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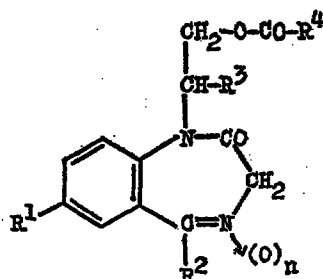


(54) BENZODIAZEPINE DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with benzodiazepine derivatives and a process for the manufacture thereof.

The benzodiazepine derivatives provided by the present invention are compounds of the general formula



, wherein R^1 represents a halogen atom or a nitro group, R^2 represents a phenyl, halophenyl or pyridyl group, R^3 represents an alkoxy group, R^4 represents a haloalkyl, alkoxyalkyl, carboxyalkyl, monoalkylamino or dialkylamino group, an alkyl group which is substituted by $-NR^6R^7$ (in which R^6 and R^7 each represent a hydrogen atom or an alkyl group or R^6 and R^7 together with the nitrogen atom to which they are attached represent a 5- or 6-membered saturated heterocyclic ring which may contain an oxygen atom) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms and n stands for zero or 1,

and salts thereof.

As used in this description and in the claims appended hereto, the term "alkyl" either alone or in combinations such as "alkoxy", "haloalkyl", "alkoxyalkyl", "carboxyalkyl" and the like includes straight-chain and branched-chain alkyl groups containing 1 to 6, preferably 1 to 4, carbon atoms such as methyl, ethyl, isopropyl and the like. The term "haloalkyl" includes monohaloalkyl, dihaloalkyl and trihaloalkyl groups. The term "halogen" includes fluorine, chlorine, bromine and iodine.

When R^4 represents a haloalkyl group, this can be, for example, a monohaloalkyl group such as chloromethyl or a dihaloalkyl group such as dichloromethyl. When R^4 represents an alkoxyalkyl group, this can be, for example, a methoxymethyl group. When R^4 represents a carboxyalkyl group, this can be, for example, an ω -carboxyalkyl

group such as 2-carboxyethyl. When R^4 represents a monoalkylamino group, this can be for example, methylamino or ethylamino. When R^4 represents an alkyl group substituted by NR^6R^7 , this can be, for example, an aminoalkyl group such as aminomethyl, a dialkylaminoalkyl group such as diethylaminomethyl or an alkyl group substituted by a 1-pyrrolidinyl, piperidino or morpholino group. When R^4 represents an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms, the hetero atoms are especially nitrogen, oxygen or sulphur atoms or a combination of any two thereof. For example, R^4 can represent an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two nitrogen atoms or one oxygen or sulphur atom or one oxygen or sulphur atom and one nitrogen atom, especially a furan, thiophene, oxazole, isoxazole, pyrazole, pyridine or pyridazine heterocycle which may be substituted by one or two alkyl groups. Examples of such heterocycles are the 2-furyl group, the 4-methyl-5-oxazolyl group, the 5-methyl-3-isoxazolyl group, the 1,5-dimethyl-3-pyrazolyl group, the 2-, 3- or 4-pyridyl group, the 2-pyridazinyl group and the 2-thienyl group.

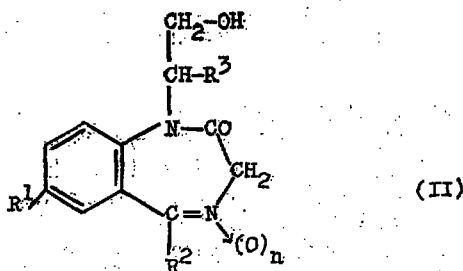
Among the compounds of formula I, those are preferred in which R^1 represents a chlorine atom or a nitro group. When R^2 represents a halophenyl group, the halo substituent is preferably present in the 2-position of the phenyl ring. When R^2 represents a pyridyl group, the 2-pyridyl group is preferred. Further preferred compounds are those in which R^2 represents a phenyl, 2-chlorophenyl or 2-fluorophenyl group. Examples of preferred values for R^4 are: pyridyl (especially 3-pyridyl and 2-pyridyl), pyrazinyl (e.g. 2-pyrazinyl), halomethyl (e.g. chloromethyl), carboxyalkyl (e.g. 2-carboxyethyl), alkoxyalkyl (e.g. methoxymethyl) and alkylamino (e.g. methylamino and ethylamino). Typical examples of preferred compounds of formula I are

2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl picolinate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl pyrazine-2-carboxylate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methoxyacetate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl ethylcarbamate and
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-(2-methoxyethyl methylcarbamate.

A particularly preferred compound is 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate.

According to the process provided by the present invention, the benzodiazepine derivatives aforesaid (that is to say, the compounds of formula I and their salts) are manufactured by

(a) converting the primary hydroxy group in the side-chain of a compound of the general formula



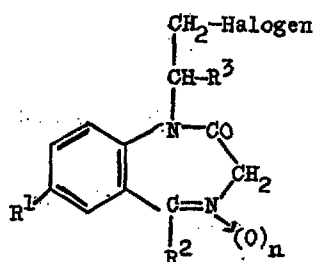
, wherein R^1 , R^2 , R^3 and n have the significance given earlier, into a group of the formula



(III)

, wherein R^4 has the significance given earlier,
by reaction with a suitable acylating agent or

- 5 (b) for the manufacture of a compound of formula I in which R^4 represents a
haloalkyl or alkoxyalkyl group, an alkyl group which is substituted by $-\text{NR}^6\text{R}^7$ (R^6
and R^7 having the significance given earlier) or an optionally substituted 5- or 6-
membered aromatic heterocycle containing one or two hetero atoms, replacing the
aliphatically-bound halogen atom in the side-chain of a compound of the general for-
mula



(IV)

, wherein R^1 , R^2 , R^3 and n have the significance given earlier,
by a group of the formula

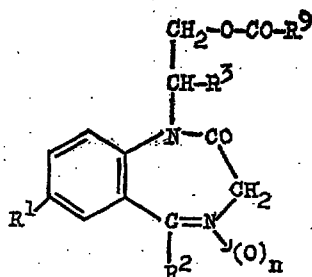


(V)

- 15 , wherein R^8 represents a haloalkyl or alkoxyalkyl group, an alkyl group which
is substituted by $-\text{NR}^6\text{R}^7$ (R^6 and R^7 having the significance given earlier) or
an optionally substituted 5- or 6-membered aromatic heterocycle containing one
or two hetero atoms,

or

- 20 (c) for the manufacture of a compound of formula I in which R^4 represents an alkyl
group which is substituted by $-\text{NR}^6\text{R}^7$ (R^6 and R^7 having the significance given
earlier), reacting a compound of the general formula



(VI)

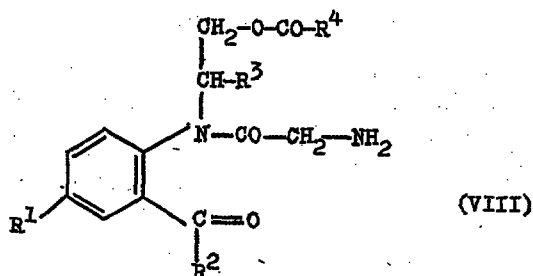
- 25 , wherein R^1 , R^2 , R^3 and n have the significance given earlier and R^9 represents
an alkyl group which is substituted by a suitable leaving atom or group,
with an amine of the general formula



(VII)

, wherein R^6 and R^7 have the significance given earlier,
or

(d) for the manufacture of a compound of formula I in which n stands for zero, cyclising a compound of the general formula



, wherein R¹, R², R³ and R⁴ have the significance given earlier,

5

or

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(e) for the manufacture of a compound of formula I in which n stands for 1, oxidising in the 4-position a corresponding compound of formula I in which n stands for zero
or

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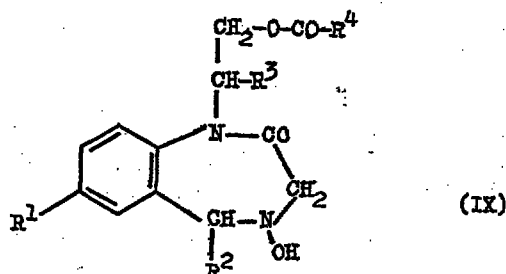
(f) for the manufacture of a compound of formula I in which n stands for zero, deoxygenating in the 4-position a corresponding compound of formula I in which n stands for 1
or

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(g) for the manufacture of a compound of formula I in which n stands for zero, dehydrating a compound of the general formula

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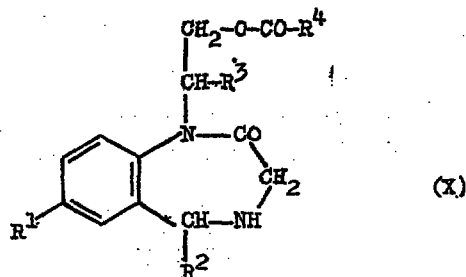


, wherein R¹, R², R³ and R⁴ have the significance given earlier,
or

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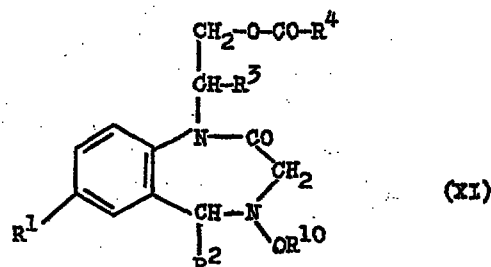
(h) for the manufacture of a compound of formula I in which n stands for zero, oxidising or dehydrogenating a compound of the general formula

