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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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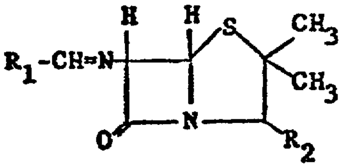
(19)

(54) 6-(SUBSTITUTED AMINO)-PENAM DERIVATIVES

(71) We, CIBA-GEIGY AG, a Swiss body corporate, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement—

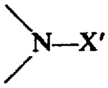
The invention relates to a novel therapeutically valuable 6 - amino - penam compounds, processes for their preparation and pharmaceutical preparations which contain the novel compounds, and also certain uses thereof.

The novel 6 - amino - penam compounds are those of the formula



(I)

wherein R_1 is an azapolycycloalkyl radical bonded via the ring nitrogen atom and containing at least one *endo*-bridge atom and a total of 7 to 12 ring atoms and which radical R_1 can contain a double bond and/or, an oxa group or a group



wherein X_1 denotes hydrogen or lower alkyl, and/or, which radical R_1 can contain free, esterified or etherified hydroxyl bonded to a ring carbon atom, and wherein R_2 is free carboxyl or carboxyl esterified by a physiologically detachable group, and salts of such compounds.

The radical R_1 is in particular aza - bi- and aza - tri - cycloalkyl having a total of 8 to 11 ring atoms.

Such radicals are, in particular, azabicycloalkyl or azabicycloalkenyl, such as azabicyclooctyl, for example 8-azabicyclo[3.2.1]oct - 8 - yl and 2 - azabicyclo[2.2.2]oct - 2 - yl, or azabicyclononyl, especially 3 - azabicyclo[3.2.2]non - 3 - yl and 9 - azabicyclo[3.3.1]non - 9 - yl; oxaazabicycloalkyl or diazabicycloalkyl, such as oxaaza- or diazabicyclononyl, especially 3,7 - diazabicyclo[3.3.1]non - 3 - yl azatricycloalkyl, such as azatricyclodecyl, especially 2 - azatricyclo[3.3.1.1.^{3,7}]dec - 2 - yl, 4 - azatricyclo[5.2.1.0^{2,6}]dec - 4 - yl or 3 - azatricyclo[5.2.1.0^{1,5}]dec - 3 - yl, or azatricycloundecyl, especially 4 - azatricyclo[5.2.2.0^{2,6}]undec - 4 - yl or 8 - azatricyclo[4.3.2.0^{1,6}]undec - 8 - yl; azatricycloalkenyl, such as azatricyclodecenyl, especially 4 - azatricyclo[5.2.1.$0^{2,6}$]dec - 8 - en - 4 - yl, and also azatricycloundecenyl, especially 4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - en - 4 - yl or 8 - azatricyclo[4.3.2.$0^{1,6}$]undec - 3 - en - 8 - yl; oxaazatricycloalkyl, such as oxaazatricyclodecyl, especially 10 - oxa - 3 - azatricyclo[5.2.1.$0^{1,5}$]dec - 3 - yl or 10 - oxa - 4 - azatricyclo[5.2.1.$0^{2,6}$]dec - 4 - yl, and diazatricycloalkyl, for example 3,10 - diazatricyclo[5.2.1.$0^{1,5}$]dec - 3 - yl.

The above compounds have been named in accordance with the currently valid nomenclature which has been laid down by the IUPAC (International Union of Pure and Applied Chemistry) and a commentary on which is given, for example, in D. Hellwinkel ("Die systematische Nomenklatur der organischen Chemie" ("Systematic Nomenclature in Organic Chemistry'), Springer-Verlag, Berlin, 1974, pages 23—28).

Particularly preferred radicals R_1 are the radicals which are bonded via the ring nitrogen and are derived from substituted or unsubstituted 8 - azabicyclo[3.2.1]octane, 9 - azabicyclo[3.3.7]nonane, 3,7 - diaza - bicyclo[3.3.7]nonane, 2 - azabicyclo[2.2.2]octane and 3 - azabicyclo[3.2.2]nonane, and also, in particular, the radicals derived from an azatricycloalkane, such as 7 - azatricyclo[5.2.2.$0^{2,6}$]undecane and from an azatricycloalkene, such as 7 - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - ene.

An additional ring nitrogen atom which may be present is either bonded by all three valencies in the ring system, in which case it can be present as a bridge head atom or can participate in a ring double bond, or is bonded, by its third valency, to a radical X_1 which is outside the ring and is hydrogen or lower alkyl.

In this specification, radicals qualified by the term "lower" contain 1 to 8 and preferably 1 to 4 carbon atoms.

Lower alkyl is, for example, in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl or tert.-butyl, and also n-pentyl, n-hexyl, n-heptyl or n-octyl.

The radical X_1 is preferably methyl.

The azapolycycloalkyl radical R_1 can be substituted by a free, esterified or etherified hydroxyl which is bonded to any desired ring carbon atom, preferred ring carbon atoms being those which are not a bridge head atom and especially those which are separated by 1—3 ring atoms from the aza nitrogen atom which bonds the radical R_1 to the penicilliminomethylene radical; for example, the free, esterified or etherified hydroxyl is preferably in the 3-position in 8 - azabicyclo[3.2.1]oct - 8 - yl, preferably in the 9-position in the 3,7 - diazabicyclo[3.3.1]non - 3 - yl and preferably in the 3- or 7-position in 9 - azabicyclo[3.3.1]non - 9 - yl.

An esterified hydroxyl is acyloxy or hydroxyl esterified by a hydrogen halide acid, i.e. halogen.

Halogen is in particular chlorine or bromine and also iodine or fluorine.

Acyl is the monovalent acyl radical of a carboxylic acid, of a carbonic acid half-derivative or of a sulphonic acid, preferably having up to 18 carbon atoms, especially the monovalent acyl radical of a substituted or unsubstituted aliphatic carboxylic acid including substituted or unsubstituted araliphatic or heterocyclylaliphatic carboxylic acid or of an unsubstituted or substituted aromatic or heterocyclic carboxylic acid and also the monovalent acyl radical of a carbonic acid helf-derivative or of a substituted aliphatic or aromatic sulphonic acid.

Substituted or unsubstituted aliphatic carboxylic acids, are in particular, lower alkanecarboxylic acids which are unsubstituted or substituted by carboxyl, lower alkoxycarbonyl, carbamoyl or carbamoyl substituted by lower alkyl, and/or by substituted or unsubstituted basic amino. Substituted or unsubstituted basic amino is, in particular, amino, mono- or di-lower alkylamino or amino cyclically disubstituted by lower alkylene or by lower alkylene interrupted by one of the groups O, NH or N-lower alkyl. Lower alkylene contains up to 6, and preferably 4—5, carbon atoms and is, for example, tetramethylene, pentamethylene or hexamethylene, whilst lower alkylene interrupted by a hetero-group is in particular oxa-lower alkylene, for example 3 - oxa - pentamethylene, and aza-lower alkylene, for example 3-azapentamethylene or 3 - methyl - 3 - azapentamethylene.

Substituted or unsubstituted aromatic-aliphatic carboxylic acids are in particular phenyl-lower alkanecarboxylic acids which are unsubstituted or substituted by lower alkyl, halogen, lower alkoxy or especially carboxyl, lower alkoxycarbonyl or carbamoyl in the phenyl radical or are unsubstituted or substituted by amino or hydroxyl in the lower alkane side chain. Substituted or unsubstituted aromatic carboxylic acids are, in particular, benzoic acids which are unsubstituted or substituted, like the above aromatic-aliphatic carboxylic acids, in the phenyl radical. Substituted or unsubstituted heterocyclic-aliphatic carboxylic acids are, in particular, α-amino acids.

Substituted or unsubstituted heterocyclic carboxylic acids are derived, in particular, from mono, di- or tri-azacylic six-membered ring compounds which are unsubstituted or monosubstituted or disubstituted by hydroxyl, such as pyridine, pyrimidine, pyrazine, pyridazine or triazine, and also from thiophene or furane.

The monovalent acyl radical of a carbonic acid half-derivative is, for example, lower alkoxycarbonyl which is unsubstituted or substituted, such as monosubstituted tri-substituted by halogen, especially chlorine, and also carbamoyl which is unsubstituted or monosubstituted or disubstituted by lower alkyl.

Substituted or unsubstituted aliphatic sulphonic acids are, in particular, lower alkanesulphonic acids, and also lower alkanesulphonic acids which are unsubstituted or substituted by amino or substituted basic amino, such as methanesulphonic acid or taurine. Aromatic sulphonic acids are substituted or unsubstituted benzene- or naphthalene-sulphonic acids, for example benzenesulphonic acid, toluenesulphonic acid, such as o- or p-toluenesulphonic acid, or naphthalenesulphonic acid, such as α- or β-naphthalenesulphonic acid.

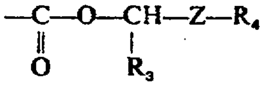
Examples of esterified hydroxyl groups are halogen, for example chlorine or bromine, lower alkanoyloxy, for example formyloxy, acetoxy or pivaloyloxy, and also substituted lower alkanoyloxy, such as lower alkanoyloxy substituted by carboxyl, lower alkoxycarbonyl, for example methoxycarbonyl, or amino, which can be disubstituted by lower alkyl, for example dimethylamino, for example carboxyacetoxy, methoxycarbonylacetoxy or dimethylamino-acetoxy, and also substituted lower alkanoyloxy radicals derived from naturally occurring amino acids and their D- and D,L-stereoisomers, for example glycyloxy, alanyloxy or β-alanyloxy, and also phenyl-lower alkanoyloxy, which is unsubstituted or substituted by amino or hydroxyl, for example phenylacetoxy, phenylglycyloxy or mandeloyloxy, benzoyloxy which is unsubstituted or substituted by carboxyl, for example benzoyloxy or o- or p-carboxybenzoyloxy, pyridine-, pyrimidine- or pyridazine-carbonyloxy which is unsubstituted or monosubstituted to disubstituted by hydroxyl, for example pyridylcarbonyloxy, such as nicotinoyloxy, 2,6 - dihydroxy - 4 - pyrimidylcarbonyloxy, 2,4 - dihydroxy - 5 - pyrimidylcarbonyloxy or 3 - hydroxy - 6 - pyridazinylcarbonyloxy, it being possible for the last-mentioned hydroxy-substituted radicals also to be in their tautomeric hydroxyoxo or oxo forms, lower alkoxycarbonyloxy which is unsubstituted or monosubstituted to trisubstituted by chlorine, for example methoxycarbonyloxy or trichloroethoxycarbonyloxy, carbamoyloxy which is unsubstituted or monosubstituted or disubstituted by lower alkyl, for example carbamoyloxy or N,N - dimethylcarbamoyloxy, substituted or unsubstituted lower alkanesulphonyloxy, for example methanesulphonyloxy, and aromatic sulphonyloxy, for example benzenesulphonyloxy, o- or p-toluenesulphonyloxy or α- or β-naphthalenesulphonyloxy.

An etherified hydroxyl group is substituted or unsubstituted lower alkoxy, such as substituted or unsubstituted methoxy or ethoxy, or phenoxy. Substituted lower alkoxy is, for example, substituted by lower alkoxy, by halogen, by carboxyl, by substituted or unsubstituted basic amino radicals or by up to three phenyl or anisyl radicals.

Examples of etherified hydroxyl groups are methoxy, ethoxy, benzyloxy, benzhydryloxy, trityloxy and also carboxylower alkoxy, such as 2-carboxymethoxy or 2-carboxypropoxy, or lower alkoxy substituted by one of the basic amino groups defined above, such as 2-aminoethoxy, 2-aminoisopropoxy, dimethylaminoethoxy, 2-piperidinoethoxy, 2-morpholinoisopropoxy or 2 - (4 - methylpiperazino) - ethoxy.

The radical R_2 can be carboxyl or a carboxyl esterified by a physiologically detachable group.

A carboxyl group esterified by a physiologically detachable group can be any desired physiologically detachable and physiologically acceptable esterified carboxyl group which is known per se and is, for example, lower alkoxycarbonyl substituted by amino, di-lower alkylamino or acylamino, for example β-aminoethoxycarbonyl, β-dimethylaminoethoxycarbonyl, β-acetamidoethoxycarbonyl or β-carbamoylethoxycarbonyl, but preferably a group of the general formula



$$-\underset{\substack{\| \\ O}}{C}-O-\underset{\substack{| \\ R_3}}{CH}-Z-R_4 \qquad (A)$$

in which R_3 is hydrogen or a lower alkyl radical having 1—3 carbon atoms, R_4 is the acyl radical of a substituted or unsubstituted mono-, di- or polycarboxylic acid, or of an aliphatic or aromatic sulphonic acid having up to 18 carbon atoms, lower alkoxy carbonyl, lower alkyl substituted by hydroxyl, lower alkoxy, amino, di-lower alkylamino, cycloalkyl having 3—7 carbon atoms, phenyl, phenyl substituted by chlorine, hydroxyl or methoxy, phenyl-lower alkyl, wherein phenyl is substituted by chlorine, hydroxyl or methoxy or a five-membered or six-membered heterocyclic structure which has 1 to 2 ring oxygen, sulphur or nitrogen atoms in the position adjacent to the bonding carbon atom, and Z is oxygen, sulfur, sulphinyl, sulphonyl, imino or lower alkylimino or in which the grouping $-CH(R_3)-Z-R_4$ or $-Z-R_4$ is a constituent of a heterocyclic ring system, or a salt of such a compound.

Examples of such esterified carboxyl groups of the formula (A) which are particularly easily splittable under physiological conditions and are physiologically acceptable are known from numerous patent specifications.

Preferred groups (A) are, for example, those in which R_3 is hydrogen or methyl, Z is oxygen or sulphur and R_4 is the substituted or unsubstituted acyl radical of a monocarboxylic acid, for example lower alkanoyl which is unsubstituted or substituted by hydroxyl, lower alkoxy, such as methoxy, halogen, such as chlorine, lower alkylthio, such as methylthio, amino or di-lower alkylamino, such as dimethylamino, for example acetyl, pivaloyl, glycyl, L-valyl, L-leucyl, L-seryl, methoxyacetyl or methylthioacetyl, cyclopropylcarbonyl, benzoyl, chlorobenzoyl, p-(N,N-diisopropylaminosulphonyl)-benzoyl, thienylcarbonyl, furylcarbonyl or acryloyl; or in which R_4 is lower alkyl which is unsubstituted or substituted, such as methyl, ethyl, methoxymethyl, ethoxymethyl, β-hydroxyethyl, β-aminoethyl or β-dimethylaminoethyl.

