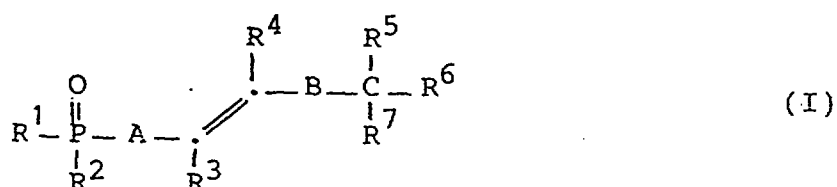


The invention relates to novel unsaturated amino acids, to salts thereof, to processes for the manufacture of these novel substances, to pharmaceutical compositions comprising these substances, and to the use of these substances and of compositions comprising them.

The compounds according to the invention are compounds of the formula I



in which the carbon-carbon double bond is in the trans-configuration and R¹ represents hydroxy or etherified hydroxy, R² represents hydrogen, alkyl, hydroxy or etherified hydroxy, R³ represents hydrogen, alkyl, haloalkyl, hydroxyalkyl, lower alkoxyalkyl, arylalkyl, lower alkenyl, halogen or aryl, R⁴ represents hydrogen, alkyl or aryl, R⁵ represents hydrogen or alkyl, R⁶ represents carboxy, esterified carboxy or amidated carboxy, R⁷ represents amino or amino substituted by alkyl or by acyl, A represents unsubstituted or alkyl-substituted α,ω-alkylene having from 1 to 3 carbon atoms, B represents a bond, and "lower" radicals contain up to and including 8 carbon atoms, and salts thereof.

The compounds of the formula I contain at least one chiral centre and may be in the form of enantiomers or enantiomeric mixtures, such as racemates, and if they contain more than one chiral centre, they may also be in the form of diastereoisomers or diastereoisomeric mixtures.

The carbon-carbon double bond of the compounds according to the invention is in the trans-configuration in relation to R³ and R⁴, or in relation to A and B, that is to say the compounds of the formula I are compounds of the E-series.

Compounds of the formula I in which R^2 represents hydrogen are phosphonous acids, those in which R^2 represents alkyl are phosphinic acids, and those in which R^2 represents hydroxy are phosphonic acids. In the names of the compounds of the formula I that are to be regarded as substituted carboxylic acids the prefixes "phosphino" (R^2 represents hydrogen), "phosphonyl" (R^2 represents alkyl) and "phosphono" (R^2 represents hydroxy) are used.

α,ω -Alkylene having from 1 to 3 carbon atoms is methylene, 1,2-ethylene or 1,3-propylene. α,ω -Alkylene substituted by alkyl is substituted at any position. Thus, methylene substituted by alkyl is, for example, 1,1-ethylene, 1,1-butylene or 1,1-octylene, 1,2-ethylene substituted by alkyl is, for example, 1,2-propylene, 1,2-butylene, 2,3-butylene, 1,2-pentylene or 1,2-nonylene, and 1,3-propylene substituted by alkyl is, for example, 1,3-butylene, 1,3-pentylene or 1,3-decylene.

Acyl-substituted amino R^7 may be acylamino or diacylamino. Alkyl-substituted amino R^7 is mono- or di-lower alkylamino.

In a corresponding acylamino group acyl is, for example, the acyl radical of an organic acid having, for example, up to 18 carbon atoms, especially of an alkane-carboxylic acid that is unsubstituted or substituted, for example by halogen, amino or by phenyl, or of a benzoic acid that is unsubstituted or substituted, for example by halogen, lower alkoxy or by nitro, or of a carboxylic acid semiester. Such acyl groups are, for example, lower alkanoyl, such as formyl, acetyl or propionyl, halo-lower alkanoyl, such as 2-haloacetyl, especially 2-fluoro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, aroyl, such as unsubstituted or substituted benzoyl, for example benzoyl, halobenzoyl, such as 4-chlorobenzoyl, lower alkoxybenzoyl, such as 4-methoxybenzoyl, or nitrobenzoyl, such as 4-nitrobenzoyl.

Especially suitable is also lower alkenyloxycarbonyl, for example allyloxycarbonyl, or lower alkoxycarbonyl that is unsubstituted or substituted in the 1- or 2-position, such as lower alkoxycarbonyl, for example methoxy- or ethoxy-carbonyl, unsubstituted or substituted benzyloxycarbonyl, for example benzyloxycarbonyl or 4-nitrobenzyloxycarbonyl, or aroylmethoxycarbonyl in which the aroyl group represents benzoyl that is unsubstituted or substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl or bromophenacyloxycarbonyl.

Acyl in a corresponding acylamino group may represent especially alkanoylamino substituted by amino and/or by phenyl, carbamoyl, carboxy, imidazolyl, lower alkylthio, tetrahydropyrrolyl, hydroxy, indolyl or by hydroxyphenyl, so that it is also to be understood as meaning, for example, the acyl radicals of amino acids, for example of the naturally occurring amino acids, such as alanine, asparagine, aspartic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine; also included are the acyl radicals of oligopeptides, for example di- or tri-peptides, such as oligopeptides made from alanine, asparagine or aspartic acid.

In a diacylamino group diacyl represents, for example, two acyl radicals as defined above, or diacyl is, for example, the acyl radical of an organic dicarboxylic acid having, for example, up to 12 carbon atoms, especially of a corresponding aromatic dicarboxylic acid, such as phthalic acid. Such a group is especially phthalimido.

Esterified carboxy is, for example, carboxy esterified by an aliphatic or araliphatic alcohol, such as an unsubstituted or substituted lower alkanol or phenyl-lower alkanol, such as corresponding lower alkoxy- or phenyl-lower alkoxy-carbonyl. Esterified carboxy is preferably pharmaceutically acceptable esterified carboxy, such as, for example, esterified carboxy that can be converted under physiological conditions into

carboxy. These esters of the formula I may also be called prodrug esters.

Carboxy esterified in a pharmaceutically acceptable manner represents preferably, for example, lower alkoxy-carbonyl; lower alkoxy-carbonyl substituted in a position higher than the α -position by amino, mono- or di-lower alkylamino or by hydroxy; lower alkoxy-carbonyl substituted by carboxy, for example α -carboxy-substituted lower alkoxy-carbonyl; lower alkoxy-carbonyl substituted by lower alkoxy-carbonyl, for example α -lower alkoxy-carbonyl-substituted lower alkoxy-carbonyl, aryl-lower alkoxy-carbonyl, for example unsubstituted or substituted benzyloxy-carbonyl, or pyridylmethoxy-carbonyl; lower alkanoyloxy-substituted methoxy-carbonyl, for example pivaloyloxymethoxy-carbonyl; lower alkoxy-methoxy-carbonyl substituted by lower alkanoyloxy or by lower alkoxy; bicyclo[2.1.1]heptyloxy-carbonyl-substituted methoxy-carbonyl, such as bornyloxy-carbonylmethoxy-carbonyl; 3-phthalidoxycarbonyl; 3-phthalidoxycarbonyl substituted by lower alkyl, lower alkoxy or by halogen; or lower alkoxy-carbonyloxy-lower alkoxy-carbonyl, for example 1-(methoxy- or ethoxy-carbonyloxy)ethoxy-carbonyl.

Especially preferred prodrug esters are, for example, lower alkyl esters having up to four carbon atoms, such as, for example, butyl or ethyl esters, lower alkanoyloxymethyl esters, such as, for example, pivaloyloxymethyl ester, lower alkyl esters that are substituted in a position higher than the α -position by di-lower alkylamino and have from two to four carbon atoms in each lower alkyl group, such as, for example, 2-diethyl-aminoethyl ester, and pyridylmethyl esters, such as 3-pyridylmethyl ester.

In amidated carboxy the amino group represents, for example, amino that is unsubstituted or monosubstituted by hydroxy or mono- or di-substituted by aliphatic radicals, such as amino, hydroxyamino, mono- or di-lower alkylamino or lower alkyleneamino having from 5 to 7 ring members. Amidated carboxy is preferably pharmaceutically

acceptable amidated carboxy, such as, for example, amidated carboxy that can be converted under physiological conditions into carboxy.

Preferred pharmaceutically acceptable amides are compounds of the formula I in which the carboxy group is in the form of carbamoyl, lower alkylcarbamoyl, for example ethylcarbamoyl, di-lower alkylcarbamoyl, for example diethylcarbamoyl, or in the form of di-lower alkylamino-lower alkylcarbamoyl, for example in the form of (2-diethylaminoethyl)carbamoyl or in the form of (3-diethylaminopropyl)carbamoyl.

Etherified hydroxy is, for example, hydroxy etherified by an aliphatic alcohol, such as hydroxy etherified by a lower alkanol, lower alkenol or lower alkinol each of which is unsubstituted or substituted by halogen or in a position higher than the α -position by hydroxy, oxo, lower alkoxy, lower alkanoyloxy and/or by mono- or di-lower alkylamino, and represents, for example, lower alkoxy, halo-lower alkoxy, or corresponding hydroxy-, oxo-, lower alkoxy-, lower alkanoyloxy- or mono- or di-lower alkylamino-lower alkoxy. Compounds in which R^1 and/or R^2 represents etherified hydroxy are esters of the phosphoric acid group and, depending on the meaning of R^2 , are phosphonous acid esters, phosphinic acid esters or phosphonic acid esters. Preferred esters are the lower alkyl esters and hydroxy-lower alkyl esters.

Salts of compounds according to the invention are especially pharmaceutically acceptable non-toxic salts of compounds of the formula I. Such salts are formed, for example, from the carboxy group present in compounds of the formula I, and are especially metal or ammonium salts, such as alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and also ammonium salts with ammonia or suitable organic amines, such as lower alkylamines, for example methylamine, diethylamine or triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethyl-

amine, bis-(2-hydroxyethyl)-amine, tris-(hydroxymethyl)-methyllamine or tris-(2-hydroxyethyl)-amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, lower alkylenediamines, for example ethylenediamine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, benzyltrimethylammonium hydroxide, dibenzylamine or N-benzyl-3-phenylethylamine. Compounds of the formula I having a primary or secondary amino group may also form acid addition salts, for example with preferably pharmaceutically acceptable inorganic acids, such as hydrohalic acids, for example hydrochloric acid or hydrobromic acid, sulphuric acid, nitric acid or phosphoric acid, or with suitable organic carboxylic or sulphonc acids, for example acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, fumaric acid, maleic acid, tartaric acid, oxalic acid, citric acid, pyruvic acid, benzoic acid, mandelic acid, malic acid, ascorbic acid, pamoic acid, nicotinic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, benzenesulphonic acid, 4-toluenesulphonic acid or naphthalenesulphonic acid.

It is possible to use also pharmaceutically unsuitable salts for isolation or purification. Only the pharmaceutically acceptable non-toxic salts are used therapeutically, and these are therefore preferred.

