1,2-phenylene and the like), chloro-1,2-phenylene (such as 3-chloro-1,2-phenylene, 4-chloro-1,2-phenylene, 4,5-dichloro-1,2-phenylene, 3,4,5,6-tetrachloro-1,2-phenylene and the like), bromo-1,2-phenylene (such as 4-bromo-1,2-phenylene, 3,6-dibromo-1,2-phenylene and the like), or any other analogous halogeno-1,2-phenylene or esterified hydroxy-1,2-phenylene radical, trifluoromethyl-1,2-phenylene (such as 4-trifluoromethyl-1,2-phenylene and the like), mercapto-1,2-phenylene (such as 4-mercapto-1,2-phenylene and the like), etherified mercapto-1,2-phenylene, such as lower alkylmercapto-1,2-phenylene, e.g. methylmercapto-1,2-phenylene (such as 4-methylmercapto-1,2-phenylene and the like), ethylmercapto-1,2-phenylene (such as 3-ethylmercapto-1,2-phenylene and the like), or any other analogous lower alkylmercapto-1,2-phenylene radical, nitro-1,2-phenylene (such as 3-nitro-1,2-phenylene, 4-nitro-1,2-phenylene and the like), N,N-di-lower alkyl-amino-1,2-phenylene, e.g. N,N-dimethylamino-1,2-phenylene (such as 3-N,N-dimethylamino-1,2-phenylene, 4-N,N-dimethyl-amino-1,2-phenylene and the like), N-ethyl-N-methyl-amino-1,2-phenylene (such as 4-N-ethyl-N-methyl-amino-1,2-phenylene and the like), N,N-diethylamino-1,2-phenylene (such as 4-N,N-diethylamino-1,2-phenylene and the like), or any other N,N-di-lower alkyl-amino-1,2-phenylene radical, N-acyl-amino-1,2-phenylene, such as N-lower alkanoyl-amino-1,2-phenylene, e.g. N-acetylamino-1,2-

phenylene (such as 4-N-acetyl-amino-1,2-phenylene and the like), N-pivaloylamino-1,2-phenylene (such as 4-N-pivaloylamino-1,2-phenylene and the like), as well as N-benzoylamino-1,2-phenylene (such as 4-N-benzoylamino-1,2-phenylene and the like), or any other analogous N-acyl-amino-1,2-phenylene radical, or acyl-1,2-phenylene, such as lower alkanoyl-1,2-phenylene, e.g. acetyl-1,2-phenylene (such as 3-acetyl-1,2-phenylene, 4-acetyl-1,2-phenylene and the like), propionyl-1,2-phenylene-1,2-phenylene (such as 3-propionyl-1,2-phenylene and the like), butyryl-1,2-phenylene (such as 4-butyryl-1,2-phenylene and the like), pivaloyl-1,2-phenylene (such as 3-pivaloyl-1,2-phenylene and the like) or any other analogous lower alkanoyl-1,2-phenylene radical, monocyclic carbocyclic aroyl-1,2-phenylene, e.g. benzoyl-1,2-phenylene (such as 3-benzoyl-1,2-phenylene, 4-benzoyl-1,2-phenylene and the like) or any other analogous monocyclic carbocyclic aroyl-1,2-phenylene radical, monocyclic carbocyclic aryl-lower alkanoyl-1,2-phenylene, such as phenyl-lower alkanoyl-1,2-phenylene, e.g. phenylacetyl-1,2-phenylene (such as 3-phenylacetyl-1,2-phenylene and the like) or any other analogous monocyclic aryl-lower alkanoyl-1,2-phenylene radical, or any equivalent substituted 1,2-phenylene radical.

The alkylene radical represented by $-C_nH_{2n}-$ in the above formula, in which the letter n may stand for a whole number from one to seven, has preferably from one to four carbon atoms (the letter n, therefore, stands preferably for a whole number from one to four), which carbon atoms may be arranged in a straight or a branched carbon chain. Such alkylene radicals may be represented by methylene, 1,1-ethylene, 1,2-ethylene, 1-methyl-1,2-ethylene, 2-methyl-1,2-ethylene, 1,3-propylene, 1,4-butylene and the like, as well as 1,4-pentylene, 1,5-pentylene, 1,6-hexylene, 1,7-heptylene and the like.

