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GB A 2042515
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EP A 0023887
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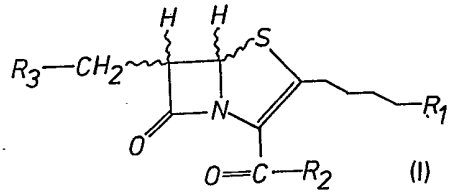
(71) Applicant
CIBA-Geigy AG, (Switzerland), Klybeckstrasse 141, 4002 Basle, Switzerland
(72) Inventors
Hans-Rudolph Pfaendler, Peter Schneider
(74) Agent and/or address for service
Kenneth D. Sparrow, CIBA-Geigy AG, Patent Dept, Tenax Road, Trafford Park, Manchester

(54) **Aminobutyl penem compounds**

(57) 2-Aminobutyl-6-hydroxymethyl-2-penem-3-carboxylic acid compounds of the formula



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in which R_1 represents an optionally substituted amino group, R_2 represents hydroxy or a radical R_2^A that together with the carbonyl group —C(=O)— forms a protected carboxy group, and R_3 represents an optionally protected hydroxy group, and their salts, their optical isomers and mixtures of these optical isomers exhibit *antibiotic* properties.

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Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

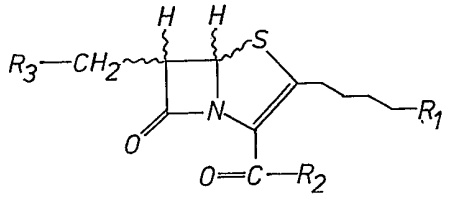
Aminobutyl compounds

The invention relates to novel 2-aminobutyl-6-hydroxymethyl-2-penem compounds, to processes for their manufacture and to pharmaceutical preparations containing such compounds.

German Offenlegungsschrift 29 50 898 and European Patent Application No. 3960 disclose 2-penem compounds that contain an amino-lower alkyl substituent in the 2-position and a 1-hydroxy-lower alkyl group in the 6-position. These compounds are valuable antibiotically-active substances that can be used especially as antibacterial antibiotics. In the mentioned specifications there are singled out as being especially preferred those penem compounds which contain a 1-hydroxyethyl group in the 6-position and thus, in addition to the two centres of asymmetry already present in the penem framework (carbon atoms 5 and 6), also possess a further centre of asymmetry at carbon atom 1′ of the side chain. The separation of the four possible pairs of enantiomers resulting therefrom generally proves to be complicated, time- and energy-consuming and, accordingly, expensive.

2-Aminobutyl-6-hydroxymethyl-2-penem compounds have not previously been disclosed. The surprising discovery has been made that such compounds exhibit a high activity when administered orally in addition to the parenteral activity. Since they have only the two centres of asymmetry that are inherent in the penem system and since, therefore, only two pairs of enantiomers are possible, the isolation of the stereoisomers that are especially pharmacologically active is facilitated to a great extent.

The invention relates especially to novel 2-aminobutyl-6-hydroxymethyl-2-penem compounds of the formula



(I)

in which

R_1 represents an optionally substituted amino group,

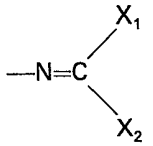
R_2 represents hydroxy or a radical R_2^A that together with the carbonyl group —C(=O)— forms a protected carboxy group, and

R_3 represents an optionally protected hydroxy group,

and to their salts, to their optical isomers and mixtures of their optical isomers, to processess for their manufacture, to pharmaceutical preparations containing such compounds and to their use as antibiotics.

Within the framework of the present description, the definitions used hereinbefore and hereinafter have preferably the following meanings:

A substituted amino group R_1 is a protected amino group or alternatively a methyleneamino group in which the methylene radical is preferably mono- or di-substituted, for example a group of the formula



(IA)

in which X_1 represents hydrogen, optionally substituted amino, for example amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, nitroamino, hydrazino or anilino; etherified hydroxy, for example lower alkoxy or phenyl-lower alkoxy; etherified mercapto, for example lower alkylthio; optionally substituted lower alkyl, for example lower alkyl, amino-lower alkyl, N-lower alkylamino-lower alkyl or N,N-di-lower alkylamino-lower alkyl; lower alkenyl; phenyl or monocyclic heteroaryl, such as corresponding 5- or 6-membered heteroaryl having 1 or 2 nitrogen atoms and/or an oxygen or sulphur atom, and X_2 represents optionally substituted amino, for example amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, nitroamino, hydrazino or anilino; etherified hydroxy, for example lower alkoxy or phenyl-lower alkoxy; or etherified mercapto, for example lower alkylthio.

In the present description, the term "lower" used in connection with definitions of groups and compounds means that, unless expressly stated otherwise, the corresponding groups and compounds contain up to 7, and preferably up to 4, carbon atoms.

Lower alkylamino is, for example, methylamino, ethylamino, n-propylamino, isopropylamino or n-butylamino, whilst di-lower alkylamino represents, for example, dimethylamino, diethylamino, di-n-propylamino or di-n-butylamino.

Lower alkyleneamino has especially from 4 to 6 carbon chain members and represents, for example, 1-pyrrolidinyl or piperidino.

Lower alkoxy is, for example, methoxy, ethoxy, n-propoxy, iospropoxy, n-butoxy or tert.-butoxy, whilst phenyl-lower alkoxy is, for example, benzyloxy.

Lower alkylthio is, for example, methylthio, ethylthio, n-propylthio, isopropylthio or n-butylthio.

Lower alkyl is, for example, methyl, ethyl n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl or tert.-butyl.

Amino-lower alkyl is, for example, 2-aminoethyl or 3-aminopropyl.

N-lower alkylamino-lower alkyl is, for example, 2-methyl- or 2-ethyl-aminoethyl, whilst N,N-di-lower alkylamino-lower alkyl is, for example, 2-dimethylaminoethyl or 2-diethylaminoethyl.

Lower alkenyl is, for example, allyl, n-propenyl or isopropenyl.

Monocyclic 5- or 6-membered heteroaryl having 1 or 2 nitrogen atoms and/or an oxygen or sulphur atom is, for example, furyl, such as 2-furyl, thienyl, such as 2-thienyl, oxazolyl, such as 2-oxazolyl, thiazolyl, such as 2- or 4-thiazolyl, pyridyl, such as 2-, 3- or 4-pyridyl, or pyrimidyl, such as 2-, 4- or 5-pyrimidyl.

Methyleneamino groups of the formula IA are, for example, correspondingly substituted guanidino groups; or isourea or isothiourea groups, imidoether or imidothioether groups, and especially amidino groups, each linked *via* a nitrogen atom to the butyl group.

In a guanidino radical of the formula IA, X_1 represents, for example, amino, lower alkylamino, for example methylamino, di-lower alkylamino, for example diethylamino, nitroamino, hydrazino or anilino, and X_2 represents, for example, amino or lower alkylamino, for example methylamino. Examples of such guanidino groups are guanidino, N-methyl-, N,N-dimethyl- or N,N,N'-trimethyl-guanidino, N-phenylguanidino or amino-guanidino.

In an isourea or isothiourea radical of the formula IA, X_1 represents especially amino, lower alkylamino, for example methylamino, di-lower alkylamino, for example dimethylamino, or anilino, and X_2 represents, for example, lower alkoxy, for example methoxy or ethoxy, or represents lower alkylthio, for example methylthio or ethylthio. Such groups are, for example, the N,N,O-trimethylisourea group or the N,N-dimethyl-S-ethyl-, N-phenyl-S-ethyl- or N,S-dimethyl-isothiourea group.

In imidoether or imidothioether radicals of the formula IA, X_2 represents, for example, lower alkoxy, for example methoxy or ethoxy, benzyloxy, or lower alkylthio, for example methylthio or ethylthio, and X_1 has the same meaning as X_2 or represents hydrogen, lower alkyl, for example methyl, or phenyl. Corresponding groups are, for example, the methyl formamidate, S-methyl thiobenzimidate, methylbenzyl oxycarbimidate or diethyl dithiocarbimidate group.

In amidino groups of the formula IA, X_1 represents, for example, hydrogen, lower alkyl, for example methyl, amino-lower alkyl, for example 2-aminoethyl, lower alkenyl, for example allyl, phenyl, thienyl, for example 2-thienyl, thiazolyl, for example 4-thiazolyl, or pyridyl, for example 2-, 3- or 4-pyridyl, and X_2 represents, for example, amino, lower alkylamino, for example methylamino or isopropylamino, di-lower alkylamino, for example dimethylamino, or lower alkyleneamino, for example piperidino. Suitable amidino groups are, for example, benzamidino, 4-pyridylcarboxamidino, 1-piperidinylmethyleneimino, or, especially, formamidino, acetamidino, N-methyl-, N-isopropyl- or N,N-dimethylformamidino.

The functional groups present in the compounds of the formula I, such as carboxy, amino or hydroxy groups, especially the amino group R_1, the carboxy group —C(=O)—R_2 and the hydroxy group R_3, are optionally protected by protecting groups that are used in penem, penicillin, cephalosporin and peptide chemistry.

Such protecting groups can be removed readily, that is to say without undesirable secondary reactions taking place, for example by solvolysis, by reduction or alternatively under physiological conditions.

Protecting groups of this type and the manner in which they are introduced and removed are described, for example, in

J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973.

T. W. Greene, "Protective Groups in Organic Synthesis" Wiley, New York, 1981,

"The Peptides", Vol. I. Schroeder and Luebke, Academic Press, London, New York, 1965, and in

Houben-Weyl, "Methoden der Organischen Chemie", Band 15/1, Georg Thieme Verlag, Stuttgart, 1974.

A protected amino group R_1 may be, for example, in the form of a readily cleavable acylamino, acylimino, etherified mercaptoamino, silylamino or stannylamino group, or in the form of an enamino, nitro or azido group.

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 alkanecarboxylic acid optionally substituted, for example by halogen or phenyl, or of a benzoic acid optionally substituted, for example by halogen, lower alkoxy or nitro, or of a carbonic 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; optionally substituted

benzoyl, for example benzoyl, halobenzoyl, such as 4-chlorobenzoyl, lower alkoxybenzoyl, such as 4-methoxybenzoyl, or nitrobenzoyl, such as 4-nitrobenzoyl. Also especially suitable are lower alkenyloxycarbonyl, for example allyloxycarbonyl, or lower alkoxycarbonyl optionally substituted in the 1- or 2-position, such as lower alkoxycarbonyl, for example methoxy- or ethoxy-carbonyl; optionally substituted benzyloxycarbonyl, for example benzyloxycarbonyl or 4-nitrobenzyloxycarbonyl; aroylmethoxycarbonyl, for example phenacyloxycarbonyl, in which the aroyl group preferably represents benzoyl optionally substituted, for example by halogen, such as bromine; 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl; or 2-(tri-substituted silyl)-ethoxycarbonyl, such as 2-tri-lower alkylsilylethoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methylsilyl)-ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl, such as 2-triphenylsilylethoxycarbonyl.

In an acylimino group, acyl 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 phthalimino.

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 silyl- or stannyl-amino group is especially an organic silyl- or stannyl-amino group in which the silicon or tin atom contains as substituent preferably lower alkyl, for example methyl, ethyl, n-butyl or tert.-butyl, also lower alkoxy, for example methoxy. Corresponding silyl or stannyl groups are especially tri-lower alkylsilyl, especially trimethylsilyl, also dimethyl-tert.-butyl-silyl, or correspondingly substituted stannyl, for example tri-n-butylstannyl. The silicon atom of a silylamino group may also be substituted by only two lower alkyl groups, for example methyl groups, and the amino, hydroxy or carboxy group of a second molecule of the formula I. Compounds having such protecting groups may be manufactured, for example, by using dimethyldichlorosilane as silylating agent.

Further protected amino groups are, for example, enamino groups that contain an electron-attracting substituent, for example a carbonyl group, at the double bond in the 2-position. Protected amino groups of this type are, for example, 1-acyl-lower alk-1-en-2-ylamino radicals in which acyl represents, 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 a carbonic acid methyl semiester or ethyl semiester, and in which lower alk-1-ene represents especially 1-propene. Corresponding protected amino groups are especailly 1-lower alkanoylprop-1-en-2-ylamino, for example 1-acetylprop-1-en-2-ylamino, or 1-lower alkoxycarbonylprop-1-en-2-ylamino, for example 1-ethoxycarbonylprop-1-en-2-ylamino.

In a protected carboxy group of the formula —C(=O)—R^A_2, R^A_2 is especially an etherified hydroxy group which together with the carbonyl grouping forms an esterified carboxy group that preferably can be cleaved readily, for example by reduction, such as hydrogenolysis, or solvolysis, such as acidolysis or, especially, by basic or neutral hydrolysis, or that can be cleaved under physiological conditions, or 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 branched in the 1-position or suitably substituted in the 1- or 2-position. Preferred carboxy groups in esterified form are, *inter alia*, lower alkoxycarbonyl, for example methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl or tert.-butoxycarbonyl, and (hetero)arylmethoxycarbonyl having from 1 to 3 aryl radicals or a 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 benzyloxycarbonyl optionally substituted, for example as mentioned above, for example 4-nitrobenzyloxycarbonyl; diphenylmethoxycarbonyl optionally substituted, for example as mentioned above, for example diphenylmethoxycarbonyl, or triphenylmethoxycarbonyl; or picolyloxycarbonyl, such as 4-picolyloxycarbonyl, or furfuryloxycarbonyl, such as 2-furfuryloxycarbonyl, each optionally substituted, for example as mentioned above. Further suitable groups are lower alkanoylmethoxycarbonyl, such as acetonyloxycarbonyl, aroylmethoxycarbonyl in which the aroyl group represents, for example, benzoyl optionally substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl; halo-lower alkoxycarbonyl, such as 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, or ω-halo-lower alkoxycarbonyl in which lower alkoxy contains from 4 to 7 carbon atoms, for example 4-chlorobutoxycarbonyl; phthalimidomethoxycarbonyl; lower alkenyloxycarbonyl, for example allyloxycarbonyl; or ethoxycarbonyl substituted in the 2-position by lower alkylsulphonyl, cyano or by tri-substituted silyl, such as tri-lower alkylsilyl or triphenylsilyl, for example 2-methylsulphonylethoxycarbonyl, 2-cyanoethoxycarbonyl, 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methylsilyl)-ethoxycarbonyl.

Further protected carboxy groups in esterified form are corresponding organic silyloxycarbonyl

groups and also corresponding organic stannyloxycarbonyl groups. In these groups, the silicon or tin atom contains as substituent preferably lower alkyl, especially methyl or ethyl, also lower alkoxy, for example methoxy. Suitable silyl or stannyl protecting groups are especially tri-lower alkylsilyl, especially trimethylsilyl or dimethyl-tert.-butyl-silyl, or correspondingly substituted stannyl groups, for example tri-n-butylstannyl.

