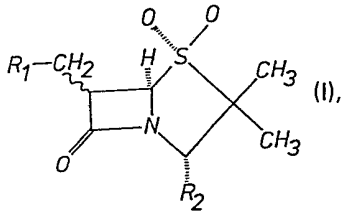
(12) UK Patent Application (19) GB (11) 2 076 812 A

(21) Application No 8114997
(22) Date of filing 15 May 1981
(30) Priority data
(31) 4017/80
(32) 22 May 1980
(33) Switzerland (CH)
(43) Application published
9 Dec 1981
(51) INT CL³
C07D 499/00 A61K 31/43
(52) Domestic classification
C2C 1313 214 220 226
22Y 247 256 25Y 275 292
29Y 30Y 314 31Y 337 351
352 357 358 360 361 364
366 367 368 36Y 389
43X 490 491 509 50Y
623 624 625 628 638 652
658 65X 678 699 761
762 800 801 80Y AA TR
YT YX
(56) Documents cited
GB 2061930A
GB 2047684A
(58) Field of search
C2C
(71) Applicants
Ciba-Geigy AG,
4002 Basle, Switzerland
(72) Inventors
Peter Schneider,
Riccardo Scartazzini
(74) Agent
Thomas Sharman,
Ciba-Geigy (UK) Limited,
Patent Dept., Tenax Road,
Trafford Park, Manchester
M17 1WT

(54) **Penam-dioxide compounds, processes for their manufacture, and their use**

(57) 2,2-Dimethylpenam-3-carboxylic acid 1,1-dioxide compounds of the formula



(I),

in which

R_1 represents hydroxy or etherified or esterified hydroxy, and

R_2 represents carboxyl or protected carboxyl,

and salts of such compounds having a salt-forming group have β-lactamase-inhibiting properties. Pharmaceutical preparations containing these compounds, optionally in combination with β-lactam antibiotics, are especially suitable for combating infections caused by β-lactamase-producing microorganisms.

Processes for the manufacture of compounds of the formula (I) and intermediates.

GB 2 076 812 A

SPECIFICATION

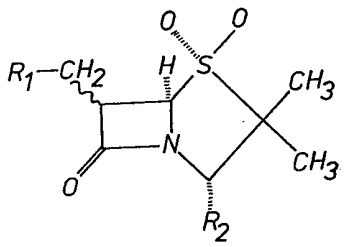
Dioxide compounds, processes for their manufacture, and their use

The invention relates to novel 2,2-dimethylpenam-3-carboxylic acid 1,1-dioxide compounds, processes for the manufacture of these compounds, their use for the inhibition of β-lactamases, pharmaceutical preparations containing such compounds optionally together with another antibiotically active β-lactam compound, and the use of such preparations.

Some 1,1-dioxides of penam-3-carboxylic acid compounds having β-lactamase-inhibiting properties are already known. For example, 2,2-dimethylpenam-3-carboxylic acid 1,1-dioxide and esters thereof are known from Belgian Patent Specification BE 867 859. The 1,1-dioxides of penam-3-carboxylic acid substituted in the 2-position optionally by a methyl group, and their esters, are described in European Patent Application 8917. Corresponding penam compounds substituted in the 6-position by an amino group are known from European Patent Application 2927 and those substituted in the 6-position by substituted hydrocarbon radicals having more than one carbon atom are known from European Patent Application 5889.

2,2-Dimethylpenam-3-carboxylic acid 1,1-dioxide compounds substituted in the 6-position by substituted methyl have not hitherto been described. The surprising discovery has been made that such compounds have, in addition to antibiotic properties, especially superior β-lactamase-inhibiting properties. They are therefore suitable, especially in combination with β-lactamase-sensitive β-lactam antibiotics, for combating infections, especially those caused by microorganisms producing β-lactamase.

The invention relates especially to 2,2-dimethylpenam-3-carboxylic acid 1,1-dioxide compounds of the formula



(I),

in which

R_1 represents hydroxy or etherified or esterified hydroxy, and

R_2 represents carboxyl or protected carboxyl,

and salts of such compounds having a salt-forming group, processes for the manufacture of these compounds, their use for inhibiting β-lactamases, pharmaceutical preparations containing such compounds optionally together with an antibiotically active β-lactam compound, and the use of such preparations.

In the present description of the invention, the term "lower" used in connection with definitions of groups and compounds, for example in groups such as lower alkyl, lower alkylene, lower alkoxy or lower alkanoyl, or in compounds such as lower alcohol and the like, means that the respective groups or compounds, unless expressly defined otherwise, contain up to 6, preferably up to 4, C-atoms.

An etherified hydroxy group R_1 is a group R_1^a—O—, in which R_1^a represents especially an optionally substituted hydrocarbon radical or an organic silyl or stannyl group.

An optionally substituted hydrocarbon radical R_1^a has up to 18 C-atoms and is, for example, a lower aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aromatic or araliphatic radical, which may be substituted, for example, by lower alkyl, lower alkoxy, halogen, oxo, hydroxy, optionally functionally modified carboxy, optionally lower alkylated amino or a corresponding protected group, or alternatively by heterocyclyl.

A lower aliphatic radical R_1^a is, for example, lower alkyl, especially having from 1—6, preferably from 1—4, C-atoms, for example methyl, ethyl, propyl or butyl, lower alkenyl, especially having from 2—5 C-atoms, for example vinyl, propenyl or butenyl, or lower alkynyl, especially having from 2—5 C-atoms, for example ethynyl or propynyl.

A cycloaliphatic radical R_1^a is cycloalkyl having from 3—8, especially from 3—6, C-atoms, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

A cycloaliphatic-aliphatic radical R_1^a is one of the mentioned aliphatic radicals that is substituted by one of the mentioned cycloaliphatic radicals, for example cyclopropylmethyl or -ethyl, or cyclohexylmethyl or -ethyl.

An aromatic radical R_1^a is especially phenyl or naphthyl.

An araliphatic radical R_1^a is one of the mentioned aliphatic radicals that is substituted by one to

three of the mentioned aromatic radicals, for example mono-, di- or triphenyl-lower alkyl, for example benzyl, phenethyl, diphenylmethyl or trityl.

Of the substituted hydrocarbon radicals R_1^a, the following may be mentioned: lower alkoxy-lower alkyl, for example methoxymethyl, 1- or 2-methoxyethyl and 1- or 2-ethoxyethyl, halo-lower alkyl, for example 2-fluoro-, 2-chloro-, 2-bromo- and 2-iodoethyl, oxo-lower alkyl, for example acetonyl, optionally protected, for example acylated, hydroxy-lower alkyl, for example 2-hydroxyethyl and acetoxyethyl, optionally esterified carboxy-lower alkyl, for example 2-carboxymethyl and 2-ethoxycarbonylmethyl, amino- and mono- or di-lower alkylamino-lower alkyl, for example 2-aminoethyl, 2-methylaminoethyl, 2-dimethylaminoethyl and acylamino-lower alkyl, for example 2-acetamidoethyl, lower alkylphenyl, for example tolyl and xylyl, lower alkoxyphenyl, for example methoxyphenyl, halophenyl, for example fluoro- or chlorophenyl, hydroxyphenyl, carboxyphenyl and aminophenyl, in which the substituents may be in the o-, m- or p-position of the phenyl nucleus, phenacetyl, and heterocyclyl-lower alkyl, especially heterocyclylmethyl, in which heterocyclyl represents, for example, furyl, thienyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thiatriazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyridazinyl or pyrimidyl, each of which is optionally substituted, for example, by lower alkyl, hydroxy, esterified hydroxy, halogen, sulpho, amidated sulpho, amino or aminomethyl, for example 2-furyl-, 5-aminomethyl-2-furyl-, 2-thienyl-, 5-aminomethyl-2-thienyl, 2-imidazolyl-, 1,2,3-triazol-4-yl-, 2-amino-1,3-thiazol-5-ylmethyl, or 5-amino-1,2,4-thiadiazol-3-ylmethyl.

An organic silyl or stannyl group R_1^a is especially one in which the silicon or tin atom, respectively, preferably contains as substituents lower alkyl, especially methyl, also lower alkoxy, for example methoxy, and/or halogen, for example chlorine. Corresponding silyl or stannyl groups are especially tri-lower alkylsilyl, especially trimethylsilyl, also dimethyl-tert.-butyl-silyl, lower alkoxy-lower alkyl-halo-silyl, for example methoxymethyl-chloro-silyl, or di-lower alkyl-halo-silyl, for example dimethyl-chloro-silyl, or correspondingly substituted stannyl, for example tri-n-butylstannyl.

An esterified hydroxy group R_1 is a group R_1^b—O—, in which R_1^b represents the acyl radical of an organic carboxylic or sulphonic acid or of an inorganic acid.

The acyl radical R_1^b of an organic carboxylic acid has up to 19 C-atoms, and includes also the acyl radical of a semiester of carbonic acid and of an optionally substituted carbamic acid. Such acyl radicals have, for example, the formula H—CO—, R_1^a—CO—, heterocyclyl-CO—, R_1^a—O—CO, H_2N—CO— and $R_1^aR_1^aN$—CO—, in which R_1^a and heterocyclyl have the meanings given above.

The acyl radical R_1^b of an organic sulphonic acid has, for example, the formula R_1^a—SO_2—, in which R_1^a has the meanings given above of an optionally substituted hydrocarbon radical.

The acyl radical R_1^b of an inorganic acid is, for example, that of an oxygen-containing sulphuric or phosphoric acid, for example $HOSO_2$— or H_2PO_3—.

Preferably, R_1 represents hydrogen, lower alkoxy, for example methoxy, phenyl-lower alkoxy, for example benzyloxy, or alternatively lower alkanoyloxy, for example formyloxy or acetoxy, aminothiazolylcarbonyloxy, for example 2-amino-1,3-thiazol-4-ylcarbonyloxy, aminothiadiazolylcarbonyloxy, for example 5-amino-1,2,4-thiadiazol-3-ylcarbonyloxy, lower alkoxycarbonyloxy, for example methoxycarbonyloxy or ethoxycarbonyloxy, carbamoyloxy, N-mono- or N,N-di-lower alkylcarbamoyloxy, for example N-methylcarbamoyloxy or N,N-dimethylcarbamoyloxy, lower alkanesulphonyloxy, for example methanesulphonyloxy, arenesulphonyloxy, for example benzenesulpohonyloxy or toluenesulphonyloxy, or hydroxysulphonyloxy (or a salt thereof, for example the sodium salt).

R_1 is especially hydroxy.

The functional groups present in compounds of the formula (I), especially carboxyl and amino groups, but also hydroxy and sulpho groups, are optionally protected by protecting groups that are used in penicillin, cephalosporin and peptide chemistry.

Such protecting groups can be split off readily, i.e. without undesired side reactions taking place, for example by solvolysis, reduction, photolysis or alternatively under physiological conditions.

Protecting groups of this type and also the manner in which they are split off are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, in "The Peptides", vol. I, Schröder and Lubke, Academic Press, London, New York, 1965, and in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, vol. 15/1, Georg Thieme Verlag, Stuttgart, 1974.

Thus, carboxyl groups, for example the carboxyl group R_2, are protected usually in esterified form, such ester groupings being readily splittable under mild conditions. Carboxyl groups protected in this manner contain as esterifying groups especially lower alkyl groups branched in the 1-position or suitably substituted in the 1- or 2-position. Preferred carboxyl groups present in esterified form are, *inter alia,* tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl; arylmethoxycarbonyl having one or two aryl radicals, these representing phenyl radicals optionally mono- or poly-substituted, for example by lower alkyl, such as tert.-lower alkyl, for example tert.-butyl, lower alkoxy, such as methoxy, hydroxy, halogen, for example chlorine, and/or by nitro, such as benzyloxycarbonyl optionally substituted, for example as indicated above, for example 4-nitrobenzyloxycarbonyl or 4-methoxybenzyloxycarbonyl, or diphenylmethoxycarbonyl optionally substituted, for example as indicated above, for example diphenylmethoxycarbonyl or di-(4-methoxyphenyl)-methoxycarbonyl; 1-lower alkoxy-lower

alkoxycarbonyl, such as methoxymethoxycarbonyl, 1-methoxyethoxycarbonyl or 1-ethoxymethoxycarbonyl; 1-lower alkylthio-lower alkoxycarbonyl, such as 1-methylthiomethoxycarbonyl or 1-ethylthioethoxycarbonyl; aroylmethoxycarbonyl in which the aroyl group represents benzoyl optionally substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl; 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl; or 2-(tri-substituted silyl)-ethoxycarbonyl, in which each of the substituents, independently of one another, represents an aliphatic, araliphatic, cycloaliphatic or aromatic hydrocarbon radical optionally substituted, for example by lower alkyl, lower alkoxy, aryl, halogen and/or nitro and having, for example, up to 15 carbon atoms, such as corresponding optionally substituted lower alkyl, phenyl-lower alkyl, cycloalkyl or phenyl, for example 2-tri-lower alkylsilylethoxycarbonyl, such as 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl, such as 2-triphenylsilylethoxycarbonyl.

Further protected carboxyl groups present in esterified form are corresponding silyloxycarbonyl groups, especially organic silyloxycarbonyl groups, and also corresponding stannyloxycarbonyl groups. In these groups, the silicon or tin atom preferably contain as substituents lower alkyl, especially methyl but also lower alkoxy, for example methoxy, and/or halogen, for example chlorine. Suitable silyl or stannyl protecting groups are especially tri-lower alkylsilyl, especially trimethylsilyl, but also dimethyl-tert.-butylsilyl, lower alkoxy-lower alkyl-halo-silyl, for example methoxy-methyl-chloro-silyl, or di-lower alkyl-halo-silyl, for example dimethyl-chloro-silyl, or correspondingly substituted stannyl groups, for example tri-n-butyl-stannyl.

Preferred protected carboxyl groups are tert.-lower alkoxycarbonyl, such as tert.-butoxycarbonyl, and especially benzyloxycarbonyl optionally substituted, for example as indicated above, such as 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl.

An esterified carboxyl group that can be split under physiological conditions is especially an acyloxymethoxycarbonyl group in which acyl represents, for example, the radical of an organic carboxylic acid, especially of an optionally substituted lower alkanecarboxylic acid, or in which acyloxymethyl forms the radical of a lactone, or alternatively 1-lower alkoxycarbonyloxy-lower alkoxycarbonyl in which lower alkyl is methyl, propyl, butyl or, especially, ethyl. Such groups are lower alkanoyloxymethoxycarbonyl, for example acetoxymethoxycarbonyl or pivaloyloxymethoxycarbonyl, amino-lower alkanoylmethoxycarbonyl, especially α-amino-lower alkanoyloxymethoxycarbonyl, for example glycyloxymethoxycarbonyl, L-valyloxymethoxycarbonyl, L-leucyloxymethoxycarbonyl, phthalidyloxycarbonyl, for example 2-phthalidyloxycarbonyl, 4-crotonolactonyl or gamma-butyrolacton-4-yl, indanyloxycarbonyl, for example 5-indanyloxycarbonyl, or 1-ethoxycarbonyloxyethoxycarbonyl.