Aryl, also in definitions such as aroyl or aryl-lower alkoxy-carbonyl, represents aromatic hydrocarbon radicals which are unsubstituted or substituted by lower alkyl, hydroxy, protected hydroxy, lower alkoxy, halogen, amino, halo-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl or by nitro, and is, for example, unsubstituted or correspondingly substituted 1- or 2-naphthyl, but preferably unsubstituted or correspondingly substituted phenyl, such as phenyl, lower alkylphenyl, for example methylphenyl, hydroxyphenyl, halophenyl, for example 4-

halophenyl, such as 4-chlorophenyl, benzyloxyphenyl, lower alkoxyphenyl, for example methoxyphenyl, hydroxymethylphenyl, aminomethylphenyl or nitrophenyl.

The general terms used hereinbefore and hereinafter, unless defined otherwise, have the following meanings:

The term "lower" indicates that correspondingly defined groups or compounds contain up to and including 8, preferably up to and including 4, carbon atoms.

Alkyl represents, for example, lower alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert.-butyl, and also n-pentyl, n-hexyl, n-heptyl or n-octyl, preferably methyl, but may also represent C₉-C₁₂-alkyl, such as nonyl, decyl, undecyl or dodecyl.

Arylalkyl represents, for example aryl-lower alkyl in which aryl has the meanings given hereinbefore, and is especially, for example, unsubstituted phenyl-lower alkyl, such as benzyl or 1- or 2-phenylethyl.

Lower alkenyl contains preferably up to 6 carbon atoms and is bonded by way of an sp³-hybridised carbon atom, and may be, for example, 2-propenyl, 2- or 3-butenyl or 3-pentenyl, but may also be vinyl.

Lower alkoxy represents especially methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert.-butoxy.

Halogen preferably has an atomic number of up to 35 and is especially chlorine, also fluorine or bromine, but may also be iodine.

Protected hydroxy is hydroxy that is esterified, for example hydroxy esterified in the form of an acyl group, such as lower alkanoyloxy, benzyloxycarbonyloxy or lower-alkoxycarbonyloxy, or etherified hydroxy, for example 2-tetrahydropyranyloxy or benzyloxy, and also lower alkoxy.

Halo-lower alkyl is, for example, halomethyl, such as fluoromethyl, trifluoromethyl or 1- or 2-chloroethyl.

Hydroxy-lower alkyl is, for example, mono- or di-hydroxy-lower alkyl, carries the hydroxy group(s),

for example, especially in a position higher than the α -position and represents, for example, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy- or 2,3-dihydroxy-propyl, 4-hydroxy- or 2,4-dihydroxy-butyl, or 5-hydroxy-, 2,5-dihydroxy- or 3,5-dihydroxy-pentyl.

Lower alkoxy-lower alkyl is, for example, mono- or di-lower alkoxy-lower alkyl, carries the lower alkoxy group(s), for example, especially in a position higher than the α -position and is, for example, 2-methoxy-, 2-ethoxy-, 2-propoxy- or 2-isopropoxy-ethyl, 3-methoxy- or 3-ethoxy-propyl or 3,3-dimethoxy-, 3,3-diethoxy-, 2,3-dimethoxy- or 2,3-diethoxy-propyl or 4,4-dimethoxy-butyl, and also methoxy-, ethoxy-, dimethoxy-, or propoxy- or isopropoxy-methyl.

Amino-lower alkyl is, for example, aminomethyl or 1- or 2-aminoethyl.

Lower alkanoyloxy is, for example, acetoxy, propionyloxy or butyryloxy, or also formyloxy or pivaloyloxy.

Lower alkoxycarbonyl is, for example, methoxycarbonyl or ethoxycarbonyl.

Aryl-lower alkoxycarbonyl is preferably phenyl-lower alkoxycarbonyl, for example benzyloxycarbonyl or 1- or 2-phenylethoxycarbonyl.

Mono- or di-lower alkylamino is, for example, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino or butylamino.

From Agric. Biol. Chem. 40, 1905-6 (1976), Agric. Biol. Chem. 41, 573-9 (1977) and JP-A1-78/87 (see Chem. Abstr. 89: 195402a (1978)); Z-(D)-2-amino-5-phosphono-3-pentenoic acid and its carboxamide were already known as a peptide component of the antibiotic tripeptides plumburnycin A and B. Furthermore, it was also known, for example from US-PS-4,483,853 and GB-A-2,104,079, that aliphatic 2-amino- ω -phosphono-carboxylic acids antagonise N-methyl-D-aspartic acid (NMDA)-sensitive excitatory amino acid receptors. Specifically, 2-amino-7-phosphono-

4-heptenoic acid was also previously known from GB-A-2,104,079.

The invention is based on the discovery that the compounds of the present invention are active and selective antagonists of N-methyl-D-aspartic acid (NMDA)-sensitive excitatory amino acid receptors in mammals. They are therefore suitable for the treatment of diseases that respond to a blocking of NMDA-sensitive receptors, such as, for example, cerebral ischaemia, muscular spasms (spasticity), convulsions (epilepsy), conditions of anxiety or manic conditions.

These advantageous effects may be demonstrated in in vitro or in in vivo test arrangements. For these, preferably mammals are used, for example mice, rats or monkeys, or tissue or enzyme preparations of such mammals. The compounds may be administered enterally or parenterally, preferably orally; or subcutaneously, intravenously or intraperitoneally, for example in gelatin capsules or in the form of aqueous suspensions or solutions. The dosage to be used in vivo may range from 0.1 to 600 mg/kg, preferably from 1 to 300 mg/kg. In vitro, the compounds may be used in the form of aqueous solutions, the concentrations ranging from 10^{-4} to 10^{-8} molar solutions.

The inhibiting action on the NMDA-sensitive excitatory amino acid receptors may be determined in vitro by measuring, in accordance with G. Fagg and A. Matus, Proc. Nat. Acad. Sci., USA, 81, 6876-80 (1984), to what extent the bonding of L-³H-glutamic acid to NMDA-sensitive receptors is inhibited. In vivo, the inhibiting action on NMDA-sensitive excitatory amino acid receptors may be demonstrated by the inhibition in mice of NMDA-induced convulsions.

The anti-convulsive properties of the compounds according to the invention may furthermore be shown by their effectiveness in preventing audiogenically induced

attacks in DBA/2 mice (Chapman et al., Arzneimittelforsch. 34, 1261, 1984).

The anti-convulsive properties may furthermore be shown by the effectiveness of the compounds according to the invention as electric shock antagonists in mice or in rats.

An indication of the anxiolytic activity of the compounds of the present invention is given by their pronounced effectiveness in the conflict model according to Cook/Davidson (Psychopharmacologia 15, 159-168 (1968)).

The pronounced effectiveness of the compounds of the formula I depends to a surprisingly high extent on the configuration at the double bond. For example, the racemate of D-2-amino-5-phosphono-3-cis-pentenoic acid known from Agric. Biol. Chem. 41, 573-579 (1979), B.K. Park et al., proves, for example in its ability to bond to the NMDA-sensitive receptor, to be far inferior to the racemate of the 2-amino-5-phosphono-3-trans-pentenoic acid according to the invention (in the Examples these compounds are referred to as compounds of the "E-series").

Preferred are compounds of the formula I in which R³ represents hydrogen, alkyl or aryl.

Also preferred are the compounds of the formula I in which R¹ represents hydroxy, lower alkoxy or hydroxy-lower alkoxy, R² represents hydrogen, alkyl, hydroxy, lower alkoxy or hydroxy-lower alkoxy, R³ represents hydrogen, lower alkyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyl-lower alkyl that is unsubstituted or substituted in the phenyl moiety, lower alkenyl, halogen, or unsubstituted or substituted phenyl, R⁴ represents hydrogen, lower alkyl or unsubstituted or substituted phenyl, R⁵ represents hydrogen or lower alkyl, R⁶

represents carboxy or pharmaceutically acceptable esterified or amidated carboxy, R^7 represents amino, mono- or di-lower alkylamino, alkanoylamino or alkanoylamino substituted by halogen, by amino and/or by phenyl, carbamoyl, carboxy, imidazolyl, lower alkylthio, tetrahydropyrrolyl, hydroxy, indolyl or by hydroxyphenyl, benzoylamino or benzoylamino substituted by halogen, lower alkoxy or by nitro, or phthalimino, A represents unsubstituted or lower alkyl-substituted α,ω -alkylene having from 1 to 3 carbon atoms and B represents a bond, wherein the substituents of phenyl are selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen, amino, halo-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl and nitro, and pharmaceutically acceptable salts thereof.

Also preferred are compounds of the formula I in which R^1 to R^5 are as defined above, R^6 represents carboxy, alkoxycarbonyl, or alkoxycarbonyl substituted by amino, mono- or di-lower alkylamino, hydroxy or by lower alkanoyloxy, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, and A and B are as defined above, and pharmaceutically acceptable salts thereof.

Likewise preferred are compounds of the formula I in which R^1 , R^2 , R^5 to R^7 and A and B are as defined immediately above and in which R^3 and R^4 , independently of one another, each represents hydrogen, lower alkyl, phenyl, or phenyl substituted by lower alkyl, hydroxy, lower alkoxy, halogen, amino, halo-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl or by nitro, and pharmaceutically acceptable salts thereof.

Especially preferred are compounds of the formula I in which R^1 represents hydroxy or lower alkoxy, R^2 represents hydrogen, alkyl, hydroxy or lower alkoxy, R^3 represents hydrogen, lower alkyl, phenyl, halophenyl, or phenyl-lower alkyl, R^4 and R^5 represent hydrogen

or lower alkyl, R^6 represents carboxy, alkoxycarbonyl or hydroxy-lower alkoxycarbonyl, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, A represents unsubstituted or lower alkyl-substituted α,ω -alkylene having from 1 to 3 carbon atoms and B represents a bond, and pharmaceutically acceptable salts thereof.

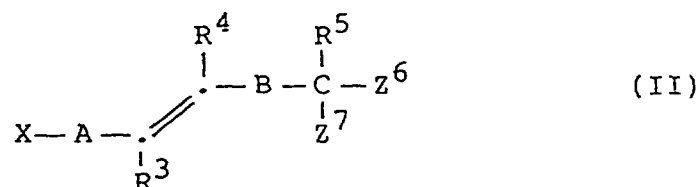
Especially preferred are compounds of the formula I in which R^1 is hydroxy, R^2 represents hydrogen, alkyl or hydroxy, R^3 represents hydrogen, lower alkyl or halophenyl, R^4 represents hydrogen or halophenyl and R^5 represents hydrogen, R^6 represents carboxy, lower alkoxycarbonyl or hydroxy-lower alkoxycarbonyl, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, A represents α,ω -alkylene having from 1 to 3 carbon atoms and B represents a bond, and pharmaceutically acceptable salts thereof.

Most especially preferred are compounds of the formula I in which R^1 is hydroxy, R^2 represents hydrogen, lower alkyl or hydroxy, R^3 represents hydrogen or lower alkyl, R^4 and R^5 represent hydrogen, R^6 represents carboxy or lower-alkoxycarbonyl, R^7 represents amino or mono-lower alkylamino, A represents α,ω -alkylene having from 1 to 3 carbon atoms and B represents a bond, and pharmaceutically acceptable salts thereof.