An esterified carboxy group that can be cleaved under physiological conditions is especially an acyloxymethoxycarbonyl group in which acyl represents, for example, the radical of an organic carboxylic acid, especially an optionally substituted lower alkanecarboxylic acid, or in which acyloxymethyl forms the radical of a lactone; 1-lower alkoxy-lower alkoxycarbonyl or alternatively 1-lower alkoxycarbonyloxy-lower alkoxycarbonyl in which lower alkyl represents, for example, methyl, propyl, butyl or, especially, ethyl, and lower alkoxy represents, for example, methoxy, ethoxy, propoxy or butoxy. Such groups are, for example, lower alkanoyloxymethoxycarbonyl, for example acetoxymethoxycarbonyl or pivaloyloxymethoxycarbonyl, amino-lower alkanoyloxymethoxycarbonyl, especially α-amino-lower alkanoyloxymethoxycarbonyl, for example glycyloxymethoxycarbonyl, *L*-valyloxymethoxycarbonyl, *L*-leucyloxymethoxycarbonyl, phthalidyloxycarbonyl, for example 3-phthalidyloxycarbonyl, 4-crotonolactonyl or 4-butyrolacton-4-yl, indanyloxycarbonyl, for example 5-indanyloxycarbonyl, 1-ethoxycarbonyloxyethoxycarbonyl, methoxymethoxycarbonyl or 1-methoxyethoxycarbonyl.

In compounds of the formula (I), a hydroxy group R_3 may be protected, for example by acyl radicals. Suitable acyl radicals are, for example, optionally substituted lower alkanoyl, for example acetyl or trifluoroacetyl, optionally substituted benzoyl, for example benzoyl, 4-nitrobenzoyl or 2,4-dinitrobenzoyl, optionally substituted lower alkoxycarbonyl, for example 2-bromoethoxycarbonyl or 2,2,2-trichloroethoxycarbonyl, or optionally substituted phenyl-lower alkoxycarbonyl, for example 4-nitrobenzyloxycarbonyl. Other hydroxy-protecting groups are, for example, tri-substituted silyl, such as tri-lower alkylsilyl, for example trimethylsilyl or tert.-butyl-dimethyl-silyl, 2-haloalkyl groups, for example 2-chloro-, 2-bromo-, 2-iodo- and 2,2,2-trichloro-ethyl, and optionally substituted 1-phenyl-lower alkyl, such as benzyl optionally substituted by halogen, for example chlorine, lower alkoxy, for example methoxy, or by nitro.

Salts of compounds according to the invention are especially pharmaceutically acceptable, non-toxic salts, such as those of compounds of the formula I in which R_2 is hydroxy. Such salts are especially metal or ammonium salts, such as alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and ammonium salts with ammonia or suitable organic amines, such as lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine 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, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, dibenzylamine or N-benzyl-β-phenethylamine. Compounds of the formula I having a basic group, for example those in which R_1 represents amino, can form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with suitable organic carboxylic or sulphonic acids, for example acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, oxalic acid, citric acid, benzoic acid, mandelic acid, malic acid, ascorbic acid, methanesulphonic acid or 4-toluenesulphonic acid. Compounds of the formula I having an acidic group and a basic group, for example those in which R_1 represents amino and R_2 represents hydroxy, can also be in the form of internal salts, that is to say in zwitterion form.

In the penem compounds of the formula I, the two asymmetric carbon atoms in the 5- and 6-positions can be in the *R*, the *S*- or the racemic *R,S*-configuration. Compounds in which the configuration of the 5-carbon atom corresponds to that of natural penicillin (5*R*-configuration) are preferred. The hydrogen atoms in the 5- and 6-positions can be in the *cis* or, preferably, in the *trans* position to one another. In the preferred configuration, the 6-hydroxymethyl substituent assumes the *S*-configuration.

The compounds of the present invention exhibit valuable pharmacological properties or may be used as intermediates for the manufacture of those compounds having valuable pharmacological properties. Compounds of the formula I in which R_1 represents an amino group of an optionally substituted methyleneamino group A, R_2 represents hydroxy or together with the carbonyl group represents an esterified carboxy group that can be cleaved under physiological conditions, and R_3 represents hydroxy, or pharmacologically acceptable salts of such compounds having salt-forming groups have anti-bacterial action. For example, *in vitro* they are effective against gram-positive and gram-negative causative organisms, for example *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus faecalis, Neisseria meningitidis, Neisseria gonorrhoeae, Enterobacteriaceae, Haemophilus influenzae, Pseudomonas aeruginosa* and *Bacteroides sp.* in minimum concentrations of from approximately 0.5 to approximately 64 μg/ml. *In vivo*, in the systemic infection of mice, for example by *Staphylococcus aureus* or *Streptococcus pyogenes*, oral administration of the compounds according to the invention results in a minimum effective dosage range of from approximately 0.65 to approximately 3 mg/kg.

The following test report illustrates the activity of compounds of the formula I with reference to selected compounds:

Test report

I. Tested compounds

The antibiotic activity of the following compounds was tested:

1. *Trans*-2-(4-aminobutyl)-6-hydroxymethylpenem-3-carboxylic acid (Example 19).
2. (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethylpenem-3-carboxylic acid (Example 28).

II. Experimental procedure

A. The antibiotic activity of the test compounds *in vitro* was determined by the agar dilution method described by Ericsson, H.M., and Sherris, S.C., *1971*, Acta Path. Microb. Scand. Section B, Suppl. No. 217, Vol. 1—90, in DST agar. The minimum concentrations found still inhibiting the growth of the test organisms (MIC=minimum inhibitory concentrations) are shown in Table I in micrograms per millilitre (μg/ml for the tested compounds.

B. The chemotherapeutic activity *in vivo* against systemic infections in female SPF, MF_2 mice was determined in accordance with the method described by Zak, O., *et al., 1979*, Drugs Exptl, Clin. Res., *5*, 45—49. The ED_{50} values found, in milligrams substance per kilogram mouse (mg/kg), for a number of micro-organisms are given in Table 2 for the test compounds, which were administered subcutaneously (s.c.) of orally (p.o.).

III. Test results

Table 1 Antibiotic activity (*in vitro*)

Micro-organism	*Test compound MIC (μg/ml)* 1	2
Staphylococcus aureus 10 B	0.2	0.5
St. aureus 2999 i^+ p^+	0.2	0.5
St. aureus 568	0.1	0.5
Streptococcus pyogenes Aronson	0.2	0.5
St. pneumoniae III/84	0.1	0.5
St. faecalis 1362/3	64	16
Neisseria meningitidis 1316	1	
N. gonorrhoeae 1317/4	0.2	
Haemophilus influenzae NCTC 4560	32	
Escherichia coli 205	32	4
E. coli 16 R^+ TEM	32	4
E. coli 576	32	4
Klebsiella pneumoniae 327	32	4
Serratia marcescens 344	32	16
Enterobacter cloacae P 99	32	4
Proteus mirabilis 774	32	16
P. rettgeri 856	128	64
Morganella morganii 2359	32	16
Pseudomonas aeruginosa ATCC 12055	32	8
Bacteroides fragilis Lo 1	1	0.5
B. fragilis 17390	1	
B. thetaiotaomicron E 50	2	
B. distanonis Am 9	8	
B. vulgatus Am 5	0.5	
Spherophorus varius Am 7	0.25	
Fusobacterium fusiforme T3/18	0.12	

Table 2 Chemotherapeutic activity (*in vivo*)

Micro-organism	*ED_{50} (mg/kg)* 1 s.c.	1 p.o.	2 s.c.	2 p.o.
Staphylococcus aureus 10 B	6	5.2	4	3
St. aureus 2999 i^+ p^+	10			
Streptococcus pyogenes Aronson	1.7	1.5	1.2	0.9

The novel compounds can therefore be used as orally or parenterally administrable antibacterial antibiotics, for example in the form of appropriate pharmaceutical preparations, for the treatment of infections.

Compounds of the formula I in which at least one of the functional groups present is in protected form, (a protected carboxy group being different from a physiologically cleavable esterified carboxy group), can be used as intermediates for the manufacture of the above-mentioned pharmacologically active compounds of the formula I.

The invention relates especially to compounds of the formula I in which R_1 represents amino, a 1-acyl-lower alk-1-en-2-ylamino radical or a mono- or di-substituted methyleneamino group, R_2 represents hydroxy or together with the carbonyl group represents an esterified carboxy group that can be cleaved under physiological conditions, and R_3 represents hydroxy, and to their salts, their optical isomers and to mixtures of their optical isomers, and their protected derivatives.

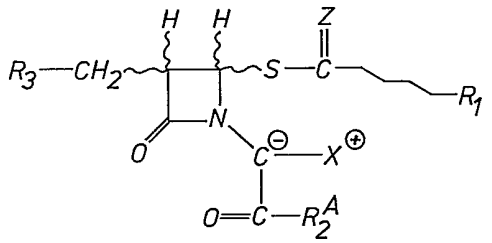
The invention relates more especially to compounds of the formula I in which R_1 represents amino, R_2 represents hydroxy, lower alkanoyloxymethoxy, amino-lower alkanoyloxymethoxy, phthalidyloxy, 4-crotonolactonyloxy, 4-butyrolacton-4-yloxy, indanyloxy, 1-lower alkoxy-lower alkoxy or 1-lower alkoxycarbonyloxy-lower alkoxy, and R_3 represents hydroxy, and to their salts, especially their pharmaceutically acceptable salts, their optical isomers and mixtures of their optical isomers.

Special mention should be made of the compound of the formula I in which R_1 represents amino, R_2 represents hydroxy, and R_3 represents hydroxy, and its optical isomers, especially the 5*R*,6*S*-isomer, and its pharmaceutically acceptable salts.

The invention relates especially to the compounds of the formula I mentioned in the Examples and to the pharmaceutically acceptable salts thereof.

The compounds of the present invention are manufactured according to processes that are known *per se*.

The novel compounds are manufactured by cyclising an ylide compound of the formula



(II)

in which R_1 represents a protected amino group, Z represents oxygen or sulphur, $X^{\oplus}$ represents either a tri-substituted phosphonio group or a di-esterified phosphono group together with a cation, R_2^A has the meaning given above, and R_3 represents an optionally protected hydroxy group, and, if desired or necessary, in a resulting compound of the formula I converting a protected amino group R_1 into the free amino group or into a different protected amino group R_1, and/or, if desired, in a resulting compound of the formula I converting a protected carboxy group —C(=O)—R_2 into the free carboxy group or into a different protected carboxy group —C(=O)—R_2, and/or, if desired, in a resulting compound of the formula I in which R_1 represents amino, converting R_1 into a substituted amino group, and/or, if necessary, converting a protected hydroxy group R_3 into the free hydroxy group R_3, or a free hydroxy group R_3 into a protected hydroxy group R_3, and/or if desired, converting a resulting compound having a salt-forming group into a salt, or a resulting salt into the free compound or into a different salt, and/or, if desired, separating a resulting mixture of isomeric compounds into the individual isomers.

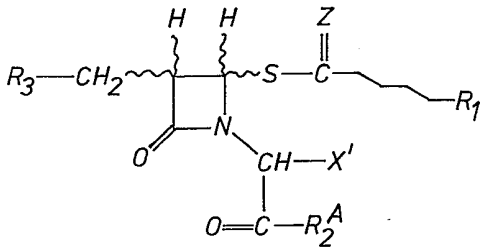
The group $X^{\oplus}$ in a starting material of the formula II is one of the phosphonio or phosphono groups customarily used in Wittig condensation reactions, especially a triarylphosphonio, for example triphenylphosphonio, or a tri-lower alkylphosphonio, for example tri-n-butylphosphonio group, or a phosphono group diesterified by lower alkyl, for example ethyl, the symbol $X^{\oplus}$ in the case of the phosphono group additionally including the cation of a strong base, especially a suitable metal ion, such as an alkali metal ion, for example a lithium, sodium or potassium ion. Preferred as group $X^{\oplus}$ are, on the one hand, triphenylphosphonio, and, on the other hand, diethylphosphono together with an alkali metal ion, for example a sodium ion.

The ylide compounds of the formula II are, in the isomeric ylene form, also termed phosphorane compounds. In phosphonio compounds of the formula II, the negative charge is neutralised by the positively charged phosphonio group. In phosphono compounds of the formula II, the negative charge is neutralised by the cation of a strong base, which ion may be, depending upon the method of manufacture of the phosphono starting material, for example, an alkali metal ion, for example a sodium, lithium or potassium ion. The phosphono starting materials are therefore used in the reaction as salts.

The ring closure can take place spontaneously, that is to say in the manufacture of the starting materials, or may be effected by heating, for example in a temperature range of approximately 30° to 160°C, preferably from approximately 50° to approximately 100°C. The reaction is preferably carried

out in a suitable inert solvent, such as in an aliphatic, cycloaliphatic or aromatic hydrocarbon, for example hexane, cyclohexane, benzene or toluene, a halogenated hydrocarbon, for example methylene chloride, an ether, for example diethyl ether, dimethoxyethane or diethylene glycol dimethyl ether, a cyclic ether, for example dioxan or tetrahydrofuran, a carboxylic acid amide, for example dimethylformamide, a di-lower alkyl sulphoxide for example dimethyl sulphoxide, or a lower alkanol, for example methanol, ethanol or tert.-butanol, or in a mixture thereof, and, if necessary, in an inert gas atmosphere, for example a nitrogen atmosphere.

A starting compound of the formula II in which $X^{\oplus}$ represents a phosphono group together with a cation is preferably manufactured *in situ* by treating a compound of the formula



(IIa),

in which X′ represents a phosphono group, with a suitable basic reagent, such as an inorganic base, for example an alkali metal carbonate, such as sodium or potassium carbonate, or an organic base, such as a tri-lower alkylamine, for example triethylamine, or a cyclic base of the amidine type, such as a corresponding diazabicycloalkene compound, for example 1,5-diazabicyclo[5.4.0]undec-5-ene.

It is preferable to use those starting materials of the formula II that result in the compounds of the formula I mentioned at the beginning as being especially preferred, for example compounds of the formula II having a 3*S*,4*R*-configuration.

For the manufacture of compounds of the formula I that contain a free amino group R_1 and/or a free carboxy group —C(=O)—R_2 and/or a free hydroxy group R_3, it is preferable to use those hydroxy-, amino- and/or carboxy-protecting groups which can be removed in one reaction step, for example by reduction, such as by hydrogenolysis.

In a compound of the formula I obtainable according to the invention having a protected amino group R_1, this group can be converted into the free amino group R_1 in a manner known *per se*, for example, depending upon the type of protecting group, preferably by means of solvolysis or reduction. For example, 2-halo-lower alkoxycarbonylamino (optionally after converting a 2-bromo-lower alkoxycarbonylamino group into a 2-iodo-lower alkoxycarbonylamino group), aroylmethoxy-carbonylamino or 4-nitrobenzyloxycarbonylamino can be cleaved by treatment with a suitable chemical reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid, or catalytically with hydrogen in the presence of a palladium catalyst. Aroylmethoxy-carbonylamino can also be cleaved by treatment with a nucleophilic, preferably salt-forming reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino may be cleaved also by treatment with an alkali metal dithionite for example sodium dithionite. Optionally substituted benzyloxy-carbonylamino can be cleaved, for example, by means of hydrogenolysis, that is to say by treatment with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst, and allyloxycarbonylamine by reaction with a palladium compound, for example tetrakis(triphenyl-phosphine)palladium, in the presence of triphenylphosphine and treatment with a carboxylic acid, for example 2-ethylhexanoic acid, or with a salt thereof. An amino group protected by an organic silyl or stannyl group can be freed, for example, by means of hydrolysis or alcoholysis, and an amino group protected by 2-halo-lower alkanoyl, for example 2-chloroacetyl, can be freed by treatment with thiourea in the presence of a base or with a thiolate salt, such as an alkali metal thiolate, of thiourea and subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting condensation product. An amino group protected by 2-substituted silylethoxycarbonyl can be converted into the free amino group by treatment with a salt of hydrofluoric acid that yields fluoride anions, such as an alkali metal fluoride, for example sodium fluoride, in the presence of a macrocyclic polyether ("Crown ether") or with a fluoride of an organic quaternary base, such as tetra-lower alkylammonium fluoride, for example tetraethylammonium fluoride. An amino group protected in the form of an azido or nitro group can be converted into free amino, for example by reduction, for example by catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as platinum oxide, palladium or Raney nickel, or by treatment with zinc in the presence of an acid, such as acetic acid. An amino group protected in the form of a phthalimido group can be converted into the free amino group by reaction with hydrazine. Furthermore, an arylthioamino group can be converted into amino by treatment with a nucleophilic reagent, such as sulphurous acid.

