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IMIDAZODIAZEPINE DERIVATIVES

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(56) Prior Art Documents
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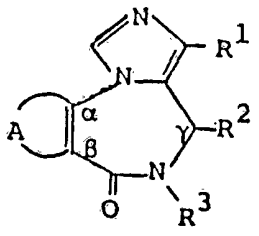
AU 71583/87 C07D 487/04
AU 21553/88 C07D 487/04

(57) Claim

1. Compounds of the general formula



I

wherein A together with the two carbon atoms denoted by α and β signifies one of the groups

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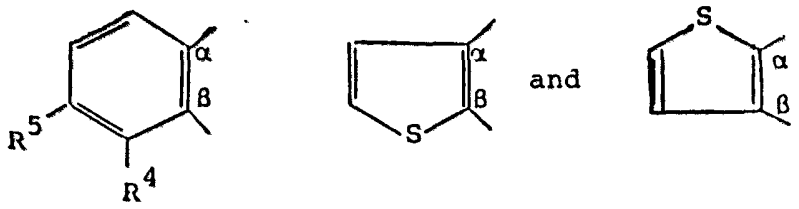

(a) (b) (c)

R^1 signifies one of the groups

$-CH=CH-R^6$ and $-C\equiv C-R^6$,

(d) (e)

R^2 signifies hydrogen and R^3 signifies lower alkyl or R^2 and R^3 together signify dimethylene or trimethylene, R^4 and R^5 each signify hydrogen, halogen, trifluoromethyl or lower alkyl and R^6 signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or di-substituted by hydroxy, lower alkoxy, (C_3-C_7)--cycloalkyl or oxo, whereby the compounds of formula I have the (S)- or (R,S)-configuration with reference to the carbon atom denoted by γ when R^2 and R^3 together signify dimethylene or trimethylene and whereby the double bond present in group (d) has the E- and/or Z-configuration when R^6 is different from hydrogen.

26. A method for treating convulsions, anxiety states, stress conditions, excitation states or sleep disorders and/or of partially or completely selectively antagonizing some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via central benzodiazepine receptors in a patient in need of said treatment, which method comprises administering to said patient an effective amount of a compound of any one of claims 1 to 16, 20 or 23 or a composition of claim 24 or claim 25.

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FORM 10

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PATENTS ACT 1952

COMPLETE SPECIFICATION

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Complete Specification for the invention entitled:

Imidazodiazepine Derivatives

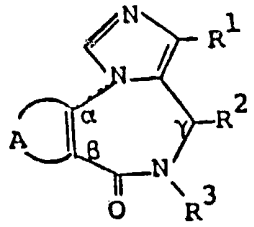
The following statement is a full description of this invention, including the best method of performing it known to me/us

5845/3

RAN 4008/339

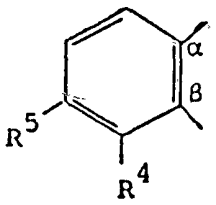
Abstract

The novel imidazodiazepine derivatives of the formula

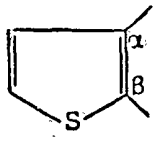


I

wherein A together with the two carbon atoms denoted by α and ß signifies one of the groups

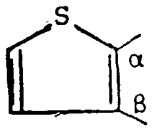


(a)



(b)

and



(c)

R^1 signifies one of the groups

$-CH=CH-R^6$ and $-C\equiv C-R^6$,

(d) (e)

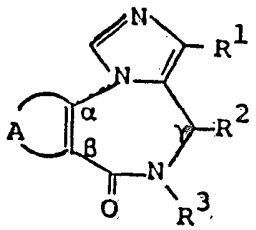
R^2 signifies hydrogen and R^3 signifies lower alkyl or R^2 and R^3 together signify dimethylene or trimethylene, R^4 and R^5 each signify hydrogen, halogen, trifluoromethyl or lower alkyl and R^6

signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or di-substituted by hydroxy, lower alkoxy, (C_3-C_7)--cycloalkyl or oxo, whereby the compounds of formula I have the (S)- or (R,S)-configuration with reference to the carbon atom denoted by γ when R^2 and R^3 together signify dimethylene or trimethylene and whereby the double bond present in group (d) has the E- and/or Z-configuration when R^6 is different from hydrogen,

possess valuable pharmacodynamic properties. They have as a common characteristic a pronounced affinity to the central benzodiazepine receptors and have either pronounced anxiolytic, anticonvulsant, muscle relaxant and sedative-hypnotic properties and/or they partially or completely selectively antagonize some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via the central benzodiazepine receptors.

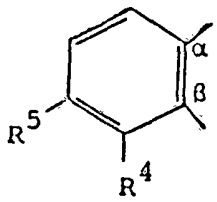
RAN 4008/339

The present invention is concerned with imidazodiazepine derivatives. In particular, it is concerned with imidazodiazepine derivatives of the general formula

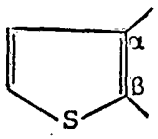


I

wherein A together with the two carbon atoms denoted by α and β signifies one of the groups

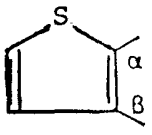


(a)



(b)

and



(c)

R^1 signifies one of the groups

$-CH=CH-R^6$ and $-C\equiv C-R^6$,

(d) (e)

R^2 signifies hydrogen and R^3 signifies lower alkyl or R^2 and R^3 together signify dimethylene or

trimethylene, R^4 and R^5 each signify hydrogen, halogen, trifluoromethyl or lower alkyl and R^6 signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or di-substituted by hydroxy, lower alkoxy, (C_3-C_7)--cycloalkyl or oxo, whereby the compounds of formula I have the (S)- or (R,S)-configuration with reference to the carbon atom denoted by γ when R^2 and R^3 together signify dimethylene or trimethylene and whereby the double bond present in group (d) has the E- and/or Z-configuration when R^6 is different from hydrogen.

These compounds are novel and are distinguished by valuable pharmacodynamic properties.

Objects of the present invention are the compounds of formula I above per se and as therapeutically active substances, a process and intermediates for their manufacture, medicaments containing a compound of formula I and a therapeutically inert carrier, the manufacture of such medicaments and the use of compounds of formula I in the control or prevention of illnesses (especially in the control or prevention of convulsions, anxiety states, stress conditions, excitation states and sleep disorders and/or in the partial or complete selective antagonism of some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via the central benzodiazepine receptors) or the use of compounds of formula I for the manufacture of medicaments, especially of medicaments for use in the just-mentioned indications.

The term "lower" is used to denote residues and compounds with up to 7, preferably up to 4, carbon atoms. The term "lower alkyl" denotes straight-chain or branched saturated hydrocarbon residues with a maximum of 7,

preferably a maximum of 4, carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl and the like. The term "lower alkoxy" denotes lower alkyl residues in the sense of the previous definition of the term "lower alkyl" which are attached via an oxygen atom. The term "aryl" denotes monocyclic aromatic hydrocarbon residues which can be substituted by lower alkyl, lower alkoxy, halogen etc. Unless indicated otherwise, the term "halogen" denotes the four halogens fluorine, chlorine, bromine and iodine.

The term "saturated hydrocarbon group" denotes open-chain and cyclic groups and combinations thereof. The open-chain groups can be straight-chain or branched. Examples of saturated lower hydrocarbon groups are: methyl, ethyl, i-propyl, t-butyl, 3-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, dicyclopropylmethyl and 1-cyclopropylethyl. Examples of saturated lower hydrocarbon residues which are mono- or disubstituted by hydroxy, lower alkoxy, (C_3-C_7)-cycloalkyl or oxo are: hydroxymethyl, methoxymethyl, dimethoxymethyl, 1-hydroxyethyl, 1-methoxyethyl, 1-hydroxypropyl, 2-hydroxy-2-propyl, 2-methoxy-2-propyl, 2-ethoxy-2-propyl, 3-hydroxy-3-pentyl, 1-hydroxy-1-cyclobutyl, 1-hydroxy-1-cyclopentyl, 1-methoxy-1-cyclopentyl, 1-oxoethyl and dicyclopropylhydroxymethyl.

When R^1 in formula I signifies a group of formula (d), then it stands, for example, for vinyl, 1-propenyl, 1-pentenyl or 2-chlorovinyl. However, R^1 in formula I preferably signifies a residue of formula (e). R^6 preferably signifies hydrogen, lower alkyl, lower hydroxyalkyl, lower alkoxyalkyl, (C_3-C_7)-cycloalkyl, hydroxy-(C_4-C_7)-cycloalkyl, lower alkoxy-(C_4-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-lower alkyl, (C_3-C_7)-cycloalkyl-lower hydroxyalkyl or (C_3-C_7)-cycloalkyl-lower alkoxyalkyl. In a particularly preferred embodiment

R^6 signifies hydrogen, lower alkyl, lower 1-hydroxyalkyl, lower 1-alkoxyalkyl, (C_3-C_7)-cycloalkyl, 1-hydroxy-(C_4-C_7)-cycloalkyl, 1-(lower alkoxy)-(C_4-C_7)-cycloalkyl or 1-[(C_3-C_7)-cycloalkyl]-lower 1-hydroxyalkyl, especially lower alkyl, lower 1-hydroxyalkyl or (C_3-C_7)-cycloalkyl, for example methyl, ethyl, i-propyl, t-butyl, 3-pentyl, hydroxymethyl, 1-hydroxyethyl, 1-hydroxypropyl, 2-hydroxy-2-propyl, 3-hydroxy-3-pentyl or cyclopropyl.

When R^2 signifies hydrogen and R^3 signifies lower alkyl, then R^3 conveniently stands for methyl. When R^2 and R^3 together signify dimethylene or trimethylene, then the carbon atom denoted by γ preferably has the (S)-configuration.

When A signifies a residue of formula (a), then conveniently one of R^4 and R^5 signifies hydrogen and the other signifies hydrogen or halogen; thus, for example, R^4 and R^5 both signify hydrogen or R^4 signifies hydrogen and R^5 signifies fluorine or R^4 signifies chlorine and R^5 signifies hydrogen.

Preferred compounds of formula I in the scope of the present invention are:

7-Chloro-4,5-dihydro-5-methyl-3-(1-propynyl)-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one;

7-chloro-4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one;

7-bromo-4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one;

7-chloro-4,5-dihydro-3-(3-hydroxy-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one;

4,5-dihydro-5-methyl-3-(1-propynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one;

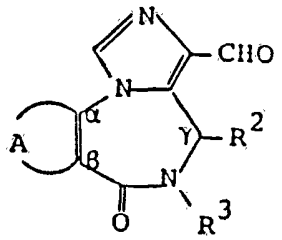
7-chloro-4,5-dihydro-5-methyl-3-(3-methyl-1-butynyl)-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one;

7-chloro-4,5-dihydro-3-(3-hydroxy-1-propynyl)-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one; and

7-chloro-3-(cyclopropylethynyl)-4,5-dihydro-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

The compounds of formula I can be manufactured in accordance with the invention by

a) reacting a compound of the general formula



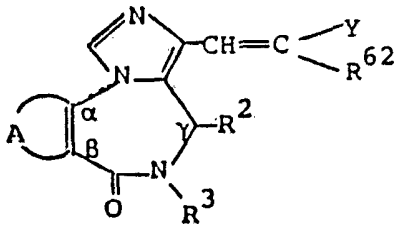
II

wherein A, R^2 and R^3 have the above significance, with a compound of the general formula

$$(Ar)_3P{=}CH\text{-}R^{61} \qquad \text{III}$$

wherein R^{61} signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or disubstituted by lower alkoxy, $(C_3\text{-}C_7)$--cycloalkyl or oxo and Ar signifies an aryl residue; or

b) dehydrohalogenating a compound of the general formula



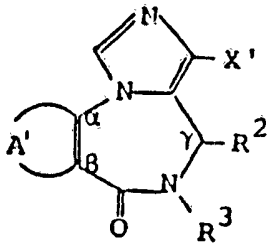
IV

wherein R^{62} signifies hydrogen or halogen and Y signifies halogen, and A, R^2 and R^3 have the above significance;

or

c) treating a compound of formula I in which R^1 signifies group (e) and R^6 signifies hydrogen with an agent yielding a saturated lower hydrocarbon residue which is optionally mono- or disubstituted by hydroxy, lower alkoxy, (C_3-C_7)-cycloalkyl or oxo, or an aryl residue or halogen; or

d) reacting a compound of the general formula



VI

wherein R^2 and R^3 have the above significance and X' signifies bromine or iodine and A' signifies a residue of formula (a), (b) or (c), with the proviso that where A' signifies a residue of formula (a) and R^4 and/or R^5 signify halogen, this halogen is fluorine or chlorine when X' signifies bromine and is

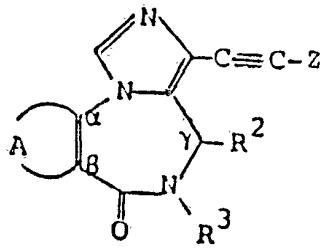
fluorine, chlorine or bromine when X' signifies iodine, with a compound of the general formula

$$HC\equiv C\text{-}R^{64} \qquad VII$$

wherein R^{64} signifies hydrogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or disubstituted by hydroxy, lower alkoxy, $(C_3\text{-}C_7)$-cycloalkyl or oxo;

or

e) cleaving off the protecting group from a compound of the general formula

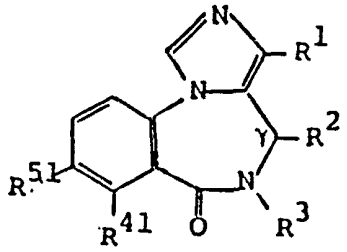


VIII

wherein R^2, R^3 and A have the above significance and Z signifies a protecting group;

or

f) replacing the amino group in a compound of the general formula



IX

wherein R^1, R^2 and R^3 have the above significance and one of R^{41} and R^{51} signifies amino and the other signifies hydrogen, halogen, trifluoromethyl or lower alkyl,

by a hydrogen or halogen atom; or

g) reducing a compound of formula I in which R^1 signifies a residue of formula (e) and in which, where A signifies a residue of formula (a), R^4 and/or R^5 do not signify iodine, to the corresponding compound of formula I in which R^1 signifies a residue of formula (d); or

h) treating a compound of formula I in which R^1 signifies a residue of formula (d) or (e) and R^6 signifies a saturated lower hydrocarbon group which is substituted by hydroxy with an agent yielding a lower alkyl residue; or

i) reducing the carbonyl group in a compound of formula I in which R^1 signifies group (d) or (e) and R^6 signifies a saturated lower hydrocarbon group which is substituted by oxo.

