

Description

The present invention relates to new cephem compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new cephem compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities, to a process for preparation thereof, to pharmaceutical composition comprising the same, and to a method for treating infectious diseases in human being or animals.

Accordingly, one object of the present invention is to provide the cephem compound and a pharmaceutically acceptable salt thereof, which are highly active against a number of pathogenic microorganisms.

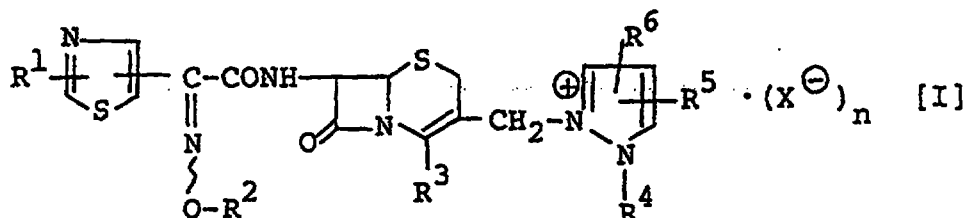
Another object of the present invention is to provide a process for the preparation of the cephem compound or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said cephem compound or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a method for treating infectious diseases caused by pathogenic microorganisms, which comprises administering said cephem compound to infected human being or animals.

Cephem compounds are generally known in the state of the art. For example, GB-A-2 037 821 discloses 7-thiazolyl group substituted cephalosporins having a monosubstituted pyrazolio group in the 3-position exhibiting an high activity against gram-negative organism. 7-Thiadiazolyl group substituted cephem compounds are disclosed in EP-A-0 062 321. Furthermore, EP-A-0 214 600 and EP-A-0 222 322 disclose cephem compounds which are substituted in the 3-position by an imidazolyl group.

The object cephem compound is novel and can be represented by the following general formula [I] :



wherein

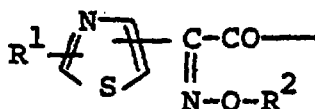
- R¹ is amino or a protected amino,
- R² is (C₁-C₆) alkyl which may have 1 to 3 halogen substituents,
- R³ is COO^o, carboxy or a protected carboxy,
- R⁴ is hydroxy(C₁-C₆)alkyl or protected hydroxy(C₁-C₆)alkyl,
- R⁵ is amino or a protected amino,
- R⁶ is hydrogen or (C₁-C₆) alkyl,
- X^o is an anion, and
- n is 0 or 1,

with proviso that

- (i) when R³ is COO^o, then n is 0, and
- (ii) when R³ is carboxy or a protected carboxy, then n is 1.

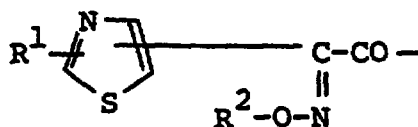
As to the object compound [I], the following points are to be noted.

That is, the object compound [I] includes syn isomer, anti isomer and a mixture thereof. Syn isomer means one geometrical isomer having the partial structure represented by the following formula :



(wherein R¹ and R² are each as defined above),

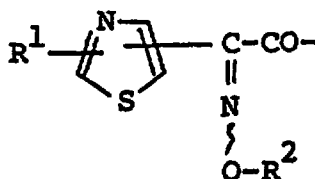
and anti isomer means the other geometrical isomer having the partial structure represented by the following formula :



(wherein R¹ and R² are each as defined above),

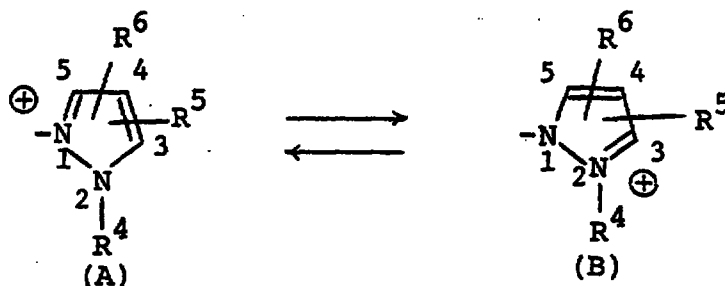
and all of such geometrical isomers and mixture thereof are included within the scope of this invention.

In the present specification and claim, the partial structure of these geometrical isomers and mixture thereof are represented for convenient sake by the following formula :



(wherein R¹ and R² are each as defined above).

Another point to be noted is that the pyrazolio moiety of the compound [I] can also exist in the tautomeric form, and such tautomeric equilibrium can be represented by the following scheme.

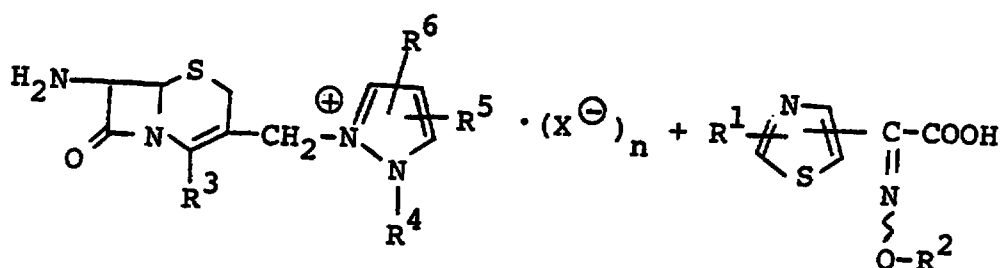


(wherein R⁴, R⁵ and R⁶ are each as defined above).

Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claim, however, the object compound [I] is represented for the convenient sake by one expression of the pyrazolio group of the formula (A).

The cephem compound [I] of the present invention can be prepared by processes as illustrated in the following reaction schemes.

Process 1

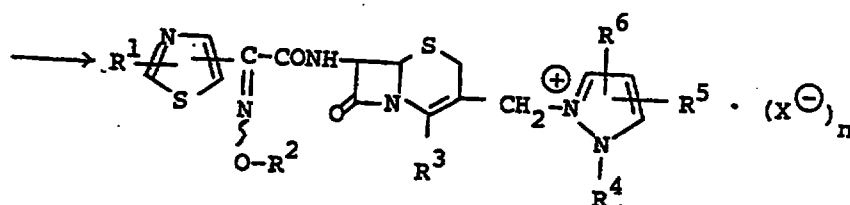


[II]

[III]

or its reactive
derivative at the
amino group,
or a salt thereof

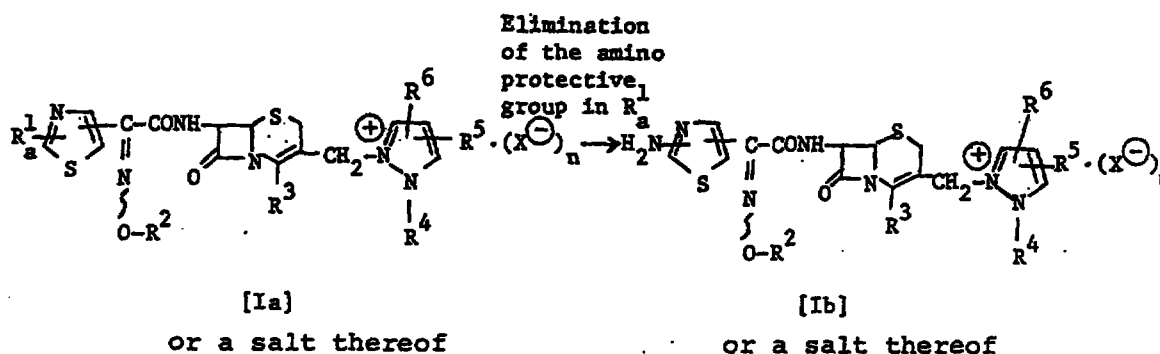
or its reactive
derivative at the
carboxy group,
or a salt thereof



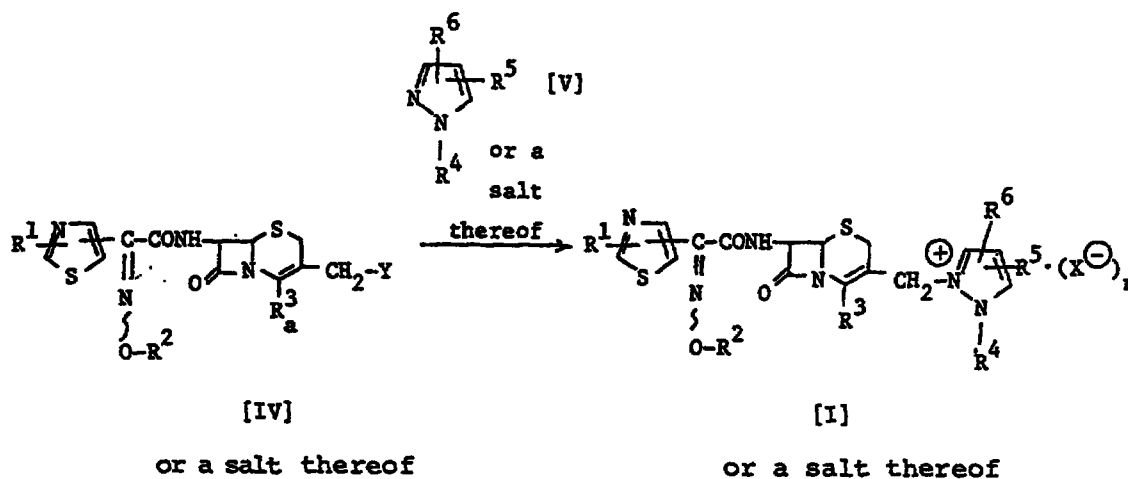
[I]

or a salt thereof

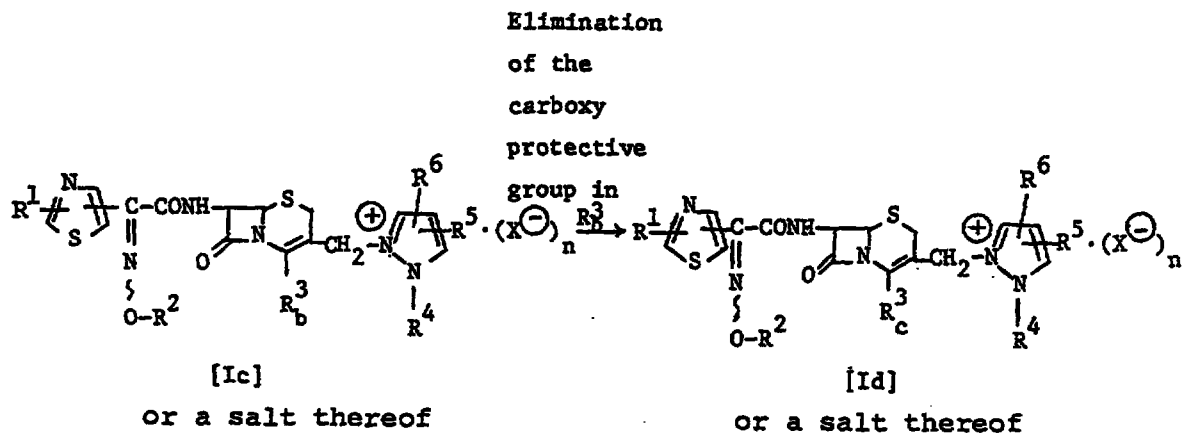
Process 2



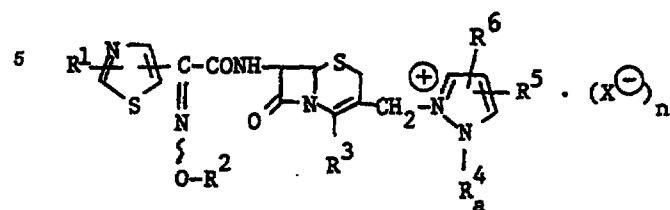
Process 3



Process 4



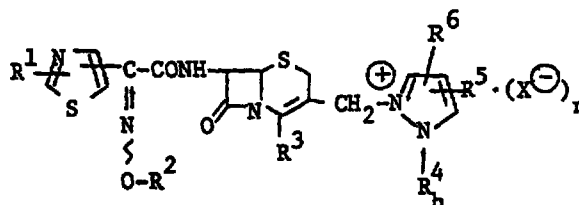
Process 5



[Ie]

or a salt thereof

Elimination of the hydroxy
protective group in R⁴

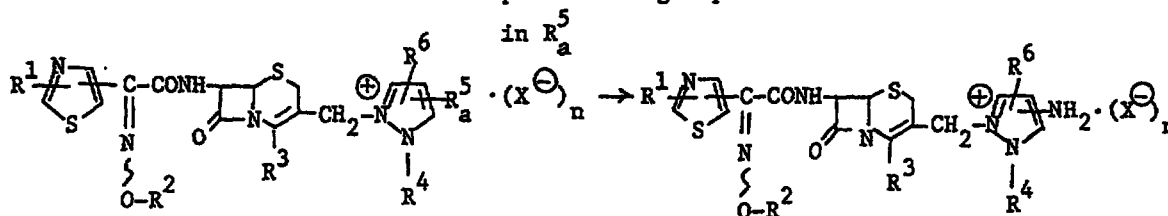


[14].

or a salt thereof

Process 6

Elimination of
the amino
protective group
in R_2^5



[Ig]

or a salt thereof

[Ih]

or a salt thereof

wherein

$R^1, R^2, R^3, R^4, R^5, R^6, X^e$ and n are

R_2^1 is

 R^3 is

R3 is

 R^3 is R^4 is

R₅⁴ is

Reis

Y is

each as defined above

a protected amino,

carboxy or a protected carboxy,

a protected carboxy,

COO⁻ or carboxy,

protected hydroxy (C₁-C₆)alkyl,

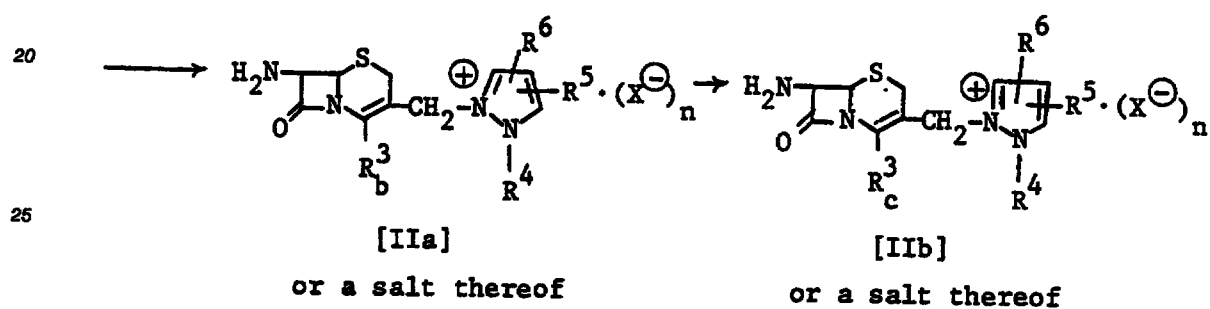
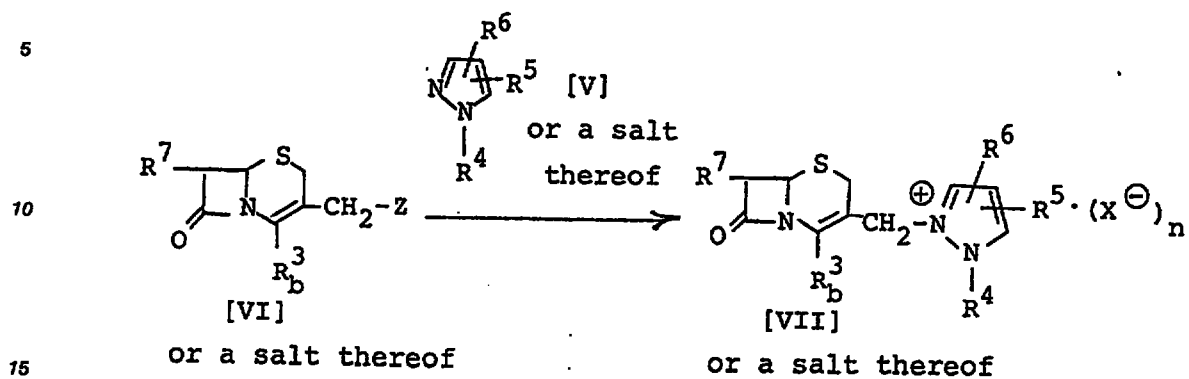
hydroxy(C₁-C₆)alkyl,

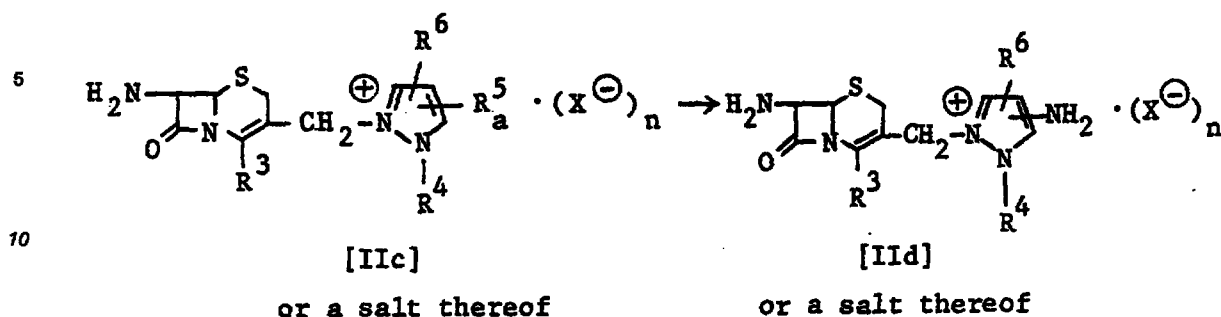
a protected amino, and

a leaving group.

