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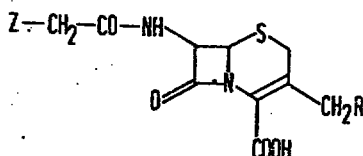
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(54) CEPHEM DERIVATIVES CONTAINING A PYRID-4-ONE NUCLEUS AND PROCESS FOR THEIR PREPARATION

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German body corporate, of 61 Darmstadt, Frankfurter Strasse 250, Germany, 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 present invention is concerned with certain novel cephem derivatives and with processes for their preparation.

According to one aspect of the present invention, we provide, as new compounds, cephem derivatives of formula I:



in which Z is a 1,4-dihydro-4-oxo-1-pyridyl radical which is unsubstituted or is mono- or poly-substituted by alkyl with 1 to 4 C atoms, alkoxy with 1 to 4 C atoms, OH, F, Cl, Br, I, NO₂ and/or NH₂,

R is H, —OCOCH₃ or —S—Het, and

Het is 3-methyl-1,2,4-thiadiazolyl-5, 5-methyl-1,3,4-oxadiazolyl-2, 5-hydroxymethyl-1,3,4-oxadiazolyl-2, 5-methyl-1,3,4-thiadiazolyl-2, 5-hydroxymethyl-1,3,4-thiadiazolyl-2, tetrazolyl-5, 1-methyltetrazolyl-5, 1,2,3-triazolyl-4-, 4-methyl-oxazolyl-2 or 1-oxido-pyridino-2, and their readily hydrolysable esters (as herein defined) and their physiologically acceptable salts.

The compounds according to the invention have excellent anti-bacterial activity against Gram-negative and Gram-positive bacteria. Compared with known semi-synthetic cephalosporins they have distinct differences with regard to the sensitivity of individual bacteria. In numerous cases, the activity of known cephalosporins is considerably surpassed by that of the new compounds so that the latter possess decisive therapeutic advantages in combating certain bacterial infections. Thus the minimum inhibitory concentration of 3 - (1 - methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dibromo - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and 3 - (1 - methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and of the potassium salts of these acids is lower, by a factor of 2 to 8, than that of Cephalothin and Cephalixin for a series of pathogens, among them *Escherichia coli*, *Salmonella typhimurium*, *Shigella krusei* and *Klebsiella pneumoniae*. Compared with Cephalothin, these compounds and 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid had, as shown by *in vivo* experiments in mice, 1 to 20 times activity (measured as DC 50) against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Salmonella newport*, *Klebsiella pneumoniae* and *Escherichia coli*. Furthermore, after parenteral administration of these compounds to dogs, serum concentrations were found which were comparable with those determined

analogously for cephalothin; 80—100% of the active compound administered was detected in the urine within 24 hours.

In the compounds according to the invention, the Z radical is preferably a 1,4-dihydro-4-oxo-1-pyridyl radical which is mono-, di- or tetra-substituted, preferably di-substituted, but may also be unsubstituted or tri-substituted. The substituents in the Z radical are preferably in the 3-position in the case of mono-substitution, in the 3- and 5- or in the 2- and 6- positions in the case of di-substitution, and in the 2-, 3- and 5-positions in the case of tri-substitution. Preferred substituents are Cl and Br, and also OH, F, I, NO₂ and NH₂. The alkyl substituent, when present, is preferably methyl, but may also be ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl. The alkoxy substituent, when present, is preferably methoxy, but may also be ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

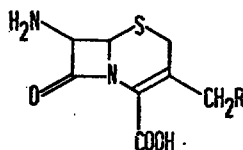
The following may be mentioned individually as preferred Z radicals, in addition to unsubstituted 1,4-dihydro-4-oxo-1-pyridyl: 3,5-dichloro-, 3,5-dibromo-, and also 3,5-difluoro-, 3,5-diiodo-, 3,5-dinitro-, 3,5-dihydroxy-, 3,5-dimethoxy-, 3,5-diamino-, 3-chloro-, 3-bromo-, 3-nitro-, 3-amino-, 3-hydroxy-, 3-methoxy-, 2,6-dimethyl-, 2,6-dimethyl-3,5-dichloro-, 2,6-dimethyl-3,5-dibromo-, 2,6-dimethyl-3,5-diiodo-, 3-chloro-5-nitro- and 3-bromo-5-nitro-, 3-chloro-5-amino-, 3-bromo-5-amino-, 3-chloro-5-hydroxy- and 3-bromo-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl. In addition, the Z group may, for example, be any of the following radicals: 3-fluoro-, 3-iodo-, 3-ethoxy-, 3-n-butoxy-, 3-methyl-, 3-ethyl-, 3-n-butyl-, 2,6-dimethyl-3-fluoro-, 2,6-dimethyl-3-chloro-, 2,6-dimethyl-3-bromo-, 2,6-dimethyl-3-iodo-, 2,6-dimethyl-3-hydroxy-, 2,6-dimethyl-3-nitro-, 2,6-dimethyl-3-amino-, 2,6-dimethyl-3-methoxy- and 2,6-dimethyl-3,5-difluoro-1,4-dihydro-4-oxo-1-pyridyl.

Among the heterocyclic radicals Het, the 1-methyl-tetrazolyl-5 radical and the 5-methyl-1,3,4-thiadiazolyl-2 radical are preferred.

The expression "readily hydrolysable esters" is used herein to refer to tert-butyl esters, trimethylsilyl esters, benzyl esters, benzhydryl esters, trichloroethyl esters, benzoylmethyl esters, p-methoxybenzyl esters, methoxymethyl esters, and pivaloyloxy-methyl esters. Of these, tert-butyl esters are particularly preferred.