Aspect a) of the process in accordance with the invention yields compounds of formula I in which R^1

signifies group (d), but in which R^6 can have only those significances which have been given above for R^{61} in connection with formula III. The compounds of formula II which are used as starting materials are known or can be prepared readily according to methods which are known per se and which are familiar to any person skilled in the art; moreover, several of the Examples hereinafter contain detailed information concerning the preparation of specific compounds of formula II. The compounds of formula III are conveniently prepared in situ, namely from corresponding phosphonium halides such as methyltriphenylphosphonium bromide, ethyltriphenylphosphonium bromide, butyltriphenylphosphonium bromide, chloromethyltriphenylphosphonium chloride etc and a strong base such as sodium amide, butyllithium and the like. For example, the reaction can be carried out by placing the respective phosphonium halide such as ethyltriphenylphosphonium bromide in an organic solvent which is inert under the reaction conditions, such as tetrahydrofuran, ether, N,N-dimethylformamide, toluene or the like, and then adding thereto an approximately equimolar amount or a slight excess of a suitable strong base, for example by adding dropwise a butyllithium solution in an organic solvent which is inert under the reaction conditions, such as n-hexane or the like. According to another embodiment, the preparation of the starting materials of formula III is conveniently effected starting from equimolar mixtures of sodium amide and a phosphonium halide such as methyltriphenylphosphonium bromide, butyltriphenylphosphonium bromide, chloromethyltriphenylphosphonium chloride and the like, some of which are commercially available; such mixtures can be used directly by taking them up in an organic solvent which is inert under the reaction conditions, such as tetrahydrofuran, ether, N,N-dimethylformamide, toluene, dioxan or the like. The solution or suspension containing a compound of formula III, which has

been obtained according to the previously described methods, is then treated with a compound of formula II. In this case it is convenient to add the compound of formula II portionwise in solid form or to add dropwise a solution of a compound of formula II in an organic solvent which is inert under the reaction conditions, such as tetrahydrofuran, dioxan, ether or the like. Depending on the nature of the compounds used as reaction components and of the solvent or solvent mixture used as the reaction medium, the reaction of the compounds of formula III with the compounds of formula II is effected at or below or above room temperature; in general, the reaction temperature conveniently lies in a range of about -50 to about +50°C. As a rule, the reaction time varies between about a half hour and some few hours.

Aspect b) of the process in accordance with the invention yields compounds of formula I in which R^1 signifies group (e), but in which R^6 can only signify hydrogen or halogen. The dehydrohalogenation is conveniently effected by means of a base, for example with an organic base which is as little nucleophilic as possible, thus conveniently with potassium tert.-butylate or the like or with a bicyclic compound such as 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene or the like or also with an inorganic base such as sodium hydride, sodium hydroxide or the like. Furthermore, the dehydrohalogenation is conveniently effected in an organic solvent which is inert under the reaction conditions, such as N,N-dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, tert.-butanol or the like, at an elevated temperature, conveniently at the boiling temperature of the reaction system; it can also be effected by means of sodium amide in liquid ammonia or by menas of a solution of sodium in a lower alcohol such as methanol, and it takes several hours, for example about 3 to about 8 hours.

In accordance with aspect c) of the process in accordance with the invention, a compound of formula I in which R^1 signifies group (e) and R^6 signifies hydrogen is firstly deprotonized by means of a strong base such as sodium hydride, potassium tert.-butylate, butyllithium or the like, which is conveniently effected in an organic solvent which is inert under the reaction conditions, such as N,N-dimethylformamide, toluene, tetrahydrofuran or the like; sodium amide in liquid ammonia or sodium hydroxide in a lower alcohol such as methanol can, however, also be used for the deprotonization. There is subsequently added thereto the agent yielding the desired residue, the nature of which depends, of course, on the desired residue to be introduced. For the introduction of a lower alkyl group there is used, for example, a lower alkyl halide such as methyl iodide, a lower dialkyl sulphate or a lower alkyl ester of a sulphonic acid such as methanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid or p-bromobenzenesulphonic acid, etc. A lower alkoxy-lower alkyl residue, a $(C_4\text{-}C_7)$-cycloalkyl residue or a $(C_3\text{-}C_7)$-cycloalkyl-lower alkyl residue can be introduced in an analogous manner, for example by means of chlorodimethyl ether, cyclohexyl bromide, cyclopropylmethyl bromide and the like. In order to introduce a hydroxyl-containing residue in which the hydroxy group is situated in the α-position, a corresponding carbonyl compound can be used; thus, for example, a hydroxymethyl group is introduced by means of formaldehyde, a 2-hydroxy--2-propyl group is introduced by means of acetone etc. A ß-hydroxy-alkyl group can be introduced conveniently by means of a corresponding epoxide, a 2-hydroxyethyl group can thus be introduced by means of ethylene oxide. A halogen atom can be introduced by means of elementary halogen. The reaction conditions depend, of course, on the nature of the reagent which is used for the introduction of each of the desired residues. If this reagent is, for

example, methyl iodide, then the reaction is conveniently effected in an organic solvent which is inert under the reaction conditions, such as N,N-dimethylformamide, tetrahydrofuran, toluene, dioxan, dimethyl sulphoxide or the like, at room temperature, and it takes a few, for example 2-5, hours.

The reaction of compounds of formulae VI and VII in accordance with aspect d) of the process in accordance with the invention is effected in the presence of a palladium(II) salt such as palladium chloride or palladium acetate, of an organophosphine such as triphenylphosphine, of copper(I) iodide and of a secondary or tertiary amine such as diethylamine or triethylamine; in place of a palladium(II) salt and an organophosphine there can also be used a suitable corresponding complex such as e.g. bis-(triphenylphosphine)-palladium(II) dichloride. As the solvent there can be used the mentioned secondary or tertiary amine itself, a halogenated hydrocarbon such as methylene chloride or the like, N,N-dimethylformamide or the like. As the compound of formula VII there is used, for example, propyne, 3,3-dimethyl-1-butyne, phenyl-acetylene, propargyl alcohol, 2-methyl-3-butyn-2-ol etc. Depending on the nature of the compound of formula VII which is used, the reaction is effected under pressure and at temperatures in a range between about room temperature and about 120°C; the reaction time amounts to about 1 to about 70 hours depending on the remaining reaction parameters. The starting materials of formula VI are known or can be prepared readily according to methods which are known per se and which are familiar to any person skilled in the art; moreover, some of the Examples hereinafter contain detailed information concerning the preparation of certain compounds of formula VI.

Aspect e) of the process in accordance with the

invention yields compounds of formula I in which R^1 signifies a residue of formula (e) and R^6 signifies hydrogen. As protecting groups which are denoted by Z in formula VIII there come into consideration, of course, only those residues which can be removed selectively without affecting other groups present in the molecule. Residues which satisfy these requirements and methods for their selective removal are familiar to the person skilled in the art. There are suitable, for example, trialkylsilyl groups such as trimethylsilyl, α-hydroxyalkyl groups such as 2-hydroxy-2-propyl etc. The cleavage of trialkylsilyl groups can be effected, for example, by means of potassium fluoride in water, by means of an alkali metal hydroxide such as potassium hydroxide in a lower alkanol such as ethanol, and/or water or the like, and the cleavage of groups such as 2-hydroxy-2-propyl can be effected conveniently under alkaline conditions, for example by means of an alkali metal hydroxide such as sodium hydroxide, an alkali metal hydride such as sodium hydride, or the like in an organic solvent which is inert under the reaction conditions, for example in an aromatic hydrocarbon such as toluene, benzene, xylene or the like. Those starting materials of formula VIII which do not fall under the scope of formula I are also novel and are likewise an object of the present invention. The preparation of such compounds can be effected in an analogous manner to the manufacture of corresponding compounds of formula I, for example in analogy to aspect d) of the process in accordance with the invention.

The replacement of an amino group by a halogen atom in accordance with aspect f) of the process in accordance with the invention can be effected by converting the amino compound of formula IX into a corresponding diazonium salt and reacting this, optionally without previous isolation, with a halide, e.g. with a chloride or bromide, in the

presence of a copper(I) salt; the manufacture of corresponding iodo compounds is effected in an analogous manner, but the presence of a copper(I) salt is not necessary. Corresponding fluoro compounds are conveniently manufactured via the corresponding diazonium tetrafluoroborate, for example by iradiation with UV light. The previously mentioned reactions are carried out in aqueous solutions at temperatures of about -10°C to about room temperature.

The replacement of the amino group by a hydrogen atom in accordance with aspect f) of the process in accordance with the invention can be carried out by reducing a corresponding diazonium salt, for example by heating in a cyclic ether such as tetrahydrofuran or dioxan or in ethanol, N,N-dimethylformamide or the like; preferably at the boiling temperature of the reaction mixture. However, an amine of formula IX can also be reacted with t-butyl nitrite, isopentyl nitrite and the like in a cyclic ether such as tetrahydrofuran or dioxan, preferably at the boiling temperature of the reaction mixture.

The starting materials of formula IX are novel and are likewise an object of the present invention. Their preparation is effected by reducing corresponding nitro compounds and these, in turn, can be obtained in analogy to the manufacture of corresponding compounds of formula I.

In accordance with aspect g) of the process in accordance with the invention, a carbon-carbon triple bond is partially reduced to a carbon-carbon double bond. Such a partial reduction can be carried out according to methods which are customary and which are familiar to any person skilled in the art, conveniently by hydrogenation in the presence of a partially inactivated catalyst, for example in the presence of a palladium catalyst pre-treated with

quinoline and/or lead. The partial hydrogenation is conveniently effected at room temperature and atmospheric pressure in an organic solvent which is inert under the reaction conditions, for example in ethyl acetate, methanol, N,N-dimethylformamide, dichloromethane etc.

In accordance with aspect h) of the process in accordance with the invention, a hydroxy group is converted into a lower alkoxy group. This is thus an etherification of a hydroxy group and methods for carrying out such an etherification are known per se and are familiar to any person skilled in the art. The etherification in accordance with the invention is conveniently effected by means of a lower alkyl halide such as methyl iodide, a lower dialkyl sulphate or a lower alkyl ester of an organic sulphonic acid such as methanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, p-bromobenzenesulphonic acid etc. The reaction is conveniently carried out in the presence of a base, for example an alkali metal hydroxide such as sodium hydroxide, and in the presence of an organic solvent which is inert under the reaction conditions, for example in N,N-dimethylformamide, dimethyl sulphoxide, toluene and the like.

In accordance with aspect i) of the process in accordance with the invention, a carbonyl group is reduced to the corresponding alcohol group. This reduction can be carried out according to methods which are known per se an which are familiar to any person skilled in the art. As the reducing agent there come into consideration, for example, an alkali metal borohydride such as sodium borohydride. Suitable solvents are e.g. lower alcohols, such as methanol and ethanol, and dimethylformamide and mixtures thereof. The reduction is conveniently carried out at room temperature.

As mentioned earlier, the compounds of formula I are novel. They possess valuable pharmacodynamic properties and have only a low toxicity. They have as a common characteristic a pronounced affinity to the central benzodiazepine receptors and have either pronounced anxiolytic, anticonvulsant, muscle relaxant and sedative-hypnotic properties and/or they partially or completely selectively antagonize some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via the central benzodiazepine receptors.