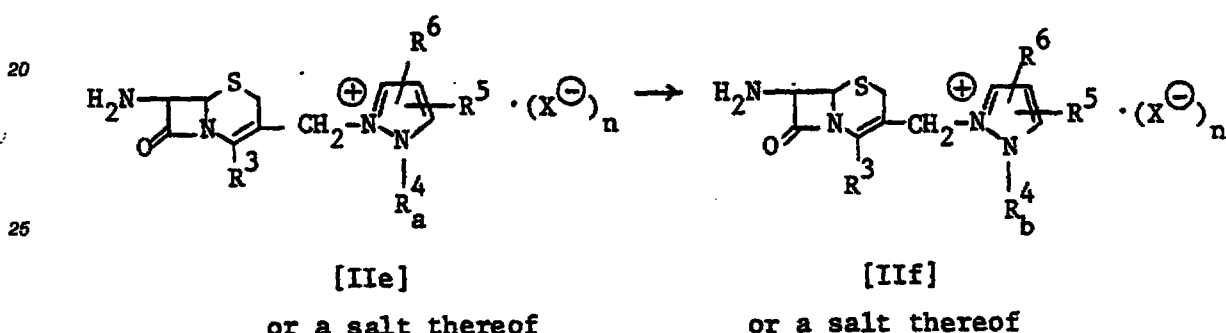
The starting compound [II] or a salt thereof is novel and can be prepared according to the following reaction schemes.

Process A





Process C



wherein

$R^3, R_b^3, R_c^3, R^4, R_a^4, R_b^4, R^5, R_a^5, R^6, X^e$ and n are
 R^7 is
 Z is

each as defined above,
a protected amino, and
a leaving group.

Some of the starting compound [V] or a salt thereof are novel and they can be prepared according to the methods disclosed in Preparations described later or similar manners thereto.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic mono or di salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt,] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt,], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt,], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate,], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate,], a salt with an amino acid [e.g. arginine salt, aspartic acid salt and glutamic acid salt, etc.].

In the above and subsequent descriptions of this specification, suitable examples of the various definitions are explained in detail as follows :

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable protective group in "a protected amino" may include ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl [e.g. benzyl, phenethyl, 1-phenylethyl, benzhydryl, trityl,], acyl as explained hereinbelow.

Suitable acyl may be aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid and sulfonic acid.

Suitable example of the acyl group thus explained may be lower alkanoyl [e.g. formyl, acetyl, propionyl, hexanoyl, pivaloyl,], mono(or di or tri)halo(lower)alkanoyl [e.g. chloroacetyl, trifluoroacetyl,], lower alkoxy carbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl,], mono(or di or tri)halo(lower)alkoxy carbonyl [e.g. chloromethoxy carbonyl, dichloroethoxycarbonyl, trichloroethoxycarbonyl,], aroyl [e.g. benzoyl, toluoyl, xyloyl, naphthoyl,], ar(lower)alkanoyl such as phenyl-

(lower)alkanoyl [e.g. phenylacetyl, phenylpropionyl,], aryloxy(alkoxy)carbonyl [e.g. phenoxy(alkoxy)carbonyl, naphthoxy(alkoxy)carbonyl,], aryloxy(lower)alkanoyl such as phenoxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl,], arylglyoxyloxy [e.g. phenylglyoxyloxy, naphthylglyoxyloxy,], ar(lower)alkoxy(alkoxy)carbonyl which may have suitable substituent(s) such as phenyl(lower)alkoxy(alkoxy)carbonyl which may have nitro or lower alkoxy [e.g. benzyloxy(alkoxy)carbonyl, phenethyloxy(alkoxy)carbonyl, p-nitrobenzyloxy(alkoxy)carbonyl, p-methoxybenzyloxy(alkoxy)carbonyl,], thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, triazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, lower alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, pentylsulfonyl, butylsulfonyl,], arylsulfonyl [e.g. phenylsulfonyl, tolylsulfonyl, xylylsulfonyl, naphthylsulfonyl,], ar(lower)alkylsulfonyl such as phenyl(lower)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl and benzhydrylsulfonyl,].

Preferable example of "a protected amino" thus defined may be ar(lower)alkylamino and lower alkanoylamino, more preferable one may be triphenyl(C₁-C₄)alkylamino and C₁-C₄ alkanoylamino, and the most preferable one may be tritylamino, formamido and acetamido.

Suitable "a protected carboxy" may be an esterified carboxy group, and concrete examples of the ester moiety in said esterified carboxy group may be the ones such as lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester,] which may have suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, 1-acetoxyethyl ester, 1-propionyloxyethyl ester, pivaloyloxymethyl ester, 2-propionyloxyethyl ester, hexanoyloxymethyl ester], lower alkanesulfonyl(lower)alkyl ester [e.g. 2-mesyloxyethyl ester,] or mono(or di or tri)halo(lower)alkyl ester [e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester]; lower alkenyl ester [e.g. vinyl ester, allyl ester]; lower alkynyl ester [e.g. ethynyl ester, propynyl ester]; ar(lower)alkyl ester which may have suitable substituent(s) [e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester,] or aryl ester which may have suitable substituent(s) [e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, 4-tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester,]; in which the preferred one may be mono or di or triphenyl(C₁-C₄)alkyl ester and the most preferred one may be benzhydryl ester.

Suitable "lower alkyl" may be straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, 2-ethylpropyl or hexyl, in which the preferred "lower alkyl" may be (C₁-C₄)alkyl and the most preferred one may be methyl.

Suitable examples of "suitable substituent(s)" in "lower alkyl which may have one or more suitable substituent(s)" may include halogen [e.g. fluoro, chloro, bromo, iodo].

Suitable examples of said lower alkyl having one or more suitable substituent(s) may include lower alkyl having one or more halogen such as fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2-chloro-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-chloromethyl-2-iodo-1-bromoethyl, 2-difluorobutyl, 1-dichloromethyl-1-methylethyl, 2-fluoro-4-chloro-5-bromopentyl, 1-difluoro-2-ethylpropyl or 2-fluoro-3-iodohexyl, in which the preferred one may be (C₁-C₄)alkyl having 1 to 3 halogen, the more preferred one may be dihalo(C₁-C₄)alkyl and the most preferred one may be difluoromethyl.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, 1-(hydroxymethyl)ethyl, 1-hydroxybutyl, 1-hydroxymethyl-1-methylethyl, 3-hydroxypentyl, 3-hydroxy-2-ethylpropyl and 6-hydroxyhexyl, in which the preferred one may be hydroxy(C₁-C₄)alkyl and the most preferred one may be 2-hydroxyethyl.

Suitable "protected hydroxy(lower)alkyl" may include acyloxy(lower)alkyl, in which suitable "acyl" moiety can be referred to the ones as exemplified for "a protected amino" before and suitable examples of said "acyloxy(lower)alkyl" may be lower alkanoyloxy(lower)alkyl [e.g. formyloxymethyl, 1-formyloxyethyl, 2-formyloxyethyl, 2-acetoxyethyl, 3-acetoxypropyl, 1-(propionyloxymethyl)ethyl, 1-butyryloxybutyl, 1-hexanoyloxybutyl, 1-pivaloyloxymethyl-1-methylethyl, 3-formyloxypentyl, 3-formyloxy-2-ethylpropyl, 6-acetoxyhexyl] or carbamoyloxy(lower)alkyl [e.g. carbamoyloxymethyl, 1-carbamoyloxyethyl, 2-carbamoyloxyethyl, 3-carbamoyloxypropyl, 1-(carbamoyloxymethyl)ethyl, 1-carbamoyloxybutyl, 1-carbamoyloxymethyl-1-methylethyl, 3-carbamoyloxypentyl, 3-carbamoyloxy-2-ethylpropyl, 6-carbamoyloxyhexyl]; in which the preferred one may be (C₁-C₄)alkanoyloxy(C₁-C₄)alkyl or carbamoyloxy(C₁-C₄)alkyl and the most preferred one may be 2-formyloxyethyl, 2-acetoxyethyl or 2-carbamoyloxyethyl.

Suitable "anion" may be formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, chloride, bromide, iodide, sulfate or phosphate.

Suitable "a leaving group" may be halogen [e.g. chlorine, bromine, iodine], acyloxy such as sulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, mesyloxy or lower alkanoyloxy [e.g. acetyloxy, propionyloxy,].

The processes for preparing the object compound of the present invention are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] or its reactive derivative at the amino group or a salt thereof with a compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound [II] may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound [II] with a carbonyl compound such as aldehyde or ketone; a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide or bis(trimethylsilyl)urea and a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene.

Suitable salts of the compound [II] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide and an activated ester. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid,], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid.] or aromatic carboxylic acid [e.g. benzoic acid]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranil ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole]. These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol,], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine or N,N-di-(lower)alkylbenzylamine.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group in R_a^1 .

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium], an alkaline earth metal [e.g. magnesium, calcium], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane or 1,8-diazabicyclo[5.4.0]-undec-7-ene.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid] is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron] or metallic compound [e.g. chromium chloride, chromium acetate] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel], cobalt catalysts [e.g. reduced cobalt, Raney cobalt], iron catalysts [e.g. reduced iron, Raney iron] and copper catalysts [e.g. reduced copper, Raney copper, Ullman copper].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the abovementioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes within the scope of the invention the case that a protected amino in R^5 is transformed into amino, the case that a protected carboxy in R^3 is transformed into carboxy and the case that protected hydroxy(lower)alkyl in R^4 is transformed into hydroxy(lower)alkyl.

40 Process 3

The object compound [I] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V] or a salt thereof.

Suitable salts of the compounds [IV] can be referred to the ones as exemplified for the compound [I].

Suitable salts of the compounds [V] may be an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate] or an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate].

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound [V] is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, organic base such as trialkylamine. The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating. The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, potassium iodide], alkali metal thiocyanate [e.g. sodium thiocyanate, potassium thiocyanate].

Anion $X^{\ominus}$ may be the one derived from a leaving group Y and may be the other one converted therefrom by a conventional method.

Process 4

The object compound [Id] or a salt thereof can be prepared by subjecting a compound [Ic] or a salt thereof to elimination reaction of the carboxy protective group in R^3 .

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that a protected amino in R^1 and/or R^5 and/or protected hydroxy(lower)alkyl in R^4 are transformed into amino and/or hydroxy(lower)alkyl, respectively during this reaction.

Process 5

The object compound [If] or a salt thereof can be prepared by subjecting a compound [Ie] or a salt thereof to elimination reaction of the hydroxy protective group in R^4 .

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the cases that a protected amino in R^1 and/or R^5 , and/or a protected carboxy in R^3 are transformed into amino, and/or carboxy, respectively during this reaction.

Process 6

The object compound [Ih] or a salt thereof can be prepared by subjecting a compound [Ig] or a salt thereof to elimination reaction of the amino protective group in R^5 .

This reaction can be carried out in a similar manner to that of Process 2 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. base, acid, catalyst, solvent, reaction temperature] of this reaction are to be referred to those as explained in Process 2.

The present invention includes within the scope of the invention the case that a protected amino in R^1 , and/or a protected carboxy in R^3 , and/or protected hydroxy(lower)alkyl in R^4 are transformed into amino, and/or carboxy, and/or hydroxy(lower)alkyl, respectively during this reaction.

The reactions in Processes A to C for preparing the starting compound [II] or a salt thereof can be carried out according to the similar manners to those explained in Processes 2 to 6 for preparing the compound [I] or a salt thereof.

Now in order to show the utility of the object compound [I], the test data on MIC (minimal inhibitory concentration) of representative compound [I] of this invention is shown in the following.

Test Method :

In vitro antibacterial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Trypticase-soy broth (10^8 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of representative test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of $\mu\text{g/ml}$ after incubation at 37°C for 20 hours.

Test Compound

(1) 7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (the compound of Example 4)

Test Result

MIC ($\mu\text{g/ml}$)	
Test Bacteria	Test Compound (1)
P. aeruginosa 26	0.39

For therapeutic administration, the object compound [I] and a pharmaceutically acceptable salt thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound [I] may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound [I] to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compound [I] of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of acetic anhydride (11.13 ml) and formic acid (5.93 ml) was stirred at ambient temperature for 30 minutes. To this solution was added 5-amino-1-(2-hydroxyethyl)pyrazole (5 g) under ice-cooling, and the mixture was stirred at 30-40°C for 1 hour. The reaction mixture was poured into a mixture of water, tetrahydrofuran and ethyl acetate and adjusted to pH 6 with aqueous sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted with a mixture of tetrahydrofuran and ethyl acetate for three times. The organic layers were combined, dried over magnesium sulfate and evaporated in vacuo to give 5-formamido-1-(2-formyloxyethyl)pyrazole (5.18 g).

IR (Nujol) : 3180, 1705, 1660 cm^{-1}

NMR (DMSO- d_6 , δ) : 4.21-4.61 (4H, m), 6.11 and 6.34 (1H, each d, J=3Hz), 7.47 (1H, d, J=3Hz), 8.00 (1H, s), 8.33 (1H, s)

Preparation 2

To a mixture of benzhydryl 7 β -tert-butoxycarbonylamino-3-chloromethyl-3-cephem-4-carboxylate (20 g) and sodium iodide (5.82 g) in N,N-dimethylformamide (20 ml) was added 5-formamido-1-(2-formyloxyethyl)pyrazole (21.34 g) at ambient temperature. After being stirred for 24 hours at the same temperature, the mixture was poured into a mixture of water and ethyl acetate. The organic layer was separated and washed with water, aqueous sodium chloride solution, and dried over magnesium sulfate. The solution was evaporated in vacuo to give benzhydryl 7 β -tert-butoxycarbonylamino-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide (29.6 g).

IR (Nujol) : 1780, 1720 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.49 (9H, s), 3.43 (2H, broad s), 4.14-4.38 (2H, m), 4.52-4.73 (2H, m), 5.15 (1H, d, J=5Hz), 5.40 (2H, broad s), 5.67 (1H, dd, J=5Hz and 8Hz), 6.88 (1H, s), 7.02 (1H, d, J=3Hz), 7.18-7.52 (10H, m), 7.94 (1H, d, J=8Hz), 7.99 (1H, s), 8.27 (1H, d, J=3Hz), 8.51 (1H, broad s)

Preparation 3

To a solution of benzhydryl 7 β -tert-butoxycarbonylamino-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide (29.5 g) and anisole (30 ml) in methylene chloride (90 ml) was added dropwise trifluoroacetic acid (60 ml) under ice-cooling. After being stirred for 1 hour at ambient temperature, the mixture was poured into a mixture of diisopropyl ether (600 ml) and ethyl acetate (600 ml). The resultant precipitate was collected by filtration to give bis(trifluoroacetic acid salts) of 7 β -amino-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (22.7 g).