A further preferred group of esterified carboxyl groups (A) which are easily splittable under physiological conditions are those in which R_3 is hydrogen or methyl, Z is imino, or lower alkylimino and R_4 is lower alkoxycarbonyl or a lower alkanoyl radical which is unsubstituted or substituted for example acetyl. Such groups are known, for example, from British Patent Specifications 1,454,726 and 1,458,234.

A further preferred group (A) is that in which the grouping $-CH(R_3)-Z-R_4$ represents a heterocyclic ring system which, together with the oxycarbonyl group, forms for example, 5 - oxo - dihydro - 2 - furfuryloxycarbonyl, 5 - oxo - tetrahydro - 2 - furfuryloxycarbonyl, phthalidyloxycarbonyl or 5,6 - dimethoxyphthalidyloxycarbonyl.

The grouping $-Z-R_4$ can also represent a heterocyclic ring system and is then, for example, a diacylimino group, such as a succinylimino, saccharimido or phthalimido group, which together with the radical $-CO-O-CH(R_3)-$ forms a group (A), for example the succinyliminomethoxycarbonyl, saccharimidomethoxycarbonyl or phthalimidomethoxycarbonyl group.

A further preferred group (A) is that in which R_3 is hydrogen or methyl, Z is sulphinyl or sulphonyl and R_4 is as defined above and in particular is lower alkyl which is unsubstituted or substituted, especially methyl or ethyl. Such radicals (A) are described, for example, in Belgian Patent Specifications 788,720, 827,858 and 831,941.

In addition to the basic amidino group $R_1-CH=N-$ and a free carboxyl group R_2, compounds of the formula I can contain further salt-forming radicals i.e. basic and/or acid radicals, in the esterified or etherified hydroxyl group which can be a substituent of the group R_1, and, according to the particular predominant neutral, basic or acid character in the total molecule, can form inner, zwitterionic salts and/or external salts with acids or bases.

In the absence of external salt-forming anions or cations, compounds of the formula I which contain acid and basic groups are in the form of inner salts, i.e. in the form of zwitterions. Compounds of the formula I which have a predominantly basic character, for example those in which R_2 is carboxyl esterified by a physiologically detachable group, can form stable 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, such as with aliphatic mono-, di- or tri-carboxylic acids, for example acetic acid, malonic acid, tartaric acid, embonic acid, citric acid or 4 - (N,N - dipropylsulphamoyl) - benzoic acid

(Probenecid), or with p-toluenesulphonic acid, α- or β-naphthalene-sulphonic acid or naphthalenedisulphonic acid, especially naphthalene - 1,5 - disulphonic acid, or with cation exchangers. Compounds of the formula I which have a predominantly acid character can form stable salts with bases. Preferred salts of this type are, in particular, pharmaceutically acceptable salts, such as alkali metal salts or alkaline earth metal salts, for example sodium salts, potassium salts, magnesium salts or calcium salts, and also ammonium salts with ammonia or suitable organic amines, the compounds used for forming the salts being, in particular, aliphatic, cycloaliphatic, cycloaliphatic-aliphatic and araliphatic primary, secondary or tertiary mono, di- or poly-amines, and also heterocyclic bases, such as tri-lower alkylamines, for example tri-ethylamine, mono, di, or tri-(hydroxy-lower alkyl)amines, for example 2 - hydroxy - ethylamine, bis - (2 - hydroxyethyl) - amine or tris - (2 - hydroxyethyl) - amine, basic aliphatic esters of carboxylic acids, for example 2-diethylaminoethyl 4-aminobenzoate, lower alkyleneamines, for example 1 - ethyl - piperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, and also bases of the pyridine type, for example pyridine, collidine or quinoline, as well as salts with anion exchangers.

The novel compounds can be in the form of mixtures of isomers, for example in the form of racemates, or in the form of pure isomers, for example in the form of optically active antipodes or in the form of the syn- or anti-compound.

The novel compounds of the formula I and their salts have a valuable pharmacological action, especially a particularly pronounced antimicrobial, especially antibacterial, action. For example, they are active against micro-organisms, such as against Gram-positive bacteria, for example *Staphylococcus aureus*, in minimum inhibitory concentrations (MIC) in vitro of from about 0.0125 mg/ml, but in particular against Gram-negative bacteria, especially enterobacteria, such as those mentioned below, in the dosage range of about 0.0002 to about 0.05 mg/ml.

For example in doses above about the MIC values indicated below, they are active in vitro against the following Gram-negative micro-organisms: *Klebsiella pneumoniae* (0.0008 mg/ml), *Salmonella typhimurium* (0.0004 mg/ml), Neisseria species, for example *Neisseria gonerrhoeae* (0.0002 mg/ml) and *Neisseria meningitidis* (0.0004 mg/ml), and Aerobacter species, for example *Aerobacter cloacae* (0.0008 mg/ml), and especially against pathogenic strains of *Escherichia coli* (0.0004 mg/ml). They are also active in vivo, for example in mice infected with *E. coli*, when administered in the dosage range of 10 to 70 mg/kg (subcutaneously) or of 20 to 150 mg/kg (perorally).

A further outstanding property of the novel compounds is the excellent action against influenza viruses, especially those of type A, for example against the strains Victoria 3/75 and Hongkong 1/68, which can be demonstrated in mice, in vivo, in a concentration range of from 1 mg/kg and especially in the range of 10 mg/kg to 250 mg/kg (perorally) or on 30 minute inhalation of a 1% strength aerosol, corresponding to 0.5 mg/mouse (per inhalation).

The compounds according to the invention are also distinguished by the fact that, in mixtures with known antimicrobial, such as antibacterial, antimycotic or antiviral, substances, for example with known antibiotics, especially β-lactam antibiotics, such as those of the penam or cephem series, and also with aminoglycoside or other antibacterial active ingredients, for example those mentioned below, they display, in a dosage range of 0.1—500 mg/kg, administered perorally, or 0.1—500 mg/kg administered parenterally, for example i.v., i.m., i.p. or s.c., of a compound of the formula I and in a mixing ratio of 1:29 to 29:1, preferably in a mixing ratio of 1:5 to 5:1, an activity which complements the antimicrobial spectrum of action or in some cases is synergistic.

For example, the compounds of the formula I, especially 6β - [(4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanic acid and pivaloyloxymethyl 6β - [(4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate, can be administered as a mixture with, and conjointly with, a β-lactam antibiotic, such as one of the penicillins amoxycillin, ampicillin, azlocillin, bacampicillin, mezlocillin, penicillin G, penicillin V, piperacillin or pivampicillin, one of the cephalosporin antibiotics cephacetrile, cephalexin, cefamandole, Cefasulbamid, cefazolin, cefoxitin, cefuroxime, 7β - (1,4 - cyclohexadienylglycylamido) - 3 - methoxy - 3 - cephem - 4 - carboxylic acid or 7β - [4 - (2 - iminothiazolidinyl) - acetamido] - 13 - [1 - (2 - dimethylaminoethyl) - tetrazolylthiomethyl] - 3 - cephem - 4 - carboxylic acid, or

7β - [3 - (methylsulphonylaminophenyl) - glycylamido] - 3 - methoxy - 3 - cephem - 4 - carboxylic acid or an aminoglycoside antibiotic, such as amikacin, gentamicin, sisomicin, Netilmicin or tobramycin, a macrolide antibiotic such as erythromycin, a sulphonamide, such as sulfamethoxazole, sulfametrole or sulfamethizole, or a mixture of a sulphonamide and trimethoprim, for example a mixture of sulfamethoxazole and trimethoprim (5:1) or of sulfametrole and trimethoprim (5:1), and also with another synthetic anti-bacterial agent, such as trimethoprim or an antiviral agent, such as those of the adamantane type, for example 1-aminoadamantane hydrochloride.

Especially for the treatment of colds, and in particular of influenza and the bacterial infections preceding, accompanying or following this, the compounds, according to the invention, of the formula I, especially 6β - [(4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanic acid or its physiologically acceptable salts or its physiologically easily splittable esters, such as the pivaloyloxymethyl ester, can be used as a mixture with one or more antimicrobial active ingredients which are customary and effective in the case of such infections, such as those substances mentioned above and/or additional symptom-alleviating substances or mixtures of active ingredients, in particular in a mixing ratio of 1:10 to 10:1. Anti-microbial active ingredients particularly suitable for this purpose are, for example, other compounds having an antiviral action, such as those of the adamantane type, for example 1-aminoadamantane, 1 - (1 - aminoethyl) - adamantane, 1′ - methyl - spiro[adamantane - 2,3′ - pyrrolidine], 1 - (ethoxymethylcarbonylamino) - adamantane or 1 - (2 - dimethylaminoethoxy - methylcarbonylamino) - adamantane or non-toxic salts, for example hydrochlorides, thereof, and also antibacterial active ingredients which are active against infections of the respiratory passages, such as ampicillin, bacampicillin, dihydroampicillin, amoxicillin, penicillin G, penicillin V, cefamandole, 7β - [4 - (2 - iminothiazolidinyl) - acetamido] - 3 - [1 - (2 - dimethylaminoethyl) - tetrazol - 5 - yl - thiomethyl] - 3 - cephem - 4 - carboxylic acid, erythromycin, Netilmycin, tobramycin, sulfamethoxazole, trimethoprim or a mixture of sulfamethoxazole and trimethoprim (5:1) or their physiologically acceptable salts. Suitable symptom-alleviating substances are, in particular, compounds which have proved useful in infections of the respiratory passages and which facilitate breathing, or mixtures thereof.

The compound of the formula I having an antiviral action can be combined in a mixture with further antimicrobial active ingredients, a symptom-alleviating compound and/or suitable pharmaceutical carriers to give combination preparations, which can be administered in the manner customary in the case of infectious diseases of the respiratory passages, for example also in the form of nosedrops, an inhalation spray, a syrup or lozenges.

The sympton-alleviating substances are known substances which facilitate breathing, in particular menthol, such as l-menthol, and are used in particular for spray (inhalation) administration.

The present invention relates preferably to those compounds of the formula I in which R_1 is aza-bi- or -tri-cyclo-alkyl which is unsubstituted or substituted by hydroxyl or esterified or etherified hydroxyl, and also can contain as a further ring hetero-atom, oxygen, or nitrogen which is bonded to the radical X_1, and/or a double bond, and R_2 is free carboxyl or carboxyl esterified by a physiologically detachable group, especially carboxyl or a carboxyl group, esterified by a physiologically detachable group, of the formula (A) or salts, especially pharmaceutically acceptable salts, of such compounds having salt-forming groups.

The invention relates especially to those compounds of the formula I in which R_1 is an azabicycloalkyl having 8—11 ring members which is bonded via the ring nitrogen atom and substituted by hydroxyl, esterified hydroxyl, such a hydroxyl esterified by a hydrogen halide, for example chlorine or bromine, unsubstituted lower alkanoyloxy, lower alkanoyloxy substituted by carboxyl, lower alkoxycarbonyl carbamoyl or by substituted or unsubstituted basic amino, benzoyloxy, which is unsubstituted or substituted by carboxyl, pyridine-, pyrimidine- or pyridazine-carbonyloxy, which are unsubstituted or substituted by one or two hydroxyl radicals, lower alkoxycarbonyloxy, which is unsubstituted or monosubstituted to trisubstituted by chlorine, carbamoyloxy, which is unsubstituted or monosubstituted or disubstituted by lower alkyl, lower alkanesulphonyloxy, or aromatic sulphonyloxy, or etherified hydroxyl, such as lower alkoxy substituted by lower alkoxy, phenoxy, halogen, especially chlorine or bromine, carboxyl or the basic amino radicals and also by up to three phenyl or anisyl radicals, such as a azabicyclooctyl, especially 8 - aza - bicyclo[3.2.1]oct - 8 - yl, and R_2 is carboxyl or an esterified carboxyl group, which is easily splittable under physiological conditions of the formula (A), in which R_3 is hydrogen or methyl, Z is oxygen and R_4 is lower alkyl which is unsubstituted or substituted by amino or di-lower alkylamino, for example methyl, ethyl, β-aminoethyl or β-dimethylaminoethyl, lower alkanoyl which is unsubstituted or substituted by amino or di-lower alkylamino, for example acetyl, pivaloyl, glycyl, L-valeryl or L-leucyl, lower alkoxycarbonyl, for example methoxycarbonyl or ethoxycarbonyl, or carbamoyl, or in which the radical (A) is phthalidyloxycarbonyl, and also salts, especially pharmacologically acceptable salts, of such compounds.

The invention also relates in particular to compounds of the formula I in which R_1 is an azabicycloalkyl which is bonded and R_2 is carboxyl, substituted or unsubstituted lower alkanoyloxymethoxycarbonyl, such as acetyloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, α-pivaloyloxyethoxycarbonyl, glycyloxymethoxycarbonyl, L-valyloxymethoxycarbonyl or L-leucyloxymethoxycarbonyl, substituted or unsubstituted lower alkoxymethoxycarbonyl, such as methoxymethoxycarbonyl, ethoxymethoxycarbonyl, α-methoxyethoxycarbonyl, methoxycarbonyloxymethoxycarbonyl, α-(ethoxycarbonyloxy-ethoxycarbonyl, carbamoyloxymethoxycarbonyl or phthalidyloxymethoxycarbonyl, and also salts, especially pharmacologically acceptable salts, of such compounds.

