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CEPHALOSPORIN DERIVATIVES AND A PROCESS FOR THE PREPARATION THEREOF

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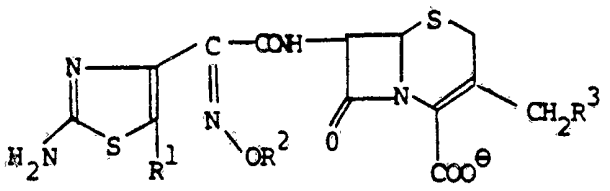
(57) Claim

1. A cephalosporin derivative of the formula I



(I)

and physiologically tolerated acid addition salts thereof, in which the R^2O group is in the syn position, and the substituents R^1, R^2 and R^3 have the following meanings:

R^1 hydrogen or halogen,

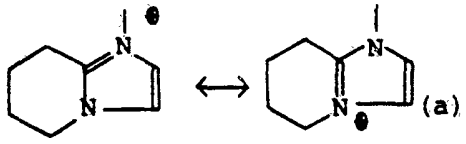
R^2 hydrogen, C_1-C_6-alkyl which can be substituted once or several times, identically or differently, by halogen, aryl, heteroaryl, C_1-C_4-alkylthio, C_1-C_4-alkoxy, nitrile or carbamoyl, in which the

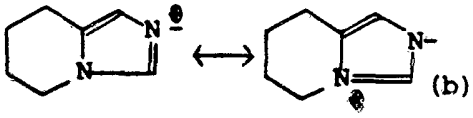
.../2

amino group can be substituted once or twice by C_1-C_4-alkyl, C_2-C_6-alkenyl which can be optionally substituted once or several times by halogen, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_4-C_7-cycloalkenyl, C_3-C_7-cycloalkylmethyl, the group of the formula

$$-(CH_2)_n-(\overset{R^4}{\underset{R^5}{C}})_m-R^6,$$

in which m and n each represents 0 or 1, and R^4 and R^5, which can be identical or different, denote hydrogen or a C_1-C_{11}-alkyl group, or form, together with the carbon to which they are bonded, a vinylidene or a C_3-C_7-cycloalkylidene group, and
R^6 denotes a carboxyl or C_1-C_4-alkyloxycarbonyl group,
R^3 a 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinium radical (a) or a 5,6,7,8-tetrahydroimidazo[1,5-a]pyridinium radical (b)


(a)


(b)

which can be substituted once or several times, identically or differently, by C_1-C_6-alkyl which can also be substituted by hydroxyl, C_1-C_6-alkyloxy, carboxyl, C_1-C_6-alkoxycarbonyl, carbamoyl or amino; C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_5-C_6-cycloalkenyl, C_3-C_6-cycloalkylmethyl; phenyl, phenoxy or benzyl, each of which can be substituted by C_1-C_4-alkyl, hydroxyl or C_1-C_4-alkoxy; C_1-C_6-alkoxy, C_1-C_6-alkylthio, sulfo, tri-

.../3

fluoromethyl, hydroxyl, mercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, carboxyl, C_1-C_6-alkoxycarbonyl, or carbamoyl which can be substituted once or twice on the nitrogen by C_1-C_6-alkyl.

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Form 10

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COMPLETE SPECIFICATION

(ORIGINAL)

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Related Art :

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Complete Specification for the invention entitled:

CEPHALOSPORIN DERIVATIVES AND A PROCESS FOR THE PREPARATION THEREOF

The following statement is a full description of this invention, including the best method of performing it known to :- us

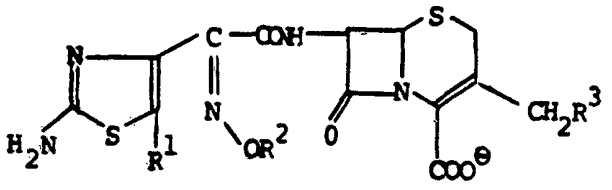
HOECHST AKTIENGESELLSCHAFT HOE 87/F 060 Dr. KA/rh

Specification

Cephalosporin derivatives and a process for the preparation thereof

The invention relates to new cephalosporin derivatives which are substituted in the 3' position of the cephem ring by a 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinium or 5,6,7,8-tetrahydroimidazo[1,5-a]pyridinium radical which is bonded via the nitrogen. They have a very good antimicrobial action against Gram-positive and Gram-negative bacteria and are thus very suitable as medicaments for the treatment of microbial infections. The invention also relates to a process for the preparation thereof, to pharmaceutical compositions containing them, and to the preparation and the use thereof for controlling bacterial infections.

Hence the invention relates to cephalosporin derivatives of the general formula I



(I)

and to the physiologically tolerated acid addition salts thereof, in which the R^2O group is in the syn position, and the substituents R^1, R^2 and R^3 have the following meanings:

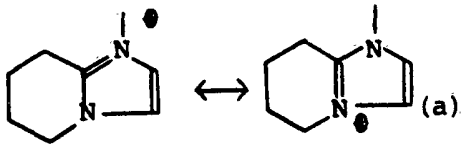
R^1 hydrogen or halogen,

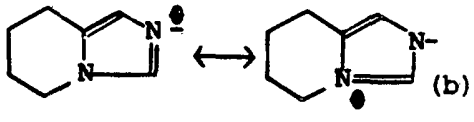
R^2 hydrogen, C_1-C_6-alkyl which can be substituted once or several times, identically or differently, by halogen, aryl, heteroaryl, C_1-C_4-alkylthio, C_1-C_4-alkoxy, nitrile or carbamoyl, in which the amino group can be substituted once or twice by C_1-C_4-

alkyl, C_2-C_6-alkenyl which can be optionally substituted once or several times by halogen, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_4-C_7-cycloalkenyl, C_3-C_7-cycloalkylmethyl, the group of the formula

$$-(CH_2)_n-(\overset{R^4}{\underset{R^5}{C}})_m-R^6,$$

in which m and n each represents 0 or 1, and R^4 and R^5, which can be identical or different, denote hydrogen or a C_1-C_{11}-alkyl group, or form, together with the carbon to which they are bonded, a vinylidene or a C_3-C_7-cycloalkylidene group, and
R^6 denotes a carboxyl or C_1-C_4-alkyloxycarbonyl group,
R^3 a 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinium radical (a) or a 5,6,7,8-tetrahydroimidazo[1,5-a]pyridinium radical (b)


(a)


(b)

which can be substituted once or several times, identically or differently, by C_1-C_6-alkyl which can also be substituted by hydroxyl, C_1-C_6-alkyloxy, carboxyl, C_1-C_6-alkoxycarbonyl, carbamoyl or amino; C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_5-C_6-cycloalkenyl, C_3-C_6-cycloalkylmethyl; phenyl, phenoxy or benzyl, each of which can be substituted by C_1-C_4-alkyl, hydroxyl or C_1-C_4-alkoxy; C_1-C_6-alkoxy, C_1-C_6-alkylthio, sulfo, trifluoromethyl, hydroxyl, mercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, carboxyl, C_1-C_6-alk-

oxycarbonyl, or carbamoyl which can be substituted once or twice on the nitrogen by C_1-C_6-alkyl.