The affinity of compounds of general formula I to the central benzodiazepine receptors was determined according to the method described in Life Science 20, 2101-2110 (1977) and Science 198, 849-851 (1977). According to this method, the inhibition of the binding of tritiated diazepam at the specific benzodiazepine receptors in the cerebral cortex by the respective test substances is ascertained. The IC_{50} ("50% inhibiting concentration") is that concentration of the respective test substance which brings about a 50 percent inhibition of the specific binding of the tritiated diazepam at the specific benzodiazepine receptors in the cerebral cortex.

The central properties of the compounds of formula I in accordance with the invention can be determined, for example, in the antipentetrazole test which is described hereinafter and which is generally recognized for recording anticonvulsant properties.

In this animal experiment the compound under investigation is administered orally to female rats weighing 60-80 g and 30 minutes later there are administered i.p. 120 mg/kg of pentetrazole, which causes emprosthotonus and tonic stretchings of the fore and/or hind limbs in unprotected experimental animals 1-4 minutes after the

injection. Ten experimental animals are used per dosage of test substance. After counting the protected experimental animals the ED_{50} is determined according to the Probit method. The ED_{50} is that dosage which protects 50% of the experimental animals from the spasmodic seizures caused by pentetrazole.

One of the typical properties of 1,4-benzodiazepines having tranquillizing activity in animal experiments is their pronounced anticonvulsant activity which can be demonstrated, for example, in the known and generally recognized pentetrazole test. This property was used to elaborate the test described hereinafter which permits the investigation of compounds which are capable of antagonizing the central properties of 1,4-benzodiazepines having tranquillizing activity.

In this test there are administered to mice one hour before the pentetrazole (120 mg/kg, i.p.) 5 mg/kg (i.p.) of diazepam (i.e. a supramaximal dosage which in the pentetrazole test on more than 900 mice protected all experimental animals from spasmodic seizures) and the compound to be tested was administered p.o. 15 minutes before the pentetrazole. The antagonistic activity of the compounds investigated, i.e. their capability to counteract the effect of the diazepam in the pentetrazole test, is determined by counting the mice which suffer spasmodic seizures in this test. The ED_{50} denotes the amount of the respective test compound in mg/kg (p.o.) which in 50% of the animals counteracts the diazepam effect in the above test.

The results which have been obtained with representative members of the class of compound defined by general formula I in the experiments described previously are compiled in the following Table. Moreover, the Table

contains data concerning the acute toxicity of some of these compounds (LD_{50} in mg/kg in the case of single oral administration to rats).

Compound	Affinity to benzodiazepine receptors IC 50, nmol/l	Antipentetrazole test ED 50 mg/kg p.o.	Antagonism of diazepam ED 50 mg/kg p.o.	Toxicity LD 50 mg/kg p.o.
A	4.5		0.24	312-625
B	24		1.5	312-625
C	2.3		0.36	>5000
D	2.4	1.5	>50	>4000
E	2.0	0.29		500-1000
F	7.6		1.2	1250-2500

A = 7-Chloro-3-ethynyl-4,5-dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one

B = 3-Ethynyl-8-fluoro-4,5-dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one

C = 7-Chloro-4,5-dihydro-5-methyl-3-(1-propynyl)-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one

D = (S)-8-Chloro-1-ethynyl-11,12,13,13a-tetrahydro-9H--imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one

E = 7-Bromo-4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)--5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one

F = 7-Chloro-4,5-dihydro-5-methyl-3-vinyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one.

A selective antagonistic component, as can be demonstrated in the case of many of the compounds of formula I, is of great therapeutic significance in that it permits the use of desired properties (e.g. anxiolytic or anticonvulsant activity) of the substances in accordance with the invention while repressing the additional properties (e.g. sedative, muscle relaxant and the activities which disturb motoric coordination) which are undesired in certain cases of administration.

The compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be carried out rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

For the manufacture of pharmaceutical preparations the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers. As such carriers there can be used for tablets, coated tablets, dragees and hard gelatine capsules, for example, lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like.

Suitable carriers for injection solutions are, for example, water, alcohols, polyols, glycerine, vegetable oils and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I and a therapeutically inert excipient are also an object of the present invention, as is a process for the manufacture of such medicaments, which comprises bringing one or more compounds of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert excipients.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable acid addition salts can be used in the control or prevention of illnesses and especially in the control of convulsions and anxiety states and/or in the partial or complete antagonism of some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via the central benzodiazepine receptors. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 100 mg comes into consideration.

Finally, as mentioned earlier, the use of compounds of formula I for the manufacture of medicaments, especially of medicaments for use in the control or prevention of convulsions, anxiety states, stress conditions, excitation states and sleep disorders and/or in the partial or complete selective antagonization of some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via the central benzodiazepine receptors is also an object of the invention.

The following Examples are intended to illustrate the present invention in more detail, but are not intended to limit its extent in any manner. All temperatures are given in degrees Celsius.

Example 1

a) 14.14 g (49.5 mmol) of ethyl 5,6-dihydro-5-methyl-6--oxo-4H -imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate in 100 ml of tetrahydrofuran are treated portionwise at the boiling temperature with 1.35 g (62 mmol) of lithium borohydride, whereupon the mixture is boiled at reflux for 6 hours. The reaction mixture is then cooled, a mixture of 20 ml of water and 20 ml of concentrated hydrochloric acid is cautiously added thereto, the mixture is heated, stirred at the boiling temperature for 30 minutes, again cooled and treated with concentrated ammonia until the reaction is alkaline. The organic solvent is distilled off on a rotary evaporator and the aqueous suspension obtained is cooled and filtered. The filter residue is washed with water and dried; there is obtained 4,5-dihydro-3-hydroxy-methyl-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 219-221°.

b) 6.73 g (27.6 mmol) of 4,5-dihydro-3-hydroxymethyl-5-

-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature for 4 hours together with 33 g (380 mmol) of manganese dioxide in 100 ml of methylene chloride. The mixture is filtered, the filter residue is rinsed thoroughly with about 1.5 l of methylene chloride and the filtrate is evaporated. There is obtained 5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3--carboxaldehyde of melting point 202-203°.

c) 13.50 g of an equimolar mixture of chloromethyltriphenylphosphonium chloride and sodium amide are stirred for 15 minutes with 50 ml of tetrahydrofuran, whereby the temperature rises to 42°. 6.2 g (25.7 mmol) of 5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3--carboxaldehyde are then added portionwise thereto, the mixture is stirred at room temperature for a further hour, filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) there is obtained 3-[(Z)-2-chlorovinyl]-4,5-dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one of melting point 197-199°.

Example 2

2.20 g (8 mmol) of 3-[(Z)-2-chlorovinyl]-4,5-dihydro--5-methyl-6H-imidazo[1,5-a][1,4[benzodiazepin-6-one are stirred at 145° for 6 hours together with 1.43 ml (9.6 mmol) of 1,8-diazabicyclo[5.4.O]undec-7-ene in 30 ml of N,N-dimethylformamide. The reaction mixture is subsequently poured into water and extracted five times with methylene chloride. The organic extracts are washed five times with water, dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and subsequent recrystallization from ethyl acetate there is obtained 3-ethynyl-4,5-dihydro-5-methyl-6H -imidazo[1,5-a][1,4]-

benzodiazepin-6-one of melting point 191-193°.

Example 3

100 g of an equimolar mixture of chloromethyltriphenylphosphonium chloride and sodium amide are stirred for 45 minutes in 450 ml of tetrahydrofuran, whereby the temperature rises to 37°. 62.23 g (229.7 mmol) of 7--chloro-5,6-dihydro-5-methyl-6-oxo -4H-imidazo[1,5-a]-[1,4]benzodiazepine-3-carboxaldehyde are then added portionwise thereto at room temperature and, after completion of the addition, the mixture is stirred for a further 1 hour. The reaction mixture is subsequently filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) there is obtained 7-chloro-3-[(Z)-2-chlorovinyl]-4,5-dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 205-207°.

Example 4

20.2 g (65.5 mmol) of 7-chloro-3-[(Z)-2-chlorovinyl]--4,5-dihydro-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 5 hours together with 11.7 ml (78.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 200 ml of N,N-dimethylformamide. The reaction mixture is subsequently poured into 800 ml of water and extracted four time with methylene chloride. The organic extracts are washed four times with water, dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and two successive crystallizations from acetonitrile and from ethyl acetate there is obtained 7-chloro-3-ethynyl-4,5-dihydro-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting

point 201-202°.

Example 5

2.72 g (10 mmol) of 7-chloro-3-ethynyl-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are dissolved in 20 ml of N,N-dimethylformamide. 1.31 g (30 mmol) of sodium hydride dispersion (55% in oil) are washed with n-hexane and then introduced at room temperature into the above solution. After 10 minutes 0.95 ml (15 mmol) of methyl iodide are added thereto and the mixture is stirred at room temperature for a further 3 hours. The reaction mixture is poured into 300 ml of water and extracted four times with methylene chloride. The organic extracts are washed four times with water and dried over magnesium sulphate. After chromatography of the residue on silica gel while eluting with ethyl acetate and recrystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro--5-methyl-3-(1-propynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 243-244°.

Example 6

6.25 g of an equimolar mixture of methyltriphenylphosphonium bromide and sodium amide are stirred for 15 minutes in 40 ml of tetrahydrofuran. 4.13 g (15 mmol) of 7-chloro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a]-[1,4]benzodiazepine-3-carboxaldehyde are then added to the yellow suspension, whereby the temperature rises to 43° and the suspension decolorizes. The mixture is stirred for a further 1 hour, filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and recrystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro-5-methyl-3-vinyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one of melting point 205-207°.

Example 7

15 g (40.4 mmol) of ethyltriphenylphosphonium bromide are placed in 60 ml of tetrahydrofuran and treated dropwise at -40° with 28 ml (45 mmol) of 1.6 molar butyllithium solution in n-hexane. The orange suspension obtained is stirred at -40° for a further 20 minutes and subsequently a solution of 10 g (36 mmol) of 7-chloro-5,6--dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine -3-carboxaldehyde in 250 ml of tetrahydrofuran is added dropwise thereto within 50 minutes at -40° to -50°. The mixture is stirred at room temperature for a further 2 hours and subsequently filtered. The filtrate is evaporated and chromatographed on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1). There are obtained 7-chloro-4,5-dihydro-5-methyl-3 -[(Z)-propenyl]-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 169.5-170.5° (from ethyl acetate/hexane) and 7-chloro-4,5--dihydro-5-methyl-3-[(E)-propenyl]-6H -imidazo[1,5-a]-[1,4]benzodiazepin-6-one of melting point 200-201° (from acetonitrile).

Example 8

25 g of an equimolar mixture of chloromethyltriphenylphosphonium chloride and sodium amide are stirred at room temperature in 120 ml of tetrahydrofuran for 20 minutes. 12.9 g (50 mmol) of 8-fluoro-5,6-dihydro-5-methyl-6-oxo--4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde are then added thereto and the mixture is stirred at room temperature for 1 hour and at the boiling temperature for 10 minutes. The mixture is cooled, filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and recrystallization from acetonitrile there is obtained 3-[(Z)-2-chlorovinyl]-8-

-fluoro-4,5-dihydro-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 220-221°.

Example 9

3.70 g (12.7 mmol) of 3-[(Z)-2-chlorovinyl]-8-fluoro--4,5-dihydro-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6--one are heated to boiling under reflux for 4 hours together with 2.26 ml (15.2 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene 30 ml of N,N-dimethylformamide. The reaction mixture is subsequently poured into 400 ml of water and extracted five times with methylene chloride. The organic extracts are washed four times with water, dried over magnesium sulphate and evaporated. The residue is dissolved in ethyl acetate, treated with charcoal and recrystallized from ethyl acetate. There is obtained 3-ethynyl-8-fluoro-4,5-dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepine-6-one of melting point 207-208°.

Example 10

40.70 g of an equimolar mixture of butyltriphenylphosphonium bromide and sodium amide are stirred at room temperature for 15 minutes in 150 ml of tetrahydrofuran. 20.73 g (80 mmol) of 8-fluoro-5,6-dihydro-5-methyl-6-oxo--4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde are then added thereto, the mixture is stirred at room temperature for a further 1.5 hours, filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and recrystallization from ethyl acetate and n-hexane there is obtained 8-fluoro-4,5--dihydro-5-methyl-3-(1-pentenyl)-6H-imidazo[1,5-a][1,4]-benzodiazepin-6-one of melting point 150-151°.

Example 11

17.5 g of an equimolar mixture of chloromethyltriphenylphosphonium chloride and sodium amide are stirred for 15 minutes in 100 ml of tetrahydrofuran, whereby the temperature rises to 33°. 11.1 g (38.58 mmol) of (S)-8-chloro-12,12a-dihydro-9-oxo-9H,11H-azeto[2,1-c]imidazo-[1,5-a][1,4]benzodiazepine-1-carboxaldehyde are then added portionwise thereto, whereby the temperature rises to 45° with the evolution of ammonia. The mixture is stirred at room temperature for a further 1 hour, filtered and the filtrate is evaporated. After chromatography on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and subsequent recrystallization from ethyl acetate there is obtained (S)-8-chloro-1-[(Z)-2-chlorovinyl]-12,12a-dihydro-9H,11H-azeto[2,1-c]imidazo[1,5-a][1,4]benzodiazepin-9-one of melting point 189-191°.