Furthermore, a free amino group R_1 can be converted into a substituted amino group in a manner known *per se*. Thus, for example, amino can be converted into acylamino R_1 by reaction with a corresponding acyl halide, such as a chloride, or into 1-lower alkanoyl- or 1-lower alkoxycarbonyl-prop-

1-en-2-ylamino by means of a β-dicarbonyl compound, such as a 1-lower alkanoylacetone or an acetoacetic acid lower alkyl ester respectively. The conversion of amino groups into amidino, guanidino, isourea, isothiourea, imido ether and imidothioether groups can be carried out, for example, according to one of the processes mentioned in German Offenlegungsschrift No. 26 52 679. Thus, for example, compounds of the formula I in which R_1 represents amino can be converted into amidines by reaction with trimethylsilyl chloride and an imidohalide of the formula $[(X_1,Y_1)C=X_2]^{\oplus}Y_2^{\ominus}$ in which Y_1 represents halogen, for example chlorine, and Y_2 represents an anion, for example chloride, and into guanidines by reaction with a substituted isourea or isothiourea of the formula $(X_1Y_3)C=X_2$ in which Y_3 represents lower alkoxy or lower alkylthio.

A compound of the formula I obtainable according to the process in which R_2 represents a radical R_2^A that together with the carbonyl group —C(=O)— forms a protected carboxy group can be converted in a manner known *per se* into a compound of the formula I in which R_2 represents hydroxy. Thus, tert.-lower alkoxycarbonyl, or lower alkoxycarbonyl substituted in the 2-position by a tri-substituted silyl group or in the 1-position by lower alkoxy, or optionally substituted diphenylmethoxycarbonyl can be converted into free carboxy, for example, by treatment with a carboxylic acid, such as formic acid or trifluoroacetic acid, optionally with the addition of a nucleophilic compound, such as phenol or anisole. Optionally substituted benzyloxycarbonyl can be cleaved, for example, by means of hydrogenolysis, that is to say by treatment with hydrogen in the presence of a metallic hydrogenation catalyst, such as a palladium catalyst. Furthermore, suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can also be converted into free carboxy by means of chemical reduction, for example by treatment with an alkali metal dithionite, for example sodium dithionite, or with a reducing metal, for example tin, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II) chloride, customarily in the presence of a hydrogen-yielding agent that together with the metal is capable of producing nascent hydrogen, such as a suitable carboxylic acid, for example a lower alkanecarboxylic acid optionally substituted, for example by hydroxy, for example acetic acid, formic acid or glycolic acid, or an alcohol or thiol, it being preferable to add water. The removal of an allyl protecting group can be effected, for example, by reaction with a palladium compound, for example tetrakis(triphenylphosphine)palladium, in the presence of triphenylphosphine and with the addition of a carboxylic acid, for example 2-ethylhexanoic acid, or a salt thereof. By treatment with a reducing metal or metal salt, as described above, it is also possible to convert 2-halo-lower alkoxycarbonyl (optionally after converting a 2-bromo-lower alkoxycarbonyl group into a corresponding 2-iodo-lower alkoxycarbonyl group), or aroylmethoxycarbonyl into free carboxy, it being possible to cleave aroylmethoxycarbonyl likewise by treatment with a nucleophilic, preferably salt-forming reagent, such as sodium thiophenolate or sodium iodide. Substituted 2-silylethoxycarbonyl can be converted into free carboxy also by treatment with a salt of hydrofluoric acid that yields the fluoride anion, such as an alkali metal fluoride, for example sodium fluoride, in the presence of a macrocyclic polyether ("Crown ether") or with a fluoride of an organic quaternary base, such as tetra-lower alkylammonium fluoride, for example tetraethylammonium fluoride. Carboxy esterified by an organic silyl or stannyl group, such as tri-lower alkylsilyl or tri-lower alkylstannyl can be freed in customary manner by solvolysis, for example by treatment with water or an alcohol. A lower alkoxycarbonyl group substituted in the 2-position by lower alkylsulphonyl or cyano can be converted into free carboxy, for example by treatment with a basic agent, such as an alkali metal or alkaline earth metal hydroxide or carbonate, for example sodium or potassium hydroxide or sodium or potassium carbonate.

On the other hand, also compounds of the formula I in which R_2 represents hydroxy can be converted into compounds of the formula I in which R_2 represents a radical R_2^A that together with the carbonyl group —C(=O)— forms a protected carboxy group, especially an esterified carboxy group. Thus, the free carboxy group can be esterified, for example, by treatment with a suitable diazo compound, such as a diazo-lower alkane, for example diazomethane, or a phenyldiazo-lower alkane, for example diphenyldiazomethane, if necessary in the presence of a Lewis acid, such as, for example, boron trifluoride, or by reaction with an alcohol suitable for esterification in the presence of an esterifying agent, such as a carbodiimide, for example dicyclohexyl carbodiimide, and carbonyldiimidazole. Esters can also be manufactured by reaction of a salt of the acid, which salt is optionally produced *in situ*, with a reactive ester of an alcohol and a strong inorganic acid, such as sulphuric acid, or a strong organic sulphonic acid, such as 4-toluenesulphonic acid. Furthermore, acid halides, such as chlorides, (manufactured, for example, by treatment with oxalyl chloride), activated esters (formed, for example, with N-hydroxynitrogen compounds, such as N-hydroxysuccinimide), or mixed anhydrides (obtained, for example, with haloformic acid lower alkyl esters, such as chloroformic acid ethyl ester or chloroformic acid isobutyl ester, or with haloacetic acid halides, such as trichloroacetyl chloride) can be converted into an esterified carboxy group by reaction with alcohols, optionally in the presence of a base, such as pyridine.

In a compound of the formula I having an esterified carboxy group, this group can be converted into a different esterified carboxy group, for example 2-chloroethoxycarbonyl or 2-bromoethoxycarbonyl: by treatment with an iodine salt, for example sodium iodide, into 2-iodoethoxycarbonyl. Furthermore, in compounds of the formula I that contain a carbonyl group protected in esterified form, the carboxy group can be removed as described above, and a resulting compound of the formula I

having a free carboxy group or a salt thereof can be converted by reaction with the reactive ester of a corresponding alcohol into a compound of the formula I in which R_2^A together with the carbonyl group represents an esterified carboxy group that can be cleaved under physiological conditions.

In compounds of the formula I obtainable according to the process in which R_3 represents a protected hydroxy group, this group can be converted into the free hydroxy group R_3 in a manner known *per se*. For example, a hydroxy group protected by a suitable acyl group or by an organic silyl or stannyl group can be freed in the same manner as a correspondingly protected amino group. A 2-halo-lower alkyl group and an optionally substituted benzyl group are removed by reduction.

Furthermore, a compound of the formula I obtainable according to the process in which R_3 represents hydroxy can be converted in a manner known *per se* into a compound of the formula I in which R_3 represents a protected hydroxy group. Thus, hydroxy can be converted by reaction with an acyl halide, for example a halide, such as the chloride, of an optionally substituted lower alkanecarboxylic acid, optionally substituted benzoic acid or an optionally substituted lower alkyl or phenyl-lower alkyl semiester of carbonic acid into optionally substituted lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy or phenyl-lower alkoxycarbonyloxy. Furthermore, by reaction with tri-substituted silyl halide or optionally substituted 1-phenyl-lower alkyl halide, compounds of the formula I can be obtained in which R_3 represents tri-substituted silyloxy or optionally substituted 1-phenyl-lower alkoxy, respectively.

Salts of compounds of the formula I having salt-forming groups can be manufactured in a manner known *per se*. Thus, salts of compounds of the formula I having a free carboxy group can be formed, for example, by treatment with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, for example the sodium salt of α-ethylcaproic acid, or with inorganic alkali or alkaline earth metal salts, for example sodium bicarbonate, or with ammonia or with a suitable organic amine, it being preferable to use stoichiometric amounts or only a small excess of the salt-forming agent. Acid addition salts of compounds of the formula I are obtained in customary manner, for example by treatment with a suitable acid or a suitable anion exchange reagent. Internal salts of compounds of the formula I in which, for example, R_1 represents amino and R_2 represents hydroxy, can be formed, for example, by neutralising salts, such as acid addition salts, to the isoelectric point, for example with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in customary manner; metal and ammonium salts, for example by treatment with suitable acids, and acid addition salts, for example by treatment with a suitable basic agent.

Resulting mixtures of isomers can be separated into the individual isomers according to methods known *per se*: mixtures of diastereoisomeric isomers, for example by fractional crystallisation, adsorption chromatography (column or thin-layer chromatography) or other suitable separating processes.

The cleaving of resulting racemates into their optical antipodes can be effected in various ways.

One of these ways consists in allowing a racemate to react with an optically active auxiliary, separating the resulting mixture of two diastereoisomeric compounds with the aid of suitable physico-chemical methods and then cleaving the individual diastereoisomeric compounds into the optically active compounds.

Racemates that are especially suitable for separation into the antipodes are those which contain an acidic group, such as, for example, racemates of compounds of the formula I in which R_2 represents hydroxy. These acidic racemates can be reacted with optically active bases, for example esters of optically active amino acids, or (—)-brucine, (+)-quinidine, (—)-quinine, (+)-cinchonine, (+)-dehydroabietylamine, (+)- and (—)-ephedrin, (+)- and (—)-1-phenylethylamine or their N-mono- or N,N-di-alkylated derivatives, to form mixtures consisting of two diastereoisomeric salts.

In racemates that contain carboxy groups, this carboxy group can also be esterified already or can become esterified by an optically active alcohol, such as (—)-menthol, (+)-borneol, (+)- or (—)-2-octanol, whereupon, when isolation of the desired diastereoisomers is complete, the carboxy group is freed.

For separation of the racemates, the hydroxy group can also be esterified by optically active acids or reactive functional derivatives thereof, diastereoisomeric esters being formed. Such acids are, for example, (—)-abietic acid, *D*(+)- and *L*(—)-malic acid, N-acylated optically active amino acid, (+)- and (—)-camphanic acid, (+)- and (—)-ketopinic acid, *L*(+)-ascorbic acid, (+)-camphoric acid, (+)-camphor-10-sulphonic acid(β), (+)- or (—)-α-bromocamphor-π-sulphonic acid, *D*(—)-quinic acid, *D*(—)-isoascorbic acid, *D*(—)- and *L*(+)-mandelic acid, (+)-1-menthoxyacetic acid, *D*(—)- and *L*(+)-tartaric acid and the di-O-benzoyl and di-O-*p*-toluyl derivatives thereof.

By reaction with optically active isocyanates, such as with (+)- or (—)-1-phenylethyl isocyanate, it is possible to convert compounds of the formula I in which R_1 represents protected amino and R_2 represents a radical R_2^A into a mixture of diastereoisomeric urethanes.

Basic racemates, for example compounds of the formula I in which R_1 represents amino, can form diastereoisomeric salts with the mentioned optically active acids.

The cleaving of the separated diastereoisomers into the optically active compounds of the formula I is also effected according to customary methods. The acids or the bases are freed from the

salts, for example, by treatment with acids or bases that are stronger than those originally used. The desired optically active compounds are obtained from the esters and urethanes, for example, after alkaline hydrolysis or after reduction with a complex hydride, such as lithium aluminium hydride.

A further method of separating the racemates consists in chromatography on optically active absorption layers, for example on cane sugar.

According to a third method, the racemates can be dissolved in optically active solvents and the more sparingly soluble optical antipode is crystallised out.

A fourth method utilises the different reactivities of the optical antipodes with respect to biological material, such as micro-organisms or isolated enzymes.

According to a fifth method, the racemates are dissolved and one of the optical antipodes is crystallised out by inoculation with a small quantity of an optically active product obtained according to one of the above methods.

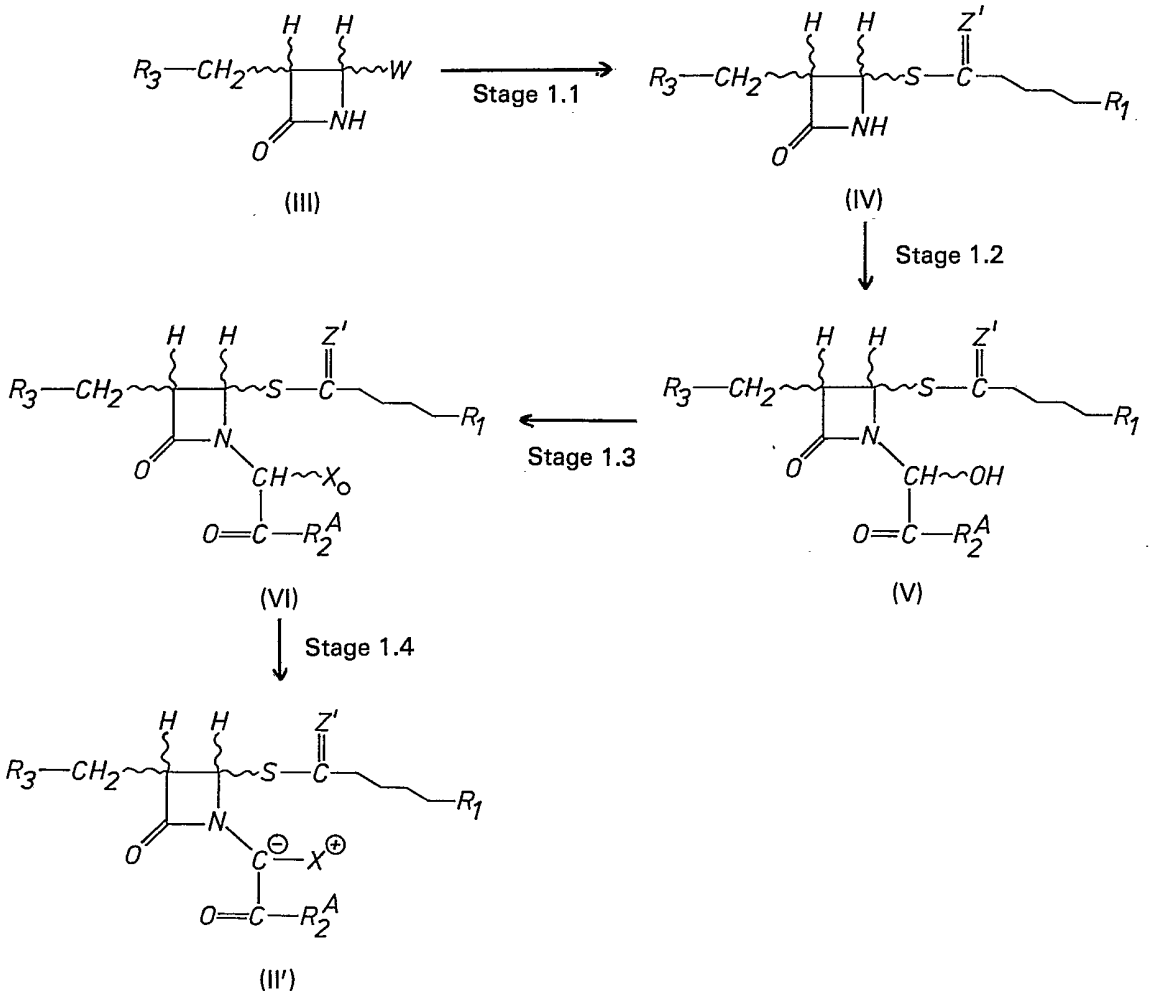
The separation of diastereoisomers into the individual racemates and of the racemates into the optical antipodes can be carried out at any stage of the process, that is to say, for example, at the stage of the starting material of the formula II or at any stage of the process for the manufacture of the starting material of the formula II that is described hereinafter.

