(12) UK Patent Application (19) GB (11) 2 080 793 A

(21) Application No **8118908**
(22) Date of filing **19 Jun 1981**
(30) Priority data
(31) **3028451**
(32) **26 Jul 1980**
(33) **Fed. Rep of Germany (DE)**
(43) Application published **10 Feb 1982**
(51) **INT CL³**
C07D 499/68
A61K 31/43 31/505 31/545
C07D 501/20
(C07D 257/00 279/00 285/00)
(C07D 499/68 239/00 277/00)
(C07D 501/20 205/00 213/00 253/00)
(52) Domestic classification
C2C 1173 1313 1314 1377 1440 1464 1601 1602 214 215 220 221 225 226 22Y 250 252 255 256 25Y 28X 292 29Y 305 30Y 322 328 32Y 33Y 340 341 342 34Y 351 352 358 360 361 362 365 366 367 368 36Y 373 37Y 385 396 397 510 51X 536 613 614 620 628 638 652 660 662 670 699 801 80Y AA KE RP SF
(56) Documents cited
None
(58) Field of search
C2C
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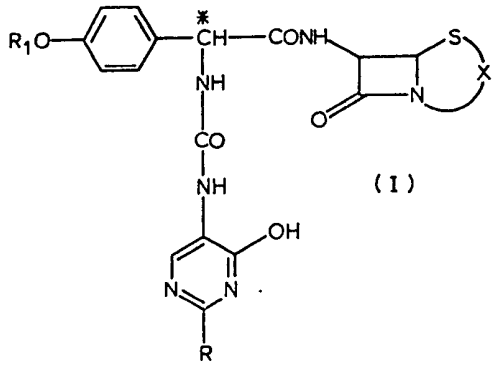
(54) **New lactams, processes for their preparation, and pharmaceutical compositions containing these compounds**

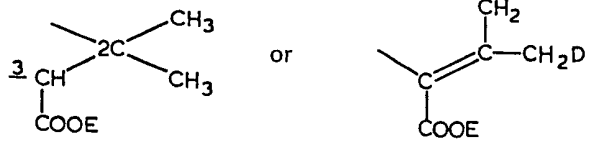
(57) Novel β-lactams of the general formula (1) are disclosed:



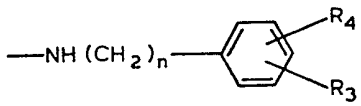
(I)

wherein:

R_1 represents an aliphatic acyl or alkoxycarbonyl group or the aminocarbonyl group, and X represents the group



wherein D represents an hydrogen atom; an acetoxy; aminocarbonyloxy; pyridinium; or 4-aminocarbonyl-pyridinium group; or a group —SHet (Het represents, for example, the 1-methyl-tetrazole-5-yl radical), and E represents an hydrogen atom or an *in vitro* or *in vivo* readily cleavable protective group, and R represents an hydrogen atom; the cyclopropyl group; a lower hydroxyalkylamino group; an amino; alkyl; or alkenylamino group; a cycloalkylamino group; or a group of the general formula:



wherein

n represents the number 0 or 1, and R_3 and R_4 represent hydrogen atoms; hydroxy; acetylamino; aminocarbonylamino; nitro; aminocarbonyl; cyano; methylsufinyl; methylsulfonyl; aminosulfonyl; or methylaminosulfonyl groups.

Salts of the compounds (I) with inorganic or organic bases, 3 processes for the preparation of these compounds and pharmaceutical compositions containing these compounds are also described.

The compounds of the general formula (I) have additionally an activity against gram-positive and especially against gram-negative bacteria and micro-organisms similar to bacteria; the compounds being distinguished especially by a broad spectrum of activity.

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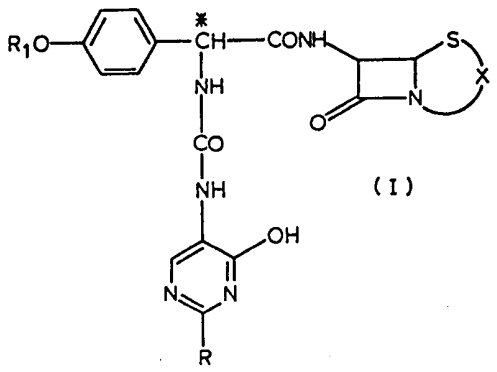
SPECIFICATION

New lactams, processes for their preparation, and pharmaceutical compositions containing these compounds

This invention relates to new β-lactams of the general formula (I):



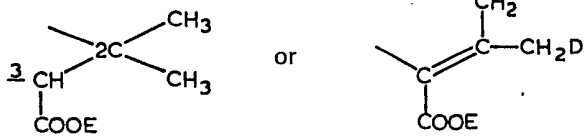
(I)

optionally, to their physiologically compatible salts with inorganic or organic bases, to processes for the preparation of these compounds, and to pharmaceutical compositions containing these compounds.

In the general formula (I):

R_1 represents an aliphatic acyl or alkoxycarbonyl group with 2 to 5 carbon atoms, or the aminocarbonyl group,

X represents the group:

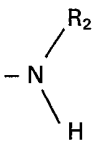


wherein;

D represents an hydrogen atom; an acetoxy, aminocarbonyloxy, pyridinium or 4-aminocarbonylpyridinium group; or the group SHet, in which Het represents the 1-methyl-tetrazole-5-yl, 1,2,4, thiadiazole-5-yl, 3-methyl-1,2,4-thiadiazole-5-yl, 1,3,4-thiadiazole-2-yl, 2-methyl-1,3,4-thiadiazole-5-yl, or 4-methyl-5,6-dioxo-1,2,4-triazine-3-yl group, and

E represents an hydrogen atom or an *in vitro* or *in vivo* readily cleavable protective group, and

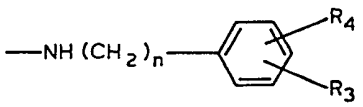
R represents an hydrogen atom; the cyclopropyl group; the 2'-hydroxyethylamino group; the 3'-hydroxypropylamino group; or the 4'-hydroxycyclohexylamino group; or a group of the general formula:



wherein:

R_2 represents hydrogen; a branched or unbranched alkyl or alkenyl group with 1 to 4 carbon atoms; or a cycloalkyl radical with 3 to 6 carbon atoms, or

R represents a group of the general formula:



wherein;

$n = 0$ or 1, and

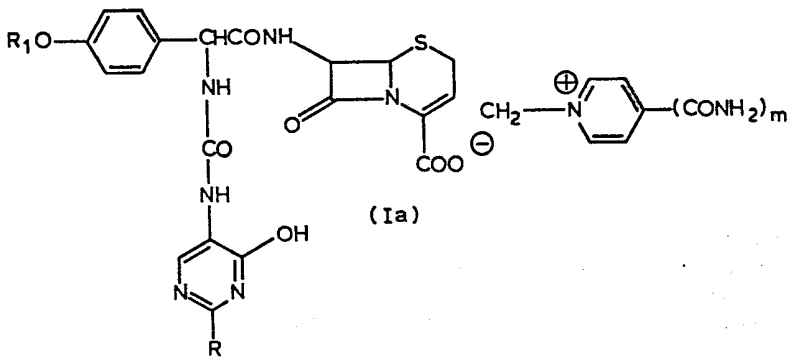
R_3 and R_4, which may be the same or different, represent hydrogen atoms; or the hydroxy; acetylamino;

aminocarbonylamino; nitro; aminocarbonyl; cyano; methylsulfinyl; methylsulfonyl; aminosulfonyl; or methylaminosulfonyl group.

Carboxyl groups protecting the group E may include, for example, those conventionally employed in the field of penicillins and cephalosporins, especially ester-forming groups which can be removed by hydrogenolysis or hydrolysis or other treatments under mild conditions as well as ester-forming groups which can be easily split off in the living organism. Examples of protective groups easily split off *in vitro* are, for example, the benzyl, diphenylmethyl, trityl, *t*-butyl, 2,2,2-trichloroethyl or trimethylsilyl group.

Where E represents a hydrogen atom, pharmaceutically compatible salts, such as, for example, alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, ammonium salts and organic amine salts, for example with triethylamine and dicyclohexylamine, also come within the scope of the invention.

If D represents pyridinium or aminocarbonyl-pyridinium, then the compounds of the invention have the general formula (Ia):



(Ia)

wherein:

m represents the number 0 or 1.

Preferred compounds are those of the general formula (I), wherein:

R_1 represents a methoxycarbonyl, ethoxycarbonyl, acetyl or aminocarbonyl group,

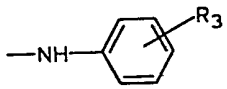
X is as defined above, in which:

E represents an hydrogen atom, and

D represents an hydrogen atom, the acetoxy group or the group SHet, in which Het represents the 1-methyltetrazole-5-yl, 1,3,4, thiadiazole-5-yl or 2-methyl-1,3,4-thiadiazole-5-yl group; and

R has the meanings given above.

An especially preferred form of the invention is that in which R represents the group of the general formula:



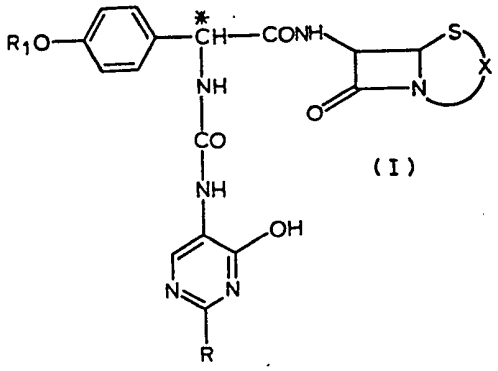
wherein:

R_3 represents the hydroxy; methylsulfinyl; methylsulfonyl; aminocarbonyl; aminocarbonylamino; aminosulfonyl; or methylaminosulfonyl group, or

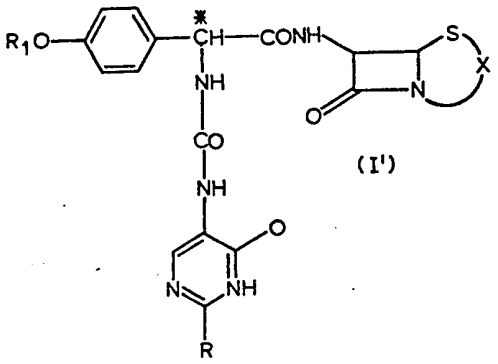
R represents the *m*-hydroxy-*p*-aminosulfonylanilino; cyclopropyl; propylamino; isopropylamino; cyclopentylamino; cyclohexylamino; 3'-hydroxy-propylamino; or 4'-hydroxycyclohexylamino group, and

R_1 and X are as defined above.