IR (Nujol) : 1780, 1715, 1660 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.53 (2H, broad s), 4.28-4.56 (2H, m), 4.78-4.99 (2H, m), 5.29 (2H, broad s), 5.53 (2H, broad s), 7.14 (1H, d, $J=3\text{Hz}$), 8.22 (1H, s), 8.46 (1H, d, $J=3\text{Hz}$), 8.63 (1H, s)

Preparation 4

Concentrated hydrochloric acid (5.67 ml) was added to a mixture of bis(trifluoroacetic acid salts) of 7 β -amino-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (10 g) in methanol (50 ml) at ambient temperature. After being stirred at the same temperature for 3 hours, the mixture was added dropwise to ethyl acetate (500 ml). The resultant precipitate was collected by filtration to give 7 β -amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate trihydrochloride (6.1 g).

IR (Nujol) : 3250, 1770, 1700, 1625 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.43 (2H, broad s), 3.52-3.88 (2H, m), 4.18-4.48 (2H, m), 5.28 (2H, broad s), 5.37 (2H, broad s), 5.97 (1H, d, $J=3\text{Hz}$), 8.18 (1H, d, $J=3\text{Hz}$)

Example 1

A mixture of N,N-dimethylformamide (0.41 ml) and phosphoryl chloride (0.49 ml) in ethyl acetate (2 ml) was stirred under ice-cooling for 30 minutes to prepare Vilsmeier reagent. 2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetic acid (1.02 g) was added to the above solution at 0-5 °C, and the mixture was stirred at the same temperature for 30 minutes to produce an activated acid solution. This activated acid solution was added to a solution of 7 β -amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate trihydrochloride (2 g) and N-(trimethylsilyl)acetamide (5.85 g) in tetrahydrofuran (40 ml) under ice-cooling, and then the mixture was stirred at 10-15 °C for 1 hour. The resultant mixture was poured into diethyl ether (500 ml), and the resulting precipitates were collected by filtration to give 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate dihydrochloride (syn isomer) (2.55 g).

IR (Nujol) : 1770, 1660 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.30 (2H, m), 3.68 (2H, m), 3.92 (3H, s), 4.31 (2H, m), 5.29 (1H, d, $J=5\text{Hz}$), 5.32 (2H, m), 5.88 (1H, dd, $J=5\text{Hz}$ and 8Hz), 5.99 (1H, d, $J=3\text{Hz}$), 7.48 (1H, s), 8.12 (1H, d, $J=3\text{Hz}$), 8.59 (1H, s), 9.81 (1H, d, $J=8\text{Hz}$)

The following compounds (Examples 2 and 3) were prepared according to a similar manner to that of Example 1.

Example 2

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1640 cm^{-1}

Example 3

7 β -[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1660 cm^{-1}

Example 4

To a solution of 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate dihydrochloride (syn isomer) (2.5 g) in methanol (12.5 ml) was added concentrated hydrochloric acid (0.88 ml) at ambient temperature. After being stirred at the same temperature for 2 hours, the mixture was poured into ethyl acetate (500 ml), and the resulting precipitate was collected by filtration. The precipitate was dissolved in water (100 ml), and adjusted to pH 2 with 5% aqueous sodium bicarbonate solution. This solution was subjected to column chromatography on macroporous non-ionic adsorption resin "Dialon HP-20" (Trademark, manufactured by Mitsubishi Chemical Industries). The object compound was eluted with 10% diisopropyl alcohol, and lyophilized to give 7 β -[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (0.43 g).

IR (Nujol) : 3300, 1770, 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 3.00 and 3.30 (2H, ABq, J=18Hz), 3.60 (2H, m), 3.83 (3H, s), 4.37 (2H, m), 5.06 (1H, d, J=5Hz), 5.18 (2H, broad s), 5.65 (1H, dd, J=5Hz and 8Hz), 5.84 (1H, d, J=3Hz), 6.71 (1H, s), 7.18 (2H, broad s), 7.38 (2H, broad s), 8.08 (1H, d, J=3Hz), 9.52 (1H, d, J=8Hz).

The following compound (Example 5) was prepared according to a similar manner to that of Example 4.

Example 5

7 β -[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1660 cm⁻¹

Example 6

To a suspension of benzhydryl 7 β -[2-(difluoromethoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer) (5 g) and sodium iodide (0.856 g) in N,N-dimethylformamide (5 ml) was added 5-formamido-1-(2-formyloxyethyl)pyrazole (4.18 g) at ambient temperature. After being stirred for 24 hours, the mixture was poured into a mixture of ethyl acetate and water. The separated organic layer was washed with water and sodium chloride aqueous solution, dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in tetrahydrofuran, and subjected to a column chromatography on an ion-exchange resin Amberlite IRA 400 (CF₃COO⁻ type) (Trademark : manufactured by Rohm and Haas Co.). The object compound was eluted with tetrahydrofuran, and evaporated in vacuo to give trifluoroacetic acid salt of benzhydryl 7 β -[2-(difluoromethoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (4.80 g).

IR (Nujol) : 1780, 1720, 1675 cm⁻¹

NMR (DMSO-d₆, δ) : 3.50 (2H, m), 3.65 (2H, m), 4.35 (2H, m), 5.25 (1H, d, J=5Hz), 5.50 (2H, broad s), 5.88 (1H, dd, J=5Hz and 8Hz), 6.91 (1H, s), 7.03 (1H, s), 7.04-7.70 (27H, m), 8.08 (1H, s), 8.33 (1H, d, J=3Hz), 8.67 (1H, s), 9.05 (1H, s), 10.05 (1H, d, J=5Hz)

The following compound (Example 7) was obtained according to a similar manner to that of Example 6.

Example 7

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1640 cm⁻¹

Example 8

To a solution of trifluoroacetic acid salt of benzhydryl 7 β -[2-(difluoromethoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (4.7 g) in methylene chloride (15 ml) and anisole (5 ml) was added trifluoroacetic acid (10 ml) under ice-cooling. After being stirred for 1.5 hours, the mixture was poured into diisopropyl ether, and the resultant precipitate was collected by filtration. The precipitate was dissolved in water,

adjusted to pH 12 with 1N sodium hydroxide aqueous solution under ice-cooling. The mixture was stirred at the same temperature for 10 minutes, and adjusted to pH 2 with 1N hydrochloric acid solution. This solution was subjected to a column chromatography on macroporous non-ionic adsorption resin "Diaion HP-20". The object compound was eluted with 10% diisopropyl alcohol, and lyophilized to give 7 β -[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[3-formamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (0.80 g).

IR (Nujol) : 3250, 1770, 1665 cm⁻¹

NMR (D₂O and DMSO-d₆, δ) : 3.11 and 3.50 (2H, ABq, J=18Hz), 3.85 (2H, m), 4.60 (2H, m), 5.22 (1H, d, J=5Hz), 5.36 (2H, broad s), 5.81 (1H, d, J=5Hz), 6.91 (1H, t, J=71Hz), 7.05 (1H, d, J=3Hz), 7.18 (1H, s), 8.24 (1H, d, J=3Hz), 8.44 (1H, s)

Example 9

To a suspension of 7 β -[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[3-formamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (0.7 g) in methanol (3.5 ml) was added concentrated hydrochloric acid (0.42 ml) at ambient temperature. After being stirred at the same temperature for 2 hours, the mixture was poured into ethyl acetate. The resulting precipitate was collected by filtration. The precipitate was dissolved in water, and adjusted to pH 2 with 5% aqueous sodium bicarbonate solution. This solution was subjected to a column chromatography on macroporous non-ionic adsorption resin "Diaion HP20". The object compound was eluted with 10% diisopropyl alcohol, and lyophilized to give 7 β -[2-(2-aminothiazol-4-yl)-2-(difluoromethoxyimino)acetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (0.41 g).

IR (Nujol) : 3300, 1760, 1660 cm⁻¹

NMR (D₂O, δ) : 3.02 and 3.35 (2H, ABq, J=18Hz), 3.78 (2H, m), 4.28 (2H, m), 4.95 and 5.16 (2H, ABq, J=16Hz), 5.16 (1H, d, J=5Hz), 5.76 (1H, d, J=5Hz), 5.92 (1H, d, J=3Hz), 6.86 (1H, t, J=69Hz), 7.16 (1H, s), 7.83 (1H, d, J=3Hz)

The following compound (Example 10) was obtained according to a similar manner to that of Example 9.

Example 10

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1640 cm⁻¹

Example 11

To a solution of 7 β -[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (6.5 g) in water (6.5 ml) was added 2N-sulfuric acid (6.5 ml) at room temperature. The mixture was stirred at room temperature to precipitate crystals. The crystals were collected by filtration and washed with ice-water and then acetone to give sulfuric acid salt of 7 β -[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (5.92 g).

NMR (DMSO-d₆, δ) : 3.13-3.83 (2H, m), 3.40-3.83 (4H, m), 5.15 (1H, d, J=5Hz), 5.05 and 5.30 (2H, ABq, J=13Hz), 5.79 (1H, d-d, J=5Hz and 8Hz), 5.88 (1H, d, J=3Hz), 6.71 (1H, s), 7.28 (2H, broad s), 7.95 (1H, d, J=3Hz), 9.57 (1H, d, J=8Hz)

Preparation 5

7 β -Amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate tri hydrochloride (66 g) was dissolved in water (264 ml). The aqueous solution was subjected to column chromatography on "Diaion HP-20" using water as eluent. Fractions containing the object compound were combined and to this combined solution was added dropwise isopropyl alcohol (1.15 l) under ice-cooling. The mixture was stirred for 1.5 hours under ice-cooling to precipitate crystals. The crystals were collected by filtration and washed with a mixture of isopropyl alcohol and water (10:1) under ice-cooling and dried over phosphorus pentoxide to give 7 β -amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate • hydrochloride • dihydrate (29.95 g).

IR (Nujol) : 3270, 1790, 1560-1635 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.43-3.77 (2H, m), 4.47-5.07 (4H, m), 5.07 (1H, d, $J=5\text{Hz}$), 5.12 and 5.38 (2H, ABq, $J=16\text{Hz}$), 5.92 (1H, d, $J=3\text{Hz}$), 7.56 (2H, broad s), 8.11 (1H, d, $J=3\text{Hz}$).

Analysis (%) Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_4\text{S}\cdot\text{HCl}\cdot 2\text{H}_2\text{O}$

Found	C:37.90, C:37.82	H:5.38, H:5.56,	N:17.00, N:16.73,	Cl:8.60 Cl:8.60
-------	---------------------	--------------------	----------------------	--------------------

Preparation 6

A mixture of acetic anhydride (44.5 ml) and formic acid (22.3 ml) was stirred at room temperature for an hour. To this mixture was added 5-amino-1-(2-hydroxyethyl)pyrazole (30 g) at 0-10°C, and the mixture was stirred under ice-cooling for 30 minutes. The mixture was poured into ice-cooled water, adjusted to pH 10.5 with 40% potassium carbonate solution, and stirred under ice-cooling for 30 minutes. The mixture was extracted with a mixture of tetrahydrofuran and ethyl acetate 6 times. The organic layer was dried over magnesium sulfate, and evaporated in vacuo to give 5-formamido-1-(2-hydroxyethyl)pyrazole (30.8 g).

mp: 109-112°C

IR (Nujol) : 3230, 1695, 1570, 1540 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.62-3.95 (2H, m), 3.98-4.32 (2H, m), 6.22 and 6.36 (1H, each d, $J=3\text{Hz}$), 7.42 (1H, d, $J=3\text{Hz}$), 8.32 and 8.36 (1H, each s).

Preparation 7

To a suspension of 5-formamido-1-(2-hydroxyethyl)pyrazole (1 g) in acetonitrile (50 ml) was added dropwise chlorosulfonyl isocyanate (0.77 ml) at -15°C ~ -20°C.

The mixture was stirred for 3 hours under ice-cooling. To the reaction mixture was added water (1 ml) and kept to stand overnight. The solution was adjusted to pH 7.5 with 5N-sodium hydroxide solution and then adjusted to pH 8.5 with 1N-sodium hydroxide solution. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran. The extract and said organic layer were combined and dried over magnesium sulfate. The solvent was distilled off and the residue was crystallized from ethyl acetate to give 5-amino-1-(2-carbamoyloxyethyl)pyrazole (0.60 g).

NMR (DMSO-d_6 , δ) : 3.83-4.35 (4H, m), 4.80-5.18 (2H, broad s), 5.32 (1H, d, $J=3\text{Hz}$), 6.33-6.87 (2H, broad s), 7.08 (1H, d, $J=3\text{Hz}$).

Preparation 8

5-Formamido-1-(2-carbamoyloxyethyl)pyrazole (3.69 g) was obtained from 5-amino-1-(2-carbamoyloxyethyl)pyrazole (3.3 g) according to a similar manner to that of Preparation 6.

NMR (DMSO-d_6 , δ) : 4.22 (4H, s), 6.17-6.40 (1H, m), 6.40-6.63 (2H, m), 7.30-7.53 (1H, m), 8.13-8.47 (1H, m).

Example 12

To a solution of benzhydryl 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer)(1.5 g) in N,N-dimethylformamide (3 ml) was added sodium iodide (0.36 g) under nitrogen atmosphere. The mixture was stirred at room temperature for 30 minutes.

Then, 5-formamido-1-(2-carbamoyloxyethyl)pyrazole (1.42 g) was added thereto and the mixture was stirred at the same temperature for 24 hours. To the reaction mixture was added a mixture of ethyl acetate (50 ml) and ice-water (30 ml). The separated organic layer was washed with water and sodium chloride aqueous solution, and dried over magnesium sulfate. The solvent was evaporated in vacuo to give benzhydryl 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-formamido-2-(2-carbamoyloxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer)(1.60 g).

Example 13

7 β -[2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-formamido-2-(2-carbamoyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (1.10 g) was obtained from benzhydryl 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-formamido-2-(2-carbamoyloxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate trifluoroacetate (syn isomer) (1.6 g) according to a similar manner to that of Example 8.

Example 14

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-carbamoyloxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (syn isomer) (0.10 g) was obtained from 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-formamido-2-(2-carbamoyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) according to a similar manner to that of Example 9.

IR (Nujol) : 3200-3300, 1760, 1710, 1650 cm⁻¹

NMR (DMSO-d₆, δ) : 3.0-3.90 (2H, m), 3.90-4.27 (4H, m), 3.82 (3H, s), 4.40-5.47 (5H, m), 5.47-5.77 (1H, m), 5.81 (1H, d, J=3Hz), 6.71 (1H, s), 6.90-7.57 (4H, m), 7.97 (1H, d, J=3Hz), 9.51 (1H, d, J=8Hz).

Preparation 9

5-Formamido-4-methyl-1-(2-formyloxyethyl)pyrazole was prepared according to a similar manner to that of Preparation 1.

IR (Nujol) : 3180, 1715, 1660 cm⁻¹

NMR (DMSO-d₆, δ) : 1.81 and 1.86 (3H, each s), 4.01-4.48 (4H, m), 7.25 and 7.40 (1H, each s), 8.06 (1H, s), 8.22 and 9.13 (1H, each s)

Preparation 10

5-Amino-1-(2-hydroxyethyl)pyrazole (5 g) was added to acetic anhydride (14.7 ml) with stirring and ice-cooling. Pyridine (6.3 ml) was added thereto. The mixture was stirred for 2 hours at 25°C.

The reaction mixture was added to a mixture of ethyl acetate (50 ml) and sodium chloride aqueous solution (50 ml). Then, an aqueous solution of sodium bicarbonate was added thereto to adjust the solution to pH 7.0. The aqueous layer was extracted with mixture of ethyl acetate and tetrahydrofuran. The extract was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 5-acetamido-1-(2-acetoxyethyl)pyrazole (5.98 g).

mp : 83-84°C

IR (Nujol) : 3270, 1750, 1670, 1565 cm⁻¹

NMR (DMSO-d₆, δ) : 1.93 (3H, s), 2.03 (3H, s), 4.22 (4H, br s), 6.13 (1H, d, J=2Hz), 7.32 (1H, d, J=2Hz), 9.76 (1H, s)

The following compounds (Preparations 11 to 13) were prepared according to a similar manner to that of Preparation 2.