Examples of suitable and particularly preferred substituents are the following:

R^1: hydrogen, fluorine, chlorine, bromine, especially hydrogen and chlorine,

R^2: a C_1-C_4-alkyl radical such as, for example, methyl, ethyl, propyl, isopropyl, butyl, especially methyl and ethyl, which can be substituted once or several times, in particular once or twice, especially by fluorine, such as, for example, monofluoromethyl or difluoromethyl; by aryl, especially by phenyl, such as, for example, benzyl, by 2- or 3- or 4-tolyl, or by 2- or 3- or 4-chlorophenyl; by heteroaryl, especially by 1,3-thiazol-4-yl, such as, for example, 1,3-thiazol-4-ylmethyl, or by imidazolyl, such as, for example, imidazol-1-ylethyl; by C_1-C_4-alkylthio, especially methylthio, such as, for example, methylthiomethyl; by C_1-C_4-alkyloxy, especially methyloxy and ethyloxy, such as, for example, methyloxymethyl, ethyloxymethyl, ethyloxyethyl; by nitrile or carbamoyl, it also being possible for the amino group to be substituted once or twice by, for example, C_1-C_2-alkyl, such as, for example, N-methyl- or N-ethyl-carbamoylmethyl or N,N-dimethyl-carbamoylmethyl,

a C_2-C_6-, preferably a C_3-C_4-alkenyl radical such as, for example, 2-propenyl or 2-butenyl, which can be substituted once or several times, preferably once or twice, by halogen, especially chlorine or bromine, such as, for example, 3-chloro-2-propenyl or 2-bromo-2-propenyl,

a C_3-C_6-alkynyl radical such as, especially, propargyl, a C_3-C_7-cycloalkyl radical such as, especially, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,

a C_3-C_7-cycloalkylmethyl radical such as,

especially, cyclopropyl- and cyclobutylmethyl,
a C_4-C_7-cycloalkenyl radical such as, especially, cyclopentenyl,

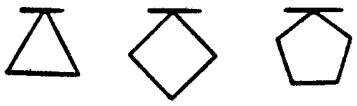
the group $-(CH_2)_n-(\overset{R^4}{\underset{R^5}{C}})_m-R^6$

R^6 denoting the group COOH, and it being possible for R^4 and R^5 to be identical or different and denote hydrogen, C_1-C_4-alkyl such as, for example, methyl, ethyl, propyl, isopropyl, butyl or sec.-butyl, preferably methyl or ethyl, especially methyl, or
it being possible for R^4 and R^5 to form, together with the carbon atom to which they are bonded, especially a vinylidene group or a C_3-C_7-cycloalkylidene group such as, for example, cyclopropylidene, cyclobutylidene, cyclopentylidene or cyclohexylidene, preferably cyclopropylidene, cyclobutylidene or cyclopentylidene,
m = 0 or 1,
n = 0 or 1, the total of m and n being 1 or 2.

Preferred examples of the group $-(CH_2)_n-(\overset{R^4}{\underset{R^5}{C}})_m-$

are the following:
in the case where n is 0 and m is 1:

$\overset{|}{C}H(CH_3)$, $\overset{|}{C}(CH_3)_2$, $\overset{|}{C}HC_2H_5$



in the case where m is 0 and n is 1: $-CH_2-$
and if n and m are 1: $-CH_2-C(=CH_2)-$.

R^3 particularly preferably represents:
a 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinium or a 5,6,7,8-tetrahydroimidazo[1,5-a]pyridinium radical, which can be

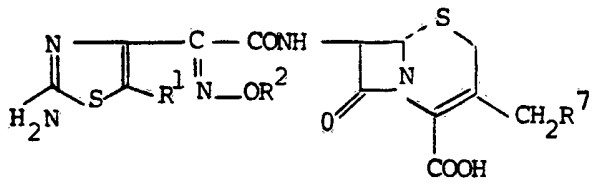
substituted once or several times, especially once or twice, preferably once, by C_1-C_3-alkyl such as, especially, methyl, ethyl, propyl or isopropyl, preferably methyl, that is to say, for example, by two methyl or two ethyl groups, it also being possible for these alkyl radicals to be substituted, preferably once. Especially suitable substituted alkyl radicals are
hydroxy-C_1-C_3-alkyl such as, especially, hydroxymethyl or hydroxyethyl,
C_1-C_2-alkyloxy-C_1-C_2-alkyl such as, especially, methyloxymethyl, ethyloxymethyl, methyloxyethyl or ethyloxyethyl,
carboxy-C_1-C_4-alkyl such as, especially, carboxymethyl and carboxyethyl;
C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl such as, especially, methyloxycarbonylmethyl, ethyloxycarbonylmethyl or methyloxycarbonylethyl;
carbamoyl-C_1-C_4-alkyl such as, especially, carbamoylmethyl or amino-C_1-C_4-alkyl such as, especially, aminomethyl or aminoethyl.

Also particularly preferred for R^3 are:
C_3-C_4-alkenyl such as, especially, allyl and butenyl, such as, for example, 2-methylallyl and 3-butenyl,
C_3-alkynyl, such as, especially, propargyl,
C_3-C_6-cycloalkyl and C_3-C_6-cycloalkylmethyl, the number of carbons relating to the cycloalkyl moiety, such as, especially, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl or cyclopropylmethyl, preferably cyclopropyl and cyclohexyl,
C_5-C_6-cycloalkenyl such as, especially, cyclopentenyl and cyclohexenyl,
phenyl, phenoxy and benzyl, each of which can also be substituted, especially by methyl, ethyl, hydroxyl, methoxy and ethoxy, such as, for example, tolyl, hydroxyphenyl, methoxyphenyl and ethoxyphenyl;
C_1-C_4-alkoxy such as, especially, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and tert.-butoxy, preferably methoxy;

C_1-C_4-alkylthio such as, especially, methylthio, ethylthio, propylthio and isopropylthio;
sulfo, trifluoromethyl, hydroxyl, mercapto and carboxyl, preference being given to carboxyl and hydroxyl,
amino, C_1-C_4-alkylamino such as, especially, methylamino and ethylamino, or di-C_1-C_4-dialkylamino such as, especially, dimethylamino or methylethylamino,
C_1-C_4-alkoxycarbonyl such as, especially, methoxycarbonyl,
carbamoyl which can be substituted once or twice on the nitrogen atom by C_1-C_4-alkyl, such as, especially, N-methyl-, N-ethyl- or N,N-dimethylcarbamoyl, preferably the unsubstituted carbamoyl.

The invention also relates to a process for the preparation of compounds of the formula I and physiologically tolerated acid addition salts thereof, which comprises

a) reaction of a compound of the general formula II



(II)

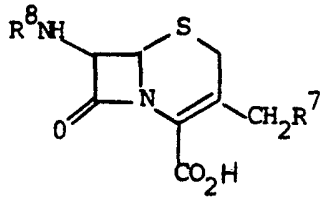
or salts thereof, in which R^1 and R^2 have the meanings mentioned in formula I, the amino group can also be protected, and R^7 denotes a group which can be replaced by tetrahydroimidazopyridine or that tetrahydroimidazopyridine derivative which corresponds to the radical R^3 of the formula I, with tetrahydroimidazopyridine or this tetrahydroimidazopyridine derivative,

α) elimination of a protective group which is present where appropriate, and

β) where necessary, conversion of the resulting product into a physiologically tolerated acid addition salt,

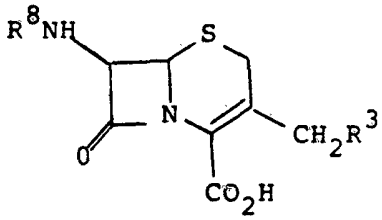
or

b) reaction of a compound of the general formula III



(III)

in which R^7 has the meaning mentioned above for the formula II, and R^8 represents hydrogen or an amino protective group, with tetrahydroimidazopyridine or the tetrahydroimidazopyridine derivative from which the radical R^3 defined in formula I derives, with formation of the compound of the general formula IV

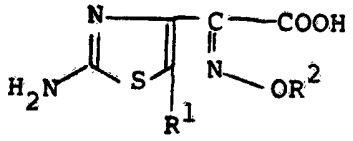


(IV)

in which R^3 and R^8 have the abovementioned meaning, and

α) elimination of an amino protective group which is present where appropriate, and

β) reaction of the compound IV in which R^8 denotes hydrogen, either as such or in the form of a reactive derivative, with a 2-syn-oxyiminoacetic acid of the general formula V



(V)

in which R^1 and R^2 have the said meaning, and the amino group can also be in protected form, or with a

derivative of this compound which is activated on the carboxyl group, and

α) elimination of a protective group which is present, where appropriate, and

β) where necessary, conversion of the resulting product of the general formula I into a physiologically tolerated acid addition salt.