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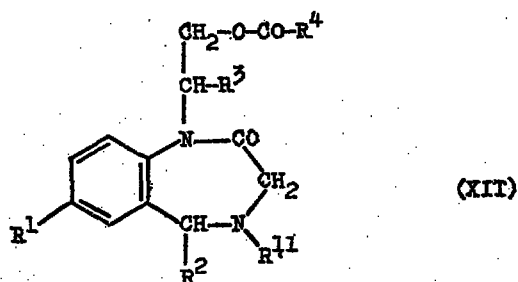
, herein R¹, R², R³ and R⁴ have the significance given earlier,
at the 4,5-bond or

- (i) for the manufacture of a compound of formula I in which n stands for zero, converting a compound of the general formula



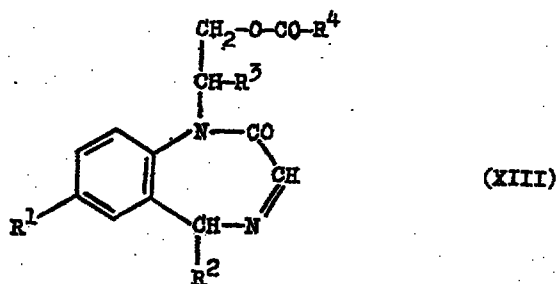
, wherein R^1 , R^2 , R^3 and R^4 have the significance given earlier and R^{10} represents an acyl group,
into the corresponding 4,5-dehydro compound by treatment with a base
or

- (j) for the manufacture of a compound of formula I in which n stands for zero, converting a compound of the general formula



, wherein R^1 , R^2 , R^3 and R^4 have the significance given earlier and R^{11} represents an alkylsulphonyl or arylsulphonyl group,
into the corresponding 4,5-dehydro compound by treatment with a strong base
or

- (k) for the manufacture of a compound of formula I in which n stands for zero, rearranging a compound of the general formula



, wherein R^1 , R^2 , R^3 and R^4 have the significance given earlier,
to the corresponding 4,5-dehydro compound and

- (l) converting a compound obtained into a salt if desired.

According to embodiment (a) of the process provided by this invention, compounds of formula I are manufactured by converting the primary hydroxy group in the side-chain of a compound of formula II into a group of formula III.

The compounds of formula II required as starting materials for embodiment (a) can be prepared by replacing the aliphatically-bound halogen atom in the side-chain of a compound of formula IV hereinbefore by a hydroxy group. This can, for example, be effected by firstly converting a compound of formula IV into the corresponding acetate and thereupon subjecting the acetate to a hydrolysis or alcoholysis in the

presence of catalytic amounts of a base. These two steps can also be carried out in a single operation. If, for example, a compound of formula IV is heated under anhydrous conditions with potassium acetate (e.g. in a mixture of toluene and dimethylformamide), there is chiefly obtained the corresponding acetoxy compound which can be subsequently hydrolysed or alcoholysed to the hydroxy compound. On the other hand, if one works in the presence of water (e.g. in dimethylformamide/water in the proportion of about 20:1), under otherwise identical conditions to those described earlier, a hydroxy compound of formula II is directly obtained.

If it is desired to manufacture a compound of formula I in which R^4 represents a monoalkylamino group in accordance with embodiment (a), a compound of formula II is reacted with an isocyanate of the general formula



(XIV)

wherein R^{12} represents an alkyl group.

Examples of isocyanates of formula XIV are methyl isocyanate, ethyl isocyanate and the like. For the manufacture of the other compounds of formula I, i.e. those in which R^4 represents a group other than a monoalkylamino group, a compound of formula II is reacted with a reactive derivative of a carboxylic acid of the general formula



(XV)

wherein R^{13} represents a haloalkyl, alkoxyalkyl, carboxyalkyl or dialkylamino group, an alkyl group which is substituted by $-NR^6R^7$ (R^6 and R^7 having the significance given earlier) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms.

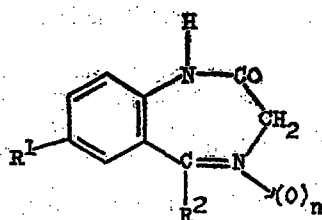
If the group R^{13} contains a primary or secondary amino group, this can carry a protecting group (e.g. a formyl group) which is removed after the acylation.

As the reactive derivative of a carboxylic acid of formula XV for the acylation of a compound of formula II there can be used, for example, an anhydride (e.g. succinic acid anhydride, chloroacetic acid anhydride and the like), an acid halide (e.g. dichloroacetyl chloride, furan-2-carboxylic acid chloride, 5-methyl-isoxazole-3-carboxylic acid chloride, isonicotinoyl chloride hydrochloride, nicotinoyl chloride and the like), an imidazolidine (e.g. picolinic acid imidazolidine, pyrazine-2-carboxylic acid imidazolidine, methoxyacetic acid imidazolidine, 4-methyloxazole-5-carboxylic acid imidazolidine, 1,5-dimethylpyrazole-3-carboxylic acid imidazolidine, nicotinic acid imidazolidine and the like) or other derivatives suitable as acylating agents.

The reaction conditions are not critical and can readily be selected by any person skilled in the art depending on the reactive derivative of the carboxylic acid or isocyanate selected as the acylating agent. For example, the reaction can be carried out at room temperature or at a temperature above or below room temperature, depending in each case on the reagent selected. In addition, the reaction is expediently carried out in a customary inert organic solvent such as a hydrocarbon (e.g. benzene, toluene and the like), a chlorinated hydrocarbon (e.g. methylene chloride and the like), an ether (e.g. tetrahydrofuran and the like), dimethylformamide, pyridine and the like.

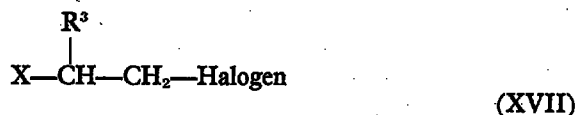
According to embodiment (b) of the process provided by this invention, the aliphatically-bound halogen atom in the side-chain of a compound of formula IV is replaced by a group of formula V.

The compounds of formula IV required as starting materials for embodiment (b) can be prepared by reacting a compound of the general formula



(XVI)

, wherein R^1 , R^2 and n have the significance given earlier, with a compound of the general formula



wherein R^3 has the significance given earlier and X represents a halogen atom. The reaction of a compound of formula XVI with a compound of formula XVII such as, for example, 1,2-dichloro-1-methoxyethane, can be carried out in an inert organic solvent such as a hydrocarbon (e.g. benzene, toluene and the like), dimethylformamide, an ether (e.g. dioxan or tetrahydrofuran), an alcohol (e.g. tert.butanol) and the like or in a mixture of such organic solvents. The reaction is suitably carried out at a temperature of, for example, between -50°C and 120°C . A compound corresponding to formula XVII in which X , instead of representing a halogen atom, represents an equivalent leaving group such as a mesyloxy, tosyloxy group or like group can be used in this reaction. It is expedient to first transform a compound of formula XVI into a 1-alkali metal derivative before the reaction with a compound of formula XVII. This 1-alkali metal derivative can, for example, be obtained with the aid of an alkali metal lower alcoholate such as sodium methylate, an alkali metal hydride such as sodium hydride, an alkali metal amide such as sodium amide and like agents. The reaction of a compound of formula XVI with a compound of formula XVII can, however, also be carried out in the presence of a base such as an alkali hydroxide (e.g. sodium hydroxide) or triethylamine.

The replacement of the aliphatically-bound halogen atom in the side-chain of a compound of formula IV by a group of formula V is expediently carried out by reaction with a suitable salt of a corresponding carboxylic acid of the general formula



wherein R^8 has the significance given earlier. If the group R^8 in formula XVIII contains a primary or secondary amino group, this can carry a protecting group (e.g. a formyl group) which is removed after the reaction with a compound of formula IV. Especially suitable salts are the silver, potassium or sodium salts as well as salts of suitable amines (e.g. trialkylamines such as triethylamine); as typical anions there may be mentioned, for example, the nicotinate, the thiophene-2-carboxylate and the formylglycinate anions. If amine salts are used, these can also be prepared in situ; that is to say, a compound of formula VI is reacted with the corresponding acid in the presence of a suitable amine. It is expedient to carry out the reaction in an inert organic solvent, for example, in a hydrocarbon such as benzene, toluene and the like, in a ketone such as acetone, methyl ethyl ketone and the like, in dimethylformamide etc. Depending on the reagents selected, the reaction can be carried out at a temperature between room temperature and the reflux temperature of the reaction mixture.

According to embodiment (c) of the process provided by this invention, a compound of formula VI is reacted with an amine of formula VII.

The compounds of formula VI required as starting materials for embodiment (c) can be prepared by acylating a compound of formula II hereinbefore with a reactive derivative of a carboxylic acid of the general formula



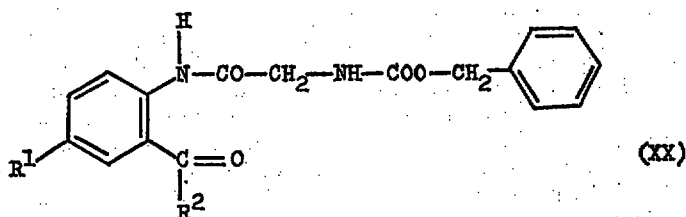
wherein R^9 has the significance given earlier. This acylation is effected in accordance with the procedure described earlier for the reaction of a compound of formula II with a reactive derivative of a carboxylic acid of formula XV or, when R^9 represents a group other than a monohaloalkyl group, in close analogy to said procedure and therefore need not be more precisely explained herein.