Outstanding are the compounds of the formula I in which R^1 and R^2 represent hydroxy, R^3 represents hydrogen or lower alkyl, R^4 and R^5 represent hydrogen, R^6 represents carboxy, R^7 represents amino, A represents methylene and B represents a bond, and the carboxylic acid lower alkyl esters and pharmaceutically acceptable salts thereof, especially the R-enantiomers thereof with reference to the atom carrying the amino group.

The compounds of the present invention may be manufactured in a manner known per se, for example as follows:

a) a compound of the formula II

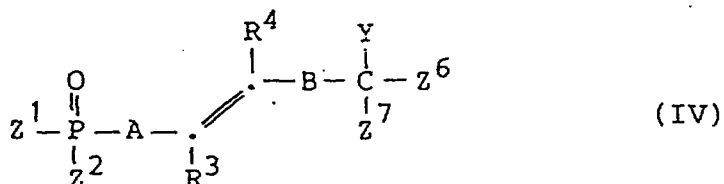


in which R^3 , R^4 , R^5 , A and B are as defined for formula I, Z^6 has the meaning of R^6 or represents protected carboxy, Z^7 has the meaning of R^7 or represents protected amino and X represents reactive esterified hydroxy, is reacted with a compound of the formula III



in which Z^1 has the meaning of R^1 or represents protected hydroxy, Z^2 has the meaning of R^2 or represents protected hydrogen or protected hydroxy, and R represents an etherifying group, or

b) in order to obtain a compound of the formula I in which R^5 represents hydrogen, in a compound of the formula IV



in which R^3 , R^4 , A and B are as defined for formula I, Z^1 has the meaning of R^1 or represents protected hydroxy, Z^2 has the meaning of R^2 or represents protected hydroxy or protected hydrogen, Z^6 has the meaning of R^6 or represents protected carboxy, Z^7 has the meaning of R^7 or represents protected amino,

and Y represents an optionally esterified carboxy group that can be replaced by hydrogen, the group Y is replaced by hydrogen, and any protected functional groups that may be present in a compound resulting from one of the preceding processes are freed and, if desired, a resulting compound of the formula I is converted into a different compound of the formula I and/or, if desired, a resulting compound of the formula I is converted into a salt or a resulting salt is converted into a different salt or into a free compound of the formula I and/or, if desired, an optical isomer is isolated from a mixture of stereoisomeric forms of a resulting compound of the formula I or of a salt thereof.

In the above-defined processes, protected hydroxy and protected amino have, for example, the meanings for protected hydroxy and for acyl-substituted amino given hereinbefore; here, protected hydroxy represents especially lower alkoxy and a protected amino represents especially lower alkanoylamino. Another preferred example of protected hydroxy is trisubstituted silyl, such as tri-lower alkylsilyl, for example trimethylsilyl or tert.-butyldimethylsilyl.

Furthermore, protected amino may also be amino substituted by substituted lower alkoxycarbonyl, such as amino substituted by 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, or by 2-(tris-substituted silyl)-ethoxycarbonyl, such as 2-tri-lower alkylsilylethoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or by 2-triarylsilylethoxycarbonyl, such as 2-triphenylsilylethoxycarbonyl, or etherified mercaptoamino or silylamino, or may be in the form of an enamino, nitro or azido group.

An etherified mercaptoamino group is especially a phenylthioamino group optionally substituted by lower alkyl, such as methyl or tert.-butyl, lower alkoxy,

such as methoxy, halogen, such as chlorine or bromine, and/or by nitro, or a pyridylthioamino group. Corresponding groups are, for example, 2- or 4-nitrophenylthioamino or 2-pyridylthioamino.

A silylamino group is especially an organic silylamino group. In such groups the silicon atom contains as substituent(s) preferably lower alkyl, for example methyl, ethyl, n-butyl or tert.-butyl, also aryl, for example phenyl. Suitable silyl groups are especially tri-lower alkylsilyl, especially trimethylsilyl or dimethyl-tert.-butylsilyl.

Enamino groups contain at the double bond in the 2-position an electron-attracting substituent, for example a carbonyl group. Protecting groups of this kind are, for example, 1-acyl-lower alk-1-en-2-yl radicals in which acyl is, for example, the corresponding radical of a lower alkanecarboxylic acid, for example acetic acid, of a benzoic acid optionally substituted, for example, by lower alkyl, such as methyl or tert.-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester, for example methyl semiester or ethyl semiester, and lower alk-1-ene is especially 1-propene. Corresponding protecting groups are especially 1-lower alkanoyl-prop-1-en-2-yl, for example 1-acetyl-prop-1-en-2-yl, or 1-lower alkoxy-carbonyl-prop-1-en-2-yl, for example 1-ethoxy-carbonyl-prop-1-en-2-yl.

Protected carboxy is customarily protected in esterified form, it being possible for the ester group to be removed under reductive, such as hydrogenolytic, or solvolytic, such as acidolytic or hydrolytic, such as acid-hydrolytic, basic-hydrolytic or neutral-hydrolytic, conditions. A protected carboxy group may furthermore be an esterified carboxy group that can be cleaved under physiological conditions or that can readily be converted into a different functionally modified carboxy group, such as into a different esterified carboxy group.

Such esterified carboxy groups contain as esterifying groups especially lower alkyl groups that are branched in the 1-position or suitably substituted in the 1- or 2-position. Preferred carboxy groups in esterified form are, inter alia, lower alkoxy-carbonyl, for example methoxycarbonyl, ethoxycarbonyl, 2-propoxycarbonyl or tert.-butoxycarbonyl, and (hetero)aryl-methoxycarbonyl having from 1 to 3 aryl radicals or having one monocyclic heteroaryl radical, these optionally being mono- or poly-substituted, for example, by lower alkyl, such as tert.-lower alkyl, for example tert.-butyl, halogen, for example chlorine, and/or by nitro. Examples of such groups are benzyl-oxy-carbonyl that is optionally substituted, for example in the manner mentioned above, for example 4-nitro-benzyloxycarbonyl, diphenylmethoxycarbonyl that is optionally substituted, for example in the manner mentioned above, for example diphenylmethoxycarbonyl, or triphenylmethoxycarbonyl, or picolyloxycarbonyl that is optionally substituted, for example in the manner mentioned above, for example 4-picolyloxycarbonyl, or furfuryloxycarbonyl, such as 2-furfuryloxycarbonyl.

Protected hydrogen Z¹ is protected in a manner known per se, such as is described, for example, in EP-A-0 009 348. Corresponding protecting groups are preferably groups of the formula $-C(C_{1-4}\text{-alkyl})(OR^a)OR^b$, preferably groups of the formula $-CH(OR^a)OR^b$ in which R^a and R^b each represents C₁₋₄-alkyl. Especially suitable is the group $-CH(OC_2H_5)_2$.

A reactive esterified hydroxy group, such as X, is a hydroxy group esterified by a strong organic acid, for example a hydroxy group esterified by an aliphatic or aromatic sulphonic acid (such as a lower alkane-sulphonic acid, especially methanesulphonic acid, trifluoromethanesulphonic acid, especially benzene-sulphonic acid, p-toluenesulphonic acid, p-bromo-benzenesulphonic acid and p-nitrobenzenesulphonic

acid) or by a strong inorganic acid, such as, especially, sulphuric acid, or a hydrohalic acid, such as hydrochloric acid or, most preferably, hydriodic acid or hydrobromic acid.

In process a), the etherifying group R is, for example, phenyl-lower alkyl, trisubstituted silyl, such as tri-lower alkylsilyl or, preferably, alkyl. The reaction is carried out in a manner known per se, especially under the known conditions of the Michaelis-Arbuzov reaction.

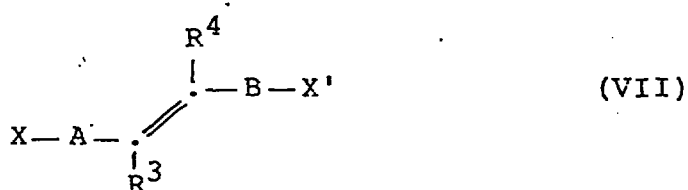
According to one variant of this process the reaction, for example, of a trialkyl phosphite of the formula III, such as triethyl phosphite, especially with compounds of the formula II in which A represents a bond, can be catalysed in a suitable manner, such as by a halide of a metal of sub-group VIII, preferably a nickel, palladium or platinum halide, especially nickel chloride.

In this process, if several of the groups Z^1 , Z^2 , Z^6 and Z^7 represent protected groups, these are advantageously so selected that they can be freed in a single step. The conditions in question under which the protected groups can be freed are preferably hydrolytic conditions, such as those of an acidic hydrolysis, for example with hydrohalic acids, such as hydrochloric acid, preferably with heating.

Working up is carried out in a manner known per se, especially two purification operations proving advantageous. Either the crude product can be converted into a readily volatile derivative, for example by silylation, and obtained as such by distillation, and can then be desilylated, or the crude product may have added to it an agent that reacts with excess acid, such as hydrohalic acid, and thus removes the acid. There come into consideration, for example, compounds to which a corresponding acid may be added, for example lower alkylene oxides (epoxides), such as propylene oxide.

It is preferable to carry out this process with compounds of the formulae II and III in which R^3 , R^4 , R^5 , A and B are as defined for formula I, z^1 represents protected hydroxy, z^2 represents lower alkyl, protected hydrogen or protected hydroxy, R represents lower alkyl, z^6 represents protected carboxy, z^7 represents protected amino and X represents reactive esterified hydroxy and, following the reaction in which the compound RX becomes free, to free the protected groups. In this case preferably z^1 represents lower alkoxy, z^2 represents lower alkyl, di-lower alkoxy-lower alkyl or lower alkoxy, R represents lower alkyl, z^6 represents lower alkoxy-carbonyl, z^7 represents formylamino and X represents halogen.

The compounds of the formula II may be manufactured, for example, by reacting N-protected amino-malonic acid esters in a manner known per se with compounds of the formula VII

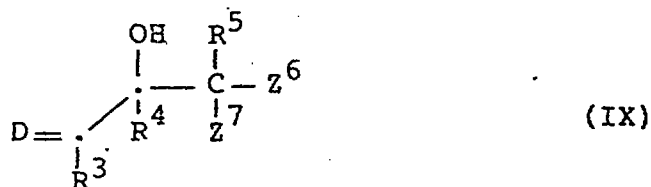


in which X and X', independently of one another, each represents reactive esterified hydroxy. The resulting compounds II' may be converted into compounds of the formula II by being decarboxylated, for example in the manner described in process b).

The starting compounds of the formula III are preferably trialkyl phosphites (z^1 = alkoxy, z^2 = alkoxy, R = alkyl) or alkylphosphonous acid dialkyl esters (z^1 = alkoxy, z^2 = alkyl, R = alkyl). They are known or can be manufactured in a manner analogous to known processes.

Compounds of the formula II in which A represents methylene optionally substituted by alkyl, B represents

a bond, X represents halogen and z^7 represents formylamino may be manufactured, for example, by reacting an α,β -unsaturated aldehyde, for example acrolein or methacrolein, with an α -isocyanoacetic acid derivative, such as, for example, an α -isocyanoacetic acid lower alkyl ester. By suitable catalysis, such as with low-valency metal salts, for example metal oxides or metal halides, such as zinc chloride, cadmium chloride, silver oxide or, preferably, copper oxide, 5-vinyl-2-oxazoline-4-carboxylic acid derivatives, for example esters, are thus obtained in a manner known per se and may be converted into the open-chained compounds of the formula IX



in which D represents methyldiene optionally substituted by alkyl. These compounds may in turn be converted by selective halogenation, such as bromination or chlorination, preferably while cooling, and with displacement of the double bond in the manner of an allylic rearrangement, into compounds of the formula II.