The β-lactams of the general formula (I) can be present in two tautomeric forms (namely of the lactim and lactam type). Which form predominates depends especially on the solvent used and on the nature of the substituent R:



(I)



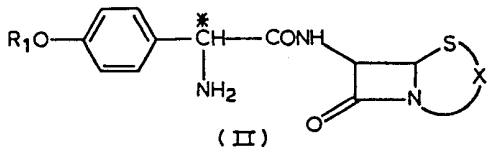
(I')

It will be understood that the compounds of the general formula (I) mentioned above always comprise both tautomers.

Due to the chiral centre denoted C+, the compounds of the invention may be present in either the R or the S configuration, or as a mixture of these two configurations. Especially preferred are those compounds having the D = R configuration. When the end-product is obtained in the D,L-form, the pure D- and L-diastereoisomers can be prepared by preparative liquid chromatography (HPCL).

The compounds of the general formula (I) may be prepared as follows:

1. Compounds of the general formula (I), wherein D has the meanings given above except for that of a pyridinium or aminocarbonylpyridinium group, by the reaction of a compound of the general formula (II):

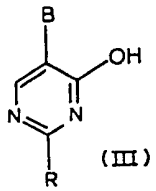


(II)

wherein:

R_1 and X have the meanings given above and

D has the meanings given above except for that of a pyridinium or aminocarbonylpyridinium group, with a pyrimidine derivative of the general formula (III):

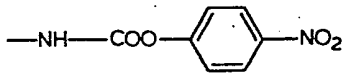


(III)

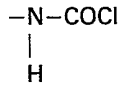
wherein:

R is as defined above and

B represents the group —NCO or a reactive derivative of the group —NHCOOH, e.g. the group —NHCOCl, —NHCOBr or



the groups —NCO and —NHCOCl being especially preferred. Also, mixtures of such pyrimidine derivatives of the general formula (III) can be used, wherein the groups B have partly one and partly another of the meanings given above, e.g., the groups —NCO and



simultaneously.

If E, in the compound of the formula (II), represents an hydrogen atom, then an inorganic or an organic salt, e.g., the triethylammonium salt or the sodium salt, can be used. The reaction can then conveniently be effected in a mixture of water with any organic solvent which is miscible with water, such as, e.g., ketones, for example, acetone, cyclic ethers, for example, tetrahydrofuran or dioxan, nitriles, for example acetonitrile, formamides, for example, dimethylformamide, dimethylsulfoxide or alcohol, for example, isopropanol, or in hexametapol. The pH value of the reaction mixture is generally kept within a pH range of from 2.0 to 9.0, preferably from 6.5 to 8.0, by the addition of bases or by the use of buffer solutions. However, it is also possible to effect the reaction in an anhydrous organic solvent, for example, an halogenated hydrocarbon such as, e.g., chloroform or methylene chloride with the addition of a base, preferably triethylamine, diethylamine or N-ethylpiperidine. Furthermore, the reaction can be effected in a mixture of water and a solvent immiscible with water, such as, e.g., an ether, for example, diethylether, an halogenated hydrocarbon, for example, chloroform or methylene chloride, carbon disulfide, a ketone, for example, isobutyl methyl ketone, an ester, for example, ethyl acetate, or aromatic solvent, for example, benzene. Again, it is generally appropriate to keep the pH value in a range of from 2.0 to 9.0, preferably from 6.5 and 8.0, by the addition of a base or the use of a buffer solution. Furthermore, it is desirable to stir the reaction mixture vigorously. The reaction can, however, also be effected in water alone in the presence of an organic or inorganic base or with the addition of a buffer.

According to a further embodiment, a silyl derivative of the compound of formula (II) may be used (for example, mono or di-trimethylsilyl derivatives silylated at the amino and/or carboxyl group, i.e., E represents a silyl group, e.g., a trimethylsilyl group). In this case, the reaction is conveniently effected in a solvent free of water and hydroxyl groups, for example in an halogenated hydrocarbon, for example, methylene chloride or chloroform, benzene, tetrahydrofuran, acetone or dimethylformamide. The addition of bases is not necessary, but it may be advantageous in individual cases in order to improve the yield and purity of the product. The optionally added bases used are, appropriately, tertiary aliphatic or aromatic amines such as, e.g., pyridine or triethylamine, or sterically hindered, non readily acylated secondary amines, such as, e.g., dicyclohexylamine.

Where E represents a protective group other than a silyl group, for example, a diphenylmethyl or pivaloyloxymethyl group, then it is generally advantageous to work in an aprotic solvent, for example, in absolute methylene chloride, chloroform, tetrahydrofuran or dimethylformamide.

The quantity of base used is determined in general by the desired adherence to a certain pH value. Where a pH value measurement or adjustment is not effected or is not possible or not appropriate due to the lack of a sufficient quantity of water in the diluting agent, preferably 1.0 to 2.0 molar equivalents of base are employed in the case of the use of a non-silylated compounds of the general formula (II). If a silylated compound is used, preferably up to 1 molar equivalent of base is employed.

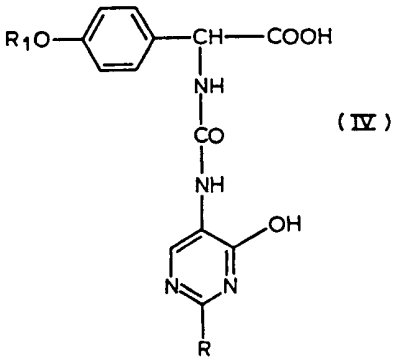
In general, any organic or inorganic base conventionally employed in organic chemistry, such as, e.g., an alkali metal or alkaline earth metal hydroxide, an alkaline earth metal oxide, an alkali metal or alkaline earth metal carbonate or bicarbonate, ammonia or a primary, secondary or tertiary aliphatic or aromatic amine as well as an heterocyclic base may be used. Mention may be made, for example, of sodium, potassium or calcium hydroxide, calcium oxide, sodium or potassium carbonate, sodium or potassium bicarbonate, diethylamine, methylethylamine, triethylamine, hydroxyethylamine, aniline, dimethylaniline, pyridine or piperidine. However, if a silylated starting material is used, the above-mentioned restrictions in respect of the type of base should be observed.

The buffer systems used may be any conventional buffer mixtures, for example, phosphate buffer, citrate buffer or tris-(hydroxymethyl)amino-methane buffer.

The reaction temperatures can be varied within a large range. In general, work is carried out between —20 and +50°C, preferably between 0 and +20°C.

The reactants of the general formulae (II) and (III) can be reacted with one another from the outset in substantially equimolar quantities. However, in individual cases, it may be appropriate to use one of the two reactants in excess to facilitate the purification of the final product or to increase the yield.

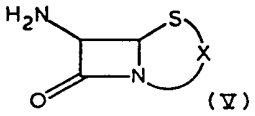
2. Compounds of the general formula (I), wherein D has the meanings given above except for that of a pyridinium or aminocarbonyl pyridinium group, by reaction of an ureidocarboxylic acid of the formula (IV):



(IV)

wherein:

R and R_1 have the meanings given above, their salts or reactive derivatives, with compounds of the general formula (V):



(V)

wherein:

X has the meanings given above, except for that of the formula in which D represents pyridinium or aminocarbonyl pyridinium.

There may be considered as reactive derivatives of ureidocarboxylic acids of the general formula (IV), for example, their acid anhydrides such as, for example, those which are derived from chloroformates, for example, ethyl or isobutyl chloroformate, or their reactive esters such as, e.g., the *p*-nitrophenyl ester or the N-hydroxy-succinimide ester, or their reactive amides such as N-carbonylimidaxole, as well as their acid halides such as, e.g., the acid chloride or their acid azides.

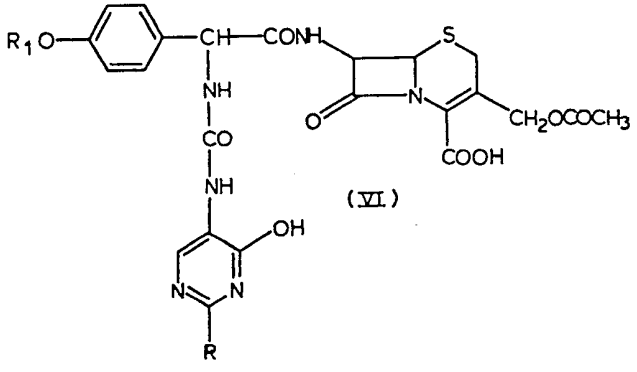
In principle, however, all linking methods known from β-lactam chemistry can be used.

The 7-aminocephalosporanic acid or penicillanic acid derivatives of the general formula (V) are advantageously employed in the form of an *in vitro* or *in vivo* readily cleavable derivative. For example, especially preferred compounds of the general formula (V) are those in which E represents the diphenylmethyl, *t*-butyl, trimethylsilyl or N,O-bis-trimethylsilyl group, or the other groups mentioned above with the exception of an hydrogen atom.

The ureidocarboxylic acids of the formula (IV), their salts and their reactive derivatives are preferably reacted with the 7-aminocephalosporanic or 6-amino-penicillanic acid derivatives in a solvent at temperatures of from −10°C to +40°C, optionally in the presence of a base. If, for example, an anhydride of the ureidocarboxylic acid, for example, the anhydride with ethyl chloroformate, is used, then the reaction is preferably effected with cooling, for example at −40 to +10°C, in the presence of a solvent such as acetone, tetrahydrofuran, dimethylformaide, chloroform, dichloromethane or hexametapol, or in a mixture of these solvents. If, for example, an N-hydroxysuccinimide ester of the ureidocarboxylic acid is reacted with the compound of formula (V), then, the reaction is preferably effected at from 0 to 20°C in the presence of a base such as, for example, triethylamine and of a solvent such as, e.g., dimethylformamide, dichloromethane or dioxan, or in a mixture of such solvents.

The reaction of an ureidocarboxylic acid of the formula (IV) itself or of its salts with compounds of the general formula (V) is effected advantageously in the presence of a condensation agent, for example, in the presence of N, N'-dicyclohexyl-carbodiimide.