A cycloaliphatic radical R_2 is preferably saturated and represents, therefore, primarily cycloalkyl. However, it may also contain one or more than one double bond, depending on the number of ring carbon atoms. A cycloalkyl group may have from five to eight, preferably from five to six, ring carbon atoms and is, therefore, primarily cyclopentyl or cyclohexyl, as well as cycloheptyl or cyclooctyl. A cycloaliphatic radical having one or more than one double bond is particularly a cycloalkenyl group, which has from five to eight, preferably from five to six, carbon atoms; cycloalkenyl groups are, for example, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl and the like, as well as 3-cycloheptenyl, 2-cyclo-octenyl and the like. The cycloaliphatic radicals are preferably unsubstituted, but may contain substituents, such as, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, or functional groups, such as halogeno, e.g. chloro, bromo and the like, lower alkoxy, e.g. methoxy, ethoxy and the like, or any other suitable functional group.

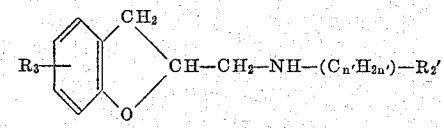
A carbocyclic aryl radical R_2 is more particularly a monocyclic carbocyclic aryl radical, e.g. phenyl or substituted phenyl, or a bicyclic carbocyclic aryl radical, e.g. 1-naphthyl, 2-naphthyl or substituted 1-naphthyl or substituted 2-naphthyl. One or more than one of the same or of different substituents may be attached to any of the positions available for substitution in a phenyl or naphthyl radical; such substituents are, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, halogeno, e.g. fluoro, chloro, bromo and the like, trifluoromethyl, nitro, amino, such as N,N-di-lower alkyl-amino and the like, or any other suitable substituent.

A heterocyclic aryl radical R_2 is preferably a monocyclic heterocyclic aryl radical, such as pyridyl, e.g. 2-pyridyl, 3-pyridyl or 4-pyridyl, thienyl, e.g. 2-thienyl and the like, furyl, e.g. 2-furyl and the like; these groups may contain additional substituents, such as, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, halogeno, e.g. fluoro, chloro, bromo and the like, or any other suitable substituent.

Salts of the new compounds of this invention are particularly acid addition salts, such as the non-toxic, pharmaceutically acceptable acid addition salts, for example, those with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, with organic carboxylic acids, e.g. formic, acetic, propionic, glycolic, malonic, maleic, hydroxymaleic, furamic, malic, tartaric, citric, ascorbic, benzoic, salicyclic, 4 - aminosalicylic, 2-phenyloxybenzoic, 2-acetoxybenzoic acid and the like, or with organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, ethane 1,2-disulfonic acid, benzene sulfonic, p-toluene sulfonic, naphthalene 2-sulfonic acid and the like. Other acid addition salts may be useful as intermediates, for example, in the purification of the free compounds or in the manufacture of other salts, as well as for identification and characterization purposes. Salts which are primarily used for identification purposes are particularly those with acidic organic compounds, e.g. picric, picrolonic, flavianic acid and the like, or with metal complex acids, e.g. phosphotungstic, phosphomolybdic, chloroplatinic, Reinecke acid and the like.

The compounds of this invention have antihypertensive properties and can, therefore, be used as antihypertensive agents, for example, in renal hypertension or similar hypertensive conditions.

A preferred group of compounds of this invention may be represented by the formula:



in which R_2' is cycloalkyl having from five to eight carbon atoms and stands primarily for cyclopentyl or cyclohexyl, or phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl or pyridyl, the group R_3 stands for hydrogen, lower alkyl, lower alkoxy, halogeno, trifluoromethyl, nitro, N,N-di-lower alkyl-amino or lower alkanoyl, and the letter n' represents a whole number from one to four, and the acid addition salts of such compounds.