According to another aspect of the present invention, we provide a process for the preparation of a cephem derivative according to the invention, which comprises:

(i) condensing a 3-CH₂R-7-amino-3-cephem-4-carboxylic acid of formula 2:



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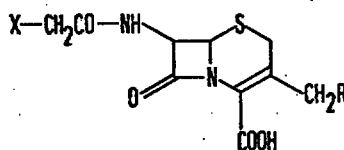
in which R has the above-stated meaning, or a functional derivative thereof, with a pyridoneacetic acid of formula 3:



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in which Z has the above-stated meaning, or a functional derivative thereof, or

(ii) condensing a 3-CH₂R-7-(X-acetamido)-3-cephem-4-carboxylic acid of formula



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in which X is Cl, Br or a reactive esterified OH group and R has the above-stated meaning, or a functional derivative thereof, with a pyridone of formula 5:



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in which Z has the above-stated meaning, or a functional derivative thereof, or

(iii) treating a compound which otherwise corresponds to formula 1 but contains at least one functionally modified OH, NH₂ or oxo group, with a solvolysing or hydrogenolysing agent in order to liberate said OH, NH₂ or oxo group.

The compound of formula 1 obtained by any of the foregoing processes may be treated, if desired, to replace R and/or Z by another R and/or Z substituent, by alkylating a hydroxyl group by treatment with an alkylating agent and/or by reducing a nitro group or an acetoxymethyl group by treatment with a reducing agent to give an amino group or a methyl group respectively, and/or by converting an acetoxy group into an —S—Het radical by treatment with a thiol of the formula Het—SH or with a corresponding mercaptide, and/or by converting a carbonyl group by treatment with an esterifying agent into a readily hydrolysable ester group.

In addition, when a salt or ester of a compound of formula 1 is obtained, it may, if desired, be solvolysed to liberate the compound of formula 1 therefrom or the compound of formula 1 obtained may, if desired, be treated with a base or an acid to form a physiologically acceptable salt thereof.

All these reactions may be carried out according to methods which are known in cephalosporin chemistry and are fully described in the literature.

The starting materials for the processes according to the invention are either known or can be prepared analogously to known compounds by methods which are in themselves known. For example, the acids 2 ($R = -S-Het$) can be obtained from 7-aminocephalosporanic acid (7-ACA: 2; $R = -OCOCH_3$) by reaction with the heterocyclic thiols of the formula $Het-SH$, which are for the most part known, or with the respective metal mercaptides, for example by reacting the corresponding alkali metal salts in hot aqueous acetone. The pyridoneacetic acids 3 can be obtained from the pyridones 5 by reacting the latter with chloroacetic acid or bromoacetic acid. The acids 4 can be obtained by methods which are in themselves known, for example from the acids 2 by reaction with a substituted acetic acid of the formula $X-CH_2COOH$ or a functional derivative thereof for example chloroacetyl chloride or bromoacetyl bromide. The X radical is preferably bromine, but it can also be Cl or a reactive esterified OH group, in particular alkylsulphonyloxy with 1 to 6 C atoms or arylsulphonyloxy with 6 to 10 C atoms, such as p-toluenesulphonyloxy. The substituted pyridones 5 can conveniently be prepared from 4-pyridone by substitution.

Suitable functional derivatives of the acids 2 and 4 are, in particular, readily hydrolysable esters, for example the tert.-butyl esters, the trimethylsilyl esters (which may be formed, for example, *in situ* from 2 or 4 and N-trimethylsilyl-acetamide) and the other esters indicated above. The salts, particularly the neutral salts, of these acids are also suitable. The alkali metal salts (for example, sodium and potassium salts), alkaline earth metal salts (for example, magnesium and calcium salts) and ammonium salts are particularly suitable. Amongst the latter, salts derived from amines, especially from tertiary amines, for example triethylamine, triethanolamine, pyridine and collidine, are preferred. These salts can be employed as such in the reaction; they can also be formed *in situ* from the acid 2 or 4 and a base, for example $NaHCO_3$, $NaHPO_4$ or triethylamine.

Suitable functional derivatives of the acids 3 are, in particular, the halides, preferably the chlorides and bromides, and also the anhydrides and mixed anhydrides as well as the azides and reactive esters, for example the esters formed with p-nitrophenol, 2,4-dinitrophenol, p-nitrophenylmercaptan, methylenecyanohydrin or N-hydroxysuccinimide. Examples of suitable mixed anhydrides of the acids 3 are, on the one hand, mixed anhydrides with lower alkanolic acids, particularly acetic acid and substituted acetic acids, for example, trichloroacetic acid, pivalic acid or cyanoacetic acid and, on the other hand, anhydrides with carbonic acid half-esters, which can be obtained, for example, by reacting the acids 3 with chloroformic acid benzyl ester, p-nitrobenzyl ester, isobutyl ester, ethyl ester or allyl ester. All these functional derivatives of 3 are preferably produced *in situ*.

Preferred functional derivatives of the pyridones 5 are their salts, for example the Na salts and K salts. These can be obtained from 5, for example, by means of metallic Na or K in a high boiling, inert solvent, such as toluene, or by means of NaH even in the cold.

The reaction of the cephem derivatives 2 or 4 (or their functional derivatives) with the pyridone derivatives 3 or 5 (or with their functional derivatives) is preferably carried out in the presence of an inert solvent. Suitable solvents are, for example, chlorinated hydrocarbons, such as methylene chloride and chloroform; ethers, such as diethyl ether, tetrahydrofuran and dioxan; ketones, such as acetone and butanone; amides such as dimethylformamide (DMF), dimethylacetamide and hexamethylphosphoric acid triamide; sulfoxides, such as dimethylsulphoxide (DMSO); water; and also organic bases or aqueous inorganic bases. Mixtures of two or more of the solvents mentioned can also be used. If it is intended to prepare a salt of a compound of

formula 1, an excess of the base required to form the desired salt is particularly suitable as the solvent, for example, triethylamine or aqueous sodium hydroxide solution.

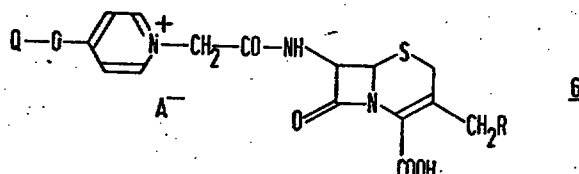
The reaction of 2 with 3 or of 4 with 5 (or their functional derivatives) is preferably carried out at a temperature of from -70° to $+80^{\circ}\text{C}$, preferably from -40° to $+30^{\circ}\text{C}$, and particularly between 0°C and room temperature. The duration of the reaction depends on the nature of the starting materials used and on the reaction temperature; it is normally between 5 minutes and 72 hours.