In formula VI, R^1 represents an alkyl group which is substituted by a suitable leaving atom or group and this leaving atom or group can be, for example, a chlorine, bromine or iodine atom or an alkylsulphonyloxy group (e.g. methanesulphonyloxy), an arylsulphonyloxy group (e.g. benzenesulphonyloxy or p-toluenesulphonyloxy) and the

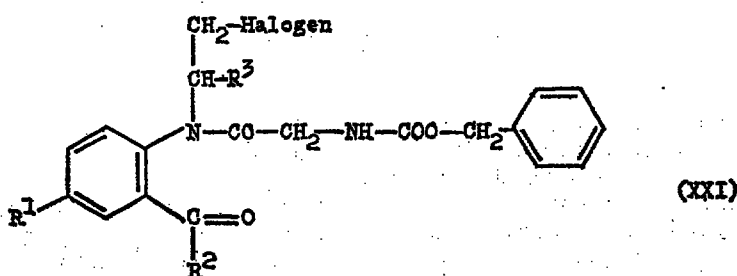
like. The reaction of a compound of formula VI with an amine of formula VII is expediently carried out in an inert organic solvent, for example, in a hydrocarbon such as benzene, toluene and the like, in a chlorinated hydrocarbon such as methylene chloride and the like, in dimethylformamide etc. Depending on the nature of the compound of formula VI and the amine of formula VII employed, the reaction can be carried out at a temperature between room temperature and the reflux temperature of the solvent.

According to embodiment (d) of the process of this invention, a compound of formula VIII is cyclised.

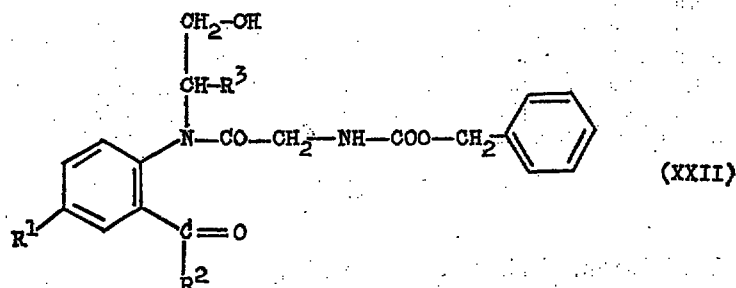
The compounds of formula VIII required as starting materials for embodiment (d) can be prepared, for example, by reacting a compound of the general formula



, wherein R^1 and R^2 have the significance given earlier, with a compound of formula XVII in an analogous manner to the procedure described earlier for the preparation of compounds of formula IV, replacing the aliphatically-bound halogen atom in a resulting compound of the general formula

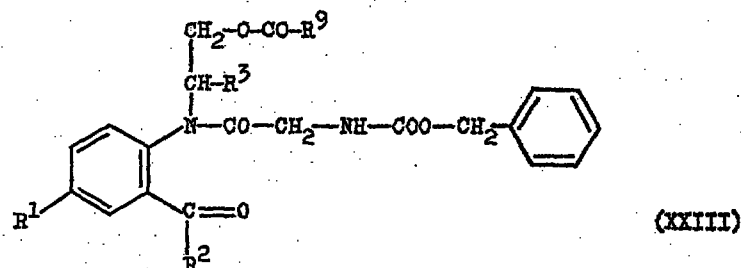


, wherein R^1 , R^2 and R^3 have the significance given earlier, by a hydroxy group in an analogous manner to the procedure described earlier for the preparation of compounds of formula II, reacting a resulting compound of the general formula



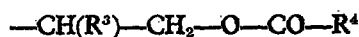
, wherein R^1 , R^2 and R^3 have the significance given earlier, with an isocyanate of formula XIV or a reactive derivative of a carboxylic acid of formula XV in an analogous manner to the procedure described earlier and thereupon cleaving off the carbobenzyloxy group. The aliphatically-bound halogen atom in a compound of formula XXI can also be replaced by a group of formula V in an analogous manner to the procedure described earlier and the carbobenzyloxy group can thereupon be cleaved off or the compound of formula XXII can be acylated with a

reactive derivative of a carboxylic acid of formula XIX in an analogous manner to the process described earlier, the so-obtained compound of the formula

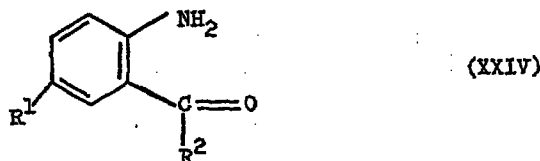


, wherein R^1 , R^2 , R^3 and R^9 have the significance given earlier, reacted with an amine of formula VII and the carbobenzyoxy group thereupon cleaved off.

According to another procedure, a substituent of the general formula



in which R^3 and R^4 have the significance given earlier can be introduced into a compound of the general formula



, wherein R^1 and R^2 have the significance given earlier, the carbobenzyoxyglycyl group introduced into the product obtained and the carbobenzyoxy group subsequently cleaved off.

The cleaving off of the carbobenzyoxy group can, for example, be carried out by catalytic hydrogenation or by means of a hydrohalic acid in the presence of acetic acid. The catalytic hydrogenation can be effected in glacial acetic acid/HCl or ethanol/HCl and the like. The cleaving off by means of a hydrohalic acid in glacial acetic acid can be carried out in the presence of an inert organic solvent such as a chlorinated hydrocarbon (e.g. methylene chloride) and the like and at a temperature between -20°C and room temperature.

If the carbobenzyoxy group is cleaved off from a compound of formula XXI, XXII or XXIII and the resulting compound is cyclised, there is obtained a corresponding compound of formula IV, II or VI respectively in which n stands for zero.

The cyclisation of a compound of formula VIII in accordance with embodiment (d) of the process can be carried out in an alkaline, neutral or acidic medium and in any desired inert organic solvent such as a hydrocarbon, a chlorinated hydrocarbon, an ether, glacial acetic acid, an alcohol, dimethylformamide and the like. Temperature and pressure are not critical factors, but it is expedient to carry out the cyclisation at temperatures in a range of ca $0^\circ-150^\circ\text{C}$.

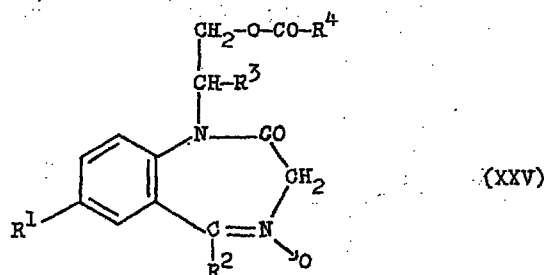
It will be appreciated that the compounds of formula VIII prepared in the manner described earlier can be cyclised to the compounds of formula I in which n stands for zero without isolation from the medium in which they are prepared.

The oxidation of a compound of formula I in which n stands for zero to a corresponding compound of formula I in which n stands for 1 (i.e. a $\text{N}^{\text{+}}$ -oxide) in accordance with embodiment (e) of the present process can be carried out using, for example, as the oxidising agent an organic peracid such as peracetic acid, trifluoroperacetic acid, perbenzoic acid, *m*-chloroperbenzoic acid, perphthalic acid and the like. The temperature for this oxidation is not critical and can therefore vary within wide limits. It is expedient to carry out the oxidation in an inert organic solvent, for example, in a halogenated hydrocarbon such as methylene chloride, in an aromatic hydrocarbon such as benzene, in an ether such as diethyl ether and the like.

The deoxidation of a compound of formula I in which n stands for 1 to a corresponding compound in which n stands for zero (i.e. a 4-desoxide) in accordance with embodiment (f) of the present process can, for example, be carried out by hydrogenation in the presence of Raney-nickel, expediently in an inert organic solvent such as a hydrocarbon (e.g. benzene or toluene), an alcohol, an ether (e.g. dioxan), ethyl acetate and the like at room temperature and normal pressure or elevated pressure. Another suitable method is treatment with a phosphorus trihalide such as phosphorus trichloride, expediently in an inert organic solvent such as a hydrocarbon (e.g. benzene and the like) or a chlorinated hydrocarbon and at room temperature, although temperatures above and below room temperature can likewise be employed. The deoxidation can also be effected with zinc and glacial acetic acid in an organic solvent such as glacial acetic acid, a chlorinated hydrocarbon, an ether, an alcohol and the like and expediently at temperatures between ca -20°C and 50°C . The use of a specific deoxidising agent is largely governed by the functional groups present in the molecule so as to avoid unfavourable side-reactions as far as possible. Thus, where a haloalkyl and/or a nitro group is present in the molecule, the deoxidation is expediently carried out with a phosphorus trihalide.

According to embodiment (g) of the process provided by the present invention, a compound of formula IX is dehydrated.

The compounds of formula IX required as starting materials for embodiment (g) can be prepared by reducing a compound of the general formula



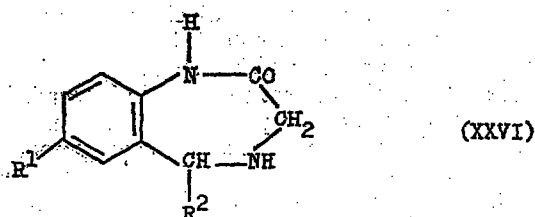
, wherein R^1 , R^2 , R^3 and R^4 have the significance given earlier, in the presence of platinum oxide.

It is expedient to carry out this reduction in an organic solvent such as glacial acetic acid, an alcohol and the like and at a temperature between ca 0°C and 50°C , preferably at room temperature.

The dehydration of a compound of formula IX in accordance with embodiment (g) yields a corresponding compound which contains a double-bond in the 4,5-position and can, for example, be carried out with a carbodiimide such as cyclohexylcarbodiimide and the like. The dehydration is expediently carried out in an inert organic solvent such as a hydrocarbon (e.g. benzene or toluene), an ether (e.g. dioxan) and the like. The dehydration is suitably carried out at a temperature of, for example, between -20°C and 100°C . In this dehydration, there is frequently observed the formation of a corresponding isomeric 3,4-dehydro compound of formula XIII. However, this latter compound can, as described in detail hereinafter, be readily isomerised to a 4,5-dehydro compound; for example, with a base such as an alkali alkoxide (e.g. sodium methoxide), triethylamine and the like.

