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2-(1,2,3,4-TETRAHYDRONAPHTHYL)-HYDRAZINES AND SALTS THEREOF

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The present invention relates to 1,2,3,4-tetrahydronaphthalene compounds, more particularly to 1,2,3,4-tetrahydro-naphthalene compounds, which contain in the 2-position a hydrazino group of the formula

—NH—NH—R_1

in which R_1 represents primarily hydrogen, as well as an acyl radical, and may also stand for lower aliphatic hydrocarbon, substituted lower aliphatic hydrocarbon, carbocyclic aryl or carbocyclic aryl-lower aliphatic hydrocarbon, or salts of such compounds, which compounds may be present in the form of mixtures of isomers, e.g. racemates and the like, or single isomers, e.g. antipodes and the like, and process for their preparation.

The group R_1 represents particularly hydrogen, i.e. the compounds of the present invention are primarily 1,2,3,4-tetrahydro-naphthalene compounds, which contain in the 2-position an N-unsubstituted hydrazino group.

Acyl groups representing the radical R_1 are primarily those of organic carboxylic acids, such as lower aliphatic carboxylic acids, e.g. formic, acetic, propionic, pivalic, dichloroacetic, methoxyacetic, N,N-dimethylamino-acetic acid and the like, as well as malonic, succinic, maleic, malic acid and halfesters thereof, carbocyclic aryl carboxylic acids, such as monocyclic carboxylic acids, e.g. benzoic, 2-hydroxy-benzoic, 2-acetoxy-benzoic, 4-methoxy-benzoic, 3,4,5-trimethoxy-benzoic, 2-ethoxy-benzoic, 2,5-dichloro-benzoic, 4-bromo-benzoic, 3-N,N-dimethylamino-benzoic, 4-nitro-benzoic, 3-methyl-benzoic, phthalic, tetrahydrophthalic acid and the like, monocyclic carbocyclic aryl-lower aliphatic hydrocarbon carboxylic acids, e.g. phenylacetic, diphenylacetic, dihydrocinnamic, cinnamic, 4-methoxy-cinnamic, ferulic acid and the like, heterocyclic carboxylic acids, particularly monocyclic heterocyclic carboxylic acids, e.g. nicotinic, isonicotinic, thienoic, furoic, 3 - (5-methyl-1,2-oxazoyl)-caroboxylic acid and the like, or any other suitable carboxylic acid.

R_1 may also stand for lower aliphatic lower hydrocarbon radicals, such as lower alkyl, particularly lower alkyl containing from one to seven carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secondary butyl, tertiary butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and the like. Other lower aliphatic hydrocarbon radicals are lower alkenyl, particularly lower alkenyl containing from three to five carbon atoms, e.g. allyl, 2-methyl-allyl, 3-methyl-allyl and the like, cycloalkyl, particularly cycloalkyl containing from five to six carbon atoms, e.g. cyclopentyl, cyclohexyl and the like, or any other suitable aliphatic hydrocarbon radicals, such as, for example, cycloalkyl-lower alkyl, in which cycloalkyl contains from five to six carbon atoms, e.g. cyclopentylmethyl, 2-cyclohexylethyl and the like. The lower aliphatic hydrocarbon radicals may also contain functional groups as substituents, such as, for example, hydroxyl, etherified hydroxyl, particularly lower alkoxy containing from one to four carbon atoms, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, or esterified hydroxyl, such as, for example, halogen, e.g. chlorine, bromine and the like, or lower alkanoyloxy, e.g. acetoxy, propionyloxy and the like, etherified mercapto, such as lower alkyl-mercapto, e.g. methylmercapto, ethylmercapto and the like, or any other suitable functional group. Other radicals representing R_1 may be carbocyclic aryl radicals, such as, for example, monocyclic carbocyclic aryl radicals, e.g. phenyl or substituted phenyl, or carbocyclic aryl-lower aliphatic hydrocarbon radicals, such as, for example, monocyclic carbocyclic aryl-lower alkyl, particularly phenyl-lower alkyl, e.g. benzyl, 1-phenylethyl, 2-phenylethyl and the like, as well as substituted phenyl lower alkyl; substituents of carbocyclic aryl radicals are, for example, lower alkyl, e.g. methyl, ethyl and the like, lower alkoxy, e.g. methoxy, ethoxy and the like, halogen, e.g. fluorine, chlorine, bromine and the like, halogeno-lower alkyl, e.g. trifluoromethyl, nitro, amino, particularly N,N-di-lower alkyl-amino, e.g. N,N-dimethylamino and the like, or any other suitable substituents.