In detail, it is particularly preferred to react an ester, preferably a tert.-butyl ester, of the acid 2 with the free pyridoneacetic acid 3, a dehydrating agent preferably also being present. Examples of suitable dehydrating agents are carbodiimides, particularly dicyclohexylcarbodiimide (DCC). Thus, for example, 7-ACA tert.-butyl ester, the acid 3 and DCC are reacted, in substantially equimolar proportions and with cooling, in an inert solvent, preferably methylene chloride, DMF, DMSO or a mixture of two or more thereof.

The reaction of 2 with a functional derivative of an acid 3 and the reaction of 4 and 5 is preferably carried out in an alkaline medium. Either the pyridone 5 is used in the form of a salt, for example an alkali metal salt, or a base is added to the reaction mixture, particularly NaHCO_3 , KHCO_3 , Na_2CO_3 , K_2CO_3 , NaOH , KOH , pyridine or a base of low nucleophilic character, for example a tertiary amine, such as triethylamine, N-methylmorpholine or ethyldiisopropylamine, or potassium tert.-butoxide.

The cephem derivatives of formula 1 can also be obtained by liberating, by methods which are in themselves known, functionally modified $\text{OH}-$, NH_2- or oxo-groups contained in a compound which otherwise corresponds to formula 1. The starting materials for this variant of the process can be obtained, for example, analogously to the methods described above, sensitive functional groups being, however, functionally modified by protective groups during the synthesis.

Examples of suitable functionally modified groups are: etherified or esterified hydroxyl groups, for example benzyloxy or acetoxy; and benzylated or acylated amino groups, for example benzylamino, benzyloxycarbonyl, tert.-butoxycarbonyl and acetylamino, which protective groups are those which are customarily used in peptide chemistry. The oxo group of the pyridone ring can be functionally modified in the form of a derivative of the corresponding enol form, for example in the form of quaternary salts of formula 6:



in which Q is a radical which can be removed solvolytically, hydrogenolytically or catalytically, particularly a readily hydrolysable ether or ester group and A is any desired anion, preferably chlorine or bromine, and in which the pyridine group can be substituted in the same way as the Z radical, and readily hydrolysable esters. The corresponding benzyl ethers and tert.-butyl ethers are particularly suitable. Instead of 6, a corresponding Zwitter ion, which can be formed by elimination of HA from 6, is also suitable.

The functionally modified groups can be liberated solvolytically, particularly hydrolytically, or hydrogenolytically by methods which are in themselves known and are described in the literature. Solvolysis, preferably a hydrolysis, may be carried out, for example with trifluoroacetic acid or with aqueous mineral acids, for example hydrochloric acid, at a temperature of from -10°C to 50°C . Hydrogenolysis of functionally modified groups, particularly the splitting off of benzyl and carbobenzyloxy radicals, is preferably carried out by hydrogenation in the presence of noble metal catalysts, such as 5–50% palladium on charcoal, or palladium oxide. Hydrogenolysis is preferably carried out at a temperature of from -10° to $+50^{\circ}\text{C}$, particularly at room temperature, and at a pressure from 1 to 100 atmospheres, preferably at normal pressure. It is possible, and is frequently desired, to direct the hydrogenolysis in such a manner that further reductive modifications in the molecule take place at the same time; for example, an acetoxymethyl group in the 3-position can be reduced to a methyl group.

If desired, in the resulting product of formula 1, an R substituent can be replaced by another R substituent and/or a Z substituent Z can be replaced by another Z substituent, by methods which are known in themselves from the literature.

For example, a hydroxyl group may be alkylated by treatment with an alkylating agent, for example with diazomethane, methyl bromide, methyl iodide, dimethyl sulphate or diethyl sulphate, ethyl chloride, bromide or iodide, n-propyl chloride, bromide or iodide, or n-butyl chloride, bromide or iodide.

A nitro group on the pyridone ring may also, for example, be reduced to an amino group. In principle, any known method for the reduction of nitro groups can be used for this purpose as long as it does not produce undesired modifications in the remainder of the molecule. Catalytic hydrogenation is particularly suitable and may be carried out, for example, with noble metal catalysts, such as palladium, at room temperature and normal pressure.

The reductive conversion of an acetoxymethyl group into a methyl group may also be carried out by hydrogenation with noble metal catalysts, such as palladium, the reaction preferably being carried out at a low temperature, but at somewhat elevated pressures (from 2 to 10 atmospheres).

If desired, several of the reductive conversions described can be carried out in one step. Thus it is possible, by hydrogenating a cephalosporanic acid *1* ($R = -\text{OCOCH}_3$) which is substituted in the Z radical by a nitro group, to prepare the corresponding desacetoxyccephalosporanic acid *1* ($R = \text{H}$) which is substituted in the Z radical by an amino group.

A resulting cephalosporanic acid of formula *1* ($R = -\text{OCOCH}_3$) may also be converted into the corresponding thioether *1* ($R = -\text{SHet}$) by reaction with a mercaptan of the formula Het-SH . A salt of the cephalosporanic acid is preferably reacted with a salt of the thiol in aqueous acetone at a temperature of from 20° to 100°C and a pH of from 4 to 8. Suitable salts are, in particular, the alkali metal salts, preferably the sodium salts.

A free carboxylic acid *1* may also be converted by esterification into a readily hydrolysable ester thereof. For example, the tert.-butyl ester is obtained by reacting the acid with isobutylene.

Conversely, the acid *1* can be liberated from a resulting salt or ester, for example by solvolysis, particularly by acid hydrolysis. The tert.-butyl esters, which are preferably obtained in the synthesis, are split, for example, by trifluoroacetic acid at a temperature of from 0° to 40°C.