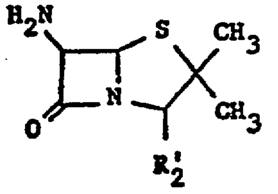
The invention relates especially to compounds of the formula I in which R_1 is an 8 - azabicyclo[3.2.1]oct - 8 - yl, 3 - azabicyclo[3.2.2]non - 3 - yl, 9 - azabicyclo[3.3.1]non - 9 - yl, 7 - methyl - 3,7 - diazabicyclo[3.3.1]non - 3 - yl, azatricycloalkyl or azatricycloalkenyl, such as 2 - azatricyclo[$3.3.1.1^{3,7}$]dec - 2 - yl, 4 - azatricyclo[$5.2.2.0^{2,6}$]undec - 4 - yl, 4 - *endo* - azatricyclo[$5.2.2.0^{2,6}$]undec - 8 - en - 4 - yl, 10 - oxa - 3 - azatricyclo[$5.2.1.0^{1,5}$]dec - 3 - yl, and 10 - methyl - 3,10 - diaza - tricyclo[$5.2.1.0^{1,5}$]dec - 3 - yl and also 3 - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl (or nortropinyl), the hydroxyl of which can be esterified by lower alkanoyl, carboxy-lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, lower alkoxycarbonyl monosubstituted to trisubstituted by chlorine, or benzoyl, nicotinoyl, carbamoyl or toluenesulphonyl or can be etherified by lower alkyl lower alkyl monosubstituted to trisubstituted by lower alkoxy, carboxyl, dilower alkylamino, or by phenyl or anisyl, the said azacyclic radicals being bonded via the aza ring nitrogen atom, and R_2 is carboxyl, acetyloxymethoxycarbonyl, methoxycarbonyloxymethoxycarbonyl, ethoxycarbonyloxymethoxycarbonyl, glycyloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, lower alkoxymethoxycarbonyl, especially methoxymethoxycarbonyl, or phthalidyloxycarbonyl, and also physiologically acceptable salts of such compounds.

The invention relates in particular to 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid, 6β - [(4 - azatricyclo[$5.2.2.0^{2,6}$]undec - 4 - yl) - methyleneamino] - penicillanic acid, 6β - [(4 - *endo* - azatricyclo[$5.2.2.0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanic acid, 6β - (3 - *endo* - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid and 6β - [(7 - methyl - 3,7 - diazabicyclo[3.3.1]non - 3 - yl) - methyleneamino] - penicillanic acid, and pivaloyloxymethyl 6β - [(4 - *endo* - azatricyclo[$5.2.2.0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate, as well as physiologically acceptable salts thereof.

The novel compounds of the formula I can be obtained by reacting a formamide or thioformamide, which can be activated, of the formula II

$$R_1{-}CH{=}X \qquad \text{(II)}$$

in which X is oxygen or sulphur and R_1 is as defined under formula I, and in which functional groups present in R_1 can be protected, or a reactive derivative of such a formamide or thioformamide, with a 6-aminopenam derivative of the formula III



(III)

wherein the 6-amino group is in a free or protected form and R_2' is free carboxyl or protected carboxyl or with an inorganic or organic salt of such compound, and in a resulting compound, wherein R_2' denotes protected carboxyl, the protected carboxyl group is converted into a free carboxyl group or a carboxyl group esterified by a physiologically detachable group, and/or, if desired, protected functional groups present are converted into the free functional groups, and/or, within the definition of the final products, a resulting compound of formula I is converted into another compound of formula I, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

Preferred reactants for use with the 6-aminopenam derivatives of the formula III are the reactive derivatives of a formamide or thioformamide of the formula II which are defined below.

Reactive derivatives of the compounds of the general formula II are, for example, formiminium salts of the formula

$$[R_1{=}CH{-}Y]^{\oplus}Z^{\ominus} \qquad \text{(IIa)}$$

in which R_1 is as defined above and any free functional groups which may be present in R_1 preferably are temporarily protected, Y is halogen, especially chlorine, or lower alkoxy which is unsubstituted or substituted by phenyl, lower alkoxy or halogen, such as chlorine, in particular methoxy, ethoxy or benzyloxy, and Z is halogen, such as chlorine, bromine or iodine, or the anionic radical of an alkylating agent, especially a monoalkyl-sulphate radical, such as a monomethyl-sulphate or monoethyl-sulphate radical, a dialkyl-phosphate radical, such as the dimethyl-phosphate radical, or the tetrafluoborate radical.

In a compound of the formula IIa, Y is in particular halogen, especially chlorine, and also lower alkoxy, especially methoxy or ethoxy, and Z is in particular halogen, especially chlorine, and also the metho- or etho-sulphate radical.

Preferred examples of starting compounds of the formula IIa are formiminium halides of the formula

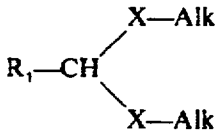
$$[R_1{=}CH{-}Hal]^{\oplus}Hal^{\ominus}$$

which can also be regarded as formamide dihalides of the formula $R_1{-}CH(Hal)_2$, and also alkylating agent adducts of the formula

$$[R_1{=}CH{-}O{-}Alk]^{\oplus}Z^{\ominus}$$

in which R_1 is as defined above and especially as defined above for preferred radicals R_1, Hal is halogen, especially chlorine, Alk is methoxy or ethoxy and Z is halogen, such as chlorine, bromine or iodine, and also the monomethyl-sulphate or monoethyl-sulphate radical.

Reactive derivatives of a formamide or thioformamide of the formula II are, for example, also formamide acetals or formamide thioacetals of the formula



$$R_1{-}CH\begin{matrix}\diagup X{-}Alk\\ \diagdown X{-}Alk\end{matrix} \qquad \text{(IIb)}$$

in which R_1 and X are as defined above and Alk is lower alkyl, which is unsubstituted or substituted by halogen, phenyl or lower alkoxy, especially methyl or ethyl.

In the compounds of the formula IIa or IIb any free functional groups which may be present in the radical R_1 can temporarily be protected, if necessary or desired.

The starting compounds of the formula III in which R_2' is a free carboxyl group, an esterified carboxyl group splittable under physiological conditions or a protected carboxyl group are known and have been described, for example, in German Offenlegungsschriften 2,055,531, 2,123,111, 2,404,587 and 2,530,299 and also in Japanese Published Specification 039958/1976 (Derwent No. 89393 X/48).

The carboxyl, amino and hydroxyl protecting groups which can be used in the starting compounds, for example those of the formulae IIa, IIb and III, are known and described in numerous patent specifications, for example in those mentioned above or in J. W. F. McOmie, "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973. Thus, examples of amino protecting groups are given in chapter 2, of hydroxyl protecting groups are given in chapter 3 and of carboxyl protecting groups are given in chapter 5 of the last-mentioned publication.

Suitable protecting groups are also mentioned in E. Schröder and Lübke, "The Peptides", volume I, Academic Press, 1965, for example on pages 72—75.

A protected carboxyl group R_2' in a starting material of the formula III is a carboxyl group esterified by a physiologically detachable group or in particular an easily splittable esterified carboxyl group or a carboxyl group in the form of an anhydride.

An easily splittable esterified carboxyl group is, for example, a lower alkoxycarbonyl which is preferably substituted, in particular in the α-position or also in the β-position, and/or branched in the α-position. Substituents of such a group are, for example, carbocyclic aryl, such as phenyl, which is unsubstituted or substituted, for example by lower alkyl, such as tert.-butyl, phenyl, hydroxyl, lower alkoxy, such as methoxy, and/or nitro, aryloxy, such as phenyloxy which is unsubstituted or substituted, for example by lower alkoxy, such as methoxy, arylcarbonyl, such as benzoyl which is unsubstituted or substituted, for example by halogen, such as bromine, or cyano or acylamino, such as diacylamino, for example phthalimino or succinylimino; such substituents are preferably in the α-position of the lower alkoxycarbonyl group and, depending on the nature of the substituents, this group can contain one, two or more such radicals. Further substituents, which are preferably in the β-position of the lower alkoxycarbonyl group, are halogen, for example chlorine, bromine or iodine, and in such radicals an individual chlorine or bromine can easily be converted to iodine before setting free a carboxyl group protected in this way. Examples of suitable lower alkyl substituents in the abovementioned substituted or unsubstituted lower alkoxycarbonyl groups are tert.-lower alkyl, for example tert.-butyl, α-phenyl-lower alkyl which can be substituted in the phenyl radical, such as benzyl, 4-methoxybenzyl or 4-nitrobenzyl, diphenylmethyl, which can be substituted in the phenyl radicals, especially by lower alkoxy, for example methoxy, such as benzhydryl or 4,4'-dimethoxydiphenylmethyl, trityl, and also tris - (p - methoxyphenyl) - methyl, bis - phenyloxy - methyl, which can be substituted in the phenyl radicals, especially by lower alkoxy, such as bis - (4 - methoxyphenyloxy) - methyl, phenacyl, which can be substituted, especially by halogen, such as 4 - bromo - phenacyl, and also cyanomethyl, diacyliminomethyl, such as phthalyliminomethyl or succinyliminomethyl, or 2 - halogeno - lower alkyl, such as 2,2,2 - trichloroethyl, 2-bromoethyl or 2-iodoethyl.

Furthermore, an easily splittable esterified carboxyl group can also be a cycloalkoxycarbonyl group, in which the α-position is preferably a bridge head carbon atom. Cycloalkyl is, for example, 1-adamantyl.

Further protected carboxyl groups R_2' are organic silyloxy- or stannyloxy-carbonyl radicals which carry 1 to 3 organic, especially aliphatic, hydrocarbon radicals, such as lower alkyl, for example methyl, ethyl, propyl or butyl or tert.-butyl, or halogeno-lower alkyl, for example chloromethyl or 2-chloroethyl, and also substituted or unsubstituted cycloaliphatic, aromatic or araliphatic hydrocarbon radicals, such as cycloalkyl, phenyl or phenyl-lower alkyl, and also etherified hydroxyl groups, for example lower alkoxy, such as methoxy or ethoxy, which, if desired, can contain halogen, such as chlorine, as further substituents. Preferred examples of such carboxyl protecting groups are tri-lower alkyl-silyl, for example trimethylsilyl or tert.-butyldimethylsilyl, tri-lower alkyl-silyl substituted by phenyl, for example trityl-dimethylsilyl, lower alkoxy-lower alkyl-halogeno-silyl, for example chloro-methoxymethylsilyl, or tri-lower alkyl-stannyl, for example tri-n-butylstannyl.

A protected carboxyl group R_2' can also be a carboxyl esterified by a phenyl radical containing substituents providing a negative polarisation. Radicals providing a negative polarisation are halogen, especially chlorine, and nitro. A suitable radical of this type is the pentachlorophenyl protecting group described in British Patent Specification 1,442,435.

A further suitably protected carboxyl is β-silylethoxycarbonyl substituted by organic radicals, for example by the radicals mentioned above with regard to silyl protecting groups, which is described in Belgian Patent Specification No. 851,576, especially β-trimethylsilylethoxycarbonyl.

A protected carboxyl group R_2' which is in the form of an anhydride is preferably a free or esterified phosphoryloxycarbonyl group, for example a O,O'-

diphenylphosphoryloxycarbonyl group, or a diphenylphosphinyloxycarbonyl group.

Preferred ester protecting groups are those which can be detached in the weakly acid to weakly basic pH range under conditions which are particularly gentle in respect of the penam ring structure, for example ester protecting groups which are easily detachable by solvolysis and are derived from tris-organosilyl alcohols, such as β-trimethylsilylethanol. Such groups are described, for example, in British Patent Specification 1,073,530, in German Offenlegungsschrift 1,800,698 or in the abovementioned Belgian patent specification.

A carboxyl group which may be present in the radical R_1 can also be protected in the manner described above for R_2' and specifically can be protected by the same or by another carboxyl protecting group.

The primary amino group in a compound of the formula III and also a primary or secondary amino group which may be present in the radical R_1 of the compound of the formula IIa or IIb can also, if necessary, advantageously temporarily be protected by one of the amino protective groups known in peptide chemistry or ion penicillin chemistry, preferably an easily detachable amino protective group. Such protecting groups can be, for example, acyl, arylmethyl, 2 - carbonyl - 1 - vinyl, arylthio or aryl-lower alkylthio groups and also arylsulphonyl groups, as well as the organic silyl or stannyl groups mentioned above.

Amino groups protected in a particularly easily splittable form are amino groups acylated by a half-ester radical of carbonic or thiocarbonic acid, for example 2-iodoethoxycarbonyl (German Offenlegungsschrift 2,126,266), 6-nitroveratryloxycarbonyl and 2-nitrobenzyloxycarbonyl (J. Amer. Chem. Soc. *92*, 6333 (1970)), 2-methylthioethoxycarbonyl (Chem. Ber. *109*, 3693 (1976)) or tert.-butyloxycarbonyl, and also by 2-acyloxymethylbenzoyl, for example 2-benzoyloxymethylbenzoyl (J. Org. Chem. *41*, 2029 (1976)) or by an aromatic phosphinic acid radical, for example diphenylphosphinyl (Tetrahedron Letters *1976*, 3623).

A hydroxyl group which may be present in a radical R_1 can also be in a temporarily protected form, especially in an easily splittable etherified or esterified form, for example in the form of a lower alkoxy group, such as a methoxy group, which is unsubstituted or substituted by lower alkoxy or lower alkylthio, for example in the form of a methoxymethoxy, methylthiomethoxy or β-methoxyethoxymethoxy group, or in the form of a 2-oxacycloalkoxy group, for example a 2-tetrahydropyranyloxy group, or of an acyloxy group, such as a lower alkanoyloxy group, for example an acetyloxy group, or in the form of an easily splittable etherified hydroxycarbonyloxy group, such as a lower alkoxycarbonyloxy group, for example a tert. - butyloxycarbonyloxy group.

The process used for the preparation of the compounds, according to the invention, of the formula I is known per se and is described in German Offenlegungsschriften 2,055,531, 2,123,111, 2,404,587 and 2,530,299.

In this process, formamides or thioformamides, of the formula II, or reactive derivatives thereof, and the compound of the formula III are reacted with one another, preferably in the presence of an inert diluent, for example of an inert, preferably polar, solvent, and, if necessary, in the presence of further reaction-promoting additives, for example strong organic bases, condensing agents and/or catalysts, at reaction temperatures of between −80 and +80°C, preferably in the temperature range below +30°C and especially with initial extensive cooling to temperatures below 0°C, if necessary in an inert gas atmosphere and in general with the exclusion of moisture.

When carrying out the process according to the invention, the reactive derivatives of a formamide or thioformamide of the formula II can be reacted with the penam compound of the formula III either after they have previously have been isolated or after they have been formed in situ from their starting materials, without prior purification and/or isolation. Thus, for example, a formamide or thioformamide of the formula II can first be reacted with a halogenating agent, such as one of the halogenating agents mentioned below which can be used for the preparation of the halogenoformiminium halides of the formula IIa, especially phosgene or oxalyl chloride, if appropriate in the presence of a strong organic base, or can first be reacted with an active acetalising agent known per se, for example a reactive ortho-ester, such as one of the ortho-esters of formic acid mentioned below, a suitable ester of pentavalent phosphorus or a reactive amide acetal, preferably dimethylformamide dimethyl acetal, and the crude reaction mixture which contains the intermediates of the formula IIa or IIb can be allowed to react further in situ with an amine of the formula III, which can be protected, in a manner analogous to that employed when the compounds used have previously been isolated, the compounds, according to the invention, of the formula I being formed.