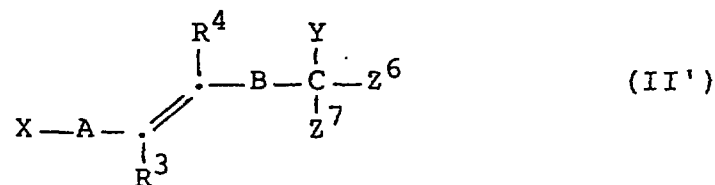
In process b), the group Y represents carboxy or esterified carboxy as defined hereinbefore, especially lower alkoxy carbonyl. Replacement of the group Y by hydrogen can be carried out, for example, under conditions under which first esterified carboxy is hydrolysed and then carboxy is replaced by hydrogen (decarboxylation), such as under hydrolytic conditions, such as those of an acidic hydrolysis, for example with hydrohalic acids, such as with hydrochloric acid, preferably while heating. In this process, if several of the groups z^1 , z^2 , z^6 and z^7 represent protected groups, these may advantageously be so selected that they can be freed together in the step in which the

hydrolysis and the decarboxylation is effected.

The replacement of the group Y by hydrogen can also be carried out without previous hydrolysis, as a dealkoxycarbonylation, for example according to A.P. Krapcho, Tetrahedron Letters 957 (1973), such as by heating in an aqueous aprotic solvent, such as dimethyl sulphoxide, in the presence of an alkali halide, such as sodium chloride.

It is preferable to carry out this process with compounds of the formula IV in which R^3 , R^4 , A and B are as defined for formula I, z^1 represents protected hydroxy, z^2 represents lower alkyl, protected hydrogen or protected hydroxy, z^6 represents protected carboxy, z^7 represents protected amino and Y represents an optionally esterified carboxy group that can be replaced by hydrogen, and for the protected groups to be freed together in the step in which the group Y is replaced by hydrogen. In this case preferably z^1 represents lower alkoxy, z^2 represents lower alkyl, di-lower alkoxy-lower alkyl or lower alkoxy, z^6 and Y represent lower alkoxycarbonyl and z^7 represents lower alkanoylamino.

The compounds of the formula IV may be manufactured, for example, analogously to process a) by reacting a compound of the formula II'



with a compound of the formula III



in which all radicals have the meanings given hereinbefore. The compounds of the formula II' may in turn be manufactured from a compound of the formula VII and an N-protected aminomalonic acid ester, as described in process a).

To convert a resulting compound of the formula I into a different compound of the formula I conversions such as the following may be carried out:

An amino group may be alkylated, and/or free carboxy may be freed from its esterified form by hydrolysis or hydrogenolysis and/or an amino group may be acylated and/or free carboxy may be esterified or amidated and/or hydroxy bonded to phosphorus may be esterified.

To convert an amino group into an alkylamino group the amino group may be alkylated by substitution, for example with a reactive esterified alkanol, such as an alkyl halide, or by reduction, such as with an aldehyde or ketone, and also catalytically activated hydrogen or, in the case of formaldehyde, advantageously with formic acid as reducing agent.

Free carboxylic acids of the formula I or salts thereof may be converted according to known processes into the corresponding esters by suitable alcohols or corresponding derivatives thereof, that is to say, into compounds of the formula I that are, for example, in the form of lower alkyl, aryl-lower alkyl, lower alkanoyloxymethyl, or lower alkoxycarbonyl-lower alkyl esters.

For the esterification, a carboxylic acid may be reacted directly with a diazoalkane, especially diazomethane, or with a corresponding alcohol in the presence of a strongly acidic catalyst (for example a hydrohalic acid, sulphuric acid or an organic sulphonic acid) and/or of a dehydrating agent (for example dicyclohexyl carbodiimide). Alternatively, the carboxylic acid may be converted into a reactive

derivative, such as into a reactive ester, or into a mixed anhydride, for example with an acid halide (for example, especially an acid chloride), and, this activated intermediate is reacted with the desired alcohol. Esterification of hydroxy bonded to phosphorus may be carried out in the manner described hereinbefore or in another manner that is known per se.

Compounds of the formula I in which R⁷ represents amino may be converted into compounds in which R⁷ represents acylamino, for example using a corresponding acid anhydride or halide, or vice versa, by processes belonging to the State of the Art and described herein in connection with protecting groups.

The above reactions are carried out according to standard methods in the presence or absence of diluents, preferably those that are inert towards the reagents and are solvents therefor, of catalysts, condensation agents and the other agents and/or in inert atmosphere, at low temperature, room temperature or elevated temperature, preferably at the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention includes furthermore those variants of the present process in which an intermediate obtainable at any stage of that process is used as starting material and the remaining steps are carried out, or the process is interrupted at any stage, or in which the starting materials are formed under the reaction conditions or in which the reactants are used in the form of their salts or optically pure antipodes. There should especially be used in these reactions those starting materials that result in the formation of the compounds mentioned hereinbefore as being especially valuable.

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

Depending on the choice of starting materials and

methods, the novel compounds may be in the form of one of the possible optical isomers or mixtures thereof, for example depending on the number of asymmetric carbon atoms they may be in the form of pure optical isomers, such as antipodes, or mixtures of optical isomers, such as racemates, or mixtures of diastereoisomers from which one antipode, if desired, may be isolated.

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

The resulting racemates (racemic diastereoisomers) may furthermore be separated into the optical antipodes according to methods known per se, for example by recrystallisation from an optically active solvent, with the aid of microorganisms or by reaction of an acidic end product with an optically active base that forms salts with the racemic acid, and separation of the salts obtained in this manner, for example on the basis of their different solubilities, into the diastereoisomers, from which the antipodes can be freed by the action of suitable agents. Basic racemic products can also be separated into the antipodes, for example by separation of the diastereoisomeric salts thereof, for example by fractional crystallisation of the d- or l-tartrates thereof. Any racemic intermediate or starting material can be separated in a similar manner.

Finally, the compounds according to the invention are obtained either in free form or in the form of their salts. Any resulting base can be converted into a corresponding acid addition salt, preferably using a pharmaceutically tolerable acid or an anion-exchange preparation, or resulting salts can be converted into

the corresponding free bases, for example using a stronger base, such as a metal or ammonium hydroxide or a basic salt, for example an alkali metal hydroxide or carbonate, or a cation-exchange preparation. A compound of the formula I can also be converted into the corresponding metal or ammonium salts. These or other salts, for example the picrates, can also be used for the purification of the resulting bases. The bases are converted into the salts, the salts are separated and the bases are freed from the salts. In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is mentioned in this Application, a corresponding salt of that compound is also included, provided that this is possible or appropriate under the given conditions.

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

The pharmaceutical preparations according to the invention are those that are suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, for the treatment or prevention of diseases that respond to the blocking of NMDA-receptors, such as, for example, cerebral ischaemia, muscular spasms (spasticity), convulsions (epilepsy), conditions of anxiety or manic conditions. They comprise an effective amount of a pharmacologically active compound of the formula I or a pharmaceutically acceptable salt thereof, on its own or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention can be used in the manufacture of pharmaceutical compositions that comprise an effective amount of the same on its own or in conjunction or admixture with excipients or carriers that are suitable for enteral or parenteral administration. Preferred are tablets and gelatin capsules that comprise the active

constituent together with a) diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, b) glidants, for example silica, talc, stearic acid, the magnesium or calcium salt thereof and/or polyethylene glycol, for tablets also c) binders, for example magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired d) dispersing or disintegrating agents, for example starches, agar, alginic acid or the sodium salt thereof, or foaming mixtures and/or e) absorbents, colouring agents, flavourings and sweeteners. Injectable preparations are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously produced from fatty emulsions or suspensions. These compositions may be sterilised and/or comprise adjuvants, such as preservatives, stabilisers, wetting agents or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. In addition they may also comprise other therapeutically valuable substances. These preparations are manufactured according to conventional mixing, granulating or coating methods and comprise approximately from 0.1 to 100 %, preferably approximately from 1 to 50 %, of the active constituent. A unit dose for a mammal weighing approximately from 50 to 70 kg may comprise between approximately 1 and 500 mg, preferably between approximately 10 and 500 mg, of active constituent.

The following Examples are intended to illustrate the invention and do not represent limitations. The temperatures are in degrees Celsius and all parts are quoted in the form of parts by weight. Unless mentioned otherwise, all evaporation is carried out under reduced pressure, preferably between approximately 2 and 13 Kilopascal (kPa).

Example 1:

8.22 g of E-2-formylamino-5-diethylphosphono-3-pentenoic acid ethyl ester are dissolved in 170 ml of 6N hydrochloric acid and the whole is heated under reflux for 22 hours. After concentration in vacuo, the oily residue is taken up in a small amount of ethanol and the mixture is again concentrated by evaporation in vacuo. This procedure is repeated a further twice. The resulting residue is dissolved in 15 ml of ethanol and 20 ml of ethanol/propylene oxide (1:1) are added dropwise. The resulting brownish-coloured precipitate is filtered off and purified by ion exchange chromatography (Dowex®50W x 8/H₂O). After concentration and lyophilisation, E-2-amino-5-phosphono-3-pentenoic acid is obtained in the form of a white amorphous powder, ¹H-NMR (D₂O): 2.39 (dd, 2H, C(5)-H); 4.27 (d, 1H, C(2)-H); 5.53 (m, 1H, C(3)-H); 5.87 (m, 1H, C(4)-H), m.p. after recrystallisation from ethanol/water 191-192°.

The starting material is manufactured as follows:

1.6 g of red copper(I) oxide are added to 200 ml of benzene. With intensive stirring, a solution of 140 g of isocyanoacetic acid ethyl ester and 84 g of freshly distilled acrolein in 200 ml of benzene is added dropwise to this suspension within a period of 10 minutes. During the course of this addition the reaction temperature is maintained between 30 and 32° by cooling with ice. When the addition is complete the mixture is maintained at 30-32° until the exothermic reaction has subsided, and then the whole is stirred for 1 hour at room temperature. After excess copper(I) oxide has been removed by filtration, the filtrate is concentrated by evaporation in vacuo at 30°.

600 ml of ether are added to the residue, and the whole is filtered over celite and concentrated to dryness by evaporation in vacuo. In this manner 5-vinyl-2-oxazoline-4-carboxylic acid ethyl ester is obtained in the form of a pale yellow oil, b.p. 100-110° (5.3 Pa).