A protected amino group may be present, for example, in the form of a readily splittable acylamino, arylmethylamino, etherified mercaptoamino, 2-acyl-lower alk-1-enylamino, silylamino or stannylamino group or in the form of an azido group.

In a corresponding acylamino group, acyl is, for example, the acyl radical of an organic carboxylic acid having, for example, up to 18 carbon atoms, especially of an alkanecarboxylic acid optionally substituted, for example by halogen or aryl, 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-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, benzoyl optionally substituted, for example by halogen, lower alkoxy or nitro, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxycarbonyl branched in the 1-position of the lower alkyl radical or suitably substituted in the 1- or 2-position, especially tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl, arylmethoxycarbonyl having one or two aryl radicals that preferably represent phenyl optionally mono- or poly-substituted, for example by lower alkyl, especially tert.-lower alkyl, such as tert.-butyl, lower alkoxy, such as methoxy, hydroxy, halogen, for example chlorine, and/or by nitro, such as optionally substituted benzyloxycarbonyl, for example 4-nitrobenzyloxycarbonyl, or substituted diphenylmethoxycarbonyl, for example benzhydryloxycarbonyl or di-(4-methoxyphenyl)-methoxycarbonyl, aroylmethoxycarbonyl in which the aroyl group preferably represents benzoyl optionally substituted, for example by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, or 2-(tri-substituted silyl)-ethoxycarbonyl, in which each of the substituents, independently of one another, represents an aliphatic, araliphatic, cycloaliphatic or aromatic hydrocarbon radical optionally substituted for example by lower alkyl, lower alkoxy, aryl, halogen or nitro, and having, for example, up to 15 carbon atoms, such as corresponding optionally substituted lower alkyl, phenyl-lower alkyl, cycloalkyl or phenyl, for example 2-tri-lower alkylsilylethoxycarbonyl, such as 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl,such as 2-triphenylsilylethoxycarbonyl.

Further acyl radicals that come into consideration as amino-protecting groups are also corresponding radicals of organic phosphoric, phosphonic or phosphinic acids, such as di-lower alkylphosphoryl, for example dimethylphosphoryl, diethylphosphoryl, di-n-propylphosphoryl or diisopropylphosphoryl, dicycloalkylphosphoryl, for example dicyclohexylphosphoryl, optionally substituted diphenylphosphoryl, for example diphenylphosphoryl, diphenyl-lower alkylphosphoryl

optionally substituted, for example by nitro, for example dibenzylphosphoryl or di-4-nitrobenzylphosphoryl, optionally substituted phenoxy-phenyl-phosphonyl, for example phenoxy-phenyl-phosphonyl, di-lower alkylphosphinyl, for example diethylphosphinyl, or optionally substituted diphenylphosphinyl, for examople diphenylphosphinyl.

In an arylmethylamino group that represents a mono-, di- or especially tri-arylmethylamino group, the aryl radicals are especially optionally substituted phenyl radicals. Such groups are, for example, benzylamino, diphenylmethylamino and especially tritylamino.

An etherified mercapto group in an amino group protected by such a radical is especially arylthio or aryllower alkylthio in which aryl is especially phenyl optionally substituted, for example by lower alkyl, such as methyl or tert.-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro. A corresponding amino-protecting group is, for example, 4-nitrophenylthio.

In a 1-acyl-lower-en-2-yl radical that may be used as an amino-protecting group, acyl is, for example, the corresponding radical of a lower alkanecarboxylic 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 nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester. Corresponding protecting groups are especially 1-lower alkanoylprop-1-en-2-yl, for example 1-acetylprop-1-en-2-yl, or 1-lower alkoxycarbonylprop-1-en-2-yl, for example 1-ethoxycarbonylprop-1-en-2-yl.

A silylamino or stannylamino group is especially an organic silylamino or stannylamino group in which the silicon or tin atom contains as substituents preferably lower alkyl, especially methyl, but also lower alkoxy, for example methoxy, and/or halogen, for example chlorine. Corresponding silyl or stannyl groups are especially tri-lower alkylsilyl, especially trimethylsilyl, but also dimethyl-tert.-butyl-silyl, lower alkoxy-lower alkyl-halo-silyl, for example methoxy-methyl-chloro-silyl, or di-lower alkyl-halo-silyl, for example dimethyl-chloro-silyl, or correspondingly substituted stannyl, for example tri-n-butylstannyl.

An amino group may also be protected in protonated form; corresponding anions that come into consideration are especially those of strong inorganic acids, such as hydrohalic acids, for example the chlorine or bromine anion, or of organic sulphonic acids, such as p-toluenesulphonic acid.

Preferred amino-protecting groups are acyl radicals of carbonic acid semiesters, especially tert.-butoxycarbonyl, benzyloxycarbonyl optionally substituted, for example as indicated, for example 4-nitrobenzyloxycarbonyl, or diphenylmethoxycarbonyl, or 2-halo-lower alkoxycarbonyl, such as 2,2,2-trichloroethoxycarbonyl, and also trityl or formyl.

Hydroxy-protecting groups are, for example, acyl radicals, such as lower alkanoyl optionally substituted, for example by halogen, such as 2,2-dichloroacetyl, or especially the acyl radicals of carbonic acid semiesters mentioned in connection with a protected amino group, especially 2,2,2-trichloroethoxycarbonyl, or the organic silyl or stannyl radicals R^a_1, also etherifying groups that can readily be split off, such as tert.-lower alkyl, for example tert.-butyl, 2-halo-lower alkyl, for example 2,2,2,-trichloro-, 2-chloro-, 2-bromo- or 2-iodo-ethyl, 2-oxa- or 2-thia aliphatic or -cycloaliphatic hydrocarbon radicals, especially 1-lower alkoxy-lower alkyl or 1-lower alkylthio-lower alkyl, for example methoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, 1-methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having from 5 to 7 ring atoms, for example 2-tetrahydrofuryl or 2-tetrahydropyranyl or corresponding thia analogues, and also optionally substituted 1-phenyl-lower alkyl, such as optionally substituted benzyl or diphenylmethyl, there coming into consideration as substituents of the phenyl radicals, for example, halogen, such as chlorine, lower alkoxy, such as methoxy, and/or nitro.

A protected sulpho group is especially an esterified sulpho group, such as a sulpho group esterified by an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aromatic or araliphatic alcohol, for examle a lower alkanol, or by a silyl or stannyl radical, such as tri-lower alkylsilyl. In a sulpho group, the hydroxy group may be etherified, for example, in the same manner as the hydroxy group in an esterified carboxy group.

Salts of compounds according to the invention are especially pharmaceutically acceptable non-toxic salts, such as those of compounds of the formula I having acid groups, for example having a free carboxyl or sulpho group. 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 also ammonium salts with ammonia or suitable organic amines, there coming into consideration for the salt formation especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines and also heterocyclic bases, 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, also bases of the pyridine type, for example pyridine, collidine or quinoline. Compounds of the formula I having a basic group 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 trifluoroacetic acid, and also with amino acids, such as arginine and lysine. If several acid or basic groups are present, mono- or poly-salts can be formed.

Compounds of the formula I having an acid group, for example a free carboxyl group, and a free basic group, for example an amino group, may also be in the form of internal salts, i.e. in zwitterion form, or one part of the molecule may be in the form of an internal salt and another part may be in the form of a normal salt.

For isolation and purification it is also possible to use pharmaceutically unacceptable salts. Only pharmaceutically acceptable non-toxic salts are used therapeutically and these are therefore preferred.

The compounds of the formula (I) have in the 3- and 5-position the R-configuration and in the 6-position the R- or S-configuration, or may alternatively be mixtures of the 6R- and 6S-configuration. Compounds with a 6R-configuration (in which the substituent R_1—CH_2— is in the β-position and the two hydrogen atoms in the 5- and 6-position are in *cis* position to one another) are preferred.

The invention relates especially to compounds of the formula (I) in which functional groups are either not protected or are protected in a form that can be split under physiological conditions, and to their pharmaceutically acceptable salts, since chiefly those compounds have the specified activity and can be used for the purpose indicated, whereas the protected compounds serve mainly as intermediates.

Special mention should be made of compounds of the formula (I) in which R_1 represents hydroxy, lower alkoxy, for example methoxy, phenyl-lower alkoxy, for example benzyloxy, lower alkanoyloxy, for example formyloxy or acetoxy, aminothiazolylcarbonyloxy, for example 2-amino-1,3-thiazol-4-ylcarbonyloxy, aminothiadiazolylcarbonyloxy, for example 5-amino-1,2,4-thiadiazol-3-ylcarbonyloxy, lower alkoxycarbonyloxy, carbamoyloxy, N-mono- or N,N-di-lower alkylcarbamoyloxy, for example N-methylcarbamoyloxy or N,N-dimethylcarbamoyloxy, lower alkanesulphonyloxy, for example methanesulphonyloxy, arenesulphonyloxy, for example benzenesulphonyloxy or toluenesulphonyloxy, or hydroxysulphonyloxy (or a salt thereof, for example the sodium salt) and R_2 represents carboxy or carboxy esterified in a form that can be split under physiological conditions, for example lower alkanoyloxymethoxycarbonyl, for example acetoxymethoxycarbonyl or pivaloyloxymethoxycarbonyl, amino-lower alkanoylmethoxy, especially α-amino-lower alkanoyloxymethoxycarbonyl, for example glycyloxymethoxycarbonyl, L-valyloxymethoxycarbonyl, L-leucyloxymethoxycarbonyl, phthalidyloxycarbonyl, for example 2-phthalidyloxycarbonyl, 4-crotonolactonyl or gamma-butyrolacton-4-yl, indanyloxycarbonyl, for example 5-indanyloxycarbonyl or 1-ethoxycarbonyloxyethoxycarbonyl, as well as the pharmaceutically acceptable salts of such compounds containing a salt-forming group, for example the alkali metal salts, for example the sodium salts, of these compounds in which R_2 represents carboxy.

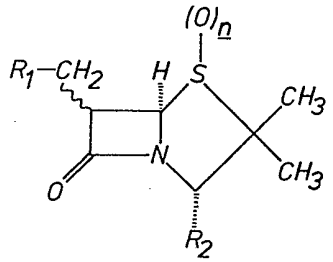
The invention relates especially to compounds of the formula (I) in which R_1 represents hydroxy, methoxy or benzyloxy and R_2 represents carboxy, and the pharmaceutically acceptable salts, for example the sodium salts, thereof.

The invention relates especially to the compounds described in the Examples, especially the compound of the formula (I) in which R_1 represents hydroxy and R_2 represents carboxy, and to the pharmaceutically acceptable salts thereof, for example the sodium salt.

The compounds of the formula (I) and salts thereof are produced in a manner known *per se*.

Compounds of the formula (I) and salts of such compounds having a salt-forming group are produced, for example, by

a) oxidising in the 1-position a compound of the formula

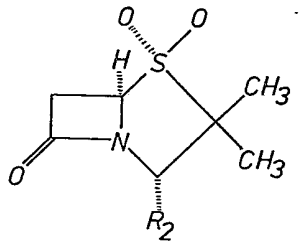


(IIa)

in which R_1 and R_2 have the meanings mentioned under formula (I) and Y represents a group that can

or

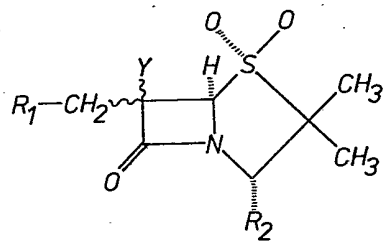
b) introducing a R_1—CH_2— group into a compound of the formula



(IIb)

in which R_2 represents a protected carboxyl group, or

c) in a compound of the formula



(IIc),

in which R_1 and R_2 have the meanings mentioned under formula (I) and Y represents a group that can be converted into a hydrogen atom, converting the Y group into a hydrogen atom,

and, if desired or necessary, converting a group R_1 in a resulting compound into a different group R_1, and/or a group R_2 into a different group R_2 and/or a resulting salt into the free compound or into a different salt and/or a resulting free compound having a salt-forming group into a salt and/or separating a resulting mixture of isomeric compounds of the formula (I) into the individual isomers.

a) *Oxidation of the 1-position:*

The oxidation of compounds of the formula (IIa) is carried out by treating with agents converting sulphide or sulphoxide groups into sulphone groups, especially with hydrogen peroxide, organic peracids, especially aliphatic percarboxylic acids, for example peracetic acid, perbenzoic acid, chloroperbenzoic acid, for example m-chloroperbenzoic acid, or monoperphthalic acid, with oxidising inorganic acids or their salts, for example nitric acid, chromic acid, potassium permanganate, or an alkali metal hypochlorite, for example sodium hypochlorite, or alternatively 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, for example 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 a mixture of these solvents, especially an aqueous mixture, for example aqueous acetic acid, at room temperature, or while cooling or gently heating, i.e. at approximately −20 to approximately +90°, preferably at approximately +18 to approximately +30°. The oxidation can alternatively be carried out in stages, by first of all oxidising at a lower temperature, i.e. at approximately −20 to approximately 0°, to the sulphoxide stage, which is optionally isolated, then, in a second step, oxidising the sulphoxide, preferably at a higher temperature, for instance at room temperature, to the sulphone, that is to say the 1,1-dioxide of the formula (I).

For working up, any excess oxidising agent still present may be eliminated by reduction, especially by treating with a reducing agent, such as a thiosulphate, for example sodium thiosulphate.

b) *Introduction of a R_1—CH_2— group:*

The group R_1—CH_2— is introduced by an alkylation reaction, for example by reacting a mono- or di-anion of a compound of the formula (IIb) with formaldehyde or a reactive functional derivative thereof and then treating the reaction product with a proton source.

Monoanions of compounds of the formula (IIb) have in the 6-position, and dianions in the 6- and in the 3-position, a negative charge instead of a hydrogen atom. Compounds of this type are usually produced *in situ*, for example by reacting a compound of the formula (IIb) with one or two moles of a metallising reagent. Suitable metallising reagents are substituted and unsubstituted alkali metal amides, alkali metal hydrides or alkali metal lower alkyl compounds, in which the alkali metal is sodium or especially lithium, for example sodium or lithium amide, lithium bis-trimethylsilylamide, sodium hydride, lithium hydride and preferably lithium diisopropylamide and butyllithium. Another method of producing monoanions consists of reacting a 6-halo compound of a compound of the formula (IIb), in which the 6-position is substituted by halogen, for example chlorine, bromine or especially iodine, with magnesium

or a Grignard reagent, for example with a lower alkylmagnesium halide, for example methylmagnesium bromide, or with activated zinc or zinc amalgam.

Reactive functional derivatives of the formaldehyde are, for example, paraformaldehyde and compounds of the formula R_1—CH_2—X in which R_1 represents an etherified or esterified hydroxy group and X is a nucleofugal leaving group, for example a halogen atom, for example chlorine, bromine or iodine, a sulphonyloxy group, for example mesyloxy or tosyloxy, or alternatively a R_1^a—O— group.