If the compound of the general formula I is to be prepared by process variant a) by nucleophilic exchange of R^7 in the compounds of the general formula II by tetrahydroimidazopyridine or one of the indicated tetrahydroimidazopyridine derivatives, the especially suitable radicals R^7 are acyloxy radicals of lower aliphatic carboxylic acids, preferably having 1 to 4 carbon atoms, such as, for example: acetoxy or propionyloxy, especially acetoxy, each of which can be optionally substituted, such as, for example: chloroacetoxy or acetylacetoxy. Other groups are also suitable for R^7, such as, for example, carbamoyloxy or a halogen atom such as, for example, chlorine, bromine or iodine.

The starting compounds used in the nucleophilic exchange reaction according to the invention are of the general formula II in which R^7 has the abovementioned meaning, or salts thereof, such as, for example, a sodium or potassium salt. The reaction is preferably carried out in a solvent, more preferably in water, formamide or in a mixture of water and organic solvent which is readily miscible with water, such as, for example, acetone, dioxane, acetonitrile, dimethylformamide, dimethyl sulfoxide or ethanol. The reaction temperature is generally in the range from about 10 to about 100°C, preferably between 20 and 80°C. The tetrahydroimidazopyridine component is added in amounts which are preferably between equimolar amounts and an excess of up to about 5-fold. The replacement of the radical R^7 is preferably facilitated by the presence of neutral salt ions,

AUSTRALIAN PATENT OFFICE

preferably of iodide or thiocyanate ions, in the reaction medium. ~~In particular~~, In particular about 10 to about 30 equivalents of potassium iodide, sodium iodide, potassium thiocyanate or sodium thiocyanate are added. The reaction is advantageously carried out near to the neutral point, preferably at a pH in the range from about 5 to about 8.

The nucleophilic exchange reaction on compounds of the general formula II can also be carried out in such a way that the reaction is undertaken in the presence of tetrahydroimidazopyridine or of the tetrahydroimidazopyridine derivatives corresponding to the radical R^3, and of tri-C_1-C_4-alkyliodosilanes such as, for example, trimethyl- or triethyliodosilane. The procedure for this can be such that the compound II in which R^7 represents, for example, acetoxy is first reacted with trimethyliodosilane under the reaction conditions mentioned hereinafter, and the formed compound II with R^7 = I is isolated and then reacted with tetrahydroimidazopyridine or the tetrahydroimidazopyridine derivative, or the 3-CH_3I compound is reacted in situ by addition of the tetrahydroimidazopyridine or its derivative. In place of trimethyliodosilane it is also possible, for example, to use a reaction mixture composed of iodine and hexamethyldisilane, which have previously been reacted at temperatures between 60 and 120°C in a manner known from the literature, resulting in trimethyliodosilane. In place of trimethyliodosilane it is also possible to use, with the same good result, triethyliodosilane which is prepared in a manner known from the literature. The reaction is carried out at temperatures between about -5° and +100°C, preferably between +10°C and +80°C.

Examples of suitable inert aprotic solvents are chlorinated hydrocarbons such as methylene chloride, chloroform, dichloroethane, trichloroethane or carbon tetrachloride, or lower alkanonitriles such as acetonitrile or propionitrile, or Frigens; in particular, methylene chloride is an excellent solvent.

AUSTRALIAN PATENT OFFICE

The tetrahydroimidazopyridine or its derivative corresponding to the radical R^3 is added in an amount which is at least stoichiometric and is up to an approximately 20-fold excess. The amounts used are preferably such that the liberated amount of hydrogen iodide is bound, and there is still at least 1 mole, preferably 1.5-5 mole, of tetrahydroimidazopyridine or its derivative available for the substitution.

Since not only the group R^7 which is to be replaced in the starting compound II but also other functional groups, such as, for example, the amino group or the carboxyl group, react with trimethyliodosilane, the latter is added in an excess which is at least two-fold and is up to about fifteen-fold, preferably three- to ten-fold.

Functional groups of these types can also be presilylated by addition of a silylating agent such as, for example, bistrimethylsilylacetamide, N-methyl-N-trimethylsilyltrifluoroacetamide, bistrimethylsilyltrifluoroacetamide, trimethylchlorosilane, hexamethyldisilazane and bistrimethylsilylurea, either without or in the presence of a base, preferably of the desired tetrahydroimidazopyridine or its derivative from which the group R^3 is derived, in the amounts described above. Subsequently, trimethyliodosilane is added in at least the stoichiometric amount or in an excess, preferably in an excess of two-fold up to ten-fold.

Where the amino group in the compounds of the formulae II and V is present in protected form, then examples of suitable amino protective groups are optionally substituted alkyl such as, for example, tert.-butyl and tert.-amyl; benzyl, p-methoxybenzyl, trityl and benzhydryl, preferably trityl; trialkylsilyl such as, for example, trimethylsilyl; optionally substituted aliphatic acyl such as, for example, formyl, chloroacetyl, bromoacetyl, trichloroacetyl and trifluoroacetyl, preferably formyl; or optionally substituted alkoxycarbonyl such as, for example,

trichloroethoxycarbonyl, benzyloxycarbonyl or tert.-butyloxycarbonyl, preferably tert.-butyloxycarbonyl and benzyloxycarbonyl; or dimethylaminomethylene.

After the exchange reaction, the protective group can be eliminated in a manner known per se, for example the trityl group by use of a carboxylic acid such as, for example, acetic acid, trifluoroacetic acid or formic acid, or the benzyloxycarbonyl group by hydrogenolysis.

The reaction products of the formula I can be isolated, for example, after addition of water or aqueous mineral acids, for example dilute HCl, HBr, HI or H_2SO_4, from the aqueous phase in a customary manner, for example by freeze-drying the aqueous phase, chromatography or precipitation by addition of organic solvents. The reaction products are preferably isolated by precipitation out of the reaction solution in the form of a sparingly soluble salt, for example a hydriodide.

In the case where R^7 represents a carbamoyloxy group the exchange reaction is carried out analogously. Where R^7 represents halogen, especially bromine or iodine, the exchange is carried out in a manner known from the literature.

Where the compound II is in the form of a reactive derivative, suitable examples are silyl derivatives formed by reaction of compounds of the general formula II with a silyl compound such as, for example, trimethylchlorosilane or bis(trimethylsilyl)acetamide. In this case, the reaction is expediently carried out in the presence of a solvent such as methylene chloride, dimethylformamide or acetonitrile.

In process variant b) the compounds of the general formula I are obtained by acylation of compounds of the general formula IV or addition salts thereof, for example with hydrochloric acid, hydrobromic acid, nitric acid,

sulfuric acid, phosphoric acid or an organic acid such as, for example, methanesulfonic acid or toluenesulfonic acid, using carboxylic acids of the general formula V or using a reactive derivative of an acid of this type.

It is not necessary in this reaction to isolate the compounds of the general formula IV. The reaction can also be carried out in such a way that compounds of the general formula III, for example 7-aminocephalosporanic acid or 3-iodomethyl-7-aminoceph-3-em-4-carboxylic acid, or reactive derivatives thereof, are reacted in a suitable solvent with the tetrahydroimidazopyridine or derivative thereof corresponding to the radical R^3 in the general formula IV, and the resulting compound of the general formula IV is acylated in situ to give the compounds of the general formula I. Starting compounds of the general formula III in which R^7 represents iodine are, according to the invention, used in this reaction. Suitable solvents are chlorinated hydrocarbons such as, for example, methylene chloride and chloroform; ethers such as, for example, diethyl ether, tetrahydrofuran and dioxane, acetonitrile and amides such as, for example, dimethylformamide and dimethylacetamide. It may also prove to be advantageous to use mixtures of the said solvents.