The carbon atoms representing the 1-position, the 3-position and the 4-position of the 1,2,3,4-tetrahydro-naphthalene nucleus may be unsubstituted and the 2-position may carry no substituent in addition to the hydrazino group; substituents, which may be attached to one or more than one of these positions, are primarily hydrocarbon radicals, such as, for example, lower alkyl, e.g. methyl, ethyl and the like, carbocyclic aryl, such as monocyclic carbocyclic aryl, e.g. phenyl or phenyl containing substituents, such as those described hereinbelow, or carbocyclic aryl-lower aliphatic hydrocarbon, such as monocyclic carbocyclic aryl-lower alkyl, for example, phenyl-lower alkyl, e.g. benzyl, diphenylmethyl, 1-phenyl-ethyl, 2-phenyl-ethyl and the like or these radicals containing substituents, such as those described hereinbelow.

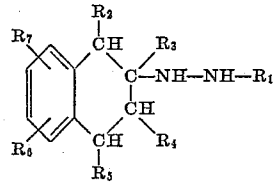
The aromatic, six-membered portion of the 1,2,3,4-tetrahydro-naphthalene nucleus may be unsubstituted or may contain one or more than one of the same or of different substituents attached to any of the four available positions. Such substituents are, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, hydroxyl, etherified hydroxyl, such as lower alkoxy containing from one to four carbon atoms, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy and the like, esterified hydroxyl, such as lower alkoxy-carbonyloxy, e.g. methoxy-carbonyloxy, ethoxy-carbonyloxy and the like, lower alkanoyloxy, e.g. acetoxy, proprionyloxy and the like, or halogeno, e.g. fluoro, chloro, bromo and the like, etherified mercapto, such as lower alkyl-mercapto, e.g. methylmercapto, ethylmercapto and the like, nitro, amino, particularly N,N-di-lower alkyl amino, e.g. N,N-dimethylamino, N,N-diethylamino and the like, halogeno-lower alkyl, e.g. trifluoromethyl and the like, or any other suitable substituent. The above-described substituents may also be attached to the carbocyclic aryl portions of any carbocyclic aryl or carbocyclic aryl-lower aliphatic substituent attached to the 1-position, 2-position, 3-position and/or the 4-position of the 1,2,3,4-tetrahydro-naphthalene nucleus.

Salts of the compounds of this invention are particularly therapeutically acceptable acid addition salts with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, with organic carboxylic acids, such as formic, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, maleic, hydroxymaleic, dihydroxymaleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, salicyclic, 4-aminosalicyclic, 2-phenoxybenzoic, 2-acetoxy-benzoic acid and the like, or with organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, p-toluene sulfonic acid and the like.

The compounds of this invention may be present in different isomeric forms depending on the number of asymmetric carbon atoms and/or the method of preparation. Having at least one asymmetric carbon atom, the compounds of this invention may be present in the form of racemates or optically active antipodes. Compounds with more than one asymmetric carbon atom may form mixtures of racemates.

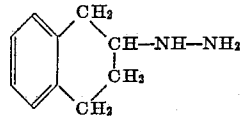
The compounds of the present invention have a strong stimulating effect due to their inhibition of amine oxidase, and can, therefore, be used as stimulating agents to overcome states of depression, lethargy and similar conditions, as, for example, in connection with mental diseases.

