

1.195.729



PATENT SPECIFICATION

NO DRAWINGS

1.195.729

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COMPLETE SPECIFICATION

Azabicycloaliphatic Compounds

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

The present invention provides an azabicycloaliphatic compound of the formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{Het}$, in which Ar represents a substituted or unsubstituted phenyl group or a substituted or unsubstituted monocyclic monoheterocyclic group of aromatic character, X denotes oxygen or a free or etherified or esterified hydroxyl group together with a hydrogen atom or a hydrocarbon radical, Alk denotes a lower alkylene radical which separates the groups represented by $-\text{C}(=\text{X})$ and Het by at least 3 carbon atoms and Het denotes a bicycloalkyleneamino group having 6 to 10 carbon atoms as ring or bridge members, which carbon atoms may be connected to one another by one or more double bonds or substituted by lower alkyl groups, and having only one ring nitrogen atom, an acid addition salt thereof and a process for the manufacture of such a compound.

The term "lower" whenever used in conjunction with an organic radical, group or compound denotes such radical, group or compound as having up to 7 carbon atoms. The number of carbon atoms preferred is up to 4.

A phenyl group represented by Ar may optionally be substituted by one, two or more identical or different substituents. Substituents may be, for example, lower alkyl groups, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, tertiary-butyl or isopentyl groups, free, etherified or esterified hydroxyl groups, for example, lower alkoxy groups, for example, methoxy, ethoxy, *n*-propoxy, isopropoxy or *n*-butoxy groups; lower alkenyloxy groups, for example, allyloxy groups; lower alkylendioxy groups, for example, methylenedioxy groups; aryloxy groups, for example, phenoxy groups; aryl-lower alkoxy groups, for example, benzyloxy groups; lower alkanoyloxy groups, for example, acetyloxy groups, halogen atoms, for example, fluorine, chlorine or bromine atoms; free or etherified mercapto groups, for example, lower alkyl-mercapto groups, for example methylmercapto or ethylmercapto groups; trifluoromethyl groups; nitro groups, amino groups, preferably tertiary amino groups, for example di-lower alkylamino groups, for example dimethylamino or diethylamino groups; and acyl groups, for example, lower alkanoyl groups, for example acetyl or propionyl groups, as well as aryl groups, for example phenyl groups or aryl-lower alkyl groups, for example benzyl groups, which may optionally contain one or more of the above substituents.

A monocyclic monoheterocyclic group of aromatic character represented by Ar is a monocyclic radical of aromatic character which contains one hetero-atom, for example, a nitrogen, oxygen or sulphur atom, as a ring member and may be, for example, a pyridyl radical, for example, a 2-pyridyl, 3-pyridyl or 4-pyridyl radical, a furyl radical, for example, a 2-furyl radical, or a thienyl radical, for example, a 2-thienyl or 3-thienyl radical. A monocyclic monoheterocyclic group represented by

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Ar may optionally be substituted like the phenyl group, but is preferably substituted by one or more lower alkyl groups and/or one or more halogen atoms.

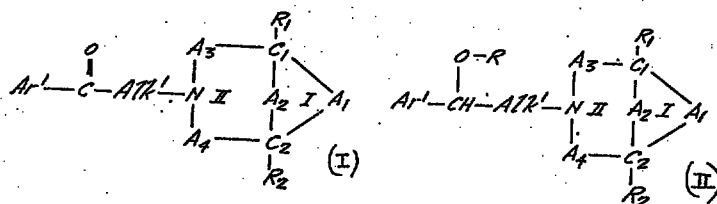
The group represented by X is preferably an oxo group. A hydroxyl group, which together with a hydrogen atom, or with a hydrocarbon radical, particularly an aliphatic, araliphatic or aromatic group, forms the group represented by X, is advantageously a free hydroxyl group; it may however also be an etherified hydroxyl group, for example a hydroxyl group etherified by a lower aliphatic hydrocarbon radical, for example, a lower alkyl or lower alkenyl group containing up to 7 carbon atoms, for example a methyl, ethyl, propyl, isopropyl or allyl group. The hydroxyl group may also be an esterified hydroxyl group, for example, a hydroxyl group esterified by an aminocarbonic, lower alkylaminocarbonic, di-lower alkylaminocarbonic or lower alkoxycarbonic acid, primarily by a lower alkanecarboxylic acid, for example, acetic acid or propionic acid. An aliphatic radical which together with the hydroxyl group forms the group represented by X is, for example, a lower alkyl radical containing up to 7 carbon atoms, whereas an araliphatic radical is preferably a phenyl-lower alkyl radical, for example, a benzyl or phenylethyl radical, and an aromatic radical is preferably a phenyl radical, in which the terms "lower alkyl" and "phenyl", for example, have the significance given above and may optionally be substituted as indicated above.

The radical represented by Alk is a lower alkylene radical containing at least 3, advantageously from 3 to 7, and preferably from 3 to 5, carbon atoms and separates the groups represented by $-C(=X)-$ and Het from one another by at least 3 carbon atoms. The radical represented by Alk may be, for example, a 1,3-propylene, 1-, 2- or 3-methyl-1,3-propylene, 2,2-, 1,2- or 1,3-dimethyl-1,3-propylene, 1,2,3-trimethyl-1,3-propylene, 1,4-butylen, 1-, 2-, or 3-methyl-1,4-butylen, 1,2-dimethyl-1,4-butylen, 1,5-pentylene, 1,6-hexylene or 1,7-heptylene radical.

A bicycloalkylene amino group represented by Het may be, for example, a 2-aza-2-bicyclo[2,2,1]heptyl, 7-aza-7-bicyclo[2,2,1]heptyl, 3-aza-3-bicyclo[3,3,0]octyl, 2-aza-2-bicyclo[2,2,2]octyl (or 2-isoquinuclidinyl), 2-aza-2-bicyclo[3,2,1]octyl, 3-aza-3-bicyclo[3,2,1]octyl (or 3-norcamphidinyl), 1,8,8-trimethyl-3-aza-3-bicyclo[3,2,1]octyl (or 3-camphidinyl), 6-aza-6-bicyclo[3,2,1]octyl, 8-aza-8-bicyclo[3,2,1]octyl (or 8-norhydrotropidinyl), 2-aza-2-bicyclo[4,3,0]nonyl, 7-aza-7-bicyclo[4,3,0]nonyl (or 4,5,6,7,8,9-hexahydro-indolinyl), 8-aza-8-bicyclo[4,3,0]nonyl (or 4,5,6,7,8,9-hexahydro-2-isoindolinyl), 3-aza-3-bicyclo[3,3,1]nonyl (or 3-isogranataninyl), 3-aza-3-bicyclo[3,2,2]nonyl, 2-aza-2-bicyclo[4,4,0]decyl (or 1,2,3,4,5,6,7,8,9,10-decahydro-1-quinolinyl), 3-aza-3-bicyclo[4,4,0]decyl (or 1,2,3,4,5,6,7,8,9,10-decahydro-2-isoquinolinyl), 3-methyl-2-aza-2-bicyclo[4,4,0]decyl, 10-aza-10-bicyclo[4,3,1]decyl (or 10-homogranataninyl), 8-aza-8-bicyclo[4,3,1]decyl, 2-aza-2-bicyclo[4,3,1]decyl, 4-aza-4-bicyclo[5,4,0]undecyl (or 2,3,4,5,6,7,8,9,10,11-decahydro-1H-3-benzazepinyl), 7-aza-bicyclo[4,3,0]nona-3-en-7-yl (or 4,7,8,9-tetrahydro-1-indolinyl), 8-aza-bicyclo[4,3,0]nona-3-en-8-yl (or 4,7,8,9-tetrahydro-2-isoindolinyl), 8-aza-bicyclo[4,3,0]non-6(10)-en-8-yl (or 4,5,6,7-tetrahydro-2-isoindolinyl), 3-aza-bicyclo[4,4,0]dec-6(11)-en-3-yl (or 1,2,3,4,5,6,7,8-octahydro-2-isoquinolinyl) or 9-aza-bicyclo[4,2,1]nona-2,4-dien-9-yl radical.