Example 12

2.21 g (6.9 mmol) of (S)-8-chloro-1-[(Z)-2-chlorovinyl]-12,12a-dihydro-9H,11H-azeto[2,1-c]imidazo-[1,5-a][1,4]benzodiazepin-9-one are heated to boiling under reflux for 4 hours together with 1.23 ml (8.3 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 30 ml of N,N-dimethylformamide. The reaction mixture is subsequently poured into 300 ml of water and extracted five times with methylene chloride. The organic extracts are washed four times with water, dried over magnesium sulphate and evaporated. After chromatography on silica gel while eluting with ethyl acetate and subsequent recrystallization from ethyl acetate there is obtained (S)-8-chloro-1-ethynyl-12,12a-dihydro-9H,11H-azeto[2,1-c]imidazo-[1,5-a][1,4]benzodiazepin-9-one of melting point 249-250°.

Example 13

8.70 g of an equimolar mixture of methyltriphenylphosphonium bromide and sodium amide are stirred for 20 minutes in 60 ml of tetrahydrofuran. 6 g (20 mmol) of (S)-8-chloro-12,12a-dihydro-9-oxo-9H,11H-azeto[2,1-c]imidazo[1,5-a][1,4]benzodiazepine-1-carboxaldehyde are then added portionwise thereto and the mixture is stirred for a further 1 hour. The mixture is subsequently filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and subsequent recrystallization from ethyl acetate there is obtained (S)-8-chloro-12,12a--dihydro-1-vinyl-9H,11H-azeto[2,1-c]imidazo[1,5-a][1,4]-benzodiazepin-9-one of melting point 171-172°.

Example 14

15 g of an equimolar mixture of chloromethyltriphenylphosphonium chloride and sodium amide are stirred in 60 ml of tetrahydrofuran for 20 minutes. 10 g (33 mmol) of (S)--8-chloro-11,12,13,13a-tetrahydro -9-oxo-9H-imidazo-[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxaldehyde are then added thereto, whereby the temperature rises rapidly to 54° with the vigorous evolution of ammonia. The mixture is stirred for a further 45 minutes, filtered and evaporated. The residue is chromatographed on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1). After recrystallization from ethyl acetate there is obtained (S)-8-chloro-1-[(Z)-2-chlorovinyl]-11,12,13,13a--tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzo-diazepin-9-one of melting point 209-210°.

Example 15

2.5 g (7.5 mmol) of (S)-8-chloro-1-[(Z)-2-chloro-

vinyl]-11,12,13,13a-tetrahydro-9H -imidazo[1,5-a]pyrrolo-[2,1-c][1,4]benzodiazepin-9-one are heated to boiling under reflux for 5 hours together with 1.66 ml (11.2 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 30 ml of N,N-dimethylformamide. The reaction mixture is subsequently poured into 400 ml of water and the crystals obtained are filtered off. After drying and recrystallization from N,N--dimethylformamide there is obtained (S)-8-chloro-1--ethynyl-11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]-pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 324-325°.

Example 16

250 mg (0.85 mmol) of (S)-8-chloro-1-ethynyl--11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c]-[1,4]benzodiazepin-9-one are suspended in 5 ml of N,N-dimethylformamide. 50 mg (1 mmol) of sodium hydride dispersion (55% in oil) are washed with n-hexane and then introduced into the above suspension. After 10 minutes 0.1 ml (1.5 mmol) of methyl iodide is added thereto and the mixture is stirred at room temperature for a further 4.5 hours. The mixture is poured into 50 ml of water and extracted four times with methylene chloride. The organic extracts are washed four times with water, dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and recrystallization from ethyl acetate and hexane there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1--propynyl-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one of melting point 205-20°.

Example 17

20.8 g of an equimolar mixture of methyltriphenylphosphonium bromide and sodium amide are stirred for 20

minutes in 80 ml of tetrahydrofuran. 15.08 g (50 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro -9-oxo-9H-imidazo-[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxaldehyde are then added portionwise thereto, whereby the temperature rises to 43° with the evolution of ammonia. The mixture is stirred at room temperature for 1 hour, filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1) and recrystallization from ethyl acetate there is obtained (S)-8-chloro--11,12,13,13a-tetrahydro-1-vinyl-9H-imidazo[1,5-a]-pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 213-215°.

Example 18

a) 2.31 g of 8-fluoro-4,5-dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one are stirred at 95° for 1.5 hours with 8.88 g (35 mmol) of iodine in 25 ml of N,N--dimethylformamide. The reaction mixture is then poured into 300 ml of water, decolorized with sodium thiosulphate solution and extracted four times with methylene chloride. The organic extracts are washed three times with water, dried over magnesium sulphate and evaporated. After recrystallization of the residue from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-3-iodo-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 187-188°.

b) 2.08 g (5.9 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are mixed in a closeable flask with 50 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 7 mg of copper(I) iodide in 20 ml of diethylamine. The mixture is cooled with an acetone/dry-ice bath and a few drops of propyne are added thereto. The flask is tightly closed and the

mixture is stirred at room temperature for 20 hours. The mixture is then again cooled to -70°, the flask is opened and left to warm to room temperature. The reaction mixture is diluted with methylene chloride and washed twice with water. The organic phase is dried over magnesium sulphate and concentrated. After two-fold recrystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-5--methyl-3-(1-propynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 219-220°.

Example 19

a) 27.3 g (100 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one are stirred at 100° for 3 hours with 88 g (350 mmol) of iodine in 200 ml of N,N-dimethylformamide. The reaction mixture is cooled, the separated product is filtered off, rinsed with ethyl acetate and, after drying, there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1--iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9--one of melting point 298-300°.

b) 3.0 g (7.5 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one, 70 mg of bis-(triphenylphophine)--palladium(II) dichloride and 10 mg of copper(I) iodide are cooled with 30 ml of diethylamine to about -60° in a pressure tube and treated with about 2 ml of propyne. The pressure tube is closed and heated to 100° for 20 hours. After cooling and opening the pressure tube the reaction mixture is taken up in methylene chloride, filtered and the filtrate is washed twice with water. The organic phase is dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and crystallization from ethyl acetate and hexane there is obtained (S)-8-chloro-11,12,13,13a-

-tetrahydro-1-(1-propynyl)-9H-imidazo[1,5-a]pyrrolo-[2,1-c][1,4]benzodiazepin-9-one of melting point 208-209°.

Example 20

a) 12.38 g (50 mmol) of 7-chloro-4,5-dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature for 40 minutes with 9.80 g (55 mmol) of N-bromosuccinimide in 80 ml of N,N-dimethylformamide. The reaction mixture is poured into 800 ml of water and the suspension obtained is filtered. The filter residue is rinsed with water and taken up in methylene chloride. The organic phase is dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and recrystallization from ethyl acetate and hexane there is obtained 3-bromo-7--chloro-4,5-dihydro-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 178-179°.

b) 3.26 g (10 mmol) of 3-bromo-7-chloro-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux overnight with 1.10 g (12 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 20 ml of diethylamine and 15 ml of methylene chloride. The reaction mixture is evaporated and the residue is dissolved in methylene chloride. After chromatography of the solution on silica gel while eluting with ethyl acetate and crystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-(3-hydroxy-3-methyl--1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 194-195°.

Example 21

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5-

-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are mixed with 1.10 g (12 mmol) of 2-methyl-3-butyn-2-ol and 20 ml of diethylamine. 70 mg of bis-(triphenylphosphine)--palladium(II) dichloride and 10 mg of copper(I) iodide are then added thereto and the mixture is stirred at room temperature for 60 hours. The reaction mixture is evaporated and the residue is dissolved in methylene chloride. The solution is washed twice with water, dried over magnesium sulphate and evaporated. After recrystallization of the residue from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-(3-hydroxy-3-methyl-1--butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 193-194°.

Example 22

660 mg (2 mmol) of 7-chloro-4,5-dihydro-3-(3-hydroxy--3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux overnight with 80 mg of sodium hydroxide in 10 ml of toluene. After evaporation of the solvent the residue is dissolved in methylene chloride and the solution is washed twice with water, dried over magnesium sulphate and evaporated. After recrystallization of the residue from ethyl acetate there is obtained 7-chloro-3-ethynyl-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 200-201°.

Example 23

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at the boiling temperature for 24 hours with 1.46 ml (12 mmol) of 3,3-dimethyl-1-butyne, 70 mg of bis--(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. After

evaporation of the reaction mixture the residue is taken up in methylene chloride and washed twice with water. The organic phase is dried over magnesium sulphate, evaporated and the residue is chromatographed on silica gel while eluting with cyclohexane/ether/isopropanol (3:3:1). After crystallization from ethyl acetate and hexane there is obtained 7-chloro-3-(3,3-dimethyl-1-butynyl)-4,5-dihydro--5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 126-128°.

Example 24

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature for 20 hours with 1.12 g (11 mmol) of phenylacetylene, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 20 ml of diethylamine. The reaction mixture is diluted with methylene chloride and washed twice with water. The organic phase is dried over magnesium sulphate and evaporated. After recrystallization of the residue from ethyl acetate there is obtained 7-chloro-4,5-dihydro--5-methyl-3-(phenylethynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 205-206°.

Example 25

a) 19.1 g (56.8 mmol) of 7-bromo-5,6-dihydro-5-methyl-6--oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid are decarboxylated at 290-300°. The melt is taken up in methylene chloride, the solution is diluted with ethyl acetate and ethanol and decolorized with animal charcoal. After evaporation and recrystallization from ethyl acetate and ethanol there is obtained 7-bromo-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 196-197°.

b) 12.80 g (44 mmol) of 7-bromo-4,5-dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at 95° for 3.5 hours with 39 g (154 mmol) of iodine in 80 ml of N,N-dimethylformamide. The reaction mixture is evaporated, the residue is taken up in methylene chloride and water and decolorized by the addition of sodium thiosulphate. The mixture is filtered and the filtrate is evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and recrystallization from methylene chloride and ethyl acetate there is obtained 7-bromo-4,5-dihydro-3-iodo-5-methyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one of melting point 203-204°.

c) 3.74 g (8.95 mmol) of 7-bromo-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at the boiling temperature for 1.5 hours with 0.80 g (9.5 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis--(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization of the residue, which remains behind upon evaporation of the eluate, from ethyl acetate there is obtained 7-bromo-4,5-dihydro-3-(3-hydroxy-3-methyl-1--butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 207-208°.

Example 26

a) 109.03 g (300 mmol) of (S)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylic acid are decarboxylated at 290°. The melt is dissolved in about 400 ml of N,N-dimethylformamide and the solution is poured into 2.5 l of water. After stirring for 30 minutes the precipitated product is filtered off, rinsed with water and dried. There is obtained (S)-8-

-bromo-11,12,13,13a-tetrahydro-9H -imidazo[1,5-a]pyrrolo-[2,1-c][1,4]benzodiazepin-9-one of melting point 232-233°.

b) 15.90 g (50 mmol) of (S)-8-bromo-11,12,13,13a-tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one are stirred at 100° for 3 hours with 44 g (175 mmol) of iodine and 14 g (100 mmol) of potassium carbonate in 100 ml of N,N-dimethylformamide. The reaction mixture is poured into 1 l of water and, after stirring for 30 minutes, the precipitated product is filtered off. The filter residue is rinsed with water, dried and recrystallized from N,N-dimethylformamide. There is obtained (S)-8--bromo-11,12,13,13a-tetrahydro-1-iodo-9H-imidazo[1,5-a]-pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 301-303°.

c) 2.22 g (5 mmol) of (S)-8-bromo-11,12,13,13a-tetrahydro-1-iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are stirred at the boiling temperature under reflux for 8 hours with 0.44 g (5 mmol) of 2-methyl--3-butyn-2-ol, 25 mg of palladium(II) acetate, 100 mg of triphenylphosphine and 10 mg of copper(I) iodide in 20 ml of triethylamine and 20 ml of N,N-dimethylformamide. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After evaporation of the eluate and recrystallization of the residue from ethyl acetate there is obtained (S)-8--bromo-11,12,13,13a-tetrahydro-1-(3-hydroxy-3-methyl-1--butynyl)-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one of melting point 227-228°.

Example 27

2.83 g (7 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are stirred at 105° for 60 hours with

1.10 g (11 mmol) of phenylacetylene, 25 mg of palladium(II) acetate, 100 mg of triphenylphosphine and 15 mg of copper(I) iodide in 40 ml of triethylamine and 20 ml of N,N-dimethylformamide. The mixture is then evaporated to dryness and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from methylene chloride and ethyl acetate there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1-(phenylethynyl)-9H-imidazo[1,5-a]pyrrolo[2,1-c]-[1,4]benzodiazepin-9-one of melting point 241-242°.