3. Cephalosporin derivatives of the general formula (I), wherein D has the meanings of an −S−Het, pyridinium or 4-aminocarbonylpyridinium group, by the reaction of a compound of the general formula (VI):



(VI)

wherein:
R_1 and R have the meanings given above, either with a compound of the general formula (VII):

$$Het - S - M \qquad (VII),$$

wherein:
Het has the meanings given above and M represents an hydrogen atom or an alkali metal or an alkaline earth metal, or with pyridine or 4-aminocarbonylpyridine. For this purpose, for example, a compound of the formula (VI) is reacted with, for example, 5-methyl-2-mercapto-1,3-4-thiadiazole in a solvent such as, for example, water, methanol, ethanol, acetone, methylethyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, dimethoxyethane, dimethylformamide, dimethylsulfoxide, or chloroform or a mixture of these solvents. Preferably, a strongly polar solvent such as, e.g., water or acetonitrile is used. In the case of water as a solvent, the pH value of the reaction solution is advantageously kept at 2 to 10 and especially at 4 to 8. The desired pH value can be adjusted by the addition of a buffer solution such as, e.g., sodium phosphate. The reaction conditions are subject to no special restrictions. Normally, the reaction is effected at a temperature in the range of 0 to 100°C for a period of a few hours.

The compounds according to the invention prepared according to the processes 1 to 3 in which E represents an *in vitro* readily cleavable protective group can be converted by methods which are known in cephalosporin or penicillin chemistry into the free carboxylic acids (E = hydrogen) of the general formula (I). Thus, for example, the trimethylsilyl group can easily be removed by aqueous hydrolysis or the diphenylmethyl ester group, for example, by hydrolytic separation with trifluoroacetic acid. This elimination of protective groups is generally known.

Also, the antibiotics of formula (I) or (I'), wherein E represents a hydrogen atom, can be converted to acyloxyalkyl esters, wherein E represents for example a pivaloyloxymethyl radical:

$$-CH_2-O\overset{\overset{O}{\|}}{C}-C(CH_3)_3,$$

by reacting an alkali metal salt of the free carboxylic acid, for example, a sodium or potassium salt, with a pivaloyloxymethyl halide of the formula:

$$Hal-CH_2-O-\overset{\overset{O}{\|}}{C}-C(CH_3)_3,$$

in which Hal represents a chlorine, bromine or iodine atom.

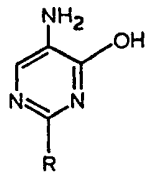
Other suitable acyloxyalkyl halides are, for example, chloromethylacetate, bromomethylproprionate and 1-bromoethylacetate.

The preparation of the acyloxyalkylates of the formula (I) is conveniently effected by reacting an alkali metal salt of the parent acid in an inert solvent with a slight molar excess of the iodo, bromo- or chloroalkylate, such as pivaloyloxymethyl iodide, preferably at ambient temperature or at slightly elevated temperature up to about 40 to 45 °C. The solvent may be, for example, acetone, tetrahydrofuran, dioxan, dimethylformamide or methylene chloride.

The further processing of the reaction mixtures obtained by the above described processes may be carried out according to the methods conventional in β-lactam chemistry, e.g., in respect of the isolation and purification of the final products, and in respect of the release of the acid and/or its conversion into salts by salification with inorganic or organic bases. In particular, in the preparation of the potassium or sodium salts, it is especially convenient to precipitate these salts from the respective alcoholic-ether solutions of the free acid by the addition of potassium or sodium 2-ethylhexanoate, or to react the free acid with the corresponding quantity of sodium bicarbonate with pH control and cooling and subsequent freeze-drying.

The starting materials of the formula (II) are known or can be prepared analogously to known compounds by methods known *per se*, for example, by the acylation of the known amino-lactams of the formula (IV), and, if desired, subsequent reaction of cephalosporanic acid derivatives of the formula (II) (D = $-OCOCH_3$) with thiols of the formula Het-SH.

The starting materials of the general formula (III) can be obtained, for example, by reacting the corresponding 5-aminopyrimidines of the formula (VIII):

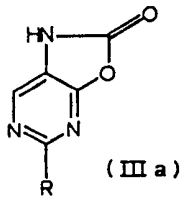

(VIII)

wherein:

R is as defined above.

with phosgene.

This reaction is preferably effected in a solvent not containing hydroxyl groups, such as tetrahydrofuran, methylene chloride, chloroform, dimethoxyethane or hexametapol, at temperatures between −40° and +60°C, preferably between −10° and +20°C. It is recommended to bind the resulting hydrogen chloride by equimolar quantities of an inert organic base such as triethylamine or pyridine. Also, pyridine in excess can be used as a solvent. If the respective aminopyrimidines of the general formula (VIII) are rather insoluble in one of the above-mentioned solvents, the phosgenation can also be effected in the heterogeneous phase. Furthermore, the aminopyrimidines of the general formula (VIII) can be converted by treatment with a silylating agent such as hexamethyldisilazane or trimethylchlorosilane/triethylamine, trimethylsilyldiethylamine or N,O-bis-trimethylsilylacetamide into an aminopyrimidine which is generally very easily soluble in the above-mentioned solvents and is mono- or poly-silylated according to the exchangeable hydrogen atoms present, and which then reacts with phosgene to form the corresponding compounds of the general formula (III). Depending on the type of solvent, the temperature value, the quantity and type of the base used, either predominantly the corresponding isocyanate or carbaminic acid halide or a mixture of these two compounds is obtained. Depending on the reaction conditions, the compound of the general formula (III) can also be present partly or wholly as a dihydrooxazolo-pyrimidine of the general formula (IIIa):

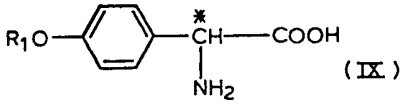

(IIIa)

isomeric to the isocyanates, or, in the case of previous silylation, depending on the nature of the substituent R, as a mono- or poly-silylated analogue.

The starting products of the general formula (III) or (IIIa), or their mixtures, which are obtained by means of phosgenation are generally readily soluble in the above-mentioned solvents, and, after removal of excess phosgene, can be reacted directly without further purification with the corresponding β-lactam derivatives of the general formula (II).

However, it is also possible to isolate the intermediate product of the general formula (IIIa), optionally to desilylate it, e.g., with a protic solvent, for example, water or methanol, to purify it on the basis of its solubility properties and to react it in the way described above.

The ureidocarboxylic acids of the general formula (IV) can easily be obtained by reacting the pyrimidine derivatives of the general formula (III) with glycine derivatives of the general formula (IX):


(IX)

wherein:

R_1 is as defined above.

The reaction is carried out at temperatures between −20° and +40°C, preferably between 0° and +20°C, in a solvent. The solvent used can be, for example, a mixture of water or an organic solvent which is miscible with water, for example, acetone, tetrahydrofuran, dioxan, acetonitrile, dimethylformamide, ethanol or dimethylsulfoxide. It may be desirable to use a hydrogen halide-binding agent, and suitable agents are, for example, trialkylamines such as, e.g, triethylamine and inorganic bases such as, e.g., dilute sodium hydroxide.

The 2- substituted 5-amino-4-hydroxypyrimidines of the general formula (VIII) are described in the DT-OS 28 08 153.0 and DT-OS 29 10 190.4.

It has been found that the compounds of the general formula (I) or (I') possess valuable pharmacological properties and exhibit good compatibility. The active compounds according to the invention can be used for the prophylaxis and chemotherapy of local and systemic infections in human and veterinary medicine.

Mention may be made as diseases which can be prevented or cured by means of the compounds according to the invention of, for example, those of the respiratory tract, the pharyngeal cavity and the

urinary passage; the compounds are active especially against pharyngitis, pneumonia, peritonitis, pyelonephritis, otitis, cystitis, endocarditis, bronchitis, arthritis and general systemic infections.

This is made possible due to the fact that these compounds have a very strong activity both *in vitro* and *in vivo* against harmful microorganisms, especially against gram-positive and gram-negative bacteria and microorganisms similar to bacteria, these compounds being distinguished especially by a broad spectrum of activity.

With these derivatives, local and/or systemic diseases can be treated and/or prevented, for example diseases caused by the following germs or by mixtures of the following germs:

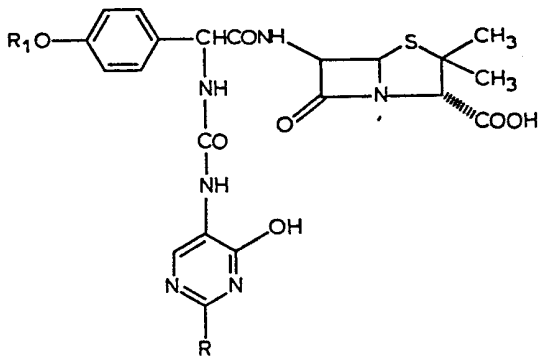
Micrococcaceae, such as *Staphylococcae;*
Lactobacteriaceae, such as *Streptococcae;*
Neisseriaceae, such as *Neisseriae;*
Corynebacteriaceae, such as *Corneybacteria;*
Enterobacteriaceae such as *Escherichiae* bacteria of the *coli* group;
Klebsiella bacteria, for example *K. pneumoniae;*
Proteae bacteria of the *proteus* group, for example *Proteus vulgaris;*
Salmonella bacteria, for example *S. thyphimurium;*
Shigella bacteria, for example *Shigella dysenteriae;*
Pseudomonas bacteria, for example *Pseudomonas aeruginosa;*
Aeromonas bacteria, for example *Aeromonas liquefaciens;*
Spirillaceae, such as *Vibrio* bacteria, for example *Vibrio cholerae;*
Parvobacteriaceae or *Brucellaceae* such as *Pasteurella* bacteria;
Brucella bacteria, for example *Brucella abortus;*
Haemophilus bacteria, for example *Haemophilus influenzae;*
Bortetella bacteria, for example *Bordetella Pertussis;*
Moraxella bacteria, for example *Moraxella lacunata;*
Bacteriodaceae, such as *Bacteroides* bacteria;
Fusiforme bacteria, for example *Fusobacterium fusiforme;*
Sphaerophorus bacteria, for example *Sphaerophorus necrophorus;*
Bacillaceae, such as aerobic spore formers, for example *Bacillus anthracis;*
anaerobic spore forming *chlostridiae,* for example *Chlostridium perfrigens;*
Spirochaetaceae, such as *Borrelia* bacteria;
Treponema bacteria, for example *Treponema pallidum;*
Leptospira bactoria, such as *Leptospira interrogans.*

The above list of germs is merely by way of example and is in no way restrictive.