According to embodiment (h) of the process provided by this invention, a compound of formula X is oxidised or dehydrogenated.

The compounds of formula X required as starting materials for embodiment (h) can be prepared from compounds of the general formula



, wherein R^1 and R^2 have the significance given earlier,

in an analogous manner to the process described earlier for the preparation of compounds of formula I from compounds of formula XVI. However, before carrying out the acylation, a protecting group such as the carbobenzoxy group must be introduced at the 4-position and subsequently hydrogenolytically removed.

The oxidation of a compound of formula X in accordance with embodiment (h) yields a corresponding compound which contains a double-bond in the 4,5-position and can, for example, be carried out with bromine, chlorine, azidocarboxylic acid esters (e.g. the diethyl ester), halosuccinimides (e.g. bromosuccinimide), haloamides (e.g. chloroacetamide) and the like. It is expedient to carry out this embodiment in an inert organic solvent such as a hydrocarbon (e.g. benzene, toluene and the like), a halogenated hydrocarbon (e.g. carbon tetrachloride), an ether (e.g. dioxan or tetrahydrofuran) and the like and advantageously at a temperature between about -30°C and 100°C .

According to embodiment (i) of the process provided by this invention, a compound of formula XI is converted into a corresponding 4,5-dihydro compound by treatment with a base.

The compounds of formula XI required as starting materials for embodiment (i) can be prepared by acylating a corresponding 4-hydroxy compound of formula IX. Suitable acylating agents are, for example, acid anhydrides such as acetic acid anhydride, acid halides and the like. It is expedient to carry out the acylation in the presence of a base such as pyridine and the like as an acid-acceptor and in an organic solvent such as a hydrocarbon, a chlorinated hydrocarbon, an ether and the like at a temperature between -50°C and 100°C . If the side-chain carries an acylatable nitrogen atom, this must be protected prior to the acylation by a carbobenzoxy group or an equivalent protecting group; the carbobenzoxy group or other protecting group being subsequently removed.

Embodiment (5), which results in the cleavage of acid from a compound of formula XI, can be carried out by treatment with a base such as an alkali hydride (e.g. sodium hydride), triethylamine, an alkali amide (e.g. sodium amide), an alkali alkoxide (e.g. sodium methoxide) and the like in an anhydrous medium. In this case, it is expedient to carry out the treatment in an inert organic solvent such as an ether, an alcohol (e.g. ethanol), a hydrocarbon (e.g. benzene or toluene), dimethylformamide and the like and at temperatures between -40°C and 120°C . The acyl group denoted by R^{10} in formula XI can be a lower alkanoyl (e.g. acetyl), aroyl (e.g. benzoyl), tosyl or mesyl group. However, in this embodiment there can also occur as an intermediate a compound of formula XIII which can be transformed into a desired compound of formula I in accordance with the methods described hereinafter.

According to embodiment (j) of the process provided by this invention, a compound of formula XII is converted into a corresponding 4,5-dehydro compound by treatment with a strong base.

The compounds of formula XII required as starting materials for embodiment (j) can be prepared by acylating a corresponding 4,5-dihydro compound of formula X; for example, by means of a mesyl or tosyl halide. It is expedient to carry out this acylation in an inert organic solvent such as a hydrocarbon (e.g. benzene), a chlorinated hydrocarbon and the like and in the presence of an acid-acceptor such as pyridine and the like and at a temperature between 0°C and the reflux temperature of the acylation mixture. If the side-chain in the compounds of formula X carries an acylatable nitrogen atom, this must (as described earlier in connection with the preparation of compounds of formula XI) be temporarily protected before the acylation by a carbobenzoxy group or an equivalent protecting group.

The cleavage of an alkylsulphonyl (e.g. mesyl) or arylsulphonyl (e.g. tosyl) group from a compound of formula XII in accordance with embodiment (j) can be carried out by treatment with a strong base such as an alkali hydride (e.g. sodium hydride), an alkali alkoxide (e.g. sodium methoxide), an alkali amide (e.g. sodium amide) and the like in an anhydrous medium. In this case, it is expedient to carry out the treatment in an inert organic solvent such as an ether, an alcohol (e.g. ethanol), a hydrocarbon (e.g. benzene or toluene), dimethylformamide and the like and at a temperature between 0°C and 120°C . In this treatment, there can also occur an isomeric compound of formula XIII which can be rearranged to a desired compound of formula I in the manner described hereinafter.

According to embodiment (k) of the process of the present invention, a compound of formula XIII is rearranged to the corresponding 4,5-dehydro compound.

The compounds of formula XIII required as starting materials for embodiment (k) can be prepared from corresponding compounds of formula XI or XII in the manner described earlier. In addition, compounds of formula XIII can be prepared

by introducing a substituent into a corresponding 1-unsubstituted compound in accordance with the methods described earlier. In this case, however, an isomerisation to a 4,5-dehydro compound can simultaneously occur.

The rearrangement (i.e. isomerisation) of a compound of formula XIII in accordance with embodiment (k) can be carried out by treatment with a base such as an alkali alcoholate (e.g. sodium methoxide), an alkali hydride (e.g. sodium hydride), triethylamine and the like. The rearrangement is expediently carried out in an inert organic solvent such as a hydrocarbon, an ether, an alcohol and the like and at a temperature between -40°C and 120°C .

It will be appreciated that the respective starting materials referred to hereinbefore need not be isolated in pure form, but can be used in the process of this invention without isolation from the medium in which they are prepared.

Compounds of formula I hereinbefore which are basic form acid addition salts with inorganic acids such as hydrochloric acid, phosphoric acid, hydrobromic acid, sulphuric acid and the like and with organic acids such as citric acid, acetic acid, formic acid, succinic acid, maleic acid, p-toluenesulphonic acid and the like.

Compounds of formula I and their pharmaceutically acceptable salts can be used as anticonvulsants, muscle relaxants, sedatives and anxiolytics.

The anticonvulsant activity is demonstrated when mice to which compounds of formula I or their salts have been administered are subjected to the pentamethylenetetrazole test according to the method of Orloff (Proc. Soc. Exptl. Biol. Med. 70 254-257 1949). The results are given as "APR 2.0" by which is meant that dosage (in mg/kg p.o.) of an anticonvulsant which brings about double the pentamethylenetetrazole consumption in comparison to an untreated control group. For example, 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate, which displays an LD_{50} of 600-1200 mg/kg (p.o.), shows in the test for anticonvulsant activity in the pentamethylenetetrazole test an APR 2.0 of 9 mg/kg p.o.; 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate (LD_{50} 2500-5000 mg/kg p.o.) shows an APR 2.0 of 2.5 mg/kg (p.o.) and 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl pyrazine-2-carboxylate (LD_{50} 1250-2500 mg/kg p.o.) shows an APR 2.0 of 2.3 mg/kg (p.o.). In contrast thereto, phenobarbital, a commonly used anticonvulsant, shows an APR 2.0 of 30 mg/kg.

The muscle relaxant activity can be demonstrated in the rotating rod test. In this test, there is determined the capability of mice, which are under the influence of a compound having muscle relaxant or sedative activity, to remain on a slowly rotating rod. The rod used has a diameter of 30 mm and rotates at 2 revolutions per minute. For the test there are selected those mice which are able to remain on the rotating rod for at least 2 minutes prior to administration of the compound to be tested. Thereafter, the selected mice are given the compound to be tested in varying dosages, introduced onto the rotating rod 30 minutes later and the time during which they are able to remain on the rotating rod is determined. That dosage which brings about a 50% reduction of the time spent on the rotating rod is denoted as the HD_{50} . For example, the aforementioned 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate shows an HD_{50} of 25 mg/kg (p.o.), 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate shows an HD_{50} of 6 mg/kg (p.o.) and 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl pyrazine-2-carboxylate shows an HD_{50} of 4 mg/kg (p.o.).

The compounds of formula I and their pharmaceutically acceptable salts can accordingly be used as medicaments; for example in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic, inert carrier material which is suitable for enteral or parenteral application such as, for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain yet other therapeutically valuable substances. The dosage follows individual requirements, but a dosage of 0.1 mg/kg to 10 mg/kg/day is preferred.

The following Examples illustrate the process provided by the invention.

EXAMPLE 1

A) The preparation of the starting material:

A solution, cooled to -20°C , of 27.1 g of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one in 150 ml of dimethylformamide is treated with 8.1 g of sodium methoxide and stirred for 5 minutes. After cooling to -40°C , 19.5 g of 1,2-dichloro-1-methoxyethane are added dropwise. Within 30 minutes, the temperature is allowed to rise to 0°C , the mixture is poured with stirring onto 500 ml of water, the precipitated material is separated off and taken up in methylene chloride. After drying over sodium sulphate, the methylene chloride solution is evaporated and the residue is crystallized from ether. Recrystallization from methanol gives 7-chloro-1-[(2-chloro-1-methoxy)ethyl]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one of melting point $152^{\circ}\text{--}154^{\circ}\text{C}$.

A solution of 36.3 g of 7-chloro-1-[(2-chloro-1-methoxy)ethyl]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one in a mixture of 400 ml of dimethylformamide and 20 ml of water is treated with 16 g of potassium acetate and boiled under reflux for 5 minutes. After cooling to 0°C the mixture is poured onto 1600 ml of water. The precipitated product is separated off and taken up in methylene chloride. The solution, after washing with water and drying over sodium sulphate, is evaporated and the residue crystallized from ether. There is obtained 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one of melting point $154^{\circ}\text{--}156^{\circ}\text{C}$. A second crystal modification melts at $190^{\circ}\text{--}192^{\circ}\text{C}$.