In all subsequent conversions of resulting compounds of the formula I, those reactions are preferred which take place under neutral, alkaline or weakly acid conditions.

The process also includes those embodiments according to which compounds formed as intermediates are used as starting materials and the remaining process steps are carried out with them, or the process is discontinued at any stage. Furthermore, starting materials can be used in the form of derivatives or can be formed *in situ*, optionally under the reaction conditions. For example, a starting material of the formula II in which Z represents oxygen can be manufactured *in situ* from a compound of the formula II in which Z represents an optionally substituted methylidene group, as described hereinafter, by ozonisation and subsequent reduction of the ozonide formed, analogously to the process (Stage 3.3) described hereinafter, whereafter the cyclisation of the compound of the formula I is effected in the reaction solution.

The starting materials of the formula II and the precursors can be manufactured as indicated in reaction schemes I, II and III.

Reaction scheme I



(III) (IV) (V) (VI) (II')

In the compounds of the formulae IV, V, VI and II', Z' represents oxygen, sulphur or alternatively a methylidene group that is optionally substituted by one or two substituents Y and can be converted by oxidation into an oxo group Z. A substituent Y of this methylidene group is an organic radical, for example optionally substituted lower alkyl, for example methyl or ethyl, cycloalkyl, for example cyclopentyl or cyclohexyl, phenyl or phenyl-lower alkyl, for example benzyl, or, especially, an esterified carboxy group, including a carboxy group esterified by an optically active alcohol, such as 1-menthol, for example one of the optionally substituted lower alkoxycarbonyl or arylmethoxycarbonyl radicals mentioned under R_2^A or alternatively 1-menthyloxycarbonyl. This methylidene group preferably carries one of the mentioned substituents. Special mention should be made of the methoxycarbonylmethylidene, ethoxycarbonylmethylidene and the 1-menthyloxycarbonylmethylidene group Z'. The latter can be used for the manufacture of optically active compounds of the formulae IV to VI and II.

In the compounds of the formula III to VI and II', the radical R_3 is preferably one of the mentioned protected hydroxy groups, for example optionally substituted 1-phenyl-lower alkoxy, optionally substituted phenyl-lower alkoxycarbonyloxy, or tri-substituted silyloxy, and R_1 preferably represents substituted amino.

Stage 1.1

A thioazetidinone of the formula IV is obtained by treating a 4-W-azetidinone of the formula III in which W represents a nucleofugal leaving group with a mercapto compound of the formula

$$R_1—(CH_2)_4—C(=Z')—SH$$

or with a salt, for example an alkali metal salt, such as a sodium or potassium salt, thereof, and, if desired, in a resulting compound of the formula IV in which R_3 represents hydroxy, converting hydroxy into protected hydroxy.

The nucleofugal leaving group W in a starting material of the formula III is a radical that can be replaced by the nucleophilic radical $R_1—(CH_2)_4—C(=Z')—S—$. Such groups W are, for example, acyloxy radicals, sulphonyl radicals $R_o—SO_2—$ in which R_o is an organic radical, or azido or halogen. In an acyloxy radical W, acyl is, for example, the radical of an organic carboxylic acid, including an optically active carboxylic acid, and represents, for example, lower alkanoyl, for example acetyl or propionyl, optionally substituted benzoyl, for example benzoyl or 2,4-dinitrobenzoyl, phenyl-lower alkanoyl, for example phenylacetyl, or the acyl radical of one of the above-mentioned optically active acids. In a sulphonyl radical $R_o—SO_2—$, R_o is, for example, lower alkyl optionally substituted by hydroxy, such as methyl, ethyl at 2-hydroxyethyl, and also correspondingly substituted optically active lower alkyl, for example (2*R*)- or (2*S*)-1-hydroxyprop-2-yl, methyl substituted by an optically active radical, such as camphoryl, or benzyl, or optionally substituted phenyl, such as phenyl, 4-bromophenyl or 4-methylphenyl. A halogen radical W is, for example, bromine, iodine or, especially, chlorine. W is preferably methyl- or 2-hydroxyethyl-sulphonyl, acetoxy or chlorine.

The nucleophilic substitution can be carried out under neutral or weakly basic conditions in the presence of water and, optionally, a water-miscible organic solvent. The basic conditions can be produced, for example, by the addition of an inorganic base, such as an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, for example sodium, potassium or calcium hydroxide, carbonate or bicarbonate. As organic solvents there may be used, for example, water-miscible alcohols, for example lower alkanols, such as methanol or ethanol, ketones, for example lower alkanones, such as acetone, amides, for example lower alkanecarboxylic acid amides, such as dimethylformamide, acetonitrile and the like. The reaction is customarily carried out at room temperature but may also be carried out at elevated or reduced temperature. The reaction can be accelerated by the addition of a salt of hydriodic acid or of thiocyanic acid, for example an alkali metal salt, such as a sodium salt.

It is possible to use in the reaction optically inactive *cis*- or *trans*-compounds of the formula III and mixtures thereof, or corresponding optically active compounds. The group being introduced, $R_1—(CH_2)_4—C(=Z')—S—$, is directed by the group $R_3—CH_2—$ preferentially into the *trans*-position, irrespective of whether W is in the *cis*- or *trans*-position to the group $R_3—CH_2—$. Although the *trans*-isomers are predominantly formed, it is occasionally possible to isolate also the *cis*-isomers. The separation of the *cis*- and *trans*-isomers is effected as described above, according to conventional methods, especially by chromatography and/or by crystallisation.

The subsequent ozonisation of a methylidene group Z' can be effected as described hereinafter. A resulting racemate of the formula IV can be separated into the optically active compounds.

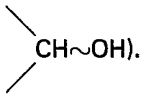
An azetidinone of the formula III in which R_3 and W each represent acetoxy is described in German Offenlegungsschrift No. 29 50 898. Other azetidinones of the formula III can be manufactured according to methods known *per se*, for example by reacting a vinyl ester of the formula $R_3—CH_2—CH=CH—W$ with chlorosulphonyl isocyanate and reacting the resulting cyclo adduct with a reducing agent, for example sodium sulphite. In this synthesis, mixtures of *cis*- and *trans*-isomers are customarily obtained which, if desired, can be separated into the pure *cis*- or *trans*-isomers, for example by chromatography and/or crystallisation or distillation. The pure *cis*- and *trans*-isomers are present in the form of racemates and can be separated into their optical antipodes, for example if acyl

in an acyloxy radical W in compounds of the formula III originates from an optically active acid. The compounds of the formula III, especially their optically active forms, can also be manufactured according to the processes given below in reaction schemes II and III.

Stage 1.2

An α-hydroxycarboxylic acid compound of the formula V is obtained by reacting a compound of the formula IV with a glyoxylic acid compound of the formula OHC—C(=O)—R_2^A or with a suitable derivative thereof, such as a hydrate, hemihydrate or semiacetal, for example a semiacetal with a lower alkanol, for example methanol or ethanol, and, if desired, in a resulting compound of the formula V in which R_3 represents hydroxy, converting hydroxy into protected hydroxy.

The compound of the formula V is customarily obtained in the form of a mixture of the two isomers (with respect to the group



It is also possible, however, to isolate the pure isomers thereof.

The addition of the glyoxylic acid ester compound to the nitrogen atom of the lactam ring is effected at room temperature or, if necessary, while heating, for example up to approximately 100°C, and in the absence of an actual condensation agent and/or without formation of a salt. When using the hydrate of the glyoxylic acid compound, water is formed which, if necessary, is removed by distillation, for example azeotropically, or by using a suitable dehydrating agent, such as a molecular sieve. It is preferable to carry out the operation in the presence of a suitable solvent, such as, for example, dioxan, toluene or dimethylformamide, or a solvent mixture, if desired or necessary in the atmosphere of an inert gas, such as nitrogen.

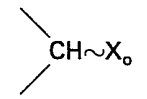
It is possible to use in the reaction pure optically inactive *cis*- or *trans*-compounds of the formula IV and mixtures thereof, or corresponding optically active compounds. A resulting racemate of the formula V can be separated into the optically active compounds.

Stage 1.3

Compounds of the formula VI in which X_o represents a reactive esterified hydroxy group, especially halogen or organic sulphonyloxy, are manufactured by, in a compound of the formula V, converting the secondary hydroxy group into a reactive esterified hydroxy group, especially into halogen, for example chlorine or bromine, or into an organic sulphonyloxy group, such as lower alkanesulphonyloxy, for example methanesulphonyloxy, or arenesulphonyloxy, for example benzene- or 4-methylbenzene-sulphonyloxy.

In the starting compounds of the formula V, R_3 preferably represents a protected hydroxy group.

The compounds of the formula VI can be obtained in the form of mixtures of the isomers (with respect to the



grouping) or in the form of pure isomers.

The above reaction is carried out by treatment with a suitable esterifying agent, for example with a thionyl halide, for example the chloride, a phosphorus oxyhalide, especially the oxychloride, a halophosphonium halide, such as triphenyl phosphono-dibromide or -diiodide, or a suitable organic sulphonic acid halide, such as the chloride, preferably in the presence of a basic agent, especially an organic basic agent, such as an aliphatic tertiary amine, for example triethylamine, diisopropylethylamine or "polystyrene Hünig base" or a heterocyclic base of the pyridine type, for example pyridine or collidine. The operation is preferably carried out in the presence of a suitable solvent, for example dioxan or tetrahydrofuran, or a solvent mixture, if necessary while cooling and/or in the atmosphere of an inert gas, such as nitrogen.

In a compound of the formula VI obtainable in this manner, a reactive esterified hydroxy group X_o can be converted into a different reactive esterified hydroxy group in a manner known *per se*. Thus, for example, a chlorine atom can be replaced by a bromine or iodine atom by treatment of the corresponding chlorine compound with a suitable bromide or iodide salt, such as lithium bromide or iodide, preferably in the presence of a suitable solvent, such as ether.

It is possible to use in the reaction pure optically inactive *cis*- or *trans*-compounds of the formula V and mixtures thereof, or corresponding optically active compounds. A resulting racemate of the formula VI can be separated into the optically active compounds.

Stage 1.4

The starting material of the formula II' is obtained by treating a compound of the formula VI in which X_o represents a reactive esterified hydroxy group with a suitable phosphine compound, such as a

tri-lower alkylphosphine, for example tri-n-butylphosphine, or a triarylphosphine, for example triphenylphosphine, or with a suitable phosphite compound, such as a tri-lower alkyl phosphite, for example triethyl phosphite, or an alkali metal di-lower alkyl phosphite, for example diethyl phosphite, it being possible, depending upon the reagent chosen, to obtain a compound of the formula II (or II') or IIa.

The above reaction is preferably carried out in the presence of a suitable inert solvent, such as a hydrocarbon, for example hexane, cyclohexane, benzene, toluene or xylene, or an ether, for example dioxan, tetrahydrofuran or diethylene glycol dimethyl ether, or a solvent mixture. Depending upon reactivity, the operation is carried out while cooling or at elevated temperature, approximately between −10° and +100°, preferably at approximately 20° to 80°, and/or in the atmosphere of an inert gas, such as nitrogen. In order to hinder oxidative processes taking place catalytic amounts of an antioxidant, for example hydroquinone, can be added.

When using a phosphine compound, the operation is customarily carried out in the presence of a basic agent, such as an organic base, for example an amine, such as triethylamine, diisopropylethylamine or "polystyrene Hünig base", and there is thus obtained directly the ylide starting material of the formula II (or II') which is formed from the corresponding phosphonium salt.

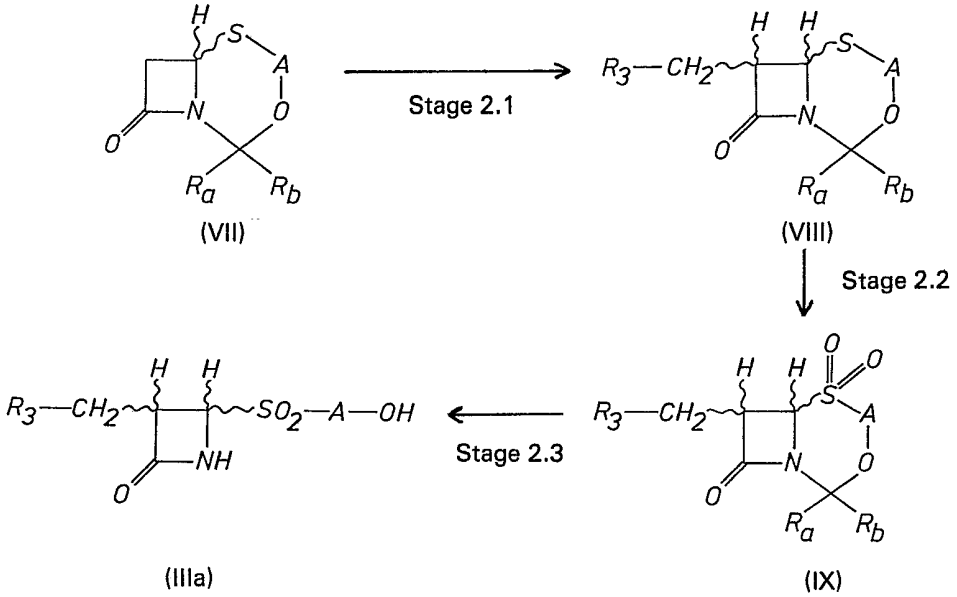
It is possible to use in the reaction pure, optically inactive *cis*- or *trans*-compounds of the formula VI and mixtures thereof, or corresponding optically active compounds. A resulting racemate of the formula II can be separated into the optically active compounds.

The ylides of the formula II' in which Z' represents oxygen or sulphur can be used directly in the cyclisation reaction for the manufacture of the end products of the formula I. It is also possible, however, in compounds of the formula II' in which R_3 represents a protected hydroxy group, for example a protected hydroxy group that can readily be cleaved by hydrolysis, such as tri-substituted silyloxy, first to remove the hydroxy-protecting group and then to use the resulting compound of the formula II' in which R_3 represents hydroxy in the cyclisation reaction. Furthermore, in compounds of the formula II' in which R_1 represents protected amino, the amino-protecting group can be removed.

In the compounds of the formulae II', IV, V and VI, an optionally substituted methylidene group Z' can be converted into the oxo group Z by ozonisation and subsequent reduction of the ozonide formed, according to the process described hereinafter in stage 3.3.

Starting compounds of the formula III in which W represents a sulphonyl radical HO—A—SO_2— can also be manufactured according to the following reaction scheme II.

Reaction scheme II



(VII) (VIII) (IX) (IIIa)

In the compounds of the formulae (VII) to (IX) and (IIIa), A represents a lower alkylene radical having 2 or 3 carbon atoms between the two hetero atoms and represents especially ethylene or 1,2-propylene, but may also represent 1,3-propylene, 1,2-, 2,3- or 1,3-butylene.