In the following tables, typical compounds according to the invention having especially good activity are listed. The penicillins mentioned can be obtained, for example, according to process 1 or 2, and the cephalosporins according to the processes 1 to 3.

TABLE 1

Penicillins of general formula



	R_1	R
1)	$CH_3OC(=O)-$	$-NH-C_6H_4-SO_2NH_2$
2)	$C_2H_5OC(=O)-$	$-NH-C_6H_4-SO_2NH_2$

TABLE I (Continued)

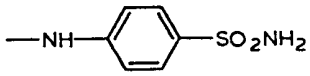
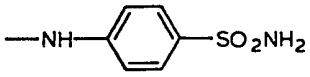
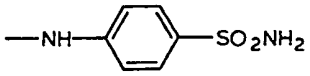
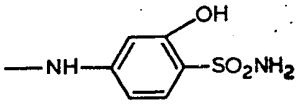
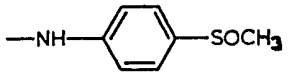
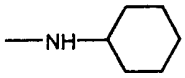
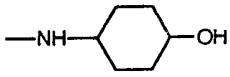
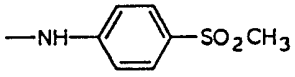
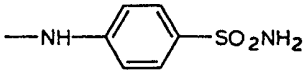
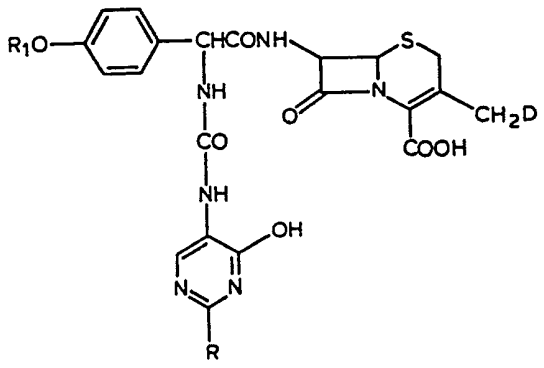
	R_1	R
3)	$CH_3C(=O)-$	
4)	$C_3H_7OC(=O)-$	
5)	$(CH_3)_2CH-CH_2OC(=O)-$	
6)	$C_2H_5-O-C(=O)-$	
7)	$CH_3-O-C(=O)-$	
8)	$C_2H_5-O-C(=O)-$	Cyclopropyl
9)	$C_2H_5-O-C(=O)-$	
10)	$C_2H_5-O-C(=O)-$	$-NH(CH_2)_3OH$
11)	CH_3CO-	
12)	$CH_3OC(=O)-$	
13)	$H_2NC(=O)-$	

TABLE 2

Cephalosporins of general formula:



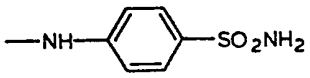
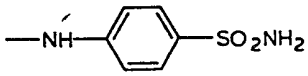
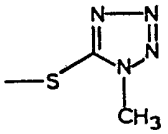
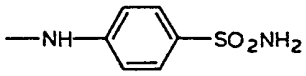
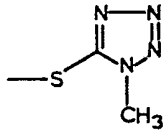
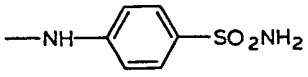
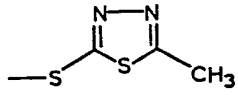
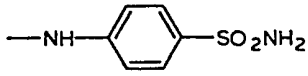
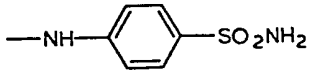
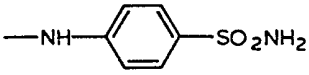
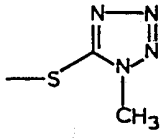
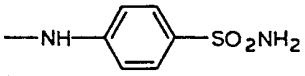
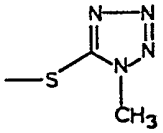
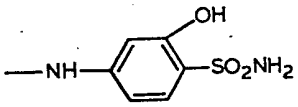
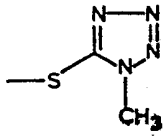
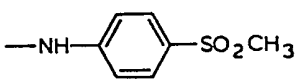
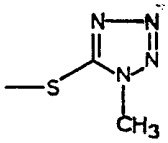
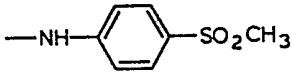
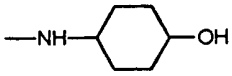
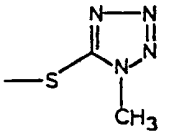
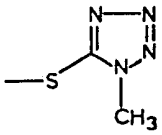
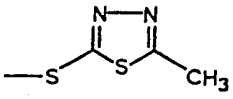
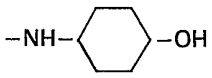
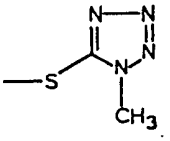
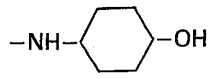
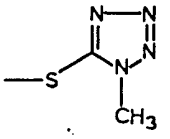
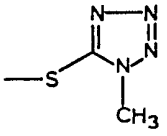
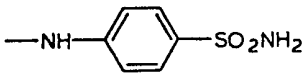
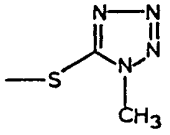
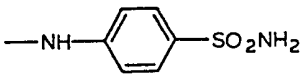
	R_1	R	D
1)	$CH_3OC(=O)-$		$-OCOCH_3$
2)	$CH_3OC(=O)-$		
3)	$C_2H_5OC(=O)-$		
4)	$C_2H_5-O-C(=O)-$		
5)	$C_2H_5-O-C(=O)-$		$-OCOCH_3$
6)	CH_3CO-		$-OCOCH_3$
7)	CH_3CO-		
8)	$C_3H_7OC(=O)-$		
9)	$C_2H_5-O-C(=O)-$		
10)	$CH_3-O-C(=O)-$		
11)	$CH_3-O-C(=O)-$		$-OCOCH_3$

TABLE 2 (Continued)

	R_1	R	D
12)	$C_2H_5-O-C(=O)-$		
13)	$C_2H_5-O-C(=O)-$	$-NH(CH_2)_3OH$	$-OCOCH_3$
14)	$C_2H_5-O-C(=O)-$	$-NH(CH_2)_3OH$	
15)	$C_2H_5-O-C(=O)-$	$-NH(CH_2)_3OH$	
16)	CH_3-CO-		
17)	$CH_3-O-C(=O)-$		
18)	$C_2H_5-O-C(=O)-$	$-NHCH(CH_3)_2$	
19)	$H_2NC(=O)-$		
20)	$H_2NC(=O)-$		$-OCOCH_3$

The activity of the β-lactam antibiotics according to the invention have been demonstrated by way of example with the following investigations:

1. *In vitro tests:*

In the investigations the method using series dilution tests in a microtiter system was applied. The substances were tested for bacteriostasis in a liquid medium. The bacteriostatic activity was investigated with the following concentrations: 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06 µg/ml. A nutrient substrate of the following composition was used: 10 g of peptone, 8 g of meat extract oxoid, 3 g of sodium chloride and 2 g of secondary sodium phosphate were made up with distilled water to 100 ml (pH 7.2 – 7.4). 1 % glucose was added only in the test against *Streptococci*. The age of the primary cultures was about 20 hours. The adjustment of the bacterial suspension was effected on a photometer (according to "Eppendorf") (test-tube diameter : 14 mm, filter: 546 nm) by reference to the turbidity of a barium sulphate comparison suspension

which was produced by means of a barium sulfate slurry obtained by the addition of 3.0 ml of 1 % barium chloride solution in 97 ml of 1 % sulphuric acid. After the adjustment, *Streptococcus* Aronson was diluted further in a ratio of 1:15, and the other test bacteria were diluted in a ratio of 1:1.500 with a common salt solution.

16 mg of the test substance were weighed in 10 ml measuring flasks and filled up to the mark with the solvent. Further succeeding dilutions were effected with distilled water or the respective solvent.

The depressions of the microtiter plates were filled with 0.2 ml of nutrient medium, 0.01 ml of the diluted test substance and a drop of bacterial suspension (0.01 ml) and incubated for 18 - 20 hours at 37°C. A solvent check was carried out continuously.

The reading was taken macroscopically, the respective limiting concentration (= the lowest concentration still having bacteriostatic activity) being determined.

The following were used as test organisms:

Staphylococcus aureus SG 511, *Escherichia coli* ATCC 11 775, *Pseudomonas aeruginosa Hamburgensis* and *Pseudomonas aeruginosa* Walter, *Serratia marcescens* ATCC 13 880, *Klebsiella pneumoniae* ATCC 10 031 and BC 6, *Proteus mirabilis* Hamburgensis, *Proteus* rettgeri, *Enterobacter cloacae* ATCC 13 047 and E. coli R+TEM (β-lactamase carrier).

In the following Table 1, the minimum inhibiting concentrations (MIC) as determined are listed for typical representatives of the compounds according to the invention:

D-α-[3-(2-p-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-p-ethoxycarbonyloxybenzylpenicillin-sodium = A

D-α-[3-(2-p-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-p-methylcarbonyloxybenzylpenicillin-sodium = B

Sodium-7-{D-α-[3-(2-p-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-p-ethoxycarbonyloxy-phenylacetamido}-3-[(1-methyltetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate = C

Sodium-7-{D-α-[3-(2-p-aminosulfonyl-anilino-4-hydroxy-5-pyrimidinyl)-ureido]-p-methyl-carbonyloxy-phenylacetamido}-3-[(1-methyltetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate = D

Minimum inhibiting concentration in µg/ml

Substance	*Staph. aureus* SG 511	*E. coli* ATCC 11775	*Pseud. Hbg.*	*Pseud.W.*	*Serr. marcesc.* ATCC 13880	*Kl. pneum.* ATCC 10031	*Kl. pneum.* BC 6	Prot. *mirab. Hbg.*	*Prot. Rettg.*	*Ent. cloacae* ATCC 13047	*E.coli* R+TEM
A	0.5	0.25	2	2	0.25	2	2	0.12	1	1	>64
B	0.5	0.25	4	2	0.5	4	2	0.12	2	1	>64
C	1	0.12	8	4	0.25	0.5	0.25	0.12	1	0.5	4
D	1	0.5	16	8	2	2	1	0.25	2	4	16
Azlocillin	2	8-16	8	8	4	32	32	2	8	32	>64
Cefuroxim	1	8	>128	>128	8	2	4	0.5	2	32	4

The compounds mentioned are distinctly superior to the comparison substances in their activity against typical gram-negative hospital bacteria, while retaining their activity against gram-positive bacteria.