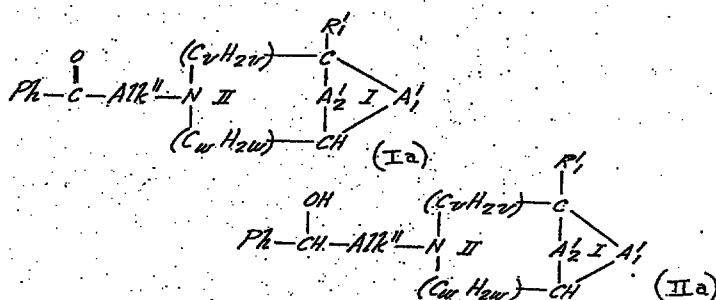
The compounds of the invention exhibit valuable pharmacological properties. In addition to adrenolytic and antihypertensive effects, they primarily show sedative, tranquillising and anti-aggressive properties, which can be demonstrated with experimental animals, for example, with mice, rats, cats, dogs and monkeys. In addition, they show anti-mescaline effects. The compounds of the invention are, therefore, useful as pharmacologically effective compounds, for example, as sedative-tranquillising, anti-aggressive agents; outstanding psychopharmacological effects are achievable with daily dosages of 0.025 g to 0.25 g. The compounds are furthermore also useful as intermediates in the manufacture of other valuable compounds, especially of pharmacologically active substances.

Compounds having particularly valuable pharmacological properties are those of formulae I and II



in which Ar' represents a phenyl, pyridyl or thienyl radical, any of which radicals may optionally be substituted by one or more substituents selected from lower alkyl, lower alkoxy, nitro and trifluoromethyl groups and halogen atoms, R denotes a hydrogen atom or a lower alkyl group and Alk' represents an alkylene group having 3 to 7 carbon atoms which separates the carbonyl or carbinol group from the nitrogen atom by 3 to 5 carbon atoms, and in which A₁ denotes an alkylene radical having 1 to 5 carbon atoms or an alkenylene radical having 2 to 5 carbon atoms which connects the C₁-carbon atom with the C₂-carbon atom, A₂ denotes a direct bond between the carbon atoms C₁ and C₂, or an alkylene radical having 1 to 3 carbon atoms, which separates the carbon atom C₁ from the carbon atom C₂ by 1 to 3 carbon atoms, each of the symbols A₃ and A₄ denotes a direct bond between the nitrogen atom and one of the bridge carbon atoms C₁ and C₂ respectively, or an alkylene radical having 1 to 4 carbon atoms which connects the nitrogen atom with the carbon atom C₁ or C₂ respectively, and each of the symbols R₁ and R₂ denotes a hydrogen atom or a lower alkyl radical, with the proviso that the azacyclic ring II contains at least 5 ring members if the carbocyclic ring I has 3 to 5 ring members, and with the further proviso that the bicycloalkylene group has 6 to 10 carbon atoms as ring members and bridge members, as well as their salts, especially their non-toxic, physiologically tolerable acid addition salts. In the above formulae, the carbon atoms of the alkylene radicals represented by A₁, A₂, A₃ and A₄ may form linear or branched carbon chains, and R₁ and R₂ preferably denote a hydrogen atom but may also represent a lower alkyl, especially methyl, as well as ethyl, *n*-propyl or isopropyl, group.

A preferred group of compounds according to the invention consists of compounds of general formulae Ia and IIa

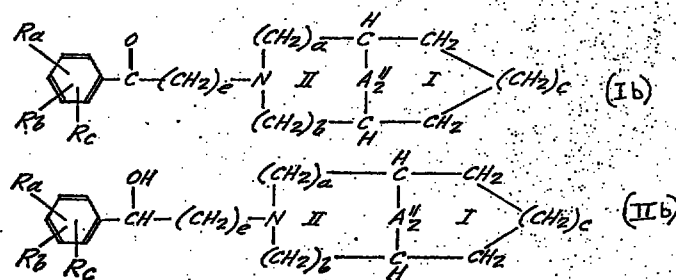


in which Ph denotes a phenyl radical optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, nitro and trifluoromethyl groups and halogen atoms, Alk'' represents an alkylene radical having 3-5 carbon atoms which separates the carbonyl or carbinol group from the nitrogen atom by at least 3 carbon atoms,

A₂' represents a radical of the formula (R₃-C-R₄)_d in which the letter d represents

0, 1 or 2, each of the symbols R₁', R₃ and R₄ represents a hydrogen atom or a methyl group, A₁' denotes a 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,2-ethenylene, 1,3-propenylenylene, 1,4-but-2-enylene or 1,4-but-1,3-dienylene radical, and each of the letters v and w denotes a number from 0 to 3, with the proviso that both the carbocyclic ring I and the azacyclic ring II have at least 5 ring members, and with the further proviso that the two rings together have 6 to 10 carbon atoms as ring and bridge members, as well as their salts, especially their non-toxic, physiologically tolerable acid addition salts.

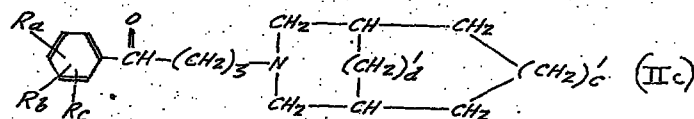
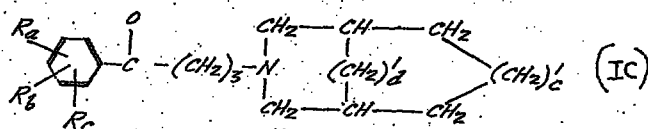
Especially outstanding sedative-tranquillising and anti-aggressive properties are shown by the compounds of the formulae Ib and IIb



in which each of the symbols R_a , R_b and R_c denotes a hydrogen atom, a lower alkyl group, preferably a methyl group, a lower alkoxy group, preferably a methoxy group, a trifluoromethyl group or a halogen atom, preferably a fluorine, chlorine or bromine

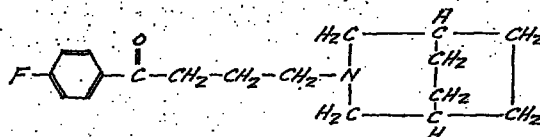
atom, and in which A_2'' represents a group of the formula $(CH_2)_d$, each of the

letters a, c and d represents a whole number from 0 to 2, the letter b stands for a whole number from 1 to 3 and the letter e represents a whole number from 3 to 5, with the proviso that each of the rings I and II has at least 5 ring members and that rings I and II together have 6 to 10 carbon atoms as ring and bridge members, primarily compounds of the formulae Ic and IIc



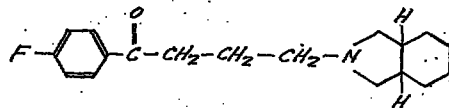
wherein R_a , R_b and R_c have the above given meaning, one or both of R_b and R_c preferably representing a hydrogen atom, and R_a preferably representing a halogen atom, especially a fluorine atom, and being located above all in the 4-position, and in which one of the letters c' and d' represents 0 and the other 2, as well as their salts, especially their non-toxic physiologically tolerable acid addition salts.

Especially outstanding sedative-tranquillizing, anti-aggressive properties are shown by 3-[4-(4-fluoro-phenyl)-4-oxo-1-n-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula



in the free form or in the form of its salts, for example, the acid addition salts, for example, the non-toxic, physiologically tolerable acid addition salts, e.g. the hydrochloride or the maleate. These compounds show excellent pharmacological activities at daily doses of 0.005 g/kg to 0.025 g/kg.

Outstanding sedative-tranquillizing and anti-aggressive effects are also shown by 2-[4-(4-fluoro-phenyl)-4-oxo-1-n-butyl]-4,5,6,7,8,9-cis-hexahydro-2-isoindoline of the formula

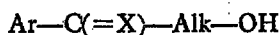


and salts thereof, especially the non-toxic, physiologically tolerable acid addition salts when administered at daily dosages of 0.025 g/kg to 0.15 g/kg.