The novel cephem derivatives are solid, crystalline or amorphous products. They form solid, frequently crystalline, alkali metal salts, ammonium salts and alkaline earth metal salts, as well as salts with organic bases such as diethylamine, triethylamine, diethanolamine, N-ethyl-diethanolamine, pyrrolidine, piperidine, N-ethylpiperidine, 1-(2-hydroxyethyl)-piperidine, morpholine, procaine, benzylamine, dibenzylamine, 1-phenyl-2-propylamine and other amines such as are customarily used for the preparation of cephalosporin salts.

Of the alkali metal salts, the sodium salts and the potassium salts are of particular importance. They can be prepared by treating a solution of an acid *1* in an organic solvent with a solution of the sodium salt or potassium salt of a fatty acid, for example diethylacetic acid or 2-ethylcaproic acid, in a solvent, for example acetone or n-butanol, or a mixture of solvents. The sodium or potassium salt which is then precipitated or after adding ether, can be filtered off.

Basic compounds of formula *1* can be converted into the corresponding acid addition salts, for example into the hydrochloride or citrates, by treatment with an acid in the customary way.

Since the compounds *1* do not have sharp melting points, they are preferably characterised by other physical characteristics, preferably by their infra-red spectra. In the infra-red spectrum, they exhibit the absorption band of the β -lactam ring at 1,760—1,800 cm^{-1} . They can also be characterised by their nuclear magnetic resonance spectra and by thin layer chromatography, for which purpose thin layer silica gel chromatographic plates F₂₅₄ manufactured by E. Merck are preferably used (a suitable migrating agent being dioxan/water 85:15).

The compounds according to the invention can be used in human or veterinary medicine in admixture with solid, liquid or semi-liquid inert, physiologically acceptable carriers or excipients. Suitable carriers are those organic and inorganic substances which are suitable for enteral, parenteral or topical administration and which do not react with the novel compounds, such as water, vegetable oils, benzyl alcohol, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, petroleum jelly or cholesterol. Compositions for enteral administration may take the form of tablets, capsules, dragees, syrups, elixirs or suppositories. For parenteral administration, the composition preferably takes the form of a solution, preferably an oily or aqueous solution, or a suspension, emulsion or implant; for topical application, ointments,

creams or powders may be used. Such compositions may, if desired, be sterilised or may contain auxiliary substances, emulsifiers, salts for controlling the osmotic pressure, buffer substances or colouring substances. They may also contain further active compounds.

When the composition is in dosage unit form, each dosage unit preferably contains from 1 to 5,000, more preferably from 200 to 2,000, mg of one or more of the novel compounds. Compositions suitable for parenteral (for example, intravenous or intramuscular) administration are preferred.

All the compounds of formula 1 mentioned in the following examples are particularly suitable for the production of pharmaceutical compositions.

In order that the invention may be more fully understood, the following Examples are given by way of illustration. In these Examples: all temperatures are in °C; the IR spectra were recorded in KBr; DMF=dimethylformamide; 7-ACA=7-aminocephalosporanic acid; and DCC=dicyclohexylcarbodiimide.

Example 1

a) A solution of 12.5 g of 7-ACA-tert.-butyl ester and 8.9 g of DCC in 100 ml of methylene chloride/DMF 1:1 was cooled to 0°. 12.8 of 3,5-dibromo-4-pyridone-1-acetic acid were added, the ice bath was removed after 5 minutes and the mixture was stirred for a further 30 minutes at 25°. The urea formed was filtered off and the filtrate was filtered through silica gel (migrating agent: ethyl acetate/1% methanol). The solvent was evaporated and the resulting 7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester was crystallised from ether.

b) 22 g of the tert.-butyl ester were dissolved in 30 ml of trifluoroacetic acid. After 30 minutes, the mixture was evaporated and the resulting 7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid was crystallised from ether.

IR: 1,780, 1,680, 1,630, 1,590, 1,220 cm⁻¹.

Analogously, there were obtained from:

4-pyridone-1-acetic acid,
2,6-dimethyl-4-pyridone-1-acetic acid,
3-methoxy-4-pyridone-1-acetic acid,
3-n-butoxy-4-pyridone-1-acetic acid,
3-hydroxy-4-pyridone-1-acetic acid,
3-fluoro-4-pyridone-1-acetic acid,
3-chloro-4-pyridone-1-acetic acid,
3-bromo-4-pyridone-1-acetic acid,
3-iodo-4-pyridone-1-acetic acid,
3,5-difluoro-4-pyridone-1-acetic acid,
3,5-dichloro-4-pyridone-1-acetic acid (this compound is the subject of our Application No. 52762/75), (Serial No. 1436990),
3,5-diiodo-4-pyridone-1-acetic acid,
2,6-dimethyl-3,5-dichloro-4-pyridone-1-acetic acid,
2,6-dimethyl-3,5-dibromo-4-pyridone-1-acetic acid,
2,6-dimethyl-3,5-diiodo-4-pyridone-1-acetic acid,
3-nitro-4-pyridone-1-acetic acid,
3,5-dinitro-4-pyridone-1-acetic acid,
3-chloro-5-nitro-4-pyridone-1-acetic acid,
3-bromo-5-nitro-4-pyridone-1-acetic acid,
3-chloro-5-amino-4-pyridone-1-acetic acid,
3-bromo-5-amino-4-pyridone-1-acetic acid,
3-methyl-5-chloro-4-pyridone-1-acetic acid,
3-methyl-5-bromo-4-pyridone-1-acetic acid,
3-chloro-5-hydroxy-4-pyridone-1-acetic acid,
3-bromo-5-hydroxy-4-pyridone-1-acetic acid,
3-bromo-5-chloro-4-pyridone-1-acetic acid, and
3-bromo-5-fluoro-4-pyridone-1-acetic acid, and
3-chloro-5-fluoro-4-pyridone-1-acetic acid,

by reaction with 7-ACA, via the corresponding tert.-butyl esters:

7-(1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(2,6-dimethyl-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-methoxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-n-butoxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,