The production of the mono- and di-anion is carried out in an inert aprotic solvent, for example in a hydrocarbon, for example hexane, benzene, toluene or xylene, a slightly polar ether, for example diethyl ether, tetrahydrofuran or dioxan, or an acid amide, for example hexamethylphosphoric acid triamide, or mixtures thereof, at temperatures of between approximately −80° and approximately room temperature, the production by means of metallising reagents, magnesium or Grignard reagents preferably being carried out at low temperatures, approximately −70° to approximately −30°, whilst the production by means of zinc is preferably carried out at approximately 0° to 30°, especially at room temperature.

The reaction of the mono- or di-anion with formaldehyde or the reactive functional derivative thereof is carried out in the same solvent or solvent mixture and under the same above-mentioned temperature conditions. The mono- or di-anion can alternatively be formed in the presence of formaldehyde or the reactive derivative thereof.

In a preferred embodiment, gaseous dry formaldehyde is conveyed at approximately −78° into a monoanion-containing reaction mixture preferably obtained by reacting a 6-halogen-substituted, especially a 6-bromine- or 6-iodine-substituted, compound of the formula IIb with a lower alkylmagnesium halide, especially methylmagnesium iodide, in an ether, especially tetrahydrofuran.

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

c) *Exchange of Y for hydrogen:*

In a compound of the formula (IIc), Y in the meaning of a group exchangeable for hydrogen is, for example, an isonitrile group C=N— or halogen, for example chlorine, iodine or, especially, bromine.

The exchange of Y for a hydrogen atom is carried out by treating with a suitable reducing agent. Suitable reducing agents are, for example, metal hydrides, especially tin hydrides, such as tri-lower alkyltin hydrides or di-lower alkyltin hydrides, especially tri-n-butyltin hydride, or alternatively triphenyltin hydride, lithium aluminium hydride or sodium borohydride, hydrogen *in statu nascendi,* for example produced from a metal and a proton source, especially zinc and acetic acid, or sodium and alcohol, for example amyl alcohol, or alternatively catalytically activated hydrogen, for example hydrogen activated by palladium-on-carbon.

The reduction is carried out in a suitable, optionally inert, solvent. Metal hydrides are used, for example, in a hydrocarbon, for example pentane, hexane, benzene, toluene or xylene, whilst the reduction with hydrogen *in statu nascendi* is carried out in the proton source employed, which may optionally be diluted by an inert solvent. The catalytic reduction can also be carried out in one of the mentioned solvents or solvent mixtures. Depending on the reducing agent used, the reduction is carried out at room temperature or reduced or elevated temperature, for instance at from −80 to +100°.

A preferred reduction process is the treatment of a compound of the formula (IIc) in which Y represents an isonitrile group or bromine with tri-n-butyltin hydride in an inert solvent, for example benzene, at room temperature to the boiling temperature of the solvent used, that is to say up to approximately 80°, optionally in the presence of a catalytic amount of azobisisobutyronitrile (D.I. John, E.J. Thomas and N.D. Tyrell, J.C.S. Chem. Comm. 1979, page 345; J.A. Aimetti, E.S. Hamanaka, D.A. Johnson and M.S. Kellogg, Tetrahedron Letters, No. 48, 1979, page 4631).

In a resulting compound of the formula (I), the substituents R_1 and R_2 can be converted within the scope of their meanings, and in any sequence, into different substituents R_1 or R_2. Thus, a hydroxy group R_1 can be converted by etherification or esterification into an etherified or esterified hydroxy group R_1^a—O— or R_1^b—O— respectively. A free carboxyl group R_2 can be esterified and an esterified carboxyl group R_2 can be converted into a free carboxyl group. Protecting groups optionally present in the radical R_1 can likewise be split off. These subsequent operations are carried out in a manner known *per se,* for example as follows:

Etherification and esterification of a hydroxy group R_1:

In a compound of the formula (I) in which the group R_2 is in the form of a functionally modified carboxyl group and other, optionally present functional groups are preferably protected, the hydroxy group R_1 can be converted in a manner known *per se* into an etherified hydroxy group R_1^a—O—.

Suitable etherifying agents are, for example, diazo compounds $R_1^aN_2$, such as optionally substituted diazo-lower alkanes, for example diazomethane, diazoethane, diazo-n-butane or diphenyldiazomethane. These reagents are used in the presence of a suitable inert solvent, such as an aliphatic, cycloaliphatic or aromatic hydrocarbon, such as hexane, cyclohexane, benzene or toluene, a halogenated aliphatic

hydrocarbon, for example methylene chloride, or an ether, such as a di-lower alkyl ether, for example diethyl ether, or a cyclic ether, for example tetrahydrofuran or dioxan, or a solvent mixture, and, depending on the diazo reagent, while cooling, at room temperature or while heating gently and also, if necessary, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Other suitable etherifying agents are esters of alcohols R_1^a—OH, especially those with strong inorganic or organic acids, such as mineral acids, for example hydrohalic acids, such as hydrochloric, hydrobromic or hydroiodic acid, also sulphuric acid or halosulphuric acids, for example fluorosulphuric acid, or strong organic sulphonic acids, such as lower alkanesulphonic acids optionally substituted, for example by halogen, such as fluorine, or aromatic sulphonic acids, such as, for example, benzenesulphonic acids optionally substituted by lower alkyl, such as methyl, by halogen, such as bromine, and/or by nitro, for example methanesulphonic acid, trifluoromethanesulphonic acid or *p*-toluenesulphonic acid. Such esters are, for example, R_1^a-halides, *inter alia* lower alkyl halides, di-R_1^a-sulphates, for example di-lower alkyl sulphates, such as dimethyl sulphate, also fluorosulphonic acid R_1^a-esters, such as fluorosulphonic acid lower alkyl esters, for example fluorosulphonic acid methyl ester, or optionally halogen-substituted methanesulphonic acid R_1^a-esters, such as methanesulphonic acid lower alkyl esters, for example trifluoromethanesulphonic acid methyl ester. They are normally used in the presence of an inert solvent, such as an optionally halogenated, such as chlorinated, aliphatic, cycloaliphatic or aromatic hydrocarbon, for example methylene chloride, an ether, such as dioxan or tetrahydrofuran, or a mixture thereof. In this process suitable condensation agents are preferably used, such as alkali metal carbonates or bicarbonates, for example sodium or potassium carbonate or bicarbonate (usually together with a sulphate), or organic bases, such as, normally sterically hindered, tri-lower alkylamines, for example N,N-diisopropyl-N-ethylamine (preferably together with halosulphonic acid lower alkyl esters or optionally halogen-substituted methanesulphonic acid lower alkyl esters), the process being carried out while cooling, at room temperature, or while heating, for example at temperatures of from approximatelyl —20° to approximately 50°C and, if necessary, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The etherification reaction described above can be considerably accelerated by phase transfer catalysis (see Dehmlow, Angewandte Chemie, vol. 5, p.187 (1974)). As phase transfer catalysts there may be used quaternary phosphonium salts and especially quaternary ammonium salts, such as optionally substituted tetraalkylammonium halides, for example tetrabutylammonium chloride, bromide or iodide, or alternatively benzyl-triethylammonium chloride, in catalytic or up to equimolar quantities. Any one of the water-immiscible solvents may be used as the organic phase, for example one of the optionally halogenated, such as chlorinated, lower aliphatic, cycloaliphatic or aromatic hydrocarbons, such as trichloroethylene or tetrachloroethylene, tetrachloroethane, carbon tetrachloride, chlorobenzene, toluene or xylene. The alkali metal carbonates or bicarbonates, for example potassium or sodium carbonate or bicarbonate, alkali metal phosphates, for example potassium phosphate, and alkali metal hydroxides, for example sodium hydroxide, suitable as condensation agents, can, in the case of base-sensitive compounds, be added to the reaction mixture titrimetrically, for example by means of an automatic titrating device, so that the pH value remains between approximately 7 and approximately 8.5 during etherification.

Other etherifying agents are suitable acetal compounds, such as *gem*-di-R_1^aO-lower alkanes, for example *germ*-di-lower alkoxy-lower alkanes, such as 2,2-dimethoxypropane, which are used in the presence of strong organic sulphonic acids, such as *p*-toluenesulphonic acid, and a suitable solvent, such as a di-lower alkyl sulphoxide or a lower alkylene sulphoxide, for example dimethyl sulphoxide; or suitable R_1^a-containing orthoesters, for example orthoformic acid tri-R_1^a-esterrs, for example orthoformic acid tri-lower alkyl esters, for example orthoformic acid triethyl ester, which are used in the presence of a strong mineral acid, for example sulphuric acid, or a strong organic sulphonic acid, such as *p*-toluenesulphonic acid, and a suitable solvent, such as an ether, for example dioxan.

Other etherifying agents are corresponding tri-substituted oxonium salt (so-called Meerwein salts), or di-substituted carbenium or halonium salts in which the substituents are the etherifying radicals R_1^a, for example tri-lower alkyloxonium salts, and also di-lower alkoxycarbenium or di-lower alkylhalonium salts, especially the corresponding salts with complex fluorine-containing acids, such as the corresponding tetrafluoroborates, hexafluorophosphates, hexafluoroantimonates or hexachloroantimonates. Such reagents are, for example, trimethyl- or triethyloxonium hexafluoroantimonate, hexachloroantimonate, hexafluorophosphate or tetrafluoroborate, dimethoxycarbenium hexafluorophosphate or dimethylbromonium hexafluoroantimonate. These etherifying agents are preferably used in an inert solvent, such as an ether or a halogenated hydrocarbon, for example diethyl ether, tetrahydrofuran or methylene chloride, or in a mixture thereof, if necessary in the presence of a base, such as an organic base, for example a preferably sterically hindered tri-lower alkylamine, for example N,N-diisopropyl-N-ethylamine, and while cooling, at room temperature or while heating gently, for example at from approximately —20°C to approximately 50°C, if necessary in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Other etherifying agents are, finally, corresponding 1-substituted 3-aryltriazene compounds, in which the substituent represents the etherifying radical R_1^a and aryl preferably represents optionally substituted phenyl, for example lower alkylphenyl, such as 4-methylphenyl. Triazene compounds of this

type are 3-aryl-1-lower alkyltriazenes, for example 3-(4-methylphenyl)-1-methyltriazene, 3-(4-methylphenyl)-1-ethyltriazene or 3-(4-methylphenyl)-1-isopropyltriazene. These reagents are usually used in the presence of inert solvents, such as optionally halogenated hydrocarbons or ethers, for example benzene, or solvent mixtures and while cooling, at room temperature or preferably at elevated temperature, for example at from approximately 20°C to approximately 100°C, if necessary in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

In a resulting compound of the formula (I), in which the group R_2 is in the form of functionally modified carboxyl and other, optionally present functional groups are preferably protected, a hydroxy group R_1 can be esterified in a manner known *per se*. Thus, the hydroxy group can be converted into an acyloxy group R_1^b—O— by treating a hydroxymethyl compound of the formula (I) with an acylating agent that introduces the desired acyl radical R_1^b of an organic carboxylic acid. In so doing, the carboxylic acid corresponding to R_1^b or a reactive derivative thereof, especially an anhydride, including a mixed or internal anhydride, of such an acid is used. Mixed anhydrides are, for example, those with hydrohalic acids, that is to say the corresponding acid halides, especially chlorides, also with hydrocyanic acid, or alternatively those with suitable carbonic acid semi-derivatives, such as corresponding semiesters (such as the mixed anhydrides formed, for example, with a haloformic acid lower alkyl ester, such as chloroformic acid ethyl ester or isobutyl ester) or with optionally substituted lower alkanecarboxylic acids, for example those containing halogen, such as chlorine (such as the mixed anhydrides formed with pivaloyl chloride or trichloroacetyl chloride). Internal anhydrides are, for example, those of organic carboxylic acids, i.e. ketenes, such as ketene or diketene, or those of carbamic acid or thiocarbamic acid, i.e. isocyanates or isothiocyanates. Further reactive derivatives of organic carboxylic acids which can be used as acylating agents are activated esters, such as suitably substituted lower alkyl esters, for example cyanomethyl ester, or suitably substituted phenyl esters, for example pentachlorophenyl ester or 4-nitrophenyl ester. The esterification can, if necessary, be carried out in the presence of suitable condensation agents; when using free carboxylic acids, for example in the presence of carbodiimide compounds, such as dicyclohexylcarbodiimide, or carbonyl compounds, such as diimidazolylcarbonyl, and when using reactive acid derivatives, for example in the presence of basic agents, such as tri-lower alkylamines, for example triethylamine, or heterocyclic bases, for example pyridine. The acylation reaction can be carried out in the absence or presence of a solvent or solvent mixture, while cooling, at room temperature or while heating and, if necessary, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere. Suitable solvents are, for example, optionally substituted, especially optionally chlorinated, aliphatic, cycloaliphatic or aromatic hydrocarbons, such as benzene and toluene, it being possible to use suitable esterifying reagents, such as acetic anhydride, also as diluents.

A hydroxy group esterified by an organic sulphonic acid R_1^b—OH, for example lower alkanesulphonic acid, such as methanesulphonic acid, or an aromatic sulphonic acid, such as *p*-toluenesulphonic acid, can be formed preferably by treating a hydroxymethyl compound of the formula (I) with a reactive sulphonic acid derivative, such as a corresponding halide, for example chloride, if necessary in the presence of an acid-neutralising basic agent, for example an inorganic or organic base, for example in a manner analogous to that of the corresponding esters with organic carboxylic acids.

A hydroxy group esterified by an inorganic acid R_1^b—OH is formed in customary manner by treating a hydroxymethyl compound of the formula (I), in which the 3-carboxyl group is preferably esterified, with the inorganic acid, optionally in the presence of a condensation agent, or with a reactive derivative, for example an anhydride or halide, thereof, or alternatively by alkylation of the inorganic acid or a salt thereof with a reactive derivative of the hydroxymethyl compound of the formula (I), for example in which R_1 represents halogen, for example chlorine, bromine or iodine. For example, in a compound of the formula (I) in which R_1 represents hydroxy and R_2 is preferably in protected form, the hydroxy group R_1 can be converted into a sulphonyloxy group $HOSO_2$—O— or a salt thereof by treatment with sulphuric acid, chlorosulphonic acid, the adduct of sulphur trioxide and a tertiary amine, for example triethylamine, or with amidosulphonic acid and optionally subsequent neutralisation, for example with sodium bicarbonate, or can be converted into a H_2PO_3—O— group or a salt thereof by treatment with concentrated phosphoric acid, optionally in the presence of a condensation agent, for example carbodiimide or trichloroacetonitrile, with a salt thereof, for example a di-tertiary ammonium phosphate, such as di-triethylammonium phosphate, or with an anhydride of phosphoric acid, for example with polyphosphoric acid, metaphosphoric acid or phosphorus (V) oxide, or a mixed anhydride, for example phosphorus oxychloride, and optionally subsequent hydrolysis and/or neutralisation.