The compounds of the present invention may be obtained by methods which are known *per se*. They may be obtained, for example, either by a) reacting a reactive ester of a compound of formula $Ar-C(=X)-Alk-OH$ with a compound of formula $H-Het$, Ar , X , Alk and Het having the above meanings or b) reacting together compounds of the formula $Ar-Y$ and $Z-Alk-Het$, in which Ar , Alk and Het have their above meanings, one of the letters Y and Z represents a positively charged metallic ion and the other represents a functionally converted carboxyl group capable of reacting with the organometallic reagent, and, where desired, converting in a resulting compound with a carbonyl group represented by $-C(=X)-$ the latter into a carbinol

group represented by $-C(=X)-$, and/or, where desired, converting in a resulting compound with a carbinol group $-C(=X)-$ the latter into a carbonyl group $-C(=O)-$ or an O-substituted carbinol group $-C(=X)-$.

Advantageously, the reactive ester of a compound of the formula



is an ester of an inorganic acid, especially a hydrogen halic acid, for example hydrochloric acid, hydrobromic acid or hydriodic acid, or sulphuric acid, or of a strong organic acid, especially a strong organic sulphonic acid, for example methanesulphonic, ethanesulphonic, *p*-toluenesulphonic, *p*-bromobenzenesulphonic, *p*- or *m*-nitrobenzenesulphonic acid. The reaction of such a reactive ester with an amine compound, for example, with an amine of formula $H-Het$ may be carried out in a manner which is in itself known, if desired, using an excess of the amine compound or working in the presence of an additional base for binding the acid liberated by the reaction or with the formation of a salt, for example, an alkali metal compound, for example a sodium compound, of the amino compound which may also take place *in situ*.

Reactive derivatives of acids which are suitable for reaction with organometallic reagents are primarily acid halides, for example chlorides or the corresponding nitriles, as well as the amides. Nitriles, that is to say compounds of formulae $N\equiv C-Alk-Het$ or $Ar-C\equiv N$, as well as the corresponding amides, are preferably converted to the desired ketones by treatment with magnesium Grignard derivatives, that is to say with compounds of formulae $Ar^{\ominus}MgHal$ or $HalMg^{\oplus}Alk-Het$ respectively, in which Hal represents a halogen atom, for example, a chlorine, bromine or iodine atom. Acid halides, that is to say compounds of formula $Hal-(=O)C-Alk-Het$ or $Ar-C(=O)-Hal$, can be reacted with the above magnesium Grignard reagents, as well as with the corresponding zinc Grignard compounds, but preferably with organocadmium compounds, for example, of the formula $[Ar]_2Cd$, to form the ketones. Furthermore, lithium salts, as reactive derivatives of acids, may also be reacted with lithium derivatives as the organometallic reagent to furnish the desired ketones.

The conversion of an oxo group represented by X to a hydroxyl group may be carried out in the usual manner. The oxo group is preferably reduced, for example, by treatment with nascent hydrogen, for example with a metal in the presence of a hydrogen-releasing material, for example, with sodium in an alcohol, or with a complex metal hydride, for example, sodium borohydride, or with catalytically activated hydrogen in the presence of a hydrogenation catalyst, for example, a platinum, palladium, rhodium, nickel or copper catalyst, for example, platinum oxide, palladium black, Raney nickel, copper chromite or rhodium on a carrier, which may be, for example, aluminium oxide or charcoal. The reduction is preferably carried out in the presence of diluents and/or solvents, and may be carried out at low, ordinary or elevated temperatures; in an open vessel or in a closed vessel under pressure. The reduction of the oxo group may also be carried out by the Meerwein-Ponndorf-Verley method, for example, in the usual manner by treatment with a lower alkanol, such as isopropanol, in the presence of a corresponding alcoholate, for example aluminium isopropylate.

The reduction of an oxo group represented by X may also be carried out with simultaneous introduction of a hydrocarbon radical, for example an aliphatic araliphatic or aromatic radical, for example, by treating a compound in which $-C(=X)-$ represents a carbonyl group, with an organometallic reagent which is suitable for the introduction of a hydrocarbon radical, for example, with a reagent analogous to the abovementioned organometallic compounds, especially with an appropriate magnesium halide Grignard reagent.

In the compounds obtained, a hydroxyl group represented by X may, if desired, be converted to an oxo group in a known manner, by treatment with a suitable oxidising agent, for example a chromium-VI compound. Furthermore, free hydroxyl groups may in the usual manner be converted into substituted, for example, etherified or esterified, hydroxyl groups. Etherification may, for example, be carried out by treatment with a diazo compound, for example a diazoalkane, for example, diazomethane or diazoethane, preferably in the presence of a suitable Lewis acid, for example fluoboric acid, aluminium chloride, boron trifluoride-etherate or an aluminium lower alkanolate. However, it is also possible to produce a metal salt and react this with a reactive ester of an alcohol, or alternatively the hydroxyl group can be converted into a reactive ester by, for example, replacing it by a halogen atom or converting it to a sulphonyloxy group, and the reactive ester may then be treated with

an alcohol, preferably in the form of a metal salt. Esterification is preferably carried out by treatment with acid halides, acid anhydrides or ketenes, optionally in the presence of condensation agents and/or bases for binding the acid which may be produced.

The reactions of the process may be carried out in the usual manner, at ordinary, lowered or raised temperature, in an open or closed vessel, optionally under pressure, in the presence or absence of diluents and/or catalysts and/or condensation agents, and/or in an inert gas atmosphere, for example, in an atmosphere of nitrogen.

Depending on the reaction conditions the compounds of the invention may be obtained in the free form or in the form of their acid addition salts, especially physiologically tolerable acid addition salts, for example those with inorganic acids, for example, hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid or phosphoric acids, or with organic acids, for example organic carboxylic acids, for example, acetic acid, propionic acid, glycolic acid, malonic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid, or isonicotinic acid, or of organic sulphonic acids, for example, methanesulphonic acid, ethanesulphonic acid, 2-hydroxy-ethanesulphonic acid, ethane-1,2-disulphonic acid, benzenesulphonic acid, *p*-toluenesulphonic acid or naphthalene-2-sulphonic acid. These acid addition salts may furthermore be used as intermediates, for example, for purifying the free compound or in the manufacture of other acid addition salts, and also for identification purposes. Acid addition salts which are especially suitable for identification purposes are, for example, those with picric, picrolonic, flavianic, phosphoric, tungstic, phosphomolybdic, chloroplatinic or perchloric acids.

The acid addition salts obtained may be converted to the free bases by known methods, for example by treatment with a base, for example a metal hydroxide, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide, with a metal carbonate, for example, sodium, potassium or calcium carbonate or bicarbonate, or with ammonia, as well as with a suitable anion exchange preparation.

Resulting acid addition salts may be converted to other acid addition salts by known methods, for example, by treatment with an anion exchange preparation or by treating a salt of an inorganic acid with a suitable metal salt, for example a sodium, barium or silver salt, of an acid, in a suitable solvent in which the resulting salt is insoluble and, therefore, precipitates from the reaction mixture.

Free bases obtained may be converted to their acid addition salts by known methods, for example, by reaction with acids, for example the acids quoted above, for example, by treating a solution of a base in a suitable inert solvent or solvent mixture with an acid or with a solution of an acid, or with a suitable anion exchange preparation.

The compounds, including their acid addition salts, may also be obtained in the form of their hydrates or may include solvent used for the crystallisation.

Because of the close relationship between the compounds of the invention in the free form and in the form of their acid addition salts, a reference in this Specification to the free compounds or to their acid addition salts is to be understood, where appropriate, as including a reference to the acid addition salts or the free compounds, respectively.

Resulting isomer mixtures may in a manner which is in itself known be separated into the individual isomers. Racemates may be resolved into the optically active *d*- and *l*-forms, for example, by crystallisation from optically active solvents or by treating the racemic compound, preferably in the presence of a suitable solvent, with an optically active acid and isolating the diastereoisomeric salts. The optically active forms of tartaric, malic, mandelic, camphor-10-sulphonic or quinic acid are suitable for this purpose. The resulting diastereoisomeric salts may be converted into other salts or into the free and optically active bases, and an optically active base may be converted to an acid addition salt by the methods described above.