In the compounds of the formulae (VII) to (IX), each of the radicals R_a and R_b represents hydrogen or an organic radical bonded *via* a carbon atom to the ring carbon atom, it being possible for the two radicals R_a and R_b to be linked to one another, and represents especially hydrogen, lower alkyl, for example methyl, ethyl, n-propyl, or isopropyl, optionally substituted phenyl, or phenyl-lower alkyl, for example benzyl, or, if taken together, represent lower alkylene preferably having from 4 to 6 carbon atoms, for example 1,4-butylene or 1,5-pentylene.

In the compounds of the formulae (VIII), (IX) and (IIIa), the radical R_3 represents hydroxy or,

preferably, one of the mentioned protected hydroxy groups, for example optionally substituted 1-phenyl-lower alkoxy, optionally substituted phenyl-lower alkoxycarbonyloxy or tri-substituted silyloxy.

Stage 2.1

A compound of the formula (VIII) is obtained by reacting a bicyclic compound of the formula (VII) with a metallating reagent and an electrophilic agent that introduces the radical $R_3—CH_2—$, then treating the resulting product with a proton source and, if desired, converting a resulting compound of the formula VIII in which R_3 represents hydroxy into a compound of the formula VIII in which R_3 represents protected hydroxy.

Suitable metallating reagents are, for example, substituted and unsubstituted alkali metal amides, alkali metal hydrides or alkali metal-lower alkyl compounds in which the alkali metal is, for example, sodium or, especially, lithium, for example sodium or lithium amide, lithium bis-trimethylsilylamide, sodium hydride lithium hydride and, preferably, lithium diisopropylamide and butyllithium.

An electrophilic agent that introduces the radical $R_3—CH_2—$ is, for example, formaldehyde, there being formed compounds of the formula (VIII) in which R_3 represents hydrogen, or a functional derivative of formaldehyde of the formula $R_3—CH_2—X$ in which X represents a nucleofugal leaving group, especially halogen, for example chlorine, bromine or iodine, or sulphonyloxy, for example methanesulphonyloxy or 4-toluenesulphonyloxy. Preferred electrophilic agents that introduce the radical $R_3—CH_2—$ are formaldehyde and optionally substituted benzyloxymethyl chloride.

Solvents suitable for the metallating reaction must not contain active hydrogen and are, for example, hydrocarbons, for example hexane, benzene, toluene or xylene, ethers, for example diethyl ether, tetrahydrofuran or dioxan, or acid amides, for examples hexamethylphosphoric acid triamide.

The metallated intermediate need not be isolated but, subsequent to the metallating reaction, can be reacted with an electrophilic agent that introduces the radical $R_3—CH_2—$. The metallating reaction takes place at temperatures of from approximately −100°C to approximately room temperature, preferably at below −30°C, and preferably in an inert gas atmosphere, such as a nitrogen atmosphere. The further reaction can take place under the same conditions. Formaldehyde is preferably introduced into the reaction mixture in gaseous, monomeric form. Monomeric formaldehyde can be obtained, for example, by thermal depolymerisation of paraformaldehyde or by thermal decomposition of formaldehydecyclohexyl hemiacetal.

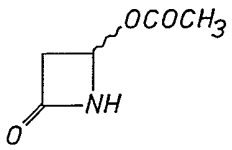
It is possible to use for the metallating reaction both the antipodes of compounds of the formula (VII) and their racemic or diastereoisomeric mixtures.

The action of the electrophilic agent that introduces the radical $R_3—CH_2—$ on the substrate generally takes place stereospecifically. If there is used as starting material an azetidinone of the formula (VII) having the *R*-configuration at carbon atom 4 of the azetidinone ring, there is produced predominantly a compound of the formula (VIII) having the *R*-configuration at carbon atom 4 and the *S*-configuration at carbon atom 3 of the azetidinone ring, that is to say the action of the electrophilic agent takes place predominantly in the *trans*-position.

After the reaction, the reaction product is treated with a proton source, for example with water, an alcohol, such as methanol or ethanol, an organic or inorganic acid, for example acetic acid, hydrochloric acid, sulphuric acid, or a similar compound that yields protons, again preferably at low temperatures.

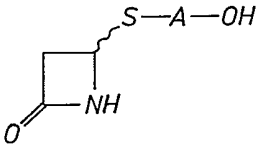
In a resulting compound of the formula (VIII) in which R_3 represents hydrogen, the hydroxy group can be protected in a manner known *per se*, for example by etherification or esterification, especially as described above.

Starting compounds of the formula (VII) can be obtained, for example by reacting an acetate of the formula



(X)

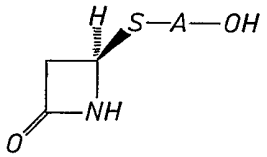
with a mercapto compound of the formula HS—A—OH, and treating the resulting thio compound of the formula



(Xa),

as described in European Patent Application No. 23887, with a carbonyl compound of the formula $(R_a,R_b)C=O$.

In the reaction of acetates of the formula (X) with mercaptans of the formula HS—A—OH that have a chirality centre in A, for example antipodes of a 2-mercaptopropan-1-ol, such as (2*R*)-2-mercaptopropan-1-ol, there are formed diastereoisomeric mixtures of compounds of the formula (Xa) which can be separated into the individual antipodes by customary methods, for example as described above. The individual antipodes, for example the (4*R*)-antipode of the formula



(Xb)

may be processed further, without the configuration being altered, to form the corresponding antipodes of the intermediates (II) to (VI), (VIII) and (IX) mentioned in reaction schemes I and II and of the end products of the formula (I). Since, as described above, the introduction of the optionally protected hydroxymethyl substituent into the azetidinone ring of the compound of the formula (VII) takes place stereospecifically (*trans*), it is possible to obtain, using compounds of the formula (Xb) as starting materials, intermediates of the formulae (II) to (VI), (VIII) and (IX) and end products of the formula (I) in which the azetidinone ring assumes the *R*-configuration in the 4-position and the *S*-configuration in the 3-position.

Stage 2.2

A sulphone of the formula IX can be manufactured by treating a thio compound of the formula III with an oxidising agent and, if desired, converting a compound of the formula IX obtainable according to the process in which R_3 represents hydroxy into a compound of the formula IX in which R_3 represents a protected hydroxy group.

Suitable oxidising agents are, for example, hydrogen peroxide, organic peracids, especially aliphatic or aromatic percarboxylic acids, for example peracetic acid, perbenzoic acid, chloroperbenzoic acid, for example 3-chloroperbenzoic acid, or monoperphthalic acid, oxidising inorganic acids and salts thereof, for example nitric acid, chromic acid, potassium permanganate, or alkali metal hypochlorites, for example sodium hypochlorite. The conversion may, however, also be effected by anodic oxidation.

The oxidation is preferably carried out in a suitable inert solvent, for example a halogenated hydrocarbon, for example methylene chloride, chloroform or carbon tetrachloride, an alcohol, for example methanol or ethanol, a ketone, for example acetone, an ether, diethyl ether, dioxan or tetrahydrofuran, an amide, for example dimethylformamide, a sulphone, for example dimethylsulphone, a liquid organic carboxylic acid, for example acetic acid, or in water or in a mixture of these solvents, especially a water-containing mixture, for example aqueous acetic acid, and at room temperature, or while cooling or gently heating, that is to say at from approximately −20° to approximately +90°C, but preferably at approximately room temperature. The oxidation may also be carried out in steps by first oxidising to the sulphoxide, which is optionally isolated, this being carried out at low temperature, that is to say at from approximately −20° to approximately 0°C, and then, in a second step preferably carried out at elevated temperature, for example at room temperature, oxidising the sulphoxide to form the sulphone of the formula (IX).

For working up, excess oxidising agent which may still be present can be destroyed by reduction, especially by treatment with a reducing agent, such as a thiosulphate, for example sodium thiosulphate.

It is possible to use in the reaction both optically inactive compounds of the formula (VIII) and corresponding optically active compounds, especially those having the 3*S*,4*R*-configuration in the azetidinone ring.

Stage 2.3

Compounds of the formula (IIIa) can be manufactured by solvolysing a bicyclic amide of the formula (IX) with a suitable solvolysis reagent and, if desired, in a compound of the formula (IIIa) obtainable according to the process, converting a free hydroxy group R_3 into a protected hydroxy group R_3.

Suitable solvolysis reagents are, for example, organic acids, for example lower alkanecarboxylic acids, such as formic acid or acetic acid, or sulphonic acids, for example 4-toluenesulphonic acid or methanesulphonic acid, mineral acids, for example sulphuric or hydrochloric acid, and also lower alkanols, for example methanol or ethanol, or lower alkanediols, for example ethylene glycol.

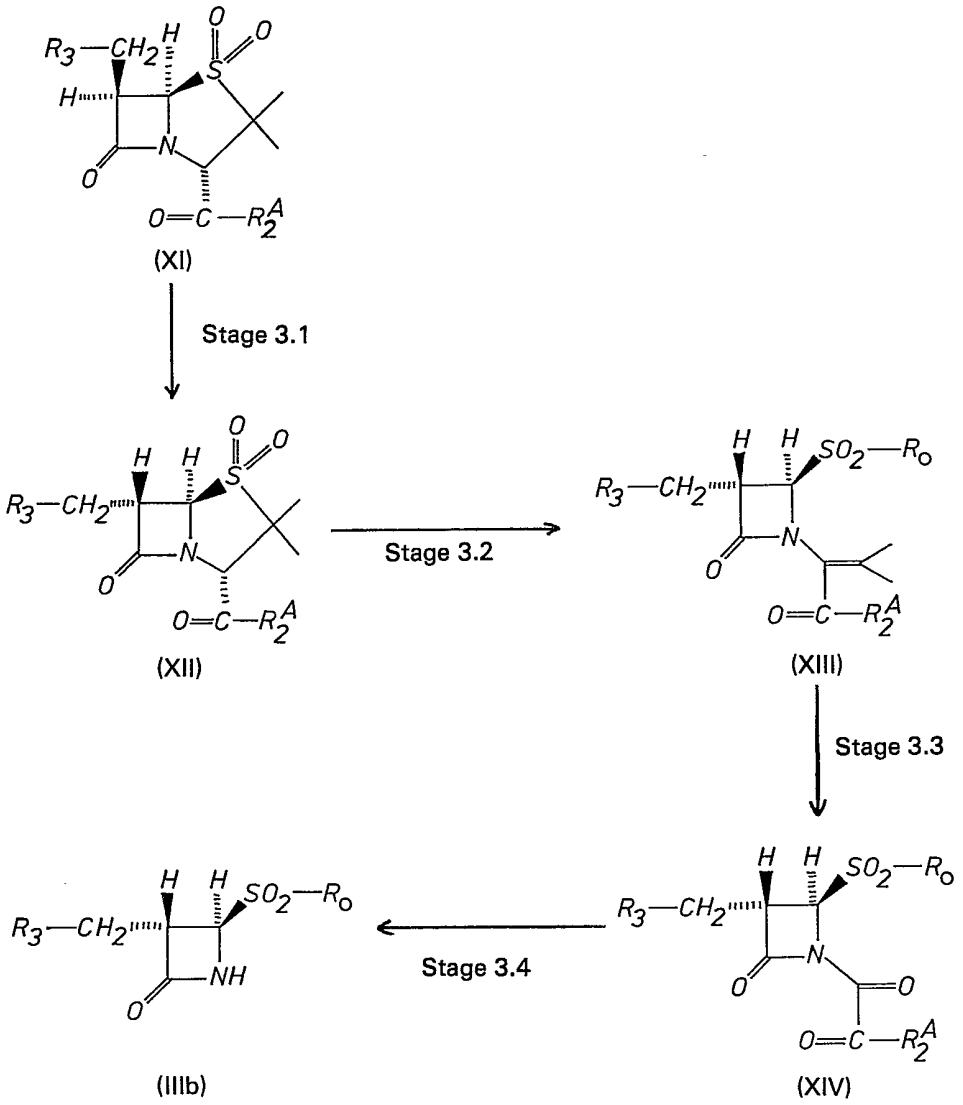
The mentioned solvolysis reagents are added undiluted or diluted with water. The solvolysis can also be carried out with pure water. The solvolysis with the acidic reagent is preferably effected in an aqueous solution of this reagent and at temperatures of from approximately −20° to approximately 150°C, preferably at from room temperature to 110°C.

It is possible to use in the reaction both optically inactive compounds of the formula (IX), for example racemates or diastereoisomeric mixtures, and corresponding optically active compounds, especially those having the 3*S*,4*R*-configuration in the azetidinone ring.

Resulting isomeric mixtures of compounds of the formulae (VIII), (IX) and (IIIa), such as racemates or diastereoisomeric mixtures, can be separated into the individual isomers, such as antipodes, in a manner known *per se*, for example as described above.

Optically active *trans*-compounds of the formula (III) that can be used according to the invention can be manufactured also according to the following reaction scheme III:

Reaction scheme III



In the compounds of the formulae (XI) to (XIV) and (IIIb), R_3 represents hydroxy or, especially, a protected hydroxy group.

Stage 3.1

Compounds of the formula (XII) are known or can be manufactured in a manner known *per se*. They can also be manufactured according to a novel process by epimerising a compound of the formula (XI) and, if desired, in a compound of the formula (XII) obtainable according to the process, converting a protected hydroxy group R_3 into a different protected hydroxy group R_3.

The epimerisation is effected, for example, in the presence of a basic agent, such as an amine, for example a tri-lower alkylamine, for example triethylamine or ethyldiisopropylamine, a tertiary amine, for example N,N-dimethylaniline, an aromatic amine, for example pyridine, or a bicyclic amine, for example 1,5-diazabicyclo[5.4.0]undec-5-ene or 1,5-diazabicyclo[4.3.0]non-5-ene, or an alkali metal-lower alkoxide, for example sodium methoxide, sodium ethoxide or potassium tert.-butoxide, in an inert solvent, for example an ether, for example diethyl ether, dimethoxyethane, tetrahydrofuran or dioxan, acetonitrile or dimethylformamide, optionally at slightly elevated or reduced temperature, for example at from 0° to 50°C, but preferably at room temperature.

In the compounds of the formula (XII) obtainable according to the process, a protected hydroxy group R_3 can be replaced by a different protected hydroxy group R_3, for example a protected hydroxy

group that can be cleaved by hydrogenolysis can be replaced by a protected hydroxy group that can be cleaved by solvolysis. Hydroxy-protecting groups are especially the above-mentioned protecting groups that can be removed by hydrogenolysis, for example 1-phenyl-lower alkyl or phenyl-lower alkoxycarbonyl, each substituted as indicated, or protecting groups that can be removed by solvolysis, for example silyl tri-substituted as indicated.

The reaction can be carried out by first removing the hydroxy-protecting group that can be removed by hydrogenolysis and then introducing into the resulting compound of the formula XII in which R_3 represents hydroxy a hydroxy-protecting group that can be removed by solvolysis.

The removal of a protecting group that can be removed by hydrogenolysis is effected, for example, with hydrogen or a hydrogen-donor, for example cyclohexene or cyclohexadiene, in the presence of a hydrogenation catalyst, such as a palladium catalyst, for example palladium-on-carbon, in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, a lower alkanol, for example methanol or ethanol, an ether, for example dioxan or tetrahydrofuran, or alternatively in water or in mixtures thereof, at a temperature of from approximately 0° to approximately 80°C, preferably at room temperature. The removal can also be carried out with a reducing metal, such as zinc, or a reducing metal alloy, for example a copper/zinc alloy, in the presence of an agent that yields protons, such as an organic acid, for example acetic acid, or alternatively a lower alkanol, for example ethanol.