Esterification of a free carboxyl group:

The conversion of free carboxyl, especially a corresponding group R_2, in a compound of the formula (I) into esterified carboxyl, especially into an esterified carboxyl group that can be split under physiological conditions, is effected according to esterification methods known *per se*, for example by reacting a compound of the formula (I) in which other, optionally present functional groups are optionally in protected form, or a reactive functional carboxy derivative, including a salt, thereof, with a corresponding alcohol or a reactive functional derivative thereof.

The esterification of free carboxyl with the desired alcohol is carried out in the presence of a

suitable condensation agent. Customary condensation agents are, for example, carbodiimides, for example N,N′-diethyl-, N,N′-dipropyl-, N,N′-dicyclohexyl- or N-ethyl-N′-(3-dimethylaminopropyl)-carbodiimide, suitable carbonyl compounds, for example carbonyldiimidazole, or 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium-3′-sulphonate and 2-tert.-butyl-5-methylisoxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline. The condensation reaction is preferably carried out in an anhydrous reaction medium, preferably in the presence of a solvent or diluent, for example methylene chloride, dimethylformamide, acetonitrile or tetrahydrofuran, and, if necessary, while cooling or heating and/or in an inert gas atmosphere.

Suitable reactive functional derivatives of the carboxyl compounds of the formula I to be esterified are, for example, anhydrides, especially mixed anhydrides, and activated esters.

Mixed anhydrides are, for example, those with inorganic acids, such as hydrohalic acids, i.e. the corresponding acid halides, for example chlorides or bromides, also hydrazoic acid, i.e. the corresponding acid azides, as well as phosphorus-containing acids, for example phosphoric acid, diethylphosphoric acid or phosphorous acid, or sulphur-containing acids, for example sulphuric acid or hydrocyanic acid. Further mixed anhydrides are, for example, those with organic carboxylic acids, such as with lower alkanecarboxylic acids optionally substituted, for example by halogen, such as fluorine or chlorine, for example pivalic acid or trichloroacetic acid, or with semiesters, especially lower alkyl semiesters of carbonic acid, such as ethyl or isobutyl semiesters of carbonic acid, or with organic, especially aliphatic or aromatic, sulphonic acids, for example *p*-toluenesulphonic acid.

Activated esters suitable for reaction with the alcohol are, for example, esters with vinylogous alcohols (i.e. enols), such as vinylogous lower alkenols, or iminomethyl ester halides, such as dimethyliminomethyl ester chloride (manufactured from carboxylic acid and dimethylchloromethylidene-iminium chloride of the formula $[(CH_3)_2N{=}CHCl]^{\oplus}Cl^{\ominus}$), or aryl esters, such as pentachlorophenyl, 4-nitrophenyl or 2,3-dinitrophenyl esters, heteromatic esters, such as benztriazole esters, for example 1-benztriazole ester, or diacylimino esters, such as succinylimino or phthalylimino ester.

The acylation with such an acid derivative, such as an anhydride, especially with an acid halide, is preferably carried out in the presence of an acid-binding agent, for example an organic base, such as an organic amine, for example a tertiary amine, such as a tri-lower alkylamine, for example trimethylamine, triethylamine or ethyldiisopropylamine, or an N,N-di-lower alkylaniline, for example N,N-dimethylaniline, or a cyclic tertiary amine, such as a N-lower alkylated morpholine, such as N-methylmorpholine, or a base of the pyridine type, for example pyridine, an inorganic base, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, for example sodium, potassium or calcium hydroxide, carbonate or bicarbonate, or an oxirane, for example a lower 1,2-alkylene oxide, such as ethylene oxide or propylene oxide.

A reactive functional derivative of the esterifying alcohol is especially a corresponding ester, preferably with a strong inorganic or organic acid, and is especially a corresponding halide, for example chloride, bromide or iodide, or a corresponding lower alkylsulphonyloxy or arylsulphonyloxy compound, such as methylsulphonyloxy or 4-methylphenylsulphonyloxy.

Such a reactive ester of an alcohol can be reacted with the free carboxyl compound of the formula I or with a salt, such as an alkali metal or ammonium salt, thereof, the reaction preferably being carried out in the presence of an acid-binding agent when using the free acid.

The above esterification reactions are carried out in an inert, usually anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, such as a formamide, for example dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or mixtures thereof, if necessary while cooling or heating, for example within a temperature range of from approximately −40°C to approximately +100°C, preferably at from approximately −10°C to approximately +40°C and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

Furthermore, the acid derivative may, if desired, be formed *in situ*. For example, a mixed anhydride is obtained by treating the carboxylic acid compound having appropriately protected functional groups, or a suitable salt thereof, such as an ammonium salt, for example with an organic amine, such as piperidine or 4-methylmorpholine, or a metal salt, for example an alkali metal salt, with a suitable acid derivative, such as the corresponding acid halide of an optionally substituted lower alkanecarboxylic acid, for example trichloroacetyl chloride, with a semiester of a carbonic acid semihalide, for example chloroformic acid ethyl ester or isobutyl ester, or with a halide of a di-lower alkylphosphoric acid, for example diethyl phosphorobromidate, and the mixed anhydride so obtained is used without isolation.

The splitting off of protecting groups:

In a resulting compound of the formula I in which one or more functional groups are protected, these, for example protected carboxyl, amino, hydroxy and/or sulpho groups, may be liberated in a manner known *per se*, optionally in stages or simultaneously, by means of solvolysis, especially hydrolysis, alcoholysis or acidolysis, or by means of reduction, especially hydrogenolysis or chemical reduction.

Thus, tert.-lower alkoxycarbonyl, or lower alkoxycarbonyl substituted in the 2-position by an organic silyl group or in the 1-position by lower alkoxy or lower alkylthio, or optionally substituted diphenylmethoxycarbonyl can be converted into free carboxyl, for example by treating with a suitable 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 liberated, for example, by means of hydrogenolysis, i.e. by treating with hydrogen in the presence of a metallic hydrogenation catalyst, such as a palladium catalyst. Furthermore, suitable substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, canb be converted into free carboxyl also be means of chemical reduction, for example by treating with an alkali metal dithionite, for example sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II) chloride, usually in the presence of a hydrogen-yielding agent that, together with the metal, is capable of producing nascent hydrogen, such as an acid, especially a suitable carboxylic acid, such as a lower alkanecarboxylic acid optionally substituted, for example by hydroxy, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic acid, 4-chloromandelic acid or tartaric acid, or of an alcohol or thiol, water preferably being added. By treating 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 carboxyl, it being possible to split aroylmethoxycarbonyl similarly by treating with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate or sodium iodide. Substituted 2-silylethoxycarbonyl can also be converted into free carboxyl by treating with a salt of hydrofluoric acid yielding the fluoride anion, such as an alkali metal fluoride, for example sodium or potassium 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 or tri-lower alkylarylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic solvent, such as dimethyl sulphoxide or N,N-dimethylacetamide. Carboxyl esterified by an organic silyl or stannyl group, such as tri-lower alkylsilyl or tri-lower alkylstannyl, for example trimethylsilyl, can be liberated in the customary manner by solvolysis, for example by treating with water, an alcohol or an acid.

A protected amino group, for example Am, is liberated in a manner known *per se* and, depending on the type of protecting groups, in various manners, preferably by solvolysis or reduction. 2-halo-lower alkoxycarbonylamino (optionally after converting a 2-bromo-lower alkoxycarbonylamino group into a 2-iodo-lower alkoxycarbonylamino group), aroylmethoxycarbonylamino or 4-nitrobenzyloxycarbonylamino can be split, for example by treating with a suitable chemical reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxycarbonylamino can also be split by treating with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino also be treating with an alkali metal dithionite, for example sodium dithionite. Optionally substituted diphenylmethoxycarbonylamino, tert.-lower alkoxycarbonylamino or 2-tri-substituted silylethoxycarbonylamino can be liberated by treating with a suitable acid, for example formic acid or trifluoroacetic acid, optionally substituted benzyloxycarbonylamino can be liberated, for example by hydrogenolysis, i.e. by treating with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst, optionally substituted triarylmethylamino, formylamino or 2-acyl-lower alk-1-en-ylamino can be liberated, for example by treating with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic acid, acetic acid or trifluoroacetic acid, optionally in the presence of water, and an amino group protected by an organic silyl or stannyl group can be liberated, for example by hydrolysis or alcoholysis. An amino group protected by 2-haloacetyl, for example 2-chloroacetyl, can be liberated by treating with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate, of thiourea and by subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting condensation product. An amino group protected by 2-substituted silylethoxycarbonyl can also be converted into the free amino group by treating with a salt of hydrofluoric acid yielding fluoride anions, as indicated above in connection with the liberation of a correspondingly protected carboxyl group. A phosphoramido, phosphonamido or phosphinamido group can be converted into the free amino group, for example by treating with a phosphorus-containing acid, such as a phosphoric, phosphonic or phosphinic acid, for example orthophosphoric acid or polyphosphoric acid, an acid ester thereof, for example monomethyl, monoethyl, dimethyl or diethyl phosphate, or monomethylphosphonic acid, of an anhydride thereof, such as phosphorus pentoxide.

An amino protected in the form of an azido group is converted into the free amino group, 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 alternatively by treating with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is carried out preferably in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or alternatively in water or a mixture of water and an organic solvent, such as an alcohol or dioxan, at approximately 20°C to 25°C, or alternatively while cooling or heating.

A hydroxy group protected by a suitable acyl group, an organic silyl or stannyl group or by optionally substituted 1-phenyl-lower alkyl is liberated in the same manner as a correspondingly

protected amino group. A hydroxy group protected by 2,2-dichloroacetyl is liberated, for example by basic hydrolysis, while a hydroxy group etherified by tert.-lower alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is liberated by acidolysis, for example by treating with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid. A 2-halo-lower alkyl group is split off by reduction.

A protected, especially esterified, sulpho group is liberated analogously to a protected carboxyl group.

The splitting reactions described are carried out under conditions known *per se*, if necessary while cooling or heating, in a closed vessel and/or in an inert gas atmosphere, for example a nitrogen atmosphere.

The methods of reductive splitting of 2-halo-lower alkoxycarbonyl and 2-halo-lower alkoxy groups, which are known *per se*, may advantageously be carried out under especially mild conditions in the presence of a catalytic amount of a transition metal complex of a corrin or porphin compound, it also being possible for groups that are normally difficult to split, for example 2-chloroethoxycarbonyl and 2-chloroethoxy groups, to be split.

Transition metal complexes of corrin and porphin compounds, which are used as catalysts to reductive splitting, are derived from those transition metals that occur in more than one valency stage, such as copper, palladium, rhodium and especially cobalt. Preferred catalysts are model compounds for the synthesis of vitamin B_{12}, for example derivatives derived from the 2,2,3,3,7,7,8,8,12,12,13,13,17,17,18,18-hexadecamethyl-10,20-diazahexahydroporphin cobalt(III) cation, and especially vitamins of the B_{12} group, and of these especially cyanocobalamin, aquocobalamin and hydroxycobalamin, and their derivatives and decomposition products, such as cobyrinic acid and its esters, corphyrinic acid, corphinic acid, cobamic acid and cobamide. The quantity of catalyst is normally from approximately 0.1 to approximately 0.001, preferably approximately 0.03 to approximately 0.003, molar equivalent, based on the component to be reduced, but with a favourable experimental arrangement, for example with an optimised electroreduction, it is possible to go far below the lowermost limit.

The reduction is carried out in a manner known *per se* by conventional methods in the presence of a proton source. The proton source used can be any inorganic or organic acid, or customary protic solvents; acids are advantageously used in a buffered form or as salts, the pH value preferably lying between approximately 4.0 and 9.5, especially between approximately 5.5 and 7.5, and more especially in the region of the neutral point.

A reducing method that recommends itself as one of the most gentle methods is cathodic electroreduction under conventional conditions, such as with a mercury cathode or some other cathode that can be generally used for electroreduction, such as a carbon cathode, in the presence of customary auxiliary electrolytes, such as ammonium and/or alkali metal salts, especially halides and perchlorates, preferably those distinguished by a good solubility in the aqueous organic medium used. There are used as solvents, besides water, customary water-miscible organic solvents, for example lower alkanols, such as methanol, ethanol and isopropyl alcohol, or dimethylformamide, and similar lower aliphatic amides, or alternatively nitriles, such as acetonitrile, ethers, such as diethyl ether, 1,2-dimethoxyethane and 1,2-diethoxyethane and cyclic ethers of the tetrahydrofuran type, ketones, such as acetone, carbonates, such as dimethyl and diethyl carbonate, and sulphoxides, such as especially dimethyl sulphoxide. The temperature of the electroreduction can vary within a wide range, that is from approximately −20°C to the boiling temperature of the reaction mixture, but preferably it is room temperature or below.

Another suitable variant of the reductive splitting is reduction by a metal, especially zinc or alternatively magnesium. For this, under certain circumstances the usual vigorous conditions can be applied, for example approximately 90% aqueous acetic acid as medium and/or elevated temperature up to the boiling point of the mixture with correspondingly shortened reaction time. Preferably, however, the reduction is carried out under the gentlest possible conditions, for example in the above-mentioned preferred pH range in the region of the neutral point and at temperatures of from approximately 0° to approximately 40°C, preferably approximately 10—25°C; normally an approximately tenfold molar excess of metal, preferably zinc in the form of zinc dust, is used, which directly before the reaction is advantageously activated in conventional manner, for example by stirring with dilute hydrochloric acid and carefully washing until neutral. To achieve the desired buffer effect, advantageously ammonium salts by hydrohalic acids can be used, especially those to be found in the respective group of the formula I to be split off. The reduction is carried out in the above-mentioned organic solvents or mixtures thereof; protic solvents are preferred. Other conventional variants of the reduction process can also be used, for example reduction with metal cations in low valency stages, for example chromium(II) salts, such as chromium(II) chloride or acetate, reduction with complex metal hydrides, for example sodium borohydride and related lower alkoxy sodium borohydrides and lower alkoxylithium borohydrides, and catalytic hydrogenation, for example with a palladium catalyst.

Preferably, when several protected functional groups are present, the protecting groups are so selected that more than one such group can be split off simultaneously, for example by acidolysis, such as by treating with trifluoroacetic acid or formic acid, or by reduction, such as by treating with zinc and

acetic acid, or with hydrogen and a hydrogenation catalyst, such as a palladium-on-carbon catalyst.

Salt formation:

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 acid groups can be formed, for example by treating 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 metal or alkaline earth metal salts, for example sodium bicarbonate, or with ammonia or a suitable organic amine, preferably stoichiometric quantities or only a small excess of the salt-forming agent being used. Acid addition salts of compounds of the formula I are obtained in the customary manner, for example by treating with an acid or a suitable anion exchange reagent. Internal salts of compounds of the formula I that contain, for example, a free carboxyl group can be formed, for example by neutralising salts, such as acid addition salts, to the isoelectric point, for example with weak bases, or by treating with liquid ion exchangers.