In the process of the present invention those starting substances are preferably used as lead to the compounds described above as being especially valuable.

The starting substances are known or are obtained in a manner which is known *per se*. Compounds of formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{NH}_2$ are, for example, obtained from the corresponding reactive esters of compounds of formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{OH}$, whereas the nitrile compounds of formula $\text{N}\equiv\text{C}-\text{Alk}-\text{Het}$ (variant b) may be formed from compounds of formula $\text{H}-\text{Het}$ (variant a), for example, by treat-

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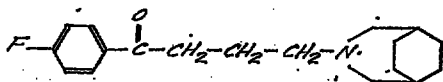
ment with a halogenalkanonitrile of formula $N\equiv C-Alk-Hal$, preferably in the presence of a base, for example, an alkali metal carbonate. The organometallic reagents are produced in a manner which is known *per se*, preferably in the presence of suitable solvents, for example ether, tetrahydrofuran, benzene and similar solvents, where necessary using reagents which initiate and/or assist the reaction.

The compounds of the present invention may be used as medicaments, for example, in the form of pharmaceutical preparations which contain these compounds in admixture or conjunction with a pharmaceutically suitable organic or inorganic solid or liquid carrier and which are suitable for enteral, for example, oral, or parenteral administration. These preparations may, for example, be in the form of tablets, dragées, capsules or in liquid form as solutions, suspensions or emulsions. They may contain adjuvants, for example preservatives, stabilisers, wetting agents or emulsifiers, salts for controlling the osmotic pressure, buffers, dyestuffs or flavouring substances. They may also contain other therapeutically valuable substances and are formulated by known methods. Compounds of the present invention may also be administered to animals in veterinary medicine in the form of suitable preparations together with a carrier suitable for veterinary use or in raising domestic animals in the form of animal fodders or animal fodder additives in admixture or conjunction with a suitable animal fodder carrier.

The following Examples illustrate the invention. Temperatures are given in degrees Centigrade.

EXAMPLE 1

A mixture of 20 g of 3-aza-bicyclo[3,2,2]nonane, 50.4 g of sodium carbonate and a few crystals of potassium iodide in 140 ml of dry toluene is treated with 44.8 g of γ -chloro-*p*-fluorobutyrophenone; the reaction mixture is boiled under reflux for 48 hours. After cooling to room temperature, 400 ml of distilled water are added, the reaction mixture is stirred for 15 minutes, the layers are separated and the toluene solution is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue is dissolved in 20 ml of isopropanol and adjusted to pH 2 by adding a solution of dry hydrogen chloride gas in isopropanol. Upon addition of 50 ml of dry ether, a crystalline solid material precipitates which, after recrystallisation from a mixture of isopropanol and ether, yields the hydrochloride of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of formula



which melts at 189—190°. The free base is obtained by adding a 1N aqueous sodium hydroxide solution to the aqueous solution of the salt, followed by extraction with toluene.

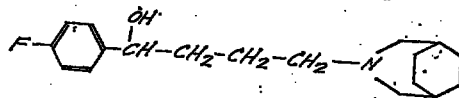
EXAMPLE 2

A solution of 7.6 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 75 ml of dry ether is added dropwise with stirring, within 30 minutes, to a solution of 4-fluorophenyl magnesium bromide (produced from 14 g 4-fluorobromobenzene and 1.92 g of magnesium) in 40 ml of dry ether. The reaction mixture is boiled under reflux for 4 hours and allowed to stand over night with exclusion of moisture. The reaction mixture is cooled to 0° and the Grignard complex is decomposed by adding dropwise 50 ml of a saturated aqueous ammonium chloride solution. The resulting suspension is filtered, the filtrate extracted with 2N aqueous sulfuric acid and the acid extract rendered basic by means of a 2N aqueous sodium hydroxide solution. The liberated base is extracted with ether; the ether extract is washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue is dissolved in dry ether and treated with a solution of dry hydrogen chloride in isopropanol. The crystalline precipitate is filtered off and recrystallised from a mixture of methanol and isopropanol to afford the hydrochloride of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, which melts at 188—189° and is identical with the compound described in Example 1.

EXAMPLE 3

A solution of 3 g of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride in 30 ml of aqueous methanol is added dropwise to a solution of 0.3 g of sodium borohydride in 20 ml of 50% aqueous methanol. The reaction

mixture is stirred for 15 minutes at room temperature and 5 hours at 70°. After cooling to room temperature, a crystalline precipitate forms, and this is filtered off and recrystallised from a mixture of isopropanol and water. One thus obtained 3-[4-(4-fluorophenyl)-4-hydroxy-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of formula



which melts at 75°.

EXAMPLE 4

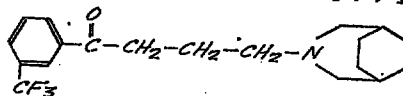
A solution of 2.2 g of 3-[4-(4-fluorophenyl)-4-hydroxy-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane in a mixture of 2 ml of isopropanol and 20 ml of dry ether is adjusted to pH 2 by adding a solution of dry hydrogen chloride gas in ethyl acetate. On cooling, a crystalline precipitate forms, which is filtered off and recrystallised from a mixture of methanol, isopropanol and ether. The 3-[4-(4-fluorophenyl)-4-hydroxy-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride so obtained melts at 216—217°.

EXAMPLE 5

A solution of 16 g of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane in 250 ml of dry ether is added dropwise to a suspension of 4 g of lithium aluminium hydride in 50 ml of dry ether; the addition is complete within 2 hours. The reaction mixture is boiled under reflux for 6 hours and allowed to stand overnight at room temperature. The excess of the hydride reagent is decomposed by successive addition of 8 ml of ethyl acetate, 8 ml of a 10% aqueous sodium hydroxide solution and 12 ml of water at 0°. The mixture obtained is filtered the filtrate is dried and evaporated to dryness, and the residue is dissolved in a 1:2 mixture of benzene and hexane, filtered through a column containing 200 g of aluminium oxide, and the filtrate evaporated to dryness. The residue is dissolved in a mixture of isopropanol and ether and the solution adjusted to pH 2 by addition of a solution of dry hydrogen chloride in isopropanol. On cooling a precipitate forms, and this is filtered off and recrystallised from a mixture of methanol, isopropanol and ether. One thus obtains 3-[4-(4-fluorophenyl)-4-hydroxy-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride, which melts at 216—217°.

EXAMPLE 6

A solution of 4 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 100 ml of dry ether is added dropwise with stirring, over the course of 30 minutes, to a solution of 3-trifluoromethylphenyl magnesium bromide (obtained from 11.6 g of 3-trifluoromethyl-bromobenzene and 1.6 of magnesium) in 40 ml of dry ether. The reaction mixture is boiled under reflux for 4 hours and allowed to stand overnight under anhydrous conditions. The reaction mixture is cooled to 0° and the Grignard complex is decomposed by adding dropwise 50 ml of a saturated aqueous ammonium chloride solution. The resulting suspension is filtered, the filtrate extracted with 2N aqueous sulphuric acid, and the acid extract rendered basic by means of a 2N aqueous caustic soda solution. The liberated base is extracted with ether; the ether extract is washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue is dissolved in dry ether and treated with a solution of dry hydrogen chloride in isopropanol. The crystalline precipitate is filtered off and recrystallised from a mixture of methanol and isopropanol. One thus obtains the hydrochloride of 3-[4-(3-trifluoromethylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of formula



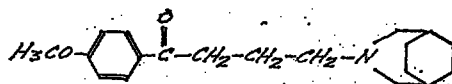
which melts at 210°. The base is obtained by adding a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt and extracting the free compound. The starting material is produced as follows:

12.36 g of γ -chlorobutyronitrile are added to a mixture of 10 g of 3-aza-bicyclo[3,2,2]nonane, 25.2 g of sodium carbonate and a few crystals of potassium iodide in 700 ml of dry toluene; the reaction mixture is boiled under reflux for 48 hours. After cooling to room temperature, 200 ml of distilled water are added; after 15 minutes stirring the layers are separated and the toluene solution is dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue is dis-

solved in ether, the solution adjusted to pH 2 by adding dry hydrogen chloride in isopropanol, and the resulting crystalline precipitate filtered off and recrystallised from a mixture of methanol and isopropanol. The 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane hydrochloride so obtained melts at 260°.