128 g of the 5-vinyl-2-oxazoline-4-carboxylic acid ethyl ester are dissolved in 70 ml of tetrahydrofuran, and 27.4 g of water and 3.5 g of triethylamine are added. The reaction mixture is stirred for 62 hours at 65-70° and, having been cooled, is taken up in 200 ml of dichloromethane. The solution is dried over 200 g of magnesium sulphate, filtered and concentrated by evaporation in vacuo. Purification by column chromatography (silica gel; hexane/ethyl acetate 3:2) of the viscous oil that remains yields 2-formylamino-3-hydroxy-4-pentenoic acid ethyl ester in the form of a diastereoisomeric mixture, m.p. 50-51°.

2.0 g of 2-formylamino-3-hydroxy-4-pentenoic acid ethyl ester in 80 ml of dry tetrahydrofuran are cooled to -78°. 2.5 ml of thionyl bromide are slowly added dropwise thereto in such a manner that the reaction temperature does not exceed -75°. When the addition is complete, the reaction solution is warmed within a period of approximately 3 hours to 0° and is stirred at that temperature for 2.5 hours. The orange-yellow solution is then poured onto 300 ml of a cold (5-10°) saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The organic extracts are dried over magnesium sulphate and concentrated by evaporation in vacuo at room temperature. The oil that remains is dissolved in 20 ml of triethyl phosphite and heated for 2 hours in vacuo (10 kPa) under reflux (55°). Excess triethyl phosphite is then distilled off under a high vacuum. Purification by column chromatography (silica gel,

ethyl acetate/hexane (2:1), then ethyl acetate) yields E-2-formylamino-5-diethylphosphono-3-pentenoic acid ethyl ester in the form of a pale yellow oil, $^1\text{H-NMR}$ (CDCl_3): 2.62 (m, 2H, C(5)-H); 5.19 (m, 1H, C(2)-H); 5.75 (m, 2H, C(3)-H and C(4)-H).

Example 2:

E-2-amino-4-methyl-5-phosphono-3-pentenoic acid is obtained by hydrolysis of E-2-formylamino-4-methyl-5-diethylphosphono-3-pentenoic acid ethyl ester in a manner analogous to that described in Example 1, $^1\text{H-NMR}$ (D_2O): 1.73 (s, 3H, CH_3); 4.55 (s, 1H, C(2)-H).

The starting material is manufactured as follows:

By reaction of isocyanoacetic acid ethyl ester with methacrolein in a manner analogous to that described in Example 1, and after subsequent fractional distillation, 5-(2-propenyl)-2-oxazoline-4-carboxylic acid ethyl ester is obtained in the form of a colourless oil, b.p. $110-130^\circ$ (5.3 Pa).

2-Formylamino-3-hydroxy-4-methyl-4-pentenoic acid ethyl ester, m.p. 67° , is obtained by hydrolysis of 5-(2-propenyl)-2-oxazoline-4-carboxylic acid ethyl ester in a manner analogous to that described in Example 1.

By reaction of 2-formylamino-3-hydroxy-4-methyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with triethyl phosphite in a manner analogous to that described in Example 1, E-2-formylamino-4-methyl-5-diethylphosphono-3-pentenoic acid ethyl ester is obtained in the form of a pale yellow oil.

Example 3:

By hydrolysis of E-2-formylamino-5-(O-ethyl-methylphosphonyl)-3-pentenoic acid ethyl ester in a

manner analogous to that described in Example 1 , after precipitation with propylene oxide E-2-amino-5-methylphosphonyl-3-pentenoic acid is obtained in the form of an amorphous white powder, $^1\text{H-NMR}$ (D_2O): 2.55 (dd, 2H, C(5)-H); 4.38 (d, 1H, C(2)-H); 5.64 (m, 1H, C(3)-H); 5.91 (m, 1H, C(4)-H).

The starting material is manufactured as follows:

By reaction of E-2-formylamino-3-hydroxy-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with methylphosphonous acid diethyl ester instead of triethyl phosphite in a manner analogous to that described in Example 1 , E-2-formylamino-5-(O-ethyl-methylphosphonyl)-3-pentenoic acid ethyl ester is obtained in the form of a colourless oil, $^1\text{H-NMR}$ (CDCl_3): 2.63 (dd, 2H, C(5)-H); 5.1 (m, 1H, C(2)-H); 5.75 (m, 2H, C(3)-H) and C(4)-H).

Example 4:

25 g of E-2-formylamino-5-O-ethyl-diethoxymethylphosphonyl-3-pentenoic acid ethyl ester are stirred under reflux for 16 hours with 500 ml of 6N hydrochloric acid and the whole is then concentrated in vacuo at 70° . The residue is suspended in 100 ml of 95% ethanol/water, 20 ml of propylene oxide are added and the product is filtered off. Recrystallisation from water yields E-2-amino-5-phosphino-3-pentenoic acid, m.p. $139-140^\circ$.

The starting material is manufactured as follows:

10 g of 2-formylamino-3-hydroxy-4-pentenoic acid ethyl ester in 50 ml of dry tetrahydrofuran are cooled to -78° . 12.7 g of thionyl chloride are added dropwise in such a manner that the reaction temperature does not exceed -75° . Subsequently, the reaction solution is warmed to -20° within a period of 3 hours and stirred at that temperature for 3 hours. The

yellow solution is then poured onto 300 ml of a cold (5°) saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The organic extracts are dried over sodium sulphate and concentrated by evaporation in vacuo at 30°. The residue is pre-purified by column chromatography (silica gel, ethyl acetate), and the light-yellow oil that remains is dissolved in 10 ml of tetrahydrofuran. After the addition of 17.0 g of diethoxymethylphosphonous acid ethyl trimethylsilyl ester, the whole is stirred for 24 hours at 35°. The dark-yellow solution is then poured onto 100 ml of a cold (5°) saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic extracts are dried over sodium sulphate and concentrated by evaporation in vacuo at 30°. After purification of the residue by column chromatography (silica gel, ethyl acetate/methanol), E-2-formylamino-5-O-ethyl-diethoxymethylphosphonyl-3-pentenoic acid ethyl ester is obtained in the form of a light-yellow oil, ¹H-NMR (CDCl₃): 2.70 (m, 2H, C(5)-H); 4.68 (q, 1H, C(2)-H); 5.20 (m, 1H, (C-P)-H); 5.80 (m, 2H, C(3)-H and C(4)-H).

Example 5:

a) 1.0 g of E-2-amino-5-phosphino-3-pentenoic acid is suspended in 20 ml of ethanol and the suspension is saturated with hydrogen chloride gas for 2 hours at 65°. After concentration, the residue is dissolved in 10 ml of ethanol, 10 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphino-3-pentenoic acid ethyl ester, m.p. 172-173°.

b) 1.0 g of E-2-amino-5-phosphino-3-pentenoic acid is suspended in 20 ml of n-butanol and the suspension

is saturated with hydrogen chloride gas for 3 hours at 60°. After concentration, the residue is dissolved in 15 ml of n-butanol, 10 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphino-3-pentenoic acid butyl ester, m.p. 160-161°.

Example 6:

a) 2.0 g of E-2-amino-5-phosphono-3-pentenoic acid are placed in 50 ml of ethanol and the whole is saturated with hydrogen chloride gas for 2 1/2 hours at 50°. After concentration, the residue is dissolved in 18 ml of ethanol, 18 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/ethanol 1:3 yields 2-amino-5-phosphono-3-pentenoic acid ethyl ester, m.p. 167-168°.

b) 2.0 g of E-2-amino-5-phosphono-3-pentenoic acid are suspended in 40 ml of n-butanol and the suspension is saturated with hydrogen chloride gas for 3 hours at 40°. After concentration, the residue is dissolved in 30 ml of n-butanol, 15 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphono-3-pentenoic acid butyl ester, m.p. 160-161°.

c) 2.0 g of E-2-amino-5-phosphono-3-pentenoic acid are suspended in 30 ml of n-octanol and the suspension is saturated with hydrogen chloride gas for 4 hours at 70°. The mixture is concentrated in vacuo at 70° to half its volume, 50 ml of diethyl ether and 15 ml of propylene oxide are added and the whole is filtered. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphono-3-pentenoic acid octyl ester, m.p. 161-162°.

d) 2.0 g of 2-amino-5-phosphono-3-pentenoic acid are suspended in 15 ml of 1-dodecanol and 25 ml of tetrahydrofuran and the suspension is saturated with hydrogen chloride gas for 4 hours at 50°. The mixture is freed of tetrahydrofuran in vacuo at 50°, 40 ml of acetone and 20 ml of propylene oxide are added and the whole is filtered. There is obtained from water/acetone 1:1, after stirring, E-2-amino-5-phosphono-3-pentenoic acid dodecyl ester, m.p. 158-159°.

e) 1.5 g of E-2-amino-5-phosphono-3-pentenoic acid are suspended in 30 ml of n-propanol and the suspension is saturated with hydrogen chloride gas for 2 1/2 hours at 50°. After concentration, the residue is dissolved in 15 ml of n-propanol, 15 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:3 yields E-2-amino-5-phosphono-3-pentenoic acid propyl ester, m.p. 161-162°.

f) 1.5 g of 2-amino-5-phosphono-3-pentenoic acid are suspended in 30 ml of n-pentanol and the suspension is saturated with hydrogen chloride gas for 3 hours at 50°. After concentration, the residue is dissolved in 15 ml of n-pentanol, 15 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphono-3-pentenoic acid pentyl ester, m.p. 160-161°.

g) 1.5 g of E-2-amino-5-phosphono-3-pentenoic acid are suspended in 30 ml of isobutanol and the suspension is saturated with hydrogen chloride gas for 3 1/2 hours at 70°. After concentration, the residue is dissolved in 10 ml of isobutanol, 10 ml of propylene oxide are added and the precipitate is filtered off. Recrysta-

llisation from water/acetone 1:1 yields E-2-amino-5-phosphono-3-pentenoic acid isobutyl ester, m.p. 163-164°.

h) 1.5 g of E-2-amino-5-phosphono-3-pentenoic acid are suspended in 30 ml of sec.-butanol and the suspension is saturated with hydrogen chloride gas for 4 hours at 75°. After concentration, the residue is dissolved in 10 ml of 2-butanol, 10 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/acetone 1:1 yields E-2-amino-5-phosphono-3-pentenoic acid sec.-butyl ester, m.p. 169-170°.

Example 7:

Manufacture of 1000 capsules, each containing 10 mg of the active substance of Example 6, with the following composition:

E-2-amino-5-phosphono-4-methyl-3-pentenoic acid	10.0 g
lactose	207.0 g
modified starch	80.0 g
magnesium stearate	3.0 g

Method: All the pulverulent constituents are sieved using a sieve having a mesh width of 0.6 mm. The active ingredient is then introduced into a suitable mixer and mixed until homogeneous first with magnesium stearate, then with lactose and starch. No. 2 gelatine capsules are each filled with 300 mg of this mixture using a capsule-filling machine.

Capsules each containing from 10 to 200 mg of the other disclosed compounds mentioned in the Examples are manufactured in an analogous manner.

Example 8:

Manufacture of 10,000 tablets, each comprising 10 mg of the active substance of Example 6, with the following composition:

E-2-amino-5-phosphono-4-methyl-3-pentenoic acid	100.00 g
lactose	2,535.00 g
corn starch	125.00 g
polyethylene glycol 6000	150.00 g
magnesium stearate	40.00 g
purified water	q.s.