Example 28

3.99 g (10 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are stirred at 100° overnight with 0.88 g (10.5 mmol) of 2-methyl-3-butyn-2-ol, 25 mg of palladium-(II) acetate, 100 mg of triphenylphosphine and 10 mg of copper(I) iodide in 40 ml of triethylamine and 20 ml of N,N-dimethylformamide. The mixture is evaporated to dryness and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1-(3-hydroxy-3-methyl-1-butynyl)-9H--imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 234-235°.

Example 29

4.18 g (10 mmol) of 7-bromo-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 2 hours with 1.12 g (11 mmol) of phenylacetylene, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The solvent is then evaporated and the residue is chromatographed on silica

gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 7-bromo-4,5-dihydro-5-methyl-3-(phenylethynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 207-209°.

Example 30

3.40 g (10 mmol) of 4,5-dihydro-3-iodo-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 1.5 hours with 0.925 g (11 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The solvent is then evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 168-169°.

Example 31

3.90 g (11.5 mmol) of 4,5-dihydro-3-iodo-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 5 hours with 0.67 g (12 mmol) of propargyl alcohol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The solvent is then evaporated, the residue is taken up in methylene chloride, the solid is filtered off and rinsed with ethyl acetate. After drying there is obtained 4,5-dihydro-3-(3-hydroxy-1-propynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 240-241°.

Example 32

1.20 g (18.6 mmol) of freshly powdered potassium

hydroxide are stirred at room temperature for 5 minutes in 15 ml of dimethyl sulphoxide. 1.65 g (5 mmol) of 7-chloro--4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one and 1.42 g (10 mmol) of methyl iodide are then added thereto in succession, whereby the temperature rises to 35°. The reaction mixture is stirred for 45 minutes and then poured into 50 ml of water. The mixture is extracted five times with methylene chloride, the combined organic phases are dried over magnesium sulphate and evaporated. After crystallization from diisopropyl ether there is obtained 7-chloro-4,5-dihydro-3-(3-methoxy-3-methyl-1-butynyl)-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 172-174°.

Example 33

7.47 g (20 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 4 hours with 1.75 g (25 mmol) of 3-butyn-2-ol, 70 mg of bis-(triphenylphospine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 50 ml of diethylamine and 20 ml of ethylene chloride. After removal of the solvent by evaporation the residue is taken up in methylene chloride and the thus--obtained suspension is suction filtered. The material obtained is washed with methylene chloride and, after recrystallization from ethyl acetate, there is obtained 7-chloro-4,5-dihydro-3-(3-hydroxy-1 -butynyl)-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 251-252°.

Example 34

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are

heated to boiling under reflux for 2 hours with 1.40 g (12.5 mmol) of 3-ethyl-1-pentyn-3-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 7-chloro-3-(3-ethyl-3-hydroxy-1 -pentynyl)-4,5-dihydro-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 186-188°.

Example 35

9.57 g (25.5 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 3 hours with 3.52 g (32 mmol) of 1-ethynylcyclopentanol, 170 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 30 mg of copper(I) iodide in 60 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After crystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-[(1 -hydroxycyclopentyl)ethynyl]-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 207-208°.

Example 36

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 5 hours with 1.09 g (13 mmol) of ethynyl-ethyl carbinol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After

recrystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-(3-hydroxy-1-pentynyl)-5 -methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 178°.

Example 37

10.0 g (26.7 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one, 140 mg of bis-(triphenylphosphine)-palladium(II) dichloride, 40 mg of copper(I) iodide and 3.4 ml (40.3 mmol) of methyl propargyl ether in 100 ml of diethylamine are heated to boiling under reflux for 3.5 hours. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 7-chloro--4,5-dihydro-3-(3-methoxy-1-propynyl)-5 -methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 154-156°.

Example 38

3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to 100° in a pressure tube for 20 hours with 0.87 g of 3-methyl-1-butyne, 70 mg of bis-(triphenylphosphine)--palladium(II) dichloride and 19 mg of copper(I) iodide in 20 ml of diethylamine and 10 ml of ethylene chloride. By evaporation of the reaction mixture and chromatography of the residue on silica gel while eluting with ethyl acetate there is obtained a mixture of product and starting material of about 2:1. In order to remove the starting material, the mixture is heated under reflux for 5 hours with 0.8 ml of 2-methyl-3-butyn-2-ol, 70 mg of bis--(triphenylphosphine)-palladium(II) dichloride and 15 mg of copper(I) iodide in 15 ml of diethylamine. By evapor-

ation of the reaction mixture and chromatography of the residue on silica gel while eluting with ethyl acetate the byproduct can be separated from the desired product. After recrystallization from ether there is obtained 7-chloro-4,5-dihydro-5-methyl-3 -(3-methyl-1-butynyl)-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 128-130°.

Example 39

3.37 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to 75° for 16 hours with 1.47 g of cyclopropylacetylene, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 20 mg of copper(I) iodide in 20 ml of diethylamine and 10 ml of ethylene chloride. By evaporation of the reaction mixture and chromatography of the residue on silica gel while eluting with ethyl acetate there is obtained a mixture of product and starting material. In order to remove the starting material, the mixture is heated under reflux for 4 hours with 1 ml of 2-methyl-3--butyn-2-ol, 70 mg of bis-(triphenylphosphine)--palladium(II) dichloride and 20 mg of copper(I) iodide in 10 ml of diethylamine and 10 ml of ethylene chloride. By evaporation of the reaction mixture and chromatography of the residue on silica gel while eluting with ethyl acetate the byproduct can be separated from the desired product. After crystallization from ethyl acetate there is obtained 7-chloro-3-(cyclopropylethynyl)-4,5 -dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 177-178°.

Example 40

4.07 g (15 mmol) of 7-chloro-3-ethynyl-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are

suspended in 30 ml of tetrahydrofuran and treated dropwise within 35 minutes at a maximum of -5° with 20 ml (30 mmol) of 1.6M butyllithium in hexane. After stirring in an ice--bath for 1.5 hours the mixture is cooled to -74° and there are added thereto 5 ml of hexamethylphosphoric acid triamide and, after 10 minutes, 3.30 g (30 mmol) of dicyclopropyl ketone. The mixture is left to come to room temperature during 6 hours and is stirred over the weekend. The reaction mixture is then poured into 200 ml of water, acidified to pH 7 with 4N hydrochloric acid and extracted four times with ethyl acetate. The combined organic extracts are washed twice with water, dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with methylene chloride/methanol (19:1) and subsequent recrystallization from ethyl acetate there is obtained 7-chloro-3-(3,3-dicyclopropyl-3-hydroxy-1-propynyl)-4,5 -dihydro-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 179-181°.

Example 41

2.72 g (10 mmol) of 7-chloro-3-ethynyl-4,5 dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are suspended in 30 ml of methanol and cooled to 10°. There are then added simultaneously thereto in portions within about 10 minutes 5 ml of 28% sodium hydroxide solution and 3 g of iodine. After stirring at room temperature for 1 hour the suspension is diluted with about 30 ml of water, suction filtered and the suction filter cake is dried. By two recrystallizations from methylene chloride and ethyl acetate and from dioxan there is obtained 7--chloro-4,5-dihydro-3-(2-iodoethynyl)-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 215-216°.

Example 42

4.0 g (69.5 mmol) of freshly powdered potassium hydroxide are stirred for 10 minutes in 40 ml of N,N-dimethylformamide and cooled to 10°. 5.48 g (17.3 mmol) of 7-chloro-4,5-dihydro-3-(3-hydroxy-1 -butynyl)-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one and 4.94 g (35 mmol) of methyl iodide are added thereto in succession, the ice-bath is removed and the mixture is stirred for a further 1 hour. The reaction mixture is poured into 200 ml of water and extracted five times with methylene chloride. The combined organic extracts are washed four times with water, dried over magnesium sulphate and evaporated. After recrystallization of the residue from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-(3--methoxy-1-butynyl)-5-methyl-6H -imidazo[1,5-a][1,4]-benzodiazepin-6-one of melting point 139-141°.

Example 43

2.35 g (42 mmol) of freshly powdered potassium hydroxide are stirred in 30 ml of dimethyl sulphoxide for 5 minutes. There are then added in succession 4.0 g (11.25 mmol) of 7-chloro-4,5-dihydro-3-[(1-hydroxycyclopentyl)ethynyl]-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one and 3.12 g (22.5 mmol) of methyl iodide and the mixture is stirred for a further 1 hour before the dimethyl sulphoxide is removed by evaporation. The residue is taken up in water and extracted three times with methylene chloride. The combined organic extracts are dried over magnesium sulphate, evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate/hexane (1:1). After recrystallization from ethyl acetate there is obtained 7-chloro-4,5-dihydro-3-[(1--methoxycyclopentyl)ethynyl]-5 -methyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one of melting point 174-175°.

Example 44

a) 3.73 g (10 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 3 hours with 1.30 g (12.5 mmol) of ethynyltrimethylsilane, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate/hexane (1:1). After crystallization from ethyl acetate and hexane there is obtained 7-chloro-4,5-dihydro-5-methyl-3-[(trimethylsilyl)ethynyl]-6H -imidazo[1,5-a][1,4]benzodiazepin--6-one of melting point 186-187°.

b) 12.7 g (37 mmol) of 7-chloro-4,5-dihydro-5-methyl-3--[(trimethylsilyl)ethynyl]-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are dissolved in 40 ml of methanol and treated with 40 ml of 1N potassium hydroxide solution. After stirring for 1 hour the methanol is distilled off and the aqueous suspension is cooled and suction filtered. After drying there is obtained 7-chloro-3-ethynyl-4,5--dihydro-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin--6-one of melting point 194-195°.

Example 45

a) 3.0 g (10.9 mmol) of 7-chloro-5,6-dihydro-5-methyl-6--oxo -4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde and 5.7 g (21.7 mmol) of triphenylphosphine are dissolved in 80 ml of methylene chloride at room temperature. Thereafter, the mixture is cooled with an ice-bath to 0° and at this temperature there is added dropwise thereto a solution of 4.0 g (12.0 mmol) of tetrabromomethane in 15 ml of methylene chloride. Thereafter, the mixture is stirred at room temperature for a further

6 hours and subsequently evaporated in a vacuum. The residue is suspended in ethyl acetate and heated under reflux for 30 minutes, cooled to 10° while stirring, suction filtered and dried. The crystalline crude product is recrystallized from alcohol and there is obtained 7-chloro-3-(2,2-dibromovinyl)-4,5 -dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one hydrobromide as white crystals of melting point 215-217°.

b) 3.3 g (6.44 mmol) of the thus-obtained compound are dissolved in 100 ml of methanol. A solution of 0.31 g (13.48 mmol) of sodium in 30 ml of methanol is added thereto. The reaction mixture is thereafter heated under reflux for 16 hours and subsequently evaporated in a vacuum. The residue is partitioned between water and methylene chloride and the aqueous phase is extracted with methylene chloride. The combined organic phases are washed with water, dried over magnesium sulphate, filtered and evaporated. The residue is dissolved in methylene chloride and chromatographed over 120 g of silica gel (in methylene chloride). Elution is carried out with a mixture of methylene chloride and ethyl acetate in the ratio 9:1, 8:2 and 7:3 (v/v). The fractions which are pure according to thin-layer chromatography are combined and recrystallized from ethyl acetate/hexane. There is obtained 3-(bromo-ethynyl)-7-chloro-4,5-dihydro-5 -methyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one as white crystals of melting point >190° (dec.).

Example 46

10.3 g (29 mmol) of acetonyltriphenylphosphonium chloride are suspended in 100 ml of tetrahydrofuran under argon. 3.3 g (29.4 mmol) of potassium tert.-butylate are added thereto and the mixture is thereafter stirred at room temperature for a further 30 minutes. After cooling

to 10° 4.0 g (14.5 mmol) of 7-chloro-5,6-dihydro-5-methyl--6-oxo-4H -imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde are added thereto and the mixture is stirred at 20° for 1 hour and under reflux for 6 hours. The reaction mixture is evaporated, the residue is partitioned between methylene chloride and water, the organic phase is washed with water and subsequently dried over magnesium sulphate, filtered and evaporated. After chromatography of the residue on silica gel with methylene chloride/ethyl acetate (8:2, 7:3 and 1:1) and subsequent recrystallization of the combined pure fractions from ethyl acetate/hexane there is obtained 7-chloro-4,5-dihydro-3--[(E)-3-oxo-1-butenyl]-5-methyl-6H -imidazo[1,5-a][1,4]-benzodiazepin-6-one as white crystals of melting point 235-237°.