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

The sulphoxide of the formula (IIa) in which the index *n* has the value 1 may be used in the 1R- or 1S-configuration or as a mixture of the two isomers.

Similarly, in a starting material of the formulae (IIa-c), the 6-position may have the R-, S- or the R,S-configuration. In the case where oxidation is involved the configuration at the 6-carbon atom is retained. If a mixture of the 6R- and 6S-compounds of the formula (IIa) is used, a mixture of the 6R- and 6S-compounds of the formula (I) is obtained. If a mixture of the 6R and 6S-compounds of the formulae (IIb) and (IIc) is used, the 6R-compound of the formula (I) is preferentially obtained.

Mixtures of isomers can be separated into the individual isomers in a manner known *per se*, for example by fractional crystallisation, chromatography, etc.

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 these, or the process is discontinued at any stage; furthermore, starting materials may be used in the form of derivatives or formed during the reaction.

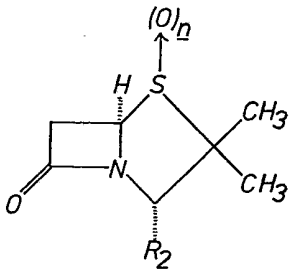
Preferably, the starting materials and the reaction conditions are so chosen that the compounds described above as being especially preferred are obtained.

Starting materials

The starting materials of the formulae (IIa) and (IIc) used in the process for the manufacture of the compounds of the present invention are novel. They may be manufactured in a manner known *per se*. The present invention relates also to these compounds together with the processes for their manufacture. Compounds of the formulae (IIa) and (IIc) in which R_2 is carboxyl or esterified carboxyl that can be split under physiological conditions and the pharmaceutically acceptable salts of such compounds having a salt-forming group have pharmaceutical properties similar to those of compounds of the formula (I).

The compounds of the formula (IIa) may be manufactured, for example, by

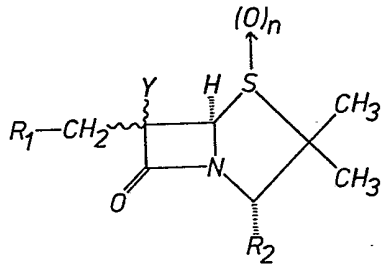
a') introducing the group $R_1—CH_2—$ into a compound of the formula



(III),

in which the index *n* has the value 0 or 1 and R_2 represents an esterified carboxyl group, or

b') in a compound of the formula



(IV),

in which R_1, R_2 and the index *n* have the meanings given under formula (IIa) and Y represents a group that can be converted into a hdyrogen atom, converting the group Y into a hydrogen atom and, if desired or necessary, in a resulting compound converting a group R_1 into a different group R_1 and/or a group R_2 into a different group R_2, and/or converting a resulting 1-sulphide into a 1-sulphoxide or a resulting 1-sulphoxide into a 1-sulphide, and/or a resulting salt into the free compound or into a different salt, and/or a resulting free compound having a salt-forming group into a salt, and/or separating a resulting mixture of isomeric compounds of the formula (I) into the individual isomers.

The introduction of a group R_1—CH_2— and the exchange of Y for hydrogen is effected analogously to the processes described under b) and c).

The compounds of the formula (IIa) that can be obtained according to processes (a') and (b') may be converted into different compounds of the formula (IIa) by subsequent operations, it being possible to use for the conversion of R_1 into a different R_1, and of R_2 into a different R_2, for the manufacture of the salts and for the manufacture of the free compounds from the salts, and for the separation of the mixture of isomers into the individual isomers the same processes as those specified for the corresponding subsequent operations in the processes for the manufacture of compounds of the formula (I).

The manufacture of the 1-sulphoxides of compounds of the formula (IIa), in which the index *n* has the value 1, from the 1-sulphides of the formula (IIa), in which the index *n* has the value 0, may also be effected analogously to the oxidation of compounds of the formula (IIa) to form sulphones of the formula (I), it being necessary correspondingly to reduce the quantity of oxidising agent if over oxidation is to be avoided.

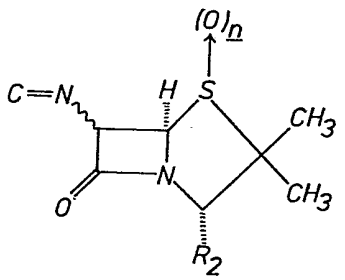
The reduction of 1-sulphoxides of the formula (IIa) to the 1-sulphides is effected by means of methods that are known in penicillin and cephalosporin chemistry, for example by treating with phosphorus trichloride or tribromide.

The compounds of the formula (IIb) are known or may be manufactured in a manner known *per se*.

The compounds of the formula (IIc) may be manufactured from compounds of the formula (IV) by oxidation analogously to process a).

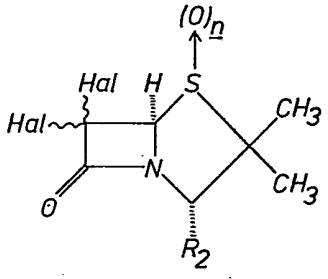
The starting compounds of the formula (III) and the 6-halo derivatives thereof are known or may be manufactured in a manner known *per se*.

The starting compounds of the formula (IV) may be manufactured in a manner known *per se*, for example, by introducing the group R_1—CH_2— into a new compound of the formula



(V)

or



(VI)

in which the index *n* has the value 0 or 1, and R_2 represents an esterified carboxyl group, for example chlorine, iodine or, especially, bromine, analogously to one of the processes mentioned under b) for the manufacture of compounds of the formula (IIa). If a compound of the formula (V) is used as starting material, the anion is produced preferably with potassium carbonate in dimethylformamide, for example according to P. H. Bentley and J. P. Clayton, J. C. S. Chem. Comm., 1974, page 278.

The compounds of the formulae (V) and (VI) are known or may be manufactured in a manner known *per se*.

The compounds of the present invention are distinguished by an excellent β-lactamase-inhibiting action which may be demonstrated, for example, *in vitro* by the inhibition of β-lactamases of *Staphylococcus aureus, Enterobacter cloacae,* pseudomonads, *Morganella morganii, Escherichia coli, Haemophilus influenzae* and *Bacteroides fragilis.* The preferred compounds especially are distinguished by an I_{50} (the concentration of the test substance that inhibits 50% of the β-lactamase) of approximately 1.2 to 0.026 μM.

As a result of this β-lactamase-inhibiting action, the compounds of the present invention increase the action of β-lactam antibiotics *in vitro* and *in vivo*, as can be ascertained by comparing the antibiotic actions of compounds of the present invention and of β-lactam antibiotics, alone and in combination with one another. For example, *in vitro*, the MIC values of 1:1 combinations of the compound of the formula (I) according to the invention, in which R_1 represents hydroxy and R_2 represents carboxy, or the sodium salt thereof with ampicillin, cefsulodin (CGP7174/E) or cefotiam (CGP14221/E) against a series of the above-mentioned, β-lactamase-producing microorganisms are significantly lower than the MIC values of the individual compounds. *In vivo,* for example when administered subcutaneously to mice infected with β-lactamase-producing microorganisms, for example with *Escherichia coli* 205 R^+ TEM or *Morganella morganii* 2359, a significant reduction in the ED_{50} values in comparison with those of the individual constituents was detected. Some of the values have been compiled in the following table:

Infecting microorganism	s.c. ED_{50} (mg/kg. mice)		
	A	B	A+B (1:1)
Esch. coli: 205 RT	100	70	14
Morganella morg. 2359	100	75	18

A = sodium salt of (3R, 5R, 6R)-2,2-dimethyl-6-hydroxy-ethylpenam--3-carboxylic acid 1,1-dioxide.

B = cefotiam.

Accordingly, the β-lactamase-inhibiting compounds of the present invention, including pharmaceutically acceptable salts thereof, are valuable in the treatment of infections in humans and animals that are produced by β-lactamase-producing microorganisms and for combating of which β-lactamase-sensitive antibiotics are used. The active compounds of the present invention may be administered either before or, especially, simultaneously with the actually effective antibiotic. The dose of β-lactamase-inhibitors according to the invention is from approximately one tenth to approximately ten times, especially approximately one fifth to approximately five times, the quantity of antibiotic to be used.

The pharmacologically acceptable compounds of the present invention can be used for the manufacture of pharmaceutical preparations which contain an effective amount of the active substance according to the invention either alone or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers and, optionally, a β-lactam antibiotic, and which are suitable for oral or for parenteral, i.e. intramuscular, subcutaneous or intraperitoneal, administration.

For the manufacture of pharmaceutical preparations that, in addition to a β-lactamase-inhibiting compound of the present invention, also contain a β-lactam antibiotic, it is possible to use any antibiotics that contain the β-lactam structure, there being preferred penicillin and cephalosporin antibiotics and also the penem antibiotics which are unstable towards β-lactamases.

Suitable penicillins and cephalosporins may be found in the synoptic publications of E. H. Flynn, Cephalosporins and Penicillins, Academic Press, New York and London, 1972; P. G. Sammess, Chem. Rev., 1976, Vol. 76, No. 1, pages 113—115; J. Cs. Jászberényi and T. E. Gunda, Progr. Med. Chem., Vol. 12, 1975, pages 395—477; J. Elks, Recent Advances in the Chemistry of β-Lactam Antibiotics, The Chemical Society, Burlington House, London W1V 0BN, 1977; the Merck Index, 9th Ed., Merck & Co. Inc., Rahway, N. J., USA, 1976, and the Encyclopaedia of Antibiotics, sec. Ed., John Wiley & Sons (1978).

Suitable penicillins are, for example, penicillin V (for example in the form of the potassium salt), benzylpenicillin (for example in the form of the potassium or sodium salt), propicillin (for example in the form of the potassium salt), epicillin, cyclacillin, azidocillin, or penicillins from the group of optionally substituted α-aminobenzylpenicillins, for example ampicillin, amoxicillin, apalcillin, pirbenicillin, hetacillin, metampicillin.or 4-acetoxyampicillin.

Suitable penicillins are also those from the groups of carboxypenicillins, sulphopenicillins, ureidopenicillins, acylureidopenicillins and methyleneaminopenicillins.

The groups of carboxy- and sulpho-penicillins include, for example, carbencillin (sodium salt), carfecillin, indanylcarbenicillin, ticarcillin (disodium salt), and sulfocillin (sulbenicillin; for example in the form of the disodium salt).

Ureidopenicillins and acylureidopenicillins suitable for the above-mentioned pharmaceutical mixtures are, for example, azlocillin, mezlocillin and furazlocillin and 6β-[D—2—(4—A—2,3-idoxo-1-piperazinocarboxamido)-phenylacetamido]-penicillanic acid, in which A is hydrogen or a substituent, especially lower alkyl, for example methyl or ethyl. Special mention should be made of piperacillin. The ureidopenicillins and acylureidopenicillins are preferably used in the form of salts, especially in the form of sodium salts.

Suitable methyleneaminopenicillins are, for example, 6β-(1-azacyclylmethyleneamino)-penicillanic acids, especially mecillinam and salts thereof, such as sodium salts, and pivmecillinam.

Suitable cephalosporins are, for example, cefaclor, cefadroxil, cefamandol, cefamandol-nafat, cefaparol, cefatrizin, cefazolin, cefonicid, cefoperazon, ceforanid, cefotaxime, cefotiam (in the form of the dihydrochloride), cefroxadin, cefsulodin, ceftezol, cephalexin, cephaloglycin, cephaloridin, cephalothin, cephapyrin (sodium salt), cephadrin, cefatriaxon, 7β-[2-(2-aminothiazol-4-yl)-2-(2-carboxyprop-2-yloxyimino)-acetamido]-2-pyridinyl-3-cephem-4-carboxylate (GR 20263), sodium salt of 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (SCE 1365), 7β-[2-(2)-aminothiazol-4-yl)-2-*syn*-methoxyimino)-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid (CGP 17845), 7β-[2-(2-aminothiazol-4-yl)-2-*syn*-methoxyimino)-acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid pivaloyloxymethyl ester (optionally in the form of the hydrochloride (CGP 18658/A)), 7β-[(2R)-2-[4-((2R-2-amino-2-carboxyethoxycarbonylamino)-phenyl]-2-hydroxyacetylamino]-3-[(1-methyl-1H-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (sodium salt; CGP 17520), and also 1-oxacephalosporins, for example 7β-[2-(*p*-hydroxyphenyl)-2-carboxyacetamido]-3-[(1-methyl-1H-tetrazol-5-yl)-thiomethyl]-1-dethia-1-oxa-3-cephem-4-carboxylic acid (disodium salt; LY 127935 or S 6059).

Suitable penam antibiotics are known from European Patent Application 3960 and include, for example, 6—R_1—2—R_2-penbem-3-carboxylic acids in which R_1 represents lower alkyl or hydroxy-lower alkyl, and R_2 represents hydrogen, optionally substituted lower alkyl or lower alkylthio, for example (5R,6R)-6-hydroxymethyl-penem-3-carboxylic acid and (5R,6R)-6-[(1R)-1-hydroxyethyl]-penem-3-carboxylic acid and salts thereof, for example the sodium salts.

In stead of the free carboxylic acids of the above-mentioned β-lactam antibiotics or salts thereof, it is also possible to use in the mixture the customary esters that can be split physiologically, for example pivaloyloxymethyl esters, acetoxymethyl esters, 1-ethoxycarbonyloxymethyl or 1-ethoxycarbonyloxyethyl esters or phthalidyl esters; instead of the above-mentioned free compounds it is also possible to use pharmaceutically acceptable salts thereof, including the internal salts and hydrates, and instead of the above-mentioned salts it is also possible to use free compounds thereof. The choice depends on the method of administration, the desired pH value and/or the desired concentration of a solution to be injected.

The ratio of the β-lactamase-inhibiting compounds of the present invention to the actually effective antibiotic in the pharmaceutical preparations according to the invention may vary within a wide range and is approximately between 1:10 and 10:1, preferably between 1:5 and 5:1, and is, for example, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, 1:5 or 1:6. The penicillin and cephalosporin antibiotics are incorporated in the preparations either in the customary quantity, in which case it is possible to achieve a longer duration of action, or alternatively in a quantity smaller than is customary, in which case, however, it is necessary to proportion the quantity such that the antibiotic activity is approximately equal to that when the preparations is administered without the addition of the β-lactamase inhibitor.

Pharmaceutical preparations or combination preparations that contain a β-lactamase-inhibiting compound of the present invention, optionally together with a β-lactam antibiotic, can be manufactured in the same manner as that known for the β-lactam antibiotics alone. In the combination preparations, the addition of the β-lactamase-inhibiting compounds according to the invention is effected within the mixture ratios specified. In combination preparations, the two active substance can either be homogeneously mixed or be arranged next to one another in separate compartments.