A pronounced stimulating effect is exhibited by 1,2,3,4-tetrahydro-naphthalene compounds of the formula



in which R_1 represents particularly hydrogen, as well as the acyl radical of a lower alkane carboxylic acid, e.g. acetic, propionic acid and the like, or a monocyclic heterocyclic carboxylic acid, e.g. nicotinic, isonicotinic, 3-(5-methyl-1,2-oxazolyl)-carboxylic acid and the like, each of the radicals R_2, R_3, R_4 and R_5 represents primarily hydrogen, as well as lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, phenyl or phenyl-lower alkyl, e.g. benzyl, 1-phenylethyl, 2-phenylethyl and the like, and each of the radicals R_6 and R_7 stands for hydrogen, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, lower alkyl-mercapto, e.g. methylmercapto, ethylmercapto and the like, halogeno, e.g. fluoro, chloro, bromo and the like, or trifluoromethyl, or therapeutically acceptable acid addition salts of such compounds, in the form of racemates or antipodes thereof.

This group of compounds may be represented by the 1,2,3,4-tetrahydro-naphthalene compound of the formula



its acyl derivatives with the previously mentioned carboxylic acids, or their therapeutically acceptable acid addition salts, which compounds may be present as in the form of racemates or antipodes.

The new compounds of this invention may be used as medicaments in the form of pharmaceutical preparations, which contain the new 1,2,3,4-tetrahydro-naphthalene compounds, or their salts, either in the form of their racemates or their antipodes in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral or parenteral administration. For making up these preparations, there may be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as capsules, tablets, dragees and the like, or in liquid form, for example, as solutions, suspensions, emulsions and the like. If desired, they may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying agents, salts for varying the osmotic pressure, buffers and the like. They may also contain, in combination, other therapeutically useful substances.

The compounds of the present invention may be prepared, for example, by replacing in a 1,2,3,4-tetrahydro-naphthalene compound, containing in the 2-position a substituent capable of being converted into a hydrazino group of the formula —NH—NH—R_1, in which R_1 has the previously-given meaning, such substituent into the desired hydrazino group of the above formula, and, if desired, acylating a resulting compound containing a hydrazino group of the formula —NH—NH_2 with a reactive derivative of an acid of the formula R_1—OH, in which R_1 represents the acyl radical of one of the above-mentioned acids, and/or, if desired, converting a hydrazino group of the formula —NH—NH—R_1, in which R_1 represents the acyl radical of one of the above-mentioned acids, into the hydrazino group of the formula

—NH—NH_2

and/or, if desired, converting a resulting salt into the free compound and/or, if desired, converting a resulting compound into a salt thereof, and/or, if desired, separating a resulting mixture of racemates into single racemates, and/or, if desired, resolving a resulting racemate into the antipodes thereof.

A substituent attached to the 2-position of the 1,2,3,4-tetrahydro-naphthalene nucleus, which may be converted into the desired hydrazino group of the formula

—NH—NH—R_1

is, for example, a reactive esterified hydroxyl group. Such hydroxyl group may be esterified with a strong inorganic acid, particularly a mineral acid, such as, for example, a hydrohalic acid, e.g. hydrochloric, hydrobromic, hydriodic acid and the like, or sulfuric acid or any other suitable mineral acid, as well as with a strong organic acid, such as, for example, an organic sulfonic acid, particularly a monocyclic carbocyclic aryl sulfonic acid, e.g. p-toluene sulfonic acid and the like. The reactive esterified hydroxyl group is, therefore, primarily a halogen, e.g. chlorine, bromine, iodine and the like, atom or a p-toluene sulfonyloxy group.

The reactive esterified hydroxyl group may be converted into the desired hydrazino group by treatment with a hydrazine of the formula H_2N—NH—R_1, in which R_1 has the previously-given meaning. Specific reagents used in the above procedure are hydrazine (for example, in the form of its hydrate), or an N-acyl-hydrazine, e.g. acetic acid hydrazide, propionic acid hydrazide, nicotinic acid hydrazide, isonicotinic acid hydrazide, 3-(5-methyl-1,2-oxazolyl)-carboxylic acid hydrazide, or any other suitable carboxylic acid hydrazide.