The acute toxicity was determined by peroral and subcutaneous administration of the compounds of Tables 1 and 2 to white laboratory mice in increasing doses.

The LD_{50} value is the dose after the administration of which 50 % of the animals had died within 8 days. All substances showed with oral administration an LD_{50} value of over 4 g/kg, with subcutaneous administration, an LD_{50} value of over 3 g/kg, that is, with 3 g/kg, no animals died, and the substances are therefore non-toxic in practice.

A series of compounds according to the invention was tested *in vivo* upon experimental infections in mice. The pathogenic bacteria used were *E.coli* ATCC 11775. An intraperitoneal infection was started with 0.2 ml of a bacterial suspension (with 5 % mucin). This corresponds to about 1.4×10^6 germs of *E. coli* bacteria per mouse. Female mice of the strain NMRI were divided into groups of 10 animals each, two groups remained untreated and the remaining groups were treated subcutaneously with various doses of the respective cephalosporins or penicillins according to the invention to determine the ED_{50} values (doses at which 50 % of the animals survived). 1 hour after the infection, the treatment was effected once.

The observation time was 7 days in both cases. The results of these tests together with representatives of the penicillins and cephalosporins according to the invention are set out in Table 2, as follows.

TABLE 2

In vivo activity in mice
E. coli infection (s.c. application)

Compound	ED_{50} (mg/kg)
A	5.5
B	4.5
C	0.6
D	3.0
Azlocillin	>100
Cefuroxim	>100

A further feature of the present invention is to provide pharmaceutical compositions which are valuable in the treatment of infectious diseases both in humans and in animals.

Preferred pharmaceutical preparations include, for example, tablets, coated tablets, capsules, granulates, suppositories, solutions, suspensions, emulsions, ointments, gels, creams, powders and sprays. Advantageously, in human and veterinary medicine, the active ingredient or a mixture of various active ingredients of the general formula (I) is administered in a dose of from 5 to 500, preferably from 10 - 200, mg/kg of body weight, in intervals of 24 hours, optionally, in the form of several single doses. A single dose will preferably contain the active ingredient according to the invention in amounts of from 1 to 250, especially 10 to 60, mg/kg of body weight. Depending on the kind and the body weight of the patient to be treated, on the kind and the seriousness of the disease, on the type of preparation and on the route of administration as well as on the period or interval over which the administration takes place, it may however be necessary to deviate from the above dosages. Thus, it may be sufficient in some cases to administer less than the above-mentioned amount of active ingredient, while, in other cases, the above-mentioned amount of active ingredient must be exceeded. The optimal dosage and type of administration of the active ingredients which are necessary in each case can easily be assessed by one skilled in the art.

The new compounds may, if desired, be used as additives to foodstuffs or to drinking water. By such administration, infections by gram-negative or gram-positive bacteria can be prevented, removed and/or treated, and also utilization of the feed can be attained. The compounds show also growth-promoting properties.

The following non-limiting examples serve to illustrate the present invention:

Example 1

D-α-[3-(2-*p*-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-ethoxycarbonyloxy-benzylpenicillin-sodium

2.8 g (0.01 mol) of 5-amino-2-*p*-aminosulfonylanilino-4-hydroxypyrimidine were suspended in 100 ml of dry tetrahydrofuran and refluxed with 8 g of trimethylsilyldiethylamine until a complete solution was obtained (10 to 30 minutes). The solution was evaporated to dryness *in vacuo*, again taken up in 100 ml of

tetrahydrofuran and dropped with ice-cooling into a solution of 1.06 g of phosgene in 70 ml of dry tetrahydrofuran. After stirring for 10 minutes at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The remaining solid product was mixed under ice-cooling with 160 ml of methanol, whereby a solution was obtained. After a short time, pure 1-hydro-5-(p-aminosulfonylanilino)-oxazolo[5,4-d]pyrimidine-2-one precipitated. The precipitate was suction-filtered and dried.

1.97 g (0.0045 mol) of D-α-amino-*p*-ethoxycarbonyloxy-benzylpenicillin were suspended in a solvent-mixture of 40 ml of tetrahydrofuran and 10 ml of water. Triethylamine was added with ice-cooling until a solution was obtained. To this solution, in portions, 1.4 g (0.0045 mol) of 1-hydro-5-(p-amino-sulfonylanilino)-oxazolo[5,4-d]pyrimidine-2-one were added, a drop in the pH value below 7 being avoided, optionally, by the addition of triethylamine. After stirring for 1 hour in the ice-bath, the reaction mixture was left until room temperature was reached, and then mixed with 20 ml of water, and the tetrahydrofuran was thereafter removed *in vacuo*. The aqueous phase was extracted once with ethyl acetate at pH 7.0 and adjusted under ice-cooling to pH 2.8 by means of 1 N hydrochloric acid. The precipitated D(−)-α-[3-(2-*p*-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-ethoxy-carbonyloxy-benzyl-penicillanic acid was suction-filtered and dried *in vacuo*. After stirring in dimethylformamide, the calculated quantity of sodium ethylhexanoate was added and the sodium salt was precipitated by dilution with ether.

Yield: 2.12 g (61.5 % of theory),
IR spectrum: 1760, 1660, 1600, 1330, 1150 cm^{-1};
NMR spectrum: (DMSO + CD_3OD), signals at ppm:
1.3 (t,3H), 1.55 (d,6H), 4.0 (s,1H), 4.25 (q, 2H), 5.40 (q,2H), 5.65 (s,1H), 7.15 (d,2H), 7.5 (d,2H), 7.7 (d,2H), 8.0 (d,2H), 8.35 (s,1H).

Example 2

D-α-[3-(2-*p*-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-acetoxy-benzylpenicillin-sodium

a) 2.36 (0.005 mol) of D(−)-α-[(2-p-aminosulfonyl-anilino-4-hydroxy-5-pyrimidinyl)-ureido]-α-(p-hydroxy-phenyl)-acetic acid were suspended in 50 ml of glacial acetic acid, and 1.75 g (0.02 mol) of acetyl chloride were added thereto.

After stirring the reaction mixture for 12 hours at 20°C further 1.75 g of acetyl chloride were added, and the mixture was then heated quickly up to 60°C, and again stirred for 1 further hour at 20°C. After the addition of 100 ml of ether, the crystals were suction-filtered, the crystalline product was triturated twice with 100 ml of ether in each case, suction-filtered and dried.

Yield: 2.4 g (93 %) of D(−)-α-[2-*p*-amino-sulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-α-(*p*-acetoxyphenyl)-acetic acid.
m.p.: 214°C (decomp.).

b) 0.46 ml (0.00425 mol) of N-methylmorpholine were added to a solution of 2.2 g (0.00425 mol) of D(−)-α-[(2-p-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-α-(p-acetoxyphenyl)-acetic acid in a mixture of 50 ml of dimethylformamide and 10 ml of methylene chloride. After cooling to −35°C, a solution of 0.41 ml (0.00425 mol) of ethyl chloroformate in 2 ml of methylene chloride was dropped into the resulting mixture.

After a reaction time of 10 minutes at −35°C, 1.34 g (0.00425 mol) of 6-amino-penicillanic acid triethylammonium salt, which were dissolved in 60 ml of methylene chloride, were added.

After stirring for 30 minutes at −35°C, cooling was stopped, and the reaction mixture was heated within 30 minutes up to 20°C. Subsequently, a mixture of 200ml of water, and 200 ml of methylacetate was poured thereinto, the pH value was adjusted to 7 by means of 1N sodium hydroxide solution, and the organic phase was separated off. The aqueous phase was adjusted under ice-cooling to pH 2.8 by means of 1N hydrochloric acid, and the precipitated D(−)-α-[3-(2-*p*-amino-sulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-acetoxy-benzylpenicillanic acid was suction-filtered, washed with water and dried. The dried product was dissolved in dimethylformamide, the calculated amount of sodium-ethylexanoate was added and the sodium salt was precipitated by the addition of ether.

Yield: 2.1 g (67 % of theory),
IR spectrum: 1770, 1660, 1600, 1330, 1150 cm^{-1},
NMR spectrum: (DMSO + CD_3OD), signals at ppm:
1.55 (d,6H), 2.20 (s,3H), 4.0 (s,1H), 5.40 (q,2H), 5.60 (s,1H), 7.05 (d,2H), 7.45 (d,2H), 7.6 (d,2H), 7.95 (d,2H), 8.30 (s,1H).

Example 3

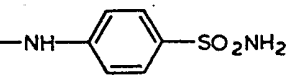
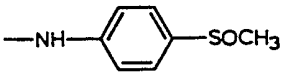
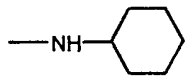
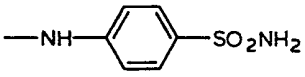
D-α-[3-(4-Hydroxy-2-{4'-hydroxycyclohexylamino}-5-pyrimidinyl)-ureido]-*p*-ethoxycarbonyloxy-benzylpenicillin-sodium

1.12 g of 5-amino-4-hydroxy-2-(4'-hydroxycyclohexylamino)-pyrimidine (5 m mol) were silylated analogously to Example 1 and reacted with phosgene. The solution of the resulting product in tetrahydrofuran was dropped into a solution of the aminopenicillin derivative prepared analogously to Example 1. Further processing was carried out analogously to Example 1.

Yield: 49 %,
IR spectrum: 1770, 1660, 1605, 1330, 1150 cm^{-1}.
NMR spectrum: (DMSO + CD_3OD) signals at ppm:

1.3 (t,3H), 1.55 (d,6H), 1.75 (m,8H), 3.6-4.1 (m,1H + s,1H + m,1H), 4.15 (q,2H), 5.45 (q,2H), 7.15 (d,2H), 7.5 (d,2H), 8.0 (s,1H).

Analogously to Examples 1 and 2, the penicillins of the following table were synthesized.