B) The process:

A stirred suspension of 10.3 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 100 ml of benzene is treated at room temperature with 4.0 g of succinic acid anhydride and 6.0 ml of triethylamine, there soon forming a clear solution. The mixture is left to stand overnight, concentrated, the residue taken up in 100 ml of 5% aqueous potassium carbonate solution, washed with ether, acidified with dilute acetic acid and the resulting oil extracted with methylene chloride. The extract is dried over sodium sulphate, concentrated and the residue is crystallized by triturating with hexane. There is obtained 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate of melting point $167^{\circ}\text{--}169^{\circ}\text{C}$. The melting point does not rise on recrystallization from acetone.

EXAMPLE 2

A stirred suspension of 10.3 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 100 ml of benzene is treated at room temperature with 5.7 g of chloroacetic acid anhydride and 6.0 ml of triethylamine and left to stand at the same temperature for 4 hours. The solution obtained is concentrated under reduced pressure, the oily residue taken up in methylene chloride and the solution obtained chromatographed on 300 g of Kieselgel with 20% ethyl acetate in methylene chloride. The uniform fractions are combined, concentrated and recrystallized from ether and hexane. There is obtained 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate of melting point $124^{\circ}\text{--}126^{\circ}\text{C}$.

EXAMPLE 3

A solution of 3.7 g of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate in 30 ml of benzene is treated with 6.0 ml of diethylamine and boiled under reflux for 2 hours. After cooling, the mixture is filtered and the filtrate evaporated in a vacuum. The oily residue is taken up in methylene chloride, the solution washed with saturated aqueous sodium chloride solution and again evaporated. The residue, dissolved in 100 ml of ether, is then treated with a slight excess of 3-N ethereal hydrogen chloride solution and left to stand overnight in a refrigerator. The crystalline precipitate is dissolved at room temperature in 70 ml of isopropanol and, after the addition of 70 ml of ether, left to stand in an ice-bath for 2 hours. There are obtained 2.8 g of N,N-diethylglycine 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl ester dihydrochloride which melts at $195^{\circ}\text{--}200^{\circ}\text{C}$ with decomposition.

EXAMPLE 4

A solution of 10.3 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 125 ml of pyridine

is treated dropwise at 30°—35°C with 10.4 g of furan-2-carboxylic acid chloride. After completion of the addition, the mixture is stirred at room temperature for a further 1 hour and then evaporated under reduced pressure. The residue is taken up in methylene chloride, the solution washed with water, dried over sodium sulphate and concentrated. The residual oil crystallizes on trituration with hexane and yields a crude product of melting point 126°—129°C. On recrystallization from ethanol, there is obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl furan - 2 - carboxylate of melting point 129°—131°C.

EXAMPLE 5

In accordance with the procedure described in Example 4, from 10.3 g of 7-chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 11.6 g of 5-methyl-isoxazole-3-carboxylic acid chloride there is obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 3 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl 5 - methyl - isoxazole - 3 - carboxylate of melting point 145°—147°C after recrystallization from ethanol.

EXAMPLE 6

6.1 g of isonicotinic acid are heated at 50°—55°C for 1 hour with 60 ml of thionyl chloride. The solution is concentrated, the residue slurried with benzene and again concentrated. The crude isonicotinoyl chloride hydrochloride thus obtained is added portionwise at 30°—35°C to a solution of 5.15 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 75 ml of pyridine and the mixture is stirred at room temperature for 1 hour. The precipitate is filtered off by suction and washed with methylene chloride. The filtrate is concentrated in a vacuum, the residue is partitioned between water and methylene chloride, the methylene chloride phase is dried over sodium sulphate and concentrated. The remaining oil crystallizes from ether and gives a crude product of melting point 174°—178°C. Recrystallization from ethanol yields 3.2 g of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl isonicotinate of melting point 177°—179°C.

EXAMPLE 7

A suspension of 3.45 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 50 ml of benzene and 5 ml of pyridine is treated with 2.5 ml of nicotinoyl chloride and stirred at room temperature for 16 hours. After concentration in a vacuum, the residue is partitioned between water and methylene chloride, the organic phase washed with bicarbonate solution, dried over sodium sulphate and evaporated. The residual oil crystallizes from ether and, after recrystallization from ethyl acetate/hexane, gives 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate of melting point 138°—140°C. After further recrystallization from ethyl acetate/hexane, the melting point rises to 140°—142°C.

EXAMPLE 8

After the addition of 5.76 g of picolinic acid, a slurry of 8.0 g of N,N'-carbonyl-diimidazole in 40 ml of tetrahydrofuran is stirred at room temperature under nitrogen for 2 hours, whereby there is obtained a clear solution of picolinic acid imidazolidine. Meanwhile, a solution of imidazole-sodium is prepared from 0.16 g of sodium and 1.6 g of imidazole in 20 ml of tetrahydrofuran by heating under reflux with exclusion of moisture and, after cooling to room temperature, is treated with a suspension of 8.1 g of 7 - chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 50 ml of methylene chloride. The prepared solution of picolinic acid-imidazolidine is then added to this mixture at room temperature and the resulting mixture is stirred overnight. The precipitate is then filtered off and the filtrate evaporated in a vacuum. The oily residue is taken up in methylene chloride, the solution washed with sodium bicarbonate solution and water, dried over sodium sulphate and concentrated. The residual oil crystallizes on trituration with ether and, after recrystallization from ethanol/ether, yields 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl picolinate of melting point 151°—153°C.

EXAMPLE 9

In accordance with the procedure described in Example 8, from 8.1 g of 7-

chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H-1,4 - benzodiazepin - 2 - one and 5.8 g of pyrazine-2-carboxylic acid there are obtained 4.6 g of 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl pyrazine - 2 - carboxylate which melts at 113°—116°C with decomposition after recrystallization from methanol.

EXAMPLE 10

In the same manner as described in Example 8, from 8.1 g of 7 - chloro - 1,3-dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 4.2 g of methoxyacetic acid there is obtained an oily product which, after chromatography on 200 g of Kieselgel with 20% ethyl acetate in methylene chloride and subsequent recrystallization from ether/hexane, gives 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl methoxyacetate of melting point 103°—105°C.

EXAMPLE 11

A suspension of 3.45 g of 7 - chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 20 ml of pyridine is treated dropwise at room temperature with 20 ml of ethyl isocyanate and subsequently boiled at reflux for 2 hours. The clear solution is then concentrated to dryness under reduced pressure. The oily residue is dissolved in methylene chloride, washed with 5% potassium carbonate solution and with saturated sodium chloride solution, dried over sodium sulphate and evaporated. The residual oil crystallizes on trituration with hexane and, after recrystallization from ether/hexane, gives 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl ethylcarbamate of melting point 117°—119°C.

EXAMPLE 12

In accordance with the procedure described in Example 11, from 3.45 g of 7 - chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 20 ml of methyl isocyanate there is obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl methyl carbamate which melts at 134°—136°C after recrystallization from ether/hexane.

EXAMPLE 13

In an analogous manner to that described in Example 8, from 8.1 g of 7 - chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 5.95 g of 4-methyl-5-oxazole-carboxylic acid there is obtained an oily product which is purified by chromatography on 200 g of Kieselgel with a mixture of acetone/toluene/glacial acetic acid (50:50:1). After recrystallization from ethanol, the uniform fractions yield 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl 4-methyl-oxazole-5-carboxylate of melting point 151°—154°C (decomposition).

EXAMPLE 14

In an analogous manner to that described in Example 8, from 8.1 g of 7 - chloro - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 6.6 g of 1,5-dimethyl-3-pyrazole-carboxylic acid there is obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl 1,5 - dimethyl - pyrazole - 3 - carboxylate which melts at 195°—197°C with decomposition after repeated recrystallization from ethanol.

EXAMPLE 15

A suspension of 10.3 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 150 ml of benzene and 15 ml of pyridine is treated with 11 g of dichloroacetyl chloride and stirred at room temperature for 6 hours. After concentration in a vacuum, the residue is taken up in methylene chloride, chromatographed on 450 g of Kieselgel with 20% ethyl acetate in methylene chloride and recrystallized from ether/hexane. There is obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl dichloroacetate of melting point 116°—118°C.

EXAMPLE 16

A) The preparation of the starting material:

A suspension of 28.1 g of 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one in 200 ml of methanol is treated at room temperature with 6.7 g of potassium hydroxide (in flakes). The clear solution obtained is concentrated to dryness and the residual salt dissolved in 150 ml of dimethylformamide. The mixture is cooled to -40°C, 19.5 g of 1,2-dichloro-1-methoxyethane are added dropwise and the mixture is stirred at -40°C for 5 minutes. Within 30 minutes, the temperature is allowed to rise to 0°C, the mixture is poured with stirring onto 500 ml of water, the precipitated product is filtered off by suction and taken up in methylene chloride. After drying over sodium sulphate, the methylene chloride solution is evaporated and the residue crystallized from ether. There is obtained 1 - [(2 - chloro - 1 - methoxy)ethyl] - 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 162°—164°C.