The new compounds of this invention may be used in the form of compositions for oral or parenteral use, which contain the new compounds or the salts thereof in admixture with an organic or inorganic, solid or liquid carrier. For making up such compositions there are employed substances which do not react with the new compounds, such as water, gelatin, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols, petroleum jelly or any other known carrier used for such preparations. The latter may be in solid form, for example, as tablets, dragees, capsules and the like, or in liquid form, for example, as solutions, suspensions, emulsions and the like, and, if desired, may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying, coloring, flavoring agents and the like, salts for varying the osmotic pressure, buffers, etc. They may also contain, in combination, other useful substances.

The compounds of this invention may be prepared according to methods known per se. I prefer to manufacture these compounds by treating an amine of the formula $R_2-(C_nH_{2n})-NH_2$, in which R_2 and the letter n have the previously-given meaning, with a compound of the formula R_1-CH_2-X, in which R_1 has the previously-given meaning, and X represents a reactive esterified hydroxyl group, and, if desired, converting a resulting salt into a free compound or into another salt, and/or, if desired, converting a free compound into a salt thereof, and/or, if desired, introducing a substituent into the car-

bocyclic aryl portion of the 2,3-dihydro-benzofurane nucleus, and/or, if desired, converting a substituent attached to the carbocyclic aryl portion of the 2,3-dihydro-benzofuran nucleus into another substituent.

The reactive esterified hydroxyl group X in a compound of the formula $R_1—CH_2—X$ is particularly a hydroxyl group esterified with a strong inorganic acid, such as a mineral acid, particularly a hydrohalic acid, e.g. hydrochloric, hydrobromic, hydriodic acid and the like, as well as sulfuric acid and the like, or a strong organic acid, particularly a strong organic sulfonic acid, such as a monocyclic carbocyclic aryl sulfonic acid, e.g. p-toluene sulfonic acid and the like, or a lower alkane sulfonic acid, e.g. methane sulfonic acid, ethane sulfonic acid and the like. The group X in the above formula is above all represented by halogeno having an atomic weight greater than 19, such as chloro, bromo or iodo.

The reaction is preferably carried out by treating the amine with the reactive ester compound in such a way that an excess of the amine is always present. Alcohols, such as lower alkanols, e.g. methanol, ethanol and the like, or any other suitable direct diluent may serve as solvents. If necessary, an alkaline reagent, such as an alkali metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, or an organic base, e.g. pyridine and the like, may be used to neutralize the generated acid.

The reaction is preferably performed at an elevated temperature, if necessary, in a closed vessel under pressure and/or in the atmosphere of an inert gas, e.g. nitrogen.

The starting materials used in the above reaction are known or may be prepared according to methods used for the preparation of the known compounds.

The compounds of this invention may also be prepared by reacting a compound of the formula $R_1—CH_2—NH_2$, in which R_1 has the previously-given meaning, with a compound of the formula $R_2—(C_nH_{2n})—X$, in which R_2, X and the letter n have the previously-given meaning, if desired, carrying out the optional steps.

This reaction is carried out according to the previously-described procedure; the starting materials are known or may be prepared according to procedures used for the known compounds.

The compounds of this invention may also be obtained by converting in a compound of the formula

$$R_1—CO—NH—(C_nH_{2n})—R_2$$

in which R_1, R_2 and the letter n have the previously-given meaning, the carbonyl group into methylene, and, if desired, carrying out the optional steps.

Conversion of the carbonyl portion of the amide group into methylene is carried out according to known methods, particularly by treatment with a reducing reagent capable of converting the carbonyl portion of the amide grouping into methylene. Such reducing reagents are especially alkali metal aluminum hydrides or alkaline earth metal aluminum hydrides, particularly lithium aluminum hydride as well as sodium aluminum hydride and the like; if necessary, these reagents may be used in the presence of an activator, for example, aluminum chloride and the like. The reaction is carried out in the presence of a suitable solvent, for example, an ether, e.g. diethylether, tetrahydrofuran and the like, and, if necessary, at an elevated temperature, for example, at the refluxing temperature of the solvent. Conversion of the carbonyl group into methylene may also be achieved by electrolytically reducing the amide on a suitable cathode, such as mercury, lead, nickel cathode and the like, using a proper anode and suitable catholyte and anolyte media. Conversion of the carbonyl portion in an amide group into methylene may also be carried out by treatment with hydrogen in the presence of a suitable catalyst, e.g. certain copper catalysts and the like.