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- 7-(3-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-fluoro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-bromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-iodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3,5-difluoro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
IR: 1,760, 1,730, 1,700, 1,670, 1,600, 1,390, 1,220 cm^{-1} ;
7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid, K salt,
IR: 1,770, 1,620, 1,580, 1,290, 1,240 cm^{-1} ;
7-(2,6-dimethyl-3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalo-
sporanic acid,
7-(2,6-dimethyl-3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalo-
sporanic acid,
7-(2,6-dimethyl-3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalo-
sporanic acid,
7-(3-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3,5-dinitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid, K salt,
IR: 1,780, 1,730, 1,680, 1,620, 1,520, 1,330, 1,230 cm^{-1} ;
7-(3-chloro-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-bromo-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-chloro-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-bromo-5-acetamino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic
acid,
7-(3-methyl-5-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic
acid,
7-(3-methyl-5-bromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic
acid,
7-(3-chloro-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic
acid,
7-(3-bromo-5-hydroxy-1,4-dihydro-4-oxo-1-pyridylacetamido)-cephalosporanic
acid,
7-(3-bromo-5-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
7-(3-bromo-5-fluoro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid,
and
7-(3-chloro-5-fluoro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic
acid.

c) 6.78 g of the resulting 7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-
cephalosporanic acid were dissolved in 60 ml of saturated aqueous sodium bicarbonate
solution at a pH of less than 7 and 1.2 g of 1-methyltetrazole-5-thiol in 20 ml of
acetone were added. The reaction solution was stirred under nitrogen for 2 hours at
80° and a pH of 6.3. The acetone was then removed, the solution washed with ether
and acidified to pH 2 and the resulting 3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3,5-
dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid was fil-
tered off and dried. K salt, IR: 1,765, 1,630, 1,600, 1,390, 1,360, 1,220 cm^{-1} .
The following were obtained analogously from the corresponding cephalosporanic
acids:

- 3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(1,4-dihydro-4-oxo-1-pyridyl-
acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(2,6-dimethyl-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-methoxy-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-n-butoxy-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-hydroxy-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-fluoro-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-chloro-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptopmethyl)-7-(3-bromo-1,4-dihydro-4-oxo-1-
pyridyl-acetamido)-3-cephem-4-carboxylic acid,

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- 3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-iodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3,5-difluoro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid, K salt, IR: 1,770, 1,690, 1,630, 1,590, 1,220 cm^{-1} ;
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid, K salt, IR: 1,760, 1,660, 1,610, 1,570, 1,390, 1,360, 1,210 cm^{-1} ;
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(2,6-dimethyl-3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(2,6-dimethyl-3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(2,6-dimethyl-3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3,5-dinitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-chloro-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-bromo-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-chloro-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-bromo-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-chloro-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-bromo-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid, and
3-(1-methyltetrazolyl-5-mercaptomethyl)-7-(3-bromo-5-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid.

Analogously, there were obtained from the following:

- 3-methyl-1,2,4-thiadiazole-5-thiol,
5-methyl-1,3,4-oxadiazole-2-thiol,
5-hydroxymethyl-1,3,4-oxadiazole-2-thiol,
5-methyl-1,3,4-thiadiazole-2-thiol,
5-hydroxymethyl-1,3,4-thiadiazole-2-thiol,
tetrazole-5-thiol,
1,2,4-triazole-4-thiol,
4-methyl-oxazole-2-thiol, and
2-mercaptopyridine-N-oxide,

by reaction with the corresponding cephalosporanic acids:

- 3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt,
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt,
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-bromo-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid Na salt, IR: 1,770, 1,700, 1,650, 1,620, 1,530, 1,370, 1,335, 1,300, 1,235 cm^{-1} ;
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-chloro-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid Na salt, IR: 1,765, 1,655, 1,615, 1,365, 1,330, 1,290, 1,230 cm^{-1} ;
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-bromo-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-chloro-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,

	3-(3-methyl-1,2,4-thiadiazolyl-5-mercapto-methyl)-7-(3-bromo-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
	3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-chloro-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
5	3-(3-methyl-1,2,4-thiadiazolyl-5-mercaptomethyl)-7-(3-bromo-5-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	5
	3-(5-methyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,755, 1,675, 1,580, 1,470, 1,380, 1,345, 1,210 cm ⁻¹ ;	
10	3-(5-methyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,680, 1,620, 1,590, 1,380, 1,350, 1,210 cm ⁻¹ ;	10
	3-(5-methyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,675, 1,605, 1,345, 1,200 cm ⁻¹ ;	
15	3-(5-hydroxymethyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	15
	3-(5-hydroxymethyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
20	3-(5-hydroxymethyl-1,3,4-oxadiazolyl-2-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	20
	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid; K salt, IR: 1,770, 1,690, 1,640, 1,590, 1,380, 1,220 cm ⁻¹ ;	
25	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,690, 1,620, 1,590, 1,390, 1,360, 1,220 cm ⁻¹ ;	25
	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
30	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3-bromo-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid Na salt, IR: 1,770, 1,695, 1,650, 1,620, 1,375, 1,330, 1,230 cm ⁻¹ ;	30
	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3-chloro-5-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid Na salt, IR: 1,765, 1,660, 1,620, 1,385, 1,330, 1,235 cm ⁻¹ ;	
35	3-(5-methyl-1,3,4-thiadiazolyl-2-mercapto-methyl)-7-(3-bromo-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	35
	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3-chloro-5-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
40	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3-bromo-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	40
	3-(5-methyl-1,3,4-thiadiazolyl-2-mercapto-methyl)-7-(3-chloro-5-hydroxy-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
45	3-(5-methyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3-bromo-5-chloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	45
	3-(5-hydroxymethyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	
50	3-(5-hydroxymethyl-1,3,4-thiadiazolyl-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,	50
	3-(tetrazolyl-5-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,630, 1,590, 1,220 cm ⁻¹ ;	
55	3-(tetrazolyl-5-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,630, 1,590, 1,220 cm ⁻¹ ;	55
	3-(tetrazolyl-5-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt,	
60	3-(1,2,3-triazolyl-4-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,680, 1,630, 1,590, 1,360, 1,220 cm ⁻¹ ;	60
	3-(1,2,3-triazolyl-4-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,620, 1,590, 1,390, 1,360, 1,220 cm ⁻¹ ;	
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- 3-(1,2,3-triazolyl-4-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,670, 1,620, 1,360, 1,220 cm^{-1} ;
- 5 3-(4-methyl-oxazolyl-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, 5
- 3-(4-methyloxazolyl-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt,
- 3-(4-methyloxazolyl-2-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid,
- 10 3-(1-oxido-pyridino-2-mercaptomethyl)-7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid, 10
- 3-(1-oxido-pyridino-2-mercaptomethyl)-7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid K salt, IR: 1,760, 1,680, 1,620, 1,580, 1,470, 1,350, 1,220 cm^{-1} ; and
- 15 3-(1-oxido-pyridino-2-mercaptomethyl)-7-(3,5-diiodo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-3-cephem-4-carboxylic acid. 15