Other N-substituted hydrazines which may be used in the above reaction, are, for example, N-lower alkyl-hydrazines, e.g. N-methyl-hydrazine, N-ethyl-hydrazine, N-n-propyl-hydrazine, N-isopropyl-hydrazine and the like, N-cycloalkyl-hydrazine, in which cycloalkyl contains from five to six ring carbon atoms, e.g. N-cyclopentyl-hydrazine, N-cyclohexyl-hydrazine and the like, N-phenyl-hydrazine, N-phenyl-lower alkyl-hydrazine, e.g. N-benzyl-hydrazine, N-(1-phenylethyl)-hydrazine, N-(2-phenylethyl)-hydrazine and the like.

The reaction of the 2-substituted 1,2,3,4-tetrahydro-naphthalene compound with the hydrazine compound is preferably carried out in the presence of a solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol, n-propanol, isopropanol and the like, a monocyclic carbocyclic hydrocarbon, e.g. benzene, toluene and the like, a halogenated lower aliphatic hydrocarbon, e.g. chloroform and the like, an ether, e.g. p-dioxane and the like, or any other suitable solvent, at room temperature, or, preferably, at an elevated temperature, if necessary, in a closed vessel under pressure and/or, in the presence of an acid adsorbent; metal or alkaline earth metal carbonate, e.g. sodium, potassium, calcium carbonate and the like, may be added to the reaction mixture to remove generated acid from the medium.

The starting materials used in the above modification, may be prepared according to known methods. For example, a 2-hydroxy-1,2,3,4-tetrahydro-naphthalene compound may be converted into the corresponding 2-halogeno-1,2,3,4-tetrahydro-naphthalene compound (in which the halogen atom represents the reactive esterified hydroxyl group) by treatment with a halogenating reagent,

such as, for example, phosphorus halide, e.g. phosphorus pentachloride, phosphorus tribromide and the like, a thionyl halide, e.g. thionyl chloride, thionyl bromide and the like, or any other suitable reagent, or with the esterifying acid itself, e.g. hydrobromic acid and the like. An iodine atom may be introduced, for example, by treatment of the corresponding 2-chloro-1,2,3,4-tetrahydro-naphthalene or 2-bromo-1,2,3,4-tetrahydro-naphthalene compound with an alkali metal iodide, e.g. sodium iodide and the like, in a suitable solvent, such as, for example, acetone and the like. A sulfonyloxy group, particularly the p-toluene sulfonyloxy group, may be formed by treating the 2-hydroxy-1,2,3,4-tetrahydro-naphthalene compound with a sulfonic acid halide, e.g. p-toluene sulfonyl chloride and the like, preferably in the presence of an organic base, e.g. pyridine and the like.

A further group attached to the 2-position of the 1,2,3,4-tetrahydro-naphthalene nucleus of the starting material, which is capable of being converted into the desired hydrazino group, may be an oxo group of the formula =O. Its conversion into the desired amino group of the formula —NH—NH—R_1 may be carried out by treatment of the 1,2,3,4-tetrahydro-naphthalen-2-one compound with the hydrazine compound of the formula H_2N—NH—R_1, in which R_1 has the previously-given meaning, or a salt thereof, to form a 2-hydrazono-1,2,3,4-tetrahydro-naphthalene compound, which upon treatment with a reducing reagent is converted into the desired hydrazino compound. The two steps, i.e. treatment with the hydrazine compound and reduction, may also be carried out simultaneously.