Example 47

2.4 g (7.6 mmol) of 7-chloro-4,5-dihydro-3-[(E)-3-oxo--1-butenyl]-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin--6-one are dissolved in 50 ml of dimethylformamide while warming. Thereafter, the solution is diluted with 280 ml of ethanol. 0.6 g (15.8 mmol) of sodium borohydride is added to this solution and the mixture is stirred at 20° for 2.5 hours, thereafter a further 0.2 g of sodium borohydride is added thereto. After a total reaction period of 4.5 hours the mixture is evaporated in a vacuum. The residue, which still contains dimethylformamide, is poured on to ice/water and stirred at 0° for 1 hour. The crystallizate is filtered off under suction and dried. There is obtained 7-chloro-4,5-dihydro-3-[(E)-3-hydroxy-1-butenyl]--5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one as white crystals of melting point 232-233°.

Example 48

3.57 g (10 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 6.5 hours with 0.925 g (11 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is then evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-3-(3-hydroxy-3-methyl-1--butynyl)-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 165-167°.

Example 49

8.93 g (25 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature for 24 hours with 3.03 g (27 mmol) of 3-ethyl-1-pentyn-3-ol, 100 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 20 mg of copper(I) iodide in 60 ml of diethylamine. A further 0.87 g (7.7 mmol) of 3-ethyl-1-pentyn-3-ol as well as 50 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 50 mg of copper(I) iodide are added thereto and the mixture is stirred at the boiling temperature for 0.5 hour. The reaction mixture is subsequently evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After decolorizing the crude product with active charcoal and crystallization from ethyl acetate there is obtained 8-fluoro-3-(3-ethyl-3--hydroxy-1-pentynyl)-4,5 -dihydro-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one of melting point 135-136°.

Example 50

3.57 g (10 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 4 hours with 1.22 g (12.5 mmol) of 3-methoxy-3-methyl-1-butyne, 70 mg of bis--(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-3-(3 -methoxy-3-methyl-1-butynyl)-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 149-150°.

Example 51

7 g (19.9 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 3 hours with 2.5 ml (29 mmol) of propargyl ether, 100 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 30 mg of copper(I) iodide in 70 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate there is obtained 8-fluoro--4,5-dihydro-3-(3-methoxy-1-propynyl)-5 -methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 146-147°.

Example 52

3.6 g (10 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature for 16 hours with 1.5 g (11 mmol) of p-chlorophenylacetylene, 70 mg of bis-(tri-

phenylphosphine)-palladium(II) dichloride and 15 mg of copper(I) iodide in 35 ml of diethylamine. The reaction mixture is diluted with 175 ml of methylene chloride and washed three times with water. The organic phase is dried over magnesium sulphate and evaporated. By chromatography of the residue on silica gel and subsequent recrystallization from methylene chloride and ethyl acetate there is obtained 3-[(p-chlorophenyl)ethynyl]-8-fluoro-4,5-dihydro-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 221-222°.

Example 53

3.6 g (10 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at room temperature overnight with 1.5 g (11 mmol) of o-chlorophenylacetylene, 70 mg of bis-(triphenylphosphine-palladium(II) dichloride and 15 mg of copper(I) iodide in 20 ml of diethylamine. The reaction mixture is diluted with 175 ml of methylene chloride and washed three times with water. After drying and evaporation of the solution the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (99:1). By recrystallization of the evaporated eluate there is obtained 3-[(o-chlorophenyl)ethynyl]-8-fluoro-4,5-dihydro--5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 259-261°.

Example 54

1.27 g (5 mmol) of 3-ethynyl-8-fluoro-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are suspended in 10 ml of tetrahydrofuran and treated dropwise within 20 minutes at a maximum of -5° with 6.4 ml (10 mmol) of 1.6M butyllithium in hexane. After stirring in an ice-bath for 2 hours the mixture is cooled to -70°

and there are added thereto in succession 1.7 ml of hexamethylphosphoric acid triamide and 0.6 g (10 mmol) of acetone. The mixture is left to come to room temperature within 4.5 hours, left to stand overnight and poured into about 120 ml of water. After acidification with 4N hydrochloric acid the mixture is extracted four times with ether and six times with ethyl acetate, the combined extracts are dried over magnesium sulphate and evaporated. After chromatography of the residue on silica gel while eluting with ethyl acetate and after crystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-3-(3--hydroxy-3-methyl-1-butynyl)-5 -methyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one of melting point 163-164°.

Example 55

2.55 g (10 mmol) of 3-ethynyl-8-fluoro-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are suspended in 20 ml of tetrahydrofuran and treated dropwise within 30 minutes at -5° with 13 ml (20 mmol) of 1.6M butyllithium in hexane. After stirring in an ice-bath for 2 hours the mixture is cooled to -70° and 3.4 ml of hexamethylphosphoric acid triamide and 1.68 g (20 mmol) of cyclopropyl methyl ketone are added thereto in succession. The mixture is left to come to room temperature within 4 hours, stirred overnight and poured into about 200 ml of water. After acidification with 4N hydrochloric acid the mixture is extracted five times with ethyl acetate, the combined extracts are dried over magnesium sulphate and evaporated. The residue is chromatographed on silica gel while eluting with ethyl acetate and after crystallization from ethyl acetate there is obtained 8-fluoro-3-(3-cyclopropyl-3-hydroxy-1-butynyl)-4,5 -dihydro-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 191-192°.

Example 56

3.83 g (15 mmol) of 3-ethynyl-8-fluoro-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are suspended in 30 ml of tetrahydrofuran and treated dropwise within 30 minutes at a maximum of -5° with 20 ml (30 mmol) of 1.6M butyllithium in hexane. After stirring for two hours in an ice-bath the mixture is cooled to -70° and 5 ml of hexamethylphosphoric acid triamide and 2 g (28 mmol) of cyclobutanone are added thereto in succession. The mixture is left to come to room temperature within 5 hours, stirred overnight and poured into 300 ml of water. After acidification with 4N hydrochloric acid the mixture is extracted five times with ethyl acetate. The combined organic extracts are washed with water, dried over magnesium sulphate and evaporated. By chromatography of the residue on silica gel while eluting with ethyl acetate and crystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-3-[(1 -hydroxycyclobutyl)-ethynyl]-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 177-179°.

Example 57

3.0 g (9.5 mmol) of 8-fluoro-4,5-dihydro-3-(3-hydroxy--3-methyl-1-butynyl)-5-methyl-6H -imidazo[1,5-a][1,4]-benzodiazepin-6-one are dissolved in 20 ml of N,N-dimethylformamide and treated at 3° with 2.97 g (19 mmol) of ethyl iodide and 2.13 g of freshly powdered potassium hydroxide (38 mmol). After stirring for 5 minutes the cooling bath is removed and the mixture is left to come to room temperature. The reaction mixture is then poured into 200 ml of water, acidified with 4N hydrochloric acid and extracted four times with methylene chloride. The combined extracts are washed five times with water, dried over magnesium sulphate and evaporated. By recrystallization of

the crude product from ethyl acetate and hexane there is obtained 8-fluoro-3-(3-ethoxy-3-methyl-1-butynyl)-4,5--dihydro-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 136-138°.

Example 58

a) 67.8 g (190 mmol) of 8-fluoro-4,5-dihydro-3-iodo-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 8 hours with 23.4 g (238 mmol) of ethynyltrimethylsilane, 300 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 70 mg of copper(I) iodide in 280 ml of diethylamine and 25 ml of ethylene chloride. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with chloroform/ethyl acetate (3:1). By recrystallization from ethyl acetate there is obtained 8-fluoro-4,5-dihydro-5-methyl-3 -[(trimethylsilyl)ethynyl]-6H -imidazo-[1,5-a][1,4]benzodiazepin-6-one of melting point 184-185°.

b) In analogy to Example 44b), from the above compound there is obtained 3-ethynyl-8-fluoro-4,5-dihydro-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one (see Example 9).

Example 59

a) 4.0 g (15.43 mmol) of 8-fluoro-5,6-dihydro-5-methyl-6--oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde and 8.1 g (30.88 mmol) of triphenylphosphine are dissolved in 150 ml of methylene chloride at room temperature. Thereafter, the mixture is cooled with an ice-bath to 0° and at this temperature there is added dropwise thereto a solution of 5.6 g (16.88 mmol) of tetrabromomethane in 20 ml of methylene chloride. Thereafter, the mixture is stirred at room temperature for a further 4 hours and subsequently evaporated. The suspension obtained is cooled

to 0°, suction filtered and dried in a vacuum. The crude product is recrystallized from ethanol. There is obtained 3-(2,2-dibromovinyl)-8-fluoro-4,5 -dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one hydrobromide as white crystals of melting point >260° (dec.).

b) 3.4 g (6.85 mmol) of the above compound are dissolved in 100 ml of methanol. A solution of 0.33 g (14.35 mmol) of sodium in 30 ml of methanol is added thereto. Thereafter, the reaction mixture is heated under reflux for 16 hours and subsequently evaporated in a vacuum. The residue is partitioned between water and methylene chloride and the aqueous phase is extracted with methylene chloride. The combined organic phases are washed with water, dried over magnesium sulphate, filtered and evaporated. The residue is recrystallized from ethyl acetate/hexane. There is obtained 3-(bromoethynyl)-8--fluoro-4,5-dihydro-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one as white crystals of melting point 167°.

Example 60

6.78 g (20 mmol) of 4,5-dihydro-3-iodo-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to 100° in a pressure tube overnight with 80 mg of bis-(triphenylphosphine)-palladium(II) dichloride, 30 mg of copper(I) iodide and about 2 ml of propyne in 60 ml of diethylamine. The reaction mixture is then evaporated and the residue is chromatographed on 300 g of silica gel while eluting with ethyl acetate. By recrystallization of the crude product from ethanol there is obtained 4,5-dihydro-5-methyl-3-(1--propynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 206-207°.

Example 61

6.78 g (20 mmol) of 4,5-dihydro-3-iodo-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 7 hours with 1.75 g (25 mmol) of 3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)--palladium(II) dichloride and 15 mg of copper(I) iodide in 50 ml of diethylamine and 30 ml of ethylene chloride. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. After recrystallization from ethyl acetate and hexane there is obtained 4,5-dihydro-3-(3-hydroxy-1--butynyl)-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 161-162°.

Example 62

2.92 g (10 mmol) of 3-bromo-4,5-dihydro-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to 80° in a pressure tube for 24 hours with 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride, 30 mg of copper(I) iodide and 2.5 ml (20 mmol) of 3,3-dimethyl-1--butyne in 30 ml of diethylamine and 10 ml of ethylene chloride. The reaction mixture is evaporated, the residue is taken up in methylene chloride and washed with water. The organic solution is dried over magnesium sulphate and filtered through a silica gel pad. By crystallization from hexane there is obtained 3-(3,3-dimethyl-1-butynyl)-4,5--dihydro-5-methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6--one of melting point 148-150°.

Example 63

5.05 g (90 mmol) of freshly powdered potassium hydroxide are suspended in 50 ml of N,N-dimethylformamide and cooled to 3°. 6.0 g (22.5 mmol) of 4,5-dihydro-3-(3-

-hydroxy-1-propynyl)-5-methyl-6H -imidazo[1,5-a][1,4]-benzodiazepin-6-one and 6.39 g (45 mmol) of methyl iodide are added thereto in succession, the ice-bath is removed and the mixture is stirred for a further 1 hour. The reaction mixture is poured into 200 ml of water, acidified to pH 7 with 4N hydrochloric acid and extracted five times with methylene chloride. The combined organic extracts are dried over magnesium sulphate, evaporated and after crystallization of the residue from ethyl acetate there is obtained 4,5-dihydro-3-(3-methoxy-1 -propynyl)-5-methyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 114-115°.

Example 64

4.58 g (80 mmol) of freshly powdered potassium hydroxide are suspended in 65 ml of dimethyl sulphoxide and cooled to 5°. 5.67 g (19.2 mmol) of 4,5-dihydro-3-(3--hydroxy-3-methyl-1 -butynyl)-5-methyl-6H-imidazo[1,5-a]-[1,4]benzodiazepin-6-one and 5.47 g (38.5 mmol) of methyl iodide are added thereto in succession. The cooling bath is removed and the mixture is stirred for a further 1 hour. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (19.5:0.5). After crystallization from tert.-butyl methyl ether there is obtained 4,5-dihydro-3-(3-methoxy-3-methyl-1 -butynyl)-5-methyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 136-137°.