Method: All the pulverulent constituents are sieved using a sieve having a mesh width of 0.6 mm. The active ingredient is then mixed in a suitable mixer with lactose, magnesium stearate and with half of the starch. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of polyethylene glycol in 260 ml of water. The resulting paste is added to the powders and the whole is granulated, if necessary with the addition of a further quantity of water. The granulate is dried overnight at 35°, forced through a sieve having a mesh width of 1.2 mm and pressed to form tablets that have a breaking groove.

Tablets each containing from 10 to 200 mg of one of the other disclosed compounds mentioned in the Examples are manufactured in an analogous manner.

Example 9:

E-2-amino-4-methyl-5-phosphono-3-pentenoic acid is obtained by hydrolysis of E-2-formylamino-4-methyl-5-dimethyl-phosphono-3-pentenoic acid ethyl ester in a manner analogous to that described in Example 1. For ¹H-NMR see Example 2. E-2-amino-4-methyl-5-methylphos-

phono-3-pentenoic acid, m.p. 149-150°, is obtained as a by-product in preliminary fractions.

The starting material is manufactured as follows:

By reaction of 2-formylamino-3-hydroxy-4-methyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with trimethyl phosphite in a manner analogous to that described in Example 17, E-2-formylamino-4-methyl-5-dimethylphosphono-3-pentenoic acid ethyl ester is obtained in the form of a pale yellow oil.

Example 10:

a) 2.0 g of E-2-amino-4-methyl-5-phosphono-3-pentenoic acid are placed in 50 ml of ethanol and the whole is saturated with hydrogen chloride gas for 2 1/2 hours at 50°. After concentration, the residue is dissolved in 20 ml of ethanol, 20 ml of propylene oxide are added and the precipitate is filtered off. Recrystallisation from water/ethanol (1:3) yields E-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester, m.p. 193-194°.

The following esters are obtained in an analogous manner:

- b) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid methyl ester, m.p. 193-194° [water/acetone (9:1)];
- c) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid n-propyl ester, m.p. 184-185°, (water);
- d) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid n-butyl ester, m.p. 186-187°, [water/acetone (2:1)];

- e) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid isobutyl ester, m.p. 181-182°, [water/acetone (9:1)];
- f) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid n-pentyl ester, m.p. 207-208°;
- g) E-2-amino-4-methyl-5-phosphono-3-pentenoic acid n-hexyl ester, m.p. 207-208°.

Example 11:

21 g of E-2-formylamino-4-methyl-5-O-ethyl-diethoxymethylphosphonyl-3-pentenoic acid ethyl ester are stirred for 16 hours at 80° with 400 ml of 4.35N hydrochloric acid and the whole is subsequently concentrated in vacuo at 45°. The residue is dissolved in 100 ml of ethanol and 30 ml of propylene oxide are added, and the product is filtered off. Recrystallisation from water yields E-2-amino-4-methyl-5-phosphino-3-pentenoic acid, m.p. 176-177°.

The starting material is manufactured as follows:

50 g of 2-formylamino-3-hydroxy-4-methyl-4-pentenoic acid ethyl ester in 500 ml of dry tetrahydrofuran are cooled to -78°. 89 g of thionyl chloride are added dropwise thereto in such a manner that the reaction temperature does not exceed -70°. Subsequently, the reaction solution is warmed to -10° within a period of 3 hours and is stirred for 3 hours at that temperature and then concentrated under a high vacuum at 20°.

The residue is taken up in 400 ml of dichloromethane and neutralised with saturated aqueous sodium hydrogen carbonate solution. The organic extracts are dried over sodium sulphate and concentrated by evaporation in vacuo at 30°. The residue is pre-

purified by column chromatography (silica gel, ethyl acetate) and the light-yellow oil that remains is dissolved in 30 ml of toluene. After the addition of 94 g of diethoxymethylphosphonous acid ethyl trimethylsilyl ester, the whole is stirred for 16 hours at 90°. The dark-yellow solution is poured onto ice/water, neutralised with sodium hydrogen carbonate and extracted with dichloromethane. The organic extracts are dried over sodium sulphate and concentrated by evaporation in vacuo at 30°. Purification of the residue by column chromatography (silica gel, ethyl acetate, then ethyl acetate/methanol 9:1) yields E-2-formylamino-4-methyl-5-O-ethyl-diethoxymethylphosphonyl-3-pentenoic acid ethyl ester in the form of a light-yellow oil, ¹H-NMR (CDCl₃): 2.64 (dd, 2H, C(5)-H); 4.60 (d, 1H, P-CH); 5.26 (m, 2H, C(2)-H and C(3)-H).

Example 12:

Racemate separation of E-2-amino-4-methyl-5-phosphono-3-pentenoic acid.

A solution of 1.5 ml of phenylacetyl chloride in 25 ml of 1,4-dioxan is added at 20°, within a period of 20 minutes, to 209 mg of E-2-amino-4-methyl-5-phosphono-3-pentenoic acid in 21 ml of 2N sodium hydroxide solution while stirring vigorously, and the whole is stirred for 4 hours at room temperature. The reaction solution is poured onto 250 ml of water and repeatedly extracted with dichloromethane. The aqueous phase is concentrated to 20 ml in vacuo at 40°, pre-purified by ion exchange chromatography (DOWEX®50 Wx8/water/1,4-dioxan 3:1) and concentrated in vacuo at 40°. The resulting E-2-phenylacetylamino-4-methyl-5-phosphono-3-pentenoic acid is adjusted to pH 7.5 in 150 ml of water with 2N sodium hydroxide solution and stirred for 16

hours at 37° with 250 mg of EUPERGIT-ACYLASE® After filtering in vacuo at 40°, the mixture is concentrated to 10 ml and separated by ion exchange chromatography (DOWEX®50 Wx8/water) into (D)-E-2-phenylacetyl-amino-4-methyl-5-phosphono-3-pentenoic acid and into (L)-E-2-amino-4-methyl-5-phosphono-3-pentenoic acid.

a) The aqueous phases of (L)-E-2-amino-4-methyl-5-phosphono-3-pentenoic acid are concentrated in vacuo and the residue is purified by recrystallisation from water, m.p. 196°, $[\alpha]_D^{20} = +97.1 \pm 1.9^\circ$ ($c = 0.5$; water).

b) The aqueous phases of (D)-E-2-phenylacetyl-amino-4-methyl-5-phosphono-3-pentenoic acid are concentrated in vacuo and the residue is stirred for 3.5 hours at 85° with 25 ml of 4.35N hydrochloric acid and then repeatedly extracted with dichloromethane. Concentration of the aqueous phases in vacuo and purification of the residue by ion exchange chromatography yield (D)-E-2-amino-4-methyl-5-phosphono-3-pentenoic acid, m.p. 194°, $[\alpha]_D^{20} = -96.7 \pm 1.2^\circ$ ($c = 0.8$; water).

Example 13:

2.5 g of E-2-formylamino-5-O-ethyl-methylphosphonyl-4-methyl-3-pentenoic acid ethyl ester are heated for 26 hours under nitrogen at 80° in 200 ml of 4.35N hydrochloric acid. The whole is concentrated by evaporation in vacuo and the residue is dissolved, in each case twice, in 200 ml each of water, tetrahydrofuran and ethanol, the solutions each time being concentrated by evaporation in vacuo. Dissolving in 150 ml of ethanol, the addition of 5 ml of propylene oxide in

100 ml of tetrahydrofuran/ethanol (1:1) at 0° within a period of 20 minutes, filtration of the precipitate and drying for 12 hours at 50° in vacuo yield crude E-2-amino-4-methyl-5-methylphosphonyl-3-pentenoic acid, which is purified by chromatography on 20 g of Dowex®50 Wx8 (H₂O) (amorphous white powder), ¹H-NMR (D₂O): 1.20 (d, 3H, CH₃-P); 1.75 (d, 3H, CH₃); 2.45 (d, 2H, C(5)-H); 4.50 (d, 1H, C(2)-H); 5.15 (m, 1H, C(3)-H).

The starting material is manufactured by reaction of 2-formylamino-3-hydroxy-4-methyl-4-pentenoic acid ethyl ester with thionyl bromide in the manner described in Example 18 and subsequent treatment with methylphosphonous acid diethyl ester instead of triethyl phosphite.

Example 14:

14.5 g of E-2-formylamino-2-methyl-5-diethylphosphono-3-pentenoic acid methyl ester are heated for 32 hours under nitrogen at 100-105° in 500 ml of 4.35N hydrochloric acid. Working up as in Example 29 yields E-2-amino-2-methyl-5-phosphono-3-pentenoic acid, m.p. 225-226° (from water).

The starting material is manufactured as follows:

A solution of 14.1 g of 2-isocyanopropionic acid methyl ester and 8.5 g of freshly distilled acrolein in 50 ml of tetrahydrofuran is added within a period of 20 minutes at 0-5° under nitrogen to a solution of 17 g of anhydrous zinc chloride in 75 ml of tetrahydrofuran, and the whole is stirred for 45 hours at 0-5°. The whole is poured onto 500 ml of 10% sodium hydrogen carbonate solution and extracted with 200 ml of dichloromethane. The organic phase is dried over sodium sulphate and concentrated by evaporation. Filtration of the residue over silica gel (ethyl

acetate as eluant) yields 4-methyl-5-vinyl-2-oxazoline-4-carboxylic acid methyl ester. By hydrolysis of the 4-methyl-5-vinyl-2-oxazoline-4-carboxylic acid methyl ester in a manner analogous to that described in Example 1, 2-formylamino-2-methyl-3-hydroxy-4-pentenoic acid methyl ester is obtained. By reaction of the 2-formylamino-3-hydroxy-2-methyl-4-pentenoic acid methyl ester with thionyl bromide and subsequent treatment with triethyl phosphite in the manner described in Example 1, E-2-formylamino-2-methyl-5-diethylphosphono-3-pentenoic acid methyl ester is obtained in the form of a yellow oil:

Calculated	C 46.91 %	H 7.22 %	N 4.56 %	P 10.08 %
Found	C 46.1 %	H 7.3 %	N 4.1 %	P 10.6 %

Example 15:

6.3 g of E-2-formylamino-3-methyl-5-diethylphosphono-3-pentenoic acid ethyl ester are heated for 30 hours at 100-105° under nitrogen in 400 ml of 4.35N hydrochloric acid. Working up as in Example 29 yields E-2-amino-3-methyl-5-phosphono-3-pentenoic acid in the form of a white powder, m.p. 168°, ¹H-NMR (D₂O): 1.50 (d, 3H, CH₃); 2.4 (m, 2H, CH₂); 4.30 (s, 1H, C(2)-H); 5.60 (m, 1H, C(4)-H).

The starting material is manufactured as follows: 5-Methyl-5-vinyl-2-oxazoline-4-carboxylic acid ethyl ester, b.p. 65-75° (13 Pa), is obtained by reaction of isocyanoacetic acid ethyl ester with methyl vinyl ketone in a manner analogous to that described in Example 14. By hydrolysis of the 5-methyl-5-vinyl-2-oxazoline-4-carboxylic acid ethyl ester in a manner analogous to that described in Example 17, 2-formylamino-3-hydroxy-3-methyl-4-pentenoic acid ethyl ester is obtained. Reaction of the 2-formylamino-3-hydroxy-3-

methyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with triethyl phosphite in a manner analogous to that described in Example 17 yields E-2-formylamino-3-methyl-5-diethylphosphono-3-pentenoic acid ethyl ester in the form of a colourless liquid.