The introduction of a hydroxy-protecting group that can be removed by solvolysis is effected, for example, with a compound of the formula $R_3'—X_3$ in which R_3' represents the hydroxy-protecting group and X_3 represents, for example, a reactive esterified hydroxy group, for example halogen, for example chlorine, bromine or iodine, or sulphonyloxy, such as methanesulphonyloxy, benzenesulphonyloxy or 4-toluenesulphonyloxy.

The reaction is effected in an inert solvent, such as an ether, for example diethyl ether, dioxan or tetrahydrofuran, a hydrocarbon, for example benzene or toluene, a halogenated hydrocarbon, for example methylene chloride, in dimethyl sulphoxide or acetonitrile, in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, for example sodium or potassium hydroxide or sodium or potassium carbonate, an alkali metal amide or hydride, for example sodium amide or sodium hydride, an alkali metal lower alkoxide, for example sodium methoxide or ethoxide or potassium tert.-butoxide, or an amine, for example triethylamine, pyridine or imidazole, at room temperature or at elevated or reduced temperature, for example at from approximately —20° to approximately 80°C, but preferably at room temperature.

Starting compounds of the formula (XI) are known, for example, from German Offenlegungsschrift No. 3 039 504 and from British Patent Application No. 20 61 930.

Stage 3.2

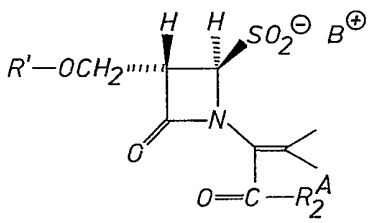
A compound of the formula (XIII) can be manufactured by treating a penam compound of the formula (XII) with a basic agent and with an esterifying agent that introduces the radical R_o.

A suitable basic agent is, for example, one of the basic agents mentioned under stage 3.1, especially one of the mentioned bicyclic amines, and also an alkali metal amide or hydride, for example sodium amide or sodium hydride.

A radical R_o is, for example, one of the organic radicals mentioned under stage 1.1, especially optionally substituted lower alkyl, for example methyl, ethyl or 2-hydroxyethyl, or benzyl.

An esterifying agent that introduces the radical R_o is, for example, a compound of the formula $R_o—X_4$ in which X_4 represents reactive esterified hydroxy, for example halogen, such as chlorine, bromine or iodine, or sulphonyloxy, such as methanesulphonyloxy, benzenesulphonyloxy or 4-toluenesulphonyloxy. For the introduction of a 2-hydroxyethyl radical, also ethylene oxide is suitable.

The reaction is preferably carried out in two steps; in the first step the penam compound of the formula (XIII) is treated with at least equimolar amounts of the basic agent and a resulting intermediate of the formula



(XIIIa)

in which $B^{\oplus}$ represents the protonated form (cation) of the basic agent, is reacted with the esterifying agent, preferably without being isolated from the reaction mixture. The reaction is carried out in an inert solvent, for example an ether, for example diethyl ether, dimethoxyethane, tetrahydrofuran or dioxan, in acetonitrile, dimethylformamide or hexamethylphosphoric acid triamide, optionally at slightly elevated or reduced temperature, for example at approximately 0° to 50°C, but preferably at room temperature. In a preferred embodiment of the process, the penam compound of the formula (XII) is

manufactured *in situ* by, as described in stage 3.1, first treating a compound of the formula (XI) with catalytic amounts of the basic agent, for example 1,5-diazabicyclo[5.4.0]-undec-5-ene, and then reacting the product with at least equimolar amounts of the same basic agent and the esterifying agent to form the compounds of the formula (XIII).

Stage 3.3

An oxalylazetidinone of the formula (XIV) can be manufactured by ozonising a compound of the formula (XIII) and cleaving the ozonide formed by reduction to form the oxo compound.

The ozonisation is customarily carried out with a mixture of ozone and oxygen in an inert solvent, such as a lower alkanol, for example methanol or ethanol, a lower alkanone, for example acetone, an optionally halogenated hydrocarbon, for example a halo-lower alkane, such as methylene chloride or carbon tetrachloride, or in a solvent mixture, including an aqueous mixture, preferably while cooling, for example at temperatures of from approximately −80° to approximately 0°C.

An ozonide obtained as intermediate is cleaved by reduction, customarily without being isolated, to form a compound of the formula XIV, there being used catalytically activated hydrogen, for example hydrogen in the presence of a heavy metal hydrogenation catalyst, such as a nickel catalyst and also a palladium catalyst, preferably on a suitable carrier, such as calcium carbonate or carbon, or chemical reducing agents, such as reducing heavy metals, including heavy metal alloys or amalgams, for example zinc, in the presence of a hydrogen-donor, such as an acid, for example acetic acid, or an alcohol, for example lower alkanol, reducing inorganic salts, such as alkali metal iodides, for example sodium iodide, or alkali metal bisulphites, for example sodium bisulphite, in the presence of a hydrogen-donor, such as an acid, for example acetic acid, or water, or reducing organic compounds, such as formic acid. As reducing agents there may also be used compounds that can readily be converted into corresponding epoxide compounds or oxides, it being possible for the epoxide formation to be effected as a result of a C—C double bond and the oxide formation in view of the presence of an oxide-forming hetero atom, such as a sulphur, phosphorus or nitrogen atom. Such compounds are, for example, suitably substituted ethene compounds (which are converted into ethylene oxide compounds in the reaction), such as tetracyanoethylene; or, especially, suitable sulphide compounds (which are converted into sulphoxide compounds in the reaction), such as di-lower alkyl sulphides, especially dimethyl sulphide; suitable organic phosphorus compounds, such as a phosphine optionally substituted by phenyl and/or lower alkyl, for example methyl, ethyl, n-propyl or n-butyl (which phosphine is converted into a phosphine oxide in the reaction), such as tri-lower alkylphosphines, for example tri-n-butylphosphine, or triphenylphosphine; and also tri-lower alkyl phosphites (which are converted into phosphoric acid tri-lower alkyl esters in the reaction), customarily in the form of corresponding alcohol adduct compounds, such as trimethyl phosphite, or phosphorous acid triamides, which optionally contain lower alkyl as substituent, such as hexa-lower alkyl phosphorous acid triamides, for example hexamethylphosphorous acid triamide, the latter preferably being in the form of a methanol adduct; and also suitable nitrogen bases (which are converted into the corresponding N-oxides in the reaction), such as heterocyclic nitrogen bases of aromatic character, for example bases of the pyridine type and, especially, pyridine itself. The cleaving of the ozonide, which customarily is not isolated, is normally effected under the same conditions as those used for its manufacture, that is to say, in the presence of a suitable solvent or solvent mixture, and while cooling or heating gently, the operation preferably being carried out at temperatures of from approximately −10° to approximately +25°C, and the reaction customarily being concluded at room temperature.

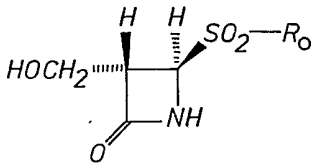
Stage 3.4

An azetidinone of the formula (IIIb) can be manufactured by solvolysing an oxalylazetidinone of the formula (XIV).

The solvolysis can be carried out in the form of hydrolysis, alcoholysis or alternatively in the form of hydrazinolysis. Hydrolysis is carried out with water, optionally in a water-miscible solvent. Alcoholysis is customarily carried out with a lower alkanol, for example methanol or ethanol, preferably in the presence of water and an organic solvent, such as a lower alkanecarboxylic acid lower alkyl ester, for example ethyl acetate, preferably at room temperature, if necessary while cooling or heating, for example at a temperature of from approximately 0° to approximately 80°C. Hydrazinolysis is carried out in conventional manner with a substituted hydrazine, for example with phenyl- or a nitrophenyl-hydrazine, such as 2-nitrophenylhydrazine, 4-nitrophenylhydrazine or 2,4-dinitrophenyl-hydrazine, which is preferably used in an approximately equimolar amount, in an organic solvent, such as an ether, for example tetrahydrofuran, dioxan, diethyl ether, an aromatic hydrocarbon, such as benzene or toluene, a halogenated hydrocarbon, such as methylene chloride, chlorobenzene or dichlorobenzene, an ester, such as ethyl acetate, and the like, at temperatures of between approximately room temperature and approximately 65°C.

In a preferred embodiment of the process, a compound of the formula (XIII) is used as starting material and is ozonised as indicated and then cleaved by reduction to form an oxalylazetidinone of the formula (XIV) which is reacted further, without being isolated from the reaction mixture, to form an azetidinone of the formula (IIIb).

In the ozonolysis there may be produced small amounts of acid which can effect the removal of a radical R_3 that can readily be removed by solvolysis, for example a tri-substituted silyl radical. The resulting compound of the formula



(IIIb')

can be separated from the protected azetidinone, for example by chromatography, and converted into the azetidinone of the formula (IIIb) by fresh reaction with the agent of the formula R_3'—X_3 that introduces the hydroxy-protecting group R_3'.

In the compounds of the formulae (II), (II'), (V), (VI) and (XII) to (XIV), a group R_2^A can be converted into a different group R_2^A according to methods known *per se*, and when so doing it is possible, taking into consideration the other functional groups which may be contained in these compounds, to use the same methods as those indicated for the conversion of this substituent in the compounds of the formula (I).

The invention relates also to novel starting materials and to novel intermediates obtainable according to the process, such as those of the formula (II) to (IV), (VIII), (IX) and (XII) to (XIV) and to the processes given for their manufacture.

The starting materials used and the reaction conditions chosen are preferably those which result in the compounds described above as being especially preferred.

The pharmacologically acceptable compounds of the present invention can be used, for example, for the manufacture of pharmaceutical preparations that contain an effective amount of the active ingredient together or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers that are suitable for oral or for parenteral, that is to say intramuscular, subcutaneous or intraperitoneal, administration.

For oral administration there are used tablets or gelatine capsules that contain the active ingredient together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol; tablets also contain binders, for example magnesium aluminium silicate, starches, such as maize, wheat, rice or arrowroot starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures or adsorbents, colourings, flavourings or sweeteners.

For parenteral administration there are suitable especially infusion solutions, preferably isotonic aqueous solutions or suspensions, it being possible to prepare these before use, for example from lyophilised preparations that contain the active ingredient alone or together with a carrier, for example mannitol. Such preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

The present pharmaceutical preparations, which, if desired, may contain other pharmacologically active substances, are manufactured in a manner known *per se*, for example by means of conventional mixing, dissolving or lyophilising processes, and contain approximately from 0.1 to 100%, especially from approximately 1 to approximately 50% or, in the case of lyophilisates, up to 100%, of the active ingredient.

Depending upon the type of infection and the condition of the infected organism, the daily dose to be administered for the treatment of a warm-blooded animal (human or animal) weighing approximately 70 kg is from approximately 0.1 g to approximately 5 g [and in the case of oral administration of (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethylpenem-3-carboxylic acid, for example two daily doses of approximately from 0.25 g to 1 g].

The following Examples serve to illustrate the invention. Temperatures are given in degrees Centigrade.

The following abbreviations are used in the Examples:

TLC: thin-layer chromatography
IR: infra-red spectrum
UV: ultraviolet spectrum
M.p.: melting point
DBU: 1,5-diazabicyclo[5.4.0]undec-5-ene

Example 1

***trans*-2,2-dimethyl-8-hydroxymethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one**

At −65° under nitrogen, a 2.0 M solution of n-butyllithium in n-hexane (0.11 mol) is added dropwise, while stirring, to a solution of 11.0 g (15.5 ml, 0.11 mol) of diisopropylamine in 200 ml of

dry tetrahydrofuran. The mixture is stirred at —65° for 15 minutes. Then, while stirring at —65°, a solution of 18.7 g (0.1 mol) of 2,2-dimethyl-3-oxa-6-thia- 1-azabicyclo[5.2.0]nonan-9-one in 80 ml of dry tetrahydrofuran is added over a period of 15 minutes. The mixture is then stirred at —65° for a further 10 minutes. Formaldehyde gas is produced in a separate flask by heating to 150° the formaldehyde/cyclohexanol adduct that is formed in conventional manner by reacting an aqueous solution of formaldehyde with cyclohexanol. An excess amount of dry formaldehyde gas is then slowly stirred through the reaction mixture at —65°. The mixture is stirred at —65° for 30 minutes. The cold reaction mixture is poured onto a mixture of 250 g of ice and 250 g of water. 250 ml of chloroform and 110 ml of 2.0 N hydrochloric acid are added. After shaking the mixture, the organic layer is separated off. After the addition of 60 g of sodium chloride, the aqueous layer is then extracted twice with chloroform. The organic solution is dried over sodium sulphate and filtered. The solvent is removed by evaporation. The resulting residue is a yellowish oily liquid.

Example 2
(5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-hydroxymethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one

This compound is obtained in a manner analogous to that described in Example 1 by reacting the metallated (5*R*,7*R*)-2,2,5-trimethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]-nonan-9-one with formaldehyde.

Example 3
***trans*-2,2-dimethyl-8-(4-nitrobenzyloxy-carbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one**

21.6 g (0.1 mol) of solid chlorocarbonic acid 4-nitrobenzyl ester are added to —10° to a solution of 22 g of crude *trans*-2,2-dimethyl-8-hydroxymethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one in 250 ml of methylene chloride. 12.2 g (0.1 mol) of solid 4-dimethylaminopyridine are added to the solution in small portions over a period of 30 minutes. The mixture is stirred at from 3 to 5° for 4 hours. The cold mixture is washed with 200 ml of 0.5 N aqueous hydrochloric acid and an aqueous sodium chloride solution.

The organic phase is dried over sodium sulphate and filtered. The solvent is removed by evaporation. The resulting residue is a yellow foam. Recrystallisation from isopropanol yields a solid.

Melting point: 82°.

Example 4
(5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one

This compound is obtained in a manner analogous to that described in Example 3 by reacting (5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-hydroxymethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one with chlorocarbonic acid 4-nitrobenzyl ester in the presence of 4-dimethylaminopyridine.

Example 5
***trans*-2,2-dimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one-6-dioxide**

At —10°, 47.8 g (0.25 mol) of *m*-chloroperbenzoic acid are added, in small portions, over a period of 30 minutes to a solution of approximately 40 g of *trans*-2,2-dimethyl-8-(4-nitrobenzyloxy-carbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one in 500 ml of methylene chloride. The mixture is then stirred at 0° for 1 hour and washed with saturated aqueous sodium bicarbonate solution, 10% strength sodium bisulphite solution and again with saturated aqueous sodium bicarbonate solution. The organic layer is dried over sodium sulphate and filtered. The solvent is removed by evaporation. The resulting residue is a solid which is recrystallised from isopropanol.

Melting point: 158°.

Example 6
(5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one-6-dioxide

This compound is obtained in a manner analogous to that described in Example 5 by reacting (5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one with *m*-chloroperbenzoic acid.

Example 7
***trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(2-hydroxyethylsulphonyl)-azetidin-2-one**

4.35 g (10 mmol) of *trans*-2,2-dimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicylo[5.2.0]nonan-9-one-6-dioxide are dissolved in 130 ml of glacial acetic acid and the solution is diluted with 30 ml of water. The temperature of the mixture is maintained at 55° for a period of 4 days. The solvent is removed by evaporation. The residue is dissolved in ethyl acetate and washed with 30 ml of aqueous sodium bicarbonate solution. The organic layer is separated off. The aqueous layer is extracted with ethyl acetate. The organic phase is dried over sodium sulphate and filtered. The solvent

is removed by evaporation. A viscous residue is obtained. Purification by chromatography and recrystallisation from isopropanol yields a solid.