The starting materials used in the above reaction may be prepared according to procedures generally used for the preparation of carboxylic acid amides, for example, by treatment of an acid halide, e.g., chloride, with an amine.

Compounds of this invention, particularly those of the formula $R_1—CH_2—NH—CH_2—(C_{n-1}H_{2n-2})—R_2$, in which R_1, R_2 and the letter n have the previously-given meaning, or salts thereof, may also be obtained by converting in a compound having the formula

$$R_1—CH_2—NH—CO—(C_{n-1}H_{2n-2})—R_2$$

in which R_1, R_2 and the letter n have the previously-given meaning, the carbonyl group into methylene, and, if desired, carrying out the optional steps.

The above reaction is carried out according to the previously-described methods, and the starting materials are prepared according to known procedures.

The compounds of the present invention may also be prepared by converting in a compound of the formula $R_1—CS—NH—(C_nH_{2n})—R_2$, in which R_1, R_2 and the letter n have the previously-given meaning, the thiocarbonyl group into methylene, and, if desired, carrying out the optional steps.

The above conversion of a thiocarbonyl group into a methylene group may be carried out according to known methods, for example, by treating the thioamide compound with freshly prepared Raney nickel in a suitable, particularly in an alcoholic, solvent, e.g., methanol, ethanol and the like, or electrolytically reducing it according to the procedure outlined hereinabove for the reduction of the amides.

The starting materials may be prepared, for example, from the previously-described amides by treatment with suitable reagents, e.g., phosphorus pentasulfide and the like.

Another method for the preparation of compounds of this invention, particularly of compounds having the formula $R_1—CH_2—NH—CH_2—(C_{n-1}H_{2n-2})—R_2$, in which R_1, R_2 and the letter n have the previously-given meaning, comprises converting in a compound having the formula $R_1—CH_2—NH—CS—(C_{n-1}H_{2n-2})—R_2$, in which R_1, R_2 and the letter n have the previously-given meaning, the thiocarbonyl group into methylene, and, if desired, carrying out the optional steps.

The above procedure is carried out as shown hereinbefore, and the starting material is prepared according to known methods.

Compounds of this invention, particularly those of the formula $R_1—CH_2—NH—CH_2—(C_{n-1}H_{2n-2})—R_2$, in which R_1, R_2 and the letter n have the previously-given meaning, or salts thereof, may also be obtained by removing in a compound of the formula

$$R_1—CH_2—N{=}CH—(C_{n-1}H_{2n-2})—R_2$$

in which R_1 and R_2 and the letter n have the previously-given meaning, the Schiff base-type N=C— double bond by reduction, and, if desired, carrying out the optional steps.

The reduction of the Schiff base-type double bond may be carried out by using catalytically activated hydrogen or a di-light metal hydride as hydrogenating agents. Catalysts containing a metal of the eighth group of the periodic system may be used in the presence of hydrogen; for example, palladium, e.g., palladium on charcoal and the like, represents a suitable metal catalyst. The reduction is carried out by treating, for example, a lower alkanol, e.g., methanol, ethanol and the like, solution of the Schiff base with hydrogen, if desired, at an increased pressure, in the presence of the catalyst.

The preferred reduction reagents, however, are light metal hydrides, particularly the alkali metal borohydrides, e.g., lithium borohydride, sodium borohydride and the like, as well as alkali metal aluminum hydrides, e.g., lithium aluminum hydride, sodium aluminum hydride

and the like, alkaline earth metal aluminum hydrides, e.g., magnesium aluminum hydride and the like, or any other suitable light metal hydride. The reduction with these reagents is preferably carried in solution, the solvents being chosen according to the reactivity of the reagent. For example, an alcohol, such as a lower alkanol, e.g., methanol, ethanol, isopropanol and the like, if desired, aqueous mixtures thereof, and the like, may be used with an alkali metal borohydride; an ether, e.g., diethylether, tetrahydrofurane and the like, is used with an alkali metal aluminum hydride. If desired, the reaction may be promoted by the addition of an activator, for example, of aluminum chloride and the like. The reaction is performed at room temperature or preferably at an elevated temperature, for example, at the boiling temperature of the solvent, and, if necessary, in the atmosphere of an inactive gas, e.g., nitrogen.