Example 16:

E-2-formylamino-5-diethylphosphono-5-methyl-3-pentenoic acid ethyl ester is hydrolysed with 4.35N hydrochloric acid in the manner described in Example 29. E-2-amino-5-methyl-5-phosphono-3-pentenoic acid is isolated in the form of an amorphous white solid mass. $^1\text{H-NMR}$ (D_2O): 1.05 (dd, 3H, CH_3); 2.45 (m, 1H, C(5)-H); 4.33 (d, 2H, C(2)-H); 5.5 and 5.9 (2m, 2H, C(3)-H and C(4)-H).

The starting material is manufactured as follows: Reaction of crotonaldehyde with isocyanoacetic acid ethyl ester in a manner analogous to that described in Example 1 yields 5-(propen-1-yl)-2-oxazoline-4-carboxylic acid ethyl ester. By hydrolysis of the 5-(propen-1-yl)-2-oxazoline-4-carboxylic acid ethyl ester analogously to Example 1, 2-formylamino-3-hydroxy-4-hexenoic acid ethyl ester is obtained. Reaction of the 2-formylamino-3-hydroxy-4-hexenoic acid ethyl ester with thionyl bromide and subsequent treatment with triethyl phosphite in a manner analogous to that described in Example 1 (12 hours) yields E-2-formylamino-5-diethylphosphono-5-methyl-3-pentenoic acid ethyl ester.

Example 17:

Hydrolysis of E-2-formylamino-4-ethyl-5-dimethylphosphono-3-pentenoic acid ethyl ester in a manner analogous to that described in Example 29 yields

E-2-amino-4-ethyl-5-phosphono-3-pentenoic acid, m.p. 176° (H₂O).

The starting material is manufactured as follows: Reaction of 2-methylene-butyraldehyde with isocyanoacetic acid ethyl ester in a manner analogous to that described in Example 1 yields 5-(buten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester. A solution of 16 g of 5-(buten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester in 100 ml of ethanol/water (1:1) is heated at the boil, under reflux, for 15 hours. The whole is concentrated by evaporation in vacuo, the residue is taken up in 200 ml of dichloromethane, dried over sodium sulphate and filtered, and the filtrate is concentrated by evaporation to yield 2-formylamino-3-hydroxy-4-ethyl-4-pentenoic acid ethyl ester.

Reaction of the 2-formylamino-3-hydroxy-4-ethyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with trimethyl phosphite in a manner analogous to that described in Example 1 yields E-2-formylamino-4-ethyl-5-dimethylphosphono-3-pentenoic acid ethyl ester.

Example 18:

Hydrolysis of E-2-formylamino-4-propyl-5-dimethylphosphono-3-pentenoic acid ethyl ester in a manner analogous to that described in Example 13 yields E-2-amino-4-propyl-5-phosphono-3-pentenoic acid, m.p. 193° (H₂O).

The starting material is manufactured as follows: Reaction of 2-methylene-pentanal with isocyanoacetic acid ethyl ester analogously to Example 1 yields 5-(penten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester. By hydrolysis of the 5-(penten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester in a manner analogous to that described in Example 17, 2-formyl-

amino-3-hydroxy-4-propyl-4-pentenoic acid ethyl ester is obtained. Reaction of the 2-formylamino-3-hydroxy-4-propyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with trimethyl phosphite in a manner analogous to that described in Example 1 yields E-2-formylamino-4-propyl-5-dimethylphosphono-3-pentenoic acid ethyl ester.

Example 19:

Hydrolysis of E-2-formylamino-4-butyl-5-dimethylphosphono-3-pentenoic acid ethyl ester in a manner analogous to that described in Example 13 yields E-2-amino-4-butyl-5-phosphono-3-pentenoic acid, m.p. 186-187° (H₂O).

The starting material is manufactured as follows: Reaction of 2-methylene-hexanal with isocyanoacetic acid ethyl ester analogously to Example 1 yields 5-(hexen-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester, which is hydrolysed in a manner analogous to that described in Example 17 to 2-formylamino-3-hydroxy-4-butyl-4-pentenoic acid ethyl ester. Reaction of the 2-formylamino-3-hydroxy-4-butyl-4-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with trimethyl phosphite analogously to Example 1 yields E-2-formylamino-4-butyl-5-dimethylphosphono-3-pentenoic acid ethyl ester.

Example 20:

Hydrolysis of E-2-formylamino-4-isopropyl-5-dimethylphosphono-3-pentenoic acid ethyl ester analogously to Example 13 yields E-2-amino-4-isopropyl-5-phosphono-3-pentenoic acid, m.p. 201° (H₂O).

The starting material is manufactured as follows: Reaction of 3-methyl-2-methylene-butanal with isocyanoacetic acid ethyl ester analogously to Example 1

yields 5-(3-methyl-buten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester, which is hydrolysed analogously to Example 17 to 2-formylamino-3-hydroxy-4-isopropyl-4-pentenoic acid ethyl ester. Subsequent treatment with thionyl bromide followed by reaction with trimethyl phosphite analogously to Example 1 yields E-2-formyl-amino-4-isopropyl-5-dimethylphosphono-3-pentenoic acid ethyl ester.

Example 21:

3.9 g of E-2-formylamino-4-tert.-butyl-5-dimethylphosphono-3-pentenoic acid ethyl ester are hydrolysed analogously to Example 29. Separation by ion exchange chromatography (Dowex®W 50, H₂O) yields 1.8 g of E-2-amino-4-tert.-butyl-5-phosphono-3-pentenoic acid and 0.075 g of Z-2-amino-4-tert.-butyl-5-phosphono-3-pentenoic acid.

E-isomer: M.p. 252-253° (H₂O); ¹H-NMR (D₂O): 0.95 (s, 9H, (CH₃)₃C); 2.65 (m, 2H, CH₂); approximately 4.7 (d, 1H, C(2)-H); 5.33 (m, 1H, C(3)-H).

(Z-isomer: ¹H-NMR (D₂O): 1.08 (s, 9H, (CH₃)₃C); 2.45 (m, 2H, CH₂); 4.95 (d, 1H, C(2)-H); 5.20 (m, 1H, C(3)-H)).

The starting material is manufactured as follows: Reaction of 3,3-dimethyl-2-methylene-butanal with isocyanoacetic acid ethyl ester in a manner analogous to that described in Example 1 yields 5-(3,3-dimethyl-buten-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester, which is hydrolysed analogously to Example 17 to 2-formylamino-3-hydroxy-4-tert.-butyl-4-pentenoic acid ethyl ester. Subsequent reaction with thionyl bromide followed by treatment with trimethyl phosphite analogously to Example 1 yields E-2-formylamino-4-tert.-butyl-5-dimethylphosphono-3-pentenoic acid ethyl ester.

Example 22:

0.44 g of E-2-formylamino-4-benzyl-5-diethylphosphono-3-pentenoic acid ethyl ester are dissolved in 8 ml of 4.5N hydrochloric acid and heated at 85° for 48 hours. After concentration in vacuo, the residue is dissolved in a small amount of ethanol and 1 ml of ethanol/propylene oxide (1:1) is added dropwise thereto. The resulting white precipitate is filtered off and, after recrystallisation from water, E-2-amino-4-benzyl-5-phosphono-3-pentenoic acid is obtained in the form of colourless needles, m.p. 196-198°.

The starting material is manufactured as follows: By reaction of isocyanoacetic acid ethyl ester with 2-benzyl-propenal in a manner analogous to that described in Example 1 and after purification by column chromatography (silica gel; dichloromethane/ethyl acetate 98:2), 5-(3-phenyl-propen-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester is obtained in the form of a colourless oil, ¹H-NMR (CDCl₃): 3.33 (s, 2H, CH₂); 4.37 (dd, 1H, C(4)-H); 4.87 (s, 1H), 5.07 (dd, 1H, C(5)-H); 5.16 (s, 1H).

By hydrolysis of the 5-(3-phenyl-propen-2-yl)-2-oxazoline-4-carboxylic acid ethyl ester in a manner analogous to that described in Example 1, 2-formylamino-3-hydroxy-4-benzyl-4-pentenoic acid ethyl ester is obtained, m.p. 87-89°.

By reaction of 2-formylamino-3-hydroxy-4-benzyl-3-pentenoic acid ethyl ester with thionyl bromide and subsequent treatment with triethyl phosphite at 100° in a manner analogous to that described in Example 1, and after chromatography (silica gel; ethyl acetate), E-2-formylamino-4-benzyl-5-diethylphosphono-3-pentenoic acid ethyl ester is obtained in the form of a colourless oil, ¹H-NMR (CDCl₃): 2.45 (d, 2H, C(5)-H); 3.80 (s, 1H, CH₂); 5.51 (m, 1H, C(3)-H).

Example 23:

0.15 g of E-2-formylamino-4-phenyl-5-diethyl-phosphono-3-pentenoic acid methyl ester are dissolved in 10 ml of 4.5N hydrochloric acid and heated at 75° for 192 hours. After concentration in vacuo, the foamy residue is dissolved in a small amount of ethanol and 1 ml of ethanol/propylene oxide (1:1) is added dropwise thereto. The resulting white precipitate is filtered off and recrystallised from water/acetone (1:2). E-2-amino-4-phenyl-5-phosphono-3-pentenoic acid is thus obtained in the form of colourless needles, m.p. 230-233°.

The starting material is manufactured as follows:

By reaction of isocyanoacetic acid methyl ester with 2-phenylacrolein in a manner analogous to that described in Example 1, and after purification by column chromatography (silica gel; dichloromethane/methanol 97.5:2.5), 5-(1-phenyl-vinyl)-2-oxazoline-4-carboxylic acid methyl ester is obtained in the form of a pale yellow oil. ¹H-NMR (CDCl₃): 3.80 (s, 3H, CH₃); 4.45 (dd, 1H, C(4)-H); 5.76 (d, 1H, C(5)-H).

By hydrolysis of the 5-(1-phenyl-vinyl)-2-oxazoline-4-carboxylic acid methyl ester in a manner analogous to that described in Example 1, 2-formyl-amino-3-hydroxy-4-phenyl-4-pentenoic acid methyl ester is obtained, m.p. 173-174°.

By reaction of the 2-formylamino-3-hydroxy-4-phenyl-4-pentenoic acid methyl ester with thionyl bromide and subsequent treatment with triethyl phosphite in a manner analogous to that described in Example 1, and after chromatography (silica gel; ethyl acetate/hexane 4:1), E-2-formylamino-4-phenyl-5-diethyl-phosphono-3-pentenoic acid methyl ester is obtained in the form of a colourless oil. ¹H-NMR (CDCl₃): 2.98 (d, 2H C(5)-H); 5.03 (dd, 1H, C(2)-H); 5.77 (dd, 1H,

C(3)-H).