The pharmacologically active compounds of the present invention are preferably used in the form of parenterally, for example intramuscularly or intravenously, administrable preparations or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions, it being possible to manufacture these before use, for example from lyophilised preparations which contain the active substance alone or together with a carrier, for example mannitol. The pharmaceutical preparations can 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 further pharmacologically valuable substances, are manufactured in a manner known *per se*, for example by means of conventional dissolving or lyophilising processes, and contain from approximately 0.1% to 100%, especially from approximately 1% to approximately 50%, and in the case of lyophilisates up to 100%, of active

substances. Compounds of the formula I, especially those in which R_2 represents an esterified carboxyl group that can be split physiologically, for example pivaloyloxymethoxycarbonyl, can also be administered orally, for example as a granulate in the form of capsules. The pharmaceutical preparations contain the active substance or, optionally, the two active substances, optionally together with suitable carriers, in doses of from approximately 0.05 g to approximately 1.0 g per dosage unit.

According to the type of infection, the condition of the infected organism and, optionally, the antibiotic activity of the β-lactam antibiotic, daily doses of from approximately 0.1 g to approximately 5 g are used for the treatment of warm-blooded animals weighing approximately 70 kg. In general, the dose for the combination preparations lies in the same order of magnitude as the dose in which the β-lactam antibiotic is used alone.

Certain compounds of the the present invention intensify the antibiotic action of some β-lactam antibiotics in a synergistic manner. In such cases the dose can be reduced.

The following Examples serve to illustrate the invention. Temperatures are given in degrees Centrigrade. TLC represents thin-layer chromatography.

EXAMPLE 1

(3R,5R,6R and 6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester.

A solution of 1.0 g (2.12 mmol) of (3R,5R,6S)-2,2-dimethyl-6-iodopenam-3-carboxylic acid diphenylmethyl ester in 25 ml of tetrahydrofuran is cooled to −78° and 1.2 ml (2.12 mmol) of a 1.8 molar solution of methylmagnesium bromide in diethyl ether is added. After 10 minutes at −78°, formaldehyde gas is passed over the solution while stirring well. After ½ hour, a TLC sample shows complete conversion. After 40 minutes, the reaction solution is neutralised with 0.4 ml of glacial acetic acid, diluted with ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 100 g of silica gel with the solvent system toluene/ethyl acetate 2:1 and yields a mixture of the 6R and 6S title compound in a ratio of 2:3.

TLC: silica gel, toluene/ethyl acetate $R_f = 0.38$

IR spectrum (CH_2Cl_2): absorption bands at 2.79, 5.63, 5.73 μ.

EXAMPLE 2

(1R,3R,5R,6R)-, (1S,3R,5R,6R)- and (1S,3R,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide.

A solution of 1.22 g (3 mmol) of a 2:3 mixture of (3R,5R,6R)- and (3R,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester in 30 ml of chloroform is cooled to −6° and 590 mg (3.09 mmol) of 90% *m*-chloroperbenzoic acid are added. After 20 minutes, the reaction solution is washed with aqueous sodium thiosulphate solution and aqueous sodium bicarbonate solution. Then aqueous phase is subsequently extracted twice with chloroform. The combined chloroform solutions are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 45 g of silica gel with the eluant system toluene/ethyl acetate 1:2. The three title compounds were eluted in the sequence given:

1. (1R,3R,5R,6R)-isomer:
   TLC: silica gel, toluene/ethyl acetate $R_f = 0.23$.
   IR spectrum (CH_2Cl_2): absorption bands at 2.75, 2.94, 5.59, 5.69 μ.
2. (1S,3R,5R,6R)-isomer:
   TLC: silica gel, toluene/ethyl acetate $R_f = 0.21$.
   IR spectrum (CH_2Cl_2): absorption bands at 2.75, 2.95, 5.57, 5.69 μ.
3. (1S,3R,5R,6S)-isomer:
   TLC: silica gel, toluene/ethyl acetate $R_f = 0.16$.
   Melting point: 135°—138°C.
   IR spectrum (CH_2Cl_2): absorption bands at 2.76, 2.9, 5.58, 5.69 μ.

EXAMPLE 3

[(3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

a) 3.81 g (9.22 mmol) of a mixture of (1R,3R,5R,6R)- and (1S,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-4-carboxylic acid diphenylmethyl ester 1-oxide are dissolved in 114 ml of chloroform and 1.86 g (10.8 mmol) of 90% *m*-chloroperbenzoic acid are added at room temperature. After stirring for 1½ hours, working up is carried out with aqueous sodium thiosulphate solution, aqueous sodium bicarbonate solution and aqueous sodium chloride solution. The aqueous phases are subsequently extracted twice with chloroform. The combined organic solutions are dried with sodium sulphate and concentrated in a rotary evaporator. The residue is dried under a high vacuum and purified by chromatography on 38 g of silica gel with the solvent system toluene/ethyl acetate 3:1. The title compound is obtained having an R_f value = 0.23 (silica gel, toluene/ethyl acetate).

IR spectrum (CH_2Cl_2): absorption bands at 2.78, 5.55, 5.68, 7.52 μ.

The same compound can also be obtained as follows:

b) 0.5 (1.26 mmol) of (3R,5R,6R)-2,2-dimethyl-4-hydroxymethylpenam-4-carboxylic acid

diphenylmethyl ester is dissolved in 13 ml of chloroform and 0.5 g (2.6 mmol) of 90% *m*-chloroperbenzoic acid is added at room temperature. After stirring for 1½ hours, working up is carried out with aqueous sodium thiosulphate solution, aqueous sodium bicarbonate solution and aqueous sodium chloride solution. The aqueous phases are subsequently extracted twice with chloroform. The combined organic solutions are dried with sodium sulphate and concentrated in a rotary evaporator. The residue is dried under a high vacuum and purified by chromatography on 10 g of silica gel with the solvent system toluene/ethyl acetate 3:1. The title compound is obtained having the same analytical data as given under a).

EXAMPLE 4

Sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide.

a) 3.34 g (7.78 mmol) of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide are dissolved in 100 ml of tetrahydrofuran, 1.3 g of Pd/C 10% is added and hydrogenation is carried out under normal pressure at room temperature. After a reaction period of 6 hours, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is taken up in water/ethyl acetate and 653 mg (7.78 mmol) of sodium bicarbonate are added. The aqueous phase is extracted three times with ethyl acetate. The organic phases are washed twice with water. After lyophilisation of the combined aqueous phases, the title compound is obtained in the form of a white powder.

IR spectrum (KBr):
absorption bands at 2.9, 5.63, 6.18, 7.19, 7.61 μ.

The same compound can also be obtained as follows:

b) 80 mg (0.41 mmol) of 90% *m*-chloroperbenzoic acid are added at room temperature to a solution of 0.1 g (0.38 mmol) of (1R,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1-oxide in 10 ml of water/tetrahydrofuran 1:1. After stirring for 1½ hours, aqueous sodium thiosulphate solution is added. The aqueous phase is adjusted to pH 6.8 with 1N sodium hydroxide solution and lyophilised. The resulting title compound is purified by chromatography on UPC_{12} plates (eluant: H_2O, $R_f = 0.58$).

c) The title compound is also obtained analogously to b), using, as starting material, 0.1 g (0.37 mmol) of the sodium salt of (1S,3R,5R,6R)-2,2-dimethyl;-6-hydroxymethylpenam-3-carboxylic acid 1-oxide dissolved in 10 ml of water/tetrahydrofuran 1:1.

d) 0.172 g (0.88 mmol) of 90% *m*-chloroperbenzoic acid is added at room temperature to a solution of 0.15 g (0.59 mmol) of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid in 10 ml of water/tetrahydrofuran 1:1. After stirring for 1½ hours, aqueous sodium thiosulphate solution is added. The aqueous phase is adjusted to pH 6.8 with 1N sodium hydroxide solution and lyophilised. The title compound is purified by chromatography on UPC_{12} plates (eluant: H_2O, R_f=0.58).

e) 821 mg (1.58 mmol) of (3R,5R,6R)-6-benzyloxymethyl-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide are dissolved in 10 ml of tetrahydrofuran, 400 mg of Pd/C 10% are added and hydrogenation is carried out under normal pressure at room temperature. After a reaction period of 6 hours, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is taken up in water/ethyl acetate and adjusted to pH 6.5 with aqueous saturated sodium bicarbonate solution. The aqueous phase is extracted three times with ethyl acetate. The organic phases are washed twice with water. After lyophilisation of the combined aqueous phases, the title compound is obtained in the form of a white powder. The IR-spectrum is identical with that of Example 4a).

EXAMPLE 5

(3,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

0.73 g of 90% *m*-chloroperbenzoic acid are added at room temperature to a solution of 1.5 g (3.6 mmol) of (1S,3R,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide in 45 ml of chloroform. After stirring for 1½ hours, working up is carried out with aqueous sodium thiosulphate solution, aqueous sodium bicarbonate solution and aqueous sodium chloride solution. The aqueous phases are extracted twice with chloroform, the combined organic solutions are dried with sodium sulphate and concentrated in a rotary evaporator. The residue is dried under a high vacuum and purified by chromatography on 16 g of silica gel with the eluant toluene/ethyl acetate 3:1. The pure title compound is obtained.

TLC: silica gel, toluene/ethyl acetate 3:1, $R_f = 0.22$.
IR spectrum (CH_2Cl_2): absorption bands at 2.76, 5.55, 5.67 μ.

EXAMPLE 6

Sodium salt of (3R,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide.

A solution of 0.82 g (1.9 mmol) of (3R,5R,6S)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic

acid diphenylmethyl ester 1,1-dioxide in 25 ml of tetrahydrofuran is hydrogenated in the presence of Pd/C 10% under normal pressure at room temperature. After a reaction period of 8 hours, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is taken up in water/ethyl acetate and 1.9 ml of 1N NaOH is slowly added (pH ~ 6.9). The aqueous phase is extracted three times with ethyl acetate. After lyophilisation of the aqueous phase, the title compound is obtained in the form of a white powder.

TLC: UPC_{12} plates, H_2O, $R_f = 0.58$

IR spectrum (KBr): absorption bands at 2.9, 5.63, 6.20 μ.

EXAMPLE 7

(1R,3R,5R,6R)- and (1S,3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide.

24.3 g (58.9 mmol) of a mixture of (1R,3R,5R,6R)- and (1S,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide are dissolved in 97 ml of dimethylformamide and, at room temperature under nitrogen, 18.31 g (117.8 mmol) of tert.-butyldimethylchlorosilane (97%) and 16.2 g (235.6 mmol) of imidazole are added. After stirring for 70 minutes, the mixture is diluted with ethyl acetate and the organic phase is washed three times with aqueous sodium chloride solution. The ethyl acetate solution is dried with sodium sulphate and concentrated in a rotary evaporator. The crude product is chromatographed on 1.1 kg of silica gel with the eluant system toluene/ethyl acetate 5:1. The two title compounds are eluted in the sequence given:

1. (1S,3R,5R,6R)-isomer:
   TLC: silica gel, toluene/ethyl acetate 5:1, $R_f = 0.54$.
   IR spectrum (CH_2Cl_2): absorption bands at 3.42, 5.61, 5.71 μ.
2. (1R,3R,5R,6R)-isomer:
   TLC: silica gel, toluene/ethyl acetate 5:1, $R_f = 0.4$.
   IR spectrum (CH_2Cl_2): absorption bands at 3.42, 5.61, 5.71 μ.

EXAMPLE 8

(1S,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide.

A solution of 3.13 g (5.9 mmol) of (1S,3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide in a mixture of 46 ml of tetrahydrofuran, 93.9 ml of acetic acid and 31 ml of water is heated at 50°C for 7 hours. The reaction solution is concentrated in a rotary evaporator and the oily residue is taken up in ethyl acetate. The organic phase is washed with aqueous sodium bicarbonate solution and then twice with saturated aqueous sodium chloride solution. After drying the organic phase over sodium sulphate, the solution is concentrated in a rotary evaporator and the crude product is purified on 76 g of silical gel with the eluant system toluene/ethyl acetate 1:1. The pure title compound is obtained.

TLC: silica gel, toluene/ethyl acetate 1:1, $R_f = 0.15$.

IR spectrum (CH_2Cl_2): absorption bands at 2.75, 2.95, 5.57, 5.68 μ.

The compound can be converted into the 1,1-dioxide analogously to Example 3.

EXAMPLE 9

(1R,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide.

(1R,3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide may be converted into the title compound analogously to Example 8.

TLC: silica gel, toluene/ethyl acetate 1:1, $R_f = 0.16$

IR spectrum (CH_2Cl_2): absorption bands at 2.75, 2.95, 5.59, 5.69 μ.

EXAMPLE 10

Sodium salt of (1S,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1-oxide.

After the addition of 1.95 g of Pd/C 10%, a solution of 1.62 g (3.92 mmol) of (1S,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide in 8 ml of tetrahydrofuran is hydrogenated at room temperature. After 5 hours, a further 2 g of Pd/C 10% are added and hydrogenation is continued for a further 22 hours. The mixture is then filtered through Hyflo and the clear solution is concentrated in a rotary evaporator. Ethyl acetate and water are added to the residue. While measuring the pH, 1N NaOH is slowly added dropwise until pH 6.9 is reached. The ethyl acetate phase is separated off and the aqueous phase is lyophilised. The sodium salt of the title compound is obtained in the form of a white power.

TLC: UPC_{12} plates, H_2O, $R_f = 0.62$

IR spectrum (Nujol): absorption bands at 3.05, 5.60, 6.20 μ.

("Nujol" is a registered Trade Mark)

EXAMPLE 11

(1R,3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid.

After the addition of 7.66 mg of Pd/C 10%, a solution of 638 mg (1.54 mmol) of (1R,3R,5R,6R)-

2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester in 8 ml of tetrahydrofuran is hydrogenated at room temperature. After 23 hours, 766 mg of Pd/C 10% are added and hydrogenation is continued for a further 7.5 hours. The reaction solution is filtered through "Hyflo" (registered Trade Mark) and concentrated in a rotary evaporator. The residue crystallises from methylene chloride.

TLC: UPC_{12} plates, H_2O, $R_f = 0.64$

IR spectrum (Nujol): absorption bands at 2.8, 5.60, 5.75 μ.

EXAMPLE 12

(3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester.

a) At 0°C under N_2, 2.8 ml (30.36 mmol) of phosphorus tribromide are added to a solution of 4.0 g (7.59 mmol) of (1S,3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide in 80 ml of methylene chloride and 20 ml of dimethylacetamide. After a reaction period of 30 minutes, cooled sodium bicarbonate solution is added. The organic phase is separated off, washed twice with saturated aqueous sodium chloride solution and dried over sodium sulphate. The solution is concentrated in a rotary evaporator and the residue is chromatographed on 45 g of silica gel with the solvent system toluene/ethyl acetate 10:1.

TLC: silica gel, toluene/ethyl acetate 10:1, $R_f = 0.61$

IR spectrum (CH_2Cl_2): absorption bands at 3.4, 5.64, 5.72 μ.

b) The same title compound is obtained analogously to a), using (1R,3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1-oxide as starting material.