Finally, it is also possible to react a preferably equimolar mixture of the amines of the formula R_1—H and III, it being possible for the amino and/or carboxyl group in III and any free functional groups which may be present in R_1—H, with the exception of the aza-amino group, temporarily to be protected, with a condensing agent which supplies the amidine carbon atom. Condensing agents which supply the amidine carbon atom are, in particular, reactive derivatives of orthoformic acid, for example orthoformates, especially aliphatic orthoformates, such as tri-lower alkyl orthoformates, corresponding thioorthoformates, di-lower alkylformamide diacetals and 1,1-dihalogenomethyl lower-alkyl ethers. Preferred derivatives of this type are trimethyl or triethyl orthoformates, trimethyl or triethyl thioorthoformates, dimethylformamide dimethylacetal and 1,1-dichlorodimethyl ether.

The process variant which proceeds via starting compounds of the formula IIa using 1,1-dichlorodimethyl ether as the condensing agent is advantageously carried out in the presence of a strong organic base and in an inert organic solvent; the process variant which proceeds via starting compounds of the formula IIb using orthoformates or thioorthoformates as the condensing agent preferably proceeds in the presence of an alkylating catalyst, such as a Lewis acid, for example zinc chloride or boron trifluoride etherate.

The reaction of a starting compound of the formula IIa, which has been isolated or has been prepared in situ, with a penam compound of the formula III is preferably carried out with temporary protection of the free functional groups and in the presence of strong organic base. The imide halide of the formula IIa and the base are used, for example, in at least approximately equivalent amounts, but the latter can advantageously also be present in excess, for example in about twice to 3 times the equivalent amount. A further equivalent of the base must be used for each free carboxyl group which may be present in an intermediate. Suitable strong organic bases are, especially, the conventional acid-binding, salt-forming tertiary amines used in organic synthesis, for example tertiary aliphatic mono- or di-amines, such as tri-lower alkylamines, for example trimethylamine, triethylamine, tripropylamine or diisopropylethylamine, and also N,N,N',N'-tetra-lower alkyl-lower alkylenediamines, for example N,N,N',N'-tetraethylethylenediamine, cyclic mono- or di-amines, such as N-substituted, for example N-lower alkylated, alkyleneamines, azaalkyleneamines or oxaalkyleneamines, for example N-methylpiperidine or N-methylmorpholine; preferably suitable salt-forming tertiary amines are especially tri-lower alkylamines, for example triethylamine or diisopropylethylamine, and also N-methylmorpholine.

Suitable inert solvents or diluents are all absolute, preferably polar, solvents. In particular, halogenated hydrocarbons, especially methylene chloride or chloroform, and also ketones, such as acetone, ethers, such as diethyl ether, anisole or tetrahydrofuran, and also aromatic hydrocarbons, for example benzene or toluene, or esters which are stable to hydrolysis, such as ethyl acetate, are suitable as the reaction medium.

In general, the starting compounds used in the above reaction are starting compounds of the formula IIa or IIb which have previously been isolated and are dissolved or suspended in one of the said inert solvents or diluents and are added to a solution of the compound of the formula III, the carboxyl group R_2 of which has previously been protected, for example by silylation, if starting materials of the formula IIa are used, after which the mixture is cooled to the said reaction temperature and the reaction is initiated or accelerated by adding the strong organic base.

In order to prepare the compounds of the formula I, it is also possible, as mentioned, to prepare the starting materials of the formula IIa in situ and to further use these direct, without prior purification or isolation. In this case, the same reaction conditions as mentioned above are maintained except that the reaction temperature is preferably chosen to be somewhat lower. Thus, for example, the reaction can be carried out at temperatures of initially −30 to −70°, after which the temperature is allowed to rise slowly.

The reaction of the starting compounds of the formula IIb with the compounds of the formula III is distinguished by the particular advantage that, a free carboxyl group in a compound of the formula III in general does not have to be protected and that the reaction also proceeds at somewhat higher temperatures, starting at about 0° and rising up to about +20 to +40°C.

In a compound of the formula I obtained by the process described, the carboxyl group R_2 and any functional group which may be present in the radical R_1 carrying a protecting group, can, if desired or necessary, be detached in a manner known per se, for example by solvolysis, reduction or photolysis, or also enzymatically.

Thus, a silyl protecting group used to protect a carboxyl, hydroxyl and/or amino group, for example the trimethylsilyl protective group, can be removed by solvolysis, for example by hydrolysis or alcoholysis, if this detaching has not already proceeded to completion during working up the reaction mixture. A carboxyl group protected by a halogeno-lower alkyl group, especially a 2,2,2-trichloroethyl group, can be converted to the carboxylate, for example by treatment with a chemical reducing agent, such as a metal, for example zinc, or a reducing metal salt, for example chromium-II chloride or chromium-II acetate, usually in the presence of an acid, for example aqueous acetic acid or formic acid, or of a preferably aqueous alcohol, and a carboxyl group esterified by an arylcarbonylmethyl group can be converted to the carboxylate by treatment with a nucleophilic scission reagent, such as sodium thiophenolate or sodium iodide. A carboxyl group esterified by a suitable arylmethyl grouping can be split, for example, by irradiation, preferably with ultraviolet light, for example of less than 290 mμ, if the arylmethyl group is, for example, a benzyl radical which can be substituted in the 3-, 4- and/or 5-position, for example by lower alkoxy and/or nitro groups, or with longer-wave ultraviolet light, for example of more than 290 mμ, if the arylmethyl group is, for example, a benzyl radical which is substituted in the 2-position by a nitro group. A carboxyl group esterified by a suitably substituted methyl group, such as tert.-butyl or diphenylmethyl, is set free in a particularly gentle manner, for example by treatment with a suitable acid agent, such as trifluoroacetic acid, if appropriate with the addition of a nucleophilic compound, such as phenol or anisole. An activated esterified carboxyl group or carboxyl group in the form of an anhydride can be split by hydrolysis with a neutral to weakly acid or weakly basic agent, which can contain water, such as acetic acid, aqueous sodium bicarbonate or an aqueous potassium phosphate buffer of pH 7 to 9, and an esterified carboxyl group which is splittable by hydrogenolysis, for example a carboxyl group esterified by benzyl, p-nitrobenzyl or p-methoxybenzyl, can be split preferably by treatment with hydrogen in the presence of a palladium catalyst.

A carboxyl or hydroxyl group protected by a benzyl protecting group, which is unsubstituted or substituted, such as monosubstituted or polysubstituted by phenyl, methoxy or nitro, can be split, more or less readily, depending on the nature of the substituents, by the action of activated hydrogen or, if desired, by a weakly acid scission agent. Thus, the benzyl ester group of the p-methoxybenzyl ester group is split by the action of activated hydrogen in an inert, preferably alcoholic, solvent, such as a lower alkanol, for example ethanol, at normal or slightly elevated temperature, and the trityl ester group of the tris - (p - methoxyphenyl) - methyl ester group is readily split by means of formic acid, which can contain water, for example at room temperature.

A carboxyl protected by a lower alkoxycarbonyl branched in the α-position, such as tert.-butoxycarbonyl, or by adamantyloxycarbonyl can likewise be set free by acidolysis, for example with lower alkanecarboxylic acids, for example acetic acid or formic acid.

In addition to the abovementioned weakly acid scission agents, further weak inorganic or organic acids or other weakly acid organic or inorganic compounds are also suitable as scission agents. Thus, polymers and adsorbents containing acid groups and also acids adsorbed on polymers are also suitable for this purpose; for example acid ion exchangers, acid adsorbents, such as silica gel or acid aluminium oxide, or insoluble or adsorbed phosphoric acids, for example metaphosphoric acids, or acid salts of phosphorus acids, and also Lewis acids in inert solvents are suitable as acidic scission agents.

A carboxyl group protected by an aryl radical containing substituents providing a negative polarisation, for example by pentachlorophenyl, can be freed from the protecting radical by mild treatment with alkali, or with an organic base, for example those mentioned above.

A β-silylethyl protecting group, for example a β-trimethylsilylethyl protecting group, is split in a mild specific manner by a fluoride solution in organic media, for example KF in the presence of a crown ether, for example 18-crown ether-6, by tetraethylammonium fluoride or by HF-pyridine, preferably in an inert polar solvent, for example dimethylformamide.

Furthermore, one of the abovementioned physiologically splittable ester groups, for example a (lower alkoxy)methyl ester group, for example a methoxymethyl ester group, or a lower alkanoyloxymethyl ester group, for example a pivaloyloxymethyl ester group, can, if desired, also be detached in vitro, enzymatically or by one of the said scission agents, especially by a weakly acid scission agent, for example one of those mentioned above, and to this extent, if desired, can also be used for the temporary protection of the carboxyl group. Compounds containing the abovementioned, and especially the last-mentioned, physiologically splittable protective groups, in particular those containing a pivaloyloxymethyl ester group, are also readily convertible in vivo, into the corresponding free carboxylic acids of the formula I and are therefore suitable for direct use as antibacterial and/or antiviral active ingredients.

The hydroxyl protecting groups used as carboxyl protective groups can also be removed in a manner known per se, for example in the manner described above.

Thus, for example, a methyl group substituted by aryl, such as trityl which is unsubstituted or substituted, such as substituted by methoxy, can be detached by the action of the abovementioned weakly acid agents, if desired in organic solvents, for example glacial acetic acid, or in a particularly gentle manner by treatment with acid ion exchangers or acid adsorbents such as silica gel or active aluminium oxide under mild conditions, for example by standing for several hours at room temperature. Preferred easily detachable hydroxyl protecting groups are the trityl group and the tris - (p - methoxyphenyl) - methyl group.

Further hydroxyl protecting groups which are particularly easily removable are derived from silyl alcohols. Thus, a trimethylsilyloxy group can already be detached, in a manner known per se, by aqueous lower alkanols, for example methanol, at normal or slightly elevated temperature.

A tetrahydropyranyl protecting group, which is particularly preferred when the protecting group has to withstand the action of basic or reducing agents, is also split easily in the presence of acid agents, for example those mentioned above.

Hydroxyl groups protected by etherification with lower alkoxy-lower alkyl can be split, for example, by treatment with zinc bromide or titanium tetrachloride in methylene chloride at room temperature and lower alkylthio-lower alkyl ethers can also be split by means of mercury-II chloride in aqueous acetonitrile or by means of methyl iodide and sodium carbonate in acetone at room temperature.

The amino protecting groups can be split in a similar manner, especially by hydrogenolysis or solvolysis, preferably acidolysis. Thus, for example, a (lower alkoxy)carbonyl group, which is preferably branched, for example the tert.-butoxycarbonyl group, can be detached in a manner known per se by treatment with acidic scission agents, for example those mentioned above, if desired in a preferably ethereal diluent, at or below room temperature.

A 2 - (benzoyloxymethyl) - benzoylamino group can be split in weakly acid or alkaline solution and/or also by hydrogenolysis in the presence of a Pd/C catalyst, and a diphenylphosphorylamino group can be split in weakly acid trifluoroacetone.

Further amino protecting groups which are also particularly easily detachable in another way are those described below. Thus, for example, the halogenoethoxycarbonyl protective group, especially the iodoethoxycarbonyl protective group, can be removed by the action of silver-I salts or mercury-I salts, such as nitrates, in an aqueous or organic medium, for example in acetone, and the methylthioethoxycarbonyl group, after methylation to dimethylsulphonioethoxycarbonyl or after oxidation to methylsulphinyl- or methylsulphonyl-ethoxycarbonyl, can be removed easily by mild treatment with alkali, and the 2,2′-dinitrodiphenylmethoxycarbonylamino, 6-nitroveratryloxycarbonylamino or 2′-nitrobenzyloxycarbonylamino group can be split quantitatively by the action of light having a wavelength of >3,200Å.

If desired or necessary, it is possible, within the definition of the end products, to convert a resulting compound of the formula I into another compound of the formula I.

Thus, in a resulting compound of the formula I, a free temporarily protected carboxyl group R_2 can be converted in a manner known per se into an esterified carboxyl group R_2 which is easily splittable under physiological conditions. The processes used for the subsequent esterification or transesterification are known.

The physiologically splittable esterified carboxyl groups R_2 can be prepared in a particularly simple manner from the corresponding carboxy compounds and the corresponding alcohol by a condensation reaction in the presence of a conventional condensing agent, such as of a carbodiimide, for example dicyclohexylcarbodiimide, or of a reactive N,N' - bis - heterocyclylurea, for example carbonyldiimidazole, for example in an inert polar solvent.

Furthermore, such esters are obtained, for example, by treatment with a suitable diazo compound, such as a diazo-lower alkane, for example diazomethane or diazobutane, or a phenyldiazo-lower alkane, for example diphenyldiazomethane, if necessary in the presence of a Lewis acid, for example boron trifluoride, or by reaction with an N,N'-disubstituted O- or S-substituted isourea or isothiourea in which an O- or S-substituent is, for example, lower alkyl especially tert.-butyl, or phenyl-lower alkyl, and N- and N'-substituents are, for example, lower alkyl, especially isopropyl, cycloalkyl or phenyl, or by any other known and suitable esterification process, such as by reaction of a salt of the acid with a reactive ester of an alcohol and a strong inorganic acid or a strong organic sulphonic acid.

Furthermore, in a resulting compound of the formula I, a free or temporarily protected hydroxyl group present in the radical R_1 can be converted in a manner known per se to an esterified or etherified hydroxyl group defined according to the invention. Esterification reactions of this type can be carried out, for example, by reacting the hydroxy compound with the corresponding carboxylic or sulphonic acid in the presence of one of the abovementioned condensing agents, or by reacting the hydroxy compound with an isocyanate, acid anhydride or acid halide, if appropriate in the presence of the abovementioned bases, and corresponding etherification reactions can be carried out, for example, by using the conventional alkylating agents.

The said esterified or etherified hydroxyl groups, the lower alkyl substituent X_1 and/or the physiologically easily splittable esterified carboxyl group R_2 are preferably already present in this form in the starting materials, if they are adequately stable, i.e. do not change when the process according to the invention is carried out.