Example 2

- 28 mg of 7-aminodesacetoxycephalosporanic acid tert.-butyl ester (obtainable from the acid and isobutylene in dioxan/ H_2SO_4 at 25°), 59 mg of 3,5-diiodo-4-pyridone-1-acetic acid and 38 mg of DCC were dissolved in 2 ml of absolute methylene chloride with ice cooling and were stirred for a further 2 hours at 25° . The reaction mixture was purified by passage through silica gel using ethyl acetate/methanol as the migration solvent and the eluate was evaporated and the residue crystallised from ether. 7-(3,5 - Diiodo - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - desacetoxycephalosporanic acid tert.-butyl ester was obtained. K salt of the free acid,
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- IR: 1,760, 1,670, 1,600, 1,400, 1,360, 1,210 cm^{-1} .

The following were obtained analogously from the corresponding pyridone-acetic acids:

- 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-desacetoxycephalosporanic acid, and
- 30 7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-desacetoxycephalosporanic acid. 30

Example 3

- a) 297 mg of 3-nitro-4-pyridone-1-acetic acid, 328 mg of 7-ACA tert.-butyl ester and 312 mg of DCC were dissolved in 3 ml of dimethylsulphoxide and were stirred for 7 minutes at 25° . The reaction mixture was poured into 100 ml of water and the resulting precipitate was filtered off with suction, dissolved as far as possible in methylene chloride, and the solution filtered through silica gel. After evaporation, 7-(3-nitro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester was obtained; IR: 1,790, 1,730, 1,710, 1,660, 1,610, 1,520, 1,380, 1,330, 1,240, 1,160 cm^{-1} . Free acid, IR: 3,300, 1,770, 1,710, 1,680, 1,660, 1,590, 1,560, 1,330, 1,250, 1,230 cm^{-1} .
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- b) 200 mg of the tert.-butyl ester were dissolved in 60 ml of methanol and were hydrogenated for 15 minutes at 25° and normal pressure in the presence of 200 mg of 5% Pd-charcoal. The catalyst was filtered off, the solution was evaporated and the residue was crystallised by means of ether. 7-(3-Amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester was obtained. Free acid, IR: 3,350, 1,780, 1,670, 1,540, 1,390, 1,240, 1,080, 1,040 cm^{-1} .
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Example 4

- 0.224 ml of trichloroacetyl chloride was added to 443 mg of 3,5-dichloro-4-pyridone-1-acetic acid in 10 ml of absolute DMF with ice cooling. After stirring for 30 minutes, a solution of 554 mg of 7-ACA and 1 g of N-trimethylsilyl-acetamide in 5 ml of DMF was added. The mixture was stirred for a further 30 minutes with ice cooling and was then poured into water and the pH adjusted to 5. After washing with ether, the pH was adjusted to 2 and the mixture was extracted with ethyl acetate; the extract was dried and evaporated and the residue was crystallised by means of ether to give 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid.
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Example 5

- 0.224 ml of trichloroacetyl chloride was added to 443 mg of 3,5-dichloro-4-pyridone-1-acetic acid in 5 ml of absolute DMF. After stirring for 30 minutes, a
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solution of 554 mg of 7-ACA and 0.84 ml of triethylamine in 20 ml of methylene chloride was added. The mixture was stirred for a further 30 minutes and then poured into water and the pH adjusted to 6. After washing with methylene chloride, the mixture was worked up in the usual manner to give 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid.

Example 6

336 mg of 3,5-dibromo-1,4-dihydro-4-oxo-1-pyridylacetyl azide were added in portions, with stirring, to a solution of 272 mg of 7-ACA and 1 ml of triethylamine in 10 ml of methylene chloride at 0°. The mixture was stirred for a further hour and filtered with suction to give 7-(3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid.

Example 7

10 g of 7-ACA were suspended in 95 ml of absolute methylene chloride, the suspension was cooled to -10°, the 7-ACA was dissolved, while stirring, by the addition of 12.9 ml of triethylamine, and the solution was stirred for a further 45 minutes at -30°. A freshly prepared solution of 3,5-dichloro-4-pyridone-1-acetyl chloride (obtained by dropwise addition of 2.68 ml of thionyl chloride to a solution of 8.12 g of 3,5-dichloro-4-pyridone-1-acetic acid in 40 ml of DMF at -40°) was then added dropwise at a temperature below -20°, and the mixture was stirred for a further 45 minutes at -20°, allowed to warm up to 0° and extracted repeatedly with aqueous sodium bicarbonate solution. The separated aqueous phases were combined and acidified with hydrochloric acid and extracted with tetrahydrofuran/ethyl acetate. The organic phases were dried over sodium sulphate and evaporated to give 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid.