Treatment with the hydrazine compound may be carried out according to known methods, for example, by treating the two reactants, if desired, in the presence of a catalytic amount of an acid, e.g. acetic acid and the like, in an inert solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like. The reduction of a resulting hydrazone compound may be accomplished by treatment with hydrogen in the presence of a catalyst containing a metal of the eighth group of the Periodic System, e.g. platinum, for example, in the form of platinum oxide, or any other suitable catalyst, whereby the reaction is preferably carried out in a closed vessel under increased pressure, and in the presence of an inert solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol and the like, as a diluent. Complex light metal hydrides, such as, for example, alkali metal aluminum hydrides, e.g. lithium aluminum hydride and the like, alkali metal borohydrides, e.g. sodium borohydride and the like, in the presence of appropriate inert solvents (for example, ethers with aluminum hydrides, lower alkanols with borohydrides), may also serve for the conversion of hydrazone compounds into the corresponding hydrazines.

Hydrazine (also used in the form of its hydrate) in the presence of hydrogen under pressure, a catalyst (e.g. platinum oxide and the like) and an inert solvent (e.g. a lower alkanol), represents a suitable reagent for the direct conversion of the 1,2,3,4-tetrahydro-naphthalin-2-one compound into the desired 2-hydrazino-1,2,3,4-tetrahydro-naphthalene derivative; other hydrazines of the formula H_2N—NH—R_1, in which R_1 represents one of the previously-described substituents other than hydrogen, may also be used in the direct transformation of the oxo group of a 1,2,3,4-tetrahydro-naphthalin-2-one compound into the desired hydrazino group.

Another group attached to the 2-position of the 1,2,3,4-tetrahydro-naphthalene nucleus, which may be converted into the hydrazino group of the formula —NH—NH—R_1, in which R_1 represents primarily hydrogen, as well as one of the other previously-mentioned groups, is, for example, an N-unsubstituted amino group of the formula —NH_2. Such amino groups may be converted into the desired hydrazino group of the above formula, for example, by treatment with a halogenoamine, primarily chloramine and the like, or any other suitable chloramine of the formula Cl—NH—R_1. These reagents, which may be formed in situ, are preferably used in the presence of an acid adsorbent condensing reagent, e.g. sodium hydroxide and the like, and an inert solvent, such as a lower alkanol, e.g. methanol, ethanol and the like, preferably while cooling.

The starting materials used in the above modification are known or, if new, may be prepared according to methods used for the known compounds.

In resulting 1,2,3,4-tetrahydro-naphthalene compounds, containing in the 2-position a hydrazino group of the formula —NH—NH—R_1, in which R_1 represents the acyl radical of a carboxylic acid, such acyl radical may be replaced by hydrogen and a 1,2,3,4-tetrahydro-naphthalene compound, containing a hydrazino group of the formula —NH—NH_2, may be recovered. Removal of the acyl group may be achieved by hydrolysis, either by treatment with an acid hydrolysis reagent, e.g. aqueous hydrochloric acid and the like, or with an alkaline hydrolysis reagent, e.g. aqueous sodium hydroxide and the like. Certain other acyl groups, such as, for example, a carbobenzoxy group, may also be removed by hydrogenolysis, for example, by the treatment with hydrogen in the presence of a catalyst, e.g. palladium black and the like, or by treatment with hydrogen bromide in acetic acid.

In a resulting 1,2,3,4-tetrahydro-naphthalene compound, a hydrazino group of the formula —NH—NH_2 in the 2-position, may be converted into a hydrazino group of the formula —NH—NH—R_1, in which R_1 stands for an acyl group; such conversion may be carried out by treatment with a reactive derivative of a carboxylic acid of the formula R_1—OH, in which R_1 represents one of the previously-described acyl groups. A reactive derivative of such acid may be, for example, a reactive ester thereof with a lower alkanol, e.g. methanol, ethanol and the like. The acylation reaction may be carried out according to known methods, for example, in the presence of a suitable inert solvent, such as a lower alkanol, e.g. methanol, ethanol and the like.