EXAMPLE 7

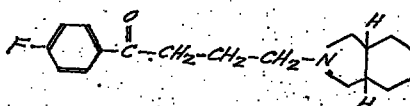
15 g of γ -chloro-*p*-methoxybutyrophenone are added to a mixture of 6 g of 3-aza-bicyclo[3,2,2]nonane, 16 g of sodium carbonate and a few crystals of potassium iodide in 400 ml of dry toluene; the reaction mixture is boiled under reflux for 48 hours. After cooling to room temperature, 200 ml of water are added and after 15 minutes stirring, the layers are separated and the toluene solution dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue is dissolved in 10 ml of isopropanol and the solution adjusted to pH 2 by adding dry hydrogen chloride in isopropanol. On adding 50 ml of dry ether a crystalline solid material separates out and this is recrystallised from a mixture of isopropanol and ether. One thus obtains the hydrochloride of 3-[4-(4-methoxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of formula



which melts at 188°. The base is obtained by adding a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt and extracting the liberated base.

EXAMPLE 8

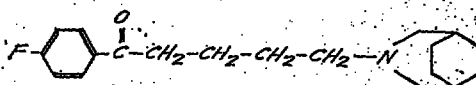
7.4 g of γ -chloro-*p*-fluorobutyrophenone is added to a mixture of 2.2 g of cis-4,5,6,7,8,9-hexahydro-isoindoline, 8 g of sodium carbonate and potassium iodide (a few crystals) in 200 ml dry toluene. The reaction mixture is boiled under reflux for 48 hours. On cooling to room temperature, 50 ml of distilled water is added and the reaction mixture is stirred for 15 minutes. The aqueous layer is separated and the toluene solution is dried over anhydrous sodium sulphate. Toluene is distilled off in vacuo and the residue is dissolved in 20 ml of isopropanol and treated with a solution of dry hydrogen chloride in isopropanol to pH 2. On addition of 100 ml of dry ether, a crystalline solid separates. This is recrystallised from a mixture of isopropanol and ether to afford the hydrochloride of cis-2-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-4,5,6,7,8,9-hexahydro-isoindoline of the formula



which melts as the hemihydrate at 158—159°. The base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 9

A solution of 10.3 g of 3-(4-cyanobutyl)-3-aza-bicyclo[3,2,2]nonane in 150 ml dry ether is added dropwise under stirring during 30 minutes to a solution of 4-fluorophenyl magnesium bromide (prepared from 2.4 g of magnesium and 17.5 g of 4-fluorobromobenzene) in 35 ml of dry ether, boiled under reflux for 6 hours and allowed to stand overnight under anhydrous conditions. The reaction mixture is cooled to 0° and the Grignard complex is decomposed by the dropwise addition of 60 ml of a saturated solution of ammonium chloride and worked up in the manner described under example 6 to yield the hydrochloride of 3-[5-(4-fluorophenyl)-5-oxo-1-*n*-pentyl]-3-aza-bicyclo[3,2,2]nonane of the formula



which melts as the dihydrate at 85—86° after recrystallisation from a mixture of isopropanol, ether and hexane. The base is prepared by addition of a 1N aqueous sodium

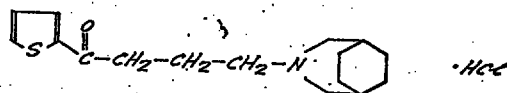
hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

The starting material is prepared as follows:

30.5 g of δ -bromovaleronitrile is added to a mixture of 15.6 g of 3-aza-bicyclo[3,2,2]nonane, 39 g of sodium carbonate and a few crystals of potassium iodide in 100 ml of dry toluene; the reaction mixture is boiled under reflux for 45 hours. On cooling to room temperature, 300 ml of distilled water is added and the reaction mixture is stirred for 15 minutes. The aqueous layer is separated and the toluene solution is dried over anhydrous sodium sulphate. Toluene is distilled off under reduced pressure, the residue is dissolved in ether and treated with a solution of dry hydrogen chloride in isopropanol to pH 2. The crystalline precipitate formed is filtered off and recrystallised from a mixture of methanol and isopropanol to afford 3-(4-cyanobutyl)-3-aza-bicyclo[3,2,2]nonane hydrochloride which melts at 278–279° (dec.).

EXAMPLE 10

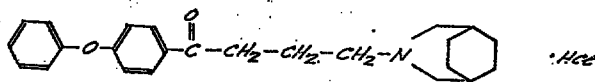
A solution of 10 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 80 ml of dry benzene is added dropwise under stirring during 30 minutes to a solution of 2-thienylmagnesium bromide (prepared from 3.6 g of magnesium and 24.3 g of 2-bromo-thiophene) in 80 ml of dry ether, boiled under reflux for 20 hours and cooled to room temperature. The reaction mixture is further cooled to 0° and the Grignard complex is decomposed by dropwise addition of 60 ml of a saturated aqueous solution of ammonium chloride and worked up in the manner described under Example 6, to afford the 3-[4-oxo-4-(2-thienyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride of the formula



which melts at 220–222° after recrystallisation from a mixture of methanol and isopropanol. The base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 11

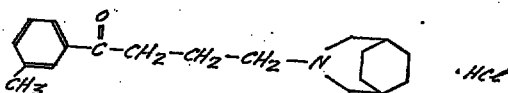
A solution of 9.6 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 80 ml of dry benzene is added dropwise under stirring during 30 minutes to a solution of 4-phenoxyphenyl magnesium bromide (prepared from 3 g of magnesium and 31.2 g of 4-bromo-diphenyl ether) in 60 ml of dry ether, boiled under reflux for 20 hours and cooled to 0°. The Grignard complex is decomposed by the dropwise addition of 60 ml of a saturated solution of ammonium chloride and worked up in the manner described under example 6, to afford 3-[4-oxo-4-(4-phenoxy-phenyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride of the formula



which melts at 237–238° after recrystallisation from a mixture of methanol and isopropanol. The base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 12

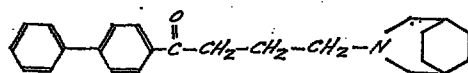
A solution of 9.8 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 80 ml dry benzene is added dropwise while stirring during 30 minutes to a solution of 3-methylphenyl magnesium bromide (prepared from 3 g of magnesium and 21.5 g of 3-bromotoluene) in 30 ml of dry ether, boiled under reflux for 20 hours under anhydrous condition. The reaction mixture is cooled to 0° and the Grignard complex is decomposed by the dropwise addition of 60 ml of saturated ammonium chloride and worked up in the manner described under example 6, to afford 3-[4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride of the formula



which melts at 183—185° after recrystallization from a mixture of methanol and ether. The base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 13

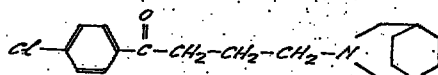
A solution of 9.8 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 75 ml of dry benzene is added dropwise while stirring during 30 minutes to a solution of 4-biphenyl magnesium bromide (prepared from 3 g of magnesium and 29.1 g of 4-bromobiphenyl) in 60 ml of dry ether, boiled under reflux for 1 hour and stirred at room temperature for 20 hours. The reaction mixture is cooled to 0°, the Grignard complex is decomposed by dropwise addition of 60 ml of a saturated aqueous solution of ammonium chloride and worked up in the manner described under example 6, to yield the hydrochloride of 3-[4-(4-biphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula



which melts at 263—265° after recrystallisation from a mixture of methanol and isopropanol. The free base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 14

A mixture of 10 g of 3-aza-bicyclo[3,2,2]nonane, 26.5 g of anhydrous sodium carbonate and a few crystals of potassium iodide in 700 ml of dry toluene is treated with 26 g of *p*,*γ*-dichlorobutyrophenone; the reaction mixture is boiled under reflux for 48 hours, then cooled to room temperature and diluted with 400 ml of water. After stirring for 15 minutes, the layers are separated and the organic solution is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue is dissolved in 25 ml of isopropanol, the solution adjusted to pH 2 by adding dry hydrogen chloride in isopropanol and on adding 150 ml of dry ether, a crystalline solid material separates out which is recrystallised from a mixture of isopropanol and ether. One thus obtains the hydrochloride of 3-[4-(4-chlorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula

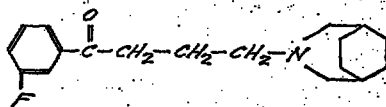


which melts at 242°. The base is obtained by adding a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt and extracting the liberated base.