EXAMPLE 13

(3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester.

a) A solution of 3.4 g (6.65 mmol) of (3R,5R,6R)-2,2-dimethyl-6-tert.-butyldimethylsilyloxymethylpenam-3-carboxylic acid diphenylmethyl ester in a mixture of 52 ml of tetrahydrofuran, 105 ml of acetic acid and 35 ml of water is heated at 50°C for 7 hours. The reaction solution is concentrated in a rotary evaporator and the oily residue is taken up in ethyl acetate. The organic phase is washed with aqueous sodium bicarbonate solution and twice with saturated sodium chloride solution. After drying the organic phase over sodium sulphate, the solution is concentrated in a rotary evaporator. The crude project is purified on 50 g of silica gel with the eluant system toluene/ethyl acetate 2:1. The title compound having a melting point of 120.5°C is obtained.

TLC: silica gel, toluene/ethyl acetate 2:1, $R_f = 0.37$

IR spectrum (CH_2Cl_2): absorption bands at 2.8, 5.65, 5.7 μ.

b) The same compound may also be obtained as follows:

A solution of 4.4 g (9.2 mmol) of (3R,5R,6R)-6-bromo-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester in 40 ml of toluene and 3.2 ml (12 mmol) of tributyltin hydride is heated at 80° under a nitrogen atmosphere for 2.5 hours. The reaction mixture is then concentrated and the residue is crystallised from hexane. Recrystallisation from methylene chloride/hexane yields and the title compound.

c) The title compound is obtained in a manner analogous to that described under b), also using (3R,5R,6R)-6-bromo-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester.

EXAMPLE 14

Sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid.

After the addition of 2.1 g of Pd/C 10%, a solution of 1.9 g (4.98 mmol) of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester in 82 ml of tetrahydrofuran is hydrogenated at room temperature. After 16 hours and again after 24 hours an additional 2.1 g of Pd/C 10% are added each time. After a total reaction period of 40 hours, the hydrogenated mixture is filtered through Hyflo and concentrated in a rotary evaporator. The oily residue is taken up in water/ethyl acetate, and 2.7 ml of 1N NaOH are carefully added (pH = 6.9). The aqueous phase is extracted three times with ethyl acetate and subsequently lyophilised. The title compound is obtained in the form of a white powder.

TLC: UPC_{12} plates, H_2O, $R_f = 0.45$

IR spectrum (Nujol): absorption bands at 2.93, 5.63, 6.27 μ.

EXAMPLE 15

(3R,5R,6R and 6S)-6-bromo-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester.

A solution of 50 g (95 mmol) of (3R,5R)-6,6-dibromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester in 370 ml of tetrahydrofuran is cooled to —78°, and 52.2 ml (95 mmol) of a 1.82

molar solution of methylmagnesium bromide in diethyl ether are added. After 10 minutes at −78°, formaldehyde gas is passed over the solution while stirring well. After 2 hours, a TLC sample shows complete conversion. 25 ml of glacial acetic acid are added and the solution is concentrated in a rotary evaporator. The residue is subsequently taken up in ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The crude phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 480 g of silica gel with the solvent system toluene/ethyl acetate (6:1). A mixture of the title compounds is obtained in a ratio of of 3(6R):1(6S).

(6R)-isomer:

TLC: silica gel, toluene/ethyl acetate (6:1), $R_f = 0.36$
IR spectrum (CH_2Cl_2): absorption bands at 2.75, 5.57, 5.70 μ.
Melting point: 144—146°.

(6S)-isomer:

TLC: silica gel, toluene/ethyl acetate (6:1), $R_f = 0.30$
IR spectrum (CH_2Cl_2): absorption bands at 2.75, 5.57, 5.70 μ.
Melting point: 158—161°.

EXAMPLE 16

(3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide.

a) 1 g of Pd/C 10% is added to 2 g (4.66 mmol) of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide in 20 ml of tetrahydrofuran and the solution is hydrogenated under normal pressure at room temperature. After a reaction period of 1 hour, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is crystallised from methylene chloride/cyclohexane. The title compound having a melting point of 150° (with decomposition) is obtained.

b) The same compound may also be obtained as follows:

2 g (3.86 mmol) of (3R,5R,6R)-6-benzyloxymethyl-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide are dissolved in 20 ml of tetrahydrofuran, 1 g of Pd/C 10% is added and the solution is hydrogenated for one hour under normal pressure at room temperature. After a reaction period of 16 hours, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is crystallised from methylene chloride/cyclohexane.

EXAMPLE 17

(3R,5R,6R)-6-benzyloxymethyl-6-bromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester.

a) A solution of 10 g (19 mmol) of (3R,5R)-6,6-dibromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester in 50 ml of tetrahydrofuran is cooled to −30°, and 10.4 ml (19 mmol) of a 1.8 molar solution of methylmagnesium bromide in diethyl ether are slowly added. After 5 minutes at −30°, 5.2 ml (38 mmol) of benzylchloromethyl ether are added. The reaction mixture is stirred for 1 hour at −30° and then heated to 0° within a period of $\frac{3}{4}$ hour. The solution is then concentrated in a rotary evaporator, the residue is taken up in ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 130 g of silica gel with toluene as eluant. Evaporation of the solvent yields the title compound.

TLC: silica gel, toluene, $R_f = 0.16$
IR spectrum (CH_2Cl_2): absorption bands at 3.45, 5.60, 5.74, 6.28 μ.

b) The same compound may also be prepared as follows:

A solution of 5 g (9.5 mmol) of (3R,5R)-6,6-dibromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester in 25 ml of tetrahydrofuran is cooled to −78°, and 5 ml (9.5 mmol) of a 1.9 molar solution of methylmagnesium bromide in diethyl ether are slowly added. After 5 minutes at −78°, 3.8 g of benzylbromomethyl ether are added. The reaction mixture is heated to room temperature within a period of 40 minutes and then concentrated in a rotary evaporator. The residue is taken up in ethyl acetate and washed with aqueous sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 70 g of silica gel with toluene as eluant. The physical-chemical data of the resulting title compound are identical with those mentioned under a).

EXAMPLE 18

(3R,5R,6R)-6-benzyloxymethyl-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester.

A solution of 2.4 g (4.24 mmol) of (3R,5R,6R)-6-benzyloxymethyl-6-bromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester and 1.5 ml (5.6 mmol) of tributyltin hydride in 20 ml of toluene is heated at 82° under a nitrogen atmosphere for 80 minutes. The reaction mixture is then concentrated and the residue crystallised from isooctane. Recrystallisation from methylene chloride/isooctane yields the title compound having a melting point of 78—80°.

TLC: silica gel, toluene/ethyl acetate (20:1), $R_f = 0.27$
IR spectrum (CH_2Cl_2): absorption bands at 3.44, 5.65, 5.73 μ.

EXAMPLE 19
(3R,5R,6R)-6-benzyloxymethyl-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

1.68 g (3.45 mmol) of (3R,5R,6R)-6-benzyloxymethyl-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester are dissolved in 16 ml of chloroform, and 1.43 g (8.3 mmol) of 90% *m*-chloroperbenzoic acid are added at room temperature. After 50 minutes, working up is carried out in succession with aqueous sodium thiosulphate solution, aqueous sodium bicarbonate solution and aqueous sodium chloride solution. The aqueous phases are extracted twice with chloroform. The combined organic solutions are dried with sodium sulphate and concentrated in a rotary evaporator. The residue is dried in a high vacuum and purified by preparative thin-layer chromatography with the solvent system toluene/ethyl acetate (20:1). The crystalline title compound having a melting point of 124—126.5° is obtained.

TLC: silica gel, toluene/ethyl acetate (20:1), $R_f = 0.52$
IR spectrum: (CH_2Cl_2): absorption bands at 3.45, 5.57, 5.71 μ.

EXAMPLE 20
(3R,5R,6R)-6-bromo-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester.

A solution of 10 g (19 mmol) of (3R,5R)-6,6-dibromo-2,2-dimethylpenam-3-carboxylic acid diphenylmethyl ester in 50 ml of tetrahydrofuran is cooled to —78°, and 9.2 ml (19 mmol) of methylmagnesium bromide in diethyl ether are added. After 5 minutes at —78°, 2.82 ml of chlorodimethyl ether are added. The reaction mixture is heated to —20° and, after 95 minutes, is concentrated in a rotary evaporator. The residue is taken up in ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 30 g of silica gel with toluene as eluant. The pure title compound is obtained.

TLC: silica gel, toluene/ethyl acetate (20:1), $R_f = 0.34$
IR spectrum (CH_2Cl_2): absorption bands at 5.62, 5.73 μ.

EXAMPLE 21
(3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester.

A solution of 7.45 g (15.1 mmol) of (3R,5R,6R)-6-bromo-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester and 5.22 ml (19.7 mmol) of tributyltin hydride in 72 ml of toluene is heated at 82° under a nitrogen atmosphere for 45 minutes. The reaction mixture is then concentrated and crystallised from hexane. Recrystallisation from methylene chloride/hexane yields the title compound having a melting point of 84°.

TLC: silica gel, toluene/ethyl acetate (20:1), $R_f = 0.31$
IR spectrum (CH_2Cl_2): absorption bands at 5.63, 5.72 μ.

EXAMPLE 22
(3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

4.8 g (11.6 mmol) of (3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester are dissolved in 48 ml of chloroform and, at 35°, 5.5 g (28.9 mmol) of 90% *m*-chloroperbenzoic acid are added. After 2.5 hours, working up is carried out with aqueous sodium bisulphate solution and sodium bicarbonate solution. The aqueous phases are subsequently extracted twice with chloroform. The combined organic solutions are dried with sodium sulphate and concentrated in a rotary evaporator. The residue is crystallised from ethyl acetate/hexane and yields the title compound having a melting point of 120—126°.

TLC: silica gel, toluene/ethyl acetate, $R_f = 0.29$
IR spectrum (CH_2Cl_2): absorption bands at 5.55, 5.69 μ.

EXAMPLE 23
(3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid 1,1-dioxide.

4.7 g (10.6 mmol) of (3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide are dissolved in 52 ml of tetrahydrofuran, 2 g of Pd/C 10% are added and the solution is hydrogenated under normal pressure at room temperature. After a reaction period of 1 hour, the catalyst is filtered off and the filtrate is concentrated in a rotary evaporator. The residue is crystallised from ethyl acetate/hexane and yields the title compound having a melting point of 145°.

TLC: UPC_{12} plates, water/acetonitrile (95:5), $R_f = 0.37$
IR spectrum (CH_2Cl_2): absorption bands at 5.55, 5.75, 7.5 μ.

EXAMPLE 24

(3R,5R,6R)-2,2-dimethyl-6-methoxymethylpenam-3-carboxylic acid 1'-ethoxycarbonyloxyethyl ester 1,1-dioxide.

12 g of sodium iodide are dissolved in 37 ml of acetone, and 2.75 ml of ethyl-1-chloroethyl carbonate are added. The mixture is stirred at room temperature for 3 hours. The solution is then added dropwise to 150 ml of methylene chloride and the inorganic salts that precipitate out are filtered off. The methylene chloride solution is concentrated to 10 ml and, at 0°, is added to a solution of 2.5 g (8.05 mmol) of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide in 40 ml of dimethylacetamide. The mixture is subsequently stirred for 3 hours at 0°, then diluted with ethyl acetate and washed three times with water. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The crude product is purified on 30 g of silica gel with the eluant system toluene/ethyl acetate (2:1). The title compound is obtained in the form of a white foam.

TLC: silica gel, toluene/ethyl acetate (2:1), $R_f = 0.48$

IR spectrum (CH_2Cl_2): absorption bands at 2.75, 5.55, 5.65 μ.

EXAMPLE 25

(3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid pivaloyloxymethyl ester 1,1-dioxide.

6 g of sodium iodide are dissolved in 20 ml of acetone, and 1.5 ml of pivalic acid chloromethyl ester are added. The mixture is stirred at room temperature for 3 hours and then added dropwise to 75 ml of methylene chloride. The inorganic salts that precipitate out are filtered off. The methylene chloride solution is concentrated to 10 ml and, at 0°, is added to a solution of 1:3 g (4 mmol) of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide in 20 ml of N,N-dimethylacetamide. The mixture is subsequently stirred for 3 hours at 0°, then diluted with ethyl acetate and washed three times with water. The organic phase is dried over sodium sulphate and concentrated in a rotary evaporator. The crude product is purified on 30 g of silica gel with the eluant system toluene/ethyl acetate (3:1). The title compound is obtained in the form of a white foam.

TLC: silica gel, toluene/ethyl acetate (3:1), $R_f = 0.2$

IR spectrum (CH_2Cl_2): absorption bands at 2.75, 5.55, 5.62, 5.68 μ.

EXAMPLE 26

(3R,5R,6R)-2,2-dimethyl-6-benzyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

169.4 g of potassium permanganate are added to a solution of 237 g (0.487 mol) of (3R,5R,6R)-2,2-dimethyl-6-benzyloxymethylpenam-3-carboxylic acid diphenylmethyl ester in 237 ml of tetrahydrofuran and 1 litre of glacial acetic acid, the reaction temperature increasing to 36°. The mixture is stirred at this temperature for $2\frac{3}{4}$ hours and then there are added, in succession, 100 ml of hydrogen peroxide solution (30%) and 4 litres of water. The title compound that precipitates out is washed with water, dissolved in ethyl acetate and washed in succession with water, aqueous sodium bicarbonate solution and water. The organic phase is dried over sodium sulphate and purified with active carbon. The resulting title compound is purified by crystallisation from ethyl acetate/hexane.

EXAMPLE 27

(3R,5R,6S and 6R)-2,2-dimethyl-6-bromo-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

A solution of 30 g (53.7 mmol) of (3R,5R)-2,2-dimethyl-6,6-dibromopenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide in 150 ml of tetrahydrofuran is cooled to −78°, and 28.2 ml (53.7 mmol) of a 1.9M solution of methylmagnesium bromide in diethyl ether are added. After 10 minutes at −78°, formaldehyde gas is passed over the solution while stirring. After 2 hours, 25 ml of glacial acetic acid are added and the solution is concentrated in a rotary evaporator. The residue is taken up in ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 250 g of silica gel with the solvent system toluene/ethyl acetate 6:1 and yields a mixture of the title compounds.

Mixture: TLC: silica gel, toluene/ethyl acetate 6:1 $R_f = 0.28$

IR spectrum (CH_2Cl_2): absorption bands at 2.74, 5.53, 5.7 μ.

EXAMPLE 28

(3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

A solution of 25 g (49.2 mmol) of a mixture of (3R,5R,6S and 6R)-2,2-dimethyl-6-bromo-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide and 15.7 ml (59 mmol) of tributyltin hydride in 250 ml of toluene is heated at 80° under a nitrogen atmosphere for 2.5 hours. The reaction mixture is concentrated and the residue is crystallised from tetrahydrofuran/hexane. Melting point 70—75°.