Example	R_1	R_2	R	Yield %	NMR spectra (DMSO + CD_3OD) signals at ppm:
4	$CH_3OC(=O)-$	H		64,5	1,55 (d,6H), 3.90 3H), 4.05 (s,1H), 5,45 (q,2H), 5.60 (s,1H), 7,10 (d,2H) 7,45 (d,2H), 7,70 (d,2H), 7.95 (d,2H), 8,35 (s,1H)
5	$CH_3OC(=O)-$	H		46	1,55 (d,6H), 2.7 (s,3H), 3.95 (s,3H), 4,0 (s,1H), 5,4 (q, 2H), 5,6 (s,1H), 7,15 (d,2H), 7,5 d,2H), 7,75 (d,2H), 8,0 (d,2H), 8,35 (s, 1H)
6	$C_2H_5OC(=O)-$	H		51	1,3 (t,3H), 1,4-2,0 (m,10+6H), 4,0 (m, 1H+ s,1H), 4,15 (q, 2H), 5,4 (q,2H), 5,65 (s,1H), 7,15 (d,2H), 7,5 (d,2H), 8,05 (s,1H)
7	$C_2H_5OC(=O)-$	H	$-NH(CH_2)_3OH$	54,5	1,3 (t,3H), 1,90 (m, 2H), 3,3 (m,2H), 3,65 (m,2H), 4,0 (s, 1H, 4,1 (q,2H), 5,45 (q,2H), 5,6 (s,1H), 7,15 (d,2H), 7,5 (d, 2H), 8,05 (s,1H)
8	$H_2NC(=O)-$	H		68	1,55 (d,6H), 4,05 (s,1H), 5,45 (q,2H + s,1H), 7,7 (d,2H), 7,95 (d,2H), 8,36 (s,1H)

Example 9

Sodium-7-D-α-[(2-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-ethoxycarbonyloxy-phenylacetamido -3-[(1-methyltetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate

a) 2,8 g (0.01 mol) of 5-amino-2-p-aminosulfonylanilino-4-hydroxy-pyrimidine were suspended in 100 ml of dry tetrahydrofuran and refluxed until complete solution with 8g of trimethylsilyldiethylamine (10 to 30 minutes). The solution was evaporated to dryness *in vacuo*, again taken up in 100 ml of tetrahydrofuran, and dropped under ice-cooling into a solution of 1.06 g of phosgene in 70 ml of dry tetrahydrofuran. After stirring for 10 minutes at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The remaining solid product was mixed under ice-cooling with 160 ml of methanol, whereby a solution was obtained. After a short time, pure 1-hydro-5-(*p*-aminosulfonylanilino)-oxazolo-[5,4-d]pyrimidine-2-one precipitated. The precipitate was suction-filtered and dried.

b) 1.4g (0.005 mol) of D(−)-α-amino-(p-ethoxycarbonyloxyphenyl)-acetic acid hydrochloride were suspended in 60 ml of tetrahydrofuran and 20 ml of 0.5 n sodium hydroxide solution were added under ice-cooling. The resulting solution was mixed in portions with 1.5 g (0.005 mol) of 1-hydro-5-(*p*-aminosulfonyl-anilino)-oxazolo[5,4-d]pyrimidine-2-one at room temperature, the pH value being kept

thereby at 8.0 - 8.3. After the addition had been completed, the reaction mixture was stirred for 1 hour at room temperature. Subsequently, 50 ml of water were added, the pH value was adjusted to 3.0 by means of 1N hydrochloric acid, and the mixture was extracted twice with 100 ml in each case of ethyl acetate.

The combined organic phases were washed with water, dried over sodium sulfate and evaporated *in vacuo*, and the solid residue was triturated with ether.

Yield: 2.4 g (88 % of theory) of D(−)-α-[(2-p-aminosulfonyl-anilino-4-hydroxy-5-pyrimidinyl)-ureido]-α-(p-ethoxycarbonyloxy-phenyl)-acetic acid.

M.p.: 210°C (decomp.).

c) 2.7 g (0.005 mol) of D(−)-α-[(2-p-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-α-(*p*-ethoxycarbonyloxyphenyl)-acetic acid and 2.47 g (0.005 mol) of 7-amino-3-[(1-methyl-tetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylic acid benzhydryl ester were dissolved in a mixture of 70 ml of dried methylene chloride and 30 ml of dimethyl formamide. Under cooling, 1.1 g (0.005 mol) of dicyclohexylcarbodiimide were added and the reaction mixture was stirred for 6 hours with ice-cooling. Subsequently, the solvent was removed *in vacuo*. The residue was extracted first with 80 ml of methanol and twice with 100 ml in each case of methylene chloride, whereby suction filtration is carried out in each case. The resulting solid product was washed with ether and dried. The benzhydryl group was split off in conventional manner by means of 10 ml of trifluoroacetic acid and 3 ml of anisole, and the cephalosporanic acid was converted to the sodium salt by means of sodium ethyl hexanoate in dimethyl formamide.

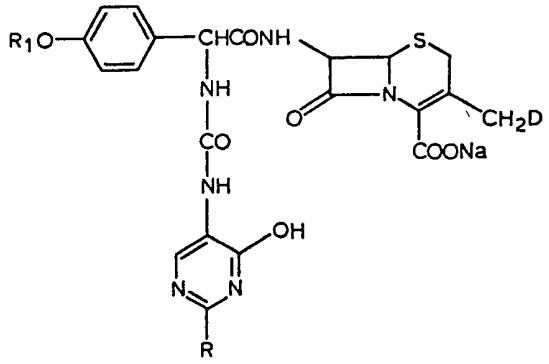
Yield of sodium salt: 2.57 g (59.5 %),

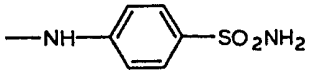
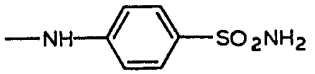
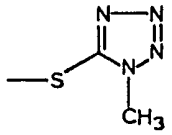
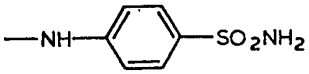
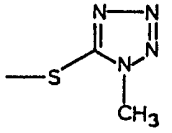
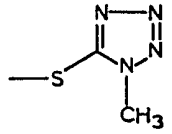
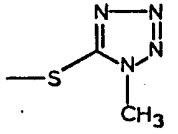
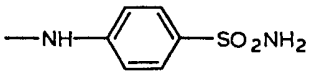
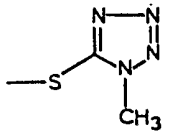
IR spectrum: 1760, 1665, 1600 cm^{-1},

NMR spectrum: (DMSO + CD_3OD) signals at ppm:

1.25 (t,3H), 3.40 (q,2H), 3.9 (s,3H), 4.0 (s,3H), 4.20 (q,2H), 4.80 (d,1H), 5.50 (s,1H), 5.6 (d,1H), 7.1 (d,2H), 7.4 - 7.7 (dd,4H), 7.9 (d,2H), 8.30 (s,1H).

Analogously, the cephalosporins of the following table were synthesized:



Example	R_1	R	D	Yield %	NMR spectrum (DMSO+CD_3OD) signals at ppm:
10	$CH_3OC(=O)-$		$-OCOCH_3$	64	2,05 (s,3H), 3,45 (q,2H), 3,90 (s,3H), 4,80 (q,2H), 4,90 (d,1H), 5,55 (s,1H), 5,65 (d,1H), 7,0 (d,2H), 7,35-7,65 (dd,4H), 7,95 (d,2H), 8,35 (s,1H).
11	$CH_3OC(=O)-$			48,5	3,50 (q,2H), 3,95 (s,3H), 4,0 (s,3H), 4,3 (q,2H), 4,95 (d,1H) 5,50 (s,1H), 5,60 (d,1H), 7,1 (d,2H), 7,4-7,7 (dd,4H), 8,0 (d,2H), 8,38 (s,1H),
12	$CH_3C(=O)-$			44	2,15 (s,3H), 3,50 (m,2H), 3,85 (s,3H), 4,25 (m,2H), 4,85 (d,1H), 5,5 (s,1H), 5,65 (d,1H), 7,0 (d,2H), 7,3-7,85 (m,6H), 8,35 (s,1H),
13	$C_2H_5OC(=O)-$	$-NH(CH_2)_3OH$		51	1,25 (t,3H), 1,90 (m,2H), 3,2 (m,2H), 3,45 (m,2H), 3,65 (m,2H), 3,95 (s,3H), 4,2 (m,2H + m,2H), 4,90 (d,1H), 5,5 (s,1H), 5,65 (d,1H), 7,1 (d,2H), 7,4 (d,2H), 8,35 (s,1H),
14	$C_2H_5OC(=O)-$	$-NHCH(CH_3)_2$		55	1,15 (d,6H), 1,3 (t,3H), 3,50 (q,2H), 3,8 (breites m, 1H), 3,95 (s,3H), 4,25 (m,4H), 4,90 (d,1H), 5,50 (s,1H), 5,65 (d,1H), 7,0-7,4 (m,4H); 8,05 (s,1H),
15	$H_2NC(=O)-$			44	3,45 (q,2H), 3,95 (s,3H), 4,25 (m,2H), 4,95 (d,1H), 5,50 (s,1H), 5,65 (d,1H), 7,1-7,4 (m,4H), 7,65 (d,2H), 7,95 (d,2H), 8,36 (s,1H).

The compounds of the general formulae (I) and (I') can be incorporated into the usual pharmaceutical preparations, such as tablets, coated tablets, capsules or ampoules. The single dose for adults in general is between 50 and 1000 mg, preferably, 100 to 500 mg, and the daily dose is between 100 and 4000 mg, preferably 250 to 2000 mg.

Example I

Tablets containing D-α-[3-(2-p-aminosulfonyl-anilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-methoxycarbonyloxy-benzyl-penicillin-sodium.

A mixture consisting of 2 kg of active ingredient, 5 kg of lactose, 1.8 kg of potato starch, 0.1 kg of magnesium stearate, and 0.1 kg of talcum was pressed into tablets in conventional manner, each tablet containing 200 mg of active ingredient.

Example II

Coated tablets containing D-α-[3-(2-p-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-methoxycarbonyloxy-benzyl-penicillin-sodium.

Analogously to Example I, tablets are pressed and are subsequently covered in conventional manner with a coating consisting of sugar, potato starch, talcum and tragacanth.

Example III

Capsules containing D-α-[3-(2-*p*-aminosulfonyl-anilino-4-hydroxy-5-pyrimidinyl)ureido]-*p*-methoxycarbonyloxy-benzyl-penicillin-sodium.

5 kg of active ingredient were filled in conventional manner into hard gelatine capsules so that each capsule contains 500 mg of active ingredient.

Example IV

Dry ampoules containing sodium 7-{D-α-[3-(2-*p*-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-methoxycarbonyloxy-phenylacetamido}-3-[(1-methyl-tetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate.