Example 65

a) 14.55 g (43 mmol) of ethyl 7-chloro-8-fluoro-5,6--dihydro-5-methyl-6-oxo-4H -imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate are heated to boiling under reflux for 15 minutes with 1.90 g (45.7 mmol) of sodium hydroxide in

80 ml of ethanol and 30 ml of water. The reaction mixture is then cooled and treated with 10.4 ml of 4N hydrochloric acid. By suction filtering the suspension obtained and drying the product there is obtained 7-chloro-8-fluoro--5,6-dihydro-6-oxo-4H -imidazo[1,5-a][1,4]benzodiazepine--3-carboxylic acid of decomposition point 260°.

b) 11.64 g (37.5 mmol) of 7-chloro-8-fluoro-5,6-dihydro--6-oxo -4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid are heated to 285° in a metal bath until the CO_2 cleavage has finished. The melt is poured into 50 ml of ethanol and the precipitated product is filtered off under suction and washed with ethanol. After drying there is obtained 7-chloro-8-fluoro-4,5-dihydro-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 234-235°.

c) 6.08 g (22.8 mmol) of 7-chloro-8-fluoro-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are stirred at 100° for 4 hours with 20 g (79.5 mmol) of iodine in 50 ml of N,N-dimethylformamide. The reaction mixture is evaporated, the residue is taken up in methylene chloride and water, decolorized with sodium thiosulphate and neutralized with sodium bicarbonate. The aqueous phase is separated and extracted four times with methylene chloride. The combined organic phases are dried over magnesium sulphate, evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate/hexane (1:1). There is obtained 7-chloro-8-fluoro--4,5-dihydro-3-iodo-5 -methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 218-219°.

d) 4.40 g (11.2 mmol) of 7-chloro-8-fluoro-4,5-dihydro-3--iodo-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 1.5 hours with 1.4 g (17 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-

-(triphenylphosphine)-palladium(II) dichloride and 20 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated, the residue is dissolved in methylene chloride and methanol and decolorized with active charcoal. By crystallization from methanol there is obtained 7-chloro-8-fluoro-4,5-dihydro-3-(3-hydroxy-3--methyl-1 -butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 208-209°.

Example 66

a) 25 g (85 mmol) of ethyl-5,6-dihydro-5,7-dimethyl-6--oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate are heated to boiling under reflux for 1 hour with 3.40 g (85 mmol) of sodium hydroxide in 200 ml of ethanol and 15 ml of water. After evaporation of the ethanol the residue is diluted with water and acidified with 21 ml of 4N hydrochloric acid. The suspension obtained is suction filtered and washed with water. By drying the filter cake there is obtained 5,6-dihydro-5,7 -dimethyl-6-oxo-4H--imidazo[1,5-a][1,4]benzodiazepine-3 -carboxylic acid of decomposition point 274-275°.

b) 22.20 g (81.8 mmol) of 5,6-dihydro-5,7-dimethyl-6-oxo--4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid are heated to 290-300° in a metal bath until the CO_2 cleavage has finished. The melt is dissolved in methylene chloride and ethanol and the solution is concentrated until methylene chloride no longer distils over. From this solution there crystallizes 4,5-dihydro-5,7 -dimethyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 224-225°.

c) 15.85 g (69.7 mmol) of 4,5-dihydro-5,7-dimethyl--6H-imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to 95° for 2.5 hours with 67 g (264 mmol) of iodine in 100 ml

of N,N-dimethylformamide. The reaction mixture is then poured into 450 ml of water, treated with methylene chloride, decolorized with sodium thiosulphate and neutralized with sodium bicarbonate. The aqueous phase is separated and extracted six times with methylene chloride. The combined organic phases are washed three times with water, dried over magnesium sulphate and evaporated. By chromatography of the residue on silica gel while eluting with ethyl acetate and recrystallization from ethyl acetate and hexane there is obtained 4,5-dihydro-3-iodo--5,7-dimethyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one of melting point 106-108°.

d) 5 g (14.2 mmol) of 4,5-dihydro-3-iodo-5,7-dimethyl-6H--imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 4.5 hours with 1.50 g (17.8 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 20 mg of copper(I) iodide in 40 ml of diethylamine. The reaction mixture is then evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. By recrystallization from ethyl acetate there is obtained 4,5-dihydro--3-(3-hydroxy-3-methyl-1-butynyl)-5,7 -dimethyl-6H--imidazo[a,5-a][1,4]benzodiazepin-6-one of melting point 165-167°.

Example 67

5.20 g (14 mmol) of 7-chloro-4,5-dihydro-3-iodo-5--methyl-6H -imidazo[1,5-a][1,4]benzodiazepin-6-one are heated to boiling under reflux for 4 hours with 1.04 g (18.5 mmol) of propargyl alcohol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 10 mg of copper(I) iodide in 35 ml of diethylamine. The reaction mixture is evaporated and the residue is suspended in methylene chloride. The suspension is suction filtered and the

filter cake is washed with ethyl acetate. After two successive recrystallizations from ethanol and N,N-dimethylformamide, respectively, there is obtained 7-chloro-4,5--dihydro-3-(3-hydroxy-1 -propynyl)-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one of melting point 250-252°.

Example 68

2.0 g (5 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H -imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are heated to boiling under reflux for 6 hours with 0.73 g (5.5 mmol) of 4-methoxyphenylacetylene, 50 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 50 mg of copper(I) iodide in 25 ml of diethylamine and 25 ml of N,N-dimethylformamide. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (99:1). After recrystallization from methylene chloride and ethyl acetate there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1-[(p-methoxyphenyl)-ethynyl]-9H -imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 186-187°.

Example 69

2.0 g (5 mmol) (S)-8-chloro-11,12,13,13a -tetrahydro-1-iodo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one are heated to boiling under reflux for 9 hours with 0.73 g (5.6 mmol) of 3-methoxyphenylacetylene, 65 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 65 mg of copper(I) iodide in 20 ml of diethylamine and 20 ml of N,N-dimethylformamide. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (99:1). By crystallization from methylene chloride and ethyl acetate there is obtained (S)-8-chloro-11,12,13,13a-tetrahydro-1-[(m-methoxyphenyl)ethynyl]-9H -imidazo[1,5-a]-

pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 204-205°.

Example 70

2.0 g (5 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H -imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are heated to boiling under reflux for 9 hours with 0.75 g (5.5 mmol) of 3-chlorophenylacetylene, 65 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 65 mg of copper(I) iodide in 20 ml of diethylamine and 20 ml of N,N-dimethylformamide. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (99.2:0.8). By recrystallization from methylene chloride and ethyl acetate there is obtained (S)-8-chloro-1-[(m--chlorophenyl)ethynyl]-11,12,13,13a -tetrahydro-9H--imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 207-209°.

Example 71

1.9 g (4.9 mmol) of (S)-8-chloro-11,12,13,13a-tetrahydro-1-iodo-9H -imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are heated to boiling under reflux for 3.5 hours with 0.71 g (5.2 mmol) of 2-chlorophenylacetylene, 65 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 65 mg of copper(I) iodide in 25 ml of diethylamine and 25 ml of N,N-dimethylformamide. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with methylene chloride/methanol (99:1). By recrystallization from methylene chloride and ethyl acetate there is obtained (S)-8-chloro-1-[(o-chloro- phenyl)ethynyl]-11,12,13,13a -tetrahydro-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 217-219°.

Example 72

a) 44.26 g (185 mmol) of (S)-11,12,13,13a-tetrahydro-9H--imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one are stirred at 100° for 4 hours with 162.8 g (645 mmol) of iodine in 300 ml of N,N-dimethylformamide. The reaction mixture is evaporated, the residue is taken up in water and methylene chloride, decolorized with sodium thiosulphate and neutralized with sodium bicarbonate. The aqueous phase is separated and extracted four times with methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated. By chromatography of the crude product on silica gel while eluting with ethyl acetate and subsequent recrystallization from methylene chloride and methanol there is obtained (S)--11,12,13,13a-tetrahydro-1-iodo-9H -imidazo[1,5-a]-pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 222-223°.

b) 3.65 g (10 mmol) of (S)-11,12,13,13a-tetrahydro-1--iodo-9H -imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin--9-one are heated to boiling under reflux for 1.5 hours with 1.26 g (15 mmol) of 2-methyl-3-butyn-2-ol, 70 mg of bis-(triphenylphosphine)-palladium(II) dichloride and 20 mg of copper(I) iodide in 30 ml of diethylamine. The reaction mixture is evaporated and the residue is chromatographed on silica gel while eluting with ethyl acetate. By recrystallization of the crude product from methanol and water there is obtained (S)-11,12,13,13a--tetrahydro-1-(3-hydroxy-3-methyl-1 -butynyl)-9H-imidazo-[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepin-9-one of melting point 128°.

Example 73

a) 27 g of 5,6-dihydro-5-methyl-4-oxo-4H-imidazo[1,5-a]-

thieno[3,2-f][1,4]diazepine-7-carboxylic acid are immersed in a flask filled with argon in a heating bath pre-heated to 280°. The substance melts with decarboxylation. After completion of the evolution of carbon dioxide (about 7 to 8 min.) the flask is cooled slightly. Even before it has solidified, the reaction mixture is mixed with 250 ml of trichloromethane. The solution is evaporated in a vacuum and the residue is recrystallized from ethyl acetate/diisopropyl ether. There is obtained 5,6-dihydro-5-methyl--4H-imidazo[1,5-a]thieno[3,2-f][1,4]diazepin-4-one of melting point 160-163°. After recrystallization from ethyl acetate the melting point amounts to 163-164°.

b) 22 g of 5,6-dihydro-5-methyl-4H-imidazo[1,5-a]thieno-[3,2-f][1,4]diazepin-4-one are dissolved in 330 ml of dimethylformamide and treated with 50.6 g of iodine. The mixture is stirred at room temperature for 24 hours and then at 30° for 18 hours. It is then poured into 9 l of saturated aqueous sodium hydrogen carbonate solution. This solution is extracted four times with trichloromethane. The trichloromethane solutions are washed in succession with aqueous sodium thiosulphate solution and with aqueous sodium chloride solution, then dried over sodium sulphate and evaporated in a vacuum. The residue is chromatographed through 2.5 kg of silica gel. An impurity is firstly eluted with trichloromethane. The main product is then eluted with trichloromethane/ethanol mixtures 199:1 and 99:1. These eluates are evaporated in a vacuum and the residue is crystallized several times from ethyl acetate/diisopropyl ether and then from ethyl acetate. There is obtained 5,6-dihydro-7-iodo-5-methyl-4H-imidazo-[1,5-a]thieno[3,2-f][1,4]diazepin-4-one of melting point 175-177°.

c) 5.52 g of 5,6-dihydro-7-iodo-5-methyl-4H-imidazo-[1,5-a]thieno[3,2-f][1,4]diazepin-4-one in 30 ml of di-

ethylamine are treated with 1.92 ml of 2-methyl-3-butyn-2-ol, 75 mg of bis-(triphenylphosphine)-palladium(II) chloride and 13 mg of copper(I) iodide. The mixture is stirred at reflux temperature for 2 hours. The reaction mixture is then evaporated in a vacuum. The residue is dissolved in dichloromethane and this solution is washed twice with water. After drying over sodium sulphate this solution is chromatographed through 300 g of silica gel. Unreacted starting material is first recovered with dichloromethane/ethanol mixtures 99:1, 98:2 and 97:3. There is then eluted with dichloromethane/ethanol mixtures 96:4 and 95:5 an oily substance which crystallizes from ethyl acetate/diethyl ether. There is obtained 5,6-dihydro-7-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-4H-imidazo[1,5-a]-thieno[3,2-f][1,4]diazepin-4-one of melting point 180-181°.

The following products are obtained in an analogous manner:

d) (S)-10,11,12,12a-Tetrahydro-1-(3-hydroxy-3-methyl-1-butynyl)-8H-imidazo[5,1-c]pyrrolo[1,2-a]thieno[2,3-e][1,4]-diazepin-8-one of melting point 145-147°;

e) 4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a]thieno[2,3-f][1,4]diazepin-6-one of melting point 198-200°;

f) (S)-10,11,12,12a-tetrahydro-1-(3-hydroxy-3-methyl-1-butynyl)-8H-imidazo[5,1-c]pyrrolo[1,2-a]thieno[3,2-e][1,4]-diazepin-8-one of melting point 142-144°.

Example 74

a) 5.1 g of 5,6-dihydro-7-iodo-5-methyl-4H-imidazo[1,5-a]-thieno[3,2-f][1,4]diazepin-4-one (prepared in accordance with Example 73) are dissolved in 47 ml of diethylamine and

20 ml of dimethylformamide, 1.75 ml of phenylacetylene, 105 mg of bis-(triphenylphosphine)-palladium(II) chloride and 17 mg of copper(I) iodide are then added. The mixture is stirred at room temperature for 2 hours and then concentrated in a vacuum. The residue is diluted with 200 ml of dichloromethane and washed twice with water. The aqueous washings are extracted twice with dichloromethane. The combined dichloromethane solutions are dried over sodium sulphate and chromatographed through 300 g of silica gel. Elution is carried out firstly with trichloromethane and trichloromethane/ethanol mixtures 199:1 and 99:1. There is then eluted with a trichloromethane/ethanol mixture 97:3 an oily substance which can be crystallized from isopropanol/water. After repeated recrystallizations from isopropanol/water there is obtained 5,6-dihydro-5-methyl-7-(phenylethynyl)-4H-imidazo[1,5-a]thieno[3,2-f][1,4]-diazepin-4-one of melting point 143-144°.