Melting point: 128°.

Example 8

(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[(2*R*)-1-hydroxy-2-propylsulphonyl]-azetidin-2-one

This compound is obtained in a manner analogous to that described in Example 7 by hydrolysing (5*R*,7*R*,8*S*)-2,2,5-trimethyl-8-(4-nitrobenzyloxycarbonyloxymethyl)-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one-6-dioxide with a solution of glacial acetic acid in water.

Example 9

***trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[5-(4-nitrobenzyloxycarbonylamino)-valeroylthio]-azetidin-2-one**

To a suspension, stirred for 30 minutes, of *trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(2-hydroxyethylsulphonyl)-azetidin-2-one (8.536 g, 22 mmol) in 14.5 ml of acetonitrile, 29 ml of acetone and 145.2 ml of phosphate buffer pH 8 there is added dropwise, while stirring, over a period of 60 minutes and at room temperature a mixture of 5-(4-nitrobenzyloxycarbonylamino)-thiovaleric acid, 26.4 ml of 1 N NaOH, 26.4 ml of water and 6 ml of acetonitrile. The mixture is then stirred at room temperature for exactly 90 minutes and the resulting milky emulsion is taken up in 250 ml of ethyl acetate. The aqueous phase is extracted with two 250 ml portions of ethyl acetate and the extracts are combined and dried over Na_2SO_4. Filtration and concentration of the solvent by evaporation *in vacuo* yield a yellowish viscous oil. Chromatography over 240 g of Merck silica gel with CH_2Cl_2/ethyl acetate (3:1) yields pure amorphous product.

IR in CH_2Cl_2: 3650, 3000, 1790, 1760, 1730, 1520, 1340, 1220 cm^{-1}.

The starting material can be prepared as follows:

a) 5-(4-nitrobenzyloxycarbonylamino)-valeric acid

Solid chloroformic acid 4-nitrobenzyl ester (28.0 g, 0.13 mol) is added at room temperature to a solution of 5-aminovaleric acid (11.7 g, 0.1 mol) in 100 ml of 1N NaOH solution, and 120 ml of 1N NaOH solution are added to the resulting beige suspension over a period of 40 minutes. The reaction mixture is then stirred at room temperature for 38 hours. The mixture is washed with two 180 ml portions of $CHCl_3$ and the aqueous phase is adjusted to pH 2 with 5N HCl. The white suspension is filtered and the residue is dried under a high vacuum. The filtrate is extracted with $CHCl_3$ (2×250 ml) and the organic phase is dried over Na_2SO_4 and concentrated by evaporation *in vacuo*. The residue is combined with the filter residue. Crystallisation from 200 ml of hot isopropanol yields, after 3 days at 0°, pure crystalline product.

Melting point: 85—87°.

b) 5-(4-nitrobenzyloxycarbonylamino)-thiovaleric acid

5-(4-nitrobenzyloxycarbonylamino)-valeric acid (59.25 g, 0.2 mol) is suspended in methylene chloride (300 ml) and dissolved by the addition of triethylamine (61.2 ml, 0.44 mol). While stirring at −10°, there is then added dropwise to this solution over a period of 30 minutes a solution of chloroformic acid isobutyl ester (28.8 ml) in methylene chloride (60 ml). After this addition, the mixture is stirred for a further 30 minutes at 0°. H_2S is then introduced at 0° for a period of 60 minutes. After removing the excess H_2S with nitrogen, the suspension is dissolved with $CHCl_3$ (1.5 l) and washed with two 250 ml portions of aqueous 2N HCl. The organic phase is extracted with 600 ml of saturated sodium bicarbonate solution and, while stirring, the aqueous phase is carefully rendered acidic with 6N aqueous HCl in an Erlenmeyer flask. The aqueous solution is extracted with two 1 l portions of $CHCl_3$ and the organic phase is dried over Na_2SO_4 and then filtered. Concentration of the solvent by evaporation *in vacuo* yields the product in the form of a yellow oil that crystallises in the refrigerator.

Melting point: approximately 35°.

Example 10

(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[5-(4-nitrobenzyloxycarbonylamino)-valeroylthio]-azetidin-2-one

Following the same procedure as that described in Example 9 and using as starting material (3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[(2*R*)-1-hydroxy-2-propylsulphonyl]-azetidin-2-one, there is obtained the title compound having an identical IR spectrum.

$[\alpha]_D^{20}$+61° (c=1, $CHCl_3$).

Example 11

2-[*trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-hydroxyacetic acid 4-nitrobenzyl ester

16.3 g of molecular sieve 4 Å are added to a mixture of 4.79 g (8.11 mmol) of *trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[5-(4-nitrobenzyloxycarbonylamino)-valeroylthio]-azetidin-2-one

and 3.10 g (12.16 mmol) of freshly prepared glyoxylic acid 4-nitrobenzyl ester ethyl hemiketal in 32 ml of toluene and 8 ml of N,N-dimethylformamide and the whole is stirred at 40° for 20 hours. The mixture is filtered and the filter residue is washed with ethyl acetate. Concentration of the filtrate by evaporation and drying at 40° under a high vacuum yield a yellowish viscous oil (8.19 g). Chromatography over 350 g of Merck silica gel with toluene/ethyl acetate (7:1) and toluene/ethyl acetate (2:1) yields the pure title compound in the form of an amorphous solid.

IR in CH_2Cl_2: 3440, 2940, 1780, 1750, 1725, 1515, 1350, 1230 cm^{-1}.

Example 12

2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-hydroxyacetic acid 4-nitrobenzyl ester

Following the same procedure as that described in Example 11 and using as starting material (3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-[5-(4-nitrobenzyloxycarbonylamino)-valeroylthio]-azetidin-2-one, there is obtained the title compound having an identical IR spectrum.

Example 13

2-[*trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-chloroacetic acid 4-nitrobenzyl ester

While stirring at −15°, to a solution of 9.6 g (12.5 mmol) of 2-[*trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-hydroxyacetic acid 4-nitrobenzyl ester in 64 ml of tetrahydrofuran there are added dropwise, in succession, 1.76 ml (24.2 mmol) of thionyl chloride and a solution of 3.4 ml of triethylamine in 5.6 ml of tetrahydrofuran, each addition being carried out over a period of 15 minutes. The white suspension is stirred at 0° for a further 30 minutes; 360 ml of methylene chloride are added and the whole is washed with 60 ml of 0.1N aqueous HCl solution and three times using 100 ml of saturated NaCl solution each time. The solution is dried over Na_2SO_4 and filtered. Concentration of the solvent by evaporation *in vacuo* yields pure product in the form of a slightly yellowish solid.

IR in CH_2Cl_2: 3440, 2940, 1785, 1750, 1720, 1520, 1345, 1230 cm^{-1}.

Example 14

2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-chloroacetic acid 4-nitrobenzyl ester

Following the same procedure as that described in Example 13 and using as starting material 2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-hydroxyacetic acid 4-nitrobenzyl ester, there is obtained the title compound having an identical IR spectrum.

Example 15

2-[*trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-triphenylphosphoranylideneacetic acid 4-nitrobenzyl ester

A solution of 3.7 g (4.67 mmol) of 2-[3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-chloroacetic acid 4-nitrobenzyl ester and 2.79 g of triphenylphosphine (10.65 mmol) in 3.9 ml of tetrahydrofuran is left to stand under nitrogen at 5° for two days. The solution is then diluted with 200 ml of methylene chloride, washed with 50 ml of saturated aqueous $NaHCO_3$ solution and the organic phase is dried over Na_2SO_4 and filtered. Concentration of the solvent by evaporation *in vacuo* yields 6.6 g of reddish oil. Chromatography over 170 g of Merck silica gel with toluene/ethyl acetate (2:1) yields a yellowish oil.

IR in CH_2Cl_2: 2940, 2440, 1755, 1725, 1515, 1355, 1230 cm^{-1}.

Example 16

2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-triphenylphosphoranylideneacetic acid 4-nitrobenzyl ester

Following the same procedure as that described in Example 15 and using as starting material 2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-chloroacetic acid 4-nitrobenzyl ester there is obtained the title compound having an identical IR spectrum.

$[\alpha]_D^{20}$ +14° (c=1, $CHCl_3$).

Example 17

***trans*-6-(4-nitrobenzyloxycarbonyloxymethyl)-2-[4-(4-nitrobenzyloxycarbonylamino)-butyl]-penem-3-carboxylic acid 4-nitrobenzyl ester**

A solution of 8.5 g (8.4 mmol) of 2-[*trans*-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-triphenylphosphoranylideneacetic acid 4-nitrobenzyl ester in 2.6 l of toluene is boiled under reflux under a nitrogen atmosphere for 25 hours.

Concentration of the solvent by evaporation and chromatography of the residue over 260 g of silica gel with toluene/ethyl acetate (3:1) yield the pure product in the form of a colourless amorphous solid.

IR in CH_2Cl_2: 3040, 2940, 1790, 1750, 1720, 1605, 1520, 1345, 1230 cm^{-1}.

Example 18

(5*R*,6*S*)-6-(4-nitrobenzyloxycarbonyloxymethyl)-2-[4-(4-nitrobenzyloxycarbonylamino)-butyl]-penem-3-carboxylic acid 4-nitrobenzyl ester

Following the same procedure as that described in Example 17 and using as starting material 2-[(3*S*,4*R*)-3-(4-nitrobenzyloxycarbonyloxymethyl)-4-(5-(4-nitrobenzyloxycarbonylamino)-valeroylthio)-2-oxoazetidinyl]-2-triphenylphosphoranylideneacetic acid 4-nitrobenzyl ester, there is obtained the title compound having an identical IR spectrum.

$[\alpha]_D^{20}$+36° (c=1, $CHCl_3$).

Example 19

***trans*-6-hydroxymethyl-2-(4-aminobutyl)-penem-3-carboxylic acid**

In a hydrogenation vessel having a bottle connected in parallel, containing KOH for CO_2 absorption, a mixture of 190 mg (0.25 mmol) of *trans*-6-(4-nitrobenzyloxycarbonyloxymethyl)-2-[4-(4-nitrobenzyloxycarbonylamino)-butyl]-penem-3-carboxylic acid 4-nitrobenzyl ester, 24 ml of dioxan and 5 ml of 0.1N aqueous HCl solution is hydrogenated over 200 mg of 10% palladium on carbon for 90 minutes at room temperature and normal pressure. During this time 39 ml of H_2 are absorbed. The mixture is filtered through Celite, concentrated by evaporation *in vacuo* to a volume of 5 ml, and to the resulting yellow suspension there is added a solution of 42 mg of $NaHCO_3$ in 1 ml of water. The solution is applied to six reverse-phase thin layer chromatography plates (L 254 OPTI—UP C—12—20, manufactured by ANTEC AG, Bennwil, Switzerland). Chromatography with CH_3CN/H_2O (2:3) and elution of the mobile UV-active fraction with CH_3CN/H_2O (4:1), partial concentration of the eluate by evaporation and lyophilisation of the aqueous solution that remains yield a colourless amorphous solid.

UV in H_2O (pH 3): λ_{max} 256 nm (2500), 318 nm (5600).

Example 20

(3*S*,5*R*,6*R*)-2,2-dimethyl-6-(tert.-butyl-dimethyl-silyloxymethyl)-penam-3-carboxylic acid methyl ester 1,1-dioxide

A solution of 23.6 g (85 mmol) of (3*S*,5*R*,6*R*)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid methyl ester 1,1-dioxide in 50 ml of dimethylformamide is stirred at room temperature for 45 minutes with 25.5 g (170 mmol) of tert-butyldimethylchlorosilane and 11.5 g (170 mmol) of imidazole. The solvent is then distilled off under a high vacuum and the residue is taken up in ethyl acetate. The solution is washed with 1N sulphuric acid and then with water and the aqueous solutions are extracted twice with ethyl acetate. The organic phase is dried over sodium sulphate and concentrated in a rotary evaporator. The product precipitates in the form of a crystalline mass.

TLC: silica gel, toluene/ethyl acetate (4:1): R_f=0.56,

IR (CH_2Cl_2): 3.4; 5.57; 5.65 μm.

Example 21

2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonyl-2-oxoazetidin-1-yl]-3-methyl-2-butenoic acid methyl ester

9 ml of DBU are added to a solution of 202 g (0.51 mol) of (3*S*,5*R*,6*R*)-2,2-dimethyl-6-(tert.-butyl-dimethyl-silyloxymethyl)-penam-3-carboxylic acid methyl ester 1,1-dioxide in 800 ml of tetrahydrofuran and the whole is stirred at room temperature for 5 minutes. A further 95 ml of DBU are then added and stirring is continued at room temperature for 30 minutes. Then, while cooling, 42.3 ml (0.68 mol) of methyl iodide are added. After a reaction period of 3 hours, the DBU hydriodide that has crystallised out is filtered off and the filtrate is concentrated. The residue is taken up in ethyl acetate and the solution is washed with 1N sulphuric acid, water and sodium bicarbonate solution. The aqueous phases are extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulphate and the solution is concentrated to a thick oil.

TLC: silica gel, toluene/ethyl acetate (4:1): R_f=0.42,

IR (CH_2Cl_2): 5.63; 5.81; 6.17 μm.

Example 22

(3*S*,4*R*)-3-hydroxymethyl-4-methylsulphonyl-azetidin-2-one and (3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonyl-azetidin-2-one

A solution of 25 g (61.7 mmol) of 2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonyl-2-oxoazetidin-1-yl]-3-methyl-2-butenoic acid methyl ester in 400 ml of methylene chloride is treated with a mixture of ozone and oxygen at −10°. The disappearance of the starting material is checked by thin-layer chromatography. When the reaction is complete, 30 ml of dimethyl sulphide are added and stirring is continued for 3 hours at room temperature. The solution is concentrated and the residue is taken up in a mixture of 160 ml of methanol, 24 ml of ethyl acetate and 3 ml of water and is heated at 70° for 40 minutes. The solvent is then removed, toluene is added

twice and the toluene is evaporated. The crystallising oil is taken up in methylene chloride and the crystals, which comprise (3*S*,4*R*)-3-hydroxymethyl-4-methylsulphonylazetidin-2-one, are isolated by filtration. The filtrate is concentrated and (3S,4R)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methyl-sulphonylazetidin-2-one is obtained in pure form by chromatography over silica gel with toluene/ethyl acetate (3:1).

(3*S*,4*R*)-3-hydroxymethyl-4-methylsulphonylazetidin-2-one

TLC: silica gel, toluene/ethyl acetate (1:1): R_f=0.36,
IR (CH_2Cl_2): 2.96; 3.54; 5.61 μm.

(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonylazetidin-2-one

TLC: silica gel, toluene/ethyl acetate (1:1): R_f=0.06.

24 g (183 mmol) of tert.-butyldimethylchlorosilane and 11 g (163 mmol) of imidazole are added at room temperature over a period of 45 minutes to a solution of 14.6 g (81.5 mmol) of 3*S*,4*R*)-3-hydroxymethyl-4-methylsulphonylazetidin-2-one in 40 ml of dimethylformamide. The solvent is then removed under a high vacuum and the residue is taken up in ethyl acetate. The organic phase is washed in succession with 1N sulphuric acid, water and sodium bicarbonate solution. The aqueous phases are extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The crystalline residue is pure (3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonylazetidin-2-one.