Preparation 11

Benzhydryl 7 β -tert-butoxycarbonylamino-3-[4-methyl-3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide

IR (Nujol) : 3250, 1780, 1710, 1680 cm⁻¹

NMR (DMSO-d₆, δ) : 1.53 (9H, s), 1.97 (3H, s), 3.51 (2H, broad s), 4.04-4.42 (2H, m), 4.52-4.78 (2H, m), 5.08 (1H, d, J=5Hz), 5.39 (2H, broad s), 5.61 (1H, dd, J=5Hz and 8Hz), 6.86 (1H, s), 7.08-7.52 (10H, m), 7.93 (1H, s), 8.18 (1H, s), 8.34 (1H, s), 9.12 (1H, s)

Preparation 12

Benzhydryl 7 β -tert-butoxycarbonylamino-3-[3-acetamido-2-(2-acetoxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide

IR (Nujol) : 1780, 1720, 1230 cm⁻¹

NMR (DMSO-d₆, δ) : 1.41 (9H, s), 1.86 (3H, s), 2.25 (3H, s), 3.40 (2H, br s), 4.0-4.4 (4H, m), 5.12 (1H, d, J=5Hz), 5.37 (2H, s), 5.60 (1H, dd, J=8Hz and 5Hz), 6.85 (1H, s), 7.24 (1H, d, J=3Hz), 7.1-7.6 (10H, m), 7.90 (1H, d, J=8Hz), 8.21 (1H, d, J=3Hz), 11.17 (1H, s)

Preparation 13

Benzhydryl 7 β -tert-butoxycarbonylamino-3-[3-formamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate iodide

IR (Nujol) : 3300, 1780, 1710, 1560, 1150 cm⁻¹

NMR (DMSO-d₆, δ) : 1.43 (9H, s), 3.53 (2H, br s), 4.0-4.5 (4H, m), 5.15 (1H, d, J=5Hz), 5.40 (2H, s), 5.55 (1H, dd, J=8Hz and 5Hz), 6.90 (1H, s), 7.01 (1H, d, J=3Hz), 7.1-7.5 (10H, m), 7.97 (1H, d, J=8Hz), 8.28 (1H, d, J=3Hz), 8.50 (1H, s)

The following compounds (Preparations 14 to 16) were prepared according to a similar manner to that of Preparation 3.

Preparation 14

Bis(trifluoroacetic acid salts) of 7 β -amino-3-[4-methyl-3-formamido-2-(2-formyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate

IR (Nujol) : 1780, 1710, 1670 cm⁻¹

NMR (DMSO-d₆, δ) : 1.98 (3H, s), 3.49 (2H, broad s), 4.22-4.48 (2H, m), 4.61-4.87 (2H, m), 5.18 (2H, broad s), 5.46 (2H, broad s), 8.05 (1H, s), 8.23 (1H, s), 8.35 (1H, s)

Preparation 15

Bis(trifluoroacetic acid salts) of 7 β -amino-3-[3-acetamido-2-(2-acetoxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate

IR (Nujol) : 1780, 1660, 1190 cm⁻¹

NMR (DMSO-d₆, δ) : 1.95 (3H, s), 2.23 (3H, s), 3.46 (2H, broad s), 4.1-4.4 (4H, m), 5.20 (2H, m), 5.46 (2H, s), 7.01 (1H, d, J=3Hz), 8.27 (1H, d, J=3Hz), 11.17 (1H, s)

Preparation 16

Bis(trifluoroacetic acid salts) of 7 β -amino-3-[3-formamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate

IR (Nujol) : 3400, 1780, 1680, 1580, 1200, 1140 cm⁻¹

NMR (DMSO-d₆, δ) : 3.70 (2H, broad s), 4.2-4.7 (4H, m), 5.23 (2H, m), 5.50 (2H, s), 7.07 (1H, d, J=3Hz), 8.35 (1H, d, J=3Hz), 8.53 (1H, s)

The following compounds (Preparations 17 and 18) were prepared according to a similar manner to that of Preparation 4.

Preparation 17

7 β -Amino-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate trihydrochloride

NMR (DMSO-d₆, δ) : 1.94 (3H, s), 3.39 (2H, broad s), 3.47-3.78 (2H, m), 4.06-4.42 (2H, m), 5.21 (4H, broad s), 7.87 (1H, s)

Preparation 18

7 β -Amino-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate trihydrochloride

IR (Nujol) : 3300, 3150, 1780, 1710, 1640, 1580 cm⁻¹

NMR (DMSO-d₆, δ) : 3.60 (2H, br s), 4.1-4.5 (4H, m), 5.23 (2H, m), 5.30 (2H, s), 5.92 (1H, d, J=3Hz), 8.07 (1H, d, J=3Hz)

The following compounds (Examples 15 to 18) were prepared according to a similar manner to that of Example 1.

Example 15

7 β -[2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3150, 1770, 1650 cm⁻¹

NMR (DMSO-d₆, δ) : 1.94 (3H, s), 3.32 (2H, broad s), 3.52-3.68 (2H, m), 3.88 (3H, s), 4.12-4.39 (2H, m), 5.14 (2H, broad s), 5.19 (1H, d, J=5Hz), 5.82 (1H, dd, J=5Hz and 8Hz), 7.36 (1H, s), 7.83 (1H, s), 8.47 (1H, s), 9.63 (1H, d, J=8Hz)

Example 16

7 β -[2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-acetoxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 1780, 1660, 1550 cm⁻¹

NMR (DMSO-d₆, δ) : 1.96 (3H, s), 2.27 (3H, s), 3.2-3.6 (2H, m), 3.87 (3H, s), 4.1-4.5 (4H, m), 5.22 (1H, d, J=5Hz), 5.43 (2H, s), 5.90 (1H, dd, J=8Hz and 5Hz), 7.00 (1H, d, J=3Hz), 7.33 (1H, s), 8.29 (1H, d, J=3Hz), 8.43 (1H, s), 9.62 (1H, d, J=8Hz)

Example 17

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660, 1605 cm⁻¹

Example 18

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1770, 1600 cm⁻¹

Example 19

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) was prepared according to a similar manner to that of Example 4.

IR (Nujol) : 3300, 1765, 1660, 1605 cm⁻¹

NMR (D₂O, δ) : 1.97 (3H, s), 3.06 and 3.37 (2H, ABq, J=18Hz), 3.73-3.93 (2H, m), 3.98 (3H, s), 4.19-4.43 (2H, s), 5.09 (2H, broad s), 5.19 (1H, d, J=5Hz), 5.89 (1H, d, J=5Hz), 6.96 (1H, s), 7.71 (1H, s)

Example 20

To a suspension of 7 β -[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-acetoxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (1.46 g) in methanol (7.3 ml) was

added conc. hydrochloric acid (0.51 ml) at room temperature. The mixture was stirred for 5 hours at room temperature.

The reaction mixture was added to ethyl acetate with stirring and ice-cooling. The produced amorphous solid was dried in vacuo, and it was dissolved in water (40 ml). The aqueous solution was adjusted to pH 13 with 1N sodium hydroxide aqueous solution with stirring at $-3 \sim 0^{\circ}\text{C}$, and stirred for 2 hours at the same temperature. The aqueous solution was adjusted to pH 2 with 1N hydrochloric acid, and subjected to column chromatography on "Diaion HP-20" and eluted with 10% aqueous isopropyl alcohol. The fractions containing the object compound were combined and concentrated to remove isopropyl alcohol, and lyophilized to give 7 β -[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) (159 mg).

mp : 160°C (dec.)

IR (Nujol) : 3200, 1770, 1600 cm^{-1}

NMR (D_2O , δ) : 2.26 (3H, s), 3.10 (1H, d, $J=18\text{Hz}$), 3.47 (1H, d, $J=18\text{Hz}$), 3.8-4.1 (4H, m), 3.95 (3H, s), 5.20 (1H, d, $J=5\text{Hz}$), 5.32 (2H, s), 5.77 (1H, d, $J=5\text{Hz}$), 6.93 (1H, d, $J=3\text{Hz}$), 6.94 (1H, s), 8.16 (1H, d, $J=3\text{Hz}$)

The following compounds (Examples 21 and 22) were prepared according to a similar manner to that of Example 6.

Example 21

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660, 1605 cm^{-1}

Example 22

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1770, 1600 cm^{-1}

The following compounds (Examples 23 to 27) were prepared according to a similar manner to that of Example 8.

Example 23

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1770, 1640 cm^{-1}

Example 24

7 β -[2-(2-Aminothiazol-4-yl)-2-(difluoromethoxyiminoacetamido)-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1760, 1660 cm^{-1}

Example 25

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-carbamoyloxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200-3300, 1760, 1710, 1650 cm^{-1}

Example 26

7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660, 1605 cm⁻¹

Example 27

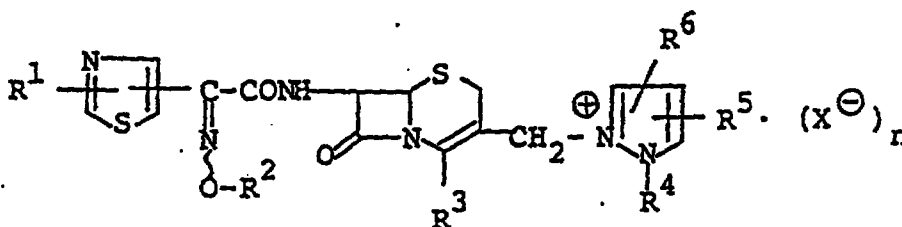
7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1770, 1600 cm⁻¹

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A cephem compound of the formula :



wherein

- R¹ is amino or a protected amino,
- R² is (C₁-C₆) alkyl which may have 1 to 3 halogen substituents,
- R³ is COO^o, carboxy or a protected carboxy,
- R⁴ is hydroxy(C₁-C₆)alkyl or protected hydroxy(C₁-C₆)alkyl,
- R⁵ is amino or a protected amino,
- R⁶ is hydrogen or (C₁-C₆) alkyl,
- X^o is an anion, and
- n is 0 or 1,

with proviso that

- (i) when R³ is COO^o, then n is 0, and
 - (ii) when R³ is carboxy or a protected carboxy, then n is 1,
- and pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

- R¹ is amino, ar(C₁-C₆)alkylamino or (C₁-C₆) alkanoylamino,
- R² is (C₁-C₆)alkyl which may have 1 to 3 halogen substituents,,
- R³ is COO^o, carboxy or ar(C₁-C₆)alkoxycarbonyl,
- R⁴ is hydroxy(C₁-C₆)alkyl, (C₁-C₆) alkanoyloxy(C₁-C₆)alkyl or carbamoyloxy(C₁-C₆)alkyl, and
- R⁵ is amino or (C₁-C₆) alkanoylamino.

3. A compound of claim 2, wherein

- R¹ is amino, and
- R³ is COO^o or carboxy.

4. A compound of claim 3, wherein

- R² is (C₁-C₆)alkyl or dihalo (C₁-C₆)alkyl.

**Example 26**

7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-methyl-3-amino-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3300, 1765, 1660, 1605 cm⁻¹

Example 27

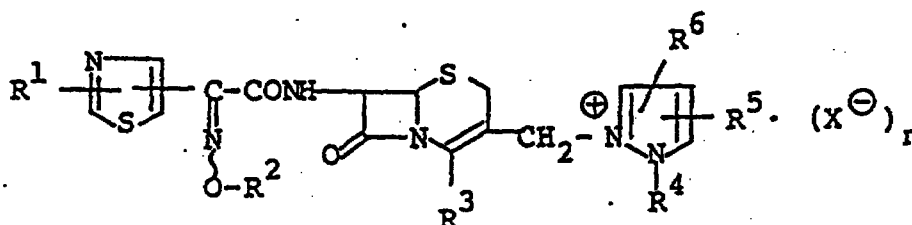
7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-acetamido-2-(2-hydroxyethyl)-1-pyrazolio]-methyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) : 3200, 1770, 1600 cm⁻¹

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A cephem compound of the formula :



wherein

- R¹ is amino or a protected amino,
- R² is (C₁-C₆) alkyl which may have 1 to 3 halogen substituents,
- R³ is COO^o, carboxy or a protected carboxy,
- R⁴ is hydroxy(C₁-C₆)alkyl or protected hydroxy(C₁-C₆)alkyl,
- R⁵ is amino or a protected amino,
- R⁶ is hydrogen or (C₁-C₆) alkyl,
- X^o is an anion, and
- n is 0 or 1,

with proviso that

- (i) when R³ is COO^o, then n is 0, and
 - (ii) when R³ is carboxy or a protected carboxy, then n is 1,
- and pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

- R¹ is amino, ar(C₁-C₆)alkylamino or (C₁-C₆) alkanoylamino,
- R² is (C₁-C₆)alkyl which may have 1 to 3 halogen substituents,,
- R³ is COO^o, carboxy or ar(C₁-C₆)alkoxycarbonyl,
- R⁴ is hydroxy(C₁-C₆)alkyl, (C₁-C₆) alkanoyloxy(C₁-C₆)alkyl or carbamoyloxy(C₁-C₆)alkyl, and
- R⁵ is amino or (C₁-C₆) alkanoylamino.

3. A compound of claim 2, wherein

- R¹ is amino, and
- R³ is COO^o or carboxy.

4. A compound of claim 3, wherein

- R² is (C₁-C₆)alkyl or dihalo (C₁-C₆)alkyl.



5. A compound of claim 4, wherein

R² is methyl or difluoromethyl,

R⁴ is 2-hydroxyethyl, 2-formyloxyethyl, 2-acetoxyethyl or 2-carbamoyloxyethyl,

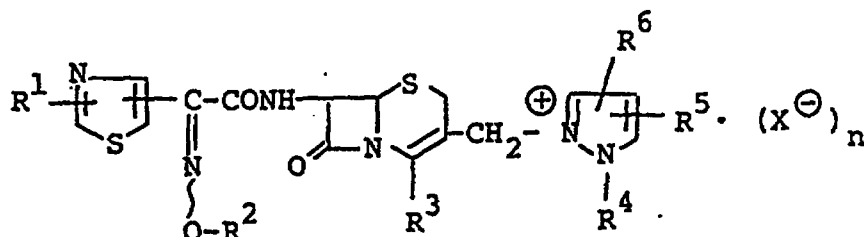
R⁵ is amino, formamido or acetamido,

and

R⁶ is hydrogen or methyl.