Example 8

a) 24 mg of NaH were added to a solution of 95 mg of 4-pyridone in 3 ml of absolute DMF. The mixture was cooled with ice and 495 mg of 7-bromoacetamido-cephalosporanic acid tert.-butyl ester were added and the whole was allowed to come to room temperature and poured into 60 ml of water. After washing with ether, the solution was extracted with methylene chloride and the extract was dried. 7-(1,4-Dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester was precipitated with ether. IR: 1,780, 1,730, 1,640, 1,560, 1,250, 1,240, 1,160 cm⁻¹.

b) 200 mg of the tert.-butyl ester were dissolved in 3 ml of trifluoroacetic acid. After standing for half an hour, the mixture was evaporated and the residue was dissolved in a little methanol and the product precipitated by means of ether. 7-(1,4-Dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid was obtained.

The corresponding cephalosporanic acids were obtained analogously, via the corresponding tert.-butyl esters, from:

2,6-dimethyl-4-pyridone,
3-methoxy-4-pyridone,
3-n-butoxy-4-pyridone,
3-hydroxy-4-pyridone,
3-fluoro-4-pyridone,
3-chloro-4-pyridone,
3-bromo-4-pyridone,
3-iodo-4-pyridone,
3,5-difluoro-4-pyridone (obtainable from 4-pyridone and CF₃OF),
3,5-dichloro-4-pyridone,
3,5-dibromo-4-pyridone,
3,5-diiodo-4-pyridone,
2,6-dimethyl-3,5-dichloro-4-pyridone,
2,6-dimethyl-3,5-dibromo-4-pyridone,
2,6-dimethyl-3,5-diiodo-4-pyridone,
3-nitro-4-pyridone,
3,5-dinitro-4-pyridone,
3-chloro-5-nitro-4-pyridone, and
3-bromo-5-nitro-4-pyridone.

c) 150 mg of the acid were dissolved in a little methanol, a methanolic solution of the potassium salt of diethylacetic acid was added and the product was precipitated with ether. The corresponding potassium salt was obtained.

d) A solution of 407 mg of 7-(1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid and 500 mg of ammonium bicarbonate in 5 ml of water was hydrogenated at 0° and 3.5 atmospheres in the presence of 30 mg of hydrated palladium oxide. After the usual working up, 7-(1,4-dihydro-4-oxo-1-pyridyl-acetamido)-desacetoxy-cephalosporanic acid was obtained.

Example 9

A solution of 535 mg of 7-(3-benzylamino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester (obtainable from 3-benzylamino-1,4-dihydro-4-oxo-1-pyridylacetic acid and 7-ACA tert.-butyl ester) in 100 ml of methanol was hydrogenated in the presence of 300 mg of 5% Pd-charcoal at 25° and normal pressure until the absorption of hydrogen ceased. The mixture was filtered and evaporated to give 7-(3-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester.

The compounds according to the invention can be formulated as pharmaceutical compositions using known procedures and materials. The following Example of a pharmaceutical composition is given by way of illustration:

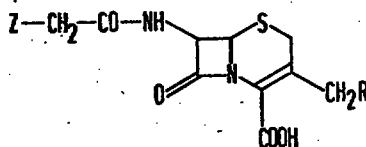
Example A: Ampoules

A solution was formed by dissolving 1 kg of the potassium salt of 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid in 3 litres of twice-distilled water, the solution was filtered under sterile conditions and filled into ampoules. The solution was then lyophilised and the ampoules closed under sterile conditions. Each ampoule contained 1 g of the said compound.

For the purpose of making up injectable solutions of this lyophilised product, ampoules of a suitable solvent were also prepared by dissolving 50 g of lidocaine hydrochloride in 3 litres of twice-distilled water and filling the solution, after filtration under sterile conditions into ampoules which were sterilised at 120° for 20 minutes. Each solution ampoule contained 50 mg of lidocaine hydrochloride in 3 ml of water, this quantity of solution being suitable for dissolving the 1 g of lyophilised product referred to above. (The lidocaine hydrochloride, a local anaesthetic, was included in the injection solution to mask pain that may be experienced on injection, particularly intramuscular injection, of the active compound).

WHAT WE CLAIM IS:—

1. Cephem derivatives of formula I:



in which Z is a 1,4-dihydro-4-oxo-1-pyridyl radical which is unsubstituted or is mono- or poly-substituted by alkyl with 1 to 4 C atoms, alkoxy with 1 to 4 C atoms, OH, F, Cl, Br, I, NO₂ and/or NH₂,

R is H, —OCOCH₃, or —S—Het, and

Het is 3-methyl-1,2,4-thiadiazolyl-5, 5-methyl-1,3,4-oxadiazolyl-2, 5-hydroxy-methyl-1,3,4-oxadiazolyl-2, 5-methyl-1,3,4-thiadiazolyl-2, 5-hydroxymethyl-1,3,4-thiadiazolyl-2, tetrazolyl-5, 1-methyltetrazolyl-5, 1,2,3-triazolyl-4, 4-methyl-oxazolyl-2 or 1-oxido-pyridino-2, and their readily hydrolysable esters (as herein defined) and their physiologically acceptable salts.

2. Cephem derivatives according to claim 1, in which Z is a 3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl radical or a 3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl radical.

3. Cephem derivatives according to claim 1, in which R is a 1-methyl-tetrazolyl-5-mercapto radical.

4. 7 - (3,5 - Dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - cephalosporanic acid.

5. 3 - (1 - Methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl-acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.

6. 3 - (1 - Methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dibromo - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.



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d) A solution of 407 mg of 7-(1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid and 500 mg of ammonium bicarbonate in 5 ml of water was hydrogenated at 0° and 3.5 atmospheres in the presence of 30 mg of hydrated palladium oxide. After the usual working up, 7-(1,4-dihydro-4-oxo-1-pyridyl-acetamido)-desacetoxy-cephalosporanic acid was obtained.

Example 9

A solution of 535 mg of 7-(3-benzylamino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester (obtainable from 3-benzylamino-1,4-dihydro-4-oxo-1-pyridylacetic acid and 7-ACA tert.-butyl ester) in 100 ml of methanol was hydrogenated in the presence of 300 mg of 5% Pd-charcoal at 25° and normal pressure until the absorption of hydrogen ceased. The mixture was filtered and evaporated to give 7-(3-amino-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid tert.-butyl ester.