Where the compounds of the general formula III are in the form of a reactive derivative, especially suitable are silyl derivatives formed by the reaction of compounds of the general formula III with silyl compounds such as, for example, trimethylchlorosilane, bis(trimethylsilyl)trifluoroacetamide etc. The base corresponding to the radical R^3 is used in an amount which is at least stoichiometric and is up to an approximately ten-fold excess, preferably 1.5 to 5 equivalents. The reaction is carried out at temperatures between about -50 and +100°C, preferably between +20 and +50°C.

The compounds of the general formula IV can also be prepared from compounds of the general formula III in which

R^7 represents, for example, acetoxy in a manner analogous to that described above for the compounds of the general formula II.

If the carboxylic acids of the general formula V, and their derivatives protected on the amino group, are themselves used as acylating agents, it is expedient to operate in the presence of a condensing agent, for example of a carbodiimide such as, for example, N,N'-dicyclohexylcarbodiimide.

Carboxylic acids of the general formula V can be activated in a particularly favorable manner by treatment with certain carboxamides and, for example, phosgene, phosphorus pentachloride, tosyl chloride, thionyl chloride or oxalyl chloride as described in, for example, German Patent 28 04 040.

Moreover, especially suitable activated derivatives of the carboxylic acids of the general formula V are halides, preferably chlorides, which are obtained in a manner known per se by treatment with halogenating agents such as, for example, phosphorus pentachloride, phosgene or thionyl chloride under the mild reaction conditions known from the literature on cephalosporin chemistry.

Further suitable activated derivatives of the carboxylic acids of the general formula V are the anhydrides and mixed anhydrides, azides, activated esters and thioesters. Particularly suitable mixed anhydrides are those with lower alkanoic acids such as, for example, acetic acid, and, particularly preferably, those with substituted acetic acids such as, for example, trichloroacetic acid, pivalic acid and cyanoacetic acid. However, also particularly suitable are the mixed anhydrides with monoesters of carbonic acid which are obtained, for example, by reaction between the carboxylic acids of the formula V in which the amino group is protected and benzyl, p-nitrobenzyl, isobutyl, ethyl or allyl chloroformate.

Suitable and preferred activated esters are those with p-nitrophenol, 2,4-dinitrophenol, methylcyanohydrin, N-hydroxysuccinimide and N-hydroxyphthalimide, especially those with 1-hydroxybenzotriazole and 6-chloro-1-hydroxybenzotriazole. Examples of particularly preferred thioesters are those with 2-mercaptobenzothiazole and 2-mercaptopyridine. It is possible to react the activated derivatives as isolated substances or in situ.

In general, the reaction of the cephem derivatives of the general formula IV with a carboxylic acid of the general formula V, or an activated derivative thereof, is carried out in the presence of an inert solvent. Especially suitable are chlorinated hydrocarbons such as, preferably, methylene chloride and chloroform; ethers such as, for example, diethyl ether and, preferably, tetrahydrofuran and dioxane; ketones such as, preferably, acetone and butanone; amides such as, preferably, dimethylformamide and dimethylacetamide, or pyridine. It may also prove to be advantageous to use mixtures of the said solvents. This is often the case where the cephem compound of the general formula IV is reacted with an activated derivative, generated in situ, of a carboxylic acid of the formula V.

The reaction of cephem compounds of the formula IV with carboxylic acids of the formula V, or activated derivatives thereof, can be carried out in a temperature range from about -80 to about +80°C, preferably between about -20°C and room temperature.

The reaction time depends on the reactants, the temperature and the solvent or solvent mixture, and is normally between 1/4 and about 72 hours.

The reaction with acid halides can, where appropriate, be carried out in the presence of an acid-binding agent in order to bind the hydrogen halide which is liberated. Especially suitable as such are tertiary amines such as,

for example, triethylamine or dimethylaniline, inorganic bases such as, for example, potassium carbonate or sodium carbonate, and alkylene oxides such as, for example, propylene oxide. The presence of a catalyst such as, for example, of dimethylaminopyridine may also, where appropriate, be advantageous. Where the amino group in the compounds of the general formula IV is in the form of a reactive derivative, it can be one known from the literature for amidations. Thus, suitable examples are silyl derivatives formed by the reaction of compounds of the general formula IV with a silyl compound such as, for example, trimethylchlorosilane or bis(trimethylsilyl)acetamide. If the reaction is carried out with such a compound activated on the amino group, it is expedient for the reaction to be carried out in an inert solvent such as, for example, methylene chloride, tetrahydrofuran or dimethylformamide.

Examples of physiologically tolerated acid addition salts of the compounds of the general formula I which may be mentioned are those with hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid or organic acids such as, for example, methanesulfonic acid, p-toluenesulfonic acid or maleic acid.

The tetrahydroimidazopyridines and other starting compounds used according to the invention are known from the literature and can be obtained by processes known from the literature.

The compounds of the general formula I, and their physiologically tolerated acid addition salts, obtained according to the invention exhibit remarkably good antibacterial efficacy against both Gram-positive and Gram-negative bacterial organisms.

Moreover, the compounds of the formula I have unexpectedly good efficacy against penicillinase- and cephalosporinase-producing bacteria. Since they also exhibit favorable

toxicological and pharmacological properties, they represent valuable chemotherapeutics.

Hence the invention also relates to drug products for the treatment of microbial infections, which contain one or more of the compounds according to the invention.

The products according to the invention can also be used in combination with other active substances, for example from the penicillin, cephalosporin or aminoglycoside series.

The compounds of the general formula I and their physiologically tolerated acid addition salts can be administered orally, intramuscularly or intravenously.

Drug products which contain one or more compounds of the general formula I as active substance can be prepared by converting the compounds of the formula I, mixed with a plurality of pharmacologically tolerated excipients or diluents such as, for example, fillers, emulsifiers, lubricants, flavorings, colorants or buffer substances, into a suitable pharmaceutical presentation such as, for example, tablets, coated tablets, capsules, or a suspension or solution suitable for parenteral administration.

Examples of excipients or diluents which may be mentioned are tragacanth, lactose, talc, agar-agar, polyglycols, ethanol and water. Examples of buffer substances are organic compounds such as, for example, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, N-methylglucamine, N-benzylphenethylamine, diethylamine or tris-(hydroxymethyl)aminomethane, or inorganic compounds such as, for example, phosphate buffer, sodium bicarbonate or sodium carbonate. Suitable and preferred for parenteral administration are suspensions or solutions in water, with or without buffer substances. It is also possible to administer the active substances as such, without

excipient or diluent, in a suitable form, for example in capsules.

Suitable doses of the compounds of the general formula I or their physiologically tolerated acid addition salts are about 0.4 to 20 g/day, preferably 0.5 to 4 g/day, for an adult of body weight approximately 60 kg.

It is possible to administer single or, in general, multiple doses, it being possible for the single dose to contain the active substance in an amount of about 50 to 1000 mg, preferably of about 100 to 500 mg.

The following examples of syn compounds which can be prepared according to the invention serve to explain the invention further, but do not confine it to them.

Example 1:

7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(5,6,7,8-tetrahydroimidazo[1,5-a]pyrid-2-ylio)methyl]-ceph-3-em-4-carboxylate

Process a) variant 1

A mixture of 0.91 g (2 mmol) of 7-[2-(2-aminothiazol-4-yl)-2-syn-methoxyiminoacetamido]cephalosporanic acid, 1.85 g (7.2 mmol) of bis(trimethylsilyl)trifluoroacetamide (BSTFA) and 5 ml of methylene dichloride is heated under reflux for 1 hour. The solution is cooled to 20°C, 1.04 g (5.2 mmol) of trimethyliodosilane are added, and stirring is continued at room temperature for 20 min. The mixture is concentrated in vacuo, the oily residue is dissolved in 4 ml of acetonitrile, and a solution of 305 mg (2.5 mmol) of 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine and 1.23 g (4.8 mmol) of BSTFA in 2 ml of acetonitrile is added. The dark-colored solution is left at room temperature for 4 hours. 0.3 ml of water is added, and the precipitate which has formed is filtered off with suction,

washed with ethanol and acetone and dried. This crude hydriodide of the title compound (yield 1.0 g) is dissolved in aqueous sodium bicarbonate solution and chromatographed on a "Lobar B" silica gel column (from Merck, Darmstadt, FRG) using acetone/water (3:1). Freeze-drying of the product fractions results in 175 mg (17 %) of the title compound as a yellowish amorphous solid.