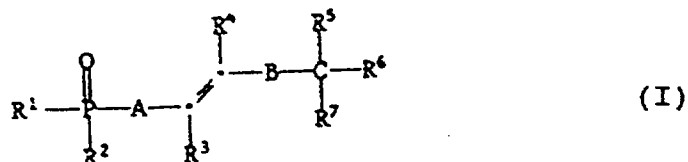
Example 24:

At 0°, 170 mg of sodium hydrogen carbonate and, within a period of 5 minutes, 50 microlitres of acetic anhydride are added to a solution of 100 mg of E-2-amino-5-phosphono-3-pentenoic acid in 6 ml of dioxan/-water (1:1). The whole is stirred for 30 minutes at 0°, approximately 2 ml of Dowex®50 H⁺ are added and filtration is carried out. The filtrate is concentrated by evaporation and purified by ion exchange chromatography (Dowex®50 H⁺). Lyophilisation of the pure fractions yields 110 mg of E-2-acetamino-5-phosphono-3-pentenoic acid, m.p. 155°.

Unless this is expressly excluded, each of the above-described compounds of the formula I can also be manufactured in accordance with any of the other processes described.

Patent Claims (for the Contracting States: BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE)

1. A compound of the formula I



in which the carbon-carbon double bond is in the trans-configuration and R^1 represents hydroxy or etherified hydroxy, R^2 represents hydrogen, alkyl, hydroxy or etherified hydroxy, R^3 represents hydrogen, alkyl, haloalkyl, hydroxyalkyl, lower alkoxyalkyl, arylalkyl, lower alkenyl, halogen or aryl, R^4 represents hydrogen, alkyl or aryl, R^5 represents hydrogen or alkyl, R^6 represents carboxy, esterified carboxy or amidated carboxy, R^7 represents amino or amino substituted by alkyl or by acyl, A represents unsubstituted or alkyl-substituted α,ω -alkylene having from 1 to 3 carbon atoms, B represents a bond, and "lower" radicals contain up to and including 8 carbon atoms, or a salt thereof.

2. A compound of the formula I according to claim 1 in which R^3 represents hydrogen, alkyl or aryl.
3. A compound of the formula I according to claim 1 in which R^6 represents lower alkoxy-carbonyl or phenyl-lower alkoxy-carbonyl.
4. A compound of the formula I according to claim 1 in which R^1 represents hydroxy, lower alkoxy or hydroxy-lower alkoxy, R^2 represents hydrogen, alkyl, hydroxy, lower alkoxy or hydroxy-lower alkoxy, R^3 represents hydrogen, lower alkyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyl-lower alkyl that



is unsubstituted or substituted in the phenyl moiety, lower alkenyl, halogen, or unsubstituted or substituted phenyl, R^4 represents hydrogen, lower alkyl or unsubstituted or substituted phenyl, R^5 represents hydrogen or lower alkyl, R^6 represents carboxy or pharmaceutically acceptable esterified or amidated carboxy, R^7 represents amino, mono- or di-lower alkylamino, alkanoylamino or alkanoylamino substituted by halogen, by amino and/or by phenyl, carbamoyl, carboxy, imidazolyl, lower alkylthio, tetrahydropyrrolyl, hydroxy, indolyl or by hydroxyphenyl, benzoylamino or benzoylamino substituted by halogen, lower alkoxy or by nitro, or phthalimino, A represents unsubstituted or lower alkyl-substituted α,ω -alkylene having from 1 to 3 carbon atoms, and B represents a bond, wherein the substituents of phenyl are selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen, amino, halo-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl and nitro, or a pharmaceutically acceptable salt thereof.

5. A compound of the formula I according to claim 3 in which R^6 represents carboxy, alkoxycarbonyl, or alkoxy-carbonyl substituted by amino, mono- or di-lower alkyl-amino, hydroxy or by lower alkanoyloxy, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, or a pharmaceutically acceptable salt thereof.

6. A compound of the formula I according to claim 4 in which R^3 and R^4 , independently of one another, each represents hydrogen, lower alkyl, phenyl, or phenyl substituted by lower alkyl, hydroxy, lower alkoxy, halogen, amino, halo-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl or by nitro, or a pharmaceutically acceptable salt thereof.



7. A compound of the formula I according to claim 1 in which R^1 represents hydroxy or lower alkoxy, R^2 represents hydrogen, alkyl, hydroxy or lower alkoxy, R^3 represents hydrogen, lower alkyl, phenyl, halophenyl or phenyl-lower alkyl, R^4 and R^5 represent hydrogen or lower alkyl, R^6 represents carboxy, alkoxycarbonyl or hydroxy-lower alkoxycarbonyl, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, A represents unsubstituted or lower alkyl-substituted α,ω -alkylene having from 1 to 3 carbon atoms, and B represents a bond, or a pharmaceutically acceptable salt thereof.

8. A compound of the formula I according to claim 1 in which R^1 is hydroxy, R^2 represents hydrogen, alkyl or hydroxy, R^3 represents hydrogen, lower alkyl or halophenyl, R^4 represents hydrogen or halophenyl and R^5 represents hydrogen, R^6 represents carboxy, lower alkoxycarbonyl or hydroxy-lower alkoxycarbonyl, R^7 represents amino, mono-lower alkylamino, lower alkanoylamino or benzoylamino, A represents α,ω -alkylene having from 1 to 3 carbon atoms, and B represents a bond, or a pharmaceutically acceptable salt thereof.

9. A compound of the formula I according to claim 1 in which R^1 is hydroxy, R^2 represents hydrogen, lower alkyl or hydroxy, R^3 represents hydrogen or lower alkyl, R^4 and R^5 represent hydrogen, R^6 represents carboxy or lower alkoxycarbonyl, R^7 represents amino or mono-lower alkylamino, A represents α,ω -alkylene having from 1 to 3 carbon atoms, and B represents a bond, or a pharmaceutically acceptable salt thereof.

10. A compound of the formula I according to claim 1 in which R^1 and R^2 represent hydroxy, R^3 represents hydrogen or lower alkyl, R^4 and R^5 represent hydrogen, R^6



represents carboxy, R⁷ represents amino, A represents methylene and B represents a bond, or a carboxylic acid lower alkyl ester or a pharmaceutically acceptable salt thereof.

11. E-2-amino-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

12. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

13. (D)-E-2-amino-4-methyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

14. E-2-amino-4-ethyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

15. E-2-amino-4-propyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

16. E-2-amino-4-butyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

17. E-2-amino-4-isopropyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

18. E-2-amino-4-benzyl-5-phosphono-3-pentenoic acid or a pharmaceutically acceptable salt thereof.

19. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethyl ester or a salt thereof.

20. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid methyl ester or a salt thereof.

21. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid



n-propyl ester or a salt thereof.

22. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid
n-butyl ester or a salt thereof.

23. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid
isobutyl ester or a salt thereof.

24. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid
n-pentyl ester or a salt thereof.

25. E-2-amino-4-methyl-5-phosphono-3-pentenoic acid
n-hexyl ester or a salt thereof.

26. A pharmaceutical preparation comprising a compound
of claim 3, 6, 8, 11 or 12 together with a pharmaceuti-
cally suitable carrier material.

27. A pharmaceutical preparation comprising a compound
of claim 1, 4, 5, 7, 9, 10 or 13 to 25 together with a
pharmaceutically suitable carrier material.

28. A compound according to claim 1 for use in a method
of therapeutically treating the human or animal body.

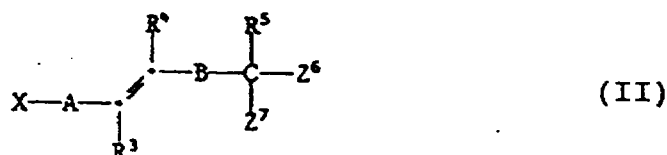
29. A compound according to claim 1 as an anti-convulsive
agent.

30. The use of a compound according to claim 1 of a
pharmaceutical preparation for use as an anti-convulsive
agent.

31. A process for the manufacture of a compound of the
formula I claimed in claim 1, or a salt thereof,
characterised in that



a) a compound of the formula II

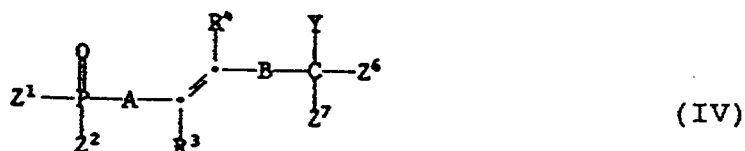


in which R^3 , R^4 , R^5 , A and B are as defined for formula I, Z^6 has the meaning of R^6 or represents protected carboxy, Z^7 has the meaning of R^7 or represents protected amino and X represents reactive esterified hydroxy, is reacted with a compound of the formula III



in which Z^1 has the meaning of R^1 or represents protected hydroxy, Z^2 has the meaning of R^2 or represents protected hydrogen or protected hydroxy, and R represents an etherifying group, or

b) in order to obtain a compound of the formula I in which R^5 represents hydrogen, in a compound of the formula IV

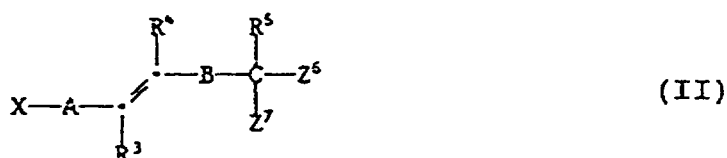


in which R^3 , R^4 , A and B are as defined for formula I, Z^1 has the meaning of R^1 or represents protected hydroxy, Z^2 has the meaning of R^2 or represents protected hydroxy or protected hydrogen, Z^6 has the meaning of R^6 or represents protected carboxy, Z^7 has the meaning of R^7 or represents protected amino, and Y represents an optionally esterified carboxy group that can be replaced by hydrogen, the group Y is replaced by hydrogen, and any protected functional groups that may be present in a



compound resulting from one of the preceding processes are freed and, if desired, a resulting compound of the formula I is converted into a different compound of the formula I and/or, if desired, a resulting compound of the formula I is converted into a salt or a resulting salt is converted into a different salt or into a free compound of the formula I and/or, if desired, an optical isomer is isolated from a mixture of stereoisomeric forms of a resulting compound of the formula I or of a salt thereof.

32. A process according to claim 31, characterised in that a compound of the formula II



in which R^3 , R^4 , R^5 , A and B are as defined for formula I, Z^6 represents protected carboxy, Z^7 represents protected amino and X represents reactive esterified hydroxy, is reacted with a compound of the formula III



in which Z^1 represents protected hydroxy, Z^2 represents lower alkyl, protected hydrogen or protected hydroxy and R represents lower alkyl, and following this reaction the protected groups are freed.

33. A process according to claim 32, in which Z^1 represents lower alkoxy, Z^2 represents lower alkyl, di-lower alkoxy-lower alkyl or lower alkoxy, R represents lower alkyl, Z^6 represents lower alkoxycarbonyl, Z^7 represents formylamino and X represents halogen.

34. A process according to claim 31 for the conversion of



a compound of the formula I in which R^6 represents carboxy into a compound of the formula I in which R^6 represents esterified carboxy.