Salts of compounds of the formula I can be prepared in a manner known per se. Thus, salts of such compounds containing acid groups can be formed, for example, by treatment with metal compounds, such as alkali metal salts of suitable carboxylic acids, for example the sodium salt of α-ethylcaproic acid, or with a dilute alkali metal hydroxide, with ammonia or with a suitable organic amine, preferably stoichiometric amounts or only a small excess of the salt-forming agent being used. Acid addition salts of compounds of the formula I containing basic groupings are obtained in a conventional manner, for example by treatment with an acid or a suitable anion exchanger. Inner salts of compounds of the formula I which contain a salt-forming amino group and 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 treatment with liquid ion exchangers.

Salts can be converted into the free compounds in a conventional manner, metal salts and ammonium salts being converted, for example, by treatment with suitable acids or cation exchangers and acid addition salts being converted by treatment with suitable basic agents or anion exchangers.

Resulting mixtures of isomers can be separated into the individual isomers by methods known per se; mixtures of diastereomers or stereoisomers, for example syn- and antiisomers, can be separated, for example, by fractional crystallisation, adsorption chromatography (column chromatography or thin layer chromatography) or other known separating processes. Resulting racemates can be resolved into the antipodes in a conventional manner, if appropriate after introducing suitable salt-forming groupings, for example by forming a mixture of diastereoisomeric salts with optically active salt-forming agents, separating the mixture into the diastereoisomeric salts and converting the salts which have been separated off into the free compounds, or by fractional crystallisation from optically active solvents.

Preferably, the starting materials used and the reaction conditions chosen are such that the compounds mentioned above as being particularly preferred are obtained.

Starting materials of the formula II in which the amino group can be substituted by a group which can be acylated are known or can be obtained according to known methods.

Thus, the compounds of the formula IIa in which Y and Z are halogen, especially chlorine, can be obtained by reacting an amine of the formula R_1—H with a reactive derivative of formic acid, such as a 1,1-dihalogenomethyl alkyl ether, for example 1,1-dichlorodimethyl ether, or by using a formamide or thioformamide of the formula II as the starting compound and reacting this in a known manner with a halogenating agent, and either isolating the halogenoformiminium halide of the formula IIa, which is obtained in both cases, or using it further in situ.

Suitable halogenating agents are conventional halogenating agents, such as inorganic or organic acid halides, preferably those which decompose into reaction products which are volatile or can be separated off easily, especially chlorides, such as oxalyl chloride, phosgene, diphosgene (trichloromethyl chloroformate), phosphorus oxychloride, phosphorus pentachloride or thionyl chloride.

The reaction is in general carried out in an inert diluent or solvent, such as those mentioned above, especially in methylene chloride, chloroform, diethyl ether or toluene, at temperatures between −10 and +30°C. Compounds of the formula IIa in which Y is lower alkoxy, especially methoxy or ethoxy, and Z is the radical of an alkylating agent, especially halogen, the mono-lower alkyl-sulphate radical or tetrafluoborate, are obtained by reacting a formamide or thioformamide of the formula II with an alkylating agent. Suitable alkylating agents are conventional alkylating agents, for example lower alkyl halides, especially methyl iodide, di-lower alkyl-sulphates, for example dimethyl sulphate and diethyl sulphate, and also onium salts, for example of fluoboric acid or fluorosilicic acid, for example triethyloxonium tetrafluoborate. This reaction can be carried out in one of the inert solvents mentioned, at normal temperature or at temperatures up to the boiling point of the solvent.

The resulting iminium ether or iminium thioether salts of the formula IIa can be isolated and purified or, as described above, produced and used further in situ.

The formamide acetals and formamide thioacetals of the formula IIb can be obtained by allowing alcohols, such as lower alkanols, for example methanol or ethanol, to act on the iminium ether or iminium thioether salts described above, preferably in the presence of basic agents, for example the abovementioned tertiary amines or alcoholates, for example sodium methylate, or by treating an amine of the formula R_1—H with an activated or reactive derivative of orthoformic acid or thioorthoformic acid, such as an ester or amide acetal thereof, for example with an orthoester of formic acid or thioformic acid, preferably in the presence of Lewis catalysts, for example with trimethyl orthoformate or triethyl orthothioformate and $ZnCl_2$ or boron trifluoride etherate, or with a dimethylformamide diacetal, for example dimethylformamide dimethyl acetal, or by treating a formamide or thioformamide of the formula II in a manner known per se with an acetalising agent, such as a trialkyloxonium tetrafluoborate, for example triethyloxonium tetrafluoborate, and, if desired, subsequently treating the reaction product with an alkaline agent, for example with sodium methylate.

The reaction conditions are known and depend in particular on the vigour of the reaction to be expected. Thus, the reaction of an iminium ether salt with sodium methylate or an alcohol in the presence of a tertiary base is preferably carried out with cooling, for example at temperatures of −70°C to +10°C, it being possible, however, also to carry out the reaction at higher temperatures, i.e. for example, of up to 75°C, if the stability of the starting materials and of the reaction products permits a higher temperature.

The other reactions, for example, the reaction of dimethylformamide dimethyl acetal with an amine of the formula R_1—H, are preferably carried out in an inert solvent, or in an excess of the orthoformic acid derivative as a diluent, and, if desired, in order to accelerate the reaction, at the boiling point of this solvent or diluent.

The formamides or thioformamides of the formula II which can be used as starting materials can be obtained from the amines of the formula R_1—H using conventional formylating agents, for example chloral, for example by warming for several hours in an inert solvent, such as chloroform.

The amines of the formula R_1—H are known or can be prepared from known starting materials in a manner known per se or in an analogous manner.

In the process according to the invention and in any additional measures which may require to be carried out and also in the preparation of the starting materials it is possible, if necessary, temporarily to protect free functional groups, which do not participate in the reaction, in the starting materials or in the compounds obtainable according to the process, in a manner known per se, as described above, for example temporarily to protect free amino groups by acylation, tritylation or silylation, free hydroxyl or mercapto groups, for example, by etherification or esterification and free carboxyl groups, for example, by esterification, including silylation, and, in each case, after the reaction has taken place, to set these groups free, if desired, in a known per se, for example as described above, especially by solvolysis or reduction.

The pharmacologically acceptable compounds of the present invention can be used, for example, to prepare pharmaceutical preparations which contain an effective amount of the active substance or a mixture, such as one of the abovementioned mixtures of active ingredients, together with or mixed with conventional inorganic or organic, solid or liquid, pharmaceutically acceptable carriers or adjuncts, and are suitable for enteral or, preferably, parenteral administration or, in the case of preparations for the treatment of infections of the respiratory passages, in particular also for topical application (for example in the form of nosedrops), administration by inhalation (for example in the form of an aerosol spray) or buccal administration (for example in the form of lozenges). Thus, tablets or gelatin capsules are used which contain the active ingredient together with adjuncts, such as carriers and fillers or diluents, for example sucrose, lactose, dextrose, mannitol, sorbitol, cellulose or cellulose derivatives, such as methylcellulose, calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate and/or glycine, and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol; tablets also contain binders, for example magnesium aluminium silicate, starches, such as maize, corn, rice or arrowroot starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, dyes, flavourings and sweeteners. Furthermore, the novel pharmacologically active compounds can be used in the form of injectable preparations, for example preparations which can be administered intravenously, or of infusion, drip or inhalation solutions. Such solutions are preferably isotonic aqueous solutions or suspensions and these can, if desired, be prepared before use from lyophilised preparations which contain the active substance on its own, as a mixture 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, solubilising agents, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical preparations of this specification which, if desired, can contain further pharmacological valuable substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilising methods, and contain from 0.1% to 100% and especially from 1% to 50% of the active ingredient, and lyophilisates contain up to approximately 100% of the active ingredient.

The following examples illustrate the invention; temperatures are in degrees Centigrade. The solvent used in thin layer chromatography is:

System A=isopropanol/formic acid/water (77:4:19) (silica gel is used as the carrier medium and ampicillin as the reference substance).

Example 1

6β - [(3 - Azabicyclo[3.3.2]non - 3 - yl) - methyleneamino] - penicillanic acid is obtained by adding 5 g of 6 - aminopenicillanic acid all at once to a solution of 6.8 g of 3 - dimethoxymethyl - 3 - azabicyclo[3.2.2]nonane and 4.3 ml of diisopropylethylamine in 100 ml of absolute methylene chloride, at 0—5° under nitrogen as a blanketing gas, stirring the mixture at 0—5° for about 10 minutes, stirring the resulting clear solution for a further 3 hours at room temperature, removing the solvent in vacuo, dissolving the residue, which has solidified as a foam, in 70 ml of acetone, whereupon crystallisation starts, after which the pH value of the solution is adjusted to 7.0 by means of toluene - 4 - sulphonic acid, and filtering off the crystals, washing then with acetone and recrystallising them from ethanol.

The compound is in the form of its inner salt; melting point 169—170° (with decomposition); $[\alpha]_D^{20}=+281\pm1^\circ$ (0.5 N sodium bicarbonate); Rf 0.37 in system A (ampicillin=0.53); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.62 (shoulder), 5.67, 5.97 and 6.28μ.

The mono-hydrochloride of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) -

methyleneamino] - penicillanic acid is obtained as follows: 3.51 g (10 mmols) of the inner salt are dissolved in 50 ml of absolute chloroform, the equimolar amount of an approximately 5% strength solution of HCl in absolute ether is added and the crystalline product which precipitates on cooling and standing is filtered off with suction and washed several times with absolute ether.

3 - Dimethoxymethyl - 3 - azabicyclo[3.2.2]nonane, which is used as the starting material, can be obtained as follows: 25 g of commercially available azabicyclononane and 25 ml of dimethylformamide dimethyl acetal are refluxed for 2 hours and volatile constituents are then distilled off under normal pressure until the temperature of the distillate is 60° and the remaining residue, which is a clear liquid, is distilled under N_2 under an oil pump vacuum. Boiling point$_{0.1}$ 70°.

Example 2

6β - [(2 - Azatricyclo$[3.3.1.1^{3,7}]$dec - 2 - yl)methyleneamino] - penicillanic acid is obtained in the form of the monohydrate by reacting 5.4 g of 2 - dimethoxymethyl - 2 - azatricyclo$[3.3.1.1^{3,7}]$decane and 3.9 ml of diisopropylethylamine with 4.6 g of 6-aminopenicillanic acid in the manner described in Example 1. The product which has crystallised out is washed with 1,4-dioxane and recrystallised from isopropanol. Melting point: 172—174°; $[\alpha]_D^{20}=+236\pm1°$ (0.5 N $NaHCO_3$); Rf 0.35 in system A (ampicillin=0.50); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.65, 5.94, 6.16 and 6.26 (shoulder) μ.

The 2 - dimethoxymethyl - 2 - azatricyclo$[3.3.1.1^{3,7}]$decane used can be obtained analogously to Example 1, using 4.6 g of 2 - azatricyclo$[3.3.1.1^{3,7}]$decane (H. Stetter and K. Heckel, Chem. Ber. *106*, 339 (1973)) and 9.5 ml of dimethylformamide dimethyl acetal as the starting materials. Boiling point$_{0.1}$ 80°.

Example 3

6β - [(3 - Aza - 10 - oxatricyclo$[5.2.1.0^{1,5}]$dec - 3 - yl) - methyl - eneamino] - penicillanic acid is obtained in the form of the hemihydrate by reacting 2.1 g of 3 - dimethoxymethyl - 3 - aza - 10 - oxa - tricyclo$[5.2.1.0^{1,5}]$decane and 1.41 ml of diisopropylethylamine with 1.65 g of 6-aminopenicillanic acid in the manner described in Example 1. The pH of the reaction solution is adjusted to 5.5—6.0 with toluene - 4 - sulphonic acid and the product which crystallises out is filtered off with suction and washed with a large amount of acetone. Melting point: 163° (with decomposition); $[\alpha]_D^{20}=+246\pm1°$ (0.5 N $NaHCO_3$), Rf 0.25 in system A (ampicillin=0.55); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.63 (shoulder), 5.67, 5.97 and 6.27μ.

The starting material is obtained as follows:

a) 16.6 g of potassium carbonate are added to 18.7 g of N benzyl - 2 - furfurylamine (R. L. Hinmann and K. L. Hamm. J. Org. Chem *23*, 529 (1955)), dissolved in 120 ml of ethanol, 12.2 g of allyl bromide are then added dropwise at room temperature in the course of 15 minutes and the mixture is refluxed for 20 hours. After cooling, the mixture is filtered, the filtrate is evaporated in vacuo, the liquid residue is dissolved in 250 ml of ether, the solution is filtered to give a clear filterate, the latter is washed twice with, in each case, 100 ml of water and dried over sodium sulphate and the ether is removed in vacuo and the residue is distilled. This gives [21.2 g=93.4%] N - allyl - N - benzyl - 2 - furfurylamine: boiling point$_{0.001}$ 82—85°.

b) 2.3 g of N - allyl - B - benzyl - 2 - furfurylamine are added to a solution of 1.4 g of oxalic acid dihydrate in 12 ml of water, the resulting white suspension is filtered and the clear filtrate is refluxed for 20 hours. N - benzyl - 3 - aza - 10 - oxa - tricyclo$[5.2.1.0^{1,5}]$dec - 8 - ene monooxalate, which precipitates in the form of slightly brownish coloured crystals on cooling, is filtered off with suction. Melting point: 195—196°.

c) 82.5 ml of ethanolic hydrochloric acid (4.88 g of HCl/100 ml) and 2. g of Pd/charcoal (containing 5% of Pd) are added to a solution of 22.7 g of the base, liberated from the above monooxalate, in 200 ml of absolute ethanol and the mixture is hydrogenated under 1—4 bars until 4.61 litres of hydrogen have been taken up, the catalyst is filtered off, the filtrate is concentrated to 50 ml in vacuo and about 30 ml of ether are added at about 40°. The crystals of 3 - aza - 10 - oxatricyclo$[5.2.1.0^{1,5}]$decane hydrochloride which precipitate and have a melting point of 172—173° are filtered off with suction and the base is liberated therefrom in the conventional manner.

d) 3 - Dimethoxymethyl - 3 - aza - 10 - oxa - tricyclo[5.2.1.0^{1,5}]decane is obtained analogously to Example 1, using 6.9 g (0.05 mol) of the above base and 15 ml (0.114 mol) of N,N-dimethylformamide dimethyl acetal as the starting materials; boiling point$_{0.1}$ 92°.