^{1}NMR (270 MHz, DMSO-d_6): δ = 1.7 - 1.83 (2H, m, CH_2); 1.83 - 1.96 (2H, m, CH_2); 2.72 - 2.82 (2H, m, CH_2); 3.06 and 3.50 (2H, AB, J=18Hz, SCH_2); 3.80 (3H, s, OCH_3); 4.12 - 4.22 (2H, m, CH_2); 4.66 and 5.14 (2H, AB, J=15Hz, $CH_2N^{\oplus}$) 5.00 (1H, d, J=5Hz, 6-H); 5.59 (1H, dd, J=5 and 8Hz, 7-H); 6.71 (1H, s,thiazole); 7.12 (2H, s, NH_2); 7.78 (1H, s, Im-H); 9.14 (1H, s, Im-H); 9.47 (1H, d, J=8Hz, NH).

Process a), variant 2

A mixture of 228 mg (0.5 mmol) of 7-[2-(2-aminothiazol-4-yl)-2-syn-methoxyiminoacetamido]cephalosporanic acid, 3.32 g (20 mmol) of potassium iodide, 610 mg (5 mmol) of 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, 3 ml of water and 1 ml of acetone is heated and stirred at 68°C for 3 hours. After the solution has been cooled, it is chromatographed on silica gel (Lobar B column, Merck) using acetone/water (3:1). The product fractions are concentrated and freeze-dried. There are obtained 65 mg (25%) of an amorphous solid which is identical in all properties to that described above.

Process b), variant 1

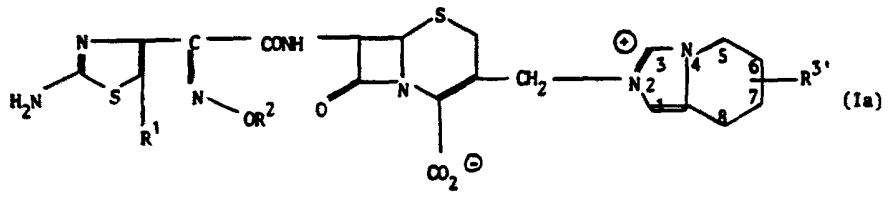
0.2 g (1 mmol) of 2-(2-aminothiazol-4-yl)-2-syn-methoxyiminoacetic acid is dissolved in 3 ml of N,N-dimethylformamide (DMF). 0.14 g (1.05 mmol) of 1-hydroxybenzotriazole hydrate and 0.21 g (1 mmol) of N,N'-dicyclohexylcarbodiimide are added and then the mixture is stirred at room temperature for 3 hours. The dicyclohexylurea is filtered off, and a solution of 268 mg (0.8 mmol) of

7-amino-3-[5,6,7,8-tetrahydroimidazo[1,5-a]pyrid-2-ylio)-methyl]ceph-3-em-4-carboxylate in 4 ml of DMF and 0.5 ml of water is added to the filtrate. After 24 hours at room temperature, the mixture is concentrated in vacuo, and the residue is chromatographed on silica gel (Lobar B, Merck) using acetone/water (3:1). Yield 206 mg (50%) of colorless solid. It is identical to the product obtained by process a).

Process b), variant 2

244 mg (2 mmol) of 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine are added to a solution of 339 mg (1 mmol) of 7-amino-3-iodomethylceph-3-em-4-carboxylic acid and 0.73 ml (3 mmol) of bistrimethylsilylacetamide in 10 ml of DMF, and the solution is left at room temperature for 2 hours. Then 0.5 ml of water and 319 mg (1 mmol) of 2-(2-aminothiazol-4-yl)-2-syn-methoxyiminoacetic acid activated as the 1-hydroxybenzotriazole ester are added, and the mixture is stirred at room temperature for a further 17 hours. The solution is concentrated in vacuo, and the oily residue is chromatographed on silica gel (Lobar B, Merck) using acetone/water (3:1). Freeze-drying of the product fractions provides 170 mg (33%) of an amorphous solid which is identical in all properties to the product obtained by process a).

The examples which are listed hereinafter are obtained in analogy to Example 1, process a) or b), as amorphous solids which correspond to the general formula Ia and in which R^1, R^2 and $R^{3'}$ have the meaning indicated in Table 1.



(Ia)

Table 1

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR (DMSO-d_6), 60 MHz: δ (ppm)=
2	H	C_2H_5	H	270MHz:1.21 (3H, t, $CH_2\underline{CH_3}$), 1.7 - 2.0 (4H, m, 2 x CH_2); 2.7 - 2.85 (2H, m, CH_2); 3.08 and 3.49 (2H, AB, J=18Hz, SCH_2); 4.07 (2H, q, $\underline{CH_2}CH_3$), 4.1 - 4.22 (2H, m, CH_2); 4.68 and 5.13 (2H, AB, J=14Hz, $CH_2N^{\oplus}$); 5.02 (1H, d, J=5Hz, 6-H); 5.62 (1H, dd, J=5 and 8Hz, 7-H), 6.70 (1H, s, thiazole); 7.20 (bs, NH_2); 7.78 and 9.14 (each 1H, s, Im H); 9.43 (1H, d, J=8Hz, NH)
3	H	CHF_2	H	1.7 - 2.0 (4H, m, 2 x CH_2); 2.7 - 2.8 (2H, m, CH_2); 3.1 - 3.6 (2H, AB, SCH_2); 3.9 - 4.2 (2H, m, CH_2); 4.4 - 5.2 (2H, AB, $CH_2N^{\oplus}$); 5.04 (1H, d, J=5Hz, 6-H); 5.62 (1H, dd, J=5 and 8Hz,

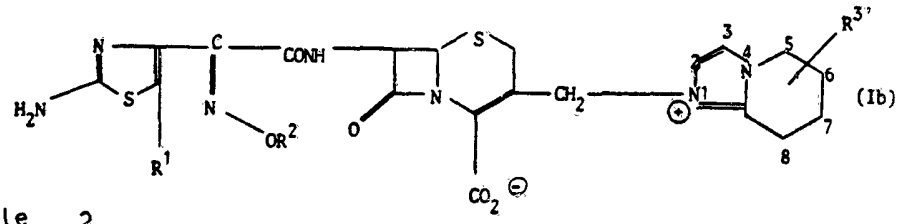
Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz: δ (ppm)=
				(1H, t, J=70Hz, CHF_2); 6.72 (1H, s, thiazole); 7.15 (2H, s, NH_2); 7.76 and 9.06 (each1H, s, Im H); 9.35 (1H, d, J=8Hz, NH);
4	H	$CH_2CH=CH_2$	H	1.7-2.0 (4H, m, 2xCH_2), 2.7-2.85 (2H,m,$\underline{CH_2}$), 3.0-3.5 (2H, AB, SCH_2); 4.1-4.2 (2H,m,CH_2), 4.55 - 4.7 (2H,m,OCH_2), 5.02 (1H, d, J=5Hz, 6-H), 4.6-6.0 (5H, m, $CH=CH_2$ and $CH_2N^{\oplus}$) 5.60 (1 H,dd, J=5 and 8 Hz, 7-H), 6.73 (1 H, s,thiazole), 7.15 (2H, s, NH_2), 7.75 and 9.03 (each1 H,s,Im H); 9.28 (1H, d, J=8Hz, NH)
5	H	$CH_2C\equiv CH$	H	1.65-2.05 (4H, m, 2xCH_2), 2.6 - 2.85 (3H, m, CH_2 and CH), 3.03 and 3.42 (2H, AB ,J = 18Hz, SCH_2),4.1 - 4.25 (2H,m,CH_2) 4.51 2H, bs, OCH_2), 4.71 and 5.16 (2H, AB, J = 15Hz, $CH_2N^{\oplus}$); 5.02 (1H, d, J=5Hz, 6-H); 5.60 (1H, dd,J= 5 and 8Hz, 7-H), 6.72 (1H, s, thiazole, 7.15 (2H, s, NH_2), 7.76 and 9.08 (each1H, s, Im H), 9.30 (1H, d, J=8Hz, NH)
6	H	CH_2CONH_2	H	1.7-2.15 (4H, m, 2 x CH_2), 2.6-2.7 (2H, m, CH_2), 3.1 - 3.4 (2H, AB,SCH_2), 4.1 - 4.22 (2H, m, CH_2), 4.42 (2H, s, OCH_2), 4.7 - 5.1 (2H, AB, $CH_2N^{\oplus}$); 5.02 (1H, d, J=5Hz, 6-H); 5.68 (1H, dd,