6. A compound of claim 5, which is 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) or its sulfuric acid salt.

7. A process for preparing a cephem compound of the formula :



wherein

R¹ is amino or a protected amino,

R² is (C₁-C₆)alkyl which may have 1 to 3 halogen substituents,

R³ is COO[⊖], carboxy or a protected carboxy,

R⁴ is hydroxy(C₁-C₆)alkyl or protected hydroxy(C₁-C₆)alkyl,

R⁵ is amino or a protected amino,

R⁶ is hydrogen or (C₁-C₆)alkyl,

X[⊖] is an anion, and

n is 0 or 1,

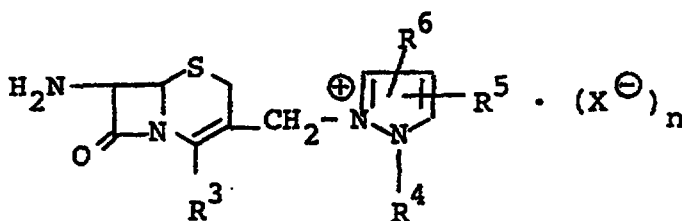
with proviso that

(i) when R³ is COO[⊖], then n is 0, and

(ii) when R³ is carboxy or a protected carboxy, then n is 1,

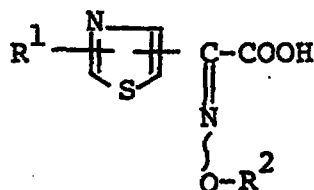
or a salt thereof, which comprises

i) reacting a compound of the formula :



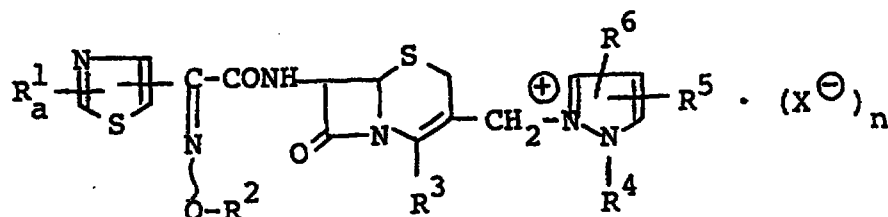
(wherein R³, R⁴, R⁵, R⁶, X[⊖] and n are each as defined above),

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula:

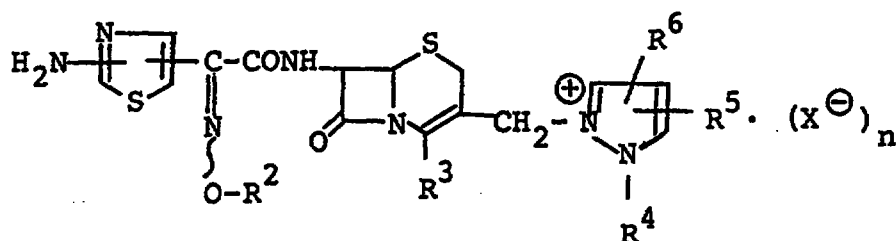




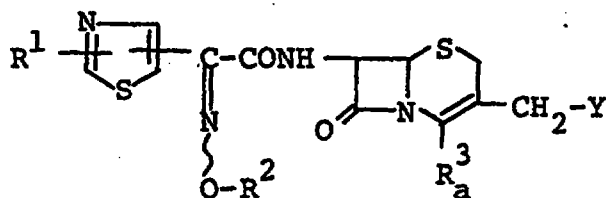
(wherein R^1 and R^2 are each as defined above)
or its reactive derivative at the carboxy group or a salt thereof, or
ii) subjecting a compound of the formula :



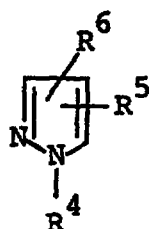
(wherein R^2 , R^3 , R^4 , R^5 , R^6 , $X^\ominus$ and n are each as defined above, and
 R^1_a is a protected amino)
or a salt thereof, to elimination reaction of the amino protective group in R^1_a , to give a compound of
the formula :



(wherein R^2 , R^3 , R^4 , R^5 , R^6 , $X^\ominus$ and n are each as defined above)
or a salt thereof, or
iii) reacting a compound of the formula :



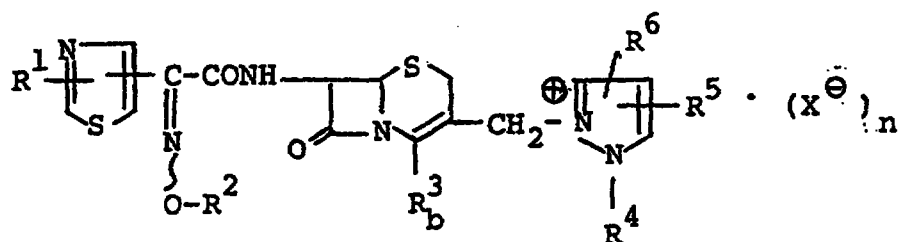
(wherein R^1 and R^2 are each as defined above,
 R^a is carboxy or a protected carboxy, and Y is a leaving group)
or a salt thereof, with a compound of the formula :



(wherein R^4 , R^5 and R^6 are each as defined above) or a salt thereof, or

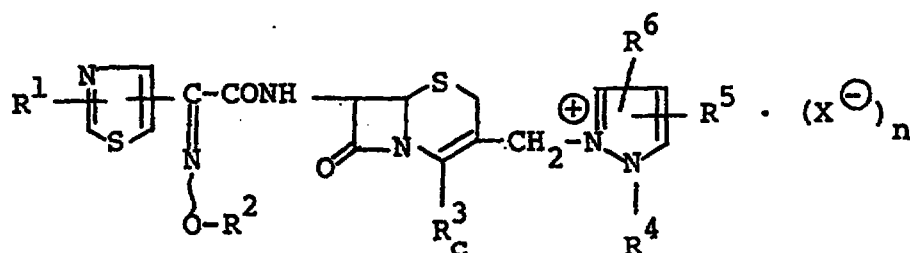


iv) subjecting a compound of the formula :



(wherein R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_b^3 is a protected carboxy)

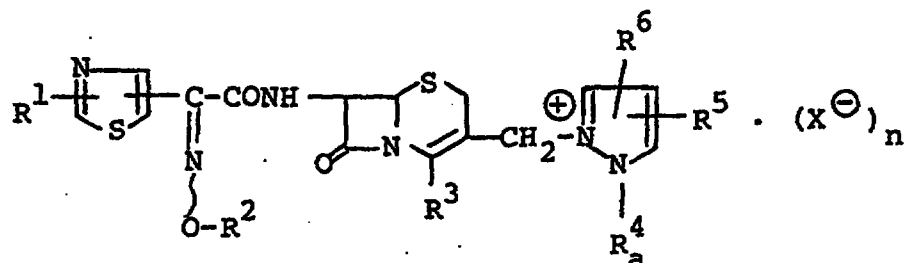
or a salt thereof, to elimination reaction of the carboxy protective group in R_b^3 , to give a compound of the formula :



(wherein R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_c^3 is $\text{COO}^\ominus$ or carboxy)

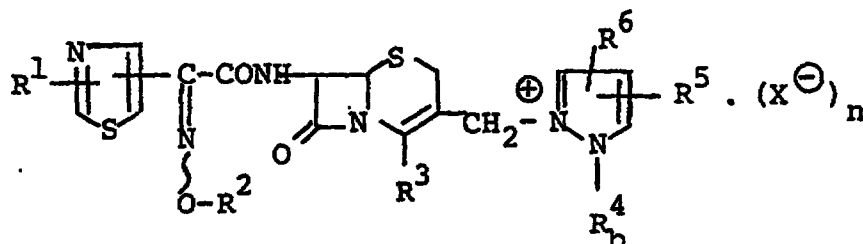
or a salt thereof, or

v) subjecting a compound of the formula :



[wherein R^1 , R^2 , R^3 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_a^4 is protected hydroxy(C_1 - C_6)alkyl]

or a salt thereof, to elimination reaction of the hydroxy protective group in R_a^4 , to give a compound of the formula :



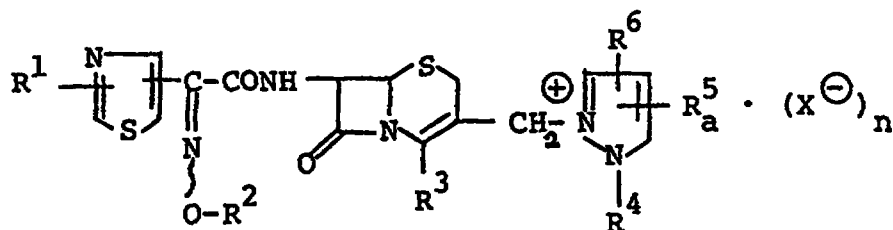
[wherein R^1 , R^2 , R^3 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and



R_b^4 is hydroxy(C_1-C_5)alkyl]

or a salt thereof, or

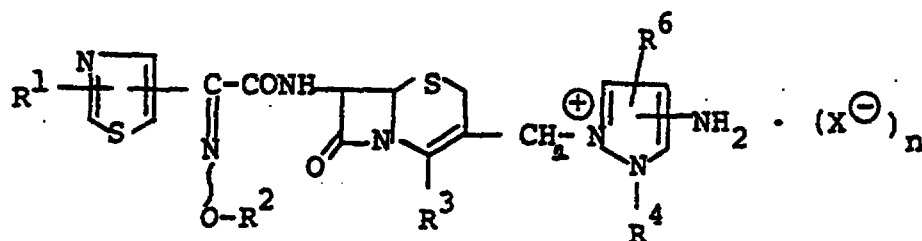
vi) subjecting a compound of the formula :



(wherein R^1 , R^2 , R^3 , R^4 , R^6 , $X^\ominus$ and n are each as defined above, and

R_a^5 is a protected amino)

or a salt thereof, to elimination reaction of the amino protective group in R_a^5 , to give a compound of the formula :



(wherein R^1 , R^2 , R^3 , R^4 , R^6 , $X^\ominus$ and n are each as defined above)

or a salt thereof.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

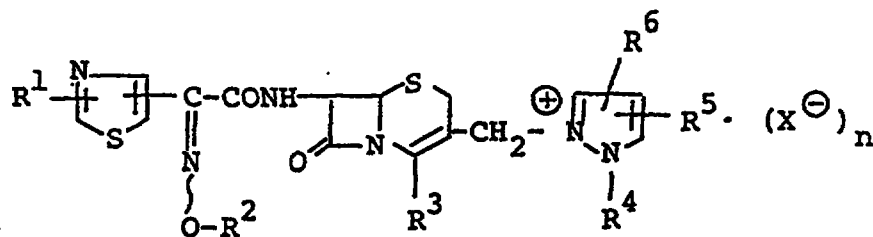
9. A compound of claim 1 or pharmaceutical acceptable salts thereof for use as a medicament.

10. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an antimicrobial agent.

11. Use of a compound of claim 1 and its pharmaceutically acceptable salt for the manufacture of a medicament for therapeutic treatment of infectious diseases.

Claims for the following Contracting State : ES

1. A process for preparing a cephem compound of the formula :



wherein

R^1 is amino or a protected amino,



R^2 is (C_1-C_6) alkyl which may have 1 to 3 halogen substituents,
 R^3 is $COO^\ominus$, carboxy or a protected carboxy,
 R^4 is hydroxy (C_1-C_6) alkyl or protected hydroxy (C_1-C_6) alkyl,
 R^5 is amino or a protected amino,
 R^6 is hydrogen or (C_1-C_6) alkyl,
 $X^\ominus$ is an anion, and
 n is 0 or 1,

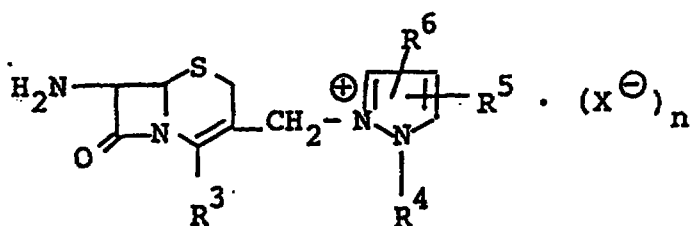
with proviso that

(i) when R^3 is $COO^\ominus$, then n is 0, and

(ii) when R^3 is carboxy or a protected carboxy, then n is 1,

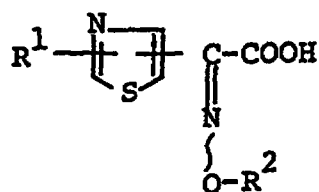
or a salt thereof, which comprises

i) reacting a compound of the formula :



(wherein R^3 , R^4 , R^5 , R^6 , $X^\ominus$ and n are each as defined above),

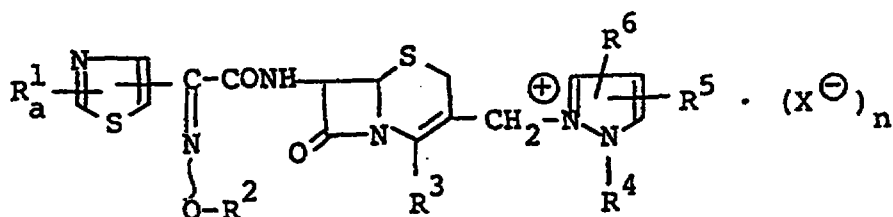
or its reactive derivative at the amino group or a salt thereof, with a compound of the formula:



(wherein R^1 and R^2 are each as defined above)

or its reactive derivative at the carboxy group or a salt thereof, or

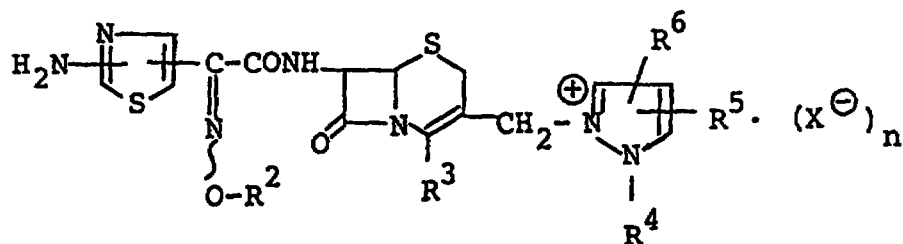
ii) subjecting a compound of the formula :



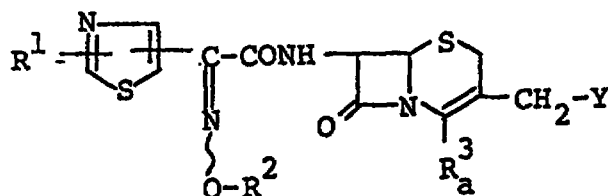
(wherein R^2 , R^3 , R^4 , R^5 , R^6 , $X^\ominus$ and n are each as defined above, and

R_a^1 is a protected amino)

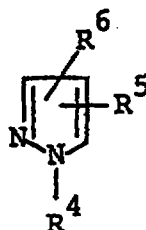
or a salt thereof, to elimination reaction of the amino protective group in R_a^1 , to give a compound of the formula :



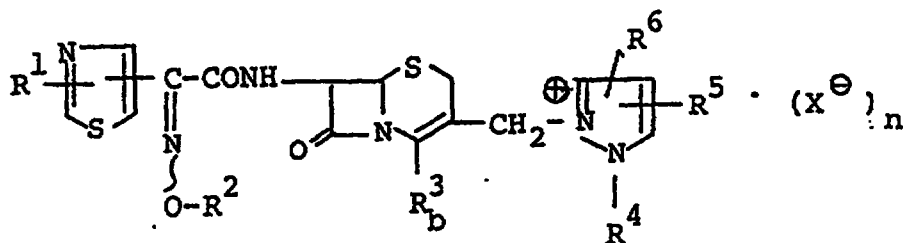
(wherein R^2 , R^3 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above)
or a salt thereof, or
iii) reacting a compound of the formula :



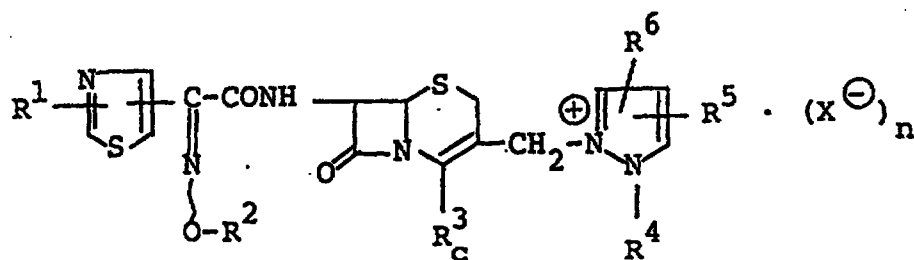
(wherein R^1 and R^2 are each as defined above,
 R^3 is carboxy or a protected carboxy, and
 Y is a leaving group)
or a salt thereof, with a compound of the formula :



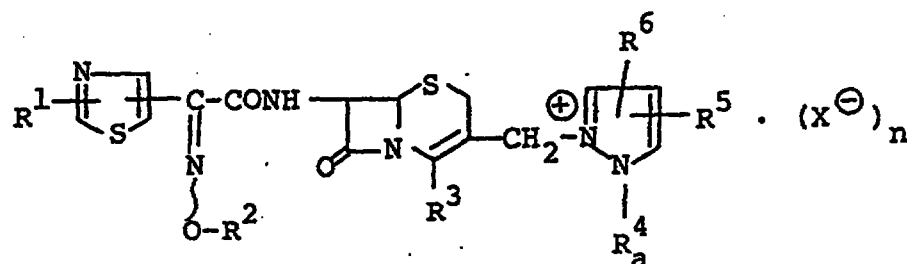
(wherein R^4 , R^5 and R^6 are each as defined above) or a salt thereof, or
iv) subjecting a compound of the formula :