The Schiff base-type starting materials may be prepared according to methods known per se, for example, by reacting a 2-aminomethyl-2,3-dihydro-benzofuran with an aldehyde, if necessary, in the presence of a solvent, such as an alcohol, for example, a lower alkanol, e.g., methanol, ethanol and the like, and /or under cooling at room temperature or at an elevated temperature.

The compounds of this invention may also be prepared by removing in a compound of the formula

$$R_1—CH=N—(C_nH_{2n})—R_2$$

in which R_1, R_2 and the letter n have the previously-given meaning, the Schiff base-type C=N— double bond by reduction, and, if desired, carrying out the optional steps.

The reductive removal of the Schiff base-type double bond is carried out as previously shown; the starting material is prepared according to known methods.

A resulting salt may be converted into the free base in the customary way, for example, by reaction with an alkaline reagent, such as a metal hydroxide, e.g. sodium hydroxide, potassium hydroxide and the like, a metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, ammonia and the like, or with a suitable hydroxyl ion exchange preparation.

A resulting salt may be converted into another salt, for example, by treating it with a metal, e.g. sodium, barium, silver and the like, salt of an acid in the presence of a suitable diluent, in which a resulting inorganic salt is insoluble, or with an anion exchange preparation.

A free base may be converted into an acid addition salt by reacting it or a solution thereof with the appropriate inorganic or organic acid, such as one of those outlined hereinbefore, or a solution thereof, and isolating the desired salt.

A substituent may be introduced into the carbocyclic aryl portion of the 2,3-dihydro-benzofuran nucleus of a resulting compound. For example, upon nitration with a suitable nitrating reagent, a nitro group may be introduced. Furthermore, a resulting compound may be reacted with an organic carboxylic acid halide, e.g. chloride and the like, in the presence of a suitable reagent, such as aluminum chloride and the like, and an organic carboxylic acid acyl radical may be introduced.

Certain substituents attached to the carbocyclic aryl portion of the 2,3-dihydro-benzofuran nucleus may be converted into other substituents. For example, a nitro group may be reduced to an amino group according to known reduction methods, for example, by controlled treatment with hydrogen in the presence of a suitable catalyst, e.g. palladium on charcoal and the like, and of an inert solvent, e.g. p-dioxane and the like. An amino group may be converted into a halogeno atom by diazotization, followed by treatment with a cuprous halide according to the Sandmeyer reaction. Or, a lower alkoxy, e.g. methoxy and the like, group may be converted into a free hydroxyl group, for example, by acidic hydrolysis with hydrobromic acid in the presence of acetic acid and the like.

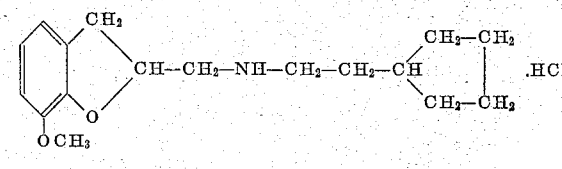
The invention also comprises any modification of the process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is(are) carried out, as well as any new intermediates.

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

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

Example 1

A mixture of 4.9 g. of 2-bromomethyl-7-methoxy-2,3-dihydro-benzofuran and 6.8 g. of 2-cyclopentylethylamine in 15 ml. of ethanol is heated in a sealed tube for four hours. The solution is concentrated under reduced pressure, and the residue is treated with water and extracted with diethyl ether. The organic solution is dried and evaporated; the residue is dissolved in ethyl acetate, anhydrous hydrogen chloride in ethyl acetate is added and the crystalline 2 - (2-cyclopentylethyl)-aminomethyl-7-methoxy-2,3-dihydro-benzofuran hydrochloride of the formula:



is recrystallized from ethanol, M.P. 160–163°; yield: 2.3 g.