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz: δ (ppm)=
				J=5 and 8Hz, 7-H); 6.76 (1H, s, thiazole); 7.10 and 7.42 (each 1H, bs, $CONH_2$); 7.23 (2H, s, NH_2); 7.76 and 9.12 (each 1H, s, Im H); 9.65 (1H, d, J=8Hz, NH)
7	Cl	CH_3	H	1.65 - 2.0 (4H, m, 2 x CH_2); 2.7 - 2.85 (2H, m, CH_2); 3.11 and 3.45 (2H, AB, J=18Hz, SCH_2); 3.83 (3H, s, OCH_3); 4.10 - 4.25 (2H, m, CH_2); 4.98 (1H, d, J=5Hz, 6-H); 5.03 and 5.13 (2H, AB, J=15Hz, $CH_2N^{\oplus}$); 5.61 (1H, dd, J=5 and 8Hz, 7-H); 7.38 (2H, s, NH_2); 7.79 and 9.13 (each 1H, s, Im H); 9.48 (1H, d, J=8Hz, NH);
8	H	H	H	1.6 - 1.9 (4H, m, 2 x CH_2); 2.7 - 2.8 (2H, m, CH_2); 3.2 - 3.4 (2H, bs, SCH_2); 4.1 - 4.2 (2H, m, CH_2); 4.7 - 4.9 (2H, AB, $CH_2N^{\oplus}$); 5.02 (1H, d, J=5Hz, 6-H); 5.62 (1H, dd, J=5 and 8Hz, 7-H); 7.15 (2H, s, NH_2); 7.75 and 8.98 (each 1H, s, Im H); 9.52 (1H, d, J=8Hz, NH)
9	H	CH_2COOH	H	(270 MHz):1.7-1.85 (2H, m, CH_2); 1.85 - 2.0 (2H, m, CH_2); 2.65 - 2.9 (2H, m, CH_2); 3.06 and 3.48 (2H, AB, J=18Hz, SCH_2); 4.05 - 4.3 (2H, m, CH_2); 4.16 (2H, d, J=5Hz, OCH_2); 4.60 and 5.69 (2H,

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6); 60MHz : δ(ppm)=
				AB, J=15Hz, $CH_2N^{\oplus}$); 4.97 (1H, d, J=5Hz, 6-H); 5.67 (1H, dd, J=5 and 8Hz, 7-H); 6.81 (1H, s, thiazole); 7.14 (2H, s, NH_2); 7.79 and 9.18 (each 1H, s, Im H); 12.10 (1H, d, J=8Hz, NH)
10	H	$C(CH_3)_2CO_2H$	H	(270MHz):1.32 and 1.41 (each 3H, s, 2 x CH_3); 1.7 - 1.82 (2H, m, CH_2); 1.82 - 1.97 (2H, m, CH_2); 2.7 - 2.88 (2H, m, CH_2); 3.06 and 3.43 (2H, AB, J=18Hz, SCH_2); 4.08 - 4.32 (2H, m, CH_2); 4.62 and 5.20 (2H, AB, J=15Hz, $CH_2N^{\oplus}$); 4.98 (1H, d, J=5Hz, 6-H), 5.72 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 7.12 (2H, s, NH_2); 7.78 and 9.21 (each 1H, s, Im H); 12.18 (1H, d, J=8Hz, NH)
11	H	$CH_2=C(CO_2H)CH_2$	H	1.65 - 1.95 (4H, m, 2 x CH_2); 2.7 - 2.9 (2H, m, CH_2, 3.0- 3.6 (2H, AB, SCH_2); 4.1 - 4.2 (2H, m, CH_2); 4.71 (2H, s, OCH_2); 4.64 and 5.08 (2H, AB, J=15Hz, $CH_2N^{\oplus}$); 5.00 (1H, d, J=5Hz, 6-H), 5.68 (1H, dd, J=5 and 8Hz, 7-H); 5.65 and 6.02 (each 1H, bs, $=CH_2$); 6.72 (1H, s, thiazole); 7.13 (2H, s, NH_2); 7.75 and 9.16 (each 1H, s, Im H); 11.85 (1H, d, J=8Hz, NH)

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz: δ (ppm)=
12	H	CH_3	6-CH_3	1.7 - 2.0 (3H, m, CH and CH_2); 2.48 (3H, s, CH_3); 2.7 - 2.85 (2H, m, CH_2); 3.02 and 3.48 (2H, AB, SCH_2); 3.81 (3H, s, OCH_3); 4.1 - 4.2 (2H, m, CH_2); 4.5 - 5.3 (2H, AB, CH_2N^+); 5.01 (1H, d, J=5Hz, 6-H); 5.60 (1H, dd, J=5 and 8Hz), 7-H); 6.72 (1H, s, thiazole); 7.15 (2H, s, NH_2); 7.76 and 9.08 (each 1H, s, Im H); 9.55 (1H, d, J=8Hz, NH);

The examples which are listed hereinafter are obtained in analogy to Example 1, process a) or b), as amorphous solids which correspond to the general formula Ib and in which R^1, R^2 and $R^{3'}$ have the meaning indicated in Table 2



(Ib)

Table 2

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz : δ (ppm)=
13	H	CH_3	H	(270MHz): 1.78 - 2.04 (4H, m, 2 x CH_2); 2.96 - 3.04 (2H, m, CH_2); 3.11 and 3.38 (2H, AB, J=18Hz, SCH_2); 3.80 (3H, s, OCH_3); 4.02 - 4.12 (2H, m, CH_2); 4.84 and 4.92 (2H, AB, J=14Hz, CH_2N^+); 5.00 (1H, d, J=5Hz, 6-H); 5.60 (1H,

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz: δ (ppm)=
				dd, J=5 and 8Hz, 7-H); 6.71 (1H, s,thiazole); 7.21 (2H, s, NH_2); 7.54 and 7.91 (each 1H, d, J=2Hz, Im H); 9.51 (1H, d, J=8Hz, NH);
14	Cl	CH_3	H	(270MHz): 1.8 - 2.05 (4H, m, 2 x CH_2); 2.95 - 3.1 (2H, m, CH_2); 3.0 - 3.4 (2H, AB, SCH_2); 3.81 (3H, s, OCH_3); 4.0 - 4.15 (2H, m, CH_2); 4.75 - 5.0 (2H, AB, $CH_2N^{\oplus}$); 4.96 (1H, d, J=5Hz, 6-H); 5.58 (1H, dd, J=5 and 8Hz, 7-H); 7.38 (2H, s, NH_2); 7.52 and 7.89 (each 1H, d, J=2Hz, Im H); 9.45 (1H, d, J=8Hz, NH)
15	H	C_2H_5	H	(270MHz): 1.21 (3H, t, $CH_2\underline{CH_3}$); 1.8 - 2.05 (4H, m, 2 x CH_2); 2.95 - 3.05 (2H, m, CH_2); 3.11 and 3.32 (2H, AAB, J=18Hz, SCH_2); 4.08 (2H, q, $\underline{CH_2}CH_3$); 4.0 - 4.15 (2H, m, CH_2); 4.84 and 4.92 (2H, AB, J=14Hz, $CH_2N^{\oplus}$); 5.01 (1H, d, J=5Hz, 6-H); 5.61 (1H, dd, J=5 and 8Hz, 7-H); 6.69 (1H, s, thiazole); 7.20 (2H, s, NH_2); 7.54 and 7.91 (each 1H, d, J=2Hz, Im H); 9.46 (1H, d, J=8Hz, NH)
16	H	CH_2CONH_2	H	(270MHz): 1.8- 2.05 (4H, m, 2 x CH_2); 2.95 - 3.05 (2H, m, CH_2); 3.21 and 3.46 (2H, AB, J=18Hz, SCH_2); 4.05 - 4.15 (2H, m, CH_2); 4.38 (2H, s, OCH_2); 4.90 and 4.95