A solution of 10 g of 1-[(2-chloro-1-methoxy)ethyl]-1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one in 100 ml of dimethylformamide is treated with 10 g of potassium acetate and heated to 110°C for 1 hour. After cooling to room temperature, the mixture is poured onto 800 ml of water. The precipitate is separated off and taken up in methylene chloride. The solution is washed with water, dried over sodium sulphate and chromatographed on 600 g of Kieselgel, firstly with 20% ethyl acetate in methylene chloride and then with ethyl acetate alone. The uniform fractions eluted with ethyl acetate yield, after recrystallization from ethanol with a small amount of active charcoal, 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 201°—203°C.

B) The process:

In an analogous manner to that described in Example 2, from 5.3 g of 1,3-dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, 2.85 g of chloroacetic acid anhydride and 3.0 ml of triethylamine, after chromatography on Kieselgel with 20% ethyl acetate in methylene chloride and recrystallization from methylene chloride/ether, there is obtained 2-(2,3 - dihydro - 7 - nitro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl chloroacetate of melting point 117°—121°C (decomposition).

EXAMPLE 17

A) The preparation of the starting material:

A suspension of 31.4 g of 7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one in 200 ml. of methanol is treated at room temperature with 6.7 g of potassium hydroxide (in flakes). 150 ml of dimethylformamide are then added (there resulting a clear solution) and the methanol is thereupon removed under reduced pressure. The mixture is then cooled to -40°C, 19.5 g of 1,2-dichloro-1-methoxyethane are added dropwise and the mixture is stirred at -40°C for 5 minutes. The temperature is allowed to rise to 0°C by itself and the mixture is poured onto 500 ml of water. The precipitated product is filtered off by suction, taken up in methylene chloride and, after drying over sodium sulphate, evaporated. The residue is chromatographed on 850 g of Kieselgel with 20% ethyl acetate in methylene chloride. After recrystallization from ethanol, the homogeneous fractions yield 7 - bromo - 1 - [(2 - chloro - 1 - methoxy)ethyl] - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 149°—151°C (decomposition).

A solution of 20.4 g of 7-bromo-1-[(2-chloro-1-methoxy)ethyl]-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one in a mixture of 200 ml of dimethylformamide and 10 ml of water is treated with 8 g of potassium acetate and boiled under reflux for 5 minutes. After cooling to 0°C, the mixture is poured onto 800 ml of water. The precipitated product is separated off and taken up in methylene chloride. The solution, after washing with water and drying over sodium sulphate, is evaporated and the residue crystallized from ether. After recrystallization from ethanol, there is obtained 7 - bromo - 1,3 - dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 198°—200°C (decomposition).

B) The process:

In the same manner as described in Example 8, from 9.13 g of 7 - bromo - 1,3-dihydro - 1 - [(2 - hydroxy - 1 - methoxy)ethyl] - 5 - (2 - pyridyl) - 2H - 1,4-benzodiazepin - 2 - one and 5.76 g of nicotinic acid there is obtained 2 - [7 - bromo - 2,3 - dihydro - 2 - oxo - 5 - (2 - pyridyl) - 1H - 1,4 - benzodiazepin - 1 yl] - 2 -

methoxyethyl nicotinate which melts at 147°—150°C with decomposition after recrystallization from isopropanol.

EXAMPLE 18

A) The preparation of the starting material:

A stirred suspension of 13.8 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 100 ml of methylene chloride is treated at room temperature with 7.8 ml of trimethylchlorosilane. There is formed a clear solution which is further stirred for 5 minutes. 8.4 ml of triethylamine are thereupon added dropwise within 15 minutes. The mixture is stirred at room temperature for a further 30 minutes, the precipitated triethylamine hydrochloride is filtered off by suction, the filtrate is washed with ice-cooled water and dried over sodium sulphate. After concentration, the oily residue is triturated with hexane, whereby crystallization occurs. After recrystallization from acetonitrile, there is obtained 7-chloro-1,3-dihydro-1-[1-methoxy-2-(trimethylsiloxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one of melting point 104°—106°C.

A solution of 8.3 g of 7-chloro-1,3-dihydro-1-[1-methoxy-2-(trimethylsiloxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one in 10 ml of methylene chloride is treated at room temperature with 5.6 g of m-chloroperbenzoic acid and stirred for 4 hours. The precipitated m-chlorobenzoic acid is filtered off by suction and the filtrate washed with 10% sodium carbonate and water. The methylene chloride solution is dried over sodium sulphate, filtered and evaporated. The residual oil (10 g) is dissolved in 20 ml of methanol, treated with 4 ml of water and left to stand at room temperature for 1 hour. The crystals filtered off by suction are washed with ethanol and ether. After recrystallization from ethanol, there is obtained 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide of melting point 210°—212°C.

B) The process:

In an analogous manner to that described in Example 1 (B), from 2.7 g of 7-chloro-1,3-dihydro-1-[(2-hydroxy-1-methoxy)ethyl]-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide, 1.0 g of succinic acid anhydride and 1.5 ml of triethylamine in 25 ml of benzene there is obtained a crude product of melting point 188°—190°C. Crystallization from methylene chloride/ether yields pure 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate 4-oxide of melting point 191°—192°C.

EXAMPLE 19

A stirred solution of 4.4 g of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate in 30 ml of methylene chloride is treated at room temperature with 2.8 g of m-chloroperbenzoic acid. The mixture is stirred for 4 hours and left to stand overnight. After concentration, the oily residue is triturated with ether, whereby crystallization occurs. Recrystallization from methylene chloride/ether yields pure 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate 4-oxide of melting point 191—192°C which is identical in all respects with the substance prepared according to Example 18.

EXAMPLE 20

A solution of 2.25 g of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl 5-methyl-isoxazole-3-carboxylate in 15 ml of methylene chloride is treated at room temperature with 1.4 g of m-chloroperbenzoic acid. The mixture is stirred for 2 hours and left to stand overnight. The precipitated m-chlorobenzoic acid is filtered off by suction and the filtrate washed with 10% sodium carbonate solution and water. The methylene chloride solution is dried over sodium sulphate, filtered and concentrated. The residual oil crystallizes from ether and gives a crude product of melting point 199°—202°C. Recrystallization from methylene chloride/ether gives pure 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl 5-methyl-isoxazole-3-carboxylate 4-oxide of melting point 210—211°C.

EXAMPLE 21

A solution of 10.9 g of 7-chloro-1-[(2-chloro-1-methoxy)ethyl]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, 4.9 g of nicotinic acid and 4.0 g of triethylamine in 100 ml of absolute dimethylformamide is boiled at reflux for 1 hour under a nitro-

5 gen atmosphere and with exclusion of moisture. The solvent is removed in a vacuum at 70°C and the residue dissolved in a mixture of 200 ml of ethyl acetate and 100 ml of water. The ethyl acetate phase is separated off, washed twice with 100 ml of ice-cold 5% sodium bicarbonate solution each time and twice with 100 ml of water each time, dried over magnesium sulphate and evaporated in a vacuum. The residue is dissolved in 30 ml of ethyl acetate and chromatographed on 200 g of Kieselgel. The column is eluted with ethyl acetate. The uniform fractions, containing 2 - (7 - chloro-2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl nicotinate, are combined and evaporated in a vacuum. After recrystallization from ethyl acetate/petroleum ether, the residue yields 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate of melting point 141°—142°C. A second crystal modification melts at 166°—167°C.

EXAMPLE 22

15 A) The preparation of the starting material:
7 - Chloro - 1 - [(2 - chloro - 1 - methoxy)ethyl] - 5 - (o - fluorophenyl) - 1,3-dihydro - 2H - 1,4 - benzodiazepin - 2 - one is obtained according to the procedure described in Example 1(A) from 14.4 g of 7-chloro-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 9.7 g of 1,2-dichloro-1-methoxyethane. It has a melting point of 170°—172°C after crystallization from acetonitrile.

20 B) The process:
A solution of 9.9 g of 7-chloro-1-[(2-chloro-1-methoxy)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one, 4.9 g of nicotinic acid and 4.0 g of triethylamine in 100 ml of absolute dimethylformamide is boiled at reflux for 1 hour under a nitrogen atmosphere and with exclusion of moisture. The solvent is removed in a vacuum at 70°C and the residue dissolved in a mixture of 400 ml of ethyl acetate and 250 ml of water. The ethyl acetate phase is separated off, washed twice with 100 ml of ice-cold 5% sodium bicarbonate solution each time and twice with 100 ml of water each time, dried over magnesium sulphate and evaporated to dryness in a vacuum. The residue is dissolved in 30 ml of ethyl acetate and chromatographed on 160 g of Kieselgel. The column is eluted with ethyl acetate. The uniform fractions, containing 2 - [7 - chloro - 5 - (o - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H-1,4 - benzodiazepin - 1 - yl] - 2 - methoxyethyl nicotinate, are combined and evaporated in a vacuum. The residue is recrystallized from alcohol and then melts at 81°—83°C. The alcohol-containing crystallizate is melted, the melt is heated at 140°C for 3 hours and, after cooling, triturated with 50 ml of ether. After filtration by suction and drying, there is obtained 2-[7-chloro-5-(o-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-1-yl]-2-methoxyethyl nicotinate of melting point 155°—156°C.

EXAMPLE 23

40 A solution of 14.5 g of 7-chloro-1-(2-chloro-1-methoxyethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, 6.4 g of thiophene-2-carboxylic acid and 5.1 g of triethylamine in 100 ml of absolute dimethylformamide is boiled at reflux for 1 hour under a nitrogen atmosphere and with exclusion of moisture and subsequently evaporated in a vacuum at 70°C. The residue is dissolved in a mixture of 500 ml of ethyl acetate and 250 ml of water. The ethyl acetate phase is separated off, washed twice with 100 ml of ice-cold 5% sodium bicarbonate solution each time and twice with 200 ml of water each time, dried over magnesium sulphate, boiled up with 1 g of active charcoal and, after filtration, evaporated in a vacuum. Recrystallization of the residue from alcohol yields 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl-1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl thiophene - 2 - carboxylate of melting point 134°—135°C.