In an aseptic location, 251 g of active ingredient were dissolved in 200 ml of distilled water for injection. The solution was filtered through a "Millipore" (registered Trade Mark) filter (pore size 0.22 μm, product of the Millipore Corporation, Bedford, USA). The solution was poured in aliquot parts of 2.0 ml into 1000 glass tubes (capacity 10 ml) and lyophilised. The glass tubes were then sealed with a rubber stopper and an aluminium cap. The glass tubes (number A) were thus obtained, each containing 250 mg of active ingredient.

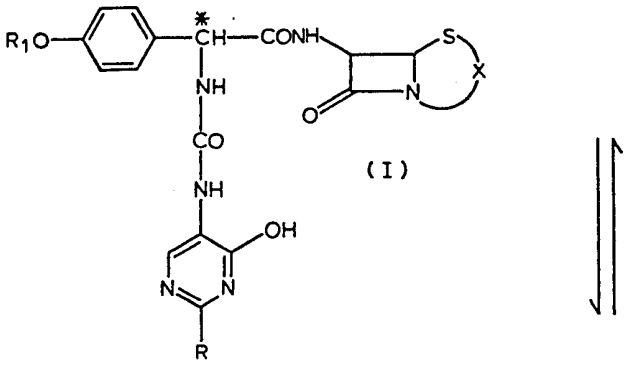
A physiological common salt solution for injection was filled in aliquot parts of 2.0 ml into ampoules and the ampoules were sealed. In this way, ampoules (number B) were obtained. The physiological common salt solution in the ampoules (number B) was poured into the glass tubes (number A), as a result of which an injectable preparation for intravenous administration was obtained.

Distilled water for injection was poured in aliquot parts of 20 ml into the glass tubes (number A) and the solution was added to 250 ml of a 5 % solution of glucose for injection. In this way, solutions for continuous infusion were prepared.

Analogously, tablets, coated tablets, capsules, and ampoules are obtainable, which contain one or more of the other active substances of formula (I) or the physiologically compatible salts of these compounds.

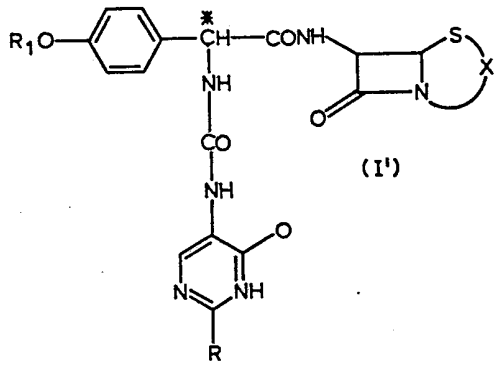
CLAIMS

1. New β-lactams of the general formulae (I) and (I'):



(I)

and



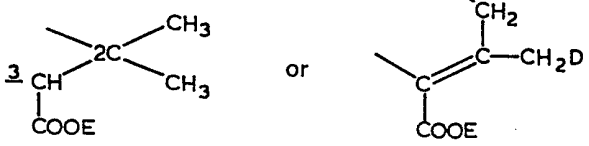
(I')

wherein:

R, R_1 and X have the following meanings:

R_1 represents an aliphatic acyl or alkoxycarbonyl group with 2 to 5 carbon atoms or the aminocarbonyl group,

X represents the group

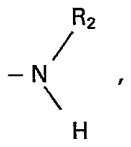


wherein:

D represents an hydrogen atom; an acetoxy; aminocarbonyloxy; pyridinium or 4-aminocarbonyl-pyridinium group; or the group -SHet, wherein Het represents the 1-methyl-tetrazole-5-yl; 1,2,4-thiadiazole-5-yl; 3-methyl-1,2,4-thiadiazole-5-yl; 1,3,4-thiadiazole-2-yl; 2-methyl-1,3,4-thiadiazole-5-yl; or 4-methyl-5,6-dioxo-1,2,4-triazine-3-yl group; and

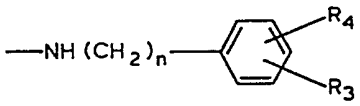
E represents an hydrogen atom or an *in vitro* or *in vivo* readily cleavable protective group, and

R represents an hydrogen atom; the cyclopropyl group; the 2'-hydroxyethylamino; 3'-hydroxypropylamino; or 4'-hydroxycyclohexylamino group; or a group of the general formula:



wherein R_2 represents an hydrogen atom, a branched or unbranched alkyl or alkenyl group with 1 to 4 carbon atoms or a cycloalkyl radical with 3 to 6 carbon atoms, or

R represents a group of the general formula:

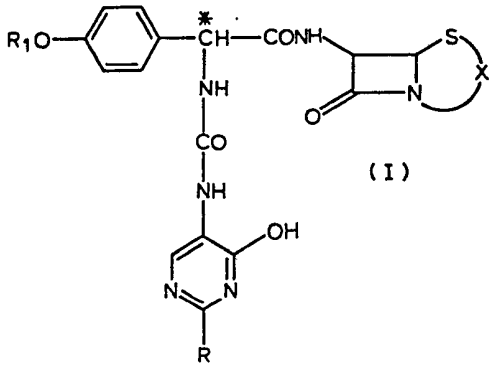


wherein:

$n = 0$ or 1, and R_3 and R_4, which may be the same or different, represent hydrogen atoms; a hydroxy; acetylamino; aminocarbonylamino; nitro; aminocarbonyl; cyano; methylsulfinyl; methylsulfonyl; aminosulfonyl or methylaminosulfonyl group, and,

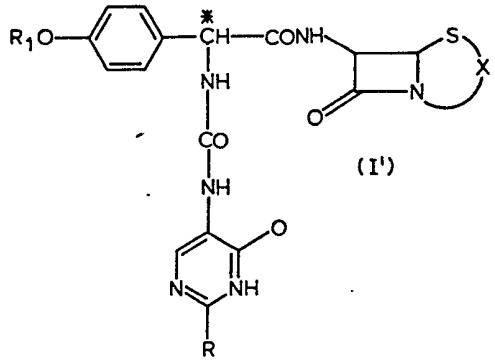
if E represents an hydrogen atom, their physiologically compatible salts with inorganic or organic bases.

2. New β-lactams of the general formulae (I) and (I'):



(I)

and



(I')

wherein:

R_1 represents a methoxycarbonyl; ethoxycarbonyl; acetyl or aminocarbonyl group;

X is defined as mentioned in claim 1, in which:

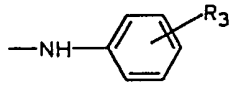
E represents an hydrogen atom; or the pivaloyloxymethyl group, and

D represents an hydrogen atom; the acetoxy group or the group -SHet, wherein Het represents the 1-methyltetrazole-5-yl; the 1,3,4-thiadiazole-5-yl; or the 2-methyl-1,3,4-thiadiazole-5-yl group; and

R has the meanings mentioned in claim 1, and,

if E represents an hydrogen atom, their physiologically compatible salts with inorganic or organic bases.

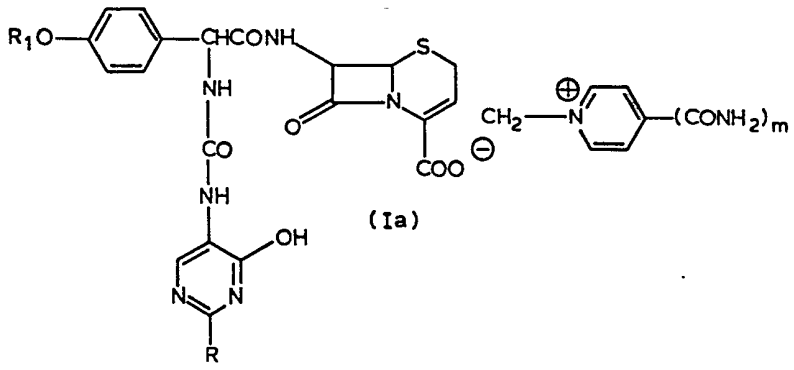
3. New β-lactams of the general formula (I) or (I') as claimed in claim 1 or 2, wherein R_1 and X are defined as claimed in claim 2, and R represents either the group of the general formula:



in which R_3 represents the hydroxy; methylsulfinyl; methylsulfonyl; aminocarbonyl; aminocarbonylamino; aminosulfonyl; or methylaminosulfonyl group, or R represents the *m*-hydroxy-*p*-aminosulfonylanilino; cyclopropyl; propylamino; isopropylamino; cyclopentylamino; cyclohexylamino; 3'-hydroxypropylamino; or 4'-hydroxycyclohexylamino group, and if E represents an hydrogen atom, their physiologically compatible salts with inorganic or organic bases.

4. New β-lactams of the general formula (I) or (I') as claimed in any one of claims 1 to 3, wherein R, R_1 and X with D have the meanings mentioned in claim 1, 2 or 3, and E as a readily cleavable group represents the benzyl; diphenylmethyl; trityl; *t*-butyl; 2,2,2-trichloroethyl; or trimethylsilyl group, or an alkanoyloxyalkyl group with 1 to 5 carbon atoms in the alkanoyl radical, with 1 to 3 carbon atoms in the alkylen radical, or the phthalidyl or indanyl group.

5. New β-lactams of the general formula (Ia):



(Ia)

wherein:

R and R_1 are defined as mentioned in any one of claims 1 to 4, and *m* represents the number 0 or 1.

6. As new compounds:

a) D-α-[3-(2-p-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-ethoxycarbonyloxy-benzylpenicillin-sodium

b) D-α-[3-(2-*p*-Aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-methylcarbonyloxy-benzylpenicillin-sodium

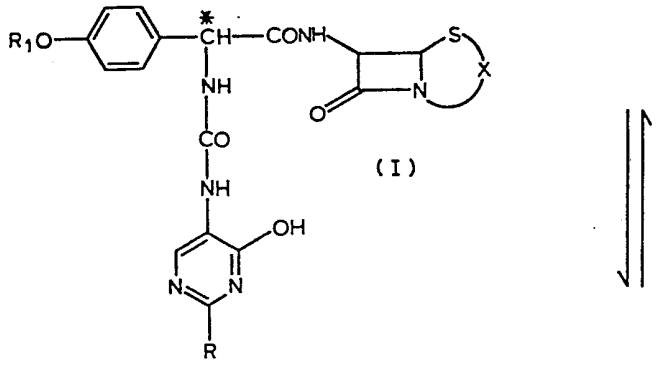
c) Sodium-7-{D-α-[3-(2-*p*-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-methylcarbonyloxy-phenylacetamido}- 3-[(1-methyl-tetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate

d) Sodium-7-{D-α-[3-(2-*p*-aminosulfonylanilino-4-hydroxy-5-pyrimidinyl)-ureido]-*p*-ethoxy-carbonyloxy-phenylacetamido}-3-[(1-methyl-tetrazole-5-yl)-thiomethyl]-ceph-3-em-4-carboxylate

and their physiologically compatible salts with inorganic or organic bases.