Example 4

6β - [(4 - Azatricyclo[5.2.2.0^{2,6}]undec - 4 - yl) - methyleneamino] - penicillanic acid is obtained in the form of the hemihydrate by reacting 9.2 g of 4 - dimethoxymethyl - 4 - azatricyclo[5.2.2.0^{2,6}]undecane and 6 ml of diisopropylethylamine with 7.6 g of 6-aminopenicillanic acid in the manner described in Example 1. The pH of the reaction solution is adjusted to 5.5—6.0 with toluene - 4 - sulphonic acid and the product which crystallises out is filtered off with suction and washed with acetone. Melting point: 166° (with decomposition); $[\alpha]_D^{20}=271\pm1°$ (0.5 N $NaHCO_3$); Rf 0.36 in system A (ampicillin=0.49); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.65, 5.95 and 6.26μ.

The starting material 4 - dimethoxymethyl - 4 - azatricyclo[5.2.2.0^{2,6}]undecane is obtained analogously to Example I using 9.1 g of 4 - azatricyclo[5.2.2.0^{2,6}]undecane (M. Fumimoto and K. Okabe, Chem. Pharm. Bull. *10*, 714 (1962)) and 20 ml of dimethylformamide dimethyl acetal as the starting materials; boiling point$_{0.3}$ 119°.

Example 5

6β - [(4 - *endo* - Azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanic acid is obtained in the form of the hemihydrate by reacting 8.7 g of 4 - dimethoxymethyl - 4 - *endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - ene and 6 ml of diisopropylethylamine with 7.2 g of 6-aminopenicillanic acid in the manner described in Example 1, dissolving the evaporation residue in 80 ml of acetone, adjusting the pH of the solution to 5.5—6.0 with 5.6 g of toluene - 4 - sulphonic acid and filtering off, with suction, the crystals which precipitate, and washing them with acetone. Melting point: 166° (with decomposition); $[\alpha]_D^{20}=+262\pm1°$ (0.5 N $NaHCO_3$); Rf 0.37 in system A (ampicillin=0.49); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.65, 5.95 and 6.26μ.

The starting material 4 - dimethoxymethyl - 4 - endo - aza - tricyclo[5.2.2.0^{2,6}]undec - 8 - ene is obtained analogously to Example 1, using 10.8 g of 4 - *endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - ene (M. Fumimoto and K. Okabe, Chem. Pharm. Bull. *10*, 714 (1962)) and 24 ml of dimethylformamide dimethyl acetal as the starting materials. Boiling point$_{0.3}$ 116°.

Example 6

6β - [(3 - *endo* - Benzhydryloxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained by stirring a suspension of 1.3 g (6 mmols) of 6-aminopenicillanic acid in a solution of 2.4 ml (11.5 mmols) of hexamethyldisilazane and 50 ml of dry methylene chloride for 15 hours under reflux, cooling the resulting clear solution, adding 2.7 g (7.2 mmols) of 3 - endo - benzhydryloxy - 8 - chloro - formiminium - 8 - azabicyclo[3.2.1]octan chloride, dissolved in 20 ml of methylene chloride, stirring the mixture for a further one hour at room temperature, adding 15 ml of water dropwise, extracting the mixture three times with cold phosphate buffer of pH 7.8 and drying the organic layer over magnesium sulphate and evaporating it in vacuo. The residue is recrystallised from ether and then melts at 130° (with decomposition); $[\alpha]_D^{20}=151\pm1°$ (1% in chloroform); Rf 0.63 in system A (ampicillin=0.56); IR spectrum (in Nujol—Registered Trade Mark), bands at 5.67, 5.89 and 6.23μ.

The starting material can be obtained as follows:

a) 3 - Benzhydryloxynortropane hydrochloride (3.6 g; 0.9 mmol) (R. Banholzer, A. Heusner and W. Schulz, Annalen der Chemie *1975*, 2227) is partitioned between 100 ml of 2 N sodium hydroxide solution and 100 ml of chloroform, the chloroform solution is dried over magnesium sulphate and concentrated to 50 ml, 1.1 ml (11.5 mmols) of anhydrous chloral are added, the mixture is stirred overnight under reflux and evaporated, the residue is triturated with absolute ether, the material which is insoluble in ether is discarded, the clear ether solution is evaporated and the residue is recrystallised from cyclohexane. The resulting N - formyl - 3 - *endo* - benzhydryloxynortropane melts at 116—118°.

b) A solution of 0.72 ml (8.4 mmols) of oxalyl chloride in 5 ml of absolute ether is added dropwise to N - formyl - 3 - *endo* - benzhydryloxynortropane (2.6 g; 8.4 mmols) in 20 ml of absolute ether, at 0—5°, with stirring, the resulting mixture is then stirred overnight at room temperature and the highly hygroscopic 3 - *endo* - benzyloxy - 8 - azabicyclo[3.2.1]octan - 8 - yl chloroformiminium chloride, chloride is dried over phosphorus-V oxide under a high vacuum.

Example 7

6β - [(3 - *endo* - Benzyloxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained by stirring a suspension of 1.09 g (5 mmols) of 6-aminopenicillanic acid in a solution of 2 ml (10 mmols) of hexamethyldisilazane and 50 ml of dry methylene chloride for 15 hours under reflux, cooling the resulting clear solution, adding 1.7 g (5.7 mmols) of 3 - *endo* - benzyloxy - 8 - azabicyclo[3.2.1]octan - 8 - yl chloroforminium chloride, dissolved in 20 ml of methylene chloride, stirring the reaction mixture for a further one hour at room temperature, adding 12 ml of water, extracting the mixture three times with cold phosphate buffer of pH 7.8 and drying the organic phase over anhydrous magnesium sulphate and evaporating it in vacuo. The residue, which has been triturated with absolute ether, melts at 128° (with decomposition), $[\alpha]_D^{20}=+216\pm1°$ (1% in chloroform); Rf 0.53 in system A (ampicillin=0.56); IR spectrum (in Nujol—Registered Trade Mark); bands at 5.63, 5.82 and 6.26μ.

The starting material can be obtained as follows:

a) 4.1 g of a dispersion of sodium hydride in oil (containing 60% of NaH) (0.102 mols of NaH) are introduced into a dry stirred flask, washed three times with dry pentane and covered with a layer of absolute dimethylformamide, a solution of 6.81 g (0.048 mol) of commercially available tropine in 100 ml of dimethylformamide is added, the mixture is warmed carefully to 75°, whereupon a vigorous evolution of hydrogen starts, and is then stirred for a further 1 hour at 75° and cooled to room temperature, 8.24 ml (0.07 mol) of benzyl bromide in 50 ml of dimethylformamide are added dropwise, with vigorous stirring, the mixture is stirred overnight at 80° and evaporated in a rotary evaporator, the resinous residue is dried under a high vacuum at 0.1 mm Hg and partitioned between 2 N HBr and methylene chloride and the organic phase is washed twice with water, dried over magnesium sulphate and evaporated and this gives a brownish residue which, when recrystallised from acetone, gives 3 - *endo* - benzyloxy - 8 - methyl - 8 - azabicyclo[3.2.1]octane hydrobromide with a melting point of 202—204°.

b) The base liberated from the above hydrobromide is dissolved in 16 ml of absolute toluene, 30 ml of phosgene in toluene (20% strength) are added and the mixture is stirred for 3 days at room temperature. A small amount of material which has precipitated is filtered off and the clear filtrate is evaporated completely, whereupon 3 - *endo* - benzyloxy - 8 - chloroformyl - 8 - azabicyclo[3.2.1]octane is obtained in the form of a clear, virtually colourless oil.

c) The above intermediate (1.6 g=0.034 mol) is suspended in 500 ml of water in a 2 litre stirred flask, the suspension is stirred under reflux for 30 minutes and filtered hot and the clear solution is evaporated completely, whereupon colourless crystals are obtained which, when recrystallised from isopropanol, give 3 - *endo* - benzyloxynortropane hydrochloride with a melting point of 223—225°.

d) 1.07 ml (1.2 mmols) of anhydrous chloral are added to the base (2.4 g=11 mmols) liberated from the above hydrochloride, in 40 ml of chloroform, the mixture is stirred overnight under reflux and evaporated and the resulting colourless oil is dissolved in methylene chloride, the solution is filtered through 100 g of silica gel and the filtrate is evaporated, whereupon N - formyl - 3 - *endo* - benzyloxynortropane is obtained in the form of a colourless oil.

e) 3 - *endo* - Benzyloxy - 8 - azabicyclo[3.2.1]octan - 8 - yl chloroformiminium chloride is obtained analogously to Example 6b) from 1.9 g (7.75 mmols) of N - formyl - 3 - *endo* - benzyloxynortropane.

Example 8

8.4 ml (60 mmols) of triethylamine and then 6.6 g (20 mmols) of 3 - *endo* - (N,N - dimethylaminoacetoxy) - 8 - azabicyclo[3.2.1]octan - 8 - yl chloroformiminium chloride in 20 ml of methylene chloride are added to 50 ml of an ice-cold solution of trimethylsilyl 6 - amino - penicillanate in methylene chloride, prepared analogously to Example 7 from 4.32 g (20 mmols) of 6-aminopenicillanic acid. The mixture is stirred for 1 hour at room temperature and poured into 100 ml of ice-cold phosphate buffer solution of pH 7.8, the organic phase is separated off, dried over $MgSO_4$ and evaporated in vacuo and the residue is triturated with diethyl ether, whereupon 6β - [(3 - *endo* - (N,N - dimethylaminoacetoxy) - 8 -

azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained in crystalline form.

The starting material is prepared as follows:

a) 6.05 g (41 mmols) of chloral are added to 5.2 g (41 mmols) of nortropine [S. P. Findlay, J. Amer. Chem. Soc. 75, 3204 (1953)] in 100 ml of chloroform and the mixture is stirred overnight at 50°. It is evaporated in vacuo and the residue is stirred with 20 ml of anhydrous diethyl ether, whereupon N-formylnortropine with a melting poing of 105—110° is obtained.

b) 5.5 ml (32 mmols) of diisopropylethylamine are added to 5 g (32 mmols) of N-formylnortropine in 100 ml of absolute benzene and the mixture is cooled to 0—5°. A solution of 2.6 ml (32 mmols) of chloroacetyl chloride in 50 ml of benzene is added dropwise to this mixture at 0—5° and the resulting mixture is then stirred for 20 hours at room temperature. The mixture is extracted with water and the organic phase is dried over $MgSO_4$ and evaporated in vacuo. The residue is extracted with diethyl ether and the ether extract is filtered through about 50 g of silica gel and evaporated, whereupon 3 - *endo* - chloroacetyloxy - 8 - formyl - 8 - azabicyclo[3.2.1]octane is obtained in the form of a light brown oil.

c) 2.3 g (10 mmols) of the above chloroacetyloxy compound and 2.5 ml of a solution of dimethylamine in benzene (20% strength) are warmed at 80° in a bomb tube overnight. The mixture is evaporated completely in vacuo and the residue is partitioned between 50 ml of ice-cold phosphate buffer solution of pH 7.4 and 50 ml of methylene chloride. The organic phase is dried and evaporated in vacuo, whereupon 3 - *endo* - (N,N - dimethylaminoacetoxy) - 8 - formyl - 8 - azabicyclo[3.2.1]octane is obtained.

d). A solution of 0.86 ml (10 mmols) of oxalyl chloride in 5 ml of diethyl ether is added dropwise at 0—5° to 2.4 g (10 mmols) of the above compound in 40 ml of absolute diethyl ether and the mixture is then stirred overnight at room temperature. 3 - *endo* - (N,N - Dimethylaminoacetoxy) - 8 - aza - bicyclo[3.2.1]octan - 8 - yl chloroformiminium chloride, which has precipitated, is highly hygroscopic and is therefore employed after drying briefly over phosphorus-V oxide under a high vacuum, without further purification.

Example 9

Analogously to Example 8, 6β - [(3 - *endo* - (2 - benzyloxycarbonylacetyloxy) - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained from 4.32 g (20 mmols) of 6-aminopenicillanic acid and 7.48 g (20 mmols) of 3 - *endo* - (2 - benzyloxycarbonylacetyloxy) - 8 - azabicyclo[3.2.1]octan - 8 - yl - chloroformiminium chloride in the presence of 5.6 ml (40 mmols) of triethylamine and is hydrogenated with palladium - on - charcoal (10% of Pd) in methanol under normal pressure. The catalyst is filtered off, the filtrate is evaporated in vacuo and the residue is crystallised from diethyl ether, whereupon 6β - [(3 - *endo* - malonyloxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained.

a) The starting material required for this reaction is obtained by adding a solution of 7.1 g (33.6 mmols) of malonic acid chloride monobenzyl ester in 50 ml of benzene to 5 g (32 mmols) of the N-formylnortropine, described in Example 8, in 200 ml of absolute benzene in the presence of 4.9 g (38 mmols) of diisopropylethylamine, at 0—5°, and then stirring the mixture overnight at room temperature. The resulting 3 - *endo* - (2 - benzyloxycarbonylacetyloxy) - 8 - formyl - 8 - azabicyclo[3.2.1]octane is isolated in the form of a brown oil by pouring the solution on to dilute sodium bicarbonate solution and ice and separating off the organic phase, drying it over $MgSO_4$ and evaporating it. For further purification, the crude material is chromatographed on 200 g of silica gel and this gives a virtually colourless oil (6.6 g=20 mmols).

b) Analogously to the method described in Example 8, 3 - *endo* - (2 - benzyloxycarbonylacetyloxy) - 8 - aza - bicyclo[3.2.1]octane - 8 - yl - chloroformiminium chloride is obtained from 6.6 g (20 mmols) of the above product, by reacting it with 1.72 ml (20 mmols) of oxalyl chloride.

Example 10

Analogously to the method described in Example 8, pure 6β - [(3 - *endo* - (2 - dimethylaminoethoxy) - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid is obtained from 4.32 g (20 mmols) of 6-aminopenicillanic acid and

5.44 g (20 mmols) of 3 - *endo* - (2 - dimethylaminoethoxy) - 8 - chloroforminiminium - 8 - azabicyclo[3.2.1]octane chloride in the presence of 5.6 g (40 mmols) of triethylamine.