3-[4-oxo-4-(4-tert-butylphenyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 244—245° after recrystallisation from methanol, is obtained by the method described in the above example by selecting the appropriate starting materials.

EXAMPLE 15

A solution of 9.6 g of 3-(3-cyanopropyl)-3-aza-bicyclo[3,2,2]nonane in 60 ml of dry benzene is added dropwise while stirring during 30 minutes to a solution of 3-fluorophenyl magnesium bromide (prepared from 3 g of magnesium and 22.5 g of 3-fluorobromobenzene) in 30 ml of ether, boiled under reflux for 20 hours and cooled to 0°. The Grignard complex is decomposed in the manner described under example 13 and the reaction mixture is worked up as described under example 6; upon treatment of the resulting free compound with maleic acid (instead of the hydrogen chloride), the maleate of 3-[4-(3-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula



is obtained, which melts at 139—140° after recrystallisation from a mixture of methanol, isopropanol and ether. The free base is prepared by addition of a 1N

aqueous sodium hydroxide solution to the aqueous solution of the above salt followed by extraction with ether.

The following compounds may be obtained by the method illustrated by choosing the appropriate starting materials:

3-[4-Oxo-4-(3-thienyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 228° after recrystallisation from a mixture of methanol, isopropanol and ether;

3-[4-(4-isopropylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 243° after recrystallisation from a mixture of methanol, isopropanol and ether;

3-[4-(4-bromo-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 267—268° after recrystallisation from methanol;

3-[4-(3,4-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 247—248° after recrystallisation from a mixture of methanol, isopropanol and ether;

3-[4-(2,4-dimethoxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 182—183° after recrystallisation from a mixture of methanol, isopropanol and ether;

3-(4-oxo-4-phenyl-1-*n*-butyl)-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 230—232° after recrystallisation from methanol;

3-[4-(4-methylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 225—226° after recrystallisation from a mixture of methanol, isopropanol and ether;

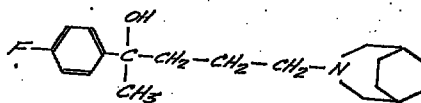
3-[4-(2,5-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 203—204° after recrystallisation from a mixture of methanol, isopropanol and ether;

3-[4-(4-hydroxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 312—313° (with decomposition) after recrystallisation from a mixture of methanol and ether; and

3-[4-(2,4-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, the hydrochloride of which melts at 203—204° after recrystallisation from a mixture of methanol, isopropanol and ether.

EXAMPLE 16

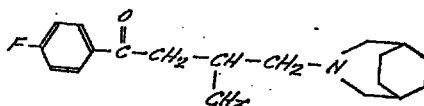
A solution of 8.7 g of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane in 60 ml of dry benzene is added to a solution of methyl lithium (prepared from 0.52 g of lithium and 10.65 g of methyl iodide) in 30 ml ether. The reaction mixture is boiled under reflux for 18 hours and worked up in the manner described under Example 6; 3-[4-(4-fluorophenyl)-4-hydroxy-4-methyl-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula



is converted into its maleate, which melts at 123° after recrystallisation from a mixture of methanol, isopropanol and ether. The free base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

EXAMPLE 17

A solution of 10.3 g of 3-(3-cyano-2-methyl-1-propyl)-3-aza-bicyclo[3,2,2]nonane in 100 ml of dry benzene is added dropwise under stirring during 30 minutes to a solution of 4-fluorophenyl magnesium bromide (prepared from 3 g of magnesium and 22 g of 4-fluorobromobenzene) in 40 ml dry ether, boiled under reflux for 20 hours and cooled to 0°. The Grignard complex is decomposed in the manner described under example 13 and the reaction mixture is worked up as shown in example 6; the maleate of 3-[4-(4-fluorophenyl)-2-methyl-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane of the formula



The starting material used in the above procedure is prepared as follows:

A mixture of 18.75 g of 3-aza-bicyclo[3,2,2]nonane, 20 g of γ -chloro- β -methylbutyronitrile, 31.8 g of anhydrous sodium carbonate and a few crystals of potassium iodide in 1200 ml of dry toluene is boiled under reflux for 48 hours. On cooling to room temperature, the solution is diluted with 600 ml of water and stirred for 15 minutes. The two layers are separated and the toluene layer is dried over anhydrous sodium sulfate, and evaporated to dryness. The residue is taken up in 100 ml of ether and a solution of hydrogen chloride in isopropanol is added until pH 2 is reached. A crystalline precipitate is formed which is filtered off and recrystallised from a mixture of methanol, isopropanol and ether to yield the 3-(3-cyano-2-methyl-1-propyl)-3-aza-bicyclo[3,2,2]nonane hydrochloride which melts at 256° (with decomposition). The free base is obtained by treating an aqueous solution of the salt with a 1N aqueous sodium hydroxide solution and extracting the liberated base.

A solution of 6 g of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane in 15 ml of isopropanol is treated with dropwise addition of 1.5 of maleic acid in 60 ml of ether at room temperature. A white crystalline granular precipitate is formed, which is filtered off and crystallised from a mixture of methanol and isopropanol to yield the maleate of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane, which melts at 132°.

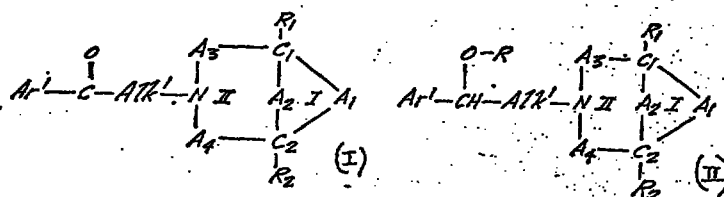
20 g of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride are thoroughly mixed with 130 g of corn starch. A paste of 30 g of corn starch and 100 g of distilled water is added to the above mixture and the product thoroughly kneaded, granulated and dried at 40°. A mixture of 14 g of talc and 6 g of magnesium stearate is added to the granules which are thoroughly mixed and then converted to tablets which contain either 0.01 g or 0.05 g of the active substance.

20 g of cis-2-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-4,5,6,7,8,9-hexahydro-isoin-doline hydrochloride and 130 g of corn starch are thoroughly mixed and treated with a paste of 30 g corn starch and 100 g of distilled water. The resulting product is well kneaded, granulated and dried at 45° and treated with 14 g of talcum and 6 g of magnesium stearate. After thoroughly mixing the granulate, it is worked up into tablets, each containing either 0.01 g or 0.05 g of the active ingredient.

1. A compound of the formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{Het}$, in which Ar represents a substituted or unsubstituted phenyl group or a substituted or unsubstituted monocyclic monoheterocyclic group of aromatic character, X denotes oxygen or a free or etherified or esterified hydroxyl group together with a hydrogen atom or a hydrocarbon radical, Alk denotes a lower alkylene radical which separates the groups represented by $-\text{C}(=\text{X})$ and Het by at least 3 carbon atoms and Het denotes a bicycloalkyleneamino group having 6 to 10 carbon atoms as ring or bridge members, which carbon atoms may be connected to one another by one or more double bonds or substituted by lower alkyl groups, and having only one ring nitrogen atom.

2. A compound of the formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{Het}$, wherein Ar, Alk and Het have the meaning given in claim 1, and X represents an oxygen atom or a free of etherified or esterified hydroxyl group together with a hydrogen atom, or an aliphatic, araliphatic or aromatic radical.