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6), 60MHz : δ (ppm)=
				(2H, AB, J=14Hz, $CH_2N^{\oplus}$); 5.08 (1H, d, J=5Hz, 6-H); 5.72 (1H, dd, J=5 and 8Hz, 7-H); 6.82 (1H, s, thiazole); 7.09 and 7.45 (each 1H, bs, $CONH_2$); 7.26 (2H, bs, NH_2); 7.56 and 7.81 (each 1H, d, J=2Hz, Im H); 9.72 (1H, d, J=8Hz, NH)
17	H	CH_2COOH	H	(270MHz): 1.85 - 2.05 (4H, m, 2 x CH_2); 2.95 - 3.05 (2H, m, CH_2); 3.07 and 3.32 (2H, AB, J=18Hz, SCH_2); 4.02 - 4.12 (2H, m, CH_2); 4.13 (2H, d, J=5Hz, OCH_2); 4.80 and 4.98 (2H, AB, J=15Hz, $CH_2N^{\oplus}$); 4.98 (1H, d, J=5Hz, 6-H); 5.62 (1H, dd, J=5 and 8Hz, 7-H); 6.82 (1H, s, thiazole); 7.15 (2H, s, NH_2); 7.54 and 8.02 (each 1H, s, Im H); 11.25 (1H, d, J=8Hz, NH);
18	H	$C(CH_3)_2CO_2H$	H	(270MHz): 1.34 and 1.43 (each 3H, s, 2 x CH_3); 1.8 - 2.05 (4H, m, 2 x CH_2); 2.95 - 3.08 (2H, m, CH_2); 3.08 and 3.38 (2H, AB, J=18Hz, SCH_2); 4.0 - 4.15 (2H, m, CH_2); 4.88 and 4.95 (2H, AB, J=15Hz, $CH_2N^{\oplus}$); 4.98 (1H, d, J=5Hz, 6-H); 5.68 (1H, dd, J=5 and 8Hz, 7-H); 6.72 (1H, s, thiazole); 7.15 (2H, s, NH_2); 7.55 and 7.94 (each 1H, s, Im H); 11.18 (1H, d, J=8Hz, NH

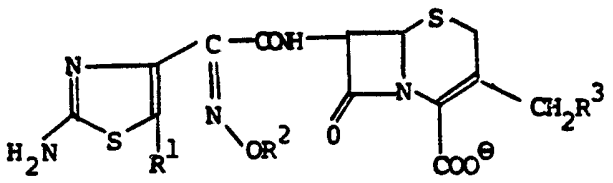
Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6): 60MHz, δ (ppm)=
19	H	CH_3	2-CH_3	1.8 - 2.1 (4H, m, 2 x CH_2); 2.35 (3H, s, CH_3); 2.9 - 3.1 (2H, m, CH_2); 3.0 - 3.5 (2H, AB, SCH_3); 3.81 (3H, s, OCH_3); 4.0 - 4.2 (2H, m, CH_2); 4.6 - 5.1 (2H, AB, $CH_2N^{\oplus}$); 5.01 (1H, d, J=5Hz, 6-H); 5.62 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 7.21 (2H, s, NH_2); 7.68 (1H, s, Im H); 9.52 (1H, d, J=8Hz, NH);
20	H	CH_3	8-OH	1.7 - 2.0 (4H, m, 2 x CH_2); 3.0 - 3.6 (2H, AB, SCH_2); 3.80 (3H, s, OCH_3); 3.9 - 4.1 (2H, m, CH_2); 4.6 - 5.2 (3H, m, $CH_2N^{\oplus}$ and CHOH); 5.02 (1H, d, J=5Hz, 6-H); 5.60 (1H, dd, J=5 and 8Hz, 7-H); 6.71 (1H, s, thiazole); 7.25 (2H, s, NH_2); 7.55 and 7.87 (each 1H, d, J=2Hz, Im H); 9.48 (1H, d, J=8Hz, NH);
21	H	CH_3	2- 	1.7 - 2.1 (4H, m, 2 x CH_2); 2.9 - 3.2 (2H, m, CH_2); 3.1 - 3.5 (2H, AB, SCH_2); 3.81 (3H, s, OCH_3); 4.0 - 4.2 (2H, m, CH_2); 4.6 - 5.1 (2H, AB, $CH_2N^{\oplus}$); 5.03 (1H, d, J=5Hz, 6-H); 5.61 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 6.90 - 8.0 (8H, m, NH_2, 5 Phenyl-H, 1 Im H); 9.50 (1H, d, J=8Hz, NH);

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6) 60MHz, δ (ppm)=
22	H	CH_3	2-(H)	1.0 - 2.1 (14H, m, 10 Cyclohexyl-H, 2 x CH_2); 2.6 - 3.1 (3H, m, CH_2, 1 Cyclohexyl-H); 3.0 - 3.5 (2H, AB, SCH_2); 3.82 (3H, s, OCH_3); 4.0 - 4.2 (2H, m, CH_2); 4.88 (2H, m, $CH_2N^{\oplus}$); 5.00 (1H, d, J=5Hz, 6-H); 5.58 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole ; 7.25 (2H, s, NH_2); 7.65 (1H, s, Im H); 9.48 (1H, d, J= 8Hz, NH)
23	H	CH_3	3-$CONH_2$	1.7 - 2.1 (4H, m, 2 x CH_2); 2.9 - 3.1 (2H, m, CH_2); 3.1 - 3.5 (2H, AB, SCH_2); 3.80 (3H, s, OCH_3); 4.0 - 4.2 (2H, m, CH_2); 4.6 - 4.9 (2H, AB, $CH_2N^{\oplus}$); 5.00 (1H, d, J=5Hz, 6-H); 5.59 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 6.9 - 7.4 (4H, 2 x NH_2); 7.78 (1H, s, Im H); 9.50 (1H, d, J=8Hz, NH);
24	H	CH_3	3-CO_2CH_3	1.7 - 2.0 (4H, m, 2 x CH_2); 2.9 - 3.1 (2H, m, CH_2); 3.0 - 3.5 (2H, AB, SCH_2); 3.73 and 3.80 (each3H, s, 2xOCH_3); 4.0 - 4.2 (2H, m, CH_2); 4.7 - 5.2 (2H, AB, $CH_2N^{\oplus}$); 5.01 (1H, d, J=5Hz, 6-H); 5.60 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 7.20 (2H, s, NH_2); 7.72 (1H, s, Im H); 9.55 (1H, d, J=8Hz, NH)