The starting material is prepared as follows:

a) 0.5 g of tetrabutylammonium bisulphate, 80 ml of toluene and 2.5 g (21 mmols) of 2-dimethylaminoethyl chloride are added to 15 ml of 50% strength sodium hydroxide solution. 3.1 g (20 mmols) of N-formylnortropine are added in portions to this mixture in the course of 1 hour, at room temperature, with stirring, and the mixture is then stirred for a further 1 hour. The organic phase is separated off, twice extracted by shaking with, in each case, 100 ml of water, dried over $MgSO_4$ and evaporated in vacuo. The crude 3 - *endo* - (2 - dimethylaminoethoxy) - 8 - formyl - 8 - azabicyclo[3.2.1]octane obtained in this way is reacted analogously to the method described in Example 9 b) with 1.72 ml (20 mmols) of oxalyl chloride and this gives 3 - *endo* - (2 - dimethylaminoethoxy) - 8 - azabicyclo[3.2.1]octan - 8 - yl - chloroformiminium chloride, which is dried over phosphorus-V oxide under a high vacuum.

Example 11

Phosgene is passed, at 0—5°, into a solution of 3.82 g (0.0115 mols) of 3 - *endo* - trichloroethoxycarbonyloxy - 8 - formyl - 8 - azabicyclo[3.2.1]octane in 150 ml of diethyl ether, in an apparatus dried under nitrogen, until no further precipitate forms. The 3 - *endo* - trichloroethoxycarbonyloxy 8 - azabicyclo[3.2.1]octan - 8 - yl - chloroformiminium chloride prepared in this way is filtered off under nitrogen and dissolved in 50 ml of chloroform and this solution is added dropwise at 0—5° in the course of 30 minutes to a solution of trimethylsilyl 6-aminopenicillanate, prepared from 2.16 g (0.01 mol) of 6-aminopenicillanic acid and hexamethyldisilazane in 100 ml of chloroform [K. W. Glombitza, Annalen der Chemie *673*, 166 (1964)]. The mixture is cooled to −10 to −15° and 3.75 ml of triethylamine are added dropwise at this temperature, whereupon a slight red coloration develops. After a further 30 minutes at this temperature, the mixture is evaporated completely at 0° and the residual solid foam is triturated with a solution of 0.5 ml of 2-butanol in 100 ml of diethyl ether. The virtually colourless powder is filtered off and dried over P_2O_5 in vacuo. 4.1 g of 6β - [3 - *endo* - trichloroethoxycarbonyloxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid with a melting point of 138° (with decomposition) are obtained in this way.

The starting material is prepared as follows:

a) 6.05 g (0.04 mol) of chloral are added to 5.2 g (0.041 mol) or nortropine in 100 ml of chloroform and the mixture is stirred for 16 hours at 50°. It is evaporated in vacuo and the residue is stirred with 20 ml of anhydrous diethyl ether, whereupon 4.4 g of N-formylnortropine with a melting point of 105—110° are obtained.

b) 11 ml (0.081 mol) of trichloroethyl chloroformate are added, at 0.5°, to 12.7 g (0.081 mol) of N-formylnortropine in 310 ml of anhydrous tetrahydrofurane. 6.6 ml (0.081 mol) of pyridine are then added dropwise in the course of 1 hour, with stirring, and the mixture is stirred for a further 1 hour at this temperature and then filtered and the filtrate is evaporated in vacuo. The residue is partitioned between water and methylene chloride and the organic phase is separated off and washed twice with water. Drying over sodium sulphate and evaporating in vacuo gives a colourless oil, which crystallises on the addition of 50 ml of diethyl ether 11.1 g of 3 - *endo* - trichloroethoxycarbonyloxy - 8 - formyl - 8 - azabicyclo[3.2.1]octane with a melting point of 115—116° are obtained in this way.

Example 12

500 mg (0.001 mol) of 6β - [(3 - *endo* - trichloroethoxycarbonyloxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid are dissolved in a mixture of 5 ml of glacial acetic acid and 5 ml of acetonitrile, and 650 mg (0.01 gram atom) of zinc powder are added to this solution at 0—5°, the addition being made in 100 mg portions in the course of 6 hours. The subsequent operations have to be carried out at 0—5°:

The excess zinc is filtered off and the filtrate is evaporated under a high vacuum. The yellow resinous residue is dissolved in 20 ml of water and hydrogen sulphide is passed into the mixture until no further precipitate forms. The mixture is filtered and the filtrate is extracted with three 50 ml portions of methylene chloride. Lyophilisation of the aqueous phase gives 135 mg of 6β - [(3 - endo -

hydroxy - 8 - aza - bicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid.

Example 13

551 mg (0.00328 mol) of N - formyl - N' - methylbispidine (=3 - formyl - 7 - methyl - 3,7 - diazabicyclo[3.3.1]nonane) are dissolved in 20 ml of diethyl ether, in an apparatus dried under nitrogen, and phosgene is passed into this solution at 0—5° until no further precipitate forms. The N - methylbispidine - yl - chloroformiminium chloride prepared in this way is filtered off under nitrogen and dissolved in 5 ml of chloroform and this solution is added dropwise at 0—5° in the course of 15 minutes to a solution of trimethylsilyl 6-aminopenicillanate, prepared from 648 mg (3.0 mmols) of 6-aminopenicillanic acid and hexamethyldisilazane in 20 ml of chloroform [K. W. Glombitza, Annalen der Chemie 673, 166 (1964)]. The mixture is stirred for a further 9 hours at this temperature and evaporated in vacuo. The resinous residue is stirred with a mixture of 0.2 ml of 2-butanol in 20 ml of diethyl ether and 909 mg of 6β - [(7 - methyl - 3,7 - diazabicyclo[3.3.1]non - 3 - yl) - methyleneamino] - penicillanic acid with a melting point of 160° (with decomposition) are obtained.

The starting material is prepared as follows:

0.527 g of chloral is added to 0.5 g (0.00358 mol) of N-methylbispidine [E. E. Smissman & P. C. Ruenitz, J. org. Chem. *41*, 1593 (1976)] dissolved in 10 ml of chloroform and the mixture is warmed at 50° for 15 hours. The cooled mixture is allowed to run through a 2 cm high column (diameter 2 cm) containing aluminium oxide and the column is rinsed with 50 ml of chloroform. After evaporating in vacuo, 551 mg of N - formyl - N' - methylbispidine are obtained and this is used without further purification.

Example 14

Pivaloyloxymethyl 6β - [(4 - *endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanate is obtained by stirring 5.0 g (0.013 mol) of 6β - [(4 - *endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanic acid (corresponding to Example 5) and 2 ml (0.015 mol) of triethylamine in 40 ml of dimethylformamide until a virtually clear solution forms, adding 1.95 g (0.013 mol) of pivaloyloxymethyl chloride all at once and stirring the mixture further overnight at room temperature, under nitrogen as a blanketing gas, removing the solvent in vacuo, stirring up the residue in ethyl acetate, filtering the resulting suspension, extracting the filtrate twice with ice-cooled saturated sodium bicarbonate solution and once with ice-water, drying it over magnesium sulphate and evaporating and recrystallising the residue, which has solidified as a foam, from 20 ml of diethyl ether.

For conversion to the hydrochloride, the above compound is dissolved in methylene chloride, the calculated amount of an ethereal solution of HCl is added and the hydrochloride is made to crystallise by adding further ether and is dried to give white crystals.

Example 15

Dry ampoules or phials containing 0.5 g of the inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid are prepared as follows:

Composition (for 1 ampoule or phial)

Inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid	0.5 g
Mannitol	0.05 g

A sterile aqueous solution of the inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid and of the mannitol is subjected to freeze-drying under aseptic conditions in 5 ml ampoules or 5 ml phials and the ampoules or phials are sealed and checked.

Dry ampoules containing the other active ingredients of the formula I described in the above examples, for example containing 6β - [(4 - azatricyclo[5.2.2.0^{2,6}]undec - 4 - yl) - methylene - amino] - penicillanic acid, 6β - [(*endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanic acid or pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanate, or a hydrate or pharamaceutically acceptable salt of these compounds, can be obtained in an analogous manner.

Example 16

Capsules containing 0.25 g of the inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid are prepared as follows:

Composition (for 1,000 capsules):

Inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid	250.000 g
Maize starch	50.000 g
Polyvinylpyrrolidone	15.000 g
Magnesium stearate	5.000 g
Ethanol	q.s.

The inner salt of 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid and the maize starch are mixed and the mixture is moistened with a solution of the polyvinylpyrrolidone in 50 g of ethanol. The moist mass is pressed through a sieve with a mesh width of 3 mm and dried at 45°. The dry granules are forced through a sieve with a mesh width of 1 mm and mixed with 5 g of magnesium stearate. The mixture is filled, in 0.320 g portions, into hard gelatin capsules.

Capsules containing other active ingredients of the formula I described in the above example, for example containing 6β - [(2 - azatricyclo[3.3.1.$1^{3,7}$]dec - 2 - yl) - methyleneamino] - penicillanic acid monohydrate and 6β - [(3 - *endo* - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid, 6β - [(4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 4 - yl) - methyleneamino] - penicillanic acid, 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanic acid or pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate, can be obtained in an analogous manner.

Example 17

Capsules which each contain 0.200 g of the hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate and 0.04 g of trimethoprim are prepared by the following procedure:

Constituents:

The hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate	200 g
Trimethoprim	40 g
Polyvinylpyrrolidone	10 g
Magnesium stearate	4 g

The hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate and the trimethoprim are mixed and the mixture is passed through a 0.84 mm sieve (20 US Standard mesh). After mixing again, the resulting powder is moistened with a solution of polyvinylpyrrolidone in 150 ml of isopropanol. The moistened mixture is granulated by passing it through a 0.84 mm sieve (20 US Standard mesh) and is then dried at 30°C. A conventional drying oven with compartments or another suitable drying apparatus, which operates, for example, on the fluid bed principle, can be used for the drying operation.

After drying, the granules are passed through a 0.70 mm sieve (25 US Standard mesh) and finally mixed with the magnesium stearate.

The granules, which are now ready to use, are filled into No. 1 hard gelatin capsules, each capsule containing about 0.260 g of granules comprising the above constituents; this corresponds to about 1,000 capsules.

Example 18

Tablets which each contain 0.200 g of the hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate and 0.020 g of trimethoprim are prepared by the following procedure:

Constituents:

The hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - enyl) - methyleneamino] - penicillanate	200 g

Trimethoprim	20 g
Polyvinylpyrrolidone	10 g
Microcrystalline cellulose	175 g
Starch	80 g
Magnesium stearate	4 g

The hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanate and the trimethoprim are mixed and sieved as indicated in Example 17. After mixing again, the resulting powder is moistened with 100 ml of a solution of polyvinylpyrrolidone in isopropanol. The moistened mixture is granulated by sieving it through a 0.84 mm sieve (20 US Standard mesh) and is then dried at 30°C. After drying, the granules are passed through a 0.70 mm sieve (25 US Standard mesh) and are then mixed with the microcrystalline cellulose, the starch and the magnesium stearate. Using presses with a diameter of 12 mm, the granules are compressed to tablets which each contain about 0.500 g of the above constituents; this corresponds to 1,000 tablets.

Example 19

Following the procedure described in Example 17, a tablet is prepared which has the following composition:

Constituents for 1,000 tablets:

Pivaloyloxymethyl 6β - [(*endo* - azatricyclo-[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanate	250 g
Trimethoprim	100 g
Polyvinylpyrrolidone	10 g
Microcrystalline cellulose	175 g
Starch	80 g
Magnesium stearate	5 g

Each tablet weighs about 0.625 g

Example 20

The following mixture is prepared for peroral administration. which can be used in particular for the treatment of infections of the respiratory passages; this mixture is intended for preparation in the form of a suspension in water or in another potable liquid immediately before use. The mixture consists of the dose of the following constituents:

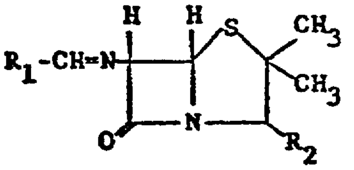
Pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.0^{2,6}]-undec - 8 - enyl) - methyleneamino] - penicillanate	100 mg
Trimethoprim	20 mg
Methylcellulose	10 mg
Sugar	2.5 mg
Saccharin sodium	8 mg
Aroma, as desired	

This dose is intended for suspension in approximately 5 ml of a suitable liquid.

In Examples 19—20, it is also possible to use, in place of the pivaloyloxymethyl ester, the hydrochloride of pivaloyloxymethyl 6β - [(*endo* - azatricyclo[5.2.2.0^{2,6}]undec - 8 - enyl) - methyleneamino] - penicillanate or one of the other compounds mentioned in Example 15 and 16, or a salt thereof.

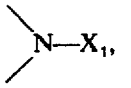
WHAT WE CLAIM IS:—

1. A 6 - amino - penam compound of the formula



(I)

wherein R_1 is an azapolycycloalkyl radical bonded via the ring nitrogen atom and containing at least one *endo*-bridge atom and a total of 7 to 12 ring atoms and which radical R_1 can contain a double bond and/or, an oxa group or a group



wherein X_1 denotes hydrogen or lower alkyl, and/or, which radical R_1 can contain free, esterified or etherified hydroxyl bonded to a ring carbon atom, and wherein R_2 is free carboxyl or carboxyl esterified by a physiologically detachable group, or a salt of such a compound.

2. A 6 - amino - penam compound of the formula I according to claim 1, wherein R_1 is an azabicycloalkyl, azabicycloalkenyl, oxaazabicycloalkyl, diazabicycloalkyl, azatricycloalkyl, azatricycloalkenyl, oxaazatricycloalkyl or diazatricycloalkyl bonded via the ring nitrogen atom and containing at least one *endo*-bridge atom and a total of 8—11 ring atoms, in which a ring carbon atom can be substituted by a free, esterified or etherified hydroxyl group and/or in which a second ring nitrogen atom which may be contained in a radical R_1 is substituted by a radical X_1, wherein X_1 denotes hydrogen or lower alkyl, and wherein R_2 is as defined in claim 1, or a salt of such a compound.

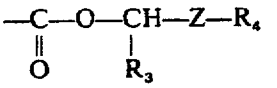
3. A 6 - amino - penam compound of formula I according to claim 1, wherein R_1 is azabicyclooctyl, azabicyclononyl, oxaazabicyclononyl, diazabicyclononyl, azatricyclodecyl, azatricycloundecyl, azatricyclodecenyl, azatricycloundecenyl, oxaazatricyclodecyl, 3,10 - diaza - tricyclo[5.2.1.$0^{1,5}$] - dec - 3 - yl, 3 - endo - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl, the hydroxyl group of which is free, esterified or etherified, or a 3,7 - diazabicyclo[3.3.1]non - 3 - yl substituted in the 7-position by lower alkyl, and wherein R_2 is as defined in claim 1, or a salt of such a compound.