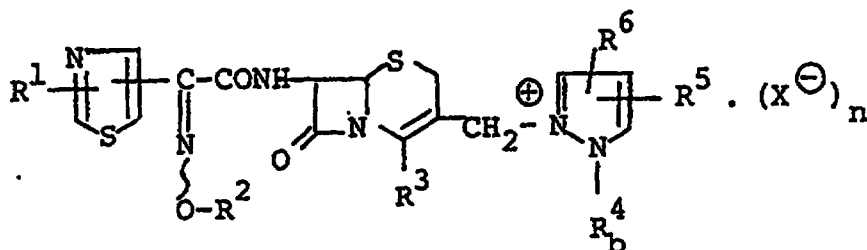
(wherein R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and
 R^3 is a protected carboxy)
or a salt thereof, to elimination reaction of the carboxy protective group in R^3 ,
to give a compound of the formula :



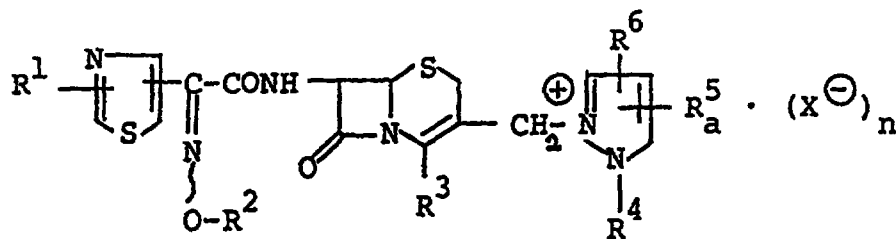
(wherein R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_c^3 is $\text{COO}^\ominus$ or carboxy) or a salt thereof, or
v) subjecting a compound of the formula :



[wherein R^1 , R^2 , R^3 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_a^4 is protected hydroxy(C_1 - C_6)alkyl] or a salt thereof, to elimination reaction of the hydroxy protective group in R_a^4 , to give a compound of the formula :



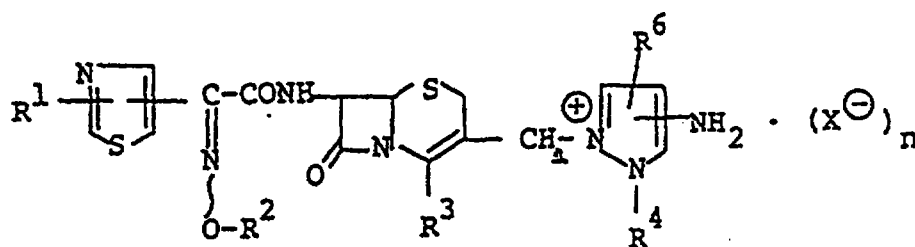
[wherein R^1 , R^2 , R^3 , R^5 , R^6 , $\text{X}^\ominus$ and n are each as defined above, and R_b^4 is hydroxy(C_1 - C_6)alkyl] or a salt thereof, or
vi) subjecting a compound of the formula :



(wherein R^1 , R^2 , R^3 , R^4 , R^5 , $\text{X}^\ominus$ and n are each as defined above, and R_a^5 is a protected amino) or a salt thereof, to elimination reaction of the amino protective group in R_a^5 , to give a compound of



the formula :



(wherein R^1 , R^2 , R^3 , R^4 , R^6 , X^- and n are each as defined above)
or a salt thereof.

2. A process of claim 1, wherein

- R^1 is amino or (C_1-C_6) alkylamino or (C_1-C_6) alkanoylamino,
 R^2 is (C_1-C_6) alkyl which may have 1 to 3 halogen substituents,
 R^3 is COO^- , carboxy or $\text{ar}(\text{C}_1-\text{C}_6)$ alkoxycarbonyl,
 R^4 is hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkanoyloxy (C_1-C_6) alkyl or carbamoyloxy (C_1-C_6) alkyl, and
 R^6 is amino or (C_1-C_6) alkanoylamino.

3. A process of claim 2, wherein

- R^1 is amino, and
 R^3 is COO^- or carboxy.

4. A process of claim 3, wherein

- R^2 is (C_1-C_6) alkyl or dihalo (C_1-C_6) alkyl.

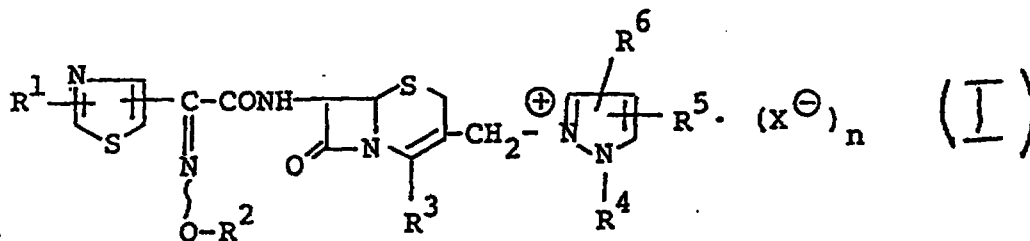
5. A process of claim 4, wherein

- R^2 is methyl or difluoromethyl,
 R^4 is 2-hydroxyethyl, 2-formyloxyethyl, 2-acetoxyethyl or 2-carbamoyloxyethyl,
 R^6 is amino, formamido or acetamido,
 and
 R^6 is hydrogen or methyl.

6. A process of claim 5, for preparing 7 β -[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) or its sulfuric acid salt.

Claims for the following Contracting State : GR

1. A process for preparing a cephem compound of the formula I :



wherein

- R^1 is amino or a protected amino,
 R^2 is (C_1-C_6) alkyl which may have 1 to 3 halogen substituents,
 R^3 is COO^- , carboxy or a protected carboxy,
 R^4 is hydroxy (C_1-C_6) alkyl or protected hydroxy (C_1-C_6) alkyl,



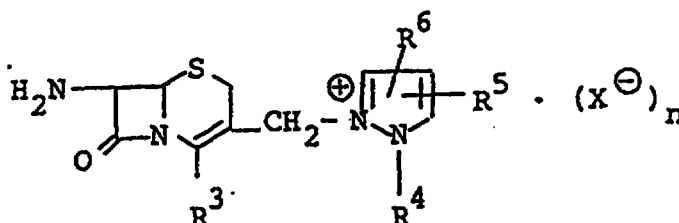
R^5 is amino or a protected amino,
 R^6 is hydrogen or (C_1-C_6) alkyl,
 X^e is an anion, and
 n is 0 or 1,

with proviso that

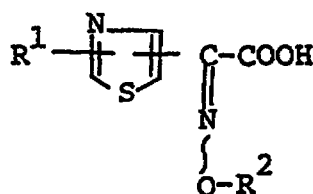
(i) when R^3 is COO^e , then n is 0, and

(ii) when R^3 is carboxy or a protected carboxy, then n is 1,
 or a salt thereof, which comprises

i) reacting a compound of the formula :



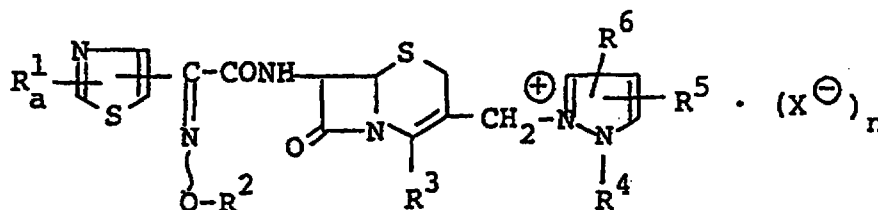
(wherein R^3 , R^4 , R^5 , R^6 , X^e and n are each as defined above),
 or its reactive derivative at the amino group
 or a salt thereof, with a compound of the formula:



(wherein R^1 and R^2 are each as defined above)

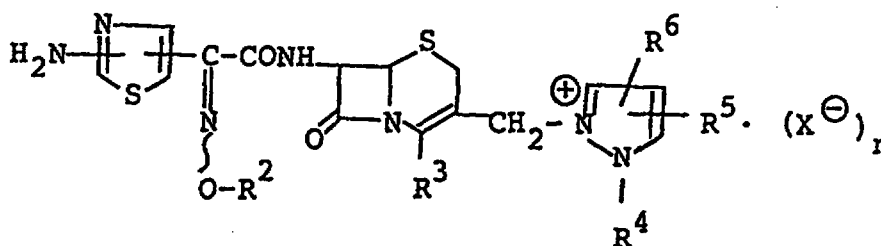
or its reactive derivative at the carboxy group or a salt thereof, or

ii) subjecting a compound of the formula :



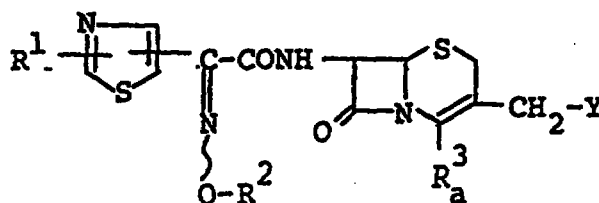
(wherein R^2 , R^3 , R^4 , R^5 , R^6 , X^e and n are each as defined above, and
 R_a^1 is a protected amino)

or a salt thereof, to elimination reaction of the amino protective group in R_a^1 , to give a compound of the formula :

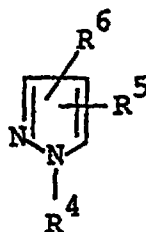




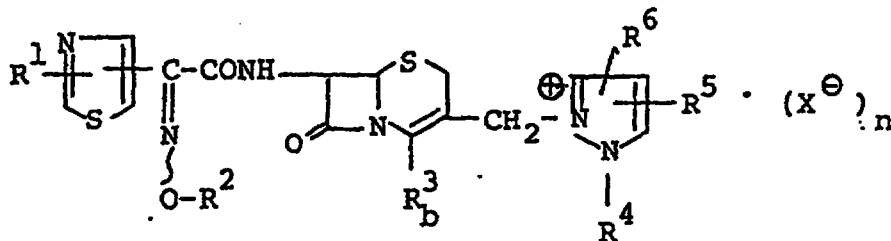
(wherein R^2 , R^3 , R^4 , R^5 , R^6 , X^e and n are each as defined above)
 or a salt thereof, or
 iii) reacting a compound of the formula :



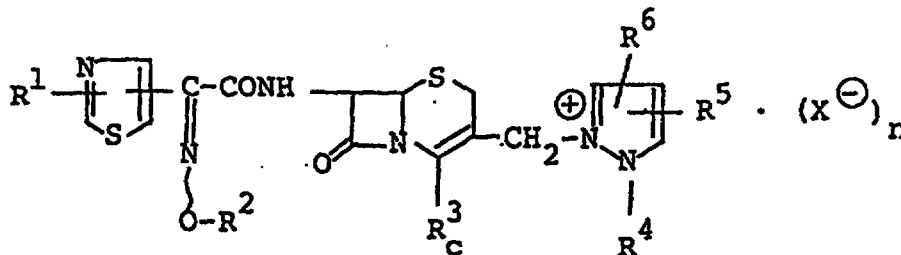
(wherein R^1 and R^2
 are each as defined above, R_a^3 is carboxy or a protected carboxy, and
 Y is a leaving group)
 or a salt thereof, with a compound of the formula :



(wherein R^4 , R^5 and R^6 are each as defined above) or a salt thereof, or
 iv) subjecting a compound of the formula :



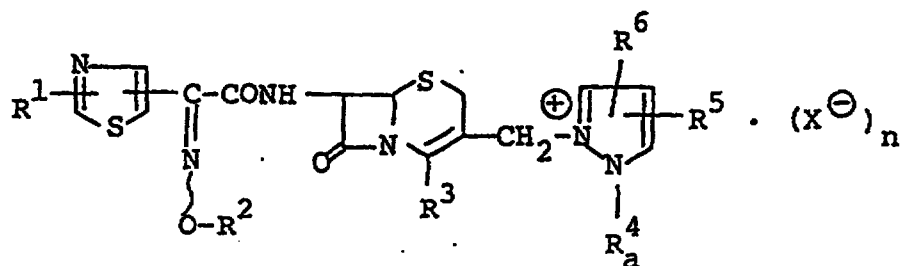
(wherein R^1 , R^2 , R^4 , R^5 , R^6 , X^e and n are each as defined above, and
 R_b^3 is a protected carboxy)
 or a salt thereof, to elimination reaction of the carboxy protective group in R_b^3 ,
 to give a compound of the formula :



(wherein R^1 , R^2 , R^4 , R^5 , R^6 , X^e and n are each as defined above, and
 R_c^3 is COO^e or carboxy)
 or a salt thereof, or



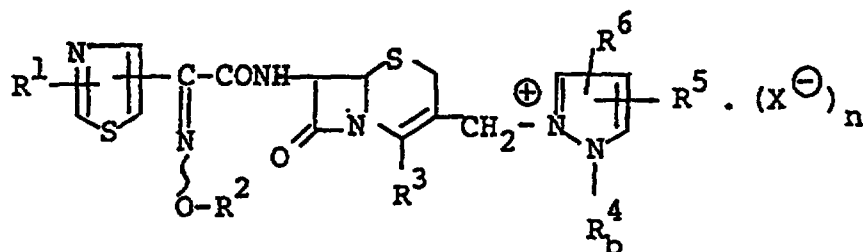
v) subjecting a compound of the formula :



[wherein R^1 , R^2 , R^3 , R^5 , R^6 , X^- and n are each as defined above, and

R_a^4 is protected hydroxy(C_1 - C_6)alkyl]

or a salt thereof, to elimination reaction of the hydroxy protective group in R_a^4 , to give a compound of the formula :

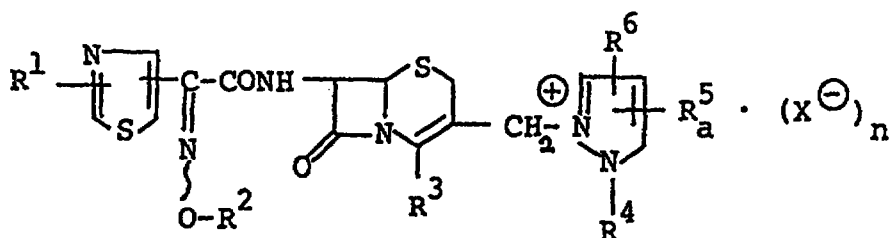


[wherein R^1 , R^2 , R^3 , R^5 , R^6 , X^- and n are each as defined above, and

R_b^4 is hydroxy(C_1 - C_6)alkyl]

or a salt thereof, or

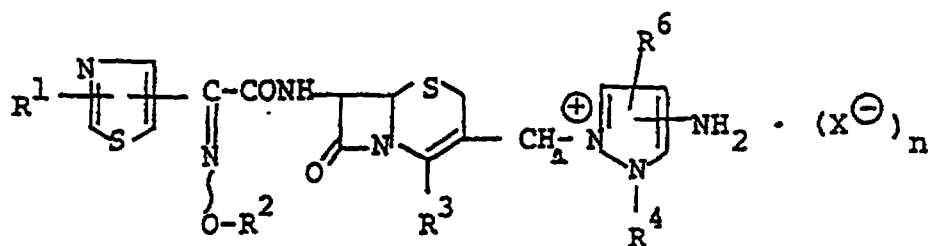
vi) subjecting a compound of the formula :



(wherein R^1 , R^2 , R^3 , R^4 , R^6 , X^- and n are each as defined above, and

R_a^5 is a protected amino)

or a salt thereof, to elimination reaction of the amino protective group in R_a^5 , to give a compound of the formula :





(wherein R^1 , R^2 , R^3 , R^4 , R^5 , $X^\ominus$ and n are each as defined above)
or a salt thereof.

2. A process of claim 1, wherein

- R^1 is amino, ar(C₁-C₆)alkylamino or (C₁-C₆)alkanoylamino,
 R^2 is (C₁-C₆)alkyl which may have 1 to 3 halogen substituents,
 R^3 is COO[⊖], carboxy or ar(C₁-C₆)alkoxycarbonyl,
 R^4 is hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkanoyloxy(C₁-C₆)alkyl or carbamoyloxy(C₁-C₆)alkyl, and
 R^5 is amino or (C₁-C₆)alkanoylamino.

3. A process of claim 2, wherein

- R^1 is amino, and
 R^3 is COO[⊖] or carboxy.

4. A process of claim 3, wherein

- R^2 is (C₁-C₆)alkyl or dihalo(C₁-C₆)alkyl.

5. A process of claim 4, wherein

- R^2 is methyl or difluoromethyl,
 R^4 is 2-hydroxyethyl, 2-formyloxyethyl, 2-acetoxyethyl or 2-carbamoyloxyethyl,
 R^5 is amino, formamido or acetamido,
 and
 R^6 is hydrogen or methyl.

