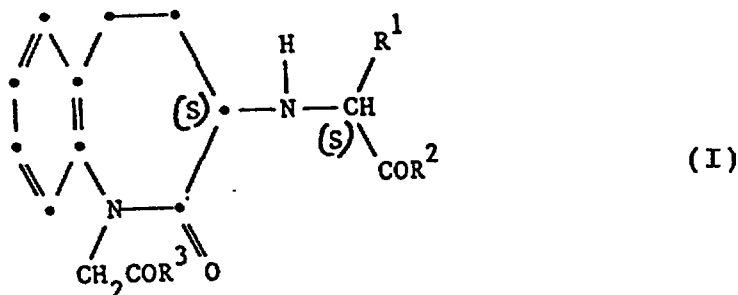


This invention relates to novel 3-(5-aminopentyl)-amino-1-benzazepin-2-one-1-alkanoic acids of the general formula I



wherein R^1 represents 4-aminobutyl, R^2 and R^3 represent, independently of each other, hydroxy or lower alkoxy, and S represents the chirality, salts, especially pharmaceutically acceptable salts thereof, processes for the manufacture of these compounds, pharmaceutical preparations containing these compounds and their therapeutic application.

The general definitions used herein have the following meanings within the scope of the present invention:

The term "lower" used above and hereinafter in connection with organic radicals and compounds defines those organic radicals and compounds having up to and including 7, preferably up to and including 4 and especially one or two, carbon atoms.

Lower alkyl contains from 1 to 7 carbon atoms, preferably from 1 to 4 carbon atoms, and is, for example, ethyl, propyl, butyl or especially methyl.

Aryl represents a carbocyclic or heterocyclic aromatic

radical, preferably phenyl unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy, lower alkylenedioxy, lower alkanoyloxy, hydroxy, halogen or by trifluoromethyl.

Cycloalkyl represents a saturated cyclic hydrocarbon radical that preferably contains from 3 to 8 carbon atoms and is, for example, cyclopentyl or cyclohexyl.

Aryl-lower alkyl represents preferably benzyl, 1- or 2-phenylethyl, 1-, 2- or 3-phenylpropyl, 1-, 2-, 3- or 4-phenylbutyl, wherein the phenyl ring is unsubstituted or mono- or di-substituted by lower alkyl, hydroxy, lower alkoxy, lower alkylenedioxy, lower alkanoyloxy, halogen or trifluoromethyl.

Lower alkoxy preferably contains from 1 to 4 carbon atoms and is, for example, methoxy, propoxy, isopropoxy or especially ethoxy.

Lower alkanoyloxy represents preferably acetoxy, propionyloxy or pivaloyloxy.

Lower alkylenedioxy represents preferably ethylenedioxy and especially methylenedioxy.

Halogen preferably represents chlorine, but may also be bromine, fluorine or iodine.

Acylated hydroxy represents preferably lower alkanoyloxy, e.g. acetyloxy, benzoyloxy substituted on the phenyl ring by lower alkyl, halogen or by lower alkoxy, e.g. by methyl, chlorine or methoxy respectively, or nicotinyl-oxy.

Etherified hydroxy represents preferably lower alkoxy,

e.g. methoxy, ethoxy or tert.-butoxy, or benzyloxy.

Trialkoxymethyl represents preferably tri-lower alkoxy-methyl, especially triethoxy- or trimethoxy-methyl.

Etherified hydroxymethyl represents preferably tertiary lower alkoxymethyl, lower alkoxy-lower alkoxymethyl, such as methoxymethoxymethyl, 2-oxa- or 2-thia-cycloalkoxy-methyl, especially 2-tetrahydropyranyloxymethyl.

The salts of compounds of formula I are derived from those compounds which have salt-forming properties. The pharmaceutically acceptable salts are preferred.

Pharmaceutically acceptable salts are preferably metal or ammonium salts of compounds of formula I wherein COR^2 and/or COR^3 represent carboxy, especially alkali metal or alkaline earth metal salts, e.g. the sodium, potassium, magnesium or calcium salt; or, advantageously, readily crystallising ammonium salts derived from ammonia or organic amines, such as mono-, di or tri-lower (alkyl, cycloalkyl or hydroxyalkyl)amines, lower alkylenediamines or (hydroxy-lower alkyl or aryl-lower alkyl)alkylammonium bases, e.g. methylamine, diethylamine, triethylamine, dicyclohexylamine, triethanolamine, ethylenediamine, tris-(hydroxymethyl)aminomethane or benzyltrimethylammonium hydroxide. These compounds of formula I form acid addition salts, preferably those of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric, phosphoric, nitric or perchloric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, gluconic, citric, ascorbic, maleic, fumaric, hydroxy-maleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic,

anthranilic, 4-hydroxybenzoic, salicylic, 4-amino-salicylic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid.

The compounds of formula I exhibit valuable pharmacological properties, e.g. cardiovascular effects caused inter alia by their inhibiting effect on the formation of angiotensin II. This effect is produced by selective inhibition of the enzyme that converts angiotensin in mammals. The compounds are therefore useful for treating diseases responsive to inhibition of the enzyme that converts angiotensin in mammals including man.

The compounds of the invention exhibit primarily hypotensive/antihypertensive activity and influence cardiac activity inter alia owing to their inhibiting action on the angiotensin-converting enzyme. These properties are demonstrable by in vitro or in vivo tests on animals, using preferably mammals, e.g. rats, cats, dogs or isolated organs thereof, as test objects. The animals may be either normotensive or hypertensive, e.g. genetically spontaneously hypertensive rats, or renally hypertensive rats or dogs, and sodium-depleted dogs. The compounds can be administered to the test animals enterally or parenterally, preferably orally or intravenously, for example in gelatin capsules or in the form of starchy suspensions or aqueous solutions. The applied dosage may lie within a range of about from 0.001 to 30 mg/kg/day, preferably about from 0.01 to 10 mg/kg/day.

The in vivo lowering effect on the blood pressure is recorded, either directly by means of a catheter placed in the test animal's femoral artery or indirectly by sphygmomanometry at the rat's tail, and with a trans-

ducer. The blood pressure is recorded in mm Hg prior to and after administration of the active ingredient.

Thus, the antihypertensive effects are demonstrable in spontaneously hypertensive rats by indirect measurement of the systolic pressure. Conscious rats are placed individually in restraint cages within a gently warmed chamber. A pulse sensor is placed inside an inflatable cuff on each rat's tail. The cuff is periodically inflated to occlude the tail artery. The pressure in the cuff is continuously reduced and the systolic pressure corresponds to that pressure in the cuff at which the pulse waves reappear. After recording control values of blood pressure and heart rate, the test compounds are administered orally once daily for 4 consecutive days. Additional blood pressure measurements are usually made 2.0, 4.0 and 23.5 hours after each daily dosing. The values are compared with those of rats treated with the carrier substance alone.

The compounds of the invention when administered intravenously or orally exhibit an inhibitory effect against the angiotensin-I-induced increase in blood pressure also in normotensive rats. Angiotensin I is hydrolysed by said converting enzyme to the potent pressor substance angiotensin II. The inhibition of said enzyme prevents the generation of angiotensin II from angiotensin I. In this manner the increase in blood pressure provoked by angiotensin I is attenuated.

The corresponding in vivo test is performed with male, normotensive rats, which are anaesthetised with sodium 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate. A femoral artery and saphenous vein are cannulated respectively for direct blood pressure measurement and intravenous administration of angiotensin I and a compound of this inven-

tion. After the basal blood pressure has stabilised, the pressure change in response to 3 challenges of 333 ng/kg angiotensin i.v., at 5 minute intervals, are determined. Such pressure changes are usually again determined 5, 10, 15, 30 and 60 minutes after intravenous administration or 1, 2, 3 and 4 hours after peroral administration of the compound to be tested, and are compared with the initial values. Any observed decrease in response of blood pressure, caused by the compounds of the invention, is an indication of angiotensin-I-converting enzyme inhibition.

The in vitro inhibition of the angiotensin-converting enzyme by the compounds of this invention can be demonstrated by a method analogous to that given in Biochim. Biophys. Acta 293, 451 (1973). According to that method, said compounds are dissolved at about 1 mM concentration in phosphate buffer. To 100 μ l of solutions of the test compound in phosphate buffer, diluted to the desired concentration, there are added 100 μ l of 5 mM hippuryl-histidyl-leucine in phosphate buffer, followed by 50 μ l of the angiotensin-converting enzyme. This enzyme is prepared from lungs of adult male rabbits in Tris buffer containing potassium chloride and magnesium chloride and also sucrose. Said solutions are incubated at 37°C for 30 minutes. The reaction is then stopped by adding 0.75 ml of 0.6N aqueous sodium hydroxide solution. At room temperature, 100 μ l of a 0.2 % solution of o-phthalaldehyde in methanol are added and, 10 minutes later, 100 μ l of 6N hydrochloric acid. These samples are compared with water in a spectrophotometer set at 360 nm, and the optical densities thereof are determined. These values are corrected for the standard curve via a conversion factor, to express nanomols of hystidyl-leucine formed during said 30 minute incubation period. The results are plotted against active ingredient concentra-

tion to determine the IC_{50} . The IC_{50} is that concentration of active ingredient which gives half the activity of a control sample containing no active ingredient.

The aforementioned advantageous properties render the compounds of the invention of great value as specific therapeutic agents for mammals including man.

Accordingly, the compounds of the invention are valuable antihypertensive agents, especially for lowering high blood pressure (regardless of etiology) and/or in cardiac conditions such as cardiac insufficiency and/or in other oedemic or ascitic diseases. They can also be used for the preparation of other valuable products, especially corresponding pharmaceutical compositions.

The invention relates especially to compounds of formula I wherein R^1 represents 4-aminobutyl, and R^2 and R^3 represent, independently of each other, hydroxy or lower alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert.-butoxy, and pharmaceutically acceptable salts thereof.

Preferred are compounds of formula I wherein R^1 represents 4-aminobutyl, and R^2 and R^3 represent, independently of each other, hydroxy, methoxy, ethoxy or tert.-butoxy, and pharmaceutically acceptable salts thereof.

Especially preferred are compounds of formula I wherein R^1 represents 4-aminobutyl, R^2 represents hydroxy, methoxy or tert.-butoxy, and R^3 represents hydroxy or ethoxy, and pharmaceutically acceptable salts, especially the hydrohalides and dihydrohalides thereof.

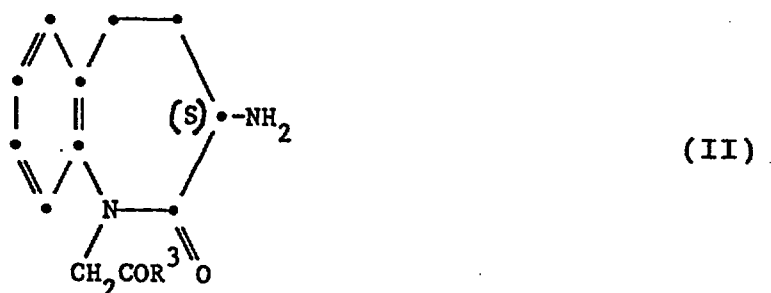
Especially preferred are compounds of formula I wherein R^1 represents 4-aminobutyl, R^2 represents hydroxy,

methoxy or tert.-butoxy when R^3 is hydroxy, and R^2 represents hydroxy or methoxy when R^3 is ethoxy, and the hydrochlorides and dihydrochlorides thereof.

Outstanding are 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one and its pharmaceutically acceptable salts.

The compounds of formula I according to the invention can be prepared in a manner known per se, e.g. as follows:

a) a compound of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R^3 has the meanings given above, is alkylated with a compound of the formula



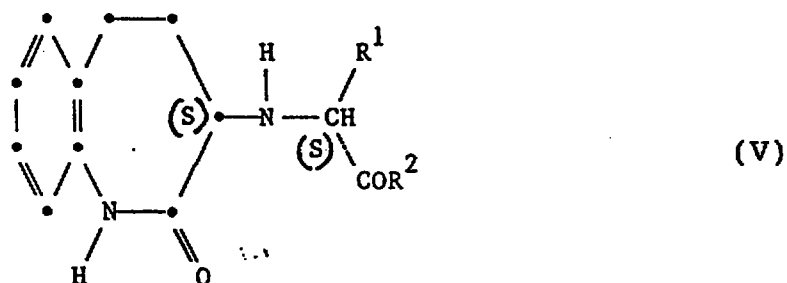
as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein Z is a reactive esterified hydroxy group and R^1 and R^2 have the meanings given above, or with a compound of the formula



wherein R^1 and R^2 have the meanings given above, in the presence of a reducing agent, with the temporary protec-

tion of the amino group and/or of hydroxy groups that may be present in any one of the radicals R^1 , R^2 and R^3 , or

b) a compound of the formula

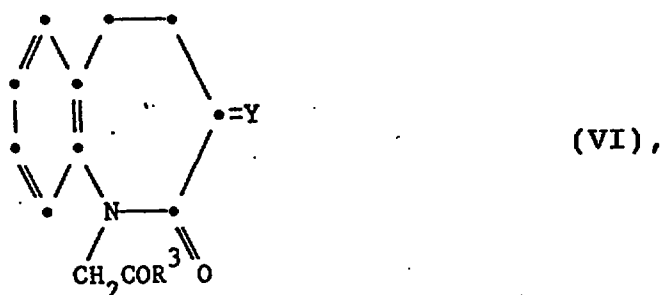


or a mixture of stereoisomers containing said compound, wherein S , R^1 and R^2 have the meanings given above, is alkylated with a compound of the formula

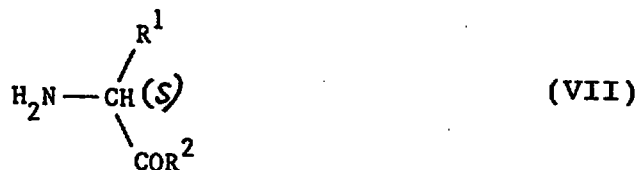


wherein Z is a reactive esterified hydroxy group and R^3 has the meanings given above, preferably with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the reactants, or

c) a compound of the formula

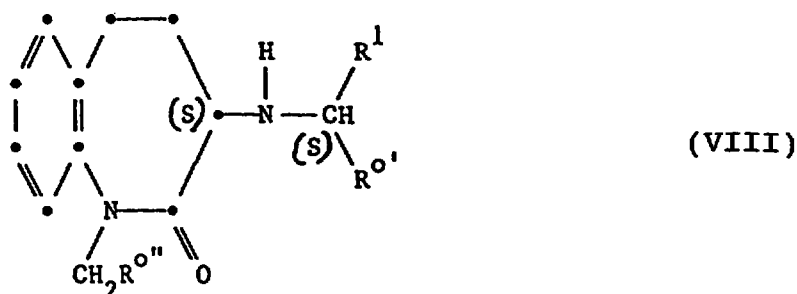


wherein Y is oxo, a reactive esterified or etherified hydroxy group Z together with hydrogen or two reactive esterified or etherified hydroxy groups Z , and R^3 has the meanings given above, is condensed with an amine of the formula



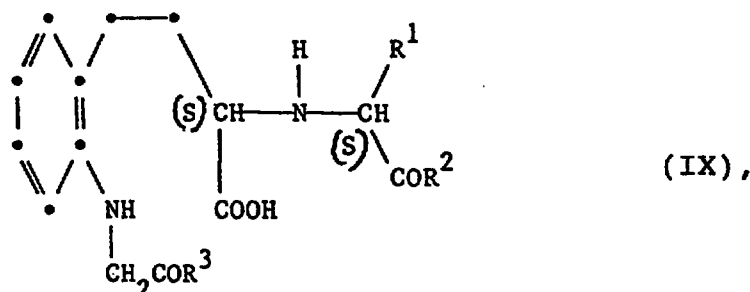
as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R^1 and R^2 have the meanings given above, with the proviso that when Y is oxo or two esterified or etherified hydroxy groups, the condensation is carried out in the presence of a reducing agent, or

d) in a compound of the formula



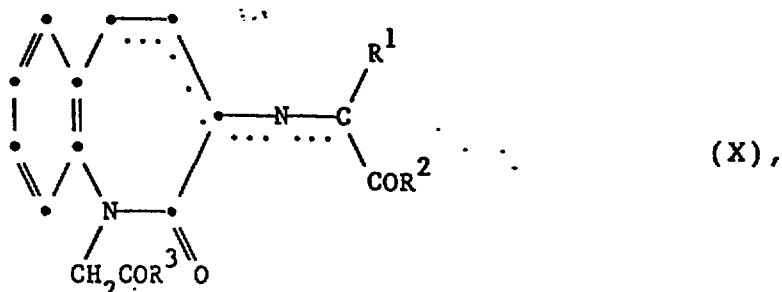
or in a mixture of stereoisomers containing said compound, wherein S and R^1 have the meanings given above, one of the symbols R^0' and R^0'' is cyano and the other is cyano or COR^2 or, as appropriate, COR^3 as defined above, the cyano group(s) is(are) subjected to solvolysis, or

e) a compound of the formula



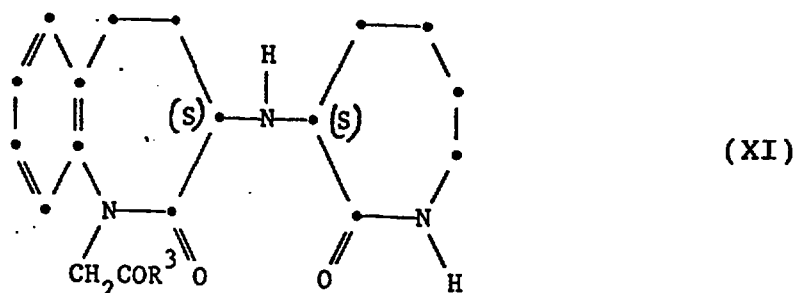
or a mixture of stereoisomers containing said compound, wherein S, R^1 , R^2 and R^3 have the meanings given above, or a reactive ester thereof, is cyclised, or

f) one or two double bonds in a compound of the formula



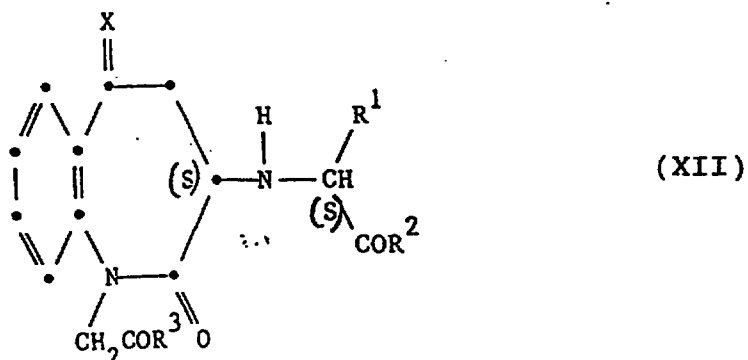
wherein said double bond(s) is(are) located between C3 and C4, C4 and C5 and/or in the side-chain between the nitrogen atom and an adjacent carbon atom, and wherein R^1 , R^2 and R^3 have the meanings given above, is(are) saturated by treatment with a reducing agent, or

g) the monocyclic lactam in a compound of the formula



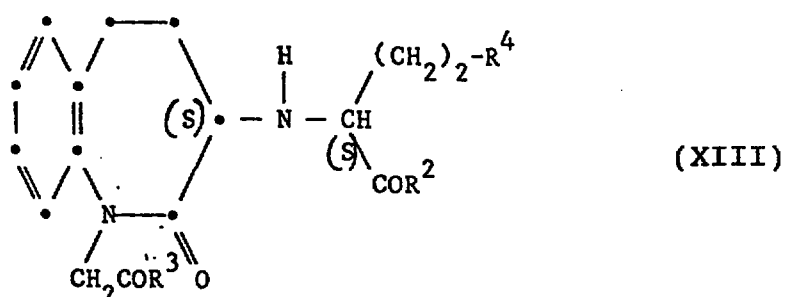
or in a mixture of stereoisomers containing said compound, wherein S and R^3 have the meanings given above, is ring-opened to give a compound of formula I wherein R^2 and R^3 are hydroxy, or

h) a compound of the formula



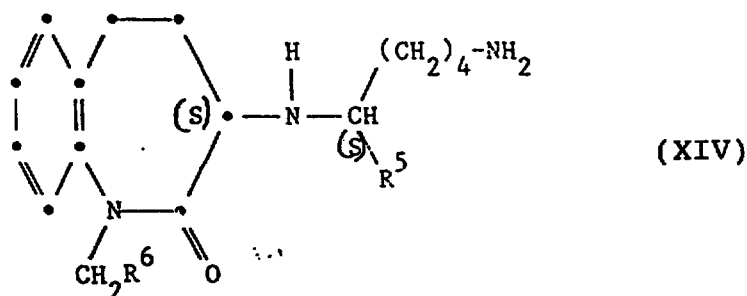
or a mixture of stereoisomers containing said compound, wherein X is oxo, protected oxo or two esterified or etherified hydroxy groups, or wherein X is hydroxy or esterified or etherified hydroxy together with a hydrogen atom, and wherein S, R¹, R² and R³ have the meanings given above, is hydrogenolysed or reduced, or

i) a compound of the formula



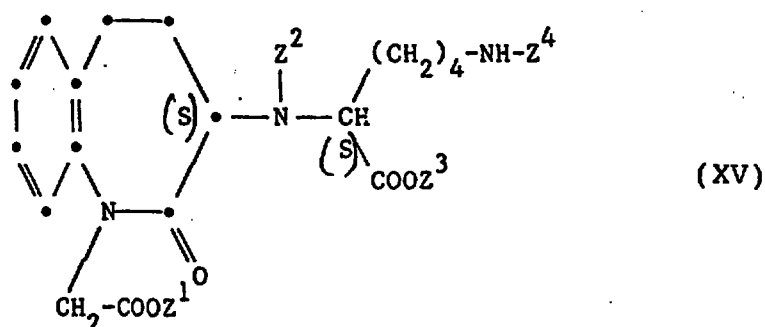
or a mixture of stereoisomers containing said compound, wherein R⁴ is a group convertible into 2-aminoethyl, and R² and R³ have the meanings given above, is converted into a compound of formula I, or

j) a compound of the formula



or a mixture of isomers containing said compound, wherein R⁵ or R⁶ is a group convertible into COR² or COR³, respectively, and the other is COR² or COR³ as appropriate, or wherein R⁵ and R⁶ are groups convertible into COR² and COR³, and wherein S has the meaning given above, is converted into a compound of the formula I, or

k) in a compound of the formula



or in a mixture of stereoisomers containing said compound, wherein at least one of the groups Z^1 to Z^4 is a protective group, remaining groups Z^2 and Z^4 are hydrogen and remaining groups Z^1 and Z^3 are hydrogen or lower alkyl, with the proviso that at least one group of the remaining groups Z^1 and Z^3 is hydrogen, and wherein S has the meaning given above, in order to obtain a compound of formula I wherein one or both of the radicals R^2 and R^3 is(are) hydroxy, the protective group(s) is(are) removed and, if desired, a resulting compound of formula I is converted into another compound of formula I and/or, if desired, a resulting compound of formula I having salt-forming properties is converted into a salt thereof or a resulting salt is converted into another salt, or a free compound is liberated from such a salt, and/or, if desired, the optical isomer of formula I that has the S,S configuration with respect to the two centres of chirality is isolated from a mixture of stereoisomeric forms containing a compound of formula I.

All of the processes for the preparation of a compound of formula I are advantageously carried out with reactive functional groups in temporarily protected form as deemed necessary in any process step under the particular circumstances by one skilled in the art.

A reactive esterified hydroxy group Z is a hydroxy group

esterified with a strong organic acid, e.g. an aliphatic or aromatic sulfonic acid (such as a lower alkanesulfonic acid, especially methanesulfonic and trifluoromethanesulfonic acid, especially benzenesulfonic acid, p-toluenesulfonic acid, p-bromobenzenesulfonic acid and p-nitrobenzenesulfonic acid) or with a strong inorganic acid, such as, especially, sulfuric acid, or a hydrohalic acid, such as hydrochloric acid or, most preferably, hydriodic acid or hydrobromic acid.

Any substitutive alkylation according to the present invention is carried out under conventional general conditions at temperatures in the range of approximately from 0°C to the boiling temperature of the reaction mixture, preferably at temperatures between room temperature and about 100°C. The reaction takes place advantageously in the presence of a solvent that is inert with respect to the reactants, such as in the presence of a chlorinated lower alkane (e.g. chloroform or methylene chloride), an acyclic or cyclic ether (e.g. diethyl ether, 1,2-dimethoxyethane, dioxane or tetrahydrofuran) and, especially, a low molecular weight tertiary amide (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, N-ethylpiperidone and hexamethylphosphoric acid triamide). Advantageously, the strong acid HZ liberated during the reaction is bound by the addition of an acid-binding agent, such as, preferably, an inorganic acid-scavenger, such as an alkali metal bicarbonate, carbonate or hydroxide, an organic quaternary ammonium salt (e.g. a tetrabutylammonium salt) or an organic tertiary base, such as triethylamine, N-ethylpiperidine, pyridine or quinoline.

An alkylation according to the invention can also be carried out under the conditions of reductive alkylation which are known per se and used in the art. In carrying

out that alkylation the starting materials are, simultaneously or in a subsequent step, reacted with a reducing agent. Among reducing agents that are used simultaneously with the alkylating agent, mention should be made of formic acid and complex metal hydrides, such as sodium cyanoborohydride; among reducing agents used predominantly in a separate subsequent operation, i.e. to reduce a preformed imine (Schiff's base), mention should be made of diborane and complex metal hydrides, such as sodium borohydride and sodium cyanoborohydride, which are added advantageously to the primary reaction mixture without isolating an intermediate, e.g. the imine. In this case, the alkylation is carried out advantageously in an organic solvent that is inert towards the reducing agent, such as in an aliphatic or cyclic ether (such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxane or tetrahydrofuran) or in an aliphatic alcohol (such as methanol, ethanol, isopropyl alcohol, glycol, glycol monomethyl ether or diethylene glycol), preferably at about from 0° to 80°C. A principal reducing agent, which can be used both simultaneously and subsequently, is hydrogen, especially catalytically activated hydrogen. The catalysts are those conventionally used as hydrogenation catalysts, preferably those of the class of noble metals (such as palladium, platinum and rhodium) on a carrier (such as calcium carbonate, aluminium oxide or barium sulfate), in a finely dispersed suspension without carrier or, in the form of complexes, in a homogeneous phase. Also, finely dispersed transition metals, e.g. Raney metals, especially Raney nickel, are very suitable catalysts for the reductive alkylation. The specific reaction conditions depend, to a large extent, on the particular hydrogenation catalyst and its precise activity, and do not differ from those generally known for hydrogenation. Temperatures ranging from room temperature to about 150°C, and pressures of hydrogen

ranging from atmospheric pressure to about 300 atmospheres may be used according to the standard procedures of the art. In addition to the inert solvents which were mentioned above in connection with the hydride reduction, low molecular weight amides, especially tertiary amides (such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, N-ethylpiperidone, hexamethylphosphoric acid triamide), and also formamide and acetamide can be used as suitable solvents.

The preformed imides referred to above are preferably prepared by condensing corresponding starting materials in an inert solvent, e.g. toluene or methylene chloride, especially in the presence of a dehydrating catalyst, e.g. boron trifluoride etherate, p-toluenesulfonic acid or molecular sieves.

In any of the alkylation processes, primary and secondary amino groups in the starting materials, except for the amino group to be alkylated, must be in a temporarily protected form during the alkylation. Suitable protecting groups and procedures for their introduction and removal are well known in the art, being elaborated in great detail in particular as general methods for the synthesis of peptides, cf. Houben-Weyl: Methoden der Organischen Chemie; 4th edition, vol. 15/I and II, E. Wünsch (editor): Synthese von Peptiden (Georg Thieme Verlag, Stuttgart; 1974). The narrower selection of the protecting groups depends on the specific purpose, it being necessary to take into account in particular the specific properties of the particular starting materials and the reaction conditions of the specific process. In cases where different functional groups have to be protected, advantageous combinations can be selected. Preferably, for example, similar amino- and carboxy-protecting groups are used in the radicals COR^2 and COR^3

and in the radical R^1 and are simultaneously removed following alkylation.

Suitable as amino-protecting groups are especially amino-protecting groups that can be removed by reduction, for example especially those of the benzyloxycarbonyl type in which the benzyloxycarbonyl group may be substituted in the aromatic moiety by halogen atoms, lower alkoxy groups and/or lower alkyl radicals and, especially, by nitro groups, such as the p-chloro- and p-bromobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-methylbenzyloxycarbonyl and, especially, p-nitrobenzyloxycarbonyl group, or alternatively the isonicotinylloxycarbonyl group. An advantageous amino-protecting group is an ethoxycarbonyl group that carries in the β -position a silyl group substituted by three hydrocarbon radicals, such as triphenylsilyl, dimethyl-tert.-butylsilyl or, especially, trimethylsilyl. A β -(trihydrocarbylsilyl)-ethoxycarbonyl group of this type, such as a β -(tri-lower alkylsilyl)-ethoxycarbonyl group, for example especially β -(trimethylsilyl)-ethoxycarbonyl, forms with the amino group to be protected a corresponding β -trihydrocarbylsilyl-ethoxycarbonylamino group (for example the β -trimethylsilylethoxycarbonylamino group), which may be removed under very specific, very mild conditions by the action of fluoride ions.

It is also possible to use groups that can be removed by acidolysis, such as the tert.-butoxycarbonyl groups and analogous groups, and also those of the aralkyl type, such as benzhydryl, di-(4-methoxy)-benzhydryl and triphenylmethyl (trityl), or certain aralkoxycarbonyl groups of the 2-(p-biphenyl)-2-propoxycarbonyl type which are described in CH-PS 509 266. It should be noted that protecting groups derived from esters of carbonic acid are in most cases also removable by basic hydroly-

sis.

For the optional temporary protection of hydroxy groups, there may advantageously be used protecting groups that can be removed by reduction, cf. the above-cited text (Houben-Weyl), and also the groups that can be removed by acidolysis, such as 2-tetrahydropyranyl, tert.-butoxycarbonyl and tert.-butyl. Preferred hydroxy-protecting groups that can be removed by reduction are, for example, benzyl groups that may be substituted in the aromatic moiety by halogen, lower alkyl, lower alkoxy and/or, especially, by nitro, especially the 4-nitrobenzyl group. It is also possible to use acyl groups that can be removed under weakly basic conditions, such as formyl or trifluoroacetyl.

For the optional protection of oxo groups, the latter are preferably protected as ketals, especially as ketals derived from lower alkanols, such as methanol or ethanol, or advantageously ethylene glycol, or as corresponding thioketals, preferably as those of 1,2-ethanedithiol. All these groups are able to free oxo groups under the conditions indicated further below.

The subsequent removal of protecting groups in accordance with the invention depends on their nature and is carried out in each case in a conventional manner known per se taking into consideration the general properties of the resulting product. If the protecting groups for amino and carboxy have been so selected that they can be removed under similar conditions, then all of these protecting groups are advantageously removed in a single operation; in special cases, however, it is possible to use different types of groups and remove each of them individually.

The groups that can be removed by reduction, especially those that contain halogenated lower alkyl radicals (for example 2,2,2-trichloroethyl radicals), isonicotinyl radicals (for example isonicotinylloxycarbonyl) and unsubstituted or substituted benzyl radicals, especially 4-nitrobenzyl radicals of any kind, are preferably removed by reduction with zinc, usually in the presence of an acid, preferably acetic acid, and with or without the addition of an inert organic solvent, usually at room temperature. The removal of a protecting group by acid hydrolysis (acidolysis) is carried out in the case of groups of the tert.-butyl type by means of hydrogen chloride, hydrogen fluoride or trifluoroacetic acid, and in the case of acid-sensitive protecting groups chiefly by means of a lower aliphatic carboxylic acid, such as formic acid and/or acetic acid, in the presence of water and, optionally, a polyhalogenated lower alkanol or lower alkanone, such as 1,1,1,3,3,3-hexafluoropropan-2-ol or hexafluoroacetone. In this manner, it is possible, for example, for an N-trityl group to be removed by an organic acid, such as formic acid, acetic acid, chloroacetic acid or trifluoroacetic acid, in aqueous or absolute trifluoroethanol as solvent (cf. DE-OS 23 46 147) or by aqueous acetic acid; for the tert.-butoxycarbonyl group to be removed by trifluoroacetic acid or hydrochloric acid; and for the 2-(p-biphenyl)-isopropoxycarbonyl group to be removed by aqueous acetic acid or, for example, by a mixture of glacial acetic acid, formic acid (82.8 % concentration) and water (7:1:2) or in accordance with the process in DE-OS 23 46 147. The β -silylethyl ester groups are preferably removed by fluoride-ion-yielding reagents, for example fluorides of quaternary organic bases, such as tetraethylammonium fluoride.

Ketalised and thioketalised oxo groups are converted into

free oxo groups by acidolysis with customary strong inorganic acids or with oxalic acid in the presence of water, the latter ones advantageously by treatment with a sulfur-binding agent, e.g. a mercury(II) salt and/or cadmium carbonate. Protecting groups that are unstable to basic conditions, for example formyl, trifluoroacetyl and carbonic acid ester groups, can be carefully removed by the action of an aqueous sodium or potassium bicarbonate or carbonate solution or also by the action of aqueous ammonia in an organic solvent, usually at room temperature. The protecting groups are preferably removed under the reaction conditions of the Examples or under analogous conditions.

In the case of the starting materials of formulae IIIA, IIIB, IV and VII wherein R^2 or R^3 represents hydroxy, an appropriate carboxylic acid salt is prepared, preferably in situ, before condensation with the desired intermediate, which is described hereinafter in detail.

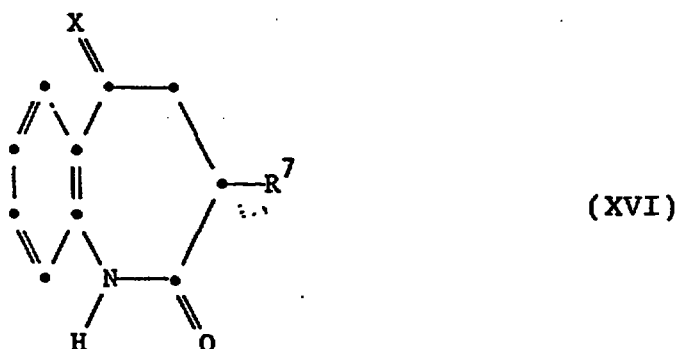
Process a) Condensation of amines of formula II with the known α -ketoacid derivatives of formula IV by reductive N-alkylation is carried out under conditions known in the art, e.g. by catalytic hydrogenation with hydrogen in the presence of platinum, palladium or nickel catalysts or with chemical reducing agents, such as simple or complex light metal hydrides, advantageously an alkali metal cyanoborohydride, such as sodium cyanoborohydride. The reductive amination with an alkali metal cyanoborohydride is preferably carried out in an inert solvent, e.g. methanol or acetonitrile, advantageously in the presence of an acid, e.g. hydrochloric acid or acetic acid, at a temperature between about 0 and 50°C, preferably room temperature.

Alkylation of amines of formula II with a reactant of

formula IIIA, well known in the art, is carried out with or without basic catalysts, such as triethylamine or potassium carbonate, in an inert solvent.

The starting materials of formulae IIIA and IV are known or, if they are unknown, can be prepared in a simple manner by conventional synthesis processes. The starting materials of formula II can be obtained by conventional synthesis processes, and advantageously in the manner which is described in more detail and exemplified for specific intermediates hereinafter.

Compounds of formula II can be obtained by condensing, under conditions of basic catalysis, a compound of the formula



wherein X represents two hydrogen atoms, one hydrogen atom and one esterified or etherified hydroxy group, oxo or oxo protected in form of a ketal or thioketal, and R^7 is amino, azido or acylamino, e.g. lower alkanoylamino or lower alkoxycarbonylamino, with a compound of the formula



wherein R^3 represents hydroxy, di-lower alkylamino, lower alkoxy, aryl-lower alkoxy, lower alkanoyloxymethoxy or lower alkoxycarbonyl-lower alkoxy, and Z represents a

reactive esterified hydroxy group; and optionally reducing, hydrogenolysing, hydrolysing or alkylating the resulting intermediate.

Compounds of formula XVI are obtained from the corresponding unsubstituted or substituted and/or derivatised 2,3,4,5-tetrahydro-1H-1-benzazepin-2-ones [J. Chem. Soc. 1937, 456; British Patent 1,359,285; Liebig's Ann. Chem. 574, 171 (1951)]. Novel, appropriately derivatised 1-benzazepin-2-one starting materials are advantageously prepared by Beckmann rearrangement of the correspondingly derivatised naphthalen-1-ones using procedures which are well known and described herein.

Said tetrahydro-1-benzazepin-2-ones are converted into the 3-halo-, e.g. 3-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-ones using processes described herein, e.g. by treatment with phosphorus pentachloride, to obtain first the 3,3-dichloro derivative, followed by hydrogenation. Substitution of said halo derivatives with a metal azide, e.g. sodium azide, and optional reduction, or substitution with ammonia and optional acylation, yields racemic compounds of formula XVI wherein R^7 is amino or acylamino.

Alternatively, compounds of formula XVI wherein R^7 represents amino or acylamino are obtained by reduction and cyclisation of an appropriately substituted and/or derivatised 4-(2-nitrophenyl)-2-aminobutyric acid and optional subsequent N-alkylation or N-acylation.

Resolution of a compound of formula XVI wherein R^7 is amino by methods well-known in the art gives the 3-(S)-enantiomer.

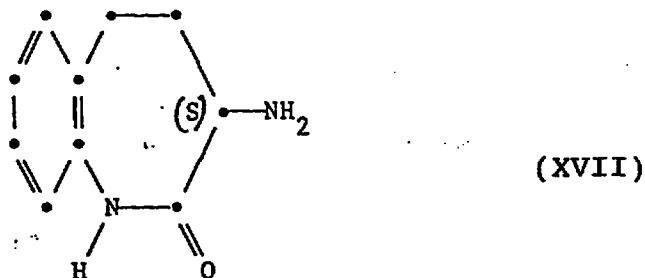
An alternative synthesis for the optically active com-

pounds of this invention starts with the natural amino acid tryptophan. For example, L-4-(2-aminophenyl)-4-oxo-2-aminobutyric acid (L-kynurenine, J. Am. Chem. Soc. 76, 1708 (1954), derived from L-tryptophan) is converted into an optically active starting material of formula XVI wherein R⁷ is acylamino, e.g. 3-(S)-tert.-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1-benzazepine-2,5-dione as described in the Australian Journal of Chemistry 33, 633-40 (1980). The lactam alkylation of a compound of formula XVI with a reactant of formula IIIB is carried out in known manner, preferably in the presence of bases, such as alkali metal hydrides, e.g. sodium or potassium hydride, alkali metal alkoxides, e.g. potassium tert.-butoxide or sodium methoxide, organo-metallic reagents, e.g. lithium diisopropylamide, or under conditions of phase-transfer catalysis, e.g. in the presence of a tetrabutylammonium salt, preferably in a solvent, e.g. tetrahydrofuran, dimethylformamide, at a temperature of preferably from 0° to 75°C.

Process b) is carried out in a conventional manner under the conditions of substitutive alkylation described hereinbefore, preferably in the presence of very strong bases, such as alkali metal hydrides (e.g. sodium or potassium hydride), alcoholates (e.g. sodium methoxide or ethoxide, potassium tert.-butoxide) or amides (e.g. lithium diisopropylamide), the above-mentioned ethers and amides being preferred as solvents.

The starting materials of formula IIIB are known or, if they are unknown, can be prepared in a simple manner by conventional synthesis processes. The starting materials of formula V can be obtained by conventional synthesis processes, and advantageously in the manner described in more detail and exemplified for specific intermediates hereinafter.

Compounds of formula V can be obtained by condensing under conditions of reductive alkylation a compound of the formula



with a compound of the formula



wherein S, R^1 and R^2 have the perviously defined meanings, or under alkylation conditions with a compound of the formula



wherein S, R^1 , R^2 and Z have the meanings previously given.

Process c), also being an alkylation reaction, is performed according to the same general considerations and under the same experimental conditions as described in detail above (substitutive alkylation or reductive alkylation). The starting materials of formula VI can be obtained by conventional processes known per se, e.g. in the manner described more specifically hereinafter.

The lysine compounds of formula VIII are known or, if they are unknown, can easily be prepared by conventional synthesis processes.

The starting materials of formula VI wherein Y represents oxo may be prepared by treating a compound of formula II with a lower alkyl nitrite, e.g. tert.-butyl nitrite, followed by a peracid, e.g. m-chloroperbenzoic acid, in an inert solvent, such as chloroform or methylene chloride, preferably at room temperature. The starting materials of formula VI wherein Y represents two reactive esterified hydroxy groups (such as dihalo, e.g. dichloro) may be prepared by first treating 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one with a halogenating agent such as phosphorous pentachloride to give e.g. the 3,3-dichloro compound, which is then alkylated with a compound of formula IIIB.

A compound of formula VI wherein Y represents one reactive esterified hydroxy group and one hydrogen atom may be prepared by hydrogenation of the corresponding compound wherein Y represents e.g. two reactive esterified hydroxy groups, such as dichloro.

Process d) is also carried out in a conventional manner under the general conditions of solvolysis, which are known to convert cyanides (nitriles) into free carboxylic acids, their salts or esters. For conversion into a free acid, hydrolysis with water is carried out advantageously in an inert organic solvent that is at least partially miscible with water, such as an ether (e.g. diethyl or diisopropyl ether, 1,2-dimethoxyethane or, especially, dioxane or tetrahydrofuran), or a lower alkanol (e.g. methanol, ethanol, isopropyl alcohol, a butyl alcohol, especially tert.-butyl alcohol), a larger amount of water being required in the latter cases in order to prevent

alcoholysis. The hydrolysis can be catalysed both by strong acids, especially inorganic acids, such as sulfuric acid or, preferably, hydrohalic acids (e.g. hydrobromic acid or, as a first choice, hydrochloric acid), and by bases, especially inorganic bases, such as hydroxides and carbonates of alkali metals, e.g. sodium and potassium hydroxide. The bases are usually employed in at least stoichiometric quantities giving rise to carboxylic acid salts as primary products. The acidic catalysts are advantageously employed in the form of a dilute aqueous solution for best results. The end products of formula I in which COR^2 and/or COR^3 represent a carboxy group esterified with a lower alkanol can be obtained by carrying out the solvolysis of the nitrile with the corresponding alcohol (alcoholysis) in the presence of a catalytic amount of an anhydrous strong acid, advantageously gaseous hydrogen chloride. Usually, excess alcohol is used as solvent; however, inert organic solvents can be added, such as acyclic and cyclic ethers (especially those mentioned above), and/or halogenated lower alkanes (especially chloroform and dichloromethane). If the alcoholysis is carried out under strictly anhydrous conditions, the primary product (imido ester) has to be hydrolysed, advantageously by adding water; on the other hand, by carrying out the alcoholysis in the presence of an approximately stoichiometric equivalent of water, the desired ester is obtained directly.

The starting materials of formula VIII can be obtained by conventional methods known per se, e.g. by a condensation analogous to that of process c) in which a starting material of formula VI is treated with an amine of the formula



wherein S and R¹ have the meanings given hereinabove. Processes a) and b) can also be used analogously for the preparation of the nitriles of formula VIII.

The cyclisation according to process variant e) can also be carried out in the manner known per se, e.g. by dehydration. Especially suitable general methods for this purpose are those developed in connection with the formation of the amide bond in peptides, as reviewed in compilative works, e.g. Houben-Weyl, Volumes 15/I and 15/II as cited hereinabove. According to one preferred modification, the amino group to be cyclised is rendered inactive by protonation (i.e. in the form of an acid addition salt), and the carboxy group is converted into an activated ester, such as that with 2,4,5-trichlorophenol, pentachlorophenol, pentafluorophenol, 2-nitrophenol or, especially, 4-nitrophenol, or with an N-hydroxy compound, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole or N-hydroxypiperidine, or alternatively with an N,N'-disubstituted isourea, such as, especially, N,N'-dicyclohexylisourea, or an analogous generally known activating agent. The cyclisation is effected by basification preferably by the addition of an organic base, for example a quaternary ammonium salt or, especially, a tertiary amine, such as triethylamine, N-ethylmorpholine or N-methylpiperidine, in order to reactivate the amino group to be cyclised by converting it into the unprotonated form. The reaction temperature is usually from -20° to +50°C, preferably approximately at room temperature, and customary solvents are used, for example dioxane, tetrahydrofuran, acetonitrile, pyridine,

dimethylformamide, dimethylacetamide, dimethyl sulfoxide, N-methylpyrrolidone, hexamethylphosphoric acid triamide, and also chloroform and methylene chloride, and expedient mixtures thereof. In a special variant of the process, the carboxy group can be directly activated in situ by the action of the free acid with a carbodiimide, such as N,N'-dicyclohexylcarbodiimide (optionally with the addition of N-hydroxysuccinimide, an unsubstituted or, for example, halogen-, methyl- or methoxy-substituted 1-hydroxybenzotriazole or 4-hydroxybenzo-1,2,3-triazine 3-oxide or N-hydroxy-5-norbornene-2,3-dicarboximide), or with N,N'-carbonyldiimidazole.

The starting materials of formula IX can be obtained according to general methods known per se, e.g. as discussed with reference to specific examples hereinafter.

Reduction according to process f) can also be carried out in a manner generally known per se for the saturation of such double bonds. More specifically, a double bond in an unsaturated starting material of formula X can be located between C3 and C4, between C4 and C5 and/or between C3 and the adjacent nitrogen atom, and/or between the nitrogen atom and the adjacent exocyclic carbon atom. The saturation of such double bonds is advantageously carried out by catalytic hydrogenation, for example under the preferred conditions discussed in detail hereinbefore, and also by metal reduction, such as zinc reduction, in neutral or acidic medium or, especially in the case of the C-N double bond, by diborane or complex hydrides, such as sodium borohydride, as mentioned hereinbefore. The unsaturated starting materials for this process variant are obtained according to generally known methods, e.g. those discussed in processes a) and c) and/or in a more specific form hereinafter.

The starting materials that have, for example, a C4-C5 double bond are prepared from starting materials that are identical in structure to the compounds of formulae II, V and VI except for having a C4-C5 double bond, in a manner analogous to that of processes a), b) or c). The latter are in turn prepared from the corresponding 5-hydroxy or 5-(esterified or etherified) hydroxy derivatives of compounds of formulae II, V and VI by elimination procedures. Said 5-substituted compounds are prepared from e.g. L-kynurenine as described herein.

The ring-opening of the caprolactam ring in a compound of formula XI according to process g) is carried out by methods known in the art, e.g. by treatment with a strong mineral acid, preferably at elevated temperature. The compound of formula I wherein R^2 and R^3 are hydroxy is obtained.

A starting material of formula XI is prepared e.g. by reductive alkylation of 3-(S)-amino- ϵ -caprolactam with a compound of formula VI according to process c).

According to process h), compounds of formula XII wherein X represents one hydrogen atom and one hydroxy group may be converted into compounds wherein X represents two hydrogen atoms, e.g. by catalytic hydrogenation of the adduct of a carbodiimide, e.g. the adduct formed by condensation of a compound wherein X represents one hydrogen and one hydroxy group with dicyclohexylcarbodiimide in the presence of cuprous chloride according to the general method described in Chem. Ber. 107, 1353 (1974).

Alternatively, the compounds wherein X represents one hydrogen atom and one hydroxy group may be first con-

verted into the corresponding compounds wherein X represents one hydrogen atom and one acylated hydroxy group, e.g. acetoxy or chloro, and subsequently reduced, e.g. by catalytic hydrogenation in the presence of a palladium catalyst, to compounds wherein X represents two hydrogen atoms.

The reduction of the oxo group in a compound of formula XII to two hydrogen atoms can advantageously be accomplished by treatment with amalgamated zinc and hydrochloric acid, or by Raney nickel desulfurisation of a corresponding dithioketal.

Compounds of formula XII wherein X represents oxo may first be converted into the corresponding compounds wherein X represents one hydrogen atom and one hydroxy group by reduction, e.g. by catalytic hydrogenation, e.g. with hydrogen in the presence of a platinum catalyst, or with a metal hydride reducing agent, such as sodium borohydride, or according to the Meerwein-Ponndorf method or a modification thereof using an alkanol, especially isopropanol, as both solvent and reducing agent and a metal alkoxide, preferably one corresponding to the reducing alcohol, such as aluminium isopropoxide, as a catalyst.

The starting materials of formula XII are prepared analogously to the processes a), b) or c) already described above, starting with e.g. L-kynurenine as described herein. For processes involving a reductive alkylation step, special measures have to be taken for starting materials that have an easily reducible functional group, such as the 5-oxo group; in order to preserve these groups, either they must be temporarily protected or selective reduction conditions, as known in the art, have to be applied; or, if a simultaneous

reduction of these groups is desired or required, vigorous reagents and/or reaction conditions are employed accordingly.

In process i) a group R^4 convertible into 2-aminoethyl is, for example, 2-nitroethyl, cyanomethyl, 2-azidoethyl, 2-carbamoylethyl, 2-hydrazinocarbonylethyl, 2-azido-carbonylethyl or 2-acylaminoethyl (preferably 2-(benzyl-oxycarbonylamino)ethyl, or 2-lower alkanoylaminoethyl), or vinyl, or the group $(CH_2)_2Z^5$ wherein Z^5 is a group convertible into amino by substitution, such as a reactive esterified group, e.g. halo (preferably bromo or iodo), or acyloxy (preferably mesyloxy).

Conversion of the group R^4 into 2-aminoethyl is carried out according to methods known in the art. For example 2-nitroethyl, cyanomethyl and 2-azidoethyl are converted into 2-aminoethyl by reduction, such as catalytic hydrogenation in an inert solvent. A group $(CH_2)_2Z^5$ is converted into 2-aminoethyl e.g. by condensation with potassium phthalimide and subsequent freeing of the amino group as known in the art, or with chloroamine. A vinyl group may be converted into 2-aminoethyl e.g. by treatment with diborane in an inert solvent, such as tetrahydrofuran, followed by treatment with chloramine. 2-Acylaminoethyl is converted into 2-aminoethyl by methods described under removal of amino-protecting groups. 2-Carbamoylethyl, 2-hydrazinocarbonylethyl and 2-azido-carbonylethyl are converted into 2-aminoethyl in known manner (e.g. Curtius degradation via an isocyanate intermediate).

The starting materials of formula XIII are prepared e.g. by processes a), b), c), e) or f) by replacing a starting material of formula IIIA, IV, V, VII, IX or X by the corresponding compound wherein R^1 represents $(CH_2)_2-R^4$.

In process j) R^5 and R^6 represent preferably groups convertible into carboxy, e.g. esterified carboxy groups, carboxy groups in form of their anhydrides, including corresponding groups of asymmetric and inner anhydrides, amidated carboxy groups, amidino groups including cyclic amidino groups, iminoether groups including cyclic iminoether groups, e.g. 2-oxazolinyl or dihydro-2-oxazolinyl groups, substituted by lower alkyl, and also hydroxymethyl, etherified hydroxymethyl, esterified hydroxymethyl (such as lower alkanoyloxymethyl), tri-alkoxymethyl, acetyl, trihaloacetyl, halomethyl, formyl, di-lower alkoxymethyl, or vinyl.

The conversion of R^5 and/or R^6 in process j) into the carboxy group is carried out in a manner known per se and as described herein and in the Examples, e.g. by solvolysis, such as hydrolysis or acidolysis (e.g. for amidated and esterified carboxy groups), or by reduction (e.g. for esterified carboxy groups). For example, trichloroethyl esters or 2-iodoethyl esters may be converted into the carboxylic acids by reduction, e.g. with zinc and a carboxylic acid in the presence of water. Benzyl esters or nitrobenzyl esters may be converted into the carboxylic acid groups by catalytic hydrogenation, the latter also with chemical reducing agents, e.g. sodium dithionite or with zinc and a carboxylic acid. A tert.-butyl ester also may be cleaved with trifluoroacetic acid.

Furthermore, compounds of formula XIV wherein R^5 and/or R^6 represents acetyl may be oxidatively cleaved to give the corresponding compounds of formula I wherein R^2 and R^3 represent hydroxy first by conversion into a compound wherein R^5 and/or R^6 represents trihaloacetyl, e.g. tribromo- or triiodo-acetyl, such as by treatment with

sodium hypobromite, followed by cleavage with e.g. an aqueous base, such as sodium hydroxide.

Compounds of formula XIV wherein R^5 and/or R^6 represents e.g. hydroxymethyl, esterified and etherified hydroxymethyl, formyl, di-lower alkoxymethyl or alkylenedioxymethyl (formyl protected in the form of an acetal, e.g. the dimethyl acetal), are oxidised with a suitable oxidising agent to the corresponding compounds of formula I wherein R^2 and/or R^3 represents hydroxy.

Compounds of formula XIV wherein R^5 and/or R^6 represents vinyl may be converted into compounds of formula I wherein R^2 and/or R^3 represents hydroxy, by e.g. first oxidising to compounds of formula XIV wherein R^5 and/or R^6 represents formyl, which are in turn oxidised to compounds of formula I wherein R^2 and/or R^3 represents hydroxy.

The hydrolysis of intermediates of formula XIV wherein R^5 and/or R^6 represents trialkoxymethyl to compounds of formula I wherein R^2 and/or R^3 represents hydroxy is preferably carried out with inorganic acids, such as hydrohalic acids or sulfuric acid.

The starting materials of formula XIV are prepared analogously to processes a), b), c), e) or f) by replacing a starting material of formula II, IIIA, IIIB, IV, V, VI, VII, IX or X by the corresponding compound wherein COR^2 and/or COR^3 represents R^5 and/or R^6 .

The removal of the amino and carboxy-protecting groups according to process k) is carried out by known methods.

The removal and the nature of the amino-protecting groups Z^2 and Z^4 is described hereinabove. The carboxy-protect-

ing groups Z^1 and Z^3 represent various radicals of the alcohol portion of mono- or di-esters of the dicarboxylic acids of formula I wherein R^2 and R^3 represent hydroxy.

The free carboxy group can be freed from an esterified carboxy in a manner generally known, especially by base-catalysed hydrolysis. Of special interest, however, are methods capable of selectively freeing one particular carboxy group represented by the symbols $-COR^2$ and $-COR^3$. In such a case, use can be made of a suitable combination of ester groups known in the art especially as carboxy-protecting groups and developed in a great variety in particular for the synthesis of peptides, c.f. Houben-Weyl, Volumes 15/I and 15/II as cited hereinabove. Radicals suitable for selective removal with the carboxy group being freed are esters derived, for example, from alcohols that yield radicals that can be removed by acidolysis, such as cyanomethyl alcohol, benzoylmethyl alcohol or tert.-butyl alcohol, but especially alcohols that yield radicals that can be removed by reduction, such as 2,2,2-trichloroethanol, benzyl alcohol and, especially, 4-nitrobenzyl alcohol, or alternatively isonicotinyl alcohol. An especially preferred class of substituted alkanols comprises ethyl alcohols that carry in the β -position a tri-substituted silyl group, such as triphenylsilyl, dimethyl-tert.-butylsilyl or, especially, trimethylsilyl. As is described, for example, in BE-PS 851 576, these alcohols are particularly suitable for selective removal because the corresponding β -silylethyl esters, for example β -(trimethylsilyl)ethyl esters, have the stability of customary alkyl esters but can be selectively removed under mild conditions by the action of fluoride ions while other esterified carboxy groups, for example alkoxycarbonyl groups, are retained.

The removal of esterifying groups depends on their nature

and is carried out in each case in a conventional manner known per se taking into consideration the properties of the other radicals involved. The groups that can be removed by reduction, especially those that contain halogenated lower alkyl radicals (for example 2,2,2-trichloroethyl radicals), isonicotinyl radicals (for example isonicotinylloxycarbonyl) and unsubstituted or substituted benzyl radicals, especially 4-nitrobenzyl radicals of any kind, are preferably removed by zinc reduction, usually in the presence of an acid, preferably acetic acid, and with or without the addition of an inert organic solvent, usually at room temperature, and those of the benzyl type, especially unsubstituted benzyl esters, also by hydrogenolysis techniques customarily used for benzyl groups.

The removal of an ester group by acid hydrolysis (acidolysis), especially in the case of the tert.-butyl type, is advantageously carried out by hydrolysis with inorganic acids, such as hydrohalic acids, trifluoroacetic acid or sulfuric acid. The β -silylethyl ester groups are preferably removed by fluoride-ion-yielding reagents, for example fluorides of quaternary organic bases, such as tetraethylammonium fluoride. Esters that are unstable to bases can be carefully removed by the rapid action of an aqueous sodium or potassium bicarbonate solution or, preferably, aqueous ammonia in an organic solvent, usually at room temperature. The ester groups are preferably removed under the reaction conditions of the Examples or under analogous conditions.

A suitable combination of the ester groups can be chosen in the earlier stages of the synthesis by appropriate selection of starting materials and reactants; a selectively removable ester group, for example, is introduced with a carboxy that is freed in the last stage.

The starting materials of formula XV are prepared according to above-described processes for the preparation of compounds of formula I starting with compounds wherein the respective amino and/or carboxy groups are protected by Z^1 to Z^4 .

For esterification, a carboxylic acid can be reacted directly with a diazoalkane, especially diazomethane, or with a corresponding alcohol in the presence of a strong acid catalyst (e.g. sulfuric acid or an organic sulfonic acid) and/or a dehydrating agent (e.g. dicyclohexylcarbodiimide). Alternatively, the carboxylic acid can be converted into a reactive derivative thereof, such as a reactive ester mentioned in connection with process e), or into a mixed anhydride, e.g. with an acid halide (e.g. especially an acid chloride), and this activated intermediate reacted with the desired alcohol.

The protecting groups are preferably removed under the reaction conditions of the Examples or under analogous conditions.

In performing the conversion of an intermediate or an end product into another intermediate or another end product, transformations such as the following are carried out: an amino group is alkylated, and/or an oxo group is converted into hydroxy (plus hydrogen) or into two hydrogen atoms by reduction, and/or hydroxy is converted into hydrogen by reduction, and/or free carboxy is freed from its esterified form by hydrolysis or hydrogenolysis, and/or an amino group is acylated and/or free carboxy is esterified, and/or amino is converted into oxo.

Conversion of compounds of formula I and/or intermediates wherein R^2 and/or R^3 is e.g. lower alkoxy, aryl-lower

alkoxy into compounds of formula I wherein R^2 and/or R^3 represents hydroxy is preferably carried out by hydrolysis with inorganic acids, such as hydrohalic acids or sulfuric acid, or with aqueous alkalis, preferably alkali metal hydroxides, such as lithium or sodium hydroxide.

Compounds of formula I and/or intermediates wherein R^2 and R^3 represent etherified hydroxy may be converted into monocarboxylic acids of formula I wherein R^2 or R^3 is hydroxy. Such conversion is carried out by selective hydrolytic or hydrogenolytic procedures known in the art, and depend upon the chemical character of the R^2 and R^3 substituents.

Free carboxylic acids of formula I or intermediates wherein R^2 and/or R^3 represent hydroxy or salts thereof may be converted by known processes into the corresponding monoesters or bisesters with the appropriate alcohols or corresponding derivatives thereof, i.e. into compounds of formula I and/or intermediates wherein R^2 and/or R^3 is e.g. lower alkoxy, aryl-lower alkoxy, lower alkanyloxy-methoxy or lower alkoxycarbonyl-lower alkoxy.

Compounds of formula I wherein R^1 represents 4-aminobutyl may be converted into compounds wherein R^1 represents 4-acylaminobutyl, or vice versa, by methods belonging to the prior art and described herein in connection with protecting groups.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably those that are inert to the reactants and are solvents thereof, of catalysts, condensing agents or other agents, and/or in inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at the boiling point of the solvents

used, under atmospheric or superatmospheric pressure.

The invention further includes any variant of the present processes in which an intermediate obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reactants are used in the form of their salts or optically pure antipodes. Mainly those starting materials that lead to the formation of the compounds indicated above as being especially valuable should be used in these reactions.

The invention also relates to novel starting materials and processes for their manufacture.

Depending on the starting materials and methods chosen, the novel compounds may be in the form of one of the possible isomers or mixtures thereof, for example, depending on the number of asymmetric carbon atoms, they may be in the form of pure optical isomers, such as antipodes, or in the form of mixtures of optical isomers, such as racemates, or in the form of mixtures of diastereoisomers from which the antipode corresponding to formula I is isolated.

Resulting mixtures of diastereoisomers and mixtures of racemates can be separated owing to the physico-chemical differences between the constituents, in known manner, into the pure isomers, diastereoisomers or racemates, for example by chromatography and/or fractional crystallisation.

Resulting racemates (racemic diastereoisomers) can furthermore be resolved into the optical antipodes by

methods known per se, for example by recrystallisation from an optically active solvent, with the aid of micro-organisms or by reacting an acidic end product with an optically active base that forms salts with the racemic acid, and separating the salts obtained in this manner, for example on the basis of their different solubilities, into the diastereoisomers, from which the antipodes can be freed by the action of suitable agents. Basic racemic products can likewise be resolved into the antipodes, for example by separation of diastereoisomeric salts thereof, e.g. by fractional crystallisation of their d- or l-tartrates. Any racemic intermediates or starting material can similarly be resolved.

The antipode leading to or corresponding to the S,S-stereoisomer of formula I is isolated.

Finally, the compounds of the invention are obtained either in free form or in the form of their salts. Any resulting base can be converted into a corresponding acid addition salt, preferably with the use of a pharmaceutically acceptable acid or anion-exchange preparation, or resulting salts can be converted into the corresponding free bases, for example with the use of a stronger base, such as a metal hydroxide or an ammonium hydroxide or a basic salt, e.g. an alkali metal hydroxide or carbonate, or a cation-exchange preparation. A compound of formula I wherein COR^2 and/or COR^3 represent carboxy can thus also be converted into the corresponding metal or ammonium salts. These or other salts, for example the picrates, can also be used for purification of the bases obtained; the bases are converted into salts, the salts are separated and the bases are freed from the salts. In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a

corresponding salt is also intended, provided that is possible or appropriate under the circumstances. Compounds of formula I wherein COR² and/or COR³ represent carboxy may be in the form of internal salts.

The compounds, including their salts, can also be obtained in the form of their hydrates or include other solvents used for the crystallisation.

The pharmaceutical preparations according to the invention are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, for the treatment or prevention of diseases responsive to inhibition of angiotensin-converting enzyme, e.g. cardiovascular diseases such as hypertension, and congestive heart failure, and comprise an effective amount of a pharmacologically active compound of formula I, or a pharmaceutically acceptable salt thereof, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for enteral or parenteral administration. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethylene glycol, for tablets also c) binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or

effervescent mixtures and/or e) absorbents, colourants, flavourings and sweeteners. Injectable preparations are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilised and/or contain adjuvants, such as preserving, stabilising, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. These preparations are prepared according to conventional mixing, granulating and/or coating methods, and contain about from 0.1 to 75 %, preferably about from 1 to 50 %, active ingredient. A unit dosage for a mammal of about 50 to 70 kg may contain about from 1 to 100 mg of the active ingredient.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Celsius, and all parts wherever given are parts by weight. Unless stated otherwise, all evaporations are performed under reduced pressure, preferably between about 20×10^{-3} and 133×10^{-3} bar (between 15 and 100 mm Hg).

In the case of compounds of formula I and derivatives wherein more than one centre of asymmetry exists, the diastereoisomeric compound of formula I is also referred to as isomer B in the relevant Examples. The respective diastereoisomeric compounds are characterised by physical properties, e.g. melting point, relative migration on chromatography, and infrared or nuclear magnetic resonance spectral properties.

The symbols A and B have been assigned to the respective isomers as follows on the basis of their relative

migration on chromatography. On the basis of migration on thin-layer chromatography and normal phase high pressure liquid chromatography employing silica gel as the stationary phase, the fast moving isomer is called isomer A and the slow moving isomer is called isomer B. On the basis of migration on reverse phase high pressure liquid chromatography the slow moving isomer is called isomer A and the fast moving isomer is called isomer B.

Example 1: A solution of 3.77 g of 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one (isomer B) in 800 ml of 80 % aqueous ethanol containing 0.5 g of 10 % palladium-on-carbon is hydrogenated at 3 atmospheres pressure for 40.5 hours. The catalyst is removed by vacuum filtration through celite and the filter cake is washed well with water. The filtrate is concentrated in vacuo. Toluene is added and the mixture is again concentrated in vacuo. This process is repeated several times, and the resulting solid is dried at 80°/0.05 mm Hg to give 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one monohydrate, m.p. 179° (decomp.), $[\alpha]_D = -174.2^\circ$ (c = 1.0 in water).

The starting material is prepared as follows:

A solution of 8 g of 3-amino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, 0.4 ml of acetic acid and 4.5 ml of tert.-butyl nitrite in 160 ml of chloroform is refluxed for 2 hours and cooled to room temperature. 6.0 g of m-chloroperbenzoic acid are added in portions with stirring, and stirring is continued for 30 minutes. The solution is washed with 100 ml of saturated aqueous sodium bicarbonate solution, 50 ml of 2N hydrochloric acid and 50 ml of water, and dried over magnesium sulfate. The solvent is removed under reduced

pressure and the residue is treated with ethyl acetate/-petroleum ether (b.p. 60-80°) to give the α -ketolactam 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-benzazepine-2,3-dione as a yellow solid, m.p. 108-110°, which is used in the next step without further purification.

To a solution of 11 g of 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione, 14 g of N- ϵ -benzyloxycarbonyllysine methyl ester hydrochloride, 6 ml of triethylamine, and 0.7 g of dibutyltin dichloride in 600 ml of methylene chloride there are added 50 g of 4 Å molecular sieve. The reaction mixture is stirred and refluxed for 40 hours. After cooling to room temperature, the reaction mixture is filtered through celite and the solvent is removed under reduced pressure. The residue is taken up in 750 ml of methanol and 28 ml of acetic acid. After 5 minutes, 3.6 g of sodium cyanoborohydride are added and the reaction mixture is stirred at room temperature for 72 hours, then acidified by the addition of 10 ml of concentrated hydrochloric acid. The solution is concentrated to dryness to give an oil which is separated by flash-chromatography using ethyl acetate/toluene (9:1). Two fractions are obtained:

a) 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (isomer A); $R_f = 0.7$, NMR ($CDCl_3$) 1.47 (m, 5H), 3.16 (m, 4H).

b) 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (isomer B); $R_f = 0.6$, NMR ($CDCl_3$) 1.30 (m, 5H), 3.06 (m, 4H).

A solution of 22.6 g of 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-(1S)-pentylamino]-1-ethoxycarbonyl-

methyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one (isomer B) and 84 ml of 1N sodium hydroxide solution in 580 ml of methanol is stirred under nitrogen at room temperature for 19 hours. The solution is concentrated and the residue is partitioned between 300 ml of water and 300 ml of ether. The organic layer is separated and the aqueous layer is washed once with 300 ml of ether. The aqueous layer is then adjusted to pH 2 with concentrated hydrochloric acid, whereupon the product slowly crystallises. The resulting solid is collected by vacuum filtration, washed well with water and dried to give 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one, m.p. 216-218° (decomp).

Example 2: A solution of 0.5 g of 3-[(5-benzyloxycarbonylamino-1-carboxy)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one hydrochloride (isomer B) in 200 ml of ethanol is hydrogenated at atmospheric pressure and room temperature over 0.5 g of 10 % palladium-on-carbon catalyst until absorption of hydrogen ceases. The catalyst is filtered off and washed with water. The combined filtrates are concentrated by evaporation and the solid material is recrystallised from methanol/ether to give the 3-[(5-amino-1-carboxy)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one hydrochloride (isomer B); m.p. 148-150° (decomposition), $[\alpha]_D = -112^\circ$ (c = 0.75 in water), representing the compound with the S,S stereochemistry. (The free compound is designated "product" in the following Examples).

The starting material is prepared as follows:

To a solution of 1.5 g of 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (isomer A) in

60 ml of methanol there are added at 0° 5 ml of 5 % aqueous sodium hydroxide solution, and the reaction mixture is stirred at room temperature for 18 hours. The solution is acidified with 2N hydrochloric acid and concentrated to dryness. 25 ml of ethanol are added and the solution concentrated to dryness. The white solid which remains is stirred with 30 ml of methylene chloride and the solid which remains is filtered off. This material is stirred with 30 ml of methylene chloride and filtered off. The combined methylene chloride solutions are concentrated by evaporation and the resulting solid is treated with ether and filtered to give 3-[(5-benzoyloxycarbonylamino-1-carboxy)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one hydrochloride (isomer A), m.p. 123-126°, $[\alpha]_D = 106^\circ$ (c = 1, methanol).

Similarly, 3-[(5-benzoyloxycarbonylamino-1-methoxycarbonyl)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (isomer B) yields 3-[(5-benzoyloxycarbonylamino-1-carboxy)-pentylamino]-carboxymethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one hydrochloride (isomer B), m.p. 107-110°, $[\alpha]_D = -88^\circ$ (c = 1.26, methanol), assigned the S,S stereochemistry.

Example 3: A solution of 1.5 g of 3-[(5-amino-methoxycarbonyl)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 100 ml of 2N hydrochloric acid is refluxed for 18 hours under a nitrogen atmosphere. The reaction mixture is evaporated to dryness under reduced pressure and the residue is treated with 10 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared as follows:

A solution of 1.5 g of 3-[(5-benzoyloxycarbonylamino-1-

methoxycarbonyl)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 250 ml of ethanol is completely hydrogenated at room temperature and atmospheric pressure over 0.5 g of 10 % palladium-on-carbon catalyst. The catalyst is filtered off and washed with 100 ml of ethanol, 100 ml of 50 % aqueous ethanol and 100 ml of water. The combined filtrates are concentrated by evaporation under reduced pressure and the resulting solid is treated with ether to give the starting material.

Example 4: A solution of 2 g of 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 150 ml of 2N hydrochloric acid is refluxed for 18 hours under a nitrogen atmosphere. The reaction mixture is evaporated to dryness under reduced pressure and the residue is treated with 15 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared as follows:

The 3-[(5-benzyloxycarbonylamino-1-tert.-butoxycarbonyl)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one employed is prepared according to the method described in Example 1 by condensation of 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione and N-ε-benzyloxycarbonyllysine tert.-butyl ester.

The 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione used for that purpose may also be prepared as follows:

5.0 kg of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one are added in portions under nitrogen to 3.03 kg of potassium tert.-butoxide in 50 litres of dry tetrahydro-

furans at such a rate that the temperature is maintained below 5°, and the reaction mixture is stirred for 1 hour after the addition has been completed. A solution of 4.38 kg of ethyl bromoacetate in 5 litres of tetrahydrofuran is then added slowly so as to maintain the temperature below 5°. The reaction mixture is then kept at room temperature overnight. 1.5 kg of Hiflo-Filteraid are added, and the reaction mixture is filtered. The filter cake is washed with tetrahydrofuran and the combined tetrahydrofuran solutions are evaporated to dryness to give 3-azido-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, which is used for the next step without further purification.

A mixture of 13.98 kg of 3-azido-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one and 1.3 kg of 5 % palladium-on-carbon in 57 litres of anhydrous ethanol is hydrogenated under 3 atmospheres pressure of hydrogen for 5 hours. The pressure reactor is vented at hourly intervals to allow accumulated nitrogen to escape. The catalyst is removed by filtration and washed with ethanol. The solution is evaporated to dryness to give 3-amino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one.

31 ml of tert.-butyl nitrite are added with stirring to a solution of 55 g of 3-amino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 1000 ml of chloroform and 2.8 ml of acetic acid. The reaction mixture is refluxed under nitrogen for 3.5 hours and then cooled to 0°. While stirring is maintained, 43.5 g of m-chloroperbenzoic acid are added in five portions over the course of half an hour. The reaction mixture is allowed to warm to room temperature and is stirred for an additional 1.5 hours. The reaction mixture is washed with 500 ml of saturated aqueous sodium bicarbonate

solution, 2 x 250 ml of concentrated aqueous ammonia solution and 250 ml of saturated aqueous sodium chloride solution. The organic solution is dried over sodium sulfate, treated with activated carbon and concentrated under reduced pressure to give an oil which is treated with ether to give 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione, m.p. 112-114°.

Dry hydrogen chloride gas is bubbled through a solution of 2.8 g of 3-[(5-benzyloxycarbonylamino-1-tert.-butoxycarbonyl)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 150 ml of ethyl acetate until thin-layer chromatography analysis indicates that no starting material remains. The solvent is removed under reduced pressure and the residue is treated with ether to give 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 124-126° (decomposition), $[\alpha]_D = -116^\circ$ (c = 1, methanol).

A solution of 0.9 g of 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 100 ml of ethanol is completely hydrogenated at room temperature and atmospheric pressure using 0.5 g of 5 % palladium-on-carbon as catalyst. The catalyst is filtered off and the solvent is removed under reduced pressure to give 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 123-125°, $[\alpha]_D = -141^\circ$ (c = 1 in methanol).

Example 5: Preparation of the product as the dihydrochloride from 3-[(5-amino-1-methoxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-

(3S)-benzazepin-2-one hydrochloride using the procedure described in Example 3.

The starting material is prepared as follows:

3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-(1S)-pentylamino]-1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 61-63°, $[\alpha]_D = -58^\circ$ (c = 1, methanol), is prepared according to the methods described in the preceding Examples by condensation of N-ε-benzyloxycarbonyllysine methyl ester and 1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione, m.p. 106-108°. The α-ketolactam is prepared using methods described above by oxidation of 3-amino-1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one.

Hydrogenation of 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-(1S)-pentylamino]-1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride according to Example 2 gives the starting material.

Example 6: Preparation of the product as the hydrochloride from 3-[(5-benzyloxycarbonylamino-1-benzyloxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one using the procedure described in Example 1. The starting material is prepared by hydrolysis of the corresponding ethyl ester (see Example 3).

Example 7: Preparation of the product as the hydrochloride from 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride using the procedure described in Example 2. The starting material is prepared by hydrolysis of the corresponding

ethyl ester.

Example 8: Preparation of the product from 3-[(5-benzyl-oxycarbonylamino-1-benzyloxycarbonyl)-(1S)-pentylamino]-1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one using the procedure described in Example 1. The starting material is prepared according to Example 1.

Example 9: A solution of 2.0 g of 3-[(5-benzyloxycarbonylamino-1-ethoxycarbonyl)-(1S)-pentylamino]-1-benzyl-oxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 150 ml of absolute ethanol is exhaustively hydrogenated using 1.0 g of 10 % palladium-on-carbon as catalyst. The catalyst is filtered off and the solvents are removed under reduced pressure to give a residue which is treated with ether to give 3-[(5-amino-1-ethoxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 85-87°, $[\alpha]_D = -149^\circ$ (c = 1, methanol).

If the hydrogenolysis is carried out in the presence of one additional mole equivalent of hydrogen chloride, the corresponding dihydrochloride salt is obtained, m.p. 203-205°, $[\alpha]_D = 143^\circ$ (c = 1.3, ethanol).

Example 10: The following procedure is used for selective hydrolysis of diesters to the corresponding 1-carboxymethyl compounds:

The diester is dissolved in ethanol and treated with a mole equivalent of potassium hydroxide solution, and the reaction mixture is stirred at room temperature for 1 hour. The solvent is removed under reduced pressure and water is added to the residue. The aqueous solution is

washed with ether, acidified with hydrochloric acid to free the free amino acid which is isolated by extraction and converted into the hydrochloride.

The following compounds are prepared:

- a) 3-[(5-benzyloxycarbonylamino-1-methoxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 102-104°, $[\alpha]_D = -116^\circ$ (c = 1, methanol) by hydrolysis of the corresponding 1-ethoxycarbonylmethyl derivative;
- b) 3-[(5-benzyloxycarbonylamino-1-ethoxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride, m.p. 104-106°, $[\alpha]_D = -113^\circ$ (c = 1, methanol) by hydrolysis of the corresponding 1-ethoxycarbonylmethyl derivative.

These compounds are converted into the corresponding compounds with a free aminopentyl group according to the method described in Example 2.

Example 11: A solution of 1.3 g of 1-ethoxycarbonylmethyl-3-(2-oxo-2,3,4,5,6,7-hexahydro-1H-(3S)-azepin-3-yl)-amino-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 150 ml of 6N hydrochloric acid is refluxed for 42 hours. The reaction mixture is evaporated to dryness under reduced pressure and the residue is boiled with 50 ml of ethyl acetate for 5 minutes. After cooling to room temperature, the solid is filtered off and boiled with 5 ml of ethyl acetate for 5 minutes. The solid is filtered off to give the product as the dihydrochloride.

The starting material is prepared by reaction of 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione with 3-(S)-aminocaprolactam as described in

Example 1.

Example 12: Hydrogen chloride gas is bubbled through a solution of 2.1 g of 3-[(5-amino-1-tert.-butoxycarbonyl)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 75 ml of ethanol, during which the solution is maintained at room temperature. The resulting solid is filtered off, dried under a high vacuum and treated with 10 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared by reaction of 1-benzyloxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione with (S)-N- ϵ -benzyloxycarbonyllysine-tert.-butyl ester followed by hydrogenation of the resulting compound according to Example 1.

Example 13: A solution of 0.7 g of N- α -[1-carboxy-3-(2-carboxymethylaminophenyl)-propyl]-(S)-lysine and 0.4 g of dicyclohexylcarbodiimide in 15 ml of dimethylformamide is maintained at room temperature for 18 hours. The reaction mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is stirred with 10 ml of water and filtered. This procedure is repeated with 2 x 10 ml of water. The combined aqueous solutions are extracted with 3 x 50 ml of ethyl acetate and then acidified with excess 2N hydrochloric acid. The solution is concentrated by evaporation under reduced pressure and the residue is treated with 2 x 10 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared by the following sequence of reactions:

A solution of 33.2 g of acetylamino malonic acid diethyl ester in 150 ml of ethanol is added to a solution of

sodium ethoxide in ethanol, prepared from 3.9 g of sodium and 200 ml of ethanol. The reaction mixture is stirred at room temperature for 30 minutes. A solution of 40.0 g of 2-nitrophenethyl bromide [J. Med. Chem. 20, 1020 (1977)], in 100 ml of ethanol is added dropwise over the course of 20 minutes. After addition has been completed, the reaction mixture is refluxed for 18 hours, then cooled to room temperature and concentrated under reduced pressure. The residue is taken up in 350 ml of water and the solution is extracted with 2 x 350 ml of ethyl acetate. The combined ethyl acetate extracts are washed with 200 ml of water and dried over magnesium sulfate. Removal of the solvent under reduced pressure gives 2-acetylamino-2-(2-nitrophenethyl)-malonic acid diethyl ester as a low-melting solid, which is used for the next step without further purification.

A solution of 80 g of 2-acetylamino-2-(2-nitrophenethyl)-malonic acid diethyl ester in 900 ml of 3N hydrochloric acid is refluxed for 12 hours. The solution is cooled and extracted with 200 ml of ethyl acetate. The aqueous solution is filtered and concentrated to dryness under reduced pressure. The residue is recrystallised from ethanol/ether to give 2-amino-4-(2-nitrophenyl)butyric acid hydrochloride, m.p. 219-221° (decomposition).

A solution of 38.0 g of 2-amino-4-(2-nitrophenyl)butyric acid hydrochloride in 1200 ml of 10 % ethanolic hydrogen chloride is refluxed with stirring for 18 hours. The reaction mixture is concentrated to dryness under reduced pressure, 250 ml of water are added, and the aqueous solution is rendered basic by the addition of 2N sodium hydroxide solution. The solution is extracted with 2 x 500 ml of dichloromethane, and the combined dichloromethane solutions are washed with 2 x 150 ml of water and dried over anhydrous magnesium sulfate. Concentra-

tion gives 2-amino-4-(2-nitrophenyl)-butyric acid ethyl ester, which is used for the next step without further purification.

To a solution of 17.4 g of 2-amino-4-(2-nitrophenyl)-butyric acid ethyl ester in 130 ml of 50 % aqueous dioxane there are added 10.5 g of triethylamine and 18.7 g of 2-(tert.-butoxycarbonyloxyimino)-2-phenyl-acetonitrile. The reaction mixture is stirred at room temperature for 4 hours and then diluted with 300 ml of water. The mixture is extracted with 2 x 150 ml of ether and the aqueous phase is acidified with ice-cold 2N hydrochloric acid and extracted with 2 x 250 ml of ethyl acetate. The ethyl acetate phases are combined, washed with 150 ml of water and dried over sodium sulfate. The solvent is evaporated off under reduced pressure to give 2-tert.-butoxycarbonylamino-4-(2-nitrophenyl)-butyric acid ethyl ester, which is used without further purification.

A solution of 13.0 g of 2-tert.-butoxycarbonylamino-4-(2-nitrophenyl)-butyric acid ethyl ester in 300 ml of ethanol is hydrogenated at room temperature and atmospheric pressure using 1 g of 10 % palladium-on-carbon as catalyst until the absorption of hydrogen ceases. The catalyst is filtered off. Evaporation of the solvent gives 2-tert.-butoxycarbonylamino-4-(2-aminophenyl)-butyric acid ethyl ester, which is used in the next step, without further purification.

A solution of 10.0 g of 2-tert.-butoxycarbonylamino-4-(2-aminophenyl)-butyric acid ethyl ester and 4.2 g of glyoxylic acid ethyl ester in 120 ml of ethanol is hydrogenated at 80° and 3 atmospheres pressure for 72 hours using 3 g of 10 % palladium-on-carbon as catalyst. The reaction mixture is cooled to room temperature and

the catalyst is filtered off. The solvent is evaporated off under reduced pressure and the residue is partitioned between 150 ml of ethyl acetate and 75 ml of water. The organic phase is dried over sodium sulfate and the solvent is evaporated off under reduced pressure to give 2-tert.-butoxycarbonylamino-4-[2-(ethoxycarbonylmethylamino)-phenyl]-butyric acid ethyl ester, which is used in the next step without further purification.

Hydrogen chloride gas is bubbled through a solution of 8.5 g of 2-tert.-butoxycarbonylamino-4-[2-(ethoxycarbonylmethylamino)-phenyl]-butyric acid ethyl ester in 150 ml of ethyl acetate for 30 minutes at room temperature. The solution is concentrated by evaporation under reduced pressure and the residue is dissolved in 100 ml of ethyl acetate. The solution is washed with 3 x 100 ml of water and dried over sodium sulfate. The solvent is evaporated off under reduced pressure to give 2-amino-4-[2-(ethoxycarbonylmethylamino)-phenyl]-butyric acid ethyl ester, which is used in the next step without further purification.

The resulting product is reacted with α -oxo- ϵ -benzyl-oxycarbonylhexanoic acid methyl ester (Tetrahedron Letters 1982, 1875) according to the method described in Example 1. Hydrolysis of the ester group as described in Example 3 followed by hydrogenation as described in Example 1 gives the starting material used for this Example.

Example 14: A solution of 0.9 g of 3-[(4-cyano-1-carboxy)-(1S)-butylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 75 ml of 10 % ethanolic ammonia is completely hydrogenated in a Parr apparatus at 2.5 atmospheres pressure over 1 g of 5 % rhodium-on-alumina. The catalyst is filtered.

off and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in 2N hydrochloric acid and again concentrated by evaporation and then treated with 10 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared by first preparing α -cyano-L- α -aminovaleric acid by the procedure of I. Mezo *et al.*, Acta. Chim. Acad. Sci. Hung. **85**, 201 (1975). This compound is converted into the ethyl ester using ethyl iodide in the presence of sodium bicarbonate in dimethylacetamide. This material is reacted with 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione as described in Example 1 and hydrolysed to the cyano-diacid as described in Example 2.

Example 15: A solution of 1.3 g of 3-[(1-carboxy-5-nitro)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 100 ml of ethanol is completely hydrogenated at room temperature and atmospheric pressure over 0.5 g of platinum oxide. The catalyst is filtered off and 25 ml of 2N hydrochloric acid are added. The solution is evaporated to dryness under reduced pressure and the resulting solid is treated with 5 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is obtained by first preparing L-6-nitro-2-aminohexanoic acid by the method of E. Bayer and K. Schmidt, Tetrahedron Letters, 2051 (1973). This substance is further processed in the same manner as the cyano-diacid in Example 14.

Example 16: Preparation of the product as the dihydrochloride from 3-[(5-acetylamino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-

benzazepin-2-one using the procedure described in Example 11.

The starting material is prepared by completely hydrogenating a solution of 3-[(1-carboxy-4-cyano)-(1S)-butyl-amino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one (see Example 14 for preparation) at room temperature and 3.4 atmospheres over Raney nickel catalyst [prepared as described by F.E. Gould *et al.*, J. Org. Chem. 25, 1658 (1960)].

Example 17: Preparation of the product as the dihydrochloride from 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-cyanomethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one using the procedure described in Example 11.

The starting material is prepared by first alkylating 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one with bromoacetonitrile and then reducing to the 3-amino-nitrile by the procedure described in Example 4. Oxidation to 1-cyanomethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione is accomplished by the procedure given in Example 1. Condensation with ϵ -benzyloxy-carbonyl-L-lysine ethyl ester, removal of the benzyl-oxycarbonyl group and hydrolysis of the ester function are carried out according to the procedures given in Examples 1 and 3.

Example 18: With stirring under an atmosphere of dry nitrogen, a solution of 0.6 ml of borane in tetrahydrofuran (1.0 M) is introduced by means of a syringe into a solution of 0.6 g of 3-[(1-carboxy)-(1S)-4-pentenyl-amino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride in 75 ml of tetrahydrofuran. The reaction mixture is maintained at room temperature for one hour, and then 1 ml of water is

added, followed by 3 ml of 3N aqueous sodium hydroxide solution and 4 ml of freshly prepared 0.31M chloramine solution. The reaction mixture is maintained at room temperature for one hour and is then acidified with 2N hydrochloric acid. The resulting precipitate is filtered off, washed with 3 x 10 ml of ethyl acetate/tetrahydrofuran (1:1) and treated with 10 ml of ethyl acetate to give the product as the dihydrochloride.

The starting material is prepared as follows:

2-Amino-5-hexenoic acid is prepared by the method of Smith and Drinkwater [J. Chem. Soc. 1305 (1971)]. This compound is esterified by reaction with ethyl iodide in the presence of sodium bicarbonate in dimethylacetamide and condensed with 1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,3-dione by the method described in Example 1. Hydrolysis of the ethyl ester using the procedure described in Example 3 gives the starting material of this Example.

Example 19: A solution of 0.6 g of 1-ethoxycarbonylmethyl-3-(2-oxo-2,3,4,5,6,7-hexahydro-1H-(3S)-azepin-3-yl)-amino-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one in 20 ml of 6N hydrochloric acid is heated under reflux overnight. The solution is cooled and concentrated to dryness to yield 3-[(5-amino-1-carboxy)-(1S)-pentyl-amino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one dihydrochloride, $[\alpha]_D = -136.9^\circ$ (1% in 1N hydrochloric acid).

The dihydrochloride of the product is converted into the product by treatment with propylene oxide in ethanol at room temperature overnight.

The starting material is prepared as follows:

A solution of 15.3 g of 3-bromo-1-ethoxycarbonylmethyl-

2,3,4,5-tetrahydro-1H-1-benzazepin-2-one and 30 g of 3-(S)- ϵ -aminocaprolactam in 400 ml of acetonitrile is heated under reflux for 48 hours. The reaction mixture is cooled to room temperature, filtered, and the filtrate is concentrated to dryness. The residue is taken up in 200 ml of methylene chloride, the methylene chloride solution is washed with 2 x 200 ml of water and then extracted with 2 x 100 ml of 2N hydrochloric acid. The acidic extract is adjusted to pH 8 by the addition of solid potassium carbonate. Extraction with methylene chloride yields 1-ethoxycarbonylmethyl-3-(2-oxo-2,3,4,5,6,7-hexahydro-1H-(3S)-azepin-3-yl)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one as a mixture of diastereoisomers. The crude product is recrystallised from methanol to yield 1-ethoxycarbonylmethyl-3-(2-oxo-2,3,4,5,6,7-hexahydro-1H-(3S)-azepin-3-yl)-amino-2,3,4,5-tetrahydro-1H-1-(1S)-benzazepin-2-one, m.p. 148-150°.

Example 20: A mixture of 1.0 g of 3-[(5-amino-1-carboxy-(1S)-pentylamino)-1-carboxymethyl-2,3-dihydro-1H-1-(3S)-benzazepin-2-one and 120 mg of palladium in 35 ml of absolute ethanol is hydrogenated at 3 atmospheres pressure until 1 mole equivalent of hydrogen has been consumed. The catalyst is removed and the reaction mixture is concentrated to dryness to give 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one.

The starting material is prepared as follows:
A solution of 0.4 g of 3-(S)-tert.-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1-benzazepine-2,5-dione [prepared from L-kynurenine as described in Australian J. Chemistry 33, 633-640 (1980)] and 0.23 g of ethyl bromoacetate in 30 ml of dry tetrahydrofuran is stirred at 0° under a dry nitrogen atmosphere. 0.254 g of potassium tert.-butoxide is added in one portion. After 1 hour at 0°, an

additional 0.23 g of ethyl bromoacetate is added and the reaction mixture is stirred at 0° for a further hour. 100 ml of water are added and the mixture is extracted with 2 x 50 ml of ethyl acetate. The combined extracts are washed with 100 ml of water, dried over magnesium sulfate and concentrated by evaporation under reduced pressure to give a yellow gum-like material which, after treatment with ether/petroleum ether (b.p. 30-60°), gives 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,5-dione, m.p. 86-88°, $[\alpha]_D = -203^\circ$ (c = 1 in dimethylformamide).

A solution of 0.14 g of 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1-benzazepine-2,5-dione and 7 mg of sodium borohydride in 10 ml of ethanol is stirred at room temperature for 18 hours. The ethanol is evaporated off under reduced pressure, and the residue is dissolved in 25 ml of dichloromethane. The solution is extracted with 2 x 20 ml of 2N hydrochloric acid and 20 ml of saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent is evaporated off under reduced pressure, and the residue is treated with ether to give 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-5-hydroxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, m.p. 167-169.5°, $[\alpha]_D = -193^\circ$ (c = 0.52 in dimethylformamide). This compound is also obtained by hydrogenation of the benzazepine-2,5-dione derivative with H₂/Pt in ethanol.

A solution of 0.75 g of methanesulfonyl chloride in 2 ml of methylene chloride is added at from -5° to -10° to a solution of 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-5-hydroxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 25 ml of methylene chloride. A solution of 1.33 g of triethylamine in 8 ml of methylene chloride is added within 10 minutes at from 0 to 5°. The result-

ing solution is stirred at room temperature for 3 days and then washed with 0.2N hydrochloric acid, water and dilute sodium bicarbonate solution. The methylene chloride solution is dried over sodium sulfate and concentrated to dryness to give 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-2,3-dihydro-1H-1-benzazepin-2-one.

Hydrogen chloride gas is bubbled through a solution of the above material in ethyl acetate for 1 hour. Nitrogen is then bubbled through this solution for 30 minutes. The ethyl acetate solution is washed with 30 ml of water and 30 ml of 1N hydrochloric acid. The ethyl acetate phase is separated off and the aqueous phases are combined. The aqueous phase is adjusted to pH 9 with dilute ammonium hydroxide and extracted with ethyl acetate; the organic phases are combined, dried over sodium sulfate and concentrated by evaporation to give, after purification, 3-(S)-amino-1-ethoxycarbonylmethyl-2,3-dihydro-1H-1-benzazepin-2-one.

Condensation of 6-benzyloxycarbonylamino-2-oxo-hexanoic acid in the presence of sodium cyanoborohydride with 3-(S)-amino-1-ethoxycarbonylmethyl-2,3-dihydro-1H-1-benzazepin-2-one yields, after separation of the isomers, 3-[(5-benzyloxycarbonylamino-1-carboxy)-(1S)-pentylamino]-1-ethoxycarbonylmethyl-2,3-dihydro-1H-1-(3S)-benzazepin-2-one.

Treatment with hydrobromic acid in acetic acid, hydrolysis with 3N hydrochloric acid and conversion into free amino acid yields 1-carboxymethyl-3-[(5-amino-1-carboxy)-(1S)-pentylamino]-2,3-dihydro-1H-1-(3S)-benzazepin-2-one.

Example 21: A mixture of 1.0 g of 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-5-chloro-2,3,4,5-

tetrahydro-1H-1-(3S)-benzazepin-2-one and 150 mg of palladium in 35 ml of absolute ethanol is hydrogenated at 3 atmospheres pressure until 1 mole equivalent of hydrogen has been consumed. The catalyst is removed by filtration and the solution is concentrated to dryness to yield 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one hydrochloride.

The starting material is prepared as follows:

A solution of 1.69 g of thionyl chloride in 5 ml of methylene chloride is added at from -5° to -10°, within 15 minutes, to a solution of 4.8 g of 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-5-hydroxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one and 2.0 g of diisopropylethylamine in 45 ml of methylene chloride. The reaction mixture is stirred at -5° for 1 hour, washed with 5 % potassium carbonate solution, dried and concentrated to dryness to yield the 5-chloro compound.

According to the procedures described in the previous Examples, 3-(S)-tert.-butoxycarbonylamino-1-ethoxycarbonylmethyl-5-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one is converted into 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-5-chloro-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one.

Example 22: Preparation of 10,000 capsules each containing 10 mg of the active ingredient.

Composition

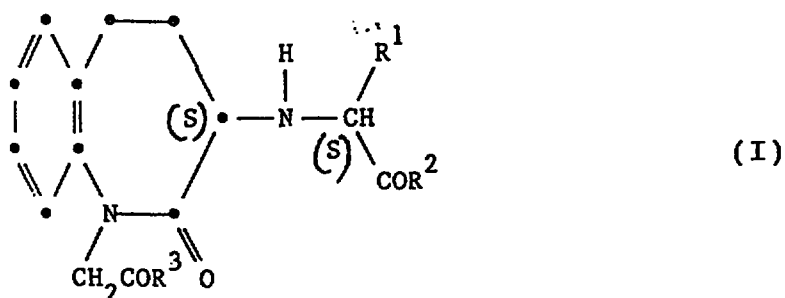
3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one	100.0 g
lactose	1900.0 g

Procedure

The pulverulent constituents are passed through a sieve of 0.6 mm mesh width. Then the active ingredient is placed in a suitable mixer and mixed with the lactose until homogenous. No. 3 capsules are each filled with 200 mg of the mixture using a filling machine.

Patent Claims for Contracting States: BE, CH, DE, FR, GB,
IT, LI, LU, NL, SE.

1. Compounds of the general formula



wherein R^1 represents 4-aminobutyl, R^2 and R^3 represent, independently of each other, hydroxy or lower alkoxy, and S represents the chirality, or salts thereof.

2. Compounds of the formula I shown in claim 1, wherein R^1 represents 4-aminobutyl, and R^2 and R^3 represent, independently of each other, hydroxy, methoxy, ethoxy or tert.-butoxy, or salts thereof.

3. Compounds of the formula I shown in claim 1, wherein R^1 represents 4-aminobutyl, R^2 represents hydroxy, methoxy or tert.-butoxy, and R^3 represents hydroxy or ethoxy, or salts thereof.

4. 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one or the salts thereof.

5. The hydrochloride and the dihydrochloride of 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one.

6. Pharmaceutical preparations containing a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, together with a pharma-



ceutically suitable carrier.

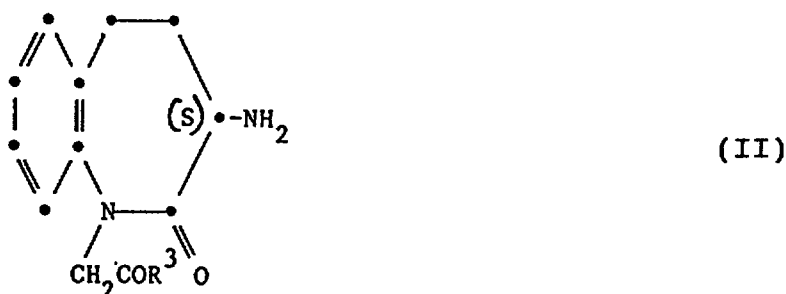
7. A compound mentioned in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof for use in a method for the therapeutic treatment of the human or animal body.

8. A compound mentioned in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof as an inhibitor of the angiotensin-converting enzyme.

9. The use of one of the compounds mentioned in claims 1 to 5 or a pharmaceutically acceptable salt thereof for the production of pharmaceutical preparations.

10. A process for the preparation of a compound of the formula I mentioned in claim 1, in which all the symbols have the meanings given in claim 1, or a salt thereof, characterised in that

a) a compound of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R³ has the meanings given above, is alkylated with a compound of the formula

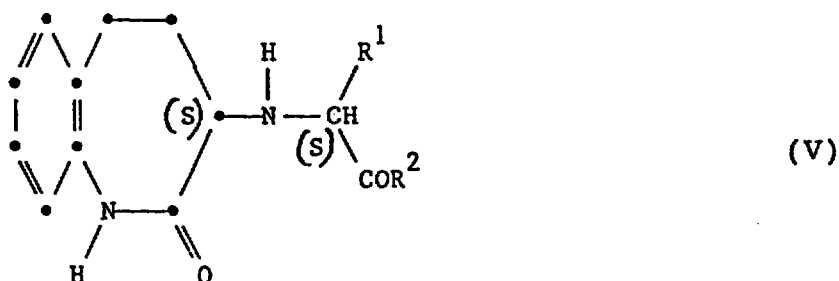


as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein Z is a reactive esterified hydroxy group and R¹ and R² have the meanings given above, or with a compound of the formula



wherein R¹ and R² have the meanings given above, in the presence of a reducing agent, with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the radicals R¹, R² and R³, or

b) a compound of the formula



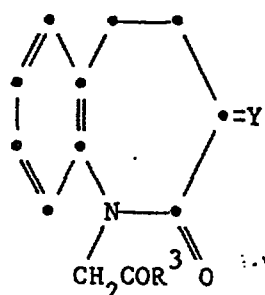
or a mixture of stereoisomers containing said compound, wherein S, R¹ and R² have the meanings given above, is alkylated with a compound of the formula



wherein Z is a reactive esterified hydroxy group and R³ has the meanings given above, preferably with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the reactants, or

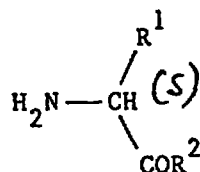
c) a compound of the formula





(VI),

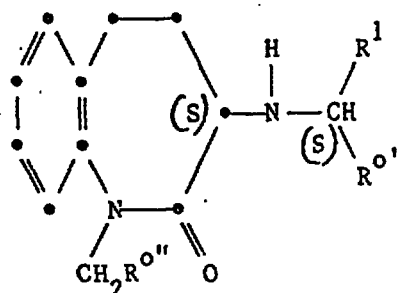
wherein Y is oxo, a reactive esterified or etherified hydroxy group Z together with hydrogen or two reactive esterified or etherified hydroxy groups Z, and R³ has the meanings given above, is condensed with an amine of the formula



(VII)

as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R¹ and R² have the meanings given above, with the proviso that when Y is oxo or two esterified or etherified hydroxy groups, the condensation is carried out in the presence of a reducing agent, or

d) in a compound of the formula

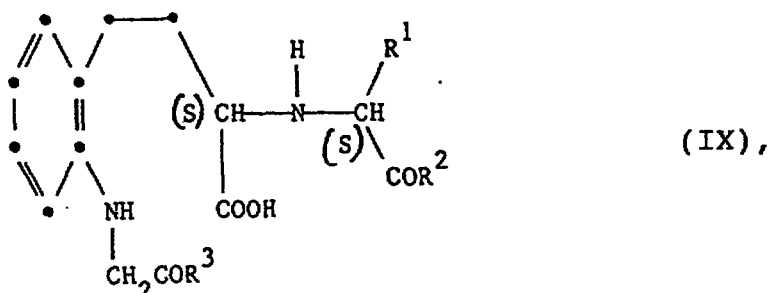


(VIII)

or in a mixture of stereoisomers containing said compound, wherein S and R¹ have the meanings given above, one of the symbols R^{0'} and R^{0''} is cyano and the other is cyano or COR² or, as appropriate, COR³ as defined above, the cyano group(s) is(are) subjected to solvolysis, or

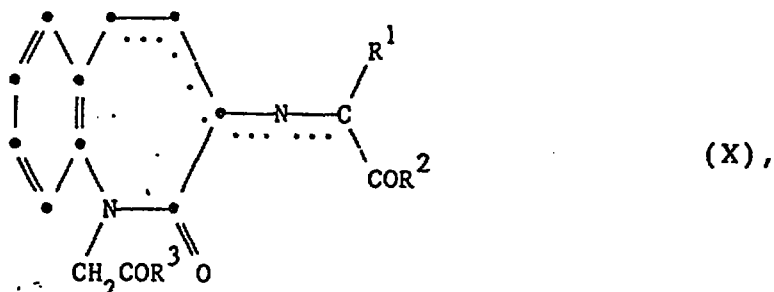


e) a compound of the formula



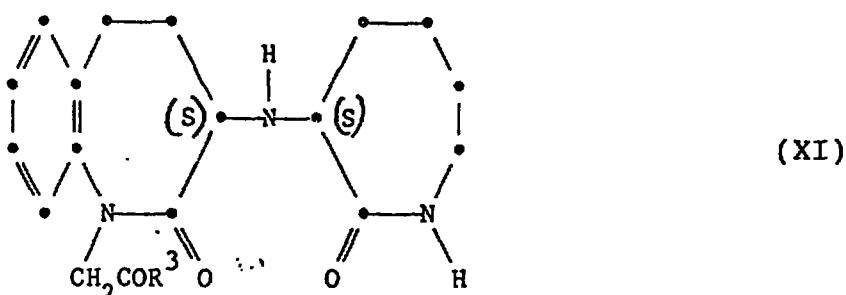
or a mixture of stereoisomers containing said compound, wherein S, R¹, R² and R³ have the meanings given above, or a reactive ester thereof, is cyclised, or

f) one or two double bonds in a compound of the formula



wherein said double bond(s) is(are) located between C3 and C4, C4 and C5 and/or in the side-chain between the nitrogen atom and an adjacent carbon atom, and wherein R¹, R² and R³ have the meanings given above, is(are) saturated by treatment with a reducing agent, or

g) the monocyclic lactam in a compound of the formula

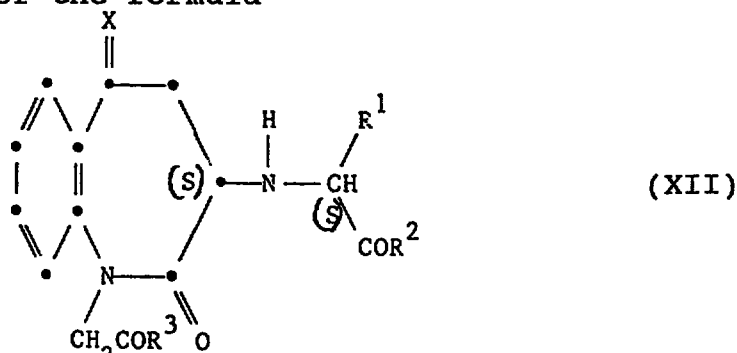


or in a mixture of stereoisomers containing said com-



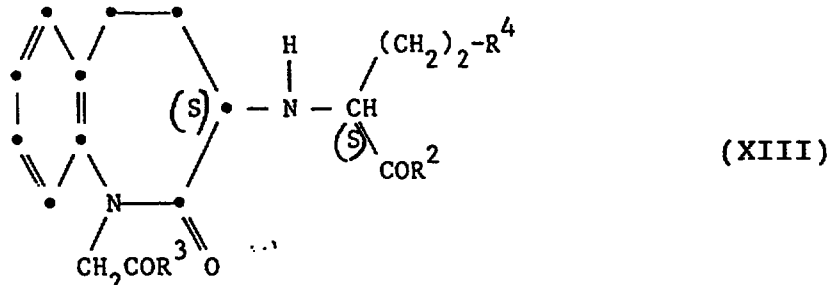
pound, wherein S and R³ have the meanings given above, is ring-opened to give a compound of formula I wherein R² and R³ are hydroxy, or

h) a compound of the formula



or a mixture of stereoisomers containing said compound, wherein X is oxo, protected oxo or two esterified or etherified hydroxy groups, or wherein X is hydroxy or esterified or etherified hydroxy together with a hydrogen atom, and wherein S, R¹, R² and R³ have the meanings given above, is hydrogenolysed or reduced, or

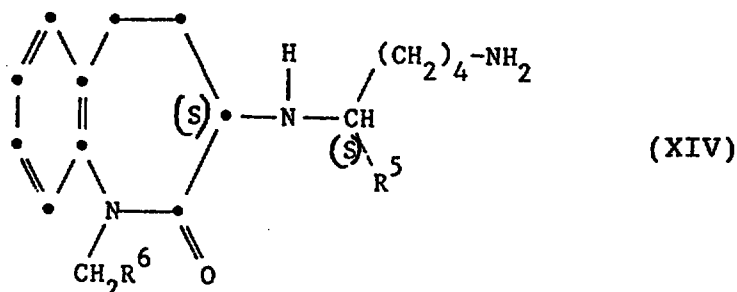
i) a compound of the formula



or a mixture of stereoisomers containing said compound, wherein R⁴ is a group convertible into 2-aminoethyl, and R² and R³ have the meanings given above, is converted into a compound of formula I, or

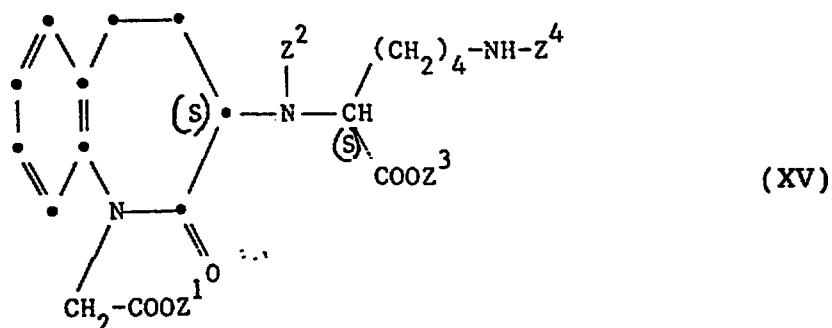
j) a compound of the formula





or a mixture of isomers containing said compound, wherein R^5 or R^6 is a group convertible into COR^2 or COR^3 , respectively, and the other is COR^2 or COR^3 as appropriate, or wherein R^5 and R^6 are groups convertible into COR^2 and COR^3 , and wherein S has the meaning given above, is converted into a compound of the formula I, or

k) in a compound of the formula



or in a mixture of stereoisomers containing said compound, wherein at least one of the groups Z^1 to Z^4 is a protective group, remaining groups Z^2 and Z^4 are hydrogen and remaining groups Z^1 and Z^3 are hydrogen or lower alkyl, with the proviso that at least one group of the remaining groups Z^1 and Z^3 is hydrogen, and wherein S has the meaning given above, in order to obtain a compound of formula I wherein one or both of the radicals R^2 and R^3 is(are) hydroxy, the protective group(s) is(are) removed and, if desired, a resulting compound of formula I is converted into another compound of formula I and/or, if desired, a resulting compound of formula I having salt-



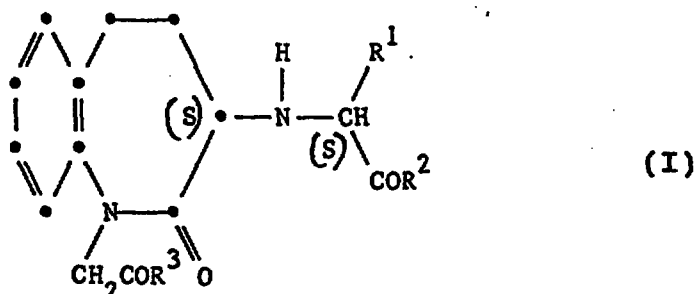
forming properties is converted into a salt thereof or a resulting salt is converted into another salt, or a free compound is freed from such a salt, and/or, if desired, the optical isomer of formula I that has the S,S configuration with respect to the two centres of chirality is isolated from a mixture of stereoisomeric forms containing a compound of formula I.

11. The compounds obtainable by the process of claim 10.



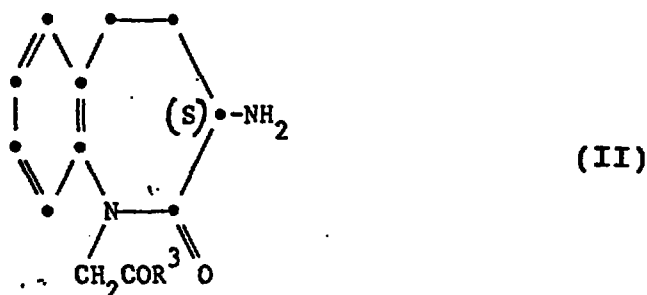
Patent Claims for Contracting State: AT

1. A process for the preparation of a 3-(5-aminopentyl)-amino-1-benzazepin-2-one-1-alkanoic acid of the general formula



wherein R^1 represents 4-aminobutyl, R^2 and R^3 represent, independently of each other, hydroxy or lower alkoxy, and S represents the chirality, or a salt thereof, characterised in that

a) a compound of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R^3 has the meanings given above, is alkylated with a compound of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein Z is a reactive esterified hydroxy group and R^1 and R^2 have the meanings given above,

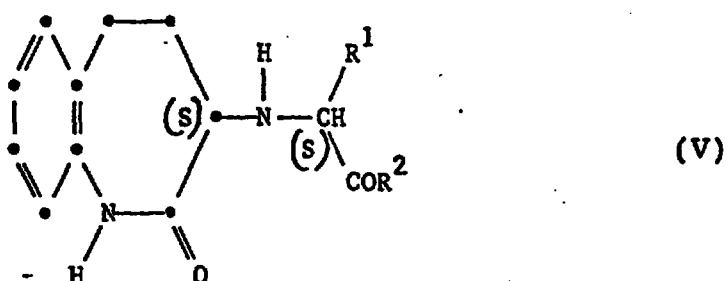


or with a compound of the formula



wherein R^1 and R^2 have the meanings given above, in the presence of a reducing agent, with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the radicals R^1 , R^2 and R^3 , or

b) a compound of the formula

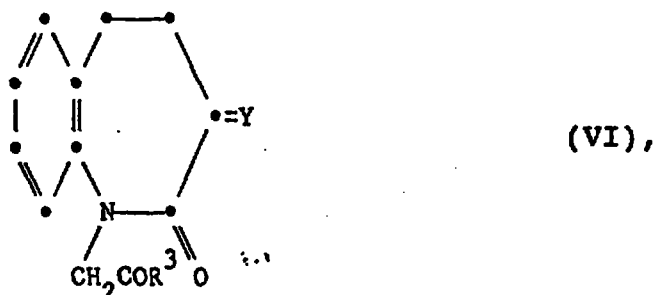


or a mixture of stereoisomers containing said compound, wherein S, R^1 and R^2 have the meanings given above, is alkylated with a compound of the formula



wherein Z is a reactive esterified hydroxy group and R^3 has the meanings given above, preferably with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the reactants, or

c) a compound of the formula

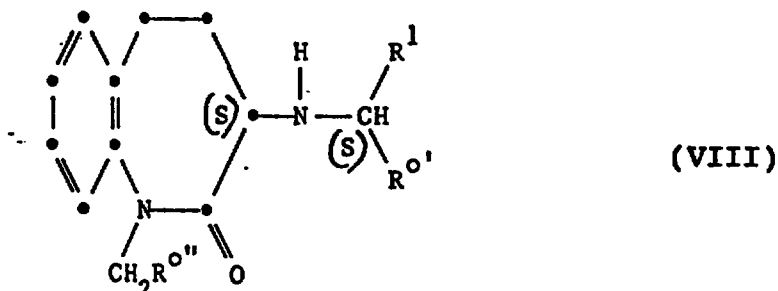


wherein Y is oxo, a reactive esterified or etherified hydroxy group Z together with hydrogen or two reactive esterified or etherified hydroxy groups Z, and R³ has the meanings given above, is condensed with an amine of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R¹ and R² have the meanings given above, with the proviso that when Y is oxo or two esterified or etherified hydroxy groups, the condensation is carried out in the presence of a reducing agent, or

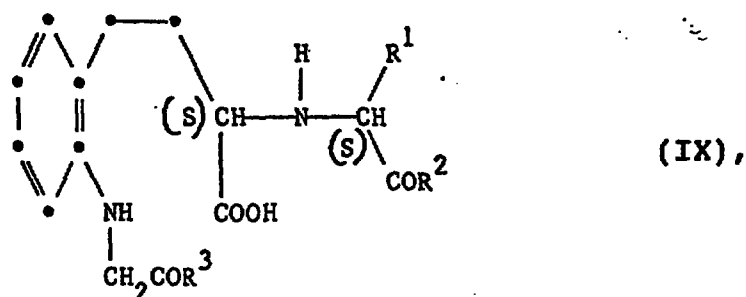
d) in a compound of the formula



or in a mixture of stereoisomers containing said compound, wherein S and R¹ have the meanings given above, one of the symbols R^{O'} and R^{O''} is cyano and the other is cyano or COR² or, as appropriate, COR³ as defined above, the cyano group(s) is(are) subjected to solvolysis, or

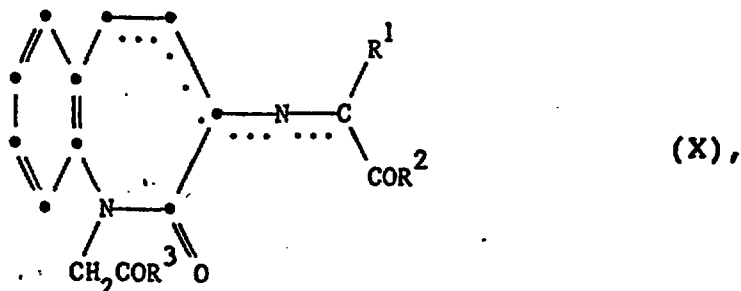
e) a compound of the formula





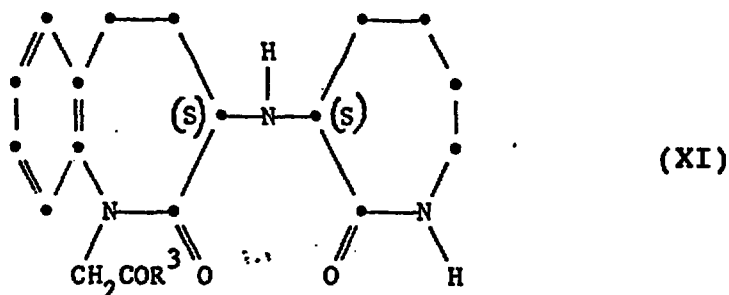
or a mixture of stereoisomers containing said compound, wherein S, R¹, R² and R³ have the meanings given above, or a reactive ester thereof, is cyclised, or

f) one or two double bonds in a compound of the formula



wherein said double bond(s) is(are) located between C3 and C4, C4 and C5 and/or in the side-chain between the nitrogen atom and an adjacent carbon atom, and wherein R¹, R² and R³ have the meanings given above, is(are) saturated by treatment with a reducing agent, or

g) the monocyclic lactam in a compound of the formula

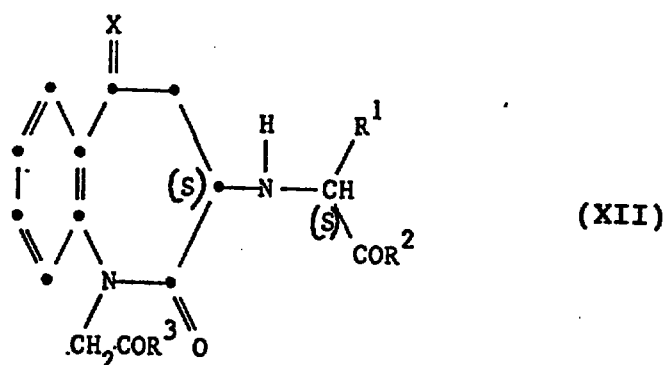


or in a mixture of stereoisomers containing said compound, wherein S and R³ have the meanings given above, is ring-opened to give a compound of formula I wherein R² and R³



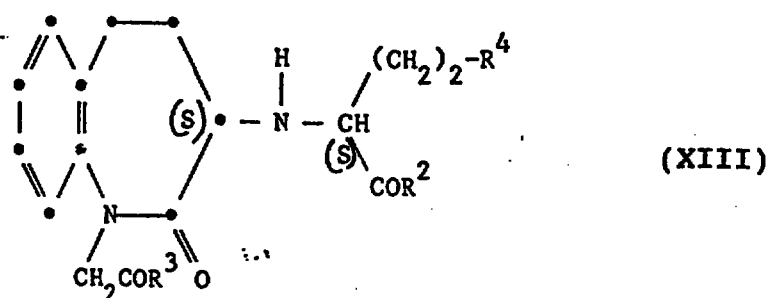
are hydroxy, or

h) a compound of the formula



or a mixture of stereoisomers containing said compound, wherein X is oxo, protected oxo or two esterified or etherified hydroxy groups, or wherein X is hydroxy or esterified or etherified hydroxy together with a hydrogen atom, and wherein S, R¹, R² and R³ have the meanings given above, is hydrogenolysed or reduced, or

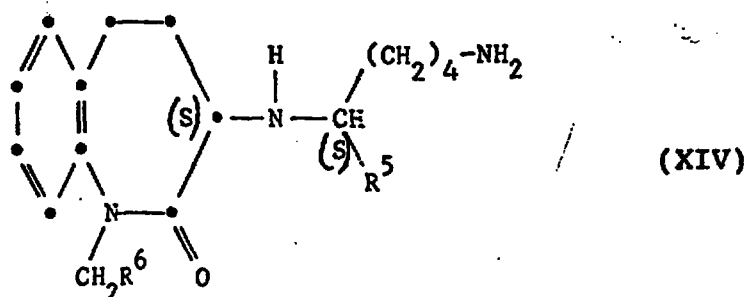
i) a compound of the formula



or a mixture of stereoisomers containing said compound, wherein R⁴ is a group convertible into 2-aminoethyl, and R² and R³ have the meanings given above, is converted into a compound of formula I, or

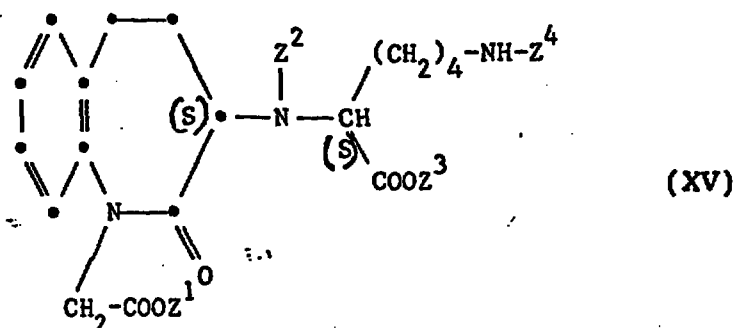
j) a compound of the formula





or a mixture of isomers containing said compound, wherein R^5 or R^6 is a group convertible into COR^2 or COR^3 , respectively, and the other is COR^2 or COR^3 as appropriate, or wherein R^5 and R^6 are groups convertible into COR^2 and COR^3 , and wherein S has the meaning given above, is converted into a compound of the formula I, or

k) in a compound of the formula



or in a mixture of stereoisomers containing said compound, wherein at least one of the groups Z^1 to Z^4 is a protective group, remaining groups Z^2 and Z^4 are hydrogen and remaining groups Z^1 and Z^3 are hydrogen or lower alkyl, with the proviso that at least one group of the remaining groups Z^1 and Z^3 is hydrogen, and wherein S has the meaning given above, in order to obtain a compound of formula I wherein one or both of the radicals R^2 and R^3 is(are) hydroxy, the protective group(s) is(are) removed and, if desired, a resulting compound of formula I is converted into another compound of formula I and/or, if desired, a resulting compound of formula I having salt-forming properties is



converted into a salt thereof or a resulting salt is converted into another salt, or a free compound is liberated from such a salt, and/or, if desired, the optical isomer of formula I that has the S,S configuration with respect to the two centres of chirality is isolated from a mixture of stereoisomeric forms containing a compound of formula I.

2. A process according to claim 1, characterised in that a compound of formula I wherein R^1 represents 4-aminobutyl, and R^2 and R^3 represent, independently of each other, hydroxy, methoxy, ethoxy or tert.-butoxy, or a salt thereof, is prepared.

3. A process according to claim 1, characterised in that a compound of formula I wherein R^1 represents 4-aminobutyl, R^2 represents hydroxy, methoxy or tert.-butoxy, and R^3 represents hydroxy or ethoxy, or a salt thereof, is prepared.

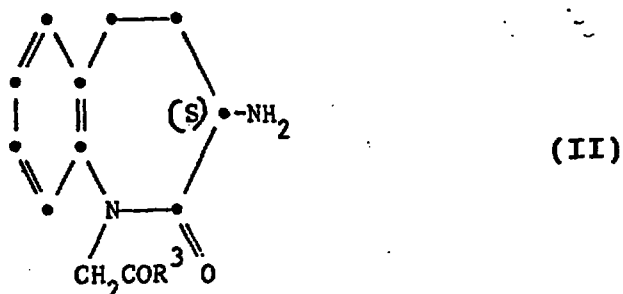
4. A process according to claim 1, characterised in that 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one or a salt thereof is prepared.

5. A process according to claim 1, characterised in that the hydrochloride or the dihydrochloride of 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one is prepared.

6. A process for the preparation of one of the compounds of formula I mentioned in claim 1, in which all the symbols have the meanings given in claim 1, or a salt thereof, characterised in that

a) a compound of the formula





as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R³ has the meanings given above, is alkylated with a compound of the formula

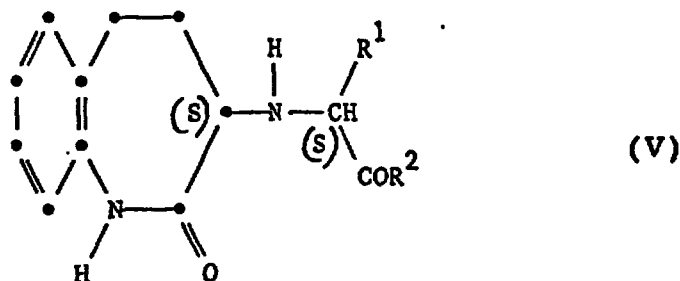


as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein Z is a reactive esterified hydroxy group and R¹ and R² have the meanings given above, or with a compound of the formula



wherein R¹ and R² have the meanings given above, in the presence of a reducing agent, with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the radicals R¹, R² and R³, or

b) a compound of the formula



or a mixture of stereoisomers containing said compound,

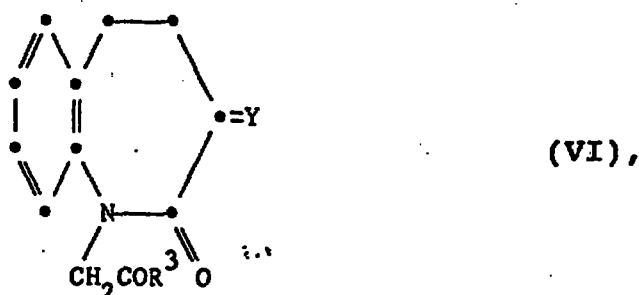


wherein S, R¹ and R² have the meanings given above, is alkylated with a compound of the formula



wherein Z is a reactive esterified hydroxy group and R³ has the meanings given above, preferably with the temporary protection of the amino group and/or of hydroxy groups that may be present in any one of the reactants, or

c) a compound of the formula



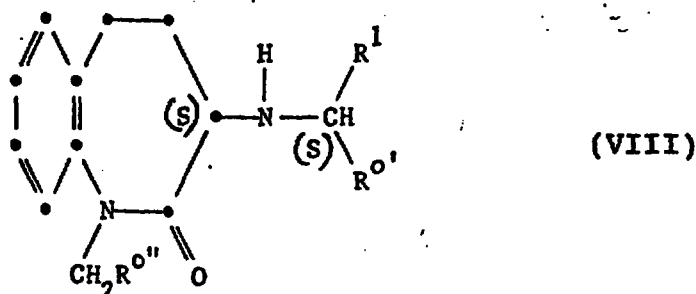
wherein Y is oxo, a reactive esterified or etherified hydroxy group Z together with hydrogen or two reactive esterified or etherified hydroxy groups Z, and R³ has the meanings given above, is condensed with an amine of the formula



as the S-enantiomer or mixture of stereoisomers containing said enantiomer, wherein R¹ and R² have the meanings given above, with the proviso that when Y is oxo or two esterified or etherified hydroxy groups, the condensation is carried out in the presence of a reducing agent, or

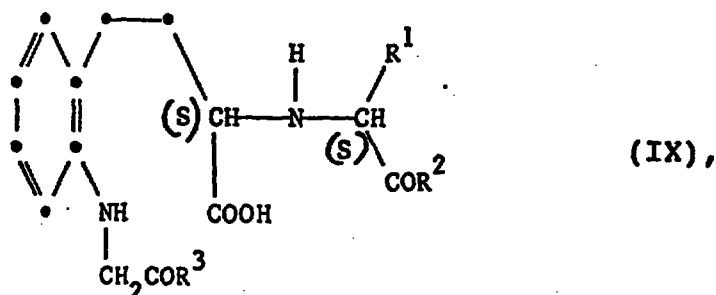
d) in a compound of the formula





or in a mixture of stereoisomers containing said compound, wherein S and R¹ have the meanings given above, one of the symbols R^{O'} and R^{O''} is cyano and the other is cyano or COR² or, as appropriate, COR³ as defined above, the cyano group(s) is(are) subjected to solvolysis, or

e) a compound of the formula



or a mixture of stereoisomers containing said compound, wherein S, R¹, R² and R³ have the meanings given above, or a reactive ester thereof, is cyclised, or

f) a compound that is structurally identical with a compound of formula I, except that it contains an additional double bond at the C3 carbon atom or in the side-chain between the nitrogen atom and the adjacent exocyclic carbon atom, is treated with a reducing agent in order to saturate said double bond, and, if desired, a resulting compound of formula I is converted into another compound of formula I and/or, if desired, a resulting compound of formula I having salt-forming properties is converted into a salt thereof or a resulting salt is converted into another salt, or a free compound is liberated from such a salt, and/or,



if desired, the optical isomer of formula I that has the S,S configuration with respect to the two centres of chirality is isolated from a mixture of stereoisomeric forms containing a compound of formula I.

7. A process according to claim 6, characterised in that a compound of claim 2 or a salt thereof is prepared.

8. A process according to claim 6, characterised in that a compound of claim 3 or a salt thereof is prepared.

9. A process according to claim 6, characterised in that 3-[(5-amino-1-carboxy)-(1S)-pentylamino]-1-carboxymethyl-2,3,4,5-tetrahydro-1H-1-(3S)-benzazepin-2-one or a salt thereof is prepared.

10. A process for the production of a pharmaceutical preparation, characterised by processing an active ingredient prepared in accordance with the invention according to any one of claims 1 to 5 with a pharmaceutical carrier.

11. A process for the production of a pharmaceutical preparation, characterised by processing an active ingredient prepared in accordance with the invention according to any one of claims 6 to 9 with a pharmaceutical carrier.