EXAMPLE 24

55 A solution of 18.2 g of 7-chloro-1-(2-chloro-1-methoxyethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, 7.2 g of formyl-glycine and 7.1 g of triethylamine in 200 ml of absolute dimethylformamide is boiled at reflux for 1 hour under a nitrogen atmosphere and with exclusion of moisture. The solvent is removed in a vacuum at 70°C and the residue dissolved in a mixture of 500 ml of ethyl acetate and 150 ml of water. The ethyl acetate phase is separated off, washed twice with 150 ml of ice-cold 5% sodium bicarbonate solution each time and twice with 250 ml of water each time, dried over magnesium sulphate and evaporated in a vacuum. The residue is dissolved in 50 ml of ethyl acetate and chromatographed on 400 g of Kieselgel. The column is eluted with ethyl acetate. The uniform fractions, containing 2 - (7-

chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl formylglycinate, are combined and evaporated to dryness in a vacuum. Recrystallization from ethyl acetate/petroleum ether gives 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl formylglycinate of melting point 110°—112°C.

A solution of 16.0 g of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl formylglycinate in 500 ml of 2-M methanolic hydrochloric acid is stirred at 25°C. for 4.5 hours and subsequently evaporated to dryness in a vacuum. The residue is taken up in 200 ml of water and the undissolved material removed by extraction with 400 ml of ethyl acetate. The ethyl acetate phase is again washed with 100 ml of water and discarded. The aqueous fractions are combined, adjusted to pH=8—9 with 5% sodium bicarbonate solution with the addition of ice and extracted twice with 300 ml of ethyl acetate each time. The ethyl acetate solution is washed twice with 200 ml of water each time, dried over magnesium sulphate and evaporated to dryness in a vacuum. The residue is recrystallized from ether/cyclohexane, there being obtained 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl glycinate of melting point 115°—116°C.

EXAMPLE 25

A solution of 500 mg of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate 4-oxide in 5 ml of chloroform is treated with 0.35 ml of phosphorus trichloride and the mixture is boiled at reflux for 2 hours. The mixture is then poured onto ice, the organic phase is separated off and washed with water. The solution is dried over sodium sulphate, evaporated to dryness and the residue is triturated with ether whereby crystallization occurs. Recrystallization from acetone yields pure 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate of melting point 167—169°C which is identical with the product manufactured according to Example 1(B).

The following Examples illustrate typical pharmaceutical preparations containing the benzodiazepine derivatives provided by this invention:

EXAMPLE A

Tablets of the following composition are manufactured:

	per tablet
2-(7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate	10 mg
Corn starch	53 mg
Lactose	150 mg
Gelatin (10% solution)	6 mg

The active ingredient (benzodiazepine derivative), the corn starch and the lactose are thickened with a 10% gelatin solution. The paste is comminuted, the granulate brought into a suitable pan and dried at 43°C. The dried granulate is passed through a comminuting machine, mixed in a mixer with the following ingredients:

Talc	6 mg
Magnesium stearate	6 mg
Corn starch	9 mg

and then compressed to tablets weighing 240 mg.

EXAMPLE B

Suppositories containing the following ingredients are manufactured:

	per 1.3 g suppository
2-(7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate	10.0 mg
Hydrogenated coconut oil	1245.0 mg
Carnauba wax	45.0 mg

The hydrogenated coconut oil and the carnauba wax are melted in a suitable vessel fitted with a glass liner and cooled to 45°C. The active ingredient (benzodiazepine derivative) is added with stirring and stirred until completely dispersed. The

mixture is then poured into suppository moulds which ensure a suppository weight of 1.3 g.

EXAMPLE C

A parenteral administration form containing the following ingredients is manufactured:

	per ml	
2-(7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate	5 mg	
Dimethylacetamide	10 %	
Benzyl alcohol	1.5 %	
Ethanol	10 %	
Water for injection ad	1 ml	

The active ingredient (benzodiazepine derivative) is dissolved in dimethylacetamide and treated with benzyl alcohol, ethanol and water. The solution is filtered through a candle filter and filled into suitable ampoules which are sealed and sterilised.

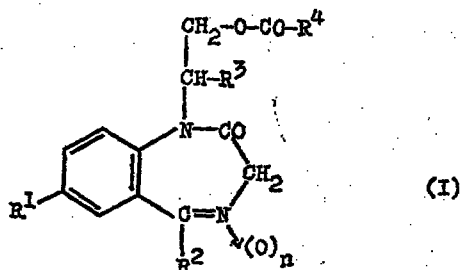
EXAMPLE D

Tablets or suppositories or parenteral administration forms are manufactured according to Examples A—C, but instead of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate, one of the following benzodiazepine derivatives is used as the active ingredient:

2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl picolinate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl pyrazine-2-carboxylate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methoxyacetate,
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl ethylcarbamate or
 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methylcarbamate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



, wherein R¹ represents a halogen atom or a nitro group, R² represents a phenyl, halophenyl or pyridyl group, R³ represents an alkoxy group, R⁴ represents a haloalkyl, alkoxyalkyl, carboxyalkyl, monoalkylamino or dialkylamino group, an alkyl group which is substituted by —NR⁶R⁷ (in which R⁶ and R⁷ each represent a hydrogen atom or an alkyl group or R⁶ and R⁷ together with the nitrogen atom to which they are attached represent a 5- or 6-membered saturated heterocyclic ring which may contain an oxygen atom) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms and n stands for zero or 1.

and salts thereof.

mixture is then poured into suppository moulds which ensure a suppository weight of 1.3 g.

EXAMPLE C

A parenteral administration form containing the following ingredients is manufactured:

	per ml	
2-(7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate	5 mg	
Dimethylacetamide	10 %	
Benzyl alcohol	1.5 %	
Ethanol	10 %	
Water for injection ad	1 ml	

The active ingredient (benzodiazepine derivative) is dissolved in dimethylacetamide and treated with benzyl alcohol, ethanol and water. The solution is filtered through a candle filter and filled into suitable ampoules which are sealed and sterilised.

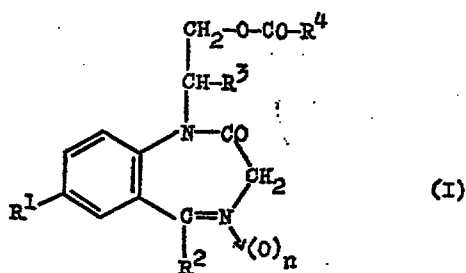
EXAMPLE D

Tablets or suppositories or parenteral administration forms are manufactured according to Examples A—C, but instead of 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate, one of the following benzodiazepine derivatives is used as the active ingredient:

- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl picolinate,
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl pyrazine-2-carboxylate,
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl chloroacetate,
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl hydrogen succinate,
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methoxyacetate,
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl ethylcarbamate or
- 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methylcarbamate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



, wherein R¹ represents a halogen atom or a nitro group, R² represents a phenyl, halophenyl or pyridyl group, R³ represents an alkoxy group, R⁴ represents a haloalkyl, alkoxyalkyl, carboxyalkyl, monoalkylamino or dialkylamino group, an alkyl group which is substituted by —NR⁶R⁷ (in which R⁶ and R⁷ each represent a hydrogen atom or an alkyl group or R⁶ and R⁷ together with the nitrogen atom to which they are attached represent a 5- or 6-membered saturated heterocyclic ring which may contain an oxygen atom) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms and n stands for zero or 1. and salts thereof.





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2. Benzodiazepine derivatives in accordance with claim 1, wherein R^1 represents a chlorine atom or a nitro group.

3. Benzodiazepine derivatives in accordance with claim 1 or claim 2, wherein R^2 represents a phenyl, 2-halophenyl or 2-pyridyl group.

5 4. Benzodiazepine derivatives in accordance with claim 3, wherein the 2-halophenyl group is a 2-chlorophenyl or 2-fluorophenyl group. 5

5. Benzodiazepine derivatives in accordance with any one of claims 1 to 4 inclusive, wherein R^4 represents an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two nitrogen atoms or one oxygen or sulphur atom or oxygen or sulphur atom and one nitrogen atom. 10

6. Benzodiazepine derivatives in accordance with claim 5, wherein R^4 represents a furan, thiophene, oxazole, isoxazole, pyrazole, pyridine or pyridazine heterocycle which is optionally substituted by 1 or 2 alkyl groups.

7. Benzodiazepine derivatives in accordance with claim 6, wherein R^4 represents a 3-pyridyl, 2-pyridyl or 2-pyrazinyl group. 15

8. Benzodiazepine derivatives in accordance with any one of claims 1 to 4 inclusive, wherein R^4 represents a halomethyl, carboxyalkyl, alkoxyalkyl or alkylamino group.

9. Benzodiazepine derivatives in accordance with claim 8, wherein R^4 represents a chloromethyl, 2-carboxyethyl, methoxymethyl, methylamino or ethylamino group. 20

10. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl nicotinate.

11. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl picolinate.

25 12. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl pyrazine - 2 - carboxylate. 25

13. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl chloroacetate.

30 14. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl hydrogen succinate. 30

15. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl methoxyacetate.

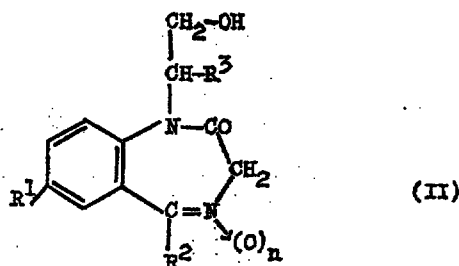
16. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl ethylcarbamate.