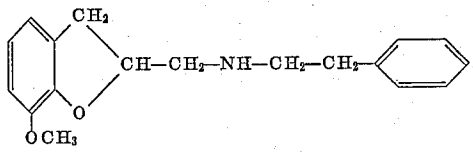
The starting material used in the above example is prepared as follows: A mixture of 124.1 g. of guaiacol, 140 g. of powdered potassium carbonate and 121.0 g. of allyl bromide in 150 ml. of acetone is refluxed while stirring for eight hours. After cooling, it is poured into 1000 ml. of water and the organic material is extracted with diethyl ether. The solvent is evaporated, and the residue is distilled under reduced pressure to yield 129.2 g. of 2-allyloxy-anisole, B.P. 90°/7 mm. After heating for 45 minutes to 230–240° and redistilling it, this material yields 119.6 g. of 2-allyl-6-methoxy-phenol, B.P. 110–115°/9 mm. Acetylation of 26.8 g. of 3-allyl-2-hydroxy-anisole with 30.6 g. of acetic acid anhydride in 24 g. of pyridine yields 29 g. of 2-acetyloxy-3-allyl-anisole, B.P. 109–111°/2.5 mm.

To a solution of 31 g. of 2-acetyloxy-3-allyl-anisole in 120 ml. of carbon disulfide is added dropwise 24.0 g. of bromine. After one hour, the reaction mixture is concentrated under reduced pressure and the residue is triturated with hexane to yield 26.0 g. of 2-acetyloxy-3-(2,3-dibromo-propyl)-anisole.

To a solution of 2-acetyloxy-3-(2,3-dibromo-propyl)-anisole in 320 ml. of ethanol is added a solution of sodium ethoxide in ethanol (prepared by dissolving 7.0 g. of sodium in 300 ml. of ethanol) dropwise while cooling. The reaction mixture is then refluxed for one hour, the solution is cooled, filtered and concentrated under reduced pressure. The residue is taken up into diethyl ether, the organic solution is washed with water, dried and concentrated. The desired 2-bromomethyl-7-methoxy-2,3-dihydro-benzofuran is purified by distilling the residue, B.P. 138°/1.5 mm.; yield: 45.25 g.

Example 2

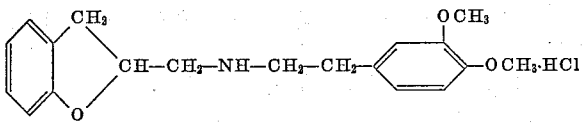
A mixture of 4.9 g. of 2-bromomethyl-7-methoxy-2,3-dihydro-benzofuran and 4.9 g. of 2-phenylethylamine in 15 ml. of ethanol is reacted as shown in Example 1; the resulting 7-methoxy-2-(2-phenylethyl)-aminoethyl-2,3-dihydro-benzofuran of the formula:



is converted into its hydrochloride by adding an anhydrous solution of hydrogen chloride in ethyl acetate to the solution of the free base in ethyl acetate and diluting it with diethyl ether; it is recrystallized repeatedly from acetone, M.P. 137–141°; yield: 2.3 g.

Example 3

To a solution of 4.3 g. of 2-bromomethyl-2,3-dihydro-benzofuran in 15 ml. of ethanol is added 7.24 g. of 2-(3,4-dimethoxy-phenyl)-ethylamine. The resulting mixture in a sealed tube is heated to 150° for four hours, and is then concentrated under reduced pressure. The residue is partitioned between diethyl ether and water; the organic solution is separated and evaporated to dryness, and the residue is dissolved in ethyl acetate. The resulting solution is acidified with a solution of hydrogen chloride in ethyl acetate; the desired 2-[2-(3,4-dimethoxy-phenyl)-ethyl] - aminomethyl - 2,3-dihydro-benzofuran hydrochloride of the formula:

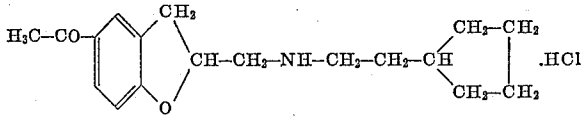


precipitates and is recrystallized from ethanol, M.P. 196–197°.

The starting material is prepared according to the procedure described by R. Adams et al., J. Am. Chem. Soc., vol. 41, p. 648 (1919).