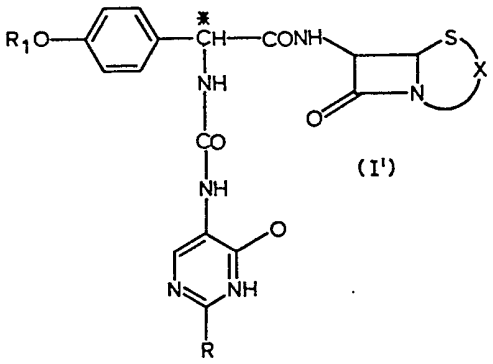
7. Pharmaceutical compositions containing one or more active ingredients of the general formula (I) or (I') or (Ia) as claimed in any one of claims 1 to 6 together with at least one pharmaceutically acceptable carrier and/or auxiliary and/or diluent.

8. A process for the preparation of new β-lactams of the general formulae (I) and (I'):



(I)

or

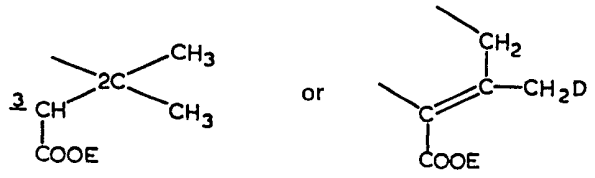


(I')

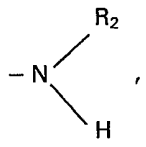
in which:

R, R_1 and X have the following meanings:

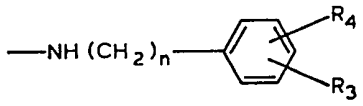
R_1 represents an aliphatic acyl or alkoxycarbonyl group with 2 to 5 carbon atoms or the aminocarbonyl group
X represents the group



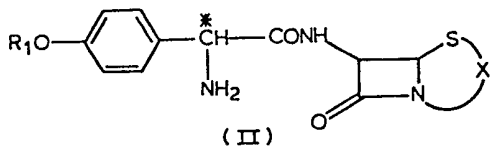
wherein:
D represents an hydrogen atom; an acetoxy; aminocarbonyloxy; pyridinium or 4-aminocarbonyl-pyridinium group; or the group -SHet, wherein Het represents the 1-methyltetrazole-5-yl; 1,2,4-thiadiazole-5-yl; 3-methyl-1,2,4-thiadiazole-5-yl; 1,3,4-thiadiazole-2-yl; 2-methyl-1,3,4-thiadiazole-5-yl; or 4-methyl-5,6-dioxo-1,2,4-triazine-3-yl group, and
E represents an hydrogen atom or an *in vitro* or *in vivo* easily cleavable protecting group;
R represents an hydrogen atom; the 3'-hydroxypropylamino; the cyclopropyl group; the 2'-hydroxypropylamino; the 4'-hydroxycylohexylamino group or a group of the general formula:



wherein R_2 represents hydrogen, a branched or unbranched alkyl or alkenyl group with 1 to 4 carbon atoms or a cycloalkyl radical with 1 to 6 carbon atoms, or
R represents a group of the general formula:

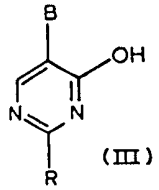


wherein
$n = 0$ or 1, and R_3 and R_4, which may be the same or different, represent hydrogen atoms; an hydroxy; acetylamino; aminocarbonylamino; nitro; amino-carbonyl; cyano; methylsufinyl; methylsulfonyl; aminosulfonyl; or methylaminosulfonyl group; and, if E represents an hydrogen atom, of their physiologicaly compatible salts with inorganic or organic bases, characterised in that
a) for the preparation of compounds of the general formula (I) or (I'), in which D has the above mentioned meanings except for that of a pyridinium or aminocarbonylpyrimidinium group, a compound of the general formula (II):



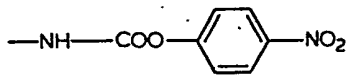
(II)

wherein:
R_1 and X have the above meanings, and D has the above meaning except for that of a pyridinium or aminocarbonylpyridinium group, is reacted with a pyrimidine derivative of the general formula (III):



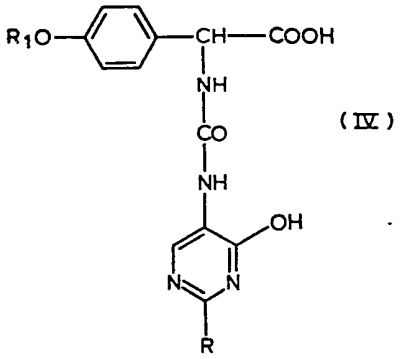
(III)

wherein
R is as defined above and B represents the group —NCO, —NHCOCl, —NHCOBr or



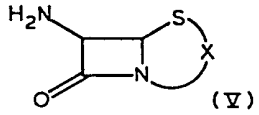
or with a mixture of such pyrimidine derivatives of the general formula (III), in which B has partly one and partly an other of the above meanings, in a solvent and at a pH range of between 2.0 and 9.0 at a temperature between −20°C and +50°C, or

b) for the preparation of a compound of the general formula (I) or (I'), in which D has the meanings mentioned above except for that of a pyridinium or aminocarbonylpyridinium group, an ureido-carboxylic acid of the general formula (IV):



(IV)

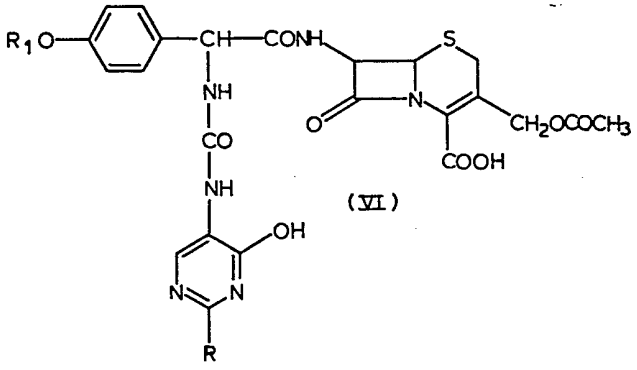
wherein R and R_1 have the above meanings or their salts or reactive derivatives, is reacted with a compound of the general formula (V):



(V)

wherein:
X has the above meanings except for that of the formula in which D represents pyridinium or amino-pyridinium, between −40°C and +40°C, in the presence of a solvent and, optionally, in the presence of a base,
or

c) for the preparation of cephalosporin derivatives of the general formula (I) or (I'), in which D represents an -S-Het, pyridinium or 4-aminocarbonyl-pyridinium group, a compound of the general formula (VI):



(VI)

which is comprised by the general formula (I) or (I') and in which R and R_1 have the above meanings, is reacted either with a compound of the general formula (VII):

Het − S − M (VII)

wherein:
Het has the above meanings and M represents an hydrogen atom or an alkali metal or alkaline earth metal or with pyridine or 4-aminocarbonylpyridine in an organic solvent or in water or in a mixture of these solvents at a pH range of the reaction solution of 2 - 10, advantageously of 4 - 8, and at a temperature in the range of 0° to 100°C, and, if desired, converting the resulting compound of the general formula (I) or (I'), in

which E represents an *in vitro* readily cleavable protective group, is thereafter converted into the free carboxylic acid of the general formula (I) or (I'), in which E represents an hydrogen atom, and/or a compound of the general formula (I) or (I'), in which E represents an hydrogen atom, is converted into its ester or, by means of an inorganic or organic base, into the corresponding salt.

9. A process as claimed in claim 8a, characterised in that a compound of the general formula (II), in which E represents an hydrogen atom, or one of its salts, with an inorganic or organic base is reacted with a compound of the general formula (III),

a) in water or in a solvent miscible with water in the presence of water in a pH range of 6.5 to 8.0, or

b) in an anhydrous solvent, or

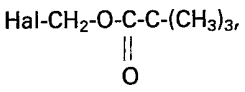
c) in a mixture of water and a solvent immiscible with water in a pH range of from 6.5 to 8.0,

or

a compound of the general formula (II), in which E represents a silyl group or another readily cleavable protective group, is reacted with a compound of the general formula (III) in an anhydrous solvent or in a solvent which is free of hydroxyl groups or an aprotic solvent, optionally in the presence of a base.

10. A process as claimed in claim 8b, characterised in that there is used as a reactive derivative of the ureidocarboxylic acid of the general formula (IV), its acid anhydride, reactive ester or reactive amide or its acid halogenide, and as a reactive ester of a compound of the general formula (V), the diphenylmethylester, the *t*-butylester, the trimethylsilylester or the N,0-bis-trimethylsilyl derivative, and in that the reaction is effected in the presence of a base and/or an organic solvent and/or a condensating agent, and, if desired, the thus obtained product of the general formula (I), in which E represents a readily cleavable protective group, is subsequently converted into a compound of the general formula (I), in which E represents an hydrogen atom.

11. A process as claimed in claim 8 for the preparation of a compound of the general formula (I) or (I'), wherein, in the group X, E represents the pivaloyloxymethyl radical, characterised in that a compound of the general formula (I) or (I'), in which E represents an hydrogen atom, is converted into its alkali metal salt, and said salt is reacted with a pivaloyloxymethyl halogenide of the general formula:



wherein:

Hal represents chlorine, bromine or iodine, in a solvent at a temperature between 20 and 45°C.

12. New β-lactams and salts thereof as claimed in claim 1 substantially as herein described with reference to any of the specific examples.

13. A process as claimed in claim 8 substantially as herein described with reference to any of the specific examples.

14. Compounds (I) and (I') and salts thereof as defined in claim 1, when prepared by a process as claimed in any of claims 8 to 11 and 13.

15. Compounds (I) and (I') and salts thereof as claimed in any of claims 1 to 6, 12 and 14 and pharmaceutical compositions as claimed in claim 7 or claim 14 for use in the treatment of microbial infections.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1982.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.