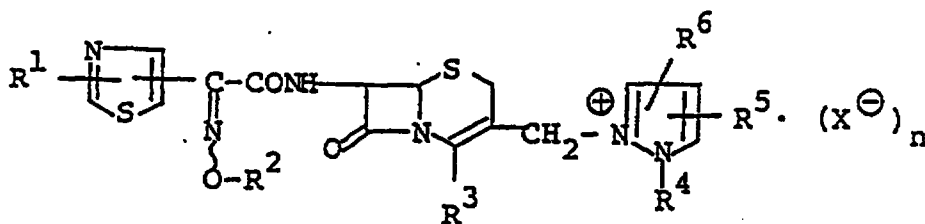
6. A process of claim 5, for preparing 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylate (syn isomer) or its sulfuric acid salt.

7. Modification of the process claimed in claim 1 which is characterized by bringing a compound of the formula I, or a non-toxic salt thereof, produced by a process claimed in claim 1, into pharmaceutical acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Cephem-Verbindung der Formel:



worin R^1 Amino oder ein geschütztes Amino ist, R^2 (C₁-C₆)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R^3 COO[⊖], Carboxy oder ein geschütztes Carboxy ist, R^4 Hydroxy(C₁-C₆)alkyl oder geschütztes Hydroxy(C₁-C₆)alkyl ist, R^5 Amino oder ein geschütztes Amino ist, R^6 Wasserstoff oder (C₁-C₆)Alkyl ist, $X^\ominus$ ein Anion ist, und n ist 0 oder 1,

mit der Bedingung, daß,

(i) wenn R^3 COO[⊖] ist, dann ist n 0 und

(ii) wenn R^3 Carboxy oder ein geschütztes Carboxy ist, dann ist n 1,

und ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, worin R^1 Amino, Ar(C₁-C₆)alkylamino oder (C₁-C₆)Alkanoylamino ist, R^2 (C₁-C₆)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R^3 COO[⊖], Carboxy oder Ar(C₁-C₆)-



alkoxycarbonyl ist, R^4 Hydroxy(C_1-C_6)alkyl, (C_1-C_6)Alkanoyloxy(C_1-C_6)alkyl oder Carbamoyloxy(C_1-C_6)alkyl ist und R^5 Amino oder (C_1-C_6)Alkanoylamino ist.

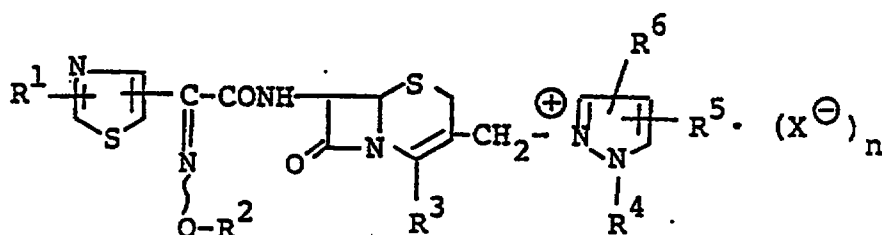
3. Verbindung nach Anspruch 2, worin R^1 Amino ist und R^3 COO^- oder Carboxy ist.

4. Verbindung nach Anspruch 3, worin R^2 (C_1-C_6)Alkyl oder Dihalogen(C_1-C_6)alkyl ist.

5. Verbindung nach Anspruch 4, worin R^2 Methyl oder Difluormethyl ist, R^4 2-Hydroxyethyl, 2-Formyloxyethyl, 2-Acetoxyethyl oder 2-Carbamoyloxyethyl ist, R^5 Amino, Formamido oder Acetamido ist und R^6 Wasserstoff oder Methyl ist.

6. Verbindung nach Anspruch 5, die 7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylat (Syn-Isomer) oder ihr Schwefelsäuresalz ist.

7. Verfahren zur Herstellung einer Cephem-Verbindung der Formel:



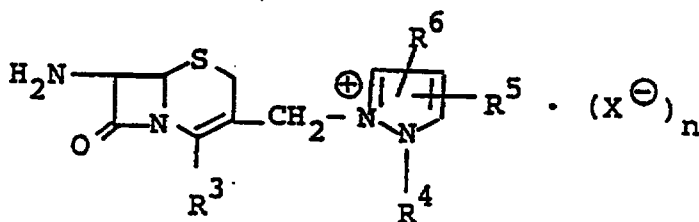
worin R^1 Amino oder ein geschütztes Amino ist, R^2 (C_1-C_6)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R^3 COO^- , Carboxy oder ein geschütztes Carboxy ist, R^4 Hydroxy(C_1-C_6)alkyl oder geschütztes Hydroxy(C_1-C_6)alkyl ist, R^5 Amino oder ein geschütztes Amino ist, R^6 Wasserstoff oder (C_1-C_6)Alkyl ist, X^- ein Anion ist und n ist 0 oder 1, mit der Bedingung, daß,

(i) wenn R^3 COO^- ist, dann ist n 0 und

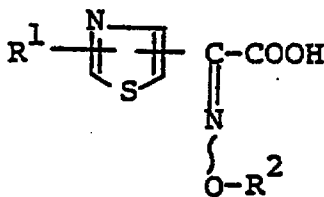
(ii) wenn R^3 Carboxy oder ein geschütztes Carboxy ist, dann ist n 1,

oder ein Salz davon, das umfaßt:

i) Reagieren einer Verbindung der Formel:



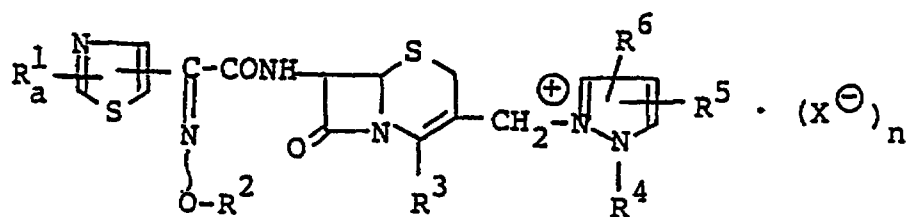
(worin R^3 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind) oder ihres reaktiven Derivates an der Aminogruppe oder eines Salz davon mit einer Verbindung der Formel:



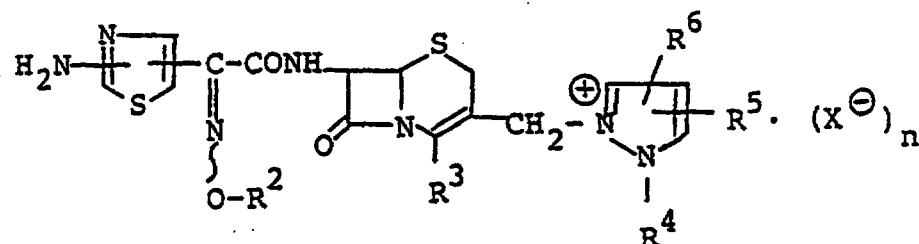
(worin R^1 und R^2 jeweils wie oben definiert sind) oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon oder



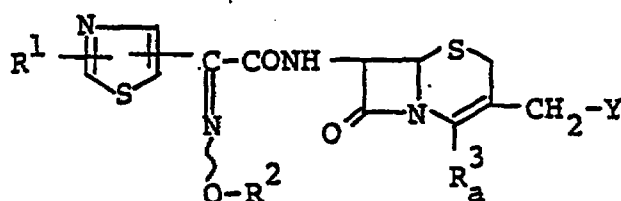
ii) Unterworfen einer Verbindung der Formel:



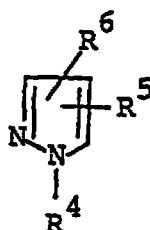
(worin R², R³, R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R¹_a ein geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R¹_a, um eine Verbindung der Formel:



(worin R^2 , R^3 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben oder iii) Reagieren einer Verbindung der Formel:



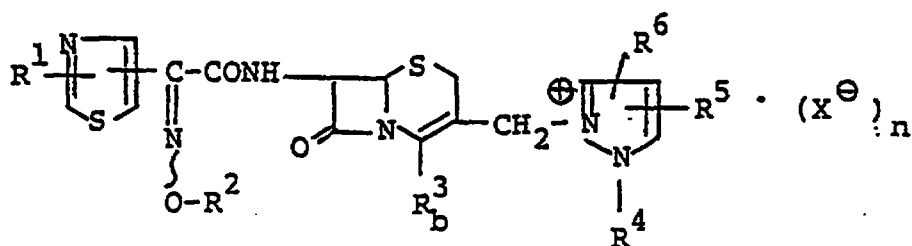
(worin R¹ und R² jeweils wie oben definiert sind, R³ Carboxy oder ein geschütztes carboxy ist und Y eine Abgangsgruppe ist) oder eines Salzes davon mit einer Verbindung der Formel:



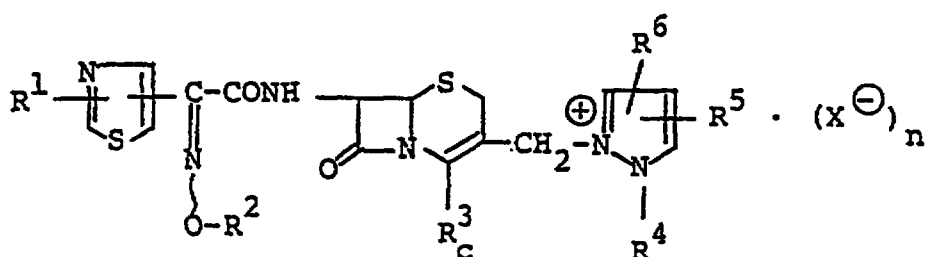
(worin R^4 , R^5 und R^6 jeweils wie oben definiert sind) oder einem Salz davon oder



iv) Unterworfen einer Verbindung der Formel:

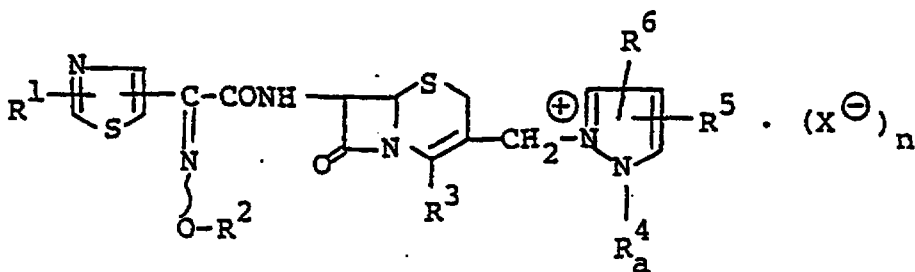


(worin R^1 , R^2 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind, und R^3_b ein geschütztes Carboxy ist) oder eines Salzes davon der Eliminierungsreaktion der Carboxyschutzgruppe in R^3_b , um eine Verbindung der Formel:

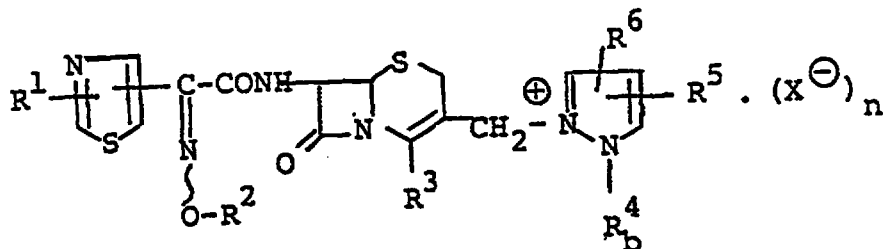


(worin R¹, R², R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R³, COO⁻ oder carboxy ist) oder ein Salz davon zu erhalten oder

v) Unterwerfen einer Verbindung der Formel:



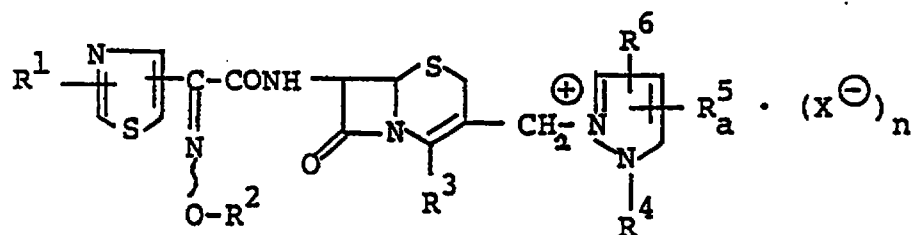
[worin R¹, R², R³, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind, und R⁴_a geschütztes Hydroxy(C₁-C₆)alkyl ist] oder eines Salzes davon der Eliminierungsreaktion der Hydroxyschutzgruppe in R⁴_a, um eine Verbindung der Formel:



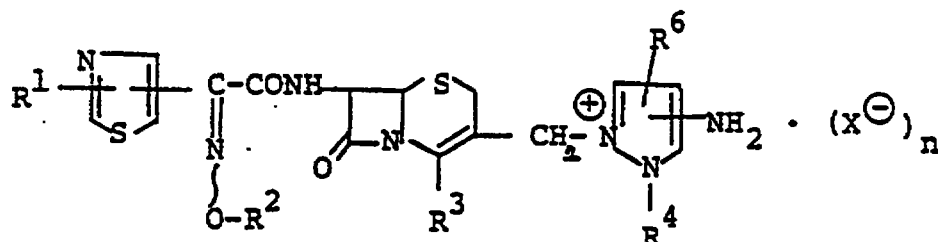
[worin R¹, R², R³, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R⁴, Hydroxy(C₁-C₆)alkyl ist] oder ein Salz davon zu ergeben oder



vi) Unterwerfen einer Verbindung der Formel:



(worin R^1 , R^2 , R^3 , R^4 , R^6 , X^- und n jeweils wie oben definiert sind und R^5_a ein geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R^5_a , um eine Verbindung der Formel:

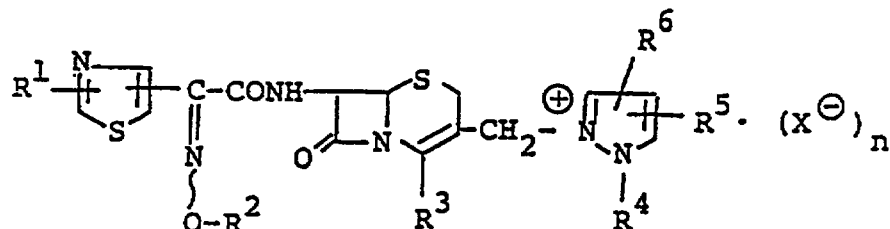


(worin R^1 , R^2 , R^3 , R^4 , R^6 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben.