Example 4

To a solution of 5.1 g. of 5-acetyl-2-bromomethyl-2,3-dihydro-benzofuran in 30 ml. of ethanol is added 4.5 g. of 2-cyclopentylethyl-amine. The reaction is carried out according to the method described in Example 3; the 5 - acetyl - 2-(2-cyclopentylethyl)-aminoethyl-2,3-dihydro-benzofuran hydrochloride of the formula:

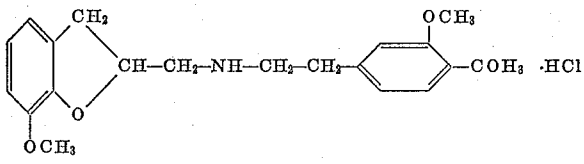


is recrystallized from isopropanol, M.P. 227–229°.

The starting material, which is prepared according to the method described by R. Adams et al., loc. cit. by starting with 4-hydroxy-benzophenone, has a boiling point of 170°/0.05 mm.

Example 5

A solution of 9.72 g. of 2-bromomethyl-7-methoxy-2,3-dihydro-benzofuran in 30 ml. of ethanol is reacted with 14.4 g. of 2-(3,4-dimethoxy-phenyl)-ethylamine according to the procedure described in Example 3; the desired 2 - [2-(3,4-dimethoxy-phenyl)-ethyl]-aminoethyl-7-methoxy-2,3-dihydro-benzofuran hydrochloride of the formula:

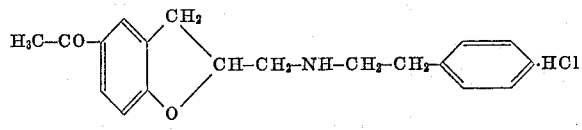


melts at 189–191° after being recrystallized twice from ethanol.

Example 6

A solution of 5.1 g. of 5-acetyl-2-bromomethyl-2,3-dihydro-benzofuran and 4.8 g. of 2-phenylethylamine in 30 ml. of ethanol is reacted as described in Example 3 to

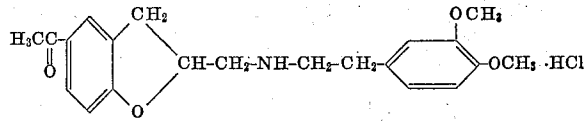
yield to 5 - acetyl-2-(2-phenylethyl)-aminomethyl-2,3-dihydro-benzofuran hydrochloride of the formula:



which is recrystallized from isopropanol, M.P. 238–242°.

Example 7

To a solution of 5.1 g. of 5-acetyl-2-bromomethyl-2,3-dihydro-benzofuran in 30 ml. of ethanol is added 7.2 g. of 2-(3,4-dimethoxy-phenyl)-ethylamine, and the mixture is reacted and worked up according to the procedure described in Example 3 to yield the 5-acetyl-2-[2-(3,4-dimethoxy - phenyl) - ethyl] - aminomethyl - 2,3 - dihydro-benzofuran hydrochloride of the formula:



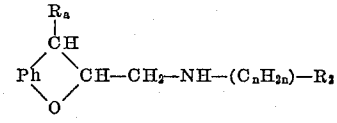
which melts at 172–175° after being recrystallized three times from isopropanol.

Other compounds, which may be prepared according to the above-described procedure using the appropriate starting materials are, for example,

2-cyclopentylmethylaminomethyl-2,3-dihydro-benzofuran,
2-cyclohexylmethylaminomethyl-2,3-dihydro-benzofuran,
2-(3-cyclohexylpropyl)-aminomethyl-2,3-dihydro-benzofuran,
2-benzylaminomethyl-2,3-dihydro-benzofuran,
2-(4-chlorobenzyl)-aminomethyl-2,3-dihydro-benzofuran,
2-(3,4-dimethoxy-benzyl)-aminomethyl-2,3-dihydro-benzofuran,
2-(1-phenylethyl)-aminomethyl-2,3-dihydro-benzofuran,
2-[1-(4-methyl-phenyl)-ethyl]-aminomethyl-2,3-dihydro-benzofuran,
2-(2-pyridyl)-methylaminomethyl-2,3-dihydro-benzofuran,
5-acetyl-2-(2-cyclohexylethyl)-aminomethyl-2,3-dihydro-benzofuran,
6-chloro-2-(2-cyclopentylethyl)-aminomethyl-2,3-dihydro-benzofuran,
2-(2-cyclopentylethyl)-aminomethyl-3-methyl-2,3-dihydro-benzofuran and the like.