Example	R^1	R^2	$R^{3'}$	^{1}H-NMR(DMSO-d_6)60MHz; δ(ppm)=
25	H	CH_3	3-COOH	1.8 - 2.1 (4H, m, 2 x CH_2); 2.9 - 3.1 (2H, m, CH_2); 3.03 - 3.6 (2H, AB, SCH_2); 3.81 (3H, s, OCH_3); 4.0 - 4.15 (2H, m, CH_2); 4.5 - 5.0 (2H, AB, $CH_2N^{\oplus}$); 5.02 (1H, d, J=5Hz, 6-H); 5.60 (1H, dd, J=5 and 8Hz, 7-H); 6.72 (1H, s, thiazole), 7.28 (2H, s, NH_2); 7.82 (1H, s, Im H); 9.68 (1H, d, J=8Hz, NH);
26	H	CH_3	8-OCH_3	1.8 - 2.0 (4H, m, 2 x CH_2); 3.1 - 3.5 (2H, AB, SCH_2); 3.75 and 3.82 (each 3H, s, 2 x OCH_3); 3.9 - 4.1 (2H, m, CH_2); 4.5 - 5.1 (3H, m, $CH_2N^{\oplus}$ and $\underline{CH}OCH_3$, 5.00 (1H, d, J=5Hz, 6-H); 5.61 (1H, dd, J=5 and 8Hz, 7-H); 6.70 (1H, s, thiazole); 7.22 (2H, s, NH_2); 7.53 and 7.90 (each 1H, d, J=2Hz, Im H); 9.52 (1H, d, J=8Hz, NH);

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A cephalosporin derivative of the formula I



(I)

and physiologically tolerated acid addition salts thereof, in which the R^2O group is in the syn position, and the substituents R^1, R^2 and R^3 have the following meanings:

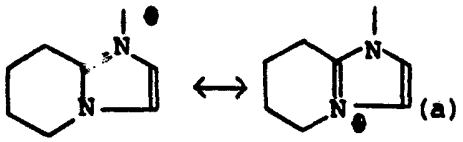
R^1 hydrogen or halogen,

R^2 hydrogen, C_1-C_6-alkyl which can be substituted once or several times, identically or differently, by halogen, aryl, heteroaryl, C_1-C_4-alkylthio, C_1-C_4-alkoxy, nitrile or carbamoyl, in which the amino group can be substituted once or twice by C_1-C_4-alkyl, C_2-C_6-alkenyl which can be optionally substituted once or several times by halogen, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, C_4-C_7-cycloalkenyl, C_3-C_7-cycloalkylmethyl, the group of the formula

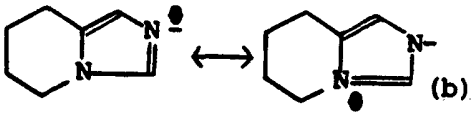
$$-(CH_2)_n-(\overset{R^4}{\underset{R^5}{C}})_m-R^6,$$

in which m and n each represents 0 or 1, and R^4 and R^5, which can be identical or different, denote hydrogen or a C_1-C_{11}-alkyl group, or form, together with the carbon to which they are bonded, a vinylidene or a C_3-C_7-cycloalkylidene group, and
R^6 denotes a carboxyl or C_1-C_4-alkyloxycarbonyl group,
R^3 a 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinium radical

(a) or a 5,6,7,8-tetrahydroimidazo[1,5-a]pyridinium radical (b)



(a)

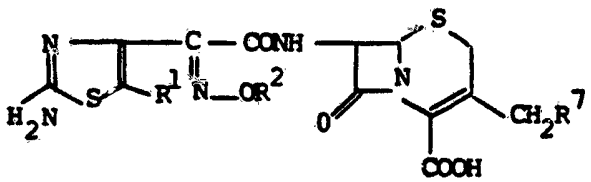


(b)

which can be substituted once or several times, identically or differently, by C_1-C_6-alkyl which can also be substituted by hydroxyl, C_1-C_6-alkyloxy, carboxyl, C_1-C_6-alkoxycarbonyl, carbamoyl or amino; C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_5-C_6-cycloalkenyl, C_3-C_6-cycloalkylmethyl; phenyl, phenoxy or benzyl, each of which can be substituted by C_1-C_4-alkyl, hydroxyl or C_1-C_4-alkoxy; C_1-C_6-alkoxy, C_1-C_6-alkylthio, sulfo, trifluoromethyl, hydroxyl, mercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, carboxyl, C_1-C_6-alkoxycarbonyl, or carbamoyl which can be substituted once or twice on the nitrogen by C_1-C_6-alkyl.

2. A process for the preparation of a cephalosporin derivative of the formula I and the physiologically tolerated acid addition salts thereof, which comprises

a) reaction of a compound of the general formula II



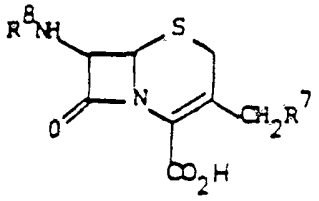
or salts thereof, in which R^1 and R^2 have the meanings mentioned in formula I, the amino group can also be

protected, and R^7 denotes a group the replacement of which can be facilitated by the presence of a neutral salt ion in an amount of 10-30 equivalents to form a protective group by tetrahydroimidzopyridine or the tetrahydroimidazopyridine derivative from which the radical R^3 defined in formula I derives, with tetrahydroimidazopyridine or this tetrahydroimidazopyridine derivative present in an amount which is between an equimolar amount and an express of up to 5-fold in the presence of a solvent

α) elimination of a protective group which is present where appropriate, and

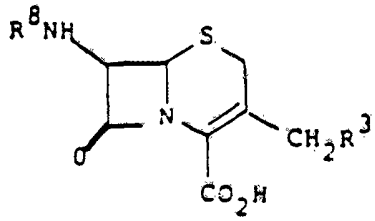
β) where necessary, conversion of the resulting product into a physiologically tolerated acid addition salt, or

b) reaction of a compound of the general formula III



(III)

in which R^7 has the meaning mentioned above for the formula II, and R^8 represents hydrogen or an amino protective group, with tetrahydroimidazopyridine or the tetrahydroimidazopyridine derivative from which the radical R^3 defined in formula I derives in an amount which is at least stoichiometric and is up to approximately tenfold excess at a temperature of -50 to +100°C with formation of the compound of the general formula IV

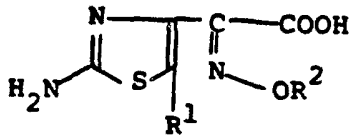


(IV)

in which R^3 and R^8 have the abovementioned meaning, and

α) elimination of an amino protective group which is present where appropriate, and

β) reaction of the compound IV in which R^8 denotes hydrogen, either as such or in the form of a reactive derivative, with a 2-syn-oxyiminoacetic acid of the general formula V



(V)

in which R^1 and R^2 have the said meaning, and the amino group can also be in protected form, or with a derivative of this compound which is activated on the carboxyl group, and

α) elimination of a protective group which is present where appropriate, and

β) where necessary, conversion of the resulting product of the general formula I into a physiologically tolerated acid addition salt.

3. A pharmaceutical product effective against bacterial infections, which contains a cephalosporin derivative of the formula I.

4. A process for the preparation of a pharmaceutical product effective against bacterial infections, which comprises converting a cephalosporin derivative of the formula I, where appropriate with pharmaceutically customary excipients or diluents, into a pharmaceutically suitable administration form.

5. The use of a cephalosporin derivative of the formula I for controlling bacterial infections.

DATED this 3rd day of March 1988.
HOECHST AKTIENGESELLSCHAFT

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PATENT ATTORNEYS
50 QUEEN STREET
MELBOURNE. VIC. 3000.

3. A pharmaceutical product effective against bacterial infections, which contains a cephalosporin derivative of the formula I in adjunct with pharmaceutically acceptable carriers or excipients.

4. A process for the preparation of a pharmaceutical product effective against bacterial infections, which comprises converting a cephalosporin derivative of the formula I, where appropriate with pharmaceutically customary excipients or diluents, into a pharmaceutically suitable administration form.

5. A method of controlling bacterial infections comprising administering to a patient suffering therefrom a pharmaceutically effective amount of a cephalosporin derivative of the formula I.

DATED this 21st day of November, 1990.

HOECHST AKTIENGESELLSCHAFT

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