35 17. 2 - (7 - Chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl methylcarbamate. 35

18. A pharmaceutical preparation comprising a compound of formula I in claim 1 or a pharmaceutically acceptable salt thereof in admixture with a compatible pharmaceutical carrier.

40 19. A process for the manufacture of the compounds claimed in claim 1 and salts thereof, which process comprises 40

(a) converting the primary hydroxy group in the side-chain of a compound of the general formula



(II)

45 or , wherein R^1 , R^2 , R^3 and n have the significance given in claim 1, 45
into a group of the formula

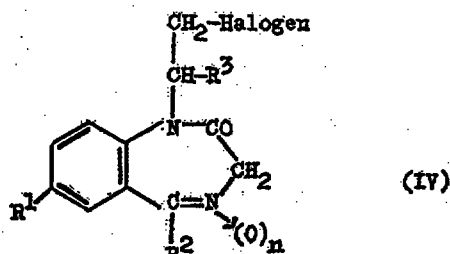


(III)

50 , wherein R^4 has the significance given in claim 1, 50
by reaction with a suitable acylating agent
(b) for the manufacture of a compound of formula I in which R^4 represents a haloalkyl or alkoxyalkyl group, an alkyl group which is substituted by $-NR^5R^6$ (R^5 and



R^7 having the significance given in claim 1) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms, replacing the aliphatically-bound halogen atom in the side-chain of a compound of the general formula

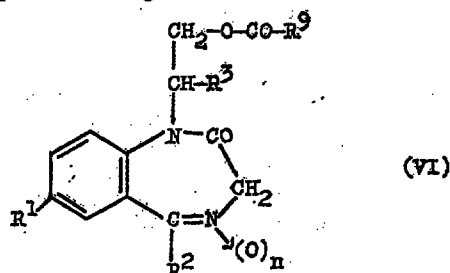


, wherein R^1 , R^2 , R^3 and n have the significance given in claim 1, by a group of the formula



, wherein R^8 represents a haloalkyl or alkoxyalkyl group, an alkyl group which is substituted by $-NR^6R^7$ (R^6 and R^7 having the significance given in claim 1) or an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two hetero atoms,

or
(c) for the manufacture of a compound of formula I in which R^4 represents an alkyl group which is substituted by $-NR^6R^7$ (R^6 and R^7 having the significance given in claim 1), reacting a compound of the general formula

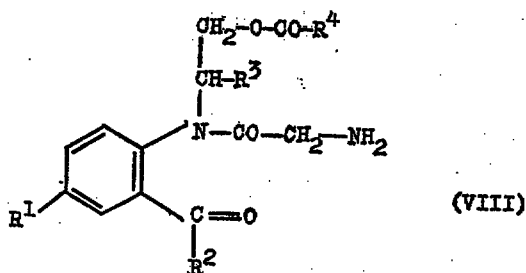


, wherein R^1 , R^2 , R^3 and n have the significance given in claim 1 and R^9 represents an alkyl group which is substituted by a suitable leaving atom or group, with an amine of the general formula



, wherein R^6 and R^7 have the significance given in claim 1,

or
(d) for the manufacture of a compound of formula I in which n stands for zero, cyclising a compound of the general formula

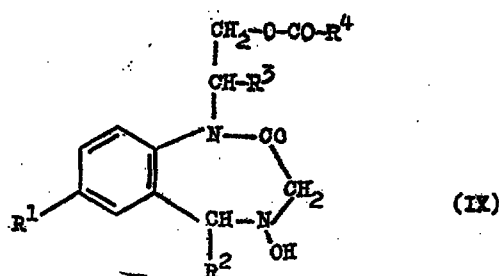


, wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1, or



- (e) for the manufacture of a compound of formula I in which n stands for 1, oxidising in the 4-position a corresponding compound of formula I in which n stands for zero or
 5 (f) for the manufacture of a compound of formula I in which n stands for zero, de-oxygenating in the 4-position a corresponding compound of formula I in which n stands for 1
 or
 (g) for the manufacture of a compound of formula I in which n stands for zero, de-hydrating a compound of the general formula

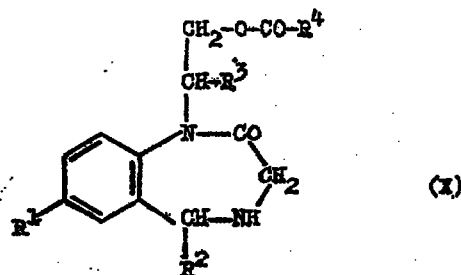
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- , wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1,
 or
 (h) for the manufacture of a compound of formula I in which n stands for zero, oxidising or dehydrogenating a compound of the general formula

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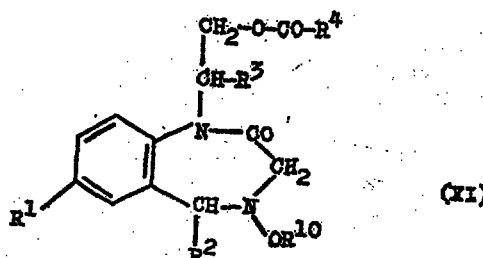
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- , wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1,
 at the 4,5-bond
 or

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- (i) for the manufacture of a compound of formula I in which n stands for zero, converting a compound of the general formula

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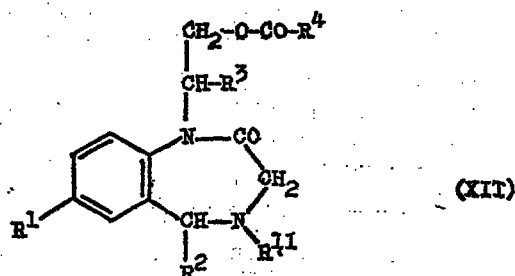
(XI)

- , wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1 and R^{10} represents an acyl group,
 into the corresponding 4,5-dehydro compound by treatment with a base
 or

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(j) for the manufacture of a compound of formula I in which n stands for zero, converting a compound of the general formula



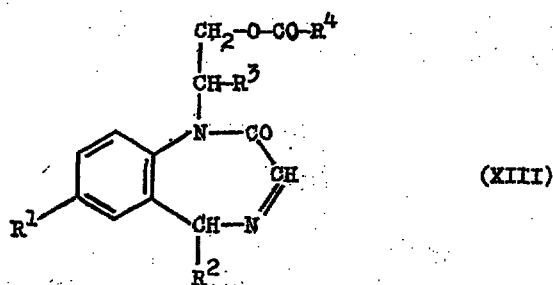
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, wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1 and R^{11} represents an alkylsulphonyl or arylsulphonyl group, into the corresponding 4,5-dehydro compound by treatment with a strong base or

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(k) for the manufacture of a compound of formula I in which n stands for zero, rearranging a compound of the general formula

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wherein R^1 , R^2 , R^3 and R^4 have the significance given in claim 1, into the corresponding 4,5-dehydro compound and

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(l) converting a compound obtained into a salt if desired.

20. A process according to claim 19, wherein R^1 represents a chlorine atom or a nitro group.

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21. A process according to claim 19 or claim 20, wherein R^2 represents a phenyl, 2-halophenyl or 2-pyridyl group.

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22. A process according to claim 21, wherein the 2-halophenyl group is a 2-chlorophenyl or 2-fluorophenyl group.

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23. A process according to any one of claims 19 to 22 inclusive, wherein R^4 represents an optionally substituted 5- or 6-membered aromatic heterocycle containing one or two nitrogen atoms or one oxygen or sulphur atom or one oxygen or sulphur atom and one nitrogen atom.

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24. A process according to claim 23, wherein R^4 represents a furan, thiophene, oxazole, isoxazole, pyrazole, pyridine or pyridazine heterocycle optionally substituted by 1 or 2 alkyl groups.

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25. A process according to claim 24, wherein R^4 represents a 3-pyridyl, 2-pyridyl or 2-pyrazinyl group.

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26. A process according to any one of claims 19 to 22 inclusive, wherein R^4 represents a halomethyl, carboxyalkyl, alkoxyalkyl or alkylamino group.

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27. A process according to claim 26, wherein R^4 represents a chloromethyl, 2-carboxyethyl, methoxymethyl, methylamino or ethylamino group.

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28. A process according to claims 19, 20, 21, 23, 24 and 25 wherein 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl nicotinate is manufactured.

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29. A process according to claims 19, 20, 21, 23, 24 and 25, wherein 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl picolinate is manufactured.



30. A process according to claims 19, 20, 21, 23, 24 and 25 wherein 2 - (7-chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl pyrazine - 2 - carboxylate is manufactured.
- 5 31. A process according to claims 19, 20, 21, 26 and 27, wherein 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl chloroacetate is manufactured. 5
32. A process according to claims 19, 20, 21, 26 and 27, wherein 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl hydrogen succinate is manufactured.
- 10 33. A process according to claims 19, 20, 21, 26 and 27, wherein 2 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 5 - phenyl - 1H - 1,4 - benzodiazepin - 1 - yl) - 2 - methoxyethyl methoxyacetate is manufactured. 10
34. A process according to claims 19, 20, 21, 26 and 27, wherein 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl ethylcarbamate is manufactured. 15
35. A process according to claims 19, 20, 21, 26 and 27, wherein 2-(7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-2-methoxyethyl methylcarbamate is manufactured.
- 20 36. A process for the manufacture of the compounds of formula I in claim 1, and salts thereof, substantially as hereinbefore described with reference to Examples 1 to 25. 20
37. Compounds of formula I in claim 1, and salts thereof, when manufactured by the process claimed in any one of claims 19 to 36 inclusive.

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