8. Pharmazeutische Zusammensetzung, die als einen aktiven Bestandteil eine Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon in Zusammenmischung mit pharmazeutisch verträglichen Trägern umfaßt.
9. Verbindung nach Anspruch 1 oder pharmazeutisch verträgliche Salze davon zur Verwendung als Medikament.
10. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als antimikrobielles Mittel.
11. Verwendung einer Verbindung nach Anspruch 1 und ihres pharmazeutisch verträglichen Salzes zur Herstellung eines Medikaments zur therapeutischen Behandlung infektiöser Krankheiten.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Cephem-Verbindung der Formel:



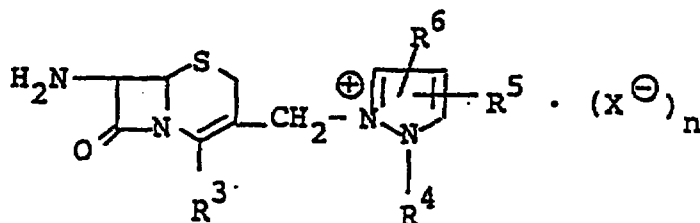
worin R^1 Amino oder ein geschütztes Amino ist, R^2 (C_1 - C_6)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R^3 COO^- , Carboxy oder ein geschütztes Carboxy ist, R^4 Hydroxy(C_1 - C_6)alkyl oder geschütztes Hydroxy(C_1 - C_6)alkyl ist, R^5 Amino oder ein geschütztes Amino ist, R^6 Wasserstoff oder (C_1 - C_6)Alkyl ist, X^- ein Anion ist, und n ist 0 oder 1,



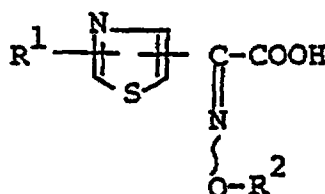
mit der Bedingung, daß,

- (i) wenn R^3 COO^- ist, dann ist n 0 und
(ii) wenn R^3 Carboxy oder ein geschütztes Carboxy ist, dann ist n 1,
oder ein Salz davon, das umfaßt:

i) Reagieren einer Verbindung der Formel:

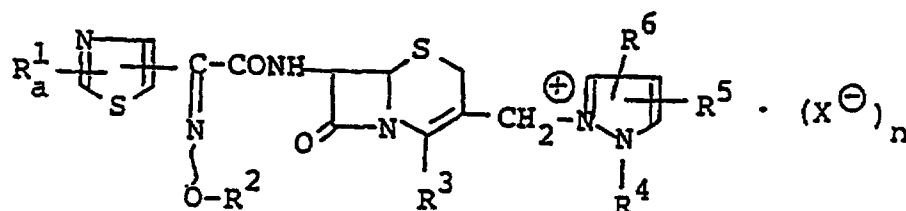


(worin R^3 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind) oder ihres reaktiven Derivates an der Aminogruppe oder eines Salz davon mit einer Verbindung der Formel:

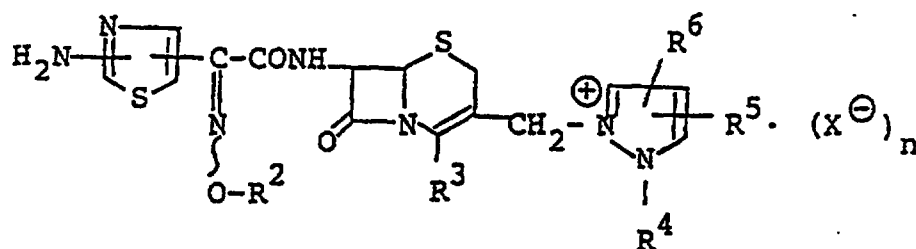


(worin R¹ und R² jeweils wie oben definiert sind) oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon oder

ii) Unterwerfen einer Verbindung der Formel:



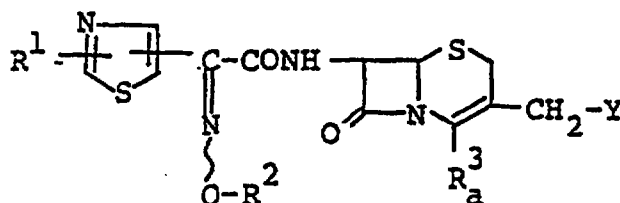
(worin R², R³, R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R^{1a} ein geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R^{1a}, um eine Verbindung der Formel:



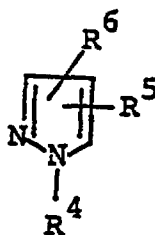
(worin R^2 , R^3 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben, oder



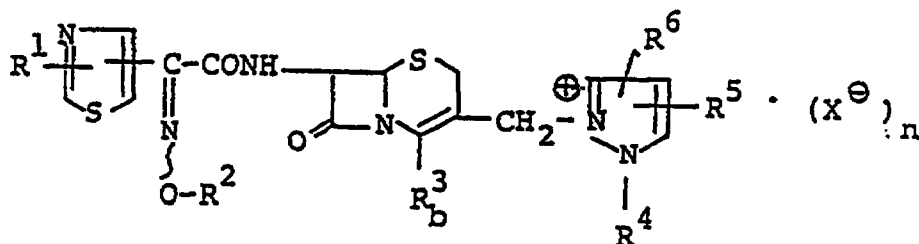
iii) Reagieren einer Verbindung der Formel:



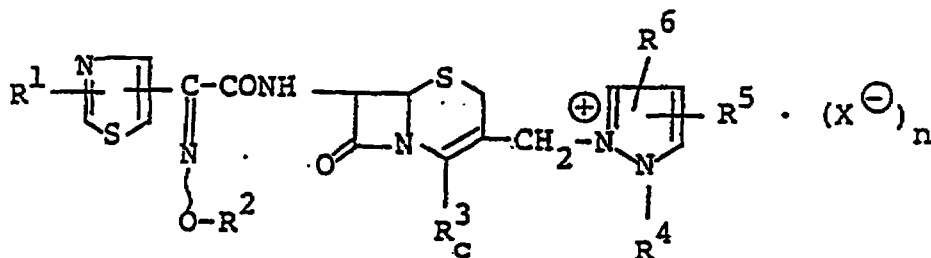
(worin R^1 und R^2 jeweils wie oben definiert sind, R^3_a Carboxy oder ein geschütztes Carboxy ist und Y eine Abgangsgruppe ist) oder eines Salzes davon mit einer Verbindung der Formel:



(worin R^4 , R^5 und R^6 jeweils wie oben definiert sind) oder einem Salz davon, oder
iv) Unterwerfen einer Verbindung der Formel:



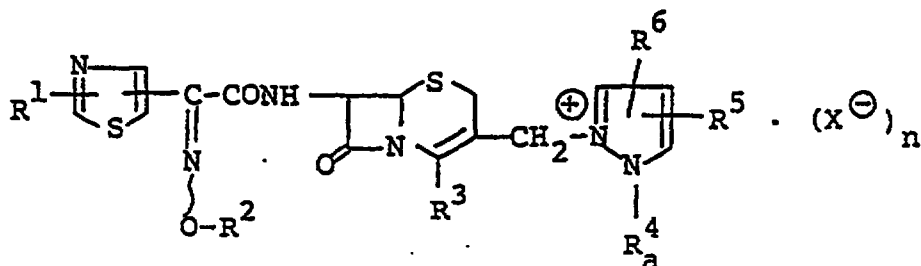
(worin R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ und n jeweils wie oben definiert sind und R^3_b ein geschütztes Carboxy ist) oder eines Salzes davon der Eliminierungsreaktion der Carboxyschutzgruppe in R^3_b um eine Verbindung der Formel:



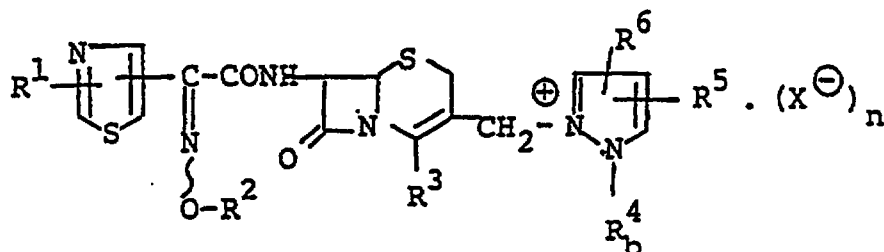
(worin R^1 , R^2 , R^4 , R^5 , R^6 , $\text{X}^\ominus$ und n jeweils wie oben definiert sind und R^3_c COO^- oder Carboxy ist) oder ein Salz davon zu erhalten oder



v) Unterwerfen einer Verbindung der Formel:

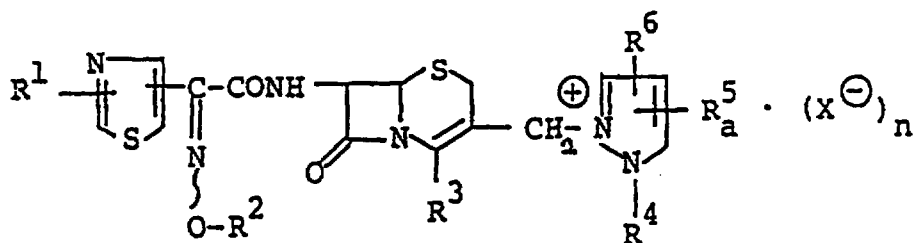


[worin R^1 , R^2 , R^3 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind und R^4_a geschütztes Hydroxy(C_1 - C_6)alkyl ist] oder eines Salzes davon der Eliminierungsreaktion der Hydroxyschutzgruppe in R^4_a , um eine Verbindung der Formel:

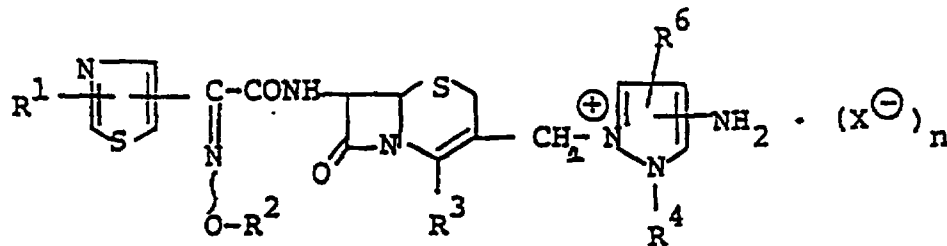


[worin R^1 , R^2 , R^3 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind und R^4_b Hydroxy(C_1 - C_6)alkyl ist] oder ein Salz davon zu ergeben oder

vi) Unterwerfen einer Verbindung der Formel:



(worin R^1 , R^2 , R^3 , R^4 , R^6 , X^- und n jeweils wie oben definiert sind, und R^5_a geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R^5_a , um eine Verbindung der Formel:



(worin R^1 , R^2 , R^3 , R^4 , R^6 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben.



2. Verfahren nach Anspruch 1, worin R¹ Amino, Ar(C₁-C₆)alkylamino oder (C₁-C₆)Alkanoylamino ist, R² (C₁-C₆)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R³ COO⁻, Carboxy oder Ar(C₁-C₆)alkoxycarbonyl ist, R⁴ Hydroxy(C₁-C₆)alkyl, (C₁-C₆)Alkanoyloxy(C₁-C₆)alkyl oder Carbamoyloxy(C₁-C₆)alkyl ist und R⁵ Amino oder (C₁-C₆)Alkanoylamino ist.

3. Verfahren nach Anspruch 2, worin R¹ Amino ist und R³ COO⁻ oder Carboxy ist.

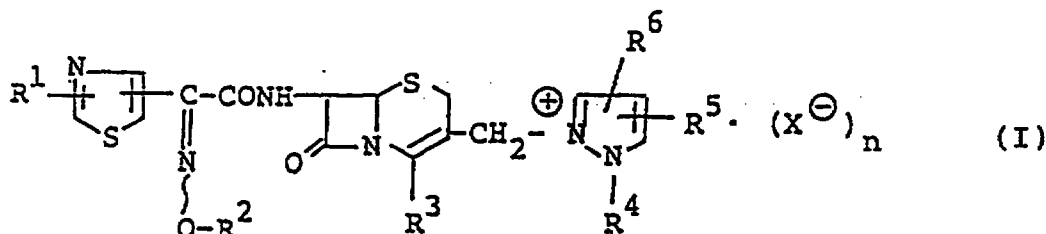
4. Verfahren nach Anspruch 3, worin R² (C₁-C₆)Alkyl oder Dihalogen(C₁-C₆)alkyl ist.

5. Verfahren nach Anspruch 4, worin R² Methyl oder Difluormethyl ist, R⁴ 2-Hydroxyethyl, 2-Formyloxyethyl, 2-Acetoxyethyl oder 2-Carbamoyloxyethyl ist, R⁵ Amino, Formamido oder Acetamido ist und R⁶ Wasserstoff oder Methyl ist.

6. Verfahren nach Anspruch 5 zur Herstellung von 7β-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylat (Syn-Isomer) oder des Schwefelsäuresalzes davon.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Cephem-Verbindung der Formel I:

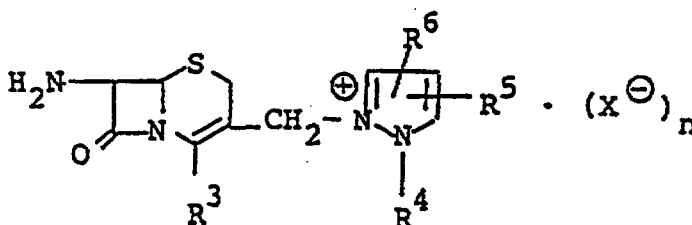


worin R¹ Amino oder ein geschütztes Amino ist, R² (C₁-C₆)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R³ COO⁻, Carboxy oder ein geschütztes Carboxy ist, R⁴ Hydroxy(C₁-C₆)alkyl oder geschütztes Hydroxy(C₁-C₆)alkyl ist, R⁵ Amino oder ein geschütztes Amino ist, R⁶ Wasserstoff oder (C₁-C₆)Alkyl ist, X⁻ ein Anion ist, und n ist 0 oder 1, mit der Bedingung, daß,

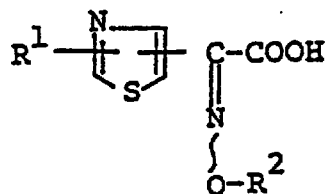
(i) wenn R³ COO⁻ ist, dann ist n 0 und

(ii) wenn R³ Carboxy oder ein geschütztes Carboxy ist, dann ist n 1, oder ein Salz davon, das umfaßt:

i) Reagieren einer Verbindung der Formel:

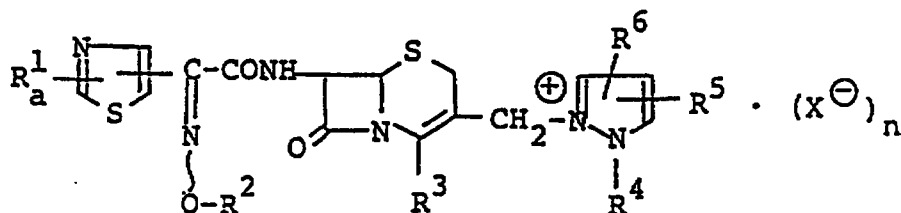


(worin R³, R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind) oder ihres reaktiven Derivates an der Aminogruppe oder eines Salz davon mit einer Verbindung der Formel:

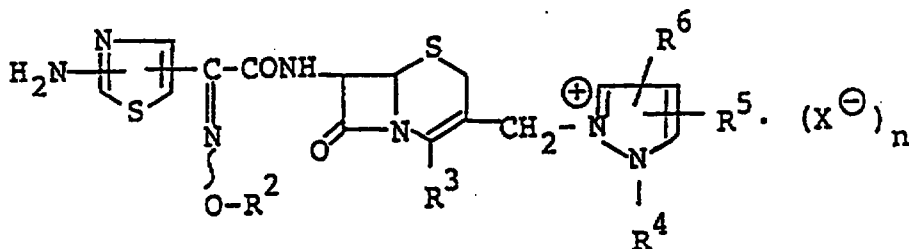


(worin R¹ und R² jeweils wie oben definiert sind) oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon oder

ii) Unterwerfen einer Verbindung der Formel:

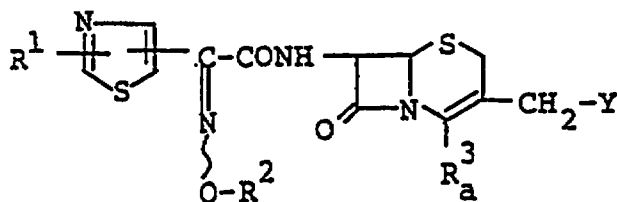


(worin R², R³, R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R¹_a ein geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R¹_a, um eine Verbindung der Formel:

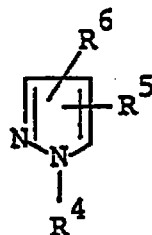


(worin R^2 , R^3 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben, oder

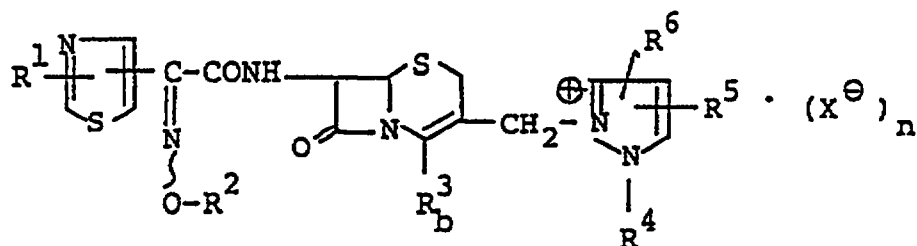
iii) Reagieren einer Verbindung der Formel:



