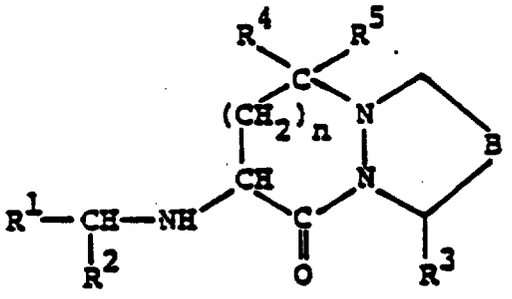
Description

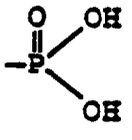
The present invention relates to bicyclic compounds, a process for their manufacture, medicaments containing these compounds as well as the use of these compounds.

In particular, the invention is concerned with bicyclic compounds of the general formula



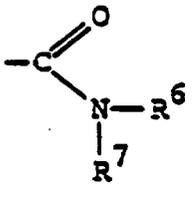
I

wherein B signifies methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$) or vinylene ($-CH=CH-$), R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylsulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl or a group of the formula



(i)

or



(ii)

R^3 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl, R^4 and R^5 each signify hydrogen or together signify an oxo group, R^6 and R^7 each signify hydrogen, alkyl or aralkyl and n signifies the number 2,

and pharmaceutically usable salts thereof.

Pyrazolopyridazines and pyridazopyridazines which likewise display an angiotensin converting enzyme inhibiting activity are described in EP-A-25941 and EP-A-42100. The pyridazodiazepines according to the Application differ in a significant manner from the previously known compounds by the presence of an amino group attached to the bicycle as well as the presence of a seven-ring in place of a five-ring and, respectively, six-ring.

The compounds of formula I contain asymmetric carbon atoms and can therefore exist as optically pure diastereomers, as diastereomeric racemates or as diastereomeric mixtures. The present invention embraces all of these forms. The compounds in accordance with the invention preferably have the (S)-configuration at each asymmetric carbon atom.

The term "alkyl" used in the present description - alone or in combination - signifies straight-chain or branched alkyl residues with 1-8, preferably 1-4, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, pentyl and hexyl. The aryl residue in aralkyl, aralkoxycarbonyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl or arylsulphonylaminoalkyl is the phenyl group which can be mono- or multiply--substituted by halogen (i.e. fluorine, chlorine, bromine or iodine), alkyl, alkoxy, trifluoromethyl or phenyl. Examples of aryl groups are phenyl, 4-chlorophenyl, p-tolyl, biphenylyl and the like and examples of aralkyl groups are benzyl, 4-chlorobenzyl, 2-phenylethyl, 3-phenylpropyl, 3-(4-chlorophenyl)propyl, 3-(4-methoxyphenyl)propyl, 4-phenylbutyl and the like. Aminomethyl, 2-aminoethyl and the like are examples of aminoalkyl groups. Methylaminomethyl, 2-methylaminoethyl, 2-ethylaminoethyl and the like can be mentioned as examples of monoalkylaminoalkyl groups and 2-dimethylaminoethyl, 2-diethylaminoethyl, 3-dimethylaminopropyl and the like can be mentioned as examples of dialkylaminoalkyl groups. An alkoxy group and the alkoxy residue in an alkoxycarbonyl group is straight-chain or branched and contains 1-8, preferably 1-4, carbon atoms. Methoxycarbonyl and ethoxycarbonyl are specific examples of alkoxycarbonyl groups.

An interesting sub-group of compounds of formula I comprises those in which R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkyl-

sulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl or alkoxycarbonyl or a group of formula (i) and R^3 signifies carboxyl or alkoxycarbonyl.

A preferred class of compounds in accordance with the invention comprises those in which B signifies methylene or ethylene. R^1 preferably signifies alkyl, aralkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, aralkoxycarbonylaminoalkyl or aralkylaminocarbonylaminoalkyl. R^2 preferably signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii). Preferably, R^3 signifies a carboxyl group.

From the above it follows that compounds of formula I in which B signifies methylene or ethylene, R^1 signifies alkyl, aralkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, aralkoxycarbonylaminoalkyl or aralkylaminocarbonylaminoalkyl, R^2 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonylamino or a group of formula (ii) and R^3 signifies carboxyl are especially preferred.

Particularly preferred compounds of general formula I are:

9-(1-Carboxy-3-phenylpropylamino)-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
8-(1-carboxy-3-phenylpropylamino)-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1--carboxylic acid,
9-(1-benzyloxycarbonyl-3-phenylpropylamino)-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-carbamoyl-3-phenylpropylamino)-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-ethylcarbamoyl-3-phenylpropylamino)octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-carboxy-4-phenylbutylamino)-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-carboxy-2-phenylethylamino)-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-carboxy-4-methylpentylamino)-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-(1-ethoxycarbonyl-4-methylpentylamino)-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,
9-[3-(4-chlorophenyl)-1-ethoxycarbonylpropylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylic acid,
9-[1-ethoxycarbonyl-3-(4-methoxyphenyl)propylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylic acid,

9-[3-(4-biphenylyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,

9-(1-ethoxycarbonyl-5-phthalimidopentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid,

8-(1-ethoxycarbonyl-3-phenylpropylamino)-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid,

9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid and

9-(5-benzyloxyformamido-1-ethoxycarbonylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

Further examples of interesting compounds of formula I are:

tert.Butyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-benzyloxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylate,

methyl 9-(1-benzyloxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

methyl 9-(1-carboxy-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

methyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

ethyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-carbamoyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-ethylcarbamoyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-ethoxycarbonyl-4-methylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-[3-(4-chlorophenyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylate,

tert.butyl 9-[1-ethoxycarbonyl-3-(4-methoxyphenyl)-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylate,

tert.butyl 9-[3-(4-biphenylyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2-]-diazepine-1-carboxylate,

tert.butyl 9-(1-ethoxycarbonyl-5-phthalimidopentyl-amino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylate,

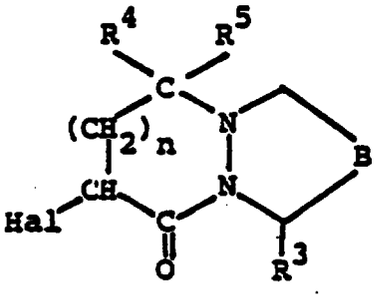
tert.butyl 8-(1-ethoxycarbonyl-3-phenylpropylamino)--2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a]-[1,2]diazepine-1-carboxylate,

benzyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate and

tert.butyl 9-(5-benzyloxyformamido-1-ethoxycarbonyl-pentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylate.

The compounds of formula I and their pharmaceutically usable salts can be manufactured in accordance with the invention by

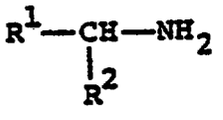
a) reacting a compound of the general formula



II

wherein B, R^3, R^4, R^5 and n have the above significance and Hal signifies halogen,

with a compound of the general formula

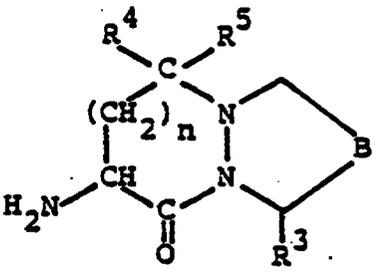


III

wherein R^1 and R^2 have the above significance,

or

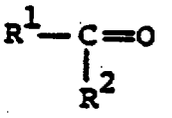
b) reductively alkylating a compound of the general formula



IV

wherein B, R^3, R^4, R^5 and n have the above significance,

with a compound of the general formula

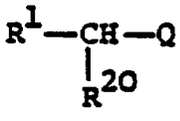


V

wherein R^1 and R^2 have the above significance,

or

c) for the manufacture of compounds of formula I in which R^2 signifies alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii) and R^3 signifies alkoxycarbonyl or aralkoxycarbonyl, reacting a compound of formula IV above in which R^3 signifies alkoxycarbonyl or aralkoxycarbonyl with a compound of the general formula



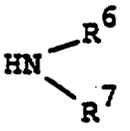
VI

wherein R^1 has the above significance, R^{20} signifies alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii) and Q signifies a leaving group,

or

d) for the manufacture of compounds of formula I in which R^2 signifies a group of formula (ii) and R^3 signifies carboxyl or tert.butoxycarbonyl, reacting a compound of

formula I in which R^2 signifies alkoxycarbonyl and R^3 signifies carboxyl or tert.butoxycarbonyl with a compound of the general formula



VII

wherein R^6 and R^7 have the above significance, or

e) for the manufacture of compounds of formula I in which B signifies ethylene, catalytically hydrogenating a compound of formula I in which B signifies vinylene, or

f) for the manufacture of compounds of formula I in which R^2 and/or R^3 signifies alkoxycarbonyl or aralkoxycarbonyl, esterifying a compound of formula I in which R^2 and/or R^3 signifies carboxyl, or

g) for the manufacture of compounds of formula I in which R^2 and/or R^3 signifies carboxyl, treating a compound of formula I in which R^2 and/or R^3 signifies alkoxycarbonyl with an acid or a base, or

h) for the manufacture of compounds of formula I in which B signifies methylene or ethylene and R^2 and/or R^3 signifies carboxyl, hydrogenating a compound of formula I in which R^2 and/or R^3 signifies aralkoxycarbonyl, or

i) for the manufacture of compounds of formula I in which R^1 signifies aminoalkyl, cleaving off the alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl group in a compound of formula I in which R^1 signifies alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl or aralkoxycarbonylaminoalkyl, and

j) if desired, separating a mixture of diastereomers obtained into the corresponding diastereomeric racemates or optically pure diastereomers and/or

k) if desired, resolving a racemate obtained into the two antipodes and

l) if desired, converting a compound of formula I obtained into a pharmaceutically usable salt.

The reaction of a compound of formula II with a compound of formula III in accordance with process

variant a) is effected in a manner known per se. Conveniently, the reaction is carried out in an inert organic solvent in the presence of an acid-binding agent. Suitable inert organic solvents are aromatic hydrocarbons such as benzene or toluene, dimethylformamide and the like. The acid-binding agent is preferably an inorganic base, especially a tertiary organic base such as triethylamine and the like. When an excess of a compound of formula III is used, then this simultaneously serves as the acid-binding agent. The reaction is conveniently carried out at an elevated temperature, for example at a temperature between about 60° and the reflux temperature of the reaction mixture.

The reductive alkylation of a compound of formula IV with a compound of formula V in accordance with process variant b) is also effected in a manner known per se. In accordance with one method, the reaction is effected in the presence of sodium cyanoborohydride in a suitable solvent such as water, a mixture of water and an alkanol, e.g. aqueous ethanol, and the like. Conveniently, the reaction is carried out under neutral reaction conditions and at approximately room temperature. In accordance with another method, the compound of formula IV is reacted with the compound of formula V and the Schiff's base obtained is catalytically hydrogenated in situ. In this catalytic hydrogenation a vinylene group B is simultaneously reduced to the ethylene group. The catalytic hydrogenation is effected under the usual reaction conditions, for example using a noble-metal catalyst such as palladium-on-carbon or Raney-nickel in an inert organic solvent such as an alkanol, e.g. ethanol, at room temperature and a pressure of 1-10 atmospheres.

The reaction of a compound of formula IV in which R^3 signifies alkoxycarbonyl or aralkoxycarbonyl with a compound of formula VI in accordance with process variant c) is conveniently effected in the presence of an inert organic solvent such as dimethylformamide, dimethyl sulphoxide, acetonitrile and the like at a temperature between about 0° and 100°C and in the presence of an acid--binding agent such as an alkali metal carbonate, e.g. sodium carbonate, a tert. organic base, e.g. triethylamine, or a basic ion exchange resin. The leaving group denoted by Q in a compound of formula VI can be, for example, a halogen atom such as a bromine atom or a sulphonate group of the formula $-O-SO_2Y$ in which Y signifies methyl, trifluoromethyl, p-tolyl and the like.

The reaction of a compound of formula I in which R^2 signifies alkoxycarbonyl and R^3 signifies carboxyl or tert.butoxycarbonyl with a compound of formula VII in accordance with process variant d) is effected in a manner

known per se, for example in water or an alcoholic medium at a low temperature, e.g. at approximately 0°C, or in a sealed tube at an elevated temperature.

The catalytic hydrogenation of a compound of formula I in which B signifies vinylene in accordance with process variant e) is also effected according to known methods. Suitable catalysts which can be used are noble metal catalysts such as palladium, platinum, ruthenium or rhodium and Raney-nickel. The noble metal catalysts can be supported on a suitable carrier material, such as palladium-on-carbon, rhodium-on-aluminium oxide and the like. The catalytic hydrogenation is effected in a conventional inert organic solvent such as an aromatic hydrocarbon, e.g. benzene, toluene, xylene etc., an alkanol, e.g. methanol, ethanol etc., or an ether e.g. dioxan etc. The catalytic hydrogenation is preferably effected at room temperature and atmospheric pressure, although it can also be carried out at an elevated temperature and/or pressure.

The esterification of a compound of formula I in which R^2 and/or R^3 signifies carboxyl in accordance with process variant f) is also effected in a manner known per se. For example, a compound of formula I in which R^2 and/or R^3 signifies carboxyl is reacted with a suitable alkanol, e.g. methanol, ethanol etc., in the presence of an acid, e.g. a mineral acid such as hydrochloric acid etc., or with a suitable diazoalkane, e.g. diazomethane or phenyldiazomethane. In accordance with an alternative embodiment, a compound of formula I in which R^2 and/or R^3 signifies carboxyl can be converted in a known manner, e.g. by reaction with thionyl chloride, phosphorus trichloride or phosphorus pentachloride, into the corresponding acid chloride which thereafter is reacted, likewise in a known manner, with a suitable alkanol. A compound of formula I in which R^2 and/or R^3 signifies carboxyl can also be reacted with isobutene in the presence of sulphuric acid, whereby there is obtained the corresponding compound of formula I in which R^2 and/or R^3 signifies tert.butoxycarbonyl.

A compound of formula I in which R^2 and/or R^3 signifies alkoxycarbonyl is converted into the corresponding compound of formula I in which R^2 and/or R^3 signifies carboxyl by reaction with an acid or a base in accordance with process variant g). This conversion is effected in a known manner, for example by reaction with an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, conveniently at a temperature between room temperature and the boiling point of the reaction mixture, or, where the alkoxycarbonyl group is the tert.butoxycarbonyl group, by treatment with anhydrous acid.

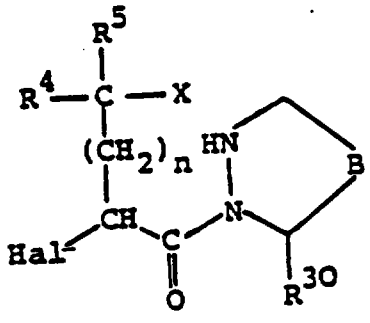
The hydrogenolysis of a compound of formula I in which R^2 and/or R^3 signifies aralkoxycarbonyl to give a compound of formula I in which B signifies methylene or ethylene and R^2 and/or R^3 signifies carboxyl in accordance with process variant h) is also effected in a known manner. In this hydrogenolysis a vinylene group B is simultaneously reduced to the ethylene group.

The cleavage in accordance with process variant i) is effected in a manner known per se, with the specific method chosen depending on the nature of the group to be cleaved off. For example, an aralkoxycarbonyl group, e.g. benzyloxycarbonyl, is cleaved off by hydrogenolysis or hydrolysis.

The separation of diastereomeric mixtures into the diastereomeric racemates or the optically pure diastereomers in accordance with process variant j) and the separation of racemates into the two optical antipodes in accordance with process variant k) are also effected according to known methods.

In accordance with process variant l), compounds of formula I can be converted into the pharmaceutically usable salts by reaction with pharmaceutically usable acids or bases. Examples of pharmaceutically usable acids are inorganic acids such as hydrohalic acids, e.g. hydrogen bromide or hydrogen chloride, sulphuric acid, phosphoric acid and nitric acid, and organic acids such as acetic acid, maleic acid, fumaric acid, tartaric acid, citric acid, methanesulphonic acid and p-toluenesulphonic acid. Examples of pharmaceutically usable bases are alkali metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides, e.g. calcium hydroxide or magnesium hydroxide, ammonium hydroxide and organic bases, e.g. dicyclohexylamine.

The compounds of formula II in which B signifies methylene or vinylene, R^3 signifies carboxyl or alkoxycarbonyl, R^4 and R^5 together signify an oxo group and n signifies the number 1, which are used as starting materials in process variant a), belong to a known class of compounds. Specific representatives which have not hitherto been described can be prepared as described in the following Examples or in analogy thereto. The remaining starting materials of formula II are novel and are also an object of the present invention. They can be prepared, for example, by cyclizing a compound of the general formula



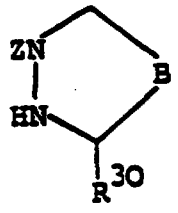
VIII

wherein R^4, R^5, n, B and Hal have the above significance and X signifies halogen and R^{30} signifies alkoxycarbonyl.

Where necessary, an alkoxycarbonyl group R^{30} in the product obtained can be converted into carboxyl or into a different alkoxycarbonyl group or an aralkoxycarbonyl group. The cyclization of a compound of formula VIII is effected according to conventional methods, for example in the presence of a suitable inert organic solvent such as dimethylformamide or tetrahydrofuran, if desired in the presence of a base such as an alkali metal carbonate, e.g. sodium carbonate, potassium carbonate etc., or a tertiary organic base, e.g. triethylamine, N-ethylmorpholine etc., at a suitable temperature between 0° and 80°C. The cyclization is conveniently carried out in situ, i.e. without isolating the compound of formula VIII from the reaction medium in which it is prepared.

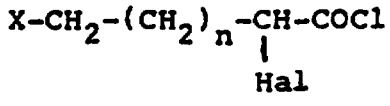
The conversion of an alkoxycarbonyl group R^{30} in the product obtained, i.e. in a compound of formula II in which R^3 signifies alkoxycarbonyl, into the carboxyl group can be carried out in an analogous manner to that given above for process variant g). The thus-obtained compound of formula II in which R^3 signifies carboxyl can then, if desired, be esterified in an analogous manner to that given above for process variant f). Alternatively thereto, a compound of formula II in which R^3 signifies alkoxycarbonyl can be trans-esterified according to known methods to give a compound of formula II in which R^3 signifies a different alkoxycarbonyl or aralkoxycarbonyl group.

The compounds of formula VIII in which R^4 and R^5 each signify hydrogen can be prepared, for example, by reacting a compound of the general formula



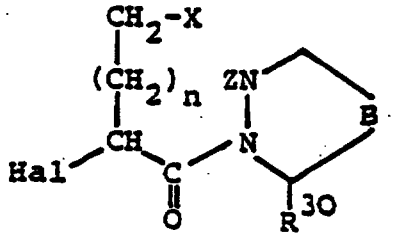
IX

with a compound of the general formula



X

and removing the benzyloxycarbonyl group in the obtained compound of the general formula



XI

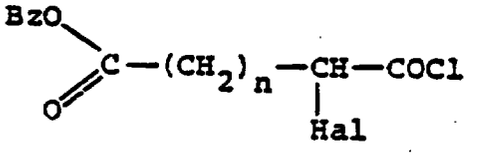
whereby in the above formulae B, R^{30}, n, X and Hal have the above significance and Z signifies benzyloxycarbonyl.

The reaction of a compound of formula IX, which is a known compound or an analogue of a known compound, with a compound of formula X, which is likewise a known compound or an analogue of a known compound, is effected according to generally known methods, for example in the presence of an inert organic solvent, e.g. a halogenated hydrocarbon such as methylene chloride, and in the presence of an acid-binding agent such as an alkali metal carbonate, e.g. sodium carbonate, or an alkali metal bicarbonate, e.g. sodium bicarbonate, at approximately room temperature.

The cleavage of the benzyloxycarbonyl group from a compound of formula XI can be effected, for example, by reaction with hydrogen bromide in glacial acetic acid at

approximately room temperature or using hydrogen in the presence of a catalyst according to known methods.

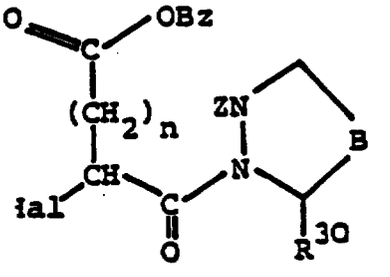
The compounds of formula VIII in which R^4 and R^5 together signify an oxo group can be prepared, for example, by reacting a compound of formula IX above with a compound of the general formula



XII

wherein n and Hal have the above significance and Bz signifies benzyl,

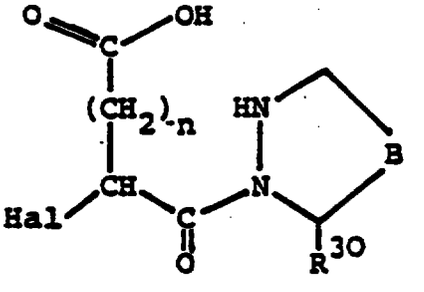
removing the benzyl and benzyloxycarbonyl groups in the resulting compound of the general formula



XIII

wherein B, R^{30}, n, Hal, Bz and Z have the above significance,

and converting the resulting acid of the general formula



XIV

wherein B, R^{30}, n and Hal have the above significance,

into the corresponding acid halide.

The reaction of a compound of formula IX with a compound of formula XII, which is a known compound or an analogue of a known compound, can be carried out in an analogous manner to that given above for the reaction of a compound of formula IX with a compound of formula X.

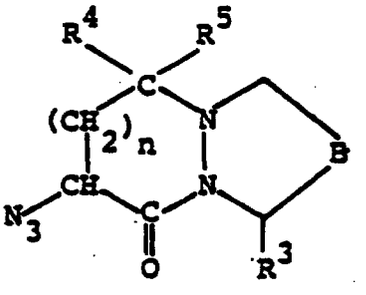
The removal of the benzyl and benzyloxycarbonyl groups from a compound of formula XIII can be carried out according to generally known methods, for example using hydrogen in the presence of a catalyst such as a noble metal catalyst, e.g. palladium-on-carbon, or, where R^{30} signifies other than tert.butoxycarbonyl, using hydrogen bromide in glacial acetic acid.

The conversion of an acid of formula XIV into the corresponding acid halide of formula VIII can also be effected according to known methods, for example using a suitable halogenating agent such as thionyl chloride, phosphorus pentachloride and the like.

The compounds of formula III which are also used as starting materials in process variant a) are known compounds or analogues of known compounds which can be prepared in a similar manner to the known compounds.

The compounds of formula IV which are used as starting materials in process variant b) are novel and are also an object of the present invention.

The compounds of formula IV can be prepared, for example, by reacting a compound of formula II with an alkali metal azide and reducing the resulting azide of the general formula



XV

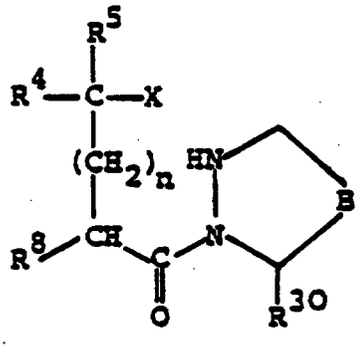
wherein B, R^3, R^4, R^5 and n have the above significance.

The reaction of a compound of formula II with an alkali metal azide, preferably sodium azide, is effected

in a known manner, for example in the presence of an inert organic solvent such as a ketone, e.g. acetone, at an elevated temperature, e.g. at the reflux temperature of the reaction mixture.

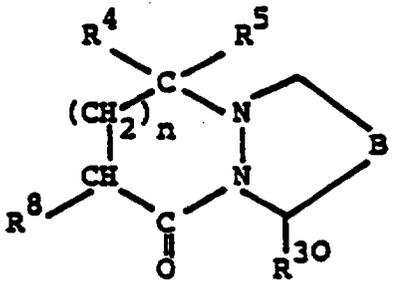
Conventional methods are used for the reduction of an azide of formula XV to a compound of formula IV. According to a preferred procedure an azide of formula XV is reacted with triphenylphosphine in a suitable inert organic solvent such as dioxan at approximately room temperature and subsequently hydrolyzed using an acid, e.g. hydrochloric acid.

The compounds of formula IV can also be obtained by cyclizing a compound of the general formula



XVI

wherein B, R^{30}, R^4, R^5, n and X have the above significance and R^8 signifies phthaloylamino, and removing the phthaloyl group from the resulting compound of the general formula



XVII

wherein B, R^{30}, R^4, R^5, R^8 and n have the above significance.

If desired, the alkoxycarbonyl group R^{30} can be converted into carboxyl, a different alkoxycarbonyl group

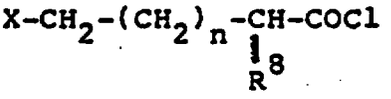
or an aralkoxycarbonyl group before or after the removal of the phthaloyl group.

The cyclization of a compound of formula XVI can be carried out according to generally known methods, for example in essentially the same manner to that given above in connection with the cyclization of a compound of formula VIII. The compounds of formula XVI are preferably cyclized in situ.

The removal of the phthaloyl group from a compound of formula XVII is also effected in a manner known per se using hydrazine, conveniently in an inert organic solvent such as an alkanol, e.g. ethanol, at room temperature or at an elevated temperature, e.g. at the reflux temperature of the reaction mixture.

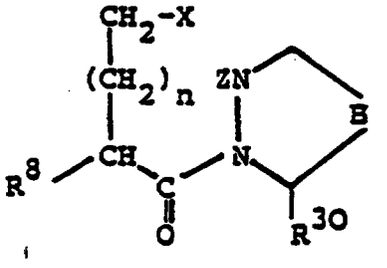
The optional conversion of an alkoxycarbonyl group R^{30} into a carboxyl group, a different alkoxycarbonyl group or an aralkoxycarbonyl group can be carried out in an analogous manner to that given above in connection with the preparation of the starting materials of formula II.

The compounds of formula XVI in which R^4 and R^5 each signify hydrogen can be obtained, for example, by reacting a compound of formula IX above with a compound of the general formula



XVIII

wherein R^8, n and X have the above significance, and cleaving off the benzyloxycarbonyl group from the resulting compound of the general formula



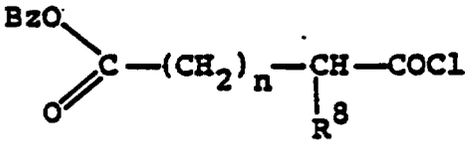
XIX

wherein B, R^{30}, R^8, n, X and Z have the above significance.

The reaction of a compound of formula IX with a compound of formula XVIII, which is a known compound or an analogue of a known compound, can be carried out in the same manner to that given above in connection with the reaction of a compound of formula IX with a compound of formula X.

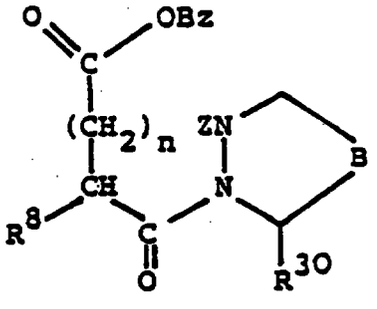
The cleavage of the benzyloxycarbonyl group from a compound of formula XIX can be effected in the same manner to that given above in connection with the cleavage of the benzyloxycarbonyl group from a compound of formula XI.

The compounds of formula XVI in which R^4 and R^5 together signify an oxo group can be prepared, for example, by reacting a compound of formula IX above with a compound of the general formula



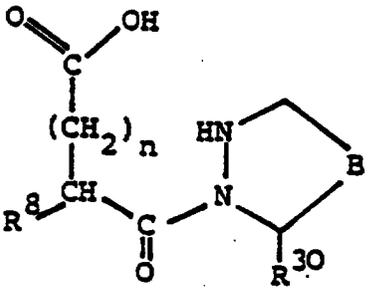
XX

wherein R^8, n and Bz have the above significance, cleaving off the benzyl and benzyloxycarbonyl groups from the resulting compound of the general formula



XXI

wherein B, R^8, R^{30}, n, Z and Bz have the above significance,
and converting the resulting acid of the general formula



XXII

wherein B, R^8, R^{30} and n have the above significance,
into the corresponding acid halide.

The reaction of a compound of formula IX with a compound of formula XX, which is a known compound or an analogue of a known compound, can be carried out under the same reaction conditions as given above in connection with the reaction of a compound of formula IX with a compound of formula X.

The cleavage of the benzyl and benzyloxycarbonyl groups from a compound of formula XXI can be effected in the same manner as given above in connection with the cleavage of these groups from a compound of formula XIII.

The conversion of an acid of formula XXII into the corresponding acid halide of formula XVI can be effected in an analogous manner to that given above in connection with the conversion of an acid of formula XIV into the corresponding acid halide.

The compounds of formulae V and VI used as starting materials in process variants b) and c) are either known compounds or analogues of known compounds which, in turn, can be prepared in a similar manner to the known compounds.

The compounds of formula VII used as starting materials in process variant d) are known.

The compounds of formula I and their pharmaceutically usable salts are valuable antihypertensives. They inhibit angiotensin converting enzyme (ACE) which is responsible for the conversion of angiotensin I into angiotensin II and are therefore useful in reducing or alleviating high blood pressure caused by angiotensin.

The activity of the present compounds in inhibiting angiotensin converting enzyme in vitro can be determined by the following test.

The method used is based on the method of Cushman and Cheung (Biochem. Pharmacol., 20, 1637-1648) incorporating the modifications of Hayakari et al. (Anal. Biochem., 84, 361-369). The substrate (hippuryl-histidyl-leucine, 2 mM) is incubated with angiotensin converting enzyme in the absence or presence of various concentrations of the test compounds in potassium phosphate buffer (pH 8.3; 100 mM), which contains sodium chloride (3 mM), for 24 minutes at 37°C (total value 500 µl). (If the test substance is an ester, then it is appropriate to cleave this by means of hog liver esterase before carrying out the test). The reaction is terminated by the addition of 3 ml of potassium phosphate buffer (pH 8.3; 200 mM) at 0°C. The mixture is subsequently treated with 2,4,6-trichloro-s--triazine (3%) in 1.5 ml of dioxan and the mixture obtained is shaken until the yellow chromophore has developed fully. The samples are subsequently centrifuged in order to remove any solid which has resulted. The yellow chromophore formed by the reaction of 2,4,6--trichloro-s-triazine with free hippuric acid is measured spectrophotometrically at 382 nm. The IC_{50} value is that concentration of a test compound which reduces by 50% the cleavage of hippuryl-histidyl-leucine by angiotensin converting enzyme under the conditions given above.

The following Table contains the results which have been obtained with representative members of the compounds of formula I in the previously described text.

Compound A: 9(S)-(1-Carboxy-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid; isomer A (see Example 1).

Compound B: 9(S)-[1(R and S)-Carboxy-4-phenylbutylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid (see Example 21).

Compound C: 9(S)-[1(R and S)-Carboxy-2-phenylethylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid (see Example 22).

Compound D: 9(S)-[1(R and S)-Carboxy-4-methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid (see Example 23).

Table

Compound	IC_{50}
A	4.2×10^{-9} M
B	1.1×10^{-8} M
C	2.6×10^{-8} M
D	1.2×10^{-8} M

The compounds of formula I and their pharmaceutically usable salts can be used as medicaments in the form of pharmaceutical preparations which contain these compounds together with suitable pharmaceutical carrier materials. As carrier materials there come into consideration for enteral, for example oral, or parenteral administration suitable organic or inorganic carrier materials, for example water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, Vaseline and the like. The pharmaceutical preparations can be made up in solid form, for example as tablets, dragees, suppositories or capsules, or in liquid form, e.g. as solutions, suspensions or emulsions. The pharmaceutical preparations can be subjected to usual pharmaceutical operations such as sterilization and/or can contain adjuvants such as preserving agents, stabilizing agents, wetting agents or emulsifying agents, salts for varying the osmotic pressure or buffers. The pharmaceutical preparations can also contain other therapeutically valuable compounds.

The compounds of formula I and their pharmaceutically usable salts can be administered to adults in a daily dosage of about 0.1 to 100 mg, preferably about 1-50 mg/kg, body weight. The daily dosage can be administered in a single dose or in divided doses. It must be emphasized here that the dosages referred to above are given by way of example and that they can be varied upwards or downwards depending on factors such as the specific properties of the compound being administered or salt being administered, the mode of administration, the severity of the indication being treated and the condition of the patient as determined by the attending physician.

The following Examples illustrate the present invention. All temperature are given in degress Celsius.

Example 1

1.25 g of 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1-(S)-carboxylic acid monohydrate

and 1.8 g of 2-oxo-4-phenylbutyric acid are dissolved in 6 ml of 2N sodium hydroxide solution at room temperature. 0.3 g of sodium cyanoborohydride is added thereto and the mixture is stirred for 50 minutes. A further 0.3 g of sodium cyanoborohydride is then added and, after a further 85 minutes, a further 0.3 g of sodium cyanoborohydride and 0.9 g of 2-oxo-4-phenylbutyric acid are added. The pH value is adjusted to 7.5-8 by the addition of sodium hydroxide solution and the mixture is left to stand for 3 days. 100 ml of diethyl ether, 20 ml of water and 30 g of Duolite C 225 ion exchange resin (H^+ form) are added and the mixture is stirred well for 100 minutes. The ethereal phase is then removed and the aqueous phase, which contains the resin, is added to a column filled with a further 10 g of the above-named resin. The column is washed with 80 ml of water and then eluted with 200 ml of water containing 2% pyridine. The eluates are evaporated, whereby there are obtained 1.1 g of crude 9(S)-[1(R and S)-carboxy-3-phenylpropylamino]octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid.

The isomer mixture is separated on Amberlite XAD 2 polystyrene resin columns with 0.1N aqueous ammonia containing 5% methanol as the eluting agent. Diastereomer A is eluted before diastereomer B; diastereomer A also has a higher Rf value on silica gel thin-layer chromatography plates which are eluted with butan-1-ol/water/acetic acid (4:1:1). In this manner there are obtained 0.32 g of diastereomer A and 0.35 g of diastereomer B in the form of ammonium salts from which the ammonia is removed by means of Duolite C 225 resin, whereby water containing 2% pyridine is used as the eluting agent.

The 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1-(S)-carboxylic acid monohydrate used as the starting material can be prepared as follows:

A) 16 g of L-glutamic acid γ-benzyl ester and 11 g of phthalic anhydride, both finely powdered, are stirred in 20 ml of toluene at reflux temperature for 2 hours. 50 ml of toluene are then added and the reaction mixture is evaporated. A further 80 ml of toluene are then added and the mixture is left to crystallize. Recrystallization from toluene yields 15 g of α(S)-2-benzyloxycarbonylethyl--1,3-dihydro-1,3-dioxo-2-isoindoleacetic acid of melting point 96-98°; $[\alpha]_D^{20} = -50.4°$ (c = 1% in methanol).

B) 56 g of α(S)-(2-benzyloxycarbonylethyl)-1,3-dihydro--1,3-dioxo-2-isoindoleacetic acid in 500 ml of dry dimethyl ether are stirred with 40 g of phosphorus pentachloride at room temperature for 2 hours. A further 2 g of phosphorus pentachloride are added, the mixture is stirred for 30 minutes, undissolved solid is filtered off and the

filtrate is evaporated. The residue is evaporated twice with toluene and thereafter dissolved in 262 ml of methylene chloride and cooled with ice/water. While stirring there are added 262 ml of methylene chloride containing 44 g of tert.butyl 1-(benzyloxycarbonyl)hexahydro-3-pyridazinecarboxylate and immediately thereafter 420 ml of satured aqueous sodium bicarbonate solution are added. The mixture is stirred at room temperature overnight, thereafter diluted with ethyl acetate and partially evaporated until the emulsion has separated. The organic phase is thereafter washed with aqueous sodium dihydrogen phosphate solution, aqueous sodium carbonate solution and sodium chloride solution, dried and evaporated. The residue is dissolved in 1040 ml of methanol and hydrogenated at atmospheric pressure over 7.4 g of 10% palladium-on-carbon until uptake of hydrogen has ceased. The catalyst is removed and the filtrate is evaporated, whereby 61 g of crude gamma(S)-(6-tert.butoxycarbonyl--hexahydro-1-pyridazinyl)-carbonyl-1,3-dioxo-2-isoindoline-butyric acid (2 diastereomers) are obtained. Crystallization from ethyl acetate/diethyl ether yields 19 g of the (S,S)-isomer of melting point 132-134°; $[\alpha]_D^{25}$ = -54.4° (c = 0.5% in methanol). Chromatography on silica gel using diethyl ether as the eluting agent yields the (S,R)-isomer of melting point 134-137° (from ethyl acetate/diethyl ether); $[\alpha]_D^{25}$ = -6.2° (c = 0.5% in methanol).

C) 2.2 g of gamma(S)-(6(S)-tert.butoxycarbonyl-hexahydro--1-pyridazinyl)-carbonyl-1,3-dioxo-2-isoindolinebutyric acid in 60 ml of dry tetrahydrofuran are stirred at 0° with 1.1 ml of N-ethylmorpholine and 1.1 g of phosphorus pentachloride. After 1 hour a further 0.2 ml of N-ethylmorpholine and 0.2 g of phosphorus pentachloride are added and, after a further 5 hours, a further 0.15 ml of N-ethylmorpholine and 0.15 g of phosphorus pentachloride are added. The reaction mixture is left to stand at room temperature overnight, evaporated, the residue is diluted with 150 ml of ethyl acetate, the solution is washed with 1N hydrochloric acid and sodium chloride solution and dried over magnesium sulphate. Evaporation of the solvent yields 2.4 g of crude tert.butyl octahydro-6,10-dioxo--9(S)-phthalimido-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate. After purification by chromatography on silica gel using ether as the eluting agent and crystallization from ethyl acetate/diethyl ether the product melts at 181-185°, $[\alpha]_D^{20}$ = -80.0° (c = 0.5% in methanol).

D) 2.4 g of tert.butyl octahydro-6,10-dioxo-9(S)--phthalimido-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate are dissolved in 20 ml of trifluoroacetic acid. After 80 minutes the mixture is evaporated and the

residue is treated twice with toluene and evaporated each time. The residue is triturated with ethyl acetate, whereby there are obtained 1.7 g of octahydro-6,10-dioxo--9(S)-phthalimido-6H-pyridazo]1,2-a][1,2]diazepine-1-(S)--carboxylic acid. A sample is recrystallized from acetone/water and melts at 307-310° (dec.); $[\alpha]_D^{20}$ = -139° (c = 0.5% in dimethylformamide).

E) 4.9 g of octahydro-6,10-dioxo-9(S)-phthalimido-6H--pyridazo]1,2-a][1,2]diazepine-1-(S)-carboxylic acid are heated for 40 minutes in 80 ml of ethanol containing 1.4 ml of hydrazine hydrate. The mixture is left to stand at room temperature overnight and thereafter evaporated. 100 ml of 2N acetic acid are added, the mixture is stirred at room temperature for 70 minutes and then filtered. The filtrate is evaporated and the residue is again evaporated with water. The residue is thereafter dissolved in 60 ml of warm water, filtered and the filtrate is concentrated. It is then diluted with 30 ml of ethanol and left to crystallize. In this manner there are obtained 2.65 g of 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-(S)-carboxylic acid monohydrate of melting point 195-200° (dec.); $[\alpha]_D^{20}$ = -174.6° (c = 0.5% in 2N hydrochloric acid).

Example 2

2.3 g of 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1-(S)-carboxylic acid monohydrate are stirred at room temperature in 25 ml of ethanol and 5 ml of water with 1.1 g of ethyl 2-oxo-4-phenylbutyrate and 0.3 g of sodium cyanoborohydride. During the next 48 hours a further 8 g of ethyl 2-oxo-4-phenylbutyrate and 1.5 g of sodium cyanoborohydride are added in 5 portions to the stirred mixture which is thereafter left to stand for 3 days. The mixture is evaporated, the residue is diluted with 120 ml of ethyl acetate and the solution obtained is extracted twice with 50 ml of water and with 5 ml of saturated aqueous sodium bicarbonate solution. The aqueous extracts are washed with 30 ml of diethyl ether, thereafter acidified (pH 3-4) and extracted with 100 ml of ethyl acetate and 50 ml of ethyl acetate. The combined organic extracts are washed with sodium chloride solution, dried over magnesium sulphate and evaporated, whereby there are obtained 3.7 g of crude 9(S)-[1(R and S)-ethoxy-carbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid in the form of a diastereomeric mixture which are separated on a silica gel thin-layer chromatography plate using diethyl ether containing 10% acetic acid as the eluent. The separation of the two diastereomers is effected by chromatography on a silica gel column using diethyl ether containing 5-15% acetic acid as the eluting agent. The

diastereomer with the lower Rf value (isomer B) is dissolved in toluene and treated with dry hydrogen chloride. The thus-obtained solid is recrystallized from ethanol/ethyl acetate, whereby there is obtained 9(S)-[1(R or S)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10--dioxo-6H-pyridazol[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrochloride of melting point 202-207° (dec.).

Example 3

In an analogous manner to that described in the first paragraph of Example 1, from 1.13 g of 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid and 2.7 g of 2-oxo-4--phenylbutyric acid there are obtained 350 mg of 8(S)-1--(carboxy-3-phenylpropylamino)-2,3,6,7,8,9-hexahydro-5,9--dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1(S)-carboxylic acid in the form of a lyophilized mixture.

The 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H--pyrazolo[1,2-a][1,2]diazepine-1(S)-carboxylic acid used as the starting material can be prepared as follows:

A) 17.2 g of tert.butyl acrylate are treated with a solution of diazomethane in diethyl ether until the yellow coloration persists for 2 minutes after the addition. The solvent is removed by evaporation, the residual oil is dissolved in 300 ml of ethanol and the solution is hydrogenated over 10% palladium-on-carbon. The catalyst is filtered off and the filtrate is evaporated. The residual oil is dissolved in 260 ml of ethyl acetate and a solution of 24 g of sodium bicarbonate in 260 ml of water is added. The mixture is cooled to 0° while stirring and treated dropwise with a solution of 18.76 g of benzyl chloroformate in 50 ml of ethyl acetate. After 1 hour the organic phase is separated, washed with 2N hydrochloric acid and sodium chloride solution, dried over magnesium sulphate and evaporated. The residual oil is chromatographed on silica gel. Elution with ethyl acetate/n-hexane (1:1) yields 10.81 g (25%) of 1-benzyl 3-tert.butyl 1,3-pyrazolidinedicarboxylate as a white solid of melting point 55-57° (from diethyl ether/n-hexane).

B) 22.02 g of α(S)-(2-benzyloxycarbonylethyl)-1,3--dihydro-1,3-dioxo-2-isoindoleacetic acid (prepared as described in Example 1) in 210 ml of dry diethyl ether are stirred with 15.01 g of phosphorus pentachloride for 2 1/2 hours. The mixture is filtered and the filtrate is evaporated. The residue is taken up twice in toluene and evaporated each time, thereafter the residue is dissolved in 110 ml of methylene chloride and the solution is cooled to 0°. The solution is then stirred at 0° and treated with a solution of 15.3 g of 1-benzyl 3-tert.butyl

1,3-pyrazolidinedicarboxylate in 110 ml of methylene chloride. 170 ml of saturated aqueous sodium bicarbonate solution are added and the mixture is stirred at room temperature for 1 hour. The organic solvent is evaporated and the residue is extracted with ethyl acetate. The extracts are washed with sodium chloride solution, dried over magnesium sulphate and evaporated. The thus-obtained oil is chromatographed on silica gel. Elution with ethyl acetate/n-hexane (1:1) yields 25.62 g (78%) of tert.butyl 1-benzyloxycarbonyl-2-(5-benzyloxycarbonyl-2-phthalimido-butyryl)-3-pyrazolidinecarboxylate (2 diastereomers) in the form of a colourless oil.

C) 24.97 g of tert.butyl 1-benzyloxycarbonyl-2-(5-benzyl-oxycarbonyl-2-phthalimidobutyryl)-3-pyrazolidinecarboxylate are dissolved in 250 ml of methanol and hydrogenated over 2 g of 10% palladium-on-carbon. The catalyst is filtered off and the filtrate is evaporated, whereby there are obtained 16 g (98%) of tert.butyl 2-(5-carboxy-2--phthalimidobutyryl)-3-pyrazolidinecarboxylate (2 diastereomers) in the form of a gum.

D) A solution of 3.45 g of tert.butyl 2-(5-carboxy-2--phthalimidobutyryl)-3-pyrazolidine carboxylate and 0.92 g of N-ethylmorpholine in 50 ml of dry tetrahydrofuran is cooled to 0° while stirring and treated with 1.66 g of phosphorus pentachloride. After 1 hour a further 0.92 g of N-ethylmorpholine and 1.66 g of phosphorus pentachloride are added and, after a further hour, a further 0.92 g of N-ethylmorpholine is added. The solvent is evaporated and the residue is partitioned between water and ethyl acetate. The organic phase is washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. The residual oil is chromato-graphed on silica gel. Elution with diethyl ether yields firstly 1.1 g (33%) of tert.butyl 2,3,6,7,8,9-hexahydro--5,9-dioxo-8(S)-phthalimido-1H,5H-pyrazolo[1,2-a][1,2]-diazepine-1(S)-carboxylate in the form of a white foam and thereafter 0.52 g (15%) of tert.butyl 2,3,6,7,8,9-hexa-hydro-5,9-dioxo-8(S)-phthalimido-1H,5H-pyrazolo[1,2-a]-[1,2]diazepine-1(R)-carboxylate in the form of a white solid of melting point 180-181° (from ethyl acetate/ n-hexane).

E) In an analogous manner to that described in Example 1 D), from 3.72 g of tert.butyl 2,3,6,7,8,9-hexa-hydro-5,9-dioxo-8(S)-phthalimido-1H,5H-pyrazolo[1,2-a]-[1,2]diazepine-1(S)-carboxylate and 30 ml of trifluoro-acetic acid there are obtained 2.09 g (65%) of 2,3,6,7,8, 9-hexahydro-5,9-dioxo-8(S)-phthalimido-1H,5H-pyrazolo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid in the form of a white solid of melting point 232-233° (from aceto-nitrile).

F) In an analogous manner to that described in Example 1 E), but using hydrazine hydrate at room temperature instead of at 70°, from 3.57 g of 2,3,6,7,8,9-hexahydro-5,9-dioxo-8(S)-phthalimido-1H,5H-pyrazolo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid there are obtained 2.0 g (88%) of 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1(S)-carboxylic acid in the form of a lyophilized solid.

Example 4

5.94 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate, 5.42 g of ethyl 2-bromo-4-phenybutanoate and 2.0 g of triethylamine are dissolved in 65 ml of acetonitrile and the solution is boiled under reflux for 17 hours. After evaporation the residue is partitioned between ethyl acetate and water. The organic phase is washed in succession with 2N aqueous acetic acid and aqueous sodium carbonate solution and thereafter evaporated. After column chromatography on silica gel using diethyl ether/n-hexane as the eluting agent there are obtained 3.1 g of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as a gum and 3.25 g of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as white crystals of melting point 55-58° after treatment with hexane.

The tert.butyl 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate used as the starting material can be prepared as follows:

8.54 g of tert.butyl octahydro-6,10-dioxo-9(S)-phthalimido-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate are suspended in 85 ml of ethanol and treated with 2 ml of hydrazine hydrate. The mixture is stirred at 20° for 2 1/2 hours and thereafter evaporated. The residue is stirred for 1 hour with 2N aqueous acetic acid and thereafter filtered. The filtrate is made basic with solid sodium carbonate and extracted with methylene chloride. The organic extracts are dried and evaporated, whereby there are obtained 5.9 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as a gum.

Example 5

131.8 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 61.6 ml of triethylamine are dissolved in 2.8 l of acetonitrile. The solution is treated with 150.9 g of ethyl

2(R)-trifluoromethanesulphonyloxy-4-phenylbutanoate (prepared from 2(R)-hydroxy-4-phenylbutyric acid according to standard methods) and the mixture is stirred at 20° for 90 minutes. The solution is evaporated and the residual oil is partitioned between ethyl acetate and water. The organic phase is dried and evaporated and the residue is filtered through a short column of silica gel using ethyl acetate/n-hexane (3:1) as the eluting agent. Evaporation of the eluate yields 187.5 g of tert.butyl 9(S)-[1(S)--ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate.

Example 6

13.7 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 29 g of ethyl 2-oxo-4-phenylbutanoate are stirred at 20° for 17 hours in 200 ml of tetrahydrofuran in the presence of 15 g of powdered 4A molecular sieve. Five 1.5 g portions of sodium cyanoborohydride are added at hourly intervals. After completion of the addition the mixture is stirred for a further 2 hours. The solvent is evaporated and the residue is partitioned between ethyl acetate and aqueous sodium carbonate solution. The organic phase is evaporated and the residue is chromatographed on silica gel, whereby diethyl ether/n-hexane is used as the eluting agent. There are thus obtained 4.8 g of tert.butyl 9(S)--[1(R)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 4.1 g of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate.

Example 7

2.0 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 4.2 g of ethyl 2-oxo-4-phenylbutanoate are dissolved in 50 ml of ethanol containing 5 ml of acetic acid. 4 g of powdered molecular sieve are added and the mixture is hydrogenated over 10% palladium-on-carbon at 20° and 4 atmospheres for 40 hours. Filtration and evaporation yields an oily residue which is chromatographed on silica gel using ethyl acetate/n-hexane as the eluting agent. In this manner there are obtained 950 mg of tert.butyl 9(S)--[1(R)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 870 mg of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate.

Example 8

860 mg of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate are dissolved in 1 ml of acetic acid and treated with 4 ml of a 45% solution of hydrogen bromide in acetic acid. The solution is left to stand at 20° for one hour and thereafter evaporated. The residue is stirred with diethyl ether and filtered, whereby there are obtained 840 mg of 9(S)-[1(S)--ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrobromide of melting point 216-218° (from ethanol/ethyl acetate).

Example 9

In an analogous manner to that described in Example 8, from 5.4 g of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there are obtained 4.41 g of 9(S)-[1(R)-ethoxycarbonyl-3-phenylpropylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine--1(S)-carboxylic acid hydrobromide of melting point 201-203° (from ethanol/ethyl acetate).

Example 10

In an analogous manner to that described in Example 7, from 5.34 g of 2-oxo-4-phenylbutyric acid and 2.97 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there are obtained 1.7 g of tert.butyl 9(S)-[1(R)-carboxy-3-phenylpropyl-amino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate and 1.75 g of tert.butyl 9(S)--[1(S)-carboxy-3-phenylpropylamino]-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate, whereby both diastereomers are isolated as gums after chromatography on silica gel.

Example 11

500 mg of tert.butyl 9(S)-[1(S)-carboxy-3-phenyl-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate are dissolved in diethyl ether and treated at 20° with a solution of phenyldiazomethane in diethyl ether. The solution is washed with aqueous sodium bicarbonate solution, dried and evaporated. The residue is chromatographed on silica gel, whereby ethyl acetate/n-hexane (1:1) is used as the elution agent. In this manner there are obtained 430 mg of tert.butyl 9(S)--[1(S)-benzyloxycarbonyl-3-phenylpropylamino]-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as a gum.

Example 12

410 mg of tert.butyl 9(S)-[1(S)-benzyloxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate are treated with 3 ml of trifluoroacetic acid. The solution is left to stand at 20° for 1 1/2 hours and thereafter evaporated. The residual foam is taken up in ethyl acetate and a solution of hydrogen chloride in ethyl acetate is added. The precipitated solid is filtered off, whereby there are obtained 330 mg of 9(S)-[1(S)-benzyloxycarbonyl-3-phenyl-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid hydrochloride as a white solid of melting point 198-202°.

Example 13

260 mg of 9(S)-[1(S)-benzyloxycarbonyl-3-phenylpropyl-amino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid is dissolved in diethyl ether and the solution is treated at 20° with a solution of diazomethane in diethyl ether. After 10 minutes the solution is washed with aqueous sodium bicarbonate solution, dried and evaporated. Chromatography of the residual gum on silica gel using ethyl acetate/hexane (1:1) as the eluting agent yields 180 mg of methyl 9(S)--[1(S)-benzyloxycarbonyl-3-phenylpropylamino]-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as a colourless gum.

Example 14

170 mg of methyl 9(S)-[1(S)-benzyloxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate are dissolved in 5 ml of acetic acid and hydrogenated over 10% palladium--on-carbon at 20° and atmospheric pressure for 17 hours. The catalyst is filtered off and the filtrate is evaporated. The residue is taken up in ethyl acetate and a solution of hydrogen chloride in ethyl acetate is added. The precipitated solid is filtered off, whereby there are obtained 85 mg of methyl 9(S)-[1(S)-carboxy-3-phenyl-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate as a white solid having a diffuse melting point.

Example 15

715 mg of 9(S)-[1(R and S)-ethoxycarbonyl-3-phenyl-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid are dissolved in diethyl ether and the solution is treated with a solution of diazomethane in diethyl ether. The diastereomers are

separated by chromatography on silica gel, whereby ethyl acetate/n-hexane (1:1) is used as the elution agent. In this manner there are obtained in the form of their crystalline hydrochloride salts from ethyl acetate methyl 9(S)-[1(R)-ethoxycarbonyl-3-phenylpropylamino]-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate hydrochloride of melting point 161-163° (dec.) and methyl 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate hydrochloride of melting point 175-178° (dec.).

Example 16

500 mg of 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid are dissolved in 30 ml of ethanol and the solution is saturated with dry hydrogen chloride. After standing at 20° for 17 hours the solution is evaporated and the residue is treated with diethyl ether. By filtration there is obtained ethyl 9(S)-[1(S)--ethoxycarbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate hydrochloride as a white solid of melting point 187-189° (dec.).

Example 17

487 mg of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate are taken up in methanol and the solution is saturated with ammonia. The mixture is left to stand at 0° for 15 days and thereafter evaporated. Chromatography of the residue on silica gel using ethyl acetate/n-hexane (3:1) as the eluting agent yields 340 mg of tert.butyl 9(S)-[1(S)-carbamoyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate as a gum.

Example 18

In an analogous manner to that described in Example 8, from 260 mg of tert.butyl 9(S)-[1(S)-carbamoyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate there are obtained 250 mg of 9(S)-[1(S)-carbamoyl-3-phenylpropylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrobromide as white crystals of melting point 170-190° (dec.); (from ethanol/ethyl acetate).

Example 19

In an analogous manner to that described in Example 17, from 487 mg of tert.butyl 9(S)-[1(S)-ethoxy-

carbonyl-3-phenylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate using ethanolic ethylamine there are obtained 260 mg of tert.butyl 9(S)-[1(S)-ethylcarbamoyl-3-phenylpropylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine--1(S)-carboxylate as a gum.

Example 20

In an analogous manner to that described in Example 8, from 210 mg of tert.butyl 9(S)-[1(S)-ethylcarbamoyl-3--phenylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there are obtained 180 mg of 9(S)-[1(S)-ethylcarbamoyl-3-phenylpropylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine--1(S)-carboxylic acid as a white solid which decomposes above 170° after crystallization from ethanol/ethyl acetate.

Example 21

In an analogous manner to that described in Example 1, from 241 mg of 9(S)-amino-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid and 576 mg of 2-oxo-5-phenylpentanoic acid there are obtained 100 mg of 9(S)-[1(R and S)-carboxy-4-phenylbutylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine--1(S)-carboxylic acid as a white solid.

Example 22

In an analogous manner to that described in Example 1, from 241 mg of 9(S)-amino-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid and 612 mg of sodium phenylpyruvate monohydrate there are obtained 110 mg of 9(S)-[1(R and S)-carboxy-2-phenylethyl-amino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid as a white solid.

Example 23

In an analogous manner to that described in Example 1, from 241 mg of 9(S)-amino-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid and 432 mg of 2-oxo-5-methylhexanoic acid there are obtained 68 mg of 9(S)-[1(R and S)-carboxy-4-methylpentylamino]--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine--1(S)-carboxylic acid as a white solid.

Example 24

In an analogous manner to that described in Example 4, from 2.97 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo-

-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 2.6 g of ethyl 2-bromo-5-methylhexanoate there are obtained 1.5 g (33%) of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-4-methylpentylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 1.6 g (35%) of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-4-methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate, both in the form of pale yellowish oils.

Example 25

In an analogous manner to that described in Example 8, from 1.0 g of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-4--methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there is obtained 0.4 g (38%) of 9(S)-[1(R)-ethoxycarbonyl-4-methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid hydrobromide as a white solid of melting point 220-221° (from ethanol/ethyl acetate).

Example 26

In an analogous manner to that described in Example 8, from 1 g of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-4-methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate there is obtained 0.74 g (70%) of 9(S)-[1(S)-ethoxycarbonyl-4-methylpentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylic acid hydrobromide as a white solid of melting point 209-210° (from ethanol/ethyl acetate).

Example 27

In an analogous manner to that described in Example 6, from 4.45 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 7.21 g of ethyl 4-(4-chlorophenyl)-2-oxo-butanoate there are obtained 2.13 g (27%) of tert.butyl 9(S)-[3-(4-chlorophenyl)-1(R)-ethoxycarbonylpropylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate in the form of white crystals of melting point 82-83° (from diethyl ether/n-hexane) and 1.49 g (19%) of tert.butyl 9(S)-[3-(4-chlorophenyl)-1(S)-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate as white crystals of melting point 86-88° (from diethyl ether/n-hexane).

Example 28

In an analogous manner to that described in Example 8, from 1.28 g of tert.butyl 9(S)-[3-(4-chlorophenyl)-1(S)-

-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate there is obtained 0.78 g (57%) of 9(S)-[3-(4-chlorophenyl)-1(S)--ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid as white crystals of melting point 224-225° (from ethanol/ethyl acetate).

Example 29

In an analogous manner to that described in Example 6, from 4.45 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 5.66 g of ethyl 4-(4-methoxyphenyl)-2-oxo-butanoate there are obtained 1.21 g (16%) of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-3-(4-methoxyphenyl)propylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as white crystals of melting point 73-74° (from diethyl ether/n-hexane) and 0.81 g (10%) of tert.butyl 9(S)-[1(S)--ethoxycarbonyl-3-(4-methoxyphenyl)propylamino]-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as white needles of melting point 100-101.5° (from diethyl ether/n-hexane).

Example 30

In an analogous manner to that described in Example 8, from 0.71 g of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-3-(4--methoxyphenyl)propylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate there is obtained 0.49 g (66%) of 9(S)-[1(S)-ethoxycarbonyl-3-(4--methoxyphenyl)propylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrobromide as a white solid of melting point 123-127° (from ethanol/ethyl acetate).

Example 31

In an analogous manner to that described in Example 6, from 4.45 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 8.46 g of ethyl 4-biphenylyl-2-oxo-butanoate there are obtained 1.83 g (22%) of tert.butyl 9(S)-[3-(4--biphenylyl)-1(R)-ethoxycarbonylpropylamino]-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as white crystals of melting point 136-139° (from diethyl ether) and 1.56 g (18%) of tert.butyl 9(S)--[3-(4-biphenylyl)-1(S)-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as white crystals of melting point 101-103° (from diethyl ether).

Example 32

In an analogous manner to that described in Example 8, from 1.36 g of tert.butyl 9(S)-[3-(4-biphenylyl)-1(S)--ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate there is obtained 0.63 g (45%) of 9(S)-[3-(4-biphenylyl)-1(S)--ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrobromide as a hygroscopic white solid.

Example 33

In an analogous manner to that described in Example 5, from 1.78 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate and 2.62 g of ethyl 2(R,S)-trifluoromethanesulphonyloxy-6--phthalimidohexanoate there are obtained 1.62 g (46%) of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-5-phthalimidopentyl-amino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate and 1.58 g (45%) of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-5-phthalimidopentylamino]-octa-hydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate, both in the form of pale yellowish oils.

Example 34

In an analogous manner to that described in Example 8, from 1.9 g of tert.butyl 9(S)-[1(R)-ethoxycarbonyl-5--phthalimidopentylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there are obtained 1.36 g (69%) of 9(S)-[1(R)-ethoxycarbonyl-5-phthalimido-pentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid hydrobromide as a white solid of melting point 207-208° (from ethanol/ethyl acetate).

Example 35

In an analogous manner to that described in Example 8, [from] 1.79 g of tert.butyl 9(S)-[1(S)-ethoxycarbonyl-5--phthalimidopentylamino]-octahydro-6,10-dioxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate there are obtained 1.36 g (74%) of 9(S)-[1(S)-ethoxycarbonyl-5-phthalimido-pentylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid hydrobromide as a white solid of melting point 227-229° (from ethanol/ethyl acetate).

Example 36

A solution of 1.15 g of tert.butyl 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]-

diazepine-1(S)-carboxylate and 3.10 g of ethyl 2-oxo-4--phenylbutanoate in 50 ml of ethanol is hydrogenated over 1.0 g of 10% palladium-on-carbon in the presence of molecular sieve at 4 atmospheres for 48 hours. The catalyst is filtered off and the filtrate is evaporated. The residue is chromatographed on silica gel, whereby there is obtained firstly 0.18 g of tert.butyl 8(S)-[1(R)--ethoxycarbonyl-3-phenylpropylamino]-2,3,6,7,8,9-hexahydro--5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1(S)--carboxylate as a pale yellowish oil and thereafter 0.19 g of tert.butyl 8(S)-[1(S)-ethoxycarbonyl-3-phenylpropyl-amino]-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo-[1,2-a][1,2]diazepine-1(S)-carboxylate as a pale yellowish oil.

The tert.butyl 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9--dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1(S)-carboxylate used as the starting material can be prepared as follows:

2.48 g of tert.butyl 2,3,6,7,8,9-hexahydro-5,9-dioxo--8(S)-phthalimido-1H,5H-pyrazolo[1,2-a][1,2]diazepine--1(S)-carboxylate [prepared as described in Example 3D)] are stirred at room temperature for half an hour in 80 ml of ethanol with 0.3 g of hydrazine hydrate. Thereafter, the reaction mixture is evaporated, 90 ml of 2N acetic acid are added, the mixture is stirred at room temperature for one hour and filtered. The filtrate is made basic with solid sodium carbonate and thereafter extracted twice with methylene chloride. The combined methylene chloride extracts are dried over magnesium sulphate and evaporated, whereby there are obtained 1.58 g (93%) of tert.butyl 8(S)-amino-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo-[1,2-a][1,2]diazepine-1(S)-carboxylate as a gum.

Example 37

A solution of 0.15 g of tert.butyl 8(S)-[1(S)-ethoxy-carbonyl-3-phenylpropylamino]-2,3,6,7,8,9-hexahydro-5,9--dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1(S)-carboxylate in 0.3 ml of acetic acid is treated at room temperature during half an hour with 1.3 ml of a 45% solution of hydrogen bromide in acetic acid. The mixture is thereafter evaporated and the residual oily solid is triturated with diethyl ether, whereby there is obtained 0.11 g (65%) of 8(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2,3,6,7,8,9--hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine--1(S)-carboxylic acid hydrobromide as a pale yellow-brown coloured solid of melting point 207-210°.

Example 38

1.27 g of benzyl 9(S)-amino-octahydro-10-oxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate, 1.36 g of

ethyl 2(R)-trifluoromethanesulphonyloxy-4-phenylbutanoate and 0.4 g of triethylamine in 10 ml of acetonitrile are stirred at room temperature for 16 hours. The solvent is evaporated and the residue is partitioned between water and ethyl acetate. The organic solution is dried over magnesium sulphate and evaporated. After purification by chromatography on silica gel using ethyl acetate/n-hexane (1:1) as the elution agent there are obtained 1.55 g of benzyl 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]--octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)--carboxylate as a colourless oil.

The benzyl 9(S)-amino-octahydro-10-oxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylate used as the starting material can be prepared as follows:

A) 2 g of α(S)-(3-bromopropyl)-1,3-dioxo-2-isoindoline-acetic acid in 15 ml of dry diethyl ether are stirred at room temperature for 1 1/2 hours with 1.34 g of phosphorus pentachloride. The solvent is evaporated and the residue is taken up twice in toluene and again evaporated and thereafter dissolved in 25 ml of methylene chloride. To this solution are added while stirring 1.64 g of tert.butyl 1-benzyloxycarbonyl-hexahydro-3-pyridazine-carboxylate in 10 ml of methylene chloride and thereafter 25 ml of saturated aqueous sodium bicarbonate solution. The reaction mixture is stirred at room temperature for 3 hours and thereafter the phases are separated. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and evaporated. After purification by chromatography on silica gel using toluene/acetonitrile (4:1) as the eluting agent there are obtained 2.4 g (75%) of 1-benzyl 3-tert.butyl 2-(5-bromo--2-phthalimidovaleryl)-1,3-pyridazinedicarboxylate (2 diastereomers) as an oil.

B) 2.37 g of 1-benzyl 3-tert.butyl 2-(5-bromo-2--phthalimidovaleryl)-1,3-pyridazinedicarboxylate (2 diastereomers) are dissolved in 25 ml of ethanol and the solution is hydrogenated at atmospheric pressure over 50 mg of 10% palladium-on-carbon until the hydrogen uptake has finished. The catalyst is filtered off and the filtrate is evaporated, whereby there are obtained 1.79 g (96%) of tert.butyl 2-(5-bromo-2-phthalimidovaleryl)-3--pyridazinecarboxylate (2 diastereomers) as an oil.

C) 15 g of tert.butyl 2-(5-bromo-2-phthalimidovaleryl)-3--pyridazinecarboxylate (2 diastereomers) are dissolved in 200 ml of dry dimethylformamide and the solution is stirred at 80° for 60 hours. The solvent is thereafter evaporated and the residue is partitioned between water and methylene chloride. The organic phase is dried over magnesium sulphate and evaporated. After purification of

the residue by chromatography on silica gel using toluene/acetic acid (4:1) as the elution agent there are obtained 3.6 g (33%) of octahydro-10-oxo-9(S)-phthalimido-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid as white crystals of melting point 256-258° (from ethyl acetate/n-hexane) and 1.4 g (13%) of octahydro-10-oxo--9(S)-phthalimido-6H-pyridazo[1,2-a][1,2]diazepine-1(R)--carboxylic acid as white crystals of melting point 241-244° (from ethyl acetate/n-hexane).

D) 3.57 g of octahydro-10-oxo-9(S)-phthalimido-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid are dissolved in 25 ml of 0.4M ethanolic sodium hydroxide solution and 0.5 g of hydrazine hydrate in 25 ml of ethanol is added. The mixture is stirred at room temperature for 4 hours and thereafter evaporated. 80 ml of 2N acetic acid are added, the mixture is stirred at room temperature for 3 hours and thereafter filtered. The filtrate is evaporated and the residue is added to a column of 40 g of Duolite C225 ion exchange resin (H^+ form). The column is eluted with water containing 2% pyridine and the eluate is evaporated, whereby there are obtained 1.7 g (75%) of 9(S)-amino-octahydro-10-oxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid as a white solid. After crystallization from water/acetonitrile the acid melts at 247-249° (dec.); $[\alpha]_D^{20}$ = -121.9° (c = 0.675% in water).

E) 1.6 g of 9(S)-amino-octahydro-10-oxo-6H-pyridazo-[1,2-a][1,2]diazepine-1(S)-carboxylic acid in 5 ml of methanol are treated with a solution of phenyldiazomethane in diethyl ether until the reaction has finished. The solvents are evaporated and the residue is partitioned between methylene chloride and 2N hydrochloric acid. The aqueous solution is made basic with potassium carbonate and extracted with methylene chloride. The organic solution is washed with sodium chloride solution, dried over magnesium sulphate and evaporated, whereby there are obtained 1.36 g of crude benzyl 9(S)-amino-octahydro-10--oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as an oil which is used without further purification.

Example 39

1.35 g of benzyl 9(S)-[1(S)-ethoxycarbonyl-3-phenyl-propylamino]-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate are dissolved in 20 ml of ethanol and the solution is hydrogenated at atmospheric pressure over 50 mg of 10% palladium-on-carbon until the uptake of hydrogen has finished. The catalyst is filtered off and the filtrate is evaporated, whereby there are obtained 1.02 g of 9(S)-[1(S)-ethoxycarbonyl-3-phenyl-propylamino]-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]-

diazepine-1(S)-carboxylic acid as a colourless oil. This oil is dissolved in 10 ml of ethyl acetate and 2 ml of 2.5N hydrogen chloride in ethyl acetate are added. 100 ml of diethyl ether are thereafter added and the mixture is stirred for one hour. The solid obtained is filtered off, whereby there is obtained 0.72 g (60%) of 9(S)-[1(S)--ethoxycarbonyl-3-phenylpropylamino]-octahydro-10-oxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid hydrochloride as a hygroscopic solid: $[\alpha]_D^{20} = -69.1°$ (c = 1% in water).

Example 40

In an analogous manner to that described in Example 4, from 1.10 g of tert.butyl 9(S)-amino-octahydro-6,10-dioxo--6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate, 1.40 g of ethyl 2-bromo-6-benzyloxyformamidohexanoate and 0.37 g of triethylamine there is obtained 0.4 g of tert.butyl 9(S)-[5-benzyloxyformamido-1(R)-ethoxycarbonylpentyl-amino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylate as a pale yellowish oil and 0.33 g of tert.butyl 9(S)-[5-benzyloxyformamido-1(S)--ethoxycarbonylpentylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate as a yellowish oil.

Example 41

By reacting tert.butyl 9(S)-[5-benzyloxyformamido--1(S)-ethoxycarbonylpentylamino]-octahydro-6,10-dioxo-6H--pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylate with trifluoroacetic acid there is obtained 9(S)-[5-benzyloxy-formamido-1(S)-ethoxycarbonylpentylamino]-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid.

The following Examples illustrate pharmaceutical compositions containing a compound in accordance with the invention:

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	per tablet
Compound of formula I	10.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg
Total weight	215.0 mg

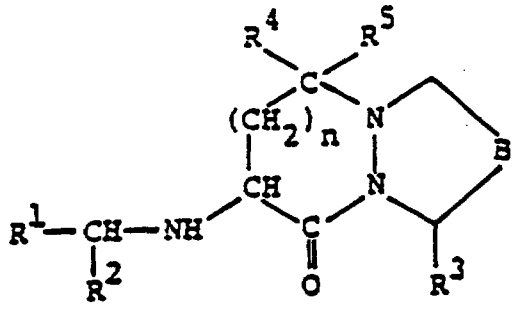
Example B

Capsules containing the following ingredients can be manufactured in an conventional manner:

Ingredients	per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg
Total weight	200.0 mg

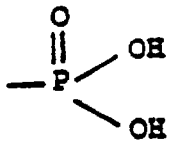
Claims

1. Compounds of the general formula



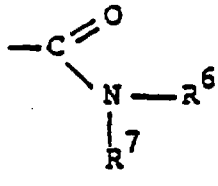
I

wherein B signifies methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$) or vinylene ($-CH=CH-$), R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylsulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl or a group of the formula



(i)

or



(ii)

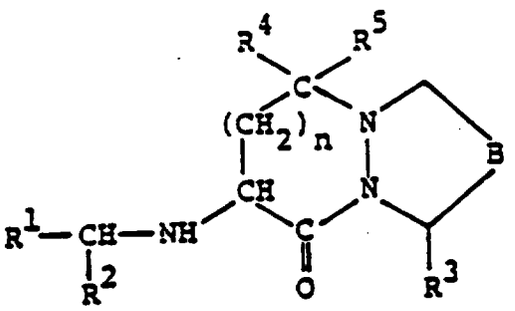
Example B

Capsules containing the following ingredients can be manufactured in an conventional manner:

Ingredients	per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg
Total weight	200.0 mg

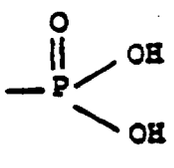
Claims

1. Compounds of the general formula



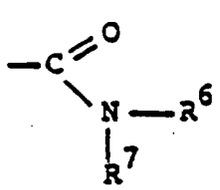
I

wherein B signifies methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$) or vinylene ($-CH=CH-$), R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylsulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl or a group of the formula



(i)

or



(ii)

R^3 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl, R^4 and R^5 each signify hydrogen or together signify an oxo group, R^6 and R^7 each signify hydrogen, alkyl or aralkyl and n signifies the number 2, whereby "aryl" signifies phenyl which is optionally mono- or multiply-substituted by halogen, alkyl, alkoxy, trifluoromethyl or phenyl and "alkyl" and "alkoxy" - alone or in combination - signify residues with 1-8 carbon atoms,
and pharmaceutically usable salts thereof.

2. Compounds according to claim 1, wherein R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylsulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl or alkoxycarbonyl or a group of formula (i) and R^3 signifies carboxyl or alkoxycarbonyl.

3. Compounds according to claim 1, wherein B signifies methylene or ethylene.

4. Compounds according to claim 1 or 3, wherein R^1 signifies alkyl, aralkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, aralkoxycarbonylaminoalkyl or arylaminocarbonylaminoalkyl.

5. Compounds according to claim 1, 3 or 4, wherein R^2 signifies carboxyl, alkoxycarbonyl, aralkoxycarbonyl or the group of formula (ii).

6. Compounds according to claim 1 or any one of claims 3-5, wherein R^3 signifies carboxyl.

7. Compounds according to claim 1 or any one of claims 3-6, wherein B signifies methylene or ethylene, R^1 signifies alkyl, aralkyl, aralkylcarbonylaminoalkyl, phthalimidoalkyl, aralkoxycarbonylaminoalkyl or arylaminocarbonylaminoalkyl, R^2 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii), R^3 signifies carboxyl and n signifies the number 2.

8. 9-(1-Carboxy-3-phenylpropylamino)-octahydro-6,10--dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

9. 9-(1-Ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylic acid.

10. 8-(1-Carboxy-3-phenylpropylamino)-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid.

11. 9-(1-Benzyloxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

12. 9-(1-Carbamoyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

13. 9-(1-Ethylcarbamoyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

14. 9-(1-Carboxy-4-phenylbutylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

15. 9-(1-Carboxy-2-phenylethylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

16. 9-(1-Carboxy-4-methylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

17. 9-(1-Ethoxycarbonyl-4-methylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

18. 9-[3-(4-Chlorophenyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylic acid.

19. 9-[1-Ethoxycarbonyl-3-(4-methoxyphenyl)propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]-diazepine-1-carboxylic acid.

20. 9-[3-(4-Biphenylyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

21. 9-(1-Ethoxycarbonyl-5-phthalimidopentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

22. 8-(1-Ethoxycarbonyl-3-phenylpropylamino)-2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a][1,2]diazepine-1-carboxylic acid.

23. 9-(1-Ethoxycarbonyl-3-phenylpropylamino)-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

24. 9-(5-Benzyloxyformamido-1-ethoxycarbonylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylic acid.

25. tert.Butyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-benzyloxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

methyl 9-(1-benzyloxycarbonyl-3-phenylpropylamino)--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

methyl 9-(1-carboxy-3-phenylpropylamino)-octahydro--6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

methyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

ethyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

tert.butyl 9-(1-carbamoyl-3-phenylpropylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

tert.butyl 9-(1-ethylcarbamoyl-3-phenylpropylamino)--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

tert.butyl 9-(1-ethoxycarbonyl-4-methylpentylamino)--octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1--carboxylate,

tert.butyl 9-[3-(4-chlorophenyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-[1-ethoxycarbonyl-3-(4-methoxyphenyl)-propylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-[3-(4-biphenylyl)-1-ethoxycarbonylpropylamino]-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

tert.butyl 9-(1-ethoxycarbonyl-5-phthalimidopentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate,

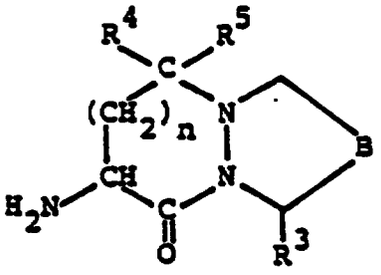
tert.butyl 8-(1-ethoxycarbonyl-3-phenylpropylamino)--2,3,6,7,8,9-hexahydro-5,9-dioxo-1H,5H-pyrazolo[1,2-a]-[1,2]diazepine-1-carboxylate,

benzyl 9-(1-ethoxycarbonyl-3-phenylpropylamino)-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate and

tert.butyl 9-(5-benzyloxyformamido-1-ethoxycarbonylpentylamino)-octahydro-6,10-dioxo-6H-pyridazo[1,2-a][1,2]diazepine-1-carboxylate.

26. A compound according to any one of claims 1-25, wherein the configuration at each asymmetric carbon atom is the S-configuration.

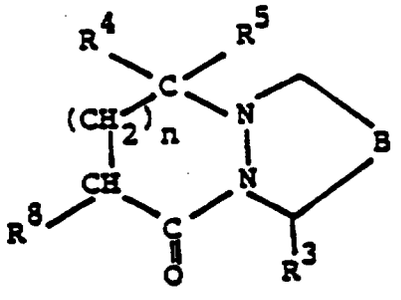
27. A compound of the general formula



IV

wherein B signifies methylene, ethylene or vinylene, R^3 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl, R^4 and R^5 each signify hydrogen or R^4 and R^5 together signify an oxo group and n signifies the number 2, whereby "aryl" signifies phenyl which is optionally mono- or multiply-substituted by halogen, alkyl, alkoxy, trifluoromethyl or phenyl and "alkyl" and "alkoxy" have 1-8 carbon atoms.

28. A compound of the general formula



XVIIa

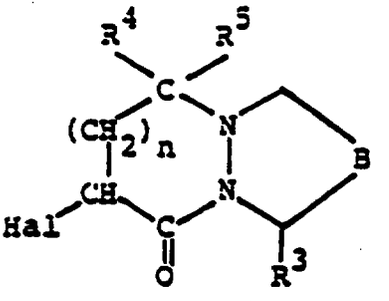
wherein B signifies methylene, ethylene or vinylene, R^3 signifies carboxyl, alkoxycarbonyl or aralkoxycarbonyl, R^4 and R^5 each signify hydrogen or R^4 and R^5 together signify an oxo group, R^8 signifies phthaloylamino and n signifies the number 2, whereby "aryl" signifies phenyl which is optionally mono- or multiply-substituted by halogen, alkyl, alkoxy, trifluoromethyl or phenyl and "alkyl" and "alkoxy" have 1-8 carbon atoms.

29. A compound according to any one of claims 1-26 or a pharmaceutically usable salt thereof as a pharmaceutically active substance.

30. A compound according to any one of claims 1-26 or a pharmaceutically usable salt thereof as an antihypertensive.

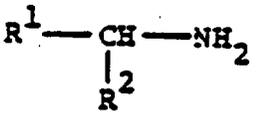
31. A process for the manufacture of compounds of formula I given in claim 1 and of pharmaceutically usable salts thereof, characterized by

a) reacting a compound of the general formula



II

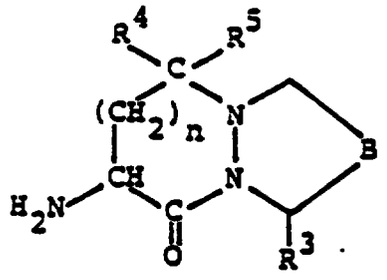
wherein B, R^3, R^4, R^5 and n have the significance given in claim 1 and Hal signifies halogen,
with a compound of the general formula



III

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

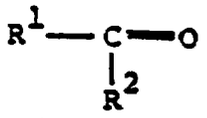
b) reductively alkylating a compound of the general formula



IV

wherein B, R^3, R^4, R^5 and n have the significance given in claim 1,

with a compound of the general formula

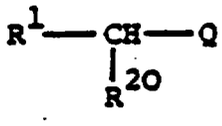


V

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

or

c) for the manufacture of compounds of formula I in which R^2 signifies alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii) and R^3 signifies alkoxycarbonyl or aralkoxycarbonyl, reacting a compound of formula IV above in which R^3 signifies alkoxycarbonyl or aralkoxycarbonyl with a compound of the general formula

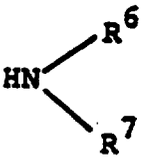


VI

wherein R^1 has the significance given in claim 1, R^{20} signifies alkoxycarbonyl or aralkoxycarbonyl or a group of formula (ii) and Q signifies a leaving group,

or

d) for the manufacture of compounds of formula I in which R^2 signifies a group of formula (ii) and R^3 signifies carboxyl or tert.butoxycarbonyl, reacting a compound of formula I in which R^2 signifies alkoxycarbonyl and R^3 signifies carboxyl or tert.butoxycarbonyl with a compound of the general formula



VII

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

or

e) for the manufacture of compounds of formula I in which B signifies ethylene, catalytically hydrogenating a compound of formula I in which B signifies vinylene, or

f) for the manufacture of compounds of formula I in which R^2 and/or R^3 signifies alkoxycarbonyl or aralkoxycarbonyl, esterifying a compound of formula I in which R^2 and/or R^3 signifies carboxyl, or

g) for the manufacture of compounds of formula I in which R^2 and/or R^3 signifies carboxyl, treating a compound of formula I in which R^2 and/or R^3 signifies alkoxycarbonyl with an acid or a base, or

h) for the manufacture of compounds of formula I in which B signifies methylene or ethylene and R^2 and/or R^3 signifies carboxyl, hydrogenating a compound of formula I in which R^2 and/or R^3 signifies aralkoxycarbonyl, or

i) for the manufacture of compounds of formula I in which R^1 signifies aminoalkyl, cleaving off the alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl group in a compound of formula I in which R^1 signifies alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl or aralkoxycarbonylaminoalkyl, and

j) if desired, separating a mixture of diastereomers obtained into the corresponding diastereomeric racemates or optically pure diastereomers and/or

k) if desired, resolving a racemate obtained into the two antipodes and

l) if desired, converting a compound of formula I obtained into a pharmaceutically usable salt.

32. A process according to claim 31, characterized in that a compound of formula I in which R^1 signifies hydrogen, alkyl, aralkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, aralkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylsulphonylaminoalkyl or arylsulphonylaminoalkyl, R^2 signifies carboxyl or alkoxycarbonyl or a group of formula (i) and R^3 signifies carboxyl or alkoxycarbonyl or a pharmaceutically usable salt thereof is manufactured according to process variants a), b), e), f), g), i), j), k) and/or l).

33. A medicament containing a compound according to any one of claims 1-26 or a pharmaceutically usable salt thereof.

34. An antihypertensive containing a compound according to any one of claims 1-26 or a pharmaceutically usable salt thereof.

35. The use of a compound according to any one of claims 1-26 or of a pharmaceutically usable salt thereof for the manufacture of an antihypertensive.

36. The use of 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]-diazepine-1(S)-carboxylic acid for the manufacture of an antihypertensive.