Example 23

(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-azetidin-2-one

A slurry of 7.0 g (32.2 mmol) of 5-allyloxycarbonylaminothiovaleric acid in 50 ml of water is cooled to 0° and 1N sodium hydroxide solution is added to pH 8. 30 ml of methylene chloride, 2.93 g (10 mmol) of 3-(tert.-butyl-dimethyl-silyloxymethyl)-4-methylsulphonylazetidin-2-one and 278 mg (1 mmol) of tetrabutylammonium chloride are then added and the two-phase system is stirred well for 3 hours at 0°. The phases are separated and are washed once each with saturated $NaHCO_3$ solution and saturated NaCl solution. The aqueous phases are extracted twice more with methylene chloride and the extracts are combined and dried over Na_2SO_4. Concentration of the solvent by evaporation *in vacuo* yields a crude product which is chromatographed over 50 g of silica gel with toluene and ethyl acetate 2:1 as eluant.

TLC: (silica gel), toluene/ethyl acetate (1:1): R_f=0.51,
IR (methylene chloride): 2.90; 2.94; 5.68; 5.88 μ.

The starting material can be prepared as follows:

6.75 g (33.6 mmol) of 5-allyloxycarbonylaminovaleric acid are dissolved in 40 ml of methylene chloride, and 10.2 ml (73.8 mmol) of triethylamine are added. While stirring at −10°, there is added dropwise to this solution over a period of 30 minutes a solution of 5.2 ml (40.3 mmol) of chloroformic acid isobutyl ester in 7 ml of methylene chloride. After this addition stirring is continued at −10° for a further 30 minutes. H_2S is then introduced at 0° for a period of 60 minutes. The solution is washed with 1N sulphuric acid and then extracted first with 50 ml and then with 30 ml of saturated sodium bicarbonate solution and, while stirring, the aqueous phase is carefully rendered acidic with 20% strength phosphoric acid in an Erlenmeyer flask. The aqueous solution is extracted three times with chloroform and the organic phase is dried over Na_2SO_4 and filtered. Concentration of the solvent by evaporation *in vacuo* and drying under a high vacuum yield 5-allyloxycarbonylaminothiovaleric acid in the form of an oil.

IR (methylene chloride): 2.94; 3.95; 5.97; 6.75 μ.

Example 24

2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-2-oxoazetidin-1-yl]-2-hydroxyacetic acid allyl ester

16 g of molecular sieve 4Å are added to a mixture of 1.9 g (4.4 mmol) of (3*S*,4R)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-azetidin-2-one and 1.9 g (13.2 mmol) of glyoxylic acid allyl ester ethyl hemiketal in 30 ml of toluene and 2 ml of N,N-dimethylformamide and the whole is stirred at room temperature for 16 hours. The mixture is filtered and the filter residue is washed with toluene. Concentration of the filtrate by evaporation and drying at 40° in a high vacuum yield the product in the form of a yellow oil.

TLC: (silica gel), toluene/ethyl acetate (2:1): R_f=0.44;
IR (methylene chloride): 2.85; 2.91; 5.65; 5.74; 5.81 μ.

Example 25

2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-2-oxoazetidin-1-yl]-2-triphenylphosphoranylideneacetic acid allyl ester

While stirring at −20°, 0.37 ml (5.14 mmol) of thionyl chloride and 0.7 ml (5.14 mmol) of triethylamine are added in succession over a period of 5 minutes to a solution of 2.35 g (4.32 mmol) of

2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-2-oxoazetidin-1-yl]-2-hydroxyacetic acid allyl ester in 60 ml of tetrahydrofuran. The white suspension is then stirred at −15° for 20 minutes; methylene chloride is added and the whole is washed with 0.1N hydrochloric acid and twice with saturated NaCl solution. The solution is dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is dissolved in 7 ml of tetrahydrofuran; 1.8 g (6.8 mmol) of triphenylphosphine and 0.6 ml (4.4 mmol) of triethylamine are added and the whole is stirred at room temperature for 16 hours. The reaction mixture is then diluted with methylene chloride and washed with saturated aqueous $NaHCO_3$ solution, and the organic phase is dried over Na_2SO_4 and filtered. Concentration of the solvent by evaporation *in vacuo* and chromatography of the residue over 50 g of silica gel with toluene/ethyl acetate 2:1 yield the pure product.

TLC: (silica gel) toluene/ethyl acetate (1:1): R_f=0.40,
IR (methylene chloride: 2.91; 5.71; 5.83; 5.95; 6.21 μ.

Example 26
2-[(3*S*,4*R*)-4-(5-allyloxycarbonylaminovaleroylthio)-3-hydroxymethyl-2-oxoazetidin-1-yl]-2-triphenylphosphoranylideneacetic acid allyl ester

A solution of 546 g (0.69 mmol) of 2-[(3*S*,4*R*)-3-(tert.-butyl-dimethyl-silyloxymethyl)-4-(5-allyloxycarbonylaminovaleroylthio)-2-oxoazetidin-1-yl]-2-triphenylphosphoranylideneacetic acid allyl ester in 12 ml of tetrahydrofuran is cooled to −10°; 536 mg (1.7 mmol) of tetrabutylammonium fluoride are added and the whole is stirred for 15 minutes. The reaction mixture is then diluted with methylene chloride and washed with aqueous $NaHCO_3$ solution and NaCl solution. The organic phase is dried over Na_2SO_4 and concentrated *in vacuo*. The residue is chromatographed over silica gel with ethyl acetate as eluant.

TLC: (silica gel) ethyl acetate: R_f=0.24,
IR (methylene chloride): 2.79; 2.90; 5.71; 5.83; 6.21 μ.

Example 27
(5*R*,6*S*)-2-(4-allyloxycarbonylaminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid allyl ester

A solution of 98 mg (0.14 mmol) of 2-[(3*S*,4*R*)-4-(5-allyloxycarbonylaminovalerolylthio)-3-hydroxymethyl-2-oxoazetidin-1-yl]-2-triphenylphosphoranylidene-acetic acid allyl ester in 10 ml of toluene is heated under nitrogen at 105° for 16 hours. Concentration of the solvent by evaporation and chromatography of the residue on a preparative silica gel plate with toluene/ethyl acetate (1:1) yield the pure product.

TLC: (silica gel) ethyl acetate: R_f=0.55;
IR (methylene chloride): 2.76; 5.58; 5.81; 6.06 μ.

Example 28
(5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid

Following the same procedure as that described in Example 19 and using as starting material (5*R*,6*S*)-6-(4-nitrobenzyloxycarbonyloxymethyl)-2-[4-(4-nitrobenzyloxycarbonylamino)-butyl]-2-penem-3-carboxylic acid 4-nitrobenzyl ester, the product is obtained.

$[\alpha]_D^{20}$+58° (c=1, H_2O/NaOH),
UV in H_2O (pH 3): λ_{max} 256 nm (2500), 318 nm (5600).

The same product can also be prepared as follows:

A solution of 46 mg (0.11 mmol) of (5*R*,6*S*)-2-(4-allyloxycarbonylaminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid allyl ester in 2 ml of methylene chloride and 1 ml of diethyl ether is stirred at room temperature for 16 hours with 20 mg (0.14 mmol) of 2-ethylhexanoic acid, 10 mg of triphenylphosphine and 6 mg of tetrakis-(triphenylphosphine)-palladium. The solution is diluted with methylene chloride and washed twice with water. The combined aqueous phases are lyophilised and the residue is chromatographed on reversed phase thin layer plates (Opti-UPC_{12}) (acetonitrile/water 2:3). Elution of the appropriate zone with acetonitrile/water (4:1), partial concentration of the eluate by evaporation and lyophilisation of the aqueous solution that remains likewise yield the end product having identical physical data.

Example 29
Sodium salt of (5*R*,6*S*)-2-[4-(1-ethoxycarbonylprop-1-en-2-ylamino)-butyl]-6-hydroxymethyl-2-penem-3-carboxylic acid

0.139 ml (1.1 mmol) of ethyl acetoacetate is added to a suspension of 0.27 mg (1 mmol) of (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid and 0.5 ml of 2M sodium hydroxide solution in 3 ml of isopropanol and the whole is stirred at room temperature for 3 hours. The product is precipitated by the addition of diethyl ether.

IR-spectrum (Nujol): absorption bands at 3.0; 5.58; 5.75 μ.

Example 30
(5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid 1-ethoxycarbonyloxyethyl ester

1.2 g of sodium iodide are dissolved in 3.7 ml of acetone, and 0.275 ml of ethyl-1-chloroethyl carbonate is added. The mixture is stirred at room temperature for 3 hours. The solution is then added dropwise to 15.0 ml of methylene chloride and the inorganic salts that form are filtered off. The methylene chloride solution is concentrated to 2 ml and, at 0°, added to a solution of 0.27 g (1 mmol) of (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid in 4 ml of dimethylacetamide. The mixture is then stirred at 0° for 3 hours, then diluted with ethyl acetate and washed 3 times with water. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The crude product is purified over 10 g of silica gel with ethyl acetate as eluant. The title compound is obtained in the form of a white foam.

IR spectrum (methylene chloride): absorption bands at 5.58; 5.75 μ.

Example 31
(5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid pivaloyloxymethyl ester

0.6 g of sodium iodide is dissolved in 2 ml of acetone, and 0.15 ml of pivalic acid chloromethyl ester is added. The mixture is stirred at room temperature for 3 hours and then added dropwise to 7.5 ml of methylene chloride. The inorganic salts that are formed are filtered off. The methylene chloride solution is concentrated to 1 ml and, at 0°, added to a solution of 0.1 g (0.4 mmol) of (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid and 0.07 ml of diisopropylethylamine in 4 ml of N,N-dimethylacetamide. The reaction mixture is then stirred at 0° for 3 hours, then diluted with ethyl acetate and washed 3 times with water. The organic phase is dried over sodium sulphate and concentrated in a rotary evaporator. The crude product is purified over 10 g of silica gel using ethyl acetate as eluant. The title compound is obtained in the form of a white foam.

IR spectrum (methylene chloride): absorption bands at 5.58; 5.75 μ.

Example 32

Dry ampoules or phials containing 0.5 g of (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid as active ingredient are manufactured as follows:

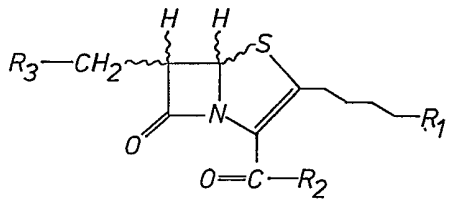
Composition (for 1 ampoule or phial)

active ingredient	0.5 g
mannitol	0.05 g

A sterile aqueous solution of the active ingredient and the mannitol in 5 ml ampoules or phials is subjected to freeze-drying under aseptic conditions and the ampoules or phials are sealed and tested.

Claims

1. 2-Aminobutyl-6-hydroxymethyl-2-penem compounds of the formula



(I),

in which

R_1 represents an optionally substituted amino group,

R_2 represents hydroxy or a radical R_2^A that together with the carbonyl group —C(=O)— forms a protected carboxy group, and

R_3 represents an optionally protected hydroxy group,

and their salts, their optical isomers and mixtures of their optical isomers.

2. Compounds of the formula I according to patent claim 1 in which R_1 represents amino, a 1-acyl-lower alk-1-en-2-ylamino radical or a mono- or di-substituted methyleneamino group, R_2 represents hydroxy or together with the carbonyl group represents an esterified carboxy group that can be cleaved under physiological conditions, and R_3 represents hydroxy, and their salts, their optical isomers and mixtures of their optical isomers.

3. Compounds of the formula I according to patent claim 1 in which R_1 represents amino, R_2 represents hydroxy, lower alkanoyloxymethoxy, amino-lower alkanoyloxymethoxy, phthalidyloxy, 4-crotonolactonyloxy, 4-butyrolacton-4-yloxy, indanyloxy, 1-lower alkoxy-lower alkoxy or 1-lower alkoxycarbonyloxy-lower alkoxy, and R_3 represents hydroxy, and their pharmaceutically acceptable salts, their optical isomers and mixtures of their optical isomers.

4. Compounds of the formula I according to any one of claims 1 to 3 in which R_1 represents amino, R_2 represents hydroxy and R_3 represents hydroxy, and their pharmaceutically acceptable salts, their optical isomers and mixtures of their optical isomers.

5. Compounds of the formula I according to patent claim 1, which in their 5-position have the *R*-configuration and in their 6-position have the *S*-configuration, and their pharmaceutically acceptable salts.

6. *Trans*-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid and pharmaceutically acceptable salts thereof according to patent claim 1.

7. (5*R*,6*S*)-2-(4-aminobutyl)-6-hydroxymethyl-2-penem-3-carboxylic acid and pharmaceutically acceptable salts thereof according to patent claim 1.

8. A compound according to claim 1 which is any one of those described in Examples 17, 18, 19, 27 and 28 herein.

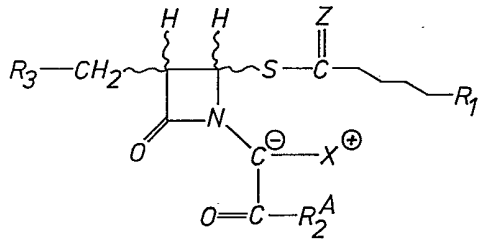
9. A compound according to claim 1 which is any one of those described in Examples 29, 30 and 31 herein.

10. A pharmaceutical preparation comprising a compound of the formula I according to patent claim 1 or a pharmaceutically acceptable salt of such a compound.

11. Use of compounds of the formula I according to patent claim 1 and of pharmaceutically acceptable salts of such compounds for the manufacture of pharmaceutical preparations.

12. A method of treating bacterial infections in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the formula I according to claim 1 or of a pharmaceutically acceptable salt thereof.

13. Process for the manufacture of compounds of the formula I according to claim 1 and of their salts, their optical isomers and mixtures of their optical isomers, characterised in that an ylide compound of the formula



(II),

in which R_1 represents a protected amino group, Z represents oxygen or sulphur, $X^{\oplus}$ represents either a tri-substituted phosphonio group or a di-esterified phosphono group together with a cation, R_2^A together with the carbonyl group —C(=O)— represents a protected carboxy group, and R_3 represents an optionally protected hydroxy group, is cyclised, and, if desired or necessary, in a resulting compound of the formula I a protected amino group R_1 is converted into the free amino group or into a different protected amino group R_1, and/or, if desired, in a resulting compound of the formula I a protected carboxy group —C(=O)—R_2 is converted into the free carboxy group or into a different protected carboxy group —C(=O)—R_2, and/or, if desired, in a resulting compound of the formula I in which R_1 represents amino, R_1 is converted into a substituted amino group, and/or, if necessary, a protected hydroxy group R_3 is converted into the free hydroxy group R_3, or a free hydroxy group R_3 is converted into a protected hydroxy group R_3, and/or, if desired, a resulting compound having a salt-forming group is converted into a salt, or a resulting salt is converted into the free compound or into a different salt, and/or, if desired, a resulting mixture of isomeric compounds is separated into the individual isomers.

14. A process for the manufacture of a compound of the formula I substantially as described in Examples 17, 18, 19, 27 and 28 herein.

15. A process for the manufacture of a compound of the formula I substantially as described in Examples 29, 30 and 31 herein.

16. A compound of the formula I according to claim 1 whenever prepared by a process as claimed in any of claims 13 to 15.

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