4. A 6 - amino - penam compound of formula I according to claim 1, wherein R_1 is 8 - azabicyclo[3.2.1]oct - 8 - yl, 3 - azabicyclo[3.2.2]non - 3 - yl, 9 - azabicyclo[3.3.1]non - 9 - yl, 7 - methyl - 3,7 - diazabicyclo[3.3.1]non - 3 - yl, 2 - azatricyclo[3.3.1.$1^{3,7}$]dec - 2 - yl, 4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 4 - yl, 4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - en - 4 - yl, 10 - oxa - 3 - azatricyclo[5.2.1.$0^{1,5}$]dec - 3 - yl, 10 - methyl - 3,10 - diaza - tricyclo - [5.2.1.$0^{1,5}$]dec - 3 - yl - or 3 - *endo* - hydroxy - 8 - azabicyclo[3.2.1] - oct - 8 - yl, the hydroxyl of which can be esterified by lower alkanoyl, carboxyl-lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, lower alkixycarbonyl monosubstituted to trisubstituted by chlorine, benzoyl, nicotinoyl, carbamoyl or toluenesulphonyl or can be etherified by lower alkyl, lower alkyl monosubstituted to trisubstituted by lower alkoxy, carboxyl, di-lower alkylamino, phenyl or anisyl, and R_2 is carboxyl, pivaloyloxymethoxycarbonyl, lower alkoxymethoxycarbonyl, or phthalidyloxycarbonyl, or a pharmaceutically acceptable salt of such a compound.

5. 6β - [(3 - *endo* - Hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid, according to claim 1, the 3-hydroxyl group of which is etherified by benzyl, benzhydryl or dimethylaminoethyl or esterified by dimethylaminoacetyl, malonyl or trichloroethoxycarbonyl, or a pharmaceutically acceptable salt thereof.

6. A physiologically splittable ester of 6β - [(4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - en - 4 - yl) - methyleneamino] - penicillanic acid or 6β - [(4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 4 - yl) - methyleneamino] - penicillanic acid, according to claim 1, or a pharmaceutically acceptable salt thereof.

7. A 6 - amino - penam compound of the formula I according to any one of claims 1 to 3, wherein R_1 is as defined in claim 1 and wherein R_2 is esterified by a physiologically detachable group of the formula



$$-\underset{\displaystyle O}{\underset{\|}{C}}-O-\underset{\displaystyle R_3}{\underset{|}{CH}}-Z-R_4 \qquad (A)$$

in which R_3 is hydrogen or a lower alkyl radical having 1—3 carbon atoms, R_4 is the acyl radical of a substituted or unsubstituted mono-, di- or poly-carboxylic acid, or of an aliphatic or aromatic sulphonic acid having up to 18 carbon atoms, lower alkoxycarbonyl, lower alkyl substituted by hydroxyl, lower alkoxy, amino, di-lower alkyl-amino, cycloalkyl having 3—7 carbon atoms, phenyl, phenyl substituted by chlorine, hydroxyl or methoxy, phenyl-lower alkyl, wherein phenyl is substituted by chlorine, hydroxyl or methoxy or a five-membered or six-membered heterocyclic structure which has 1 to 2 ring oxygen, sulphur or nitrogen atoms in the position adjacent to the bonding carbon atom, and Z is oxygen, sulfur, sulphinyl, sulphonyl, imino or lower alkylimino or in which the grouping $—CH(R_3)—Z—R_4$ or $—Z—R_4$ is a constituent of a heterocyclic ring system, or a salt of such a compound.

8. 6β - [(3 - *endo* - Hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

9. 6β - [(3 - Azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

10. 6β - [(7 - Methyl - 3,7 - diazabicyclo[3.3.1]non - 3 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

11. 6β - [(2 - Azatricyclo[3.3.1.1^{3,7}]dec - 2 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

12. 6β - [(3 - Aza - 10 - oxatricyclo[5.2.1.0^{1,5}]dec - 3 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

13. 6β - [(4 - Azatricyclo[5.2.2.0^{2,6}]undec - 4 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

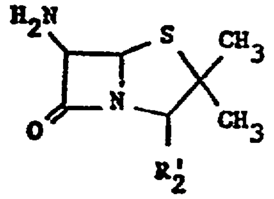
14. 6β - [(4 - *endo* - Azatricyclo[5.2.2.0^{2,6}]undec - 8 - en - 4 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof, according to claim 1.

15. Pivaloyloxymethyl - 6β - [(4 - *endo* - azatricyclo[5.2.2.0^{2,6}] - undec - 8 - enyl) - methyleneamino] - penicillanate or a pharmaceutically acceptable salt thereof, according to claim 1.

16. A process for the preparation of a 6 - amino - penam compound of formula I, wherein R_1 and R_2 are as defined in claim 1, or a salt of such a compound, which comprises reacting a formamide or thioformamide, which can be activated, of the formula II

$$R_1—CH=X \qquad (II)$$

in which X is oxygen or sulphur and R_1 is as defined under formula I, and in which functional groups present in R_1 can be protected, or a reactive derivative of such a formamide or thioformamide, with a 6-aminopenam derivative of hye formula III

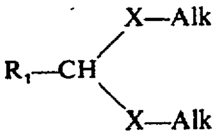


wherein the 6-amino group is in a free or protected form and R_2' is free carboxyl or protected carboxyl, or with an inorganic or organic salt of such compound, and in a resulting compound, wherein R_2' denotes protected carboxyl, the protected carboxyl group is converted into a free carboxyl group or a carboxyl group esterified by a physiologically detachable group, and/or, if desired, protected functional groups present are converted into the free functional groups, and/or, within the definition of the final products, a resulting compound of formula I is converted into another compound of formula I, and/or, if desired, a resulting mixture of isomers is converted into the single isomers.

17. A process according to claim 16, which comprises using as the reactive derivative of a formamide or thioformamide of formula II a formiminium salt of the formula

$$[R_1{=}CH—Y]^{\oplus}Z^{\ominus} \qquad (IIa)$$

in which R_1 is as defined in claim 1 and free functional groups present in R_1 can be protected, Y is halogen, or lower alkoxy which is unsubstituted or substituted by phenyl, lower alkoxy or halogen, and Z is halogen or the anionic radical of an alkylating agent, or a formamide acetal or formamide thioacetal of the formula



$$R_1\text{—}CH\begin{matrix}\diagup X\text{—}Alk \\ \diagdown X\text{—}Alk\end{matrix}$$

(IIb)

in which R_1 is as defined in claim 1 and X is as defined in claim 16 and Alk is lower alkyl, which is unsubstituted or substituted by phenyl, lower alkoxy or halogen.

18. A process according to either of claims 16 and 17, which comprises using as the reactive derivative of a formamide or thioformamide of the formula II a formiminium salt of formula IIa, in which R_1 is as defined in claim 1 and free functional groups present in R_1 can be protected, Y is chlorine, methoxy, ethoxy or benzyloxy and Z is chlorine, bromine, iodine, monomethyl-sulphate, monoethylsulphate, dimethylphosphate or tetrafluoroborate, or a formamide acetal or formamide thioacetal of formula IIb, in which R_1 is as defined in claim 1 and X is as defined in claim 16 and Alk is methyl or ethyl.

19. A process according to any one of claims 16 to 18, which comprises producing and reacting the reactive derivative of a formamide or thioformamide of the formula II which is used in situ.

20. A process according to any one of claims 16 to 19, which comprises forming the reactive derivative of a formamide or thioformamide of formula II in situ from an amine of the formula R_1—H and a condensing agent which supplies the amidine carbon atom or from a formamide or thioformamide of formula II, if necessary after the addition of reaction-promoting substances, and reacting it with an amine of the formula III which can be protected.

21. A process according to claim 20, which comprises using a reactive derivative of orthoformic acid as the condensing agent which supplies the amidine carbon atoms.

22. A process according to claim 21, which comprises using an orthoformate, thioorthoformate, di-lower alkylformamine diacetal or 1,1-dihalogenomethyl lower alkyl ether as the reactive derivative of orthoformic acid.

23. A process according to any one of claims 20 to 22, which comprises using Lewis acid and/or a strong organic base as reaction-promoting substances.

24. A process according to any one of claims 16 to 23, which comprises the preparation of a compound of formula I, wherein R_1 is as defined as in claim 2 and R_2 is as defined as in claim 1, or a salt of such compound.

25. A process according to any one of claims 16 to 23, which comprises the preparation of a compound of formula I, wherein R_1 and R_2 are as defined as in claim 4, or a pharmaceutically acceptable salt of such compound.

26. A process according to any one of claims 16 to 23, which comprises the preparation of 6β - [(3 - *endo* - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid, the 3-hydroxyl group of which is etherified by benzyl, benzhydryl or dimethylaminoethyl or sterified by dimethylaminoacetyl, malonyl or trichloroethoxycarbonyl, or a pharmaceutically acceptable salt thereof.

27. A process according to any one of claims 16 to 23, which comprises the preparation of a physiologically splittable ester of 6β - [4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - en - 4 - yl) - methyleneamino] - penicillanic acid or 6β - [(4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 4 - yl) - methyleneamino] - penicillanic acid, or a pharmaceutically acceptable salt thereof.

28. A process according to any one of claims 16 to 23, which comprises the preparation of 6β - [(3 - *endo* - hydroxy - 8 - azabicyclo[3.2.1]oct - 8 - yl) - methyleneamino] - penicillanic acid, 6β - [(3 - azabicyclo[3.2.2]non - 3 - yl) - methyleneamino] - penicillanic acid, 6β - [(7 - methyl - 3,7 - diazabicyclo[3.3.1] - non - 3 - yl) - methyleneamino] - penicillanic acid, 6β - [(2 - azatricyclo[3.3.$1^{3,7}$]dec - 2 - yl) - methyleneamino] - penicillanic acid, 6β - [(3 - aza - 10 - oxatricyclo[5.2.1.$0^{1,5}$]dec - 3 - yl) - methyleneamino] - penicillanic acid or 6β - [(4 - azatricyclo[5.2.2.$0^{2,6}$]undec - 4 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof.

29. A process according to any one of claims 16 to 23, which comprises the preparation of 6β - [(4 - *endo* - azatricyclo[5.2.2.$0^{2,6}$]undec - 8 - en - 4 - yl) - methyleneamino] - penicillanic acid or a pharmaceutically acceptable salt thereof.

30. A process according to any one of claims 16 to 23, which comprises the preparation of pivaloyloxymethyl 6β - [(3 - *endo* - azatricyclo[5.2.2.$0^{2.6}$]undec - 8 - enyl) - methyleneamino] - penicillanate or a pharmaceutically acceptable salt thereof.

31. The processes for the preparation of compounds of formula I described in examples 1 to 14.

32. The compounds of formula I obtainable by the processes of claims 16 to 30.

33. The compounds of formula I obtainable by the processes of examples 1 to 14.

34. A pharmaceutical preparation containing a compound according to claim 1 to 15 and conventional pharmaceutical additives and/or carriers.

35. A mixture containing a compound of the formula I according to any one of claims 1 to 15 and further substances having an antimicrobial action.

36. A pharmaceutical preparation containing a mixture according to claim 35 and conventional pharmaceutical additives and/or carriers.

37. The use of the substances and substance mixtures according to claims 1 to 15, and 34—36 for combatting microorganisms in warm blooded animals other than human beings.

38. The use of a compound of the formula I according to claims 1 to 15 or of a substance mixture according to either of claims 35 or 36 for the preparation of a medicament by non-chemical means.

39. A pharmaceutical preparation containing a compound of formula I and further antimicrobial active ingredients or a mixture of antibacterial substances and/or an additional substance which alleviates the symptoms in the case of infections of the respiratory passages, or a mixture of such substances, it being possible for the active substances also to be present in the form of pharmaceutically acceptable salts.

40. A pharmaceutical preparation according to claim 39, containing a compound of the formula I or pharmaceutically acceptable salt thereof, mixed with a compound of the adamantane type which has an antiviral action and/or a substance having an antibacterial action from the group of antibiotics, or a sulphonamide on its own or in combination with trimethoprim and/or a substance which facilitates breathing, it being possible for the active compounds to be present in the form of physiologically acceptable, non-toxic acid addition salts or of physiologically acceptable, non-toxic salts with bases.

41. A pharmaceutical preparation according to either of claims 39 and 40, containing a compound of the formula I or a physiologically acceptable salt, thereof and a compound of the adamantane type which has an antiviral action in combination with a compound which facilitates breathing.

42. A pharmaceutical preparation according to either of claims 39 and 40 containing a compound of the formula I or a physiologically acceptable salt thereof in combination with a 5:1 mixture of sulfamethoxazole and trimethoprim.

43. A pharmaceutical preparation according to any one of claims 39 and 40, containing further pharmacologically active compounds.

44. A pharmaceutical preparation according to either of claims 39 and 40, containing 6β - [(*endo* - azatricyclo[5.2.2.$0^{2.6}$]undec - 8 - en - 4 - yl) - methyleneamino - penicillanic acid or pivaloyloxymethyl - 6β - [(*endo* - azatricyclo[5.2.2.$0^{2.6}$]undec - 8 - en - 4 - yl) - methyleneamino - penicillanate or a physiologically acceptable salt thereof and additionally, as a compound having an antiviral action, 1 - amino - adamantane or a physiologically acceptable, non-toxic acid additon salt thereof, and/or, as a compound having an action against bacterial infections of the respiratory passages, ampicillin, bacampicillin, dihydroampicillin, amoxicillin, penicillin G, penicillin V, cefamandole, 7β - [4 - (2 - iminothiazolidinyl) - acetamido] - 3 - [1 - (2 - dimethylaminoethyl) - tetrazol - 5 - yl - thiomethyl] - 3 - cephem - 4 - carboxylic acid, erythromycin, sulfamethoxazole, trimethoprim or a 5:1 mixture of sulfamethoxazole and trimethoprim, or physiologically acceptable salts thereof.

45. A pharmaceutical preparation according to any one of claims 39 to 44 containing carriers and adjuncts, in an administration form suitable for oral, nasal or buccal administration or for administration by inhalation.

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