The compounds of this invention may be obtained in the form of the free bases or as the salts thereof. A salt may be converted into the free base, for example, by reaction with an alkaline reagent, such as aqueous alkali metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, aqueous alkali metal carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate and the like, or any other suitable alkaline reagent, or with an anion exchange resin. A free base may be converted into its therapeutically useful acid addition salts by reacting the former with one of the organic acids mentioned hereinbefore. The salt-forming reaction may be carried out, for example, by treating a solution of the free base in a solvent, such as a lower alkanol, e.g. methanol, ethanol, n-propanol and the like, an ether, e.g. diethyl ether, di-isopropyl ether and the like, a lower alkyl lower alkanolate, e.g. methyl acetate, ethyl acetate and the like, a lower alkanone, e.g. acetone, ethyl methyl ketone and the like, an aliphatic hydrocarbon, e.g. pentane, hexane and the like, a halogenated aliphatic hydrocarbon, e.g. methylene chloride, ethylene chloride and the like, a monocyclic carbocyclic aryl hydrocarbon, e.g. benzene, toluene, xylene and the like, or any other suitable solvent or solvent mixture, with the acid or a solution thereof and isolating the desired salt.

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

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

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

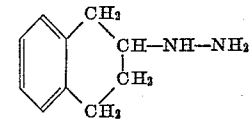
The invention also comprises any modification of the process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is(are) carried out. It also includes any new intermediates, which may be formed in one of the procedures outlined hereinbefore.

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

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 5.85 g. of 2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene and 3.1 g. of anhydrous hydrazine in ethanol is refluxed for six hours. The solvent is evaporated under reduced pressure, the residue is taken up in a small amount of water and the aqueous solution is acidified with 15 percent aqueous hydrochloric acid. The p-toluene sulfonic acid salt of 2-hydrazino-1,2,3,4-tetrahydro-naphthalene of the formula



precipitates (4.0 g.) and is recrystallized from a mixture of ethanol and ethyl ether, M.P. 151–153°.

The starting material may be prepared as follows: To a solution of 25 g. of 1,2,3,4-tetrahydro-naphthalen-2-one in 250 ml. of ethanol is slowly added 9.0 g. of sodium borohydride while stirring. After the addition is completed, the reaction mixture is refluxed for one hour and then concentrated under reduced pessure to a small volume under reduced pressure. The residue is diluted with water, the organic material is extracted with ether, the organic phase is washed twice with water, dried over magnesium sulfate and evaporated to dryness.

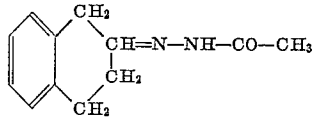
9.65 g. of p-toluene sulfonyl chloride is added to a solution of 5 g. of the resulting 2-hydroxy-1,2,3,4-tetrahydro-naphthalene in 10 ml. of pyridine. The mixture is allowed to stand at room temperature and is then poured onto ice. A white oil separates, crystallizes upon standing, is collected, washed with water and air dried. The resulting 2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene is recrystallized from a mixture of ethyl acetate and diethyl ether, M.P. 80–83°; yield: 8.85 g.

In the above reaction the 2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene may be replaced by other reactive esters of 2-hydroxy-1,2,3,4-tetrahydro-naphthalene compounds, such as, for example, 1-phenyl-2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene, 2-methyl-2-p-toluene sulfonyloxy - 1,2,3,4 - tetrahydro-naphthalene, 1-benzyl-2-p-toluene sulfonyloxy - 1,2,3,4 - tetrahydro-naphthalene, 6-chloro-2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene, 6-methoxy-2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene, 6,7 - dimethoxy - 2 - p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene, 5-methyl-2-p-toluene sulfonyloxy-1,2,3,4-tetrahydro-naphthalene, 6-trifluoromethyl-2-p-toluene sulfonyloxy-1,2,3,4 - tetrahydro-naphthalene and the like. When treated with hydrazine according to the previously-described procedure, these reactive esters of 2-hydroxy-1,2,3,4 - tetrahydro-naphthalene yield, for example, 2-hydrazino-1-phenyl-1,2,3,4-tetrahydro-naphthalene, 2-hydrazino-2-methyl-1,2,3,4-tetrahydro-naphthalene, 1-benzyl-2-hydrazino-1,2,3,4-tetrahydro-naphthalene, 6-chloro-2 - hydrazino - 1,2,3,4 - tetrahydro-naphthalene, 2-hydrazino-6-methoxy-1,2,3,4 - tetrahydro-naphthalene, 6,7-dimethoxy-2-hydrazino-1,2,3,4 - tetrahydro-naphthalene, 2-hydrazino-5-methyl-1,2,3,4-tetrahydro-naphthalene, 2-hydrazino-6-trifluoromethyl-1,2,3,4 - tetrahydro-naphthalene; and the like, in the form of their p-toluene sulfonic acid addition salts, which may be converted into free base by treatment with an alkaline reagent, e.g. sodium hydroxide.