The following products are obtained in an analogous manner:

b) (S)-10,11,12,12a-Tetrahydro-1-(phenylethynyl)-8H-imidazo-[5,1-c]pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepin-8-one of melting point 159-160°;

c) 4,5-dihydro-5-methyl-3-(phenylethynyl)-6H-imidazo[1,5-a]-thieno[2,3-f][1,4]diazepin-6-one of melting point 200-202°;

d) (S)-10,11,12,12a-tetrahydro-1-(phenylethynyl)-8H-imidazo-[5,1-c]pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepin-8-one of melting point 218-220°.

Example A

Tablets of the following composition are manufactured in the usual manner:

	mg/tablet
7-Chloro-4,5-dihydro-3-(3-hydroxy-3--methyl-1-butynyl)-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one	0.2
Lactose	140
Maize starch	50.8
Polyvinylpyrrolidine	8
Magnesium stearate	1
Tablet weight	200

Example B

Capsules of the following composition are manufactured in the usual manner:

	mg/capsule
7-Chloro-4,5-dihydro-3-(3-hydroxy-3--methyl-1-butynyl)-5-methyl-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one	0.5
Lactose	40
Maize starch	8
Talc	1
Magnesium stearate	0.5
Capsule fill weight	50

Example C

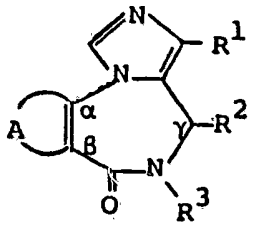
Injection solutions of the following composition are manufactured:

7-Chloro-4,5-dihydro-5-methyl-3--(1-propynyl)-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one	0.1 mg
Sodium chloride	45.0 mg
SESQUESTREN Na_2	0.5 mg
Acetic acid p.a.	0.5 mg
NaOH 1N ad pH 4.5	q.s.
Water for injection q.s. ad	5.0 ml

~~Claims~~

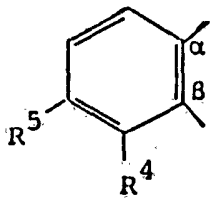
The claims defining the invention are as follows:

1. Compounds of the general formula

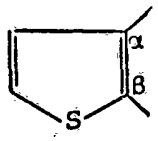


I

wherein A together with the two carbon atoms denoted by α and β signifies one of the groups

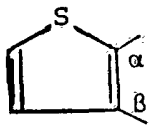


(a)



(b)

and



(c)

R^1 signifies one of the groups

$-CH=CH-R^6$ and $-C\equiv C-R^6$,

(d) (e)

R^2 signifies hydrogen and R^3 signifies lower alkyl

or R^2 and R^3 together signify dimethylene or trimethylene, R^4 and R^5 each signify hydrogen, halogen, trifluoromethyl or lower alkyl and R^6 signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or di-substituted by hydroxy, lower alkoxy, (C_3-C_7)--cycloalkyl or oxo, whereby the compounds of formula I have the (S)- or (R,S)-configuration with reference to the carbon atom denoted by γ when R^2 and R^3 together signify dimethylene or trimethylene and whereby the double bond present in group (d) has the E- and/or Z-configuration when R^6 is different from hydrogen.

2. Compounds in accordance with claim 1, wherein R^1 signifies the group $-CH=CH-R^6$ (d) and R^6 signifies hydrogen, lower alkyl, lower hydroxyalkyl, lower alkoxy-lower alkyl, (C_3-C_7)-cycloalkyl, hydroxy-(C_4-C_7)-cycloalkyl, lower alkoxy-(C_4-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-lower alkyl, phenyl or halogen or R^1 signifies the group $-C\equiv C-R^6$ (e) and R^6 signifies hydrogen, lower alkyl, lower hydroxyalkyl, lower alkoxy-lower alkyl, (C_3-C_7)-cycloalkyl, hydroxy-(C_4-C_7)-cycloalkyl, lower alkoxy-(C_4-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-lower alkyl or phenyl.

3. Compounds in accordance with claim 1 or 2, wherein R^1 signifies the group $-C\equiv C-R^6$ (e).

4. Compounds in accordance with claim 3, wherein R^6 signifies hydrogen, lower alkyl, lower hydroxyalkyl, lower alkoxyalkyl, (C_3-C_7)-cycloalkyl, hydroxy-(C_4-C_7)-cycloalkyl, lower alkoxy-(C_4-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-lower alkyl, (C_3-C_7)-cycloalkyl-lower hydroxyalkyl or (C_3-C_7)-cycloalkyl-lower alkoxyalkyl.

5. Compounds in accordance with claim 4, wherein R^6 signifies hydrogen, lower alkyl, lower 1-hydroxyalkyl, lower 1-alkoxyalkyl, (C_3-C_7)-cycloalkyl, 1-hydroxy-(C_4-C_7)-cycloalkyl, 1-(lower alkoxy)-(C_4-C_7)-cycloalkyl or 1-[(C_3-C_7)-cycloalkyl]-lower 1-hydroxyalkyl, especially lower alkyl, lower 1-hydroxyalkyl or (C_3-C_7)-cycloalkyl.

6. Compounds in accordance with any one of claims 1 to 5, wherein R^2 signifies hydrogen and R^3 signifies methyl or wherein R^2 and R^3 together signify dimethylene or trimethylene and the carbon atom denoted by γ has the (S)-configuration.

7. Compounds in accordance with any one of claims 1 to 6, wherein A signifies a residue of formula (a) and one of R^4 and R^5 signifies hydrogen and the other signifies hydrogen or halogen.

8. Compounds in accordance with claim 7, wherein R^4 and R^5 both signify hydrogen or R^4 signifies hydrogen and R^5 signifies fluorine or R^4 signifies chlorine or bromine and R^5 signifies hydrogen.

9. 7-Chloro-4,5-dihydro-5-methyl-3-(1-propynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

10. 7-Chloro-4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

11. 7-Bromo-4,5-dihydro-3-(3-hydroxy-3-methyl-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

12. 7-Chloro-4,5-dihydro-3-(3-hydroxy-1-butynyl)-5-methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

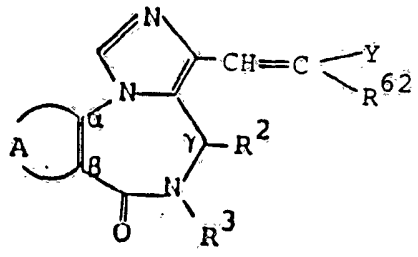
13. 4,5-Dihydro-5-methyl-3-(1-propynyl)-6H-imidazo-[1,5-a][1,4]benzodiazepin-6-one.

14. 7-Chloro-4,5-dihydro-5-methyl-3-(3-methyl-1--butynyl)-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

15. 7-Chloro-4,5-dihydro-3-(3-hydroxy-1-propynyl)-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

16. 7-Chloro-3-(cyclopropylethynyl)-4,5-dihydro-5--methyl-6H-imidazo[1,5-a][1,4]benzodiazepin-6-one.

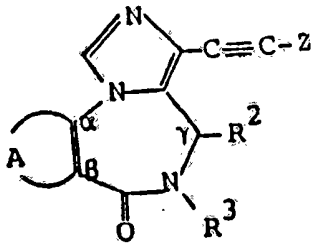
17. Compounds of the general formula



IVa

wherein Y and R^{62} each signify halogen and A, R^2 and R^3 have the significance given in claim 1.

18. Compounds of the general formula

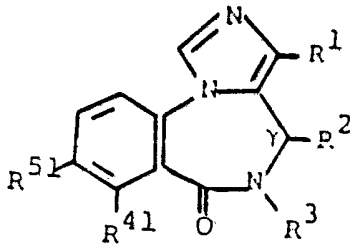


VIII

wherein Z signifies a protecting group and A, R^2 and

R^3 have the significance given in claim 1.

19. Compounds of the general formula



IX

wherein one of R^{41} and R^{51} signifies amino and the other signifies hydrogen, halogen, trifluoromethyl or lower alkyl and R^1, R^2 and R^3 have the significance given in claim 1.

20. An imidazodiazepine derivative substantially as hereinbefore described with reference to any one of the Examples 1a or c, 2 to 64, 65b, c or d, 66b, c or d or 67 to 74.

21. A process for the manufacture of a compound in accordance with any one of claims 1 to 16, which process comprises

a) reacting a compound of the general formula

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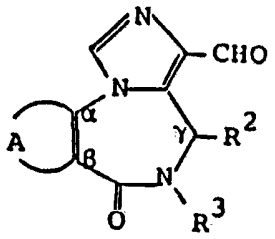


II

wherein A, R^2 and R^3 have the significance given in claim 1,

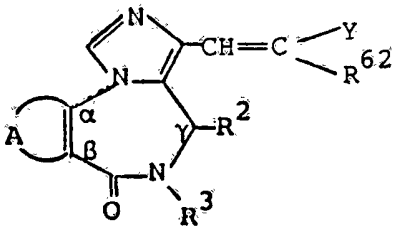
with a compound of the general formula

$$(Ar)_3P=CH-R^{61} \qquad III$$

wherein R^{61} signifies hydrogen, halogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or disubstituted by lower alkoxy, (C_3-C_7)-cycloalkyl or oxo and Ar signifies an aryl residue;

or

b) dehydrohalogenating a compound of the general formula



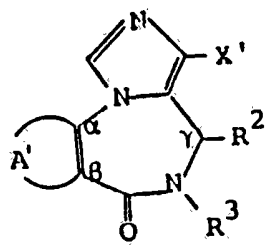
IV

wherein R^{62} signifies hydrogen or halogen and Y signifies halogen, and A, R^2 and R^3 have the significance given in claim 1;

or

c) treating a compound of formula I in which R^1 signifies group (e) and R^6 signifies hydrogen with an agent yielding a saturated lower hydrocarbon residue which is optionally mono- or disubstituted by hydroxy, lower alkoxy, (C_3-C_7)-cycloalkyl or oxo or an aryl residue or halogen; or

d) reacting a compound of the general formula



VI

wherein R^2 and R^3 have the significance given in claim 1 and X' signifies bromine or iodine and A' signifies a residue of formula (a), (b) or (c), with the proviso that where A' signifies a residue of formula (a) and R^4 and/or R^5 signify halogen, this halogen is fluorine or chlorine when X' signifies bromine and is fluorine, chlorine or bromine when X' signifies iodine,

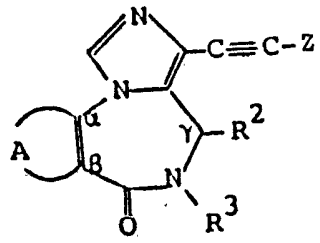
with a compound of the general formula

$$HC\equiv C-R^{64} \qquad \text{VII}$$

wherein R^{64} signifies hydrogen, aryl or a saturated lower hydrocarbon group which is optionally mono- or disubstituted by hydroxy, lower alkoxy, (C_3-C_7)-cycloalkyl or oxo;

or

e) cleaving off the protecting group from a compound of the general formula

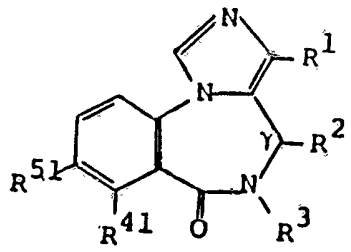


VIII

wherein R^2, R^3 and A have the significance given in claim 1 and Z signifies a protecting group;

or

f) replacing the amino group in a compound of the general formula



IX

wherein R^1, R^2 and R^3 have the significance given in claim 1 and one of R^{41} and R^{51} signifies amino and the other signifies hydrogen, halogen, trifluoromethyl or lower alkyl,

by a hydrogen or halogen atom; or

g) reducing a compound of formula I in which R^1 signifies a residue of formula (e) and in which, where A signifies a residue of formula (a), R^4 and/or R^5 do not

signify iodine, to the corresponding compound of formula I in which R^1 signifies a residue of formula (d); or

h) treating a compound of formula I in which R^1 signifies a residue of formula (d) or (e) and R^6 signifies a saturated lower hydrocarbon group which is substituted by hydroxy with an agent yielding a lower alkyl residue; or

i) reducing the carbonyl group in a compound of formula I in which R^1 signifies group (d) or (e) and R^6 signifies a saturated lower hydrocarbon group which is substituted by oxo.

22. A process of preparing an imidazodiazepine derivative which process is substantially as hereinbefore described with reference to any one of Examples 1 to 74.

23. An imidazodiazepine derivative when prepared by the process as defined in claim 21 or claim 22.

24. A pharmaceutical composition comprising a compound of any one of claims 1 to 16 together with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

25. A pharmaceutical composition substantially as hereinbefore described with reference to any one of Examples A to C.

26. A method for treating convulsions, anxiety states, stress conditions, excitation states or sleep disorders and/or of partially or completely selectively antagonizing some or all activities which 1,4-benzodiazepines having tranquillizing activity or other substances display via central benzodiazepine receptors in a patient in need of said treatment, which method comprises administering to said patient an effective amount of a compound of any one of claims 1 to 16, 20 or 23 or a composition of claim 24 or claim 25.

DATED this TWENTY-EIGHTH day of AUGUST 1990
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