The compounds according to the invention can be formulated as pharmaceutical compositions using known procedures and materials. The following Example of a pharmaceutical composition is given by way of illustration:

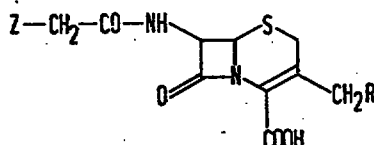
Example A: Ampoules

A solution was formed by dissolving 1 kg of the potassium salt of 7-(3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl-acetamido)-cephalosporanic acid in 3 litres of twice-distilled water, the solution was filtered under sterile conditions and filled into ampoules. The solution was then lyophilised and the ampoules closed under sterile conditions. Each ampoule contained 1 g of the said compound.

For the purpose of making up injectable solutions of this lyophilised product, ampoules of a suitable solvent were also prepared by dissolving 50 g of lidocaine hydrochloride in 3 litres of twice-distilled water and filling the solution, after filtration under sterile conditions into ampoules which were sterilised at 120° for 20 minutes. Each solution ampoule contained 50 mg of lidocaine hydrochloride in 3 ml of water, this quantity of solution being suitable for dissolving the 1 g of lyophilised product referred to above. (The lidocaine hydrochloride, a local anaesthetic, was included in the injection solution to mask pain that may be experienced on injection, particularly intramuscular injection, of the active compound).

WHAT WE CLAIM IS:—

1. Cephem derivatives of formula 1:



in which Z is a 1,4-dihydro-4-oxo-1-pyridyl radical which is unsubstituted or is mono- or poly-substituted by alkyl with 1 to 4 C atoms, alkoxy with 1 to 4 C atoms, OH, F, Cl, Br, I, NO₂ and/or NH₂,

R is H, —OCOCH₃ or —S—Het, and

Het is 3-methyl-1,2,4-thiadiazolyl-5, 5-methyl-1,3,4-oxadiazolyl-2, 5-hydroxy-methyl-1,3,4-oxadiazolyl-2, 5-methyl-1,3,4-thiadiazolyl-2, 5-hydroxymethyl-1,3,4-thiadiazolyl-2, tetrazolyl-5, 1-methyltetrazolyl-5, 1,2,3-triazolyl-4, 4-methyl-oxazolyl-2 or 1-oxido-pyridino-2, and their readily hydrolysable esters (as herein defined) and their physiologically acceptable salts.

2. Cephem derivatives according to claim 1, in which Z is a 3,5-dichloro-1,4-dihydro-4-oxo-1-pyridyl radical or a 3,5-dibromo-1,4-dihydro-4-oxo-1-pyridyl radical.

3. Cephem derivatives according to claim 1, in which R is a 1-methyl-tetrazolyl-5-mercapto radical.

4. 7 - (3,5 - Dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - cephalosporanic acid.

5. 3 - (1 - Methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl-acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.

6. 3 - (1 - Methyltetrazolyl - 5 - mercaptomethyl) - 7 - (3,5 - dibromo - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.

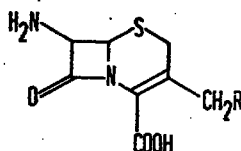
7. 3 - (5 - Methyl - 1,3,4 - thiadiazolyl - 2 - mercaptomethyl) - 7 - (3,5 - dichloro - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.

8. 3 - (5 - Methyl - 1,3,4 - thiadiazolyl - 2 - mercaptomethyl - 7 - (3,5 - dibromo - 1,4 - dihydro - 4 - oxo - 1 - pyridyl - acetamido) - 3 - cephem - 4 - carboxylic acid and the potassium salt thereof.

9. A pharmaceutical composition comprising a cephem derivative according to any of claims 1 to 8, and an inert, physiologically acceptable carrier.

10. A composition according to claim 9 in dosage unit form, each dosage unit containing from 1 to 5000 mg of said derivative.

11. A process for the preparation of a cephem derivative of formula 1 specified in claim 1, which comprises condensing a 3-CH₂R-7-amino-3-cephem-4-carboxylic acid of formula 2:



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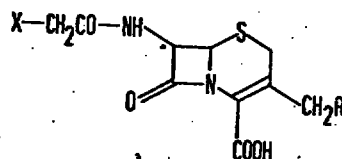
in which R has the meaning specified in claim 1, or a functional derivative thereof, with a pyridone-acetic acid of formula 3:



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in which Z has the meaning specified in claim 1, or a functional derivative thereof.

12. A process for the preparation of a cephem derivative of formula 1 specified in claim 1, which comprises condensing a 3-CH₂R-7-(X-acetamido)-3-cephem-4-carboxylic acid of formula 4:



4

in which X is Cl, Br or a reactive esterified OH group and R has the meaning specified in claim 1, or a functional derivative thereof, with a pyridone of formula 5:



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in which Z has the meaning specified in claim 1, or a functional derivative thereof.

13. A process for the preparation of a cephem derivative of formula 1 specified in claim 1, which comprises treating a compound which otherwise corresponds to formula 1 but contains at least one functionally modified OH, NH₂ or oxo group, with a solvolysing or hydrogenolysing agent in order to liberate said OH, NH₂ or oxo group.

14. A process according to any of claims 11 to 13, in which the compound of formula 1 obtained is treated to replace R and/or Z by another R and/or Z substituent, by alkylating a hydroxyl group by treatment with an alkylating agent and/or by reducing a nitro group or an acetoxymethyl group by treatment with a reducing agent to give an amino group or a methyl group respectively and/or by converting an acetoxy group into an -S-Het radical by treatment with a thiol of the formula Het-SH or with a corresponding mercaptide and/or by converting a carboxyl group by treatment with an esterifying agent into a readily hydrolysable ester group.

15. A process according to any of claims 11 to 14, in which, when a salt or ester of a compound of formula 1 is obtained, it is solvolysed to liberate the com-



pound of formula I therefrom or the compound of formula I obtained is treated with a base or an acid to form a physiologically acceptable salt thereof.

16. A process for the preparation of a cephem derivative according to claim 1 substantially as herein described in any of Examples 1 to 9.

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