Example 2

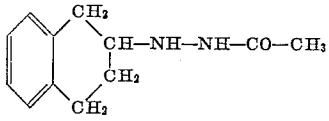
A solution of 25.0 g. of 1,2,3,4-tetrahydro-naphthalene-2-one in 30 ml. of ethanol is refluxed with 12.7 g. of acetyl-hydrazine in 50 ml. of ethanol for two hours under an atmosphere of nitrogen. The solvent is removed under reduced pressure and the crystalline residue is recrystal-

lized from a mixture of ethanol and ethyl acetate to yield the desired compound of the formula



which melts at 118–122°.

A solution of 10 g. of the above-described hydrazone in 250 ml. of acetone is hydrogenated in the presence of about 0.5 g. of platinum oxide until one mol is absorbed. The catalyst is filtered off, the solvent is evaporated under reduced pressure, the residue is diluted with water and the aqueous solution is made basic with aqueous ammonia. The organic material is extracted with ether, the ether solution is dried, the solvent is evaporated and the resulting 1-acetyl-2-(1,2,3,4-tetrahydro-2-naphthyl)-hydrazine of the formula

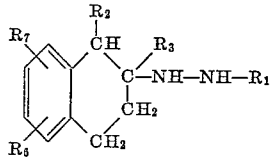


is recrystallized from ethanol, M.P. 78–80°.

The acetyl-hydrazine may be replaced by isonicotinoyl-hydrazine, the 3-(5-methyl-1,2-oxazolyl)-carboxylic acid hydrazide and the like; upon treatment with 1,2,3,4-tetrahydro-naphthalen-2-one and subsequent hydrogenation according to the above example, the 1-isonicotinoyl-2-(1,2,3,4-tetrahydro-2-naphthyl)-hydrazine, 1-[3-(5-methyl-1,2-oxazolyl)-carboxy]-2-1,2,3,4-tetrahydro-2-naphthyl)-hydrazine may be obtained.

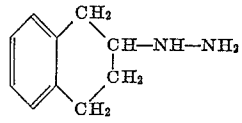
What is claimed is:

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

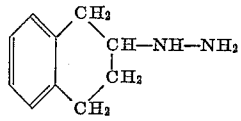


in which R_1 is a member selected from the group consisting of hydrogen, lower alkanoyl, isonicotinoyl and 5-methyl-1,2-oxazolyl-3-carbonyl, R_2 is a member selected from the group consisting of hydrogen, phenyl and benzyl, R_3 is a member selected from the group consisting of hydrogen and lower alkyl, R_6 is a member selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, chloro and trifluoromethyl, and R_7 is a member selected from the group consisting of hydrogen and lower alkoxy, and a therapeutically acceptable acid addition salt thereof.

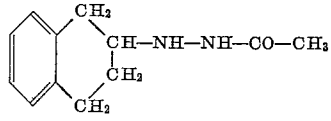
2. The compound of the formula



3. Therapeutically acceptable acid addition salts of the compound of the formula



4. The compound of the formula



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