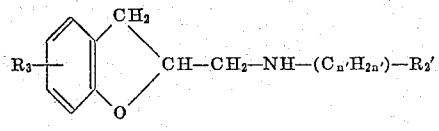
What is claimed is:

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



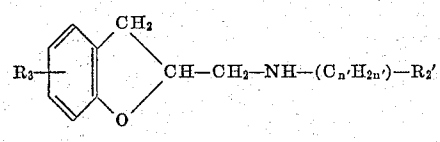
in which R_a is a member selected from the group consisting of hydrogen and lower alkyl, Ph represents a member selected from the group consisting of 1,2-phenylene, lower alkyl-1,2-phenylene, hydroxy-1,2-phenylene, lower alkoxy-1,2-phenylene, halogeno-1,2-phenylene, trifluoromethyl - 1,2 - phenylene, mercapto - 1,2 - phenylene, lower alkyl-mercapto-1,2-phenylene, nitro-1,2-phenylene, N,N-di-lower alkyl-amino-1,2-phenylene, N-lower alkanoyl-amino-1,2-phenylene, and lower alkanoyl-1,2-phenylene, the letter *n* stands for a whole number from one to seven, and R_2 stands for a member selected from the group consisting of cycloalkyl having from 5 to 8 ring carbon atoms, cycloalkenyl having from 5 to 8 ring carbon atoms, phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (halogeno)-phenyl, (trifluoromethyl)-phenyl, (nitro)-phenyl, (amino)-phenyl, pyridyl, thienyl and furyl, and an acid addition salt thereof.

2. A compound of the formula:



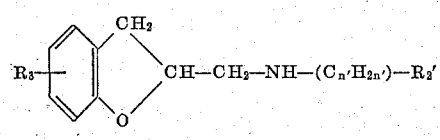
in which R_2' is phenyl, the group R_3 is lower alkoxy, and the letter n' is a whole number from one to four.

3. A compound of the formula:



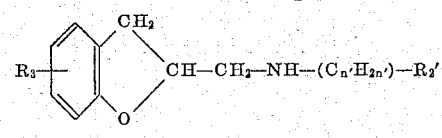
in which R_2' is (lower alkoxy)-phenyl, the group R_3 is lower alkoxy, and the letter n' is a whole number from one to four.

4. A compound of the formula:



in which R_2' stands for cycloalkyl having from 5 to 8 ring carbon atoms, the group R_3 is lower alkoxy, and the letter n' is a whole number from one to four.

5. An acid addition salt of a compound of the formula:



in which R_2' stands for cycloalkyl having from 5 to 8 ring carbon atoms, the group R_3 is lower alkoxy, and the letter n' is a whole number from one to four.

6. 2 - (2 - cyclopentylethyl)-aminomethyl-7-methoxy-2,3-dihydro-benzofuran.

7. An acid addition salt of 2-(2-cyclopentylethyl)-aminomethyl-7-methoxy-2,3-dihydro-benzofuran.

8. 7 - methoxy-2-(2-phenylethyl)-aminomethyl-2,3-dihydro-benzofuran.

9. An acid addition salt of 7-methoxy-2-(2-phenylethyl)-aminomethyl-2,3-dihydro-benzofuran.

10. 2 - [2-(3,4-dimethoxy-phenyl)-ethyl]-aminomethyl-2,3-dihydro-benzofuran.

11. An acid addition salt of 2-[2-(3,4-dimethoxy-phenyl)-ethyl]-aminomethyl-2,3-dihydro-benzofuran.

References Cited by the Examiner

Fieser: Organic Chemistry, third edition (1956), pages 46–7.

Harington (editor): Hypotensive Drugs (1958), page 11.

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