3. A compound of the formula I or formula II



in which Ar' represents a phenyl, pyridyl or thienyl radical any of which radicals



* C L M S *

1,195,729

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melts at 145—146° after recrystallisation from a mixture of methanol and ether. The free base is prepared by addition of a 1N aqueous sodium hydroxide solution to the aqueous solution of the above salt, followed by extraction with ether.

The starting material used in the above procedure is prepared as follows:

A mixture of 18.75 g of 3-aza-bicyclo[3,2,2]nonane, 20 g of γ -chloro- β -methylbutyronitrile, 31.8 g of anhydrous sodium carbonate and a few crystals of potassium iodide in 1200 ml of dry toluene is boiled under reflux for 48 hours. On cooling to room temperature, the solution is diluted with 600 ml of water and stirred for 15 minutes. The two layers are separated and the toluene layer is dried over anhydrous sodium sulfate, and evaporated to dryness. The residue is taken up in 100 ml of ether and a solution of hydrogen chloride in isopropanol is added until pH 2 is reached. A crystalline precipitate is formed which is filtered off and recrystallised from a mixture of methanol, isopropanol and ether to yield the 3-(3-cyano-2-methyl-1-propyl)-3-aza-bicyclo[3,2,2]nonane hydrochloride which melts at 256° (with decomposition). The free base is obtained by treating an aqueous solution of the salt with a 1N aqueous sodium hydroxide solution and extracting the liberated base.

EXAMPLE 18

A solution of 6 g of 3-[4-(4-fluorophenyl)-4-oxo-1-n-butyl]-3-aza-bicyclo[3,2,2]nonane in 15 ml of isopropanol is treated with dropwise addition of 1.5 of maleic acid in 60 ml of ether at room temperature. A white crystalline granular precipitate is formed, which is filtered off and crystallised from a mixture of methanol and isopropanol to yield the maleate of 3-[4-(4-fluorophenyl)-4-oxo-1-n-butyl]-3-aza-bicyclo[3,2,2]nonane, which melts at 132°.

EXAMPLE 19

20 g of 3-[4-(4-fluorophenyl)-4-oxo-1-n-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride are thoroughly mixed with 130 g of corn starch. A paste of 30 g of corn starch and 100 g of distilled water is added to the above mixture and the product thoroughly kneaded, granulated and dried at 40°. A mixture of 14 g of talc and 6 g of magnesium stearate is added to the granules which are thoroughly mixed and then converted to tablets which contain either 0.01 g or 0.05 g of the active substance.

EXAMPLE 20

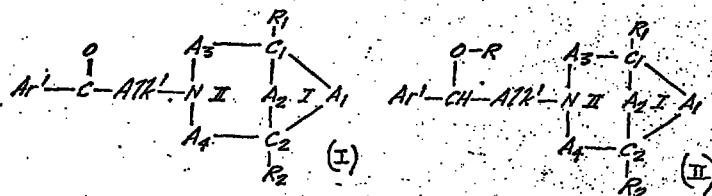
20 g of cis-2-[4-(4-fluorophenyl)-4-oxo-1-n-butyl]-4,5,6,7,8,9-hexahydro-isoin-doline hydrochloride and 130 g of corn starch are thoroughly mixed and treated with a paste of 30 g corn starch and 100 g of distilled water. The resulting product is well kneaded, granulated and dried at 45° and treated with 14 g of talcum and 6 g of magnesium stearate. After thoroughly mixing the granulate, it is worked up into tablets, each containing either 0.01 g or 0.05 g of the active ingredient.

WHAT WE CLAIM IS:—

1. A compound of the formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{Het}$, in which Ar represents a substituted or unsubstituted phenyl group or a substituted or unsubstituted monocyclic monoheterocyclic group of aromatic character, X denotes oxygen or a free or etherified or esterified hydroxyl group together with a hydrogen atom or a hydrocarbon radical, Alk denotes a lower alkylene radical which separates the groups represented by $-\text{C}(=\text{X})$ and Het by at least 3 carbon atoms and Het denotes a bicycloalkyleneamino group having 6 to 10 carbon atoms as ring or bridge members, which carbon atoms may be connected to one another by one or more double bonds or substituted by lower alkyl groups, and having only one ring nitrogen atom.

2. A compound of the formula $\text{Ar}-\text{C}(=\text{X})-\text{Alk}-\text{Het}$, wherein Ar, Alk and Het have the meaning given in claim 1, and X represents an oxygen atom or a free or etherified or esterified hydroxyl group together with a hydrogen atom, or an aliphatic, araliphatic or aromatic radical.

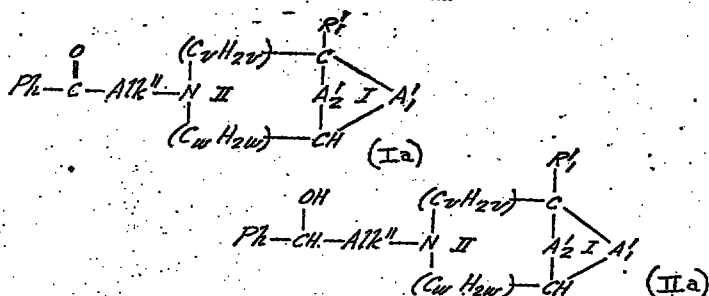
3. A compound of the formula I or formula II



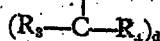
in which Ar' represents a phenyl, pyridyl or thienyl radical any of which radicals

may optionally be substituted by one or more substituents selected from lower alkyl, lower alkoxy, nitro and trifluoromethyl groups and halogen atoms, R denotes a hydrogen atom or a lower alkyl group, and Alk' represents an alkylene group having 3 to 7 carbon atoms which separates the carbonyl or carbinol group from the nitrogen atom by 3 to 5 carbon atoms, and in which A₁ denotes an alkylene radical having 1 to 5 carbon atoms or an alkenylene radical having 2 to 5 carbon atoms which connects the C₁-carbon atom with the C₂-carbon atom, A₂ denotes a direct bond between the carbon atoms C₁ and C₂, or an alkylene radical having 1 to 3 carbon atoms, which separates the carbon atom C₁ from the carbon atom C₂ by 1 to 3 carbon atoms, each of the symbols A₃ and A₄ denotes a direct bond between the nitrogen atom and one of the bridge carbon atoms C₁ and C₂ respectively, or an alkylene radical having 1 to 4 carbon atoms which connects the nitrogen atom with the carbon atom C₁ or C₂, and each of groups R₁ and R₂ denotes hydrogen or a lower alkyl radical, with the proviso that the azacyclic ring II contains at least 5 ring members if the carbocyclic ring I has 3 to 5 ring members, and with the further proviso that the bicycloalkylene group has 6 to 10 carbon atoms as ring members and bridge members.

4. A compound of the formula Ia or formula IIa

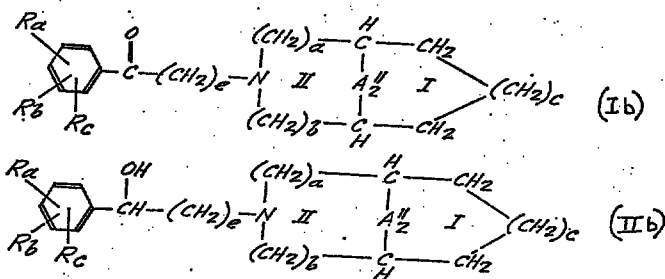


wherein Ph denotes a phenyl radical optionally substituted by one or more substituents selected from lower alkyl, lower alkoxy, nitro and trifluoromethyl groups and halogen atoms, Alk'' represents an alkylene radical having 3-5 carbon atoms which separates the carbonyl or carbinol group from the nitrogen atom by at least 3 carbon atoms, A₂' represents a radical of the formula



in which the letter d represents 0, 1 or 1, each of the symbols R₁', R₃ and R₄ represents a hydrogen atom or a methyl group, A₁' denotes a 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,2-ethenylene, 1,3-propenylene, 1,4-but-2-enylene or 1,4-but-1,3-dienylene radical, and each of the letters v and w denotes a number from 0 to 3, with the proviso that both the carbocyclic ring I and the azacyclic ring II have at least 5 ring members, and with the further proviso that the two rings together have 6 to 10 carbon atoms as ring and bridge members.