EXAMPLE 29

(3R,5R,6R)-2,2-dimethyl-6-bromo-6-benzyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

A solution of 5 g (8.96 mmol) of (3R,5R,6S and 6R)-2,2-dimethyl-6,6-dibromopenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide in 25 ml of tetrahydrofuran is cooled to −78°, and 4.7 ml (8.96 mmol) of a 1.9 molar solution of methylmagnesium bromide in diethyl ether are slowly added. After 5 minutes at −78°, 3.6 g of benzyloxymethyl bromide are added. The reaction mixture is heated to room temperature within a period of 40 minutes and is then concentrated in a rotary evaporator. The residue is taken up in ethyl acetate and washed with aqueous sodium bicarbonate solution and sodium chloride solution. The organic phases are dried over sodium sulphate and concentrated in a rotary evaporator. The residue is chromatographed on 70 g of silica gel with toluene and the title compound is obtained.

TLC: silica gel, toluene, $R_f = 0.13$

IR spectrum (CH_2Cl_2): absorption bands at 5.53, 5.74 μ.

EXAMPLE 30

(3R,5R,6R)-2,2-dimethyl-6-benzyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

A solution of 2.4 g (4 mmol) of (3R,5R,6R)-2,2-dimethyl-6-bromo-6-benzyloxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide and 1.5 ml (5.6 mmol) of tributyltin hydride in 20 ml of toluene is heater at 82° under a nitrogen atmosphere for 80 minutes. The reaction mixture is then concentrated and the residue is crystallised from isooctane. Recrystallisation from ethyl acetate/hexane yields the title compound having a melting point of 119—123°.

TLC: silica gel, toluene/ethyl acetate 6:1, $R_f = 0.52$

IR spectrum (CH_2Cl_2): absorption bands at 3.44, 5.57, 5.73 μ.

Pharmaceutical preparations

Example A Dry-filled ampoules or phials containing 1 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance are prepared as follows:

Composition (for 1000 ampoules or phials):	
active substance	1000 g
mannitol	100 g
	1100 g

The constituents are homogeneously mixed and in each case 1.1 g of the mixture is introduced into one ampoule or one phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example B Dry-filled ampoules or phials containing 2 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 0.2 g of cefotiam as active substance B are prepared as follows:

Composition (for 1000 ampoules or phials):	
active substance A	1000 g
active substance B	100 g
mannitol	100 g
	1200 g

The constituents are homogeneously mixed and in each case 2.4 g of the mixture is introduced into one ampoule or one phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example C Dry-filled ampoules or phials containing 2.0 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 0.4 g of cefotiam as active substance B are prepared as follows:

Composition (for 1000 ampoules or phials):

active substance A	2000 g
active substance B	400 g
mannitol	200 g
	2600 g

The constituents are homogeneously mixed and in each case 2.6 g of the mixture are introduced into one ampoule or phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example D Dry-filled ampoules or phials containing 2 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 1 g of cefotiam as active substance B (2:1) are prepared as follows:

Composition (for 1000 ampoules of phials):

active substance A	2000 g
active substance B	1000 g
mannitol	300 g
	3300 g

The constituents are homogeneously mixed and in each case 3.3 g of the mixture are introduced into one ampoule or phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example E Dry-filled ampoules or phials containing 1 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 1 g of cefotiam as active substance B are prepared as follows:

Compound (for 1000 ampoules or phials):

active substance A	1000 g
active substance B	1000 g
mannitol	200 g
	2200 g

The constituents are homogeneously mixed and in each case 2.2 g of the mixture are introduced into one ampoule or phial under aseptic conditons. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example F Dry-filled ampoules or phials containing 1 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 3 g of cefotiam as active substance B are prepared as follows:

Composition (for 1000 ampoules or phials):

active substance A	1000 g
active substance B	3000 g
mannitol	300 g
	4300 g

The constituents are homogeneously mixed and in each case 4.3 g of the mixture are introduced into one ampoule or phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

Example G Dry-filled ampoules or phials containing 0.25 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 1.25 g of cefotiam as active substance B are prepared as follows:

Composition (for 1000 ampoules or phials):	
active substance A	250 g
active substance B	1250 g
mannitol	200 g
	1700 g

The constituents are homogeneously mixed and in each case 1.7 g of the mixture are introduced into one ampoule or phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities or other active substance constituents according to the invention are prepared in the same manner.

Example H Dry-filled ampoules or phials containing 0.25 g of the sodium salt of (3R,5R,6R)-2,2-dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide as active substance A and 2.5 g of cefotiam as active substance B (1:10) are prepared as follows:

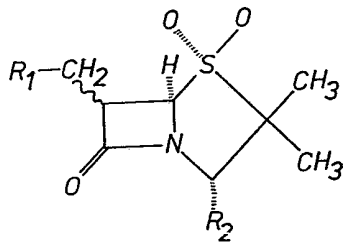
Composition (for 1000 ampoules or phials):	
active substance A	250 g
active substance B	2500 g
mannitol	200 g
	2950 g

The constituents are homogeneously mixed and in each case 2.950 g of the mixture are introduced into one ampoule or phial under aseptic conditions. The ampoules or phials are sealed and tested.

Ampoules or phials having corresponding quantities of other active substance constituents according to the invention are prepared in the same manner.

CLAIMS

1. 2,2-Dimethylpenam-3-carboxylic acid 1,1-dioxide compounds of the formula



(I),

in which

R_1 represents hydroxy or etherified or esterified hydroxy, and

R_2 represents carboxyl or protected carboxyl,

and salts of such compounds having a salt-forming group.

2. Compounds of the formula (I) according to claim 1 in which R_1 represents hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, aminothiazolylcarbonyloxy, aminothiadiazolylcarbonyloxy,

lower alkoxycarbonyloxy, carbamoyloxy, N-mono- or N,N-di-lower alkylcarbamoyloxy, lower alkanesulphonyloxy, arenesulphonyloxy, or hydroxysulphonyloxy (or a salt thereof) and R_2 represents carboxy or carboxy esterified in a form that can be split under physiological conditions, as well as the pharmaceutically acceptable salts of such compounds containing a salt-forming group.

3. Compounds of the formula (I) according to claim 1 or 2 in which R_1 represents methoxy, benzyloxy, formyloxy, acetoxy, 2-amino-1,3-thiazol-4-yl-carbonyloxy, 5-amino-1,2,4-thiadiazol-3-ylcarbonyloxy, N-methylcarbamoyloxy, N,N-dimethylcarbamoyloxy, methanesulphonyloxy, benzenesulphonyloxy or toluenesulphonyloxy.

4. Compounds of the formula (I) according to any preceding claim in which R_2 represents a lower alkanoyloxymethoxycarbonyl, amino-lower alkanoylmethoxycarbonyl, phthalidyloxycarbonyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, indanyloxycarbonyl, or 1-ethoxycarbonyloxy-ethoxycarbonyl group.

5. Compounds of the formual (I) according to any preceding claim in which R_2 represents acetoxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, 2-phthalidyloxycarbonyl or 5-indanyloxycarbonyl.

6. Compounds of the formula (I) according to any one of claims 1 to 4 in which R_2 represents an α-amino-lower alkanoyloxymethoxycarbonyl group.

7. Compounds of the formula (I) according to claim 6 in which R_2 represents glycyloxymethoxycarbonyl, L-valyloxymethoxycarbonyl or L-leucyloxymethoxycarbonyl.

8. Compounds of the formula (I) according to claim 1 in which R_1 represents hydroxy, methoxy or benzyloxy and R_2 represents carboxy, and the pharmaceutically acceptable salts thereof.

9. Compounds of the formula (I) according to claim 1 in which R_1 represents hydroxyy.

10. Compounds of the formula (I) according to any preceding claim of which the 6-position has the R-configuration.

11. (3R,5R,6R)-2,2-Dimethyl-6-hydroxymethylpenam-3-carboxylic acid diphenylmethyl ester 1,1-dioxide.

12. (3R,5R,6R)-2,2-Dimethyl-6-hydroxymethylpenam-3-carboxylic acid 1,1-dioxide sodium salt.

13. (3R,5R,6R)-2,2-Dimethyl-6-hydroxymethylpenam-3-carboxylic acid pivaloyloxymethyl ester 1,1-dioxide.

14. The pharmaceutically acceptable salts of compounds according to any one of patent claims 1—10 having a salt-forming group.

15. Pharmaceutical preparations containing a compound of the formula (I) according to any one of claims 1—12 or 14 or a pharmaceutically acceptable salt of such a compound having a salt-forming group.

16. Pharmaceutical preparations containing the compound according to claim 13.

17. Pharmaceutical preparations containing a compound of the formula (I) according to any one of patent claims 1—12 or 14 or a pharmaceutically acceptable salt of such a compound having a salt-forming group, and a β-lactam antibiotic.

18. Pharmaceutical preparations containing the compound according to claim 13 and a β-lactam antibiotic.

19. Compounds of the formula (I) and salts thereof according to any one of patent claims 1—12 or 14 for the use in a method of therapeutical treatment of the human or animal body.

20. The compound according to claim 13 for the use in a method of therapeutical treatment of the human or animal body.

21. Compounds of the formula (I) and salts thereof according to any one of claims 1—12 or 14 as β-lactamase inhibiting agents.

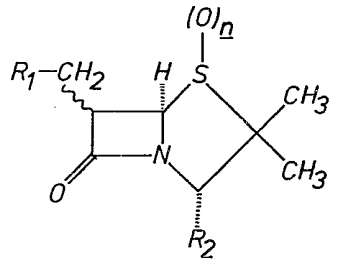
22. The compound according to claim 13 as β-lactamase inhibiting agents.

23. Use of a compound of the formula (I) according to any one of claims 1—12 and 14 and salts of such compounds having a salt-forming group for the manufacture of pharmaceutical preparations.

24. Use of a compound of the formula (I) according to claim 13 for the manufacture of pharmaceutical preparations.

25. Process for the manufacture of compounds of the formula (I) and salts of such compounds having a salt-forming group, according to claim 1, characterised in that

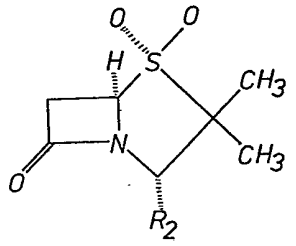
a) a compound of the formula



(IIa),

in which R_1 and R_2 have the meanings mentioned under formula (I) and the index *n* has the value 0 or 1, is oxidised in the 1-position, or

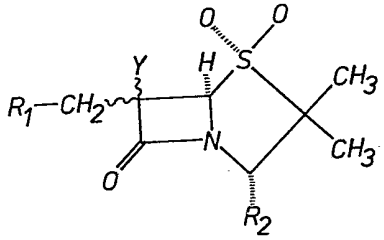
b) a R_1—CH_2— group is introduced into a compound of the formula



(IIb),

in which R_2 represents a protected carboxyl group, or

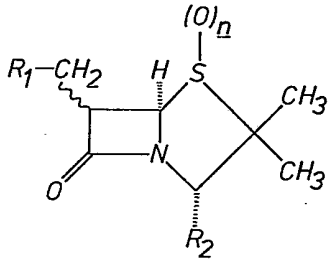
c) in a compound of the formula



(IIc),

in which R_1 and R_2 have the meanings mentioned under formula (I) and Y represents a group that can be converted into a hydrogen atom, the Y group is converted into a hydrogen atom, and, if desired or necessary, in a resulting compound a group R_1 is converted into a different group R_1, and/or a group R_2 is converted into a different group R_2 and/or a resulting salt is converted into the free compound or into a different salt and/or a resulting free compound having a salt-forming group is converted into a salt, and/or a resulting mixture of isomeric compounds of the formula (I) is separated into the individual isomers.

26. Process according to claim 25, characterised in that a compound of the formula



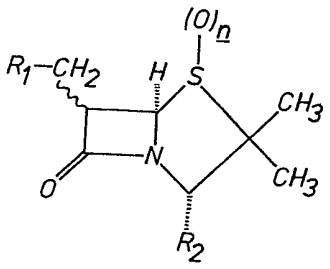
(II),

in which R_1 and R_2 have the meanings mentioned under formula (I) and the index *n* has the value 0 or 1, is oxidised in the 1-position and, if desired or necessary, in a resulting compound a group R_1 is converted into a different group R_1, and/or a group R_2 is converted into a different group R_2, and/or a resulting salt is converted into the free compound or into a different salt, and/or a resulting free compound having a salt-forming group is converted into a salt, and/or a resulting mixture of isomeric compounds of the formula (I) is separated into the individual isomers.

27. The compounds obtainable according to claim 25.

28. The compounds obtainable according to claim 26.

29. Compounds of the formula



(II),

in which

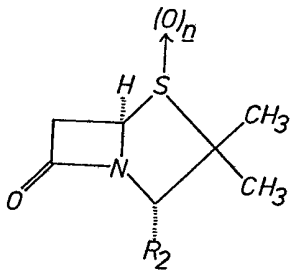
R_1 represents hydroxy or etherified or esterified hydroxy,

R_2 represents carboxyl or protected carboxyl, and the index *n* have the value 0 or 1,

and salts of such compounds having a salt-forming group.

30. Process for the manufacture of compounds of the formula (II) according to claim 29 and salts of such compounds having a salt-forming group, characterised in

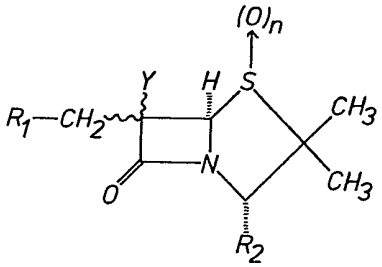
a) a R_1—CH_2— group is introduced into a compound of the formula



(III),

in which the index *n* has the value 0 or 1 R_2 represents an esterified carboxyl group, or

b) in a compound of the formula



(IV),

in which R_1, R_2 and the index *n* have the meanings mentioned under formula (II) and Y represents a group that can be converted into a hydrogen atom, the Y group is converted into a hydrogen atom, and, if desired or necessary, in a resulting compound a group R_1 is converted into a different group R_1, and/or a group R_2 is converted into a different group R_2, and/or a resulting 1-sulphide into a 1-sulphoxide or a resulting 1-sulphoxide is converted into a 1-sulphide, and/or a resulting salt is converted into the free compound having a salt-forming group is converted into a salt, and/or a resulting mixture of isomeric compounds of the formula (II) is separated into the individual isomers.

31. Compounds of the formula (I) according to claim 1 substantially as hereinbefore described with reference to any one of Examples 3—6, 16, 19 and 22—30.

32. Compounds of the formula (II) according to claim 29 substantially as hereinbefore described with reference to any one of Examples 1,2,7—15, 17, 18, 20 and 21.

33. Pharmaceutical preparations substantially as hereinbefore described with reference to any one of Examples A—H.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.