5. A compound of the formula Ib or formula IIb



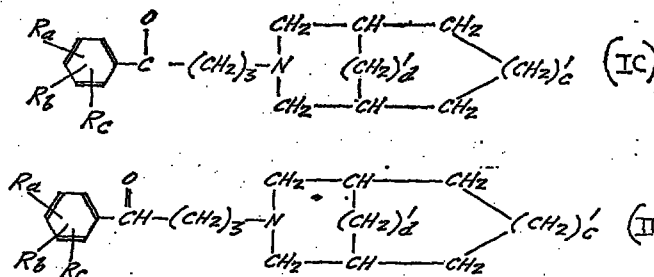
in which each of the symbols R_a, R_b and R_c represents a hydrogen atom, a lower alkyl, lower alkoxy or trifluoromethyl group or a halogen atom, and A₂' represents a group of the formula (CH₂)_d, each of the letters a, c and d represents 1 or 2, the letter b stands for a whole number from 1 to 3 and the letter e represents





6. A compound of the formula Ic or formula IIc

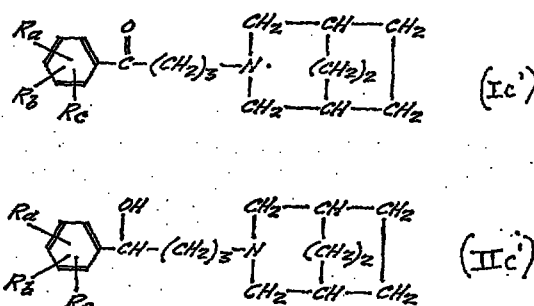
6. A compound of the formula Ic or formula IIc



7. A compound of the formula Ic or formula IIc as claimed in claim 6, wherein c' and d' have the meaning given in claim 6, R_a represents a halogen atom, and each of R_b and R_c represents a hydrogen atom.

8. A compound of the formula Ic of formula IIc as claimed in claim 6, wherein c' and d' have the meaning given in claim 6, R_a is a fluorine atom occupying the 4-position of the phenyl radical and each of R_b and R_c represents a hydrogen atom.

9. A compound of the formula Ic' or formula IIc'



wherein R_a , R_b and R_c have the meaning given in claim 5.

10. 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
11. 3-[4-(4-fluoro-phenyl)-4-hydroxy-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
12. 3-[4-(3-trifluoromethylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
13. 3-[4-(4-methoxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
14. 2-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-4,5,6,7,8,9-hexahydro-isindoline.
15. 3-[5-(4-fluoro-phenyl)-5-oxo-1-*n*-pentyl]-3-aza-bicyclo[3,2,2]nonane.
16. 3-[4-oxo-4-(2-thienyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
17. 3-[4-oxo-4-(4-phenoxyphenyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
18. 3-[4-(3-methylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
19. 3-[4-(4-biphenyl)-4-oxo-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
20. 3-[4-(4-chlorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
21. 3-[4-oxo-4-(4-tert.-butyl-phenyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
22. 3-[4-(3-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
23. 3-[4-oxo-4-(3-thienyl)-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
24. 3-[4-(4-isopropylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
25. 3-[4-(4-bromo-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
26. 3-[4-(3,4-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
27. 3-[(2,4-dimethoxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
28. 3-(4-oxo-4-phenyl-1-*n*-butyl)-3-aza-bicyclo[3,2,2]nonane.
29. 3-[4-(4-methylphenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
30. 3-[4-(2,5-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
31. 3-[4-(4-hydroxy-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.

32. 3-[4-(2,4-dimethyl-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
33. 3-[4-(4-fluorophenyl)-4-hydroxy-4-methyl-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
34. 3-[4-(4-fluorophenyl)-2-methyl-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
35. An acid addition salt of a compound as claimed in any one of claims 2, 9, 11—18.
36. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 2, 9, 11—18.
37. An acid addition salt of 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
38. A physiologically tolerable acid addition salt of 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane.
39. 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane hydrochloride.
40. 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane maleate.
41. An acid addition salt of a compound as claimed in any one of claims 1, 3, 4—8 and 19—34.
42. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 1, 3, 4—8 and 19—34.
43. A pharmaceutical preparation comprising a compound as claimed in any one of claims 2, 9, 11—18, and 36 in admixture or in conjunction with a pharmaceutically suitable carrier.
44. A pharmaceutical preparation comprising 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane or a physiologically tolerable acid addition salt thereof in admixture or in conjunction with a pharmaceutically suitable carrier.
45. A pharmaceutical preparation comprising a compound as claimed in any one of claims 1, 3, 4—8, 25—34, and 42 in admixture or in conjunction with a pharmaceutically suitable carrier.
46. A veterinary preparation comprising a compound claimed in any one of claims 2, 9, 11—18 and 36 in admixture or in conjunction with a carrier suitable for veterinary use.
47. A veterinary preparation comprising 3-[4-(4-fluorophenyl)-4-oxo-1-*n*-butyl]-3-aza-bicyclo[3,2,2]nonane or a physiologically tolerable acid addition salt thereof in admixture or in conjunction with a carrier suitable for veterinary use.
48. A veterinary preparation comprising a compound as claimed in any one of claims 1, 3, 4—8, 25—34, and 42 in admixture or in conjunction with a carrier suitable for veterinary use.
49. An animal feedstuff or animal feedstuff additive, comprising a compound as claimed in any one of claims 2, 9, 11—18, and 36 in admixture or in conjunction with an animal feedstuff carrier.
50. An animal feedstuff or animal feedstuff additive, comprising 3-[4-(4-fluoro-phenyl)-4-oxo-1-*n*-butyl]-3-aza bicyclo[3,2,2]nonane or a physiologically tolerable acid addition salt thereof in admixture or in conjunction with an animal feedstuff carrier.
51. An animal feedstuff or animal feedstuff additive, comprising a compound as claimed in any one of claims 1, 3, 4—8, 25—34 and 42 together with an animal feedstuff carrier.
52. A process for the manufacture of a compound as claimed in any one of claims 2, 9, 11—18, 35 and 36 as described hereinbefore.
53. A process for the manufacture of a compound as claimed in any one of claims 1, 3 4—8, 19—34, 41 and 42 as described hereinbefore.
54. A process for the manufacture of a compound as claimed in any one of claims 10, 37 and 38 as described hereinbefore.
55. A process for the manufacture of a compound as claimed in any one of claims 2, 9, 11—18, 35 and 36 conducted substantially as described in Examples 3—12 herein.
56. A process for the manufacture of a compound as claimed in any one of claims 1, 3, 4—8, 19—34, 41 and 42 conducted substantially as described in Examples 13—17 herein.
57. A process for the manufacture of a compound as claimed in any one of claims 10, 37 and 38 conducted substantially as described in Examples 1, 2 and 18 herein.
58. A compound as claimed in any one of claims 2, 9, 11—18, 35 and 36, whenever prepared according to a process as claimed in claim 52.



2]nonane.
bicyclo[3,2,
[3,2,2]nonane.
of claims 2, 9,
as claimed in
3-aza-bicyclo
phenyl)-4-oxo-
mane hydro-
ane maleate.
f claims 1, 3,
aimed in any
d in any one
maceutically
4-oxo-1-n-
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59. A compound as claimed in any one of claims 1, 3, 4—8, 19—34, 41 and 42, whenever prepared according to a process as claimed in claim 53.

60. A compound as claimed in any one of claims 10, 37 and 38, whenever prepared according to a process as claimed in claim 54.

61. A pharmaceutical preparation comprising a compound as claimed in claim 1, or a physiologically tolerable acid addition salt thereof, having a composition substantially as described in Example 19 or Example 20.

62. A pharmaceutical preparation as claimed in any one of claims 43 to 45, which contains, in dosage unit form, from 0.025 to 0.25 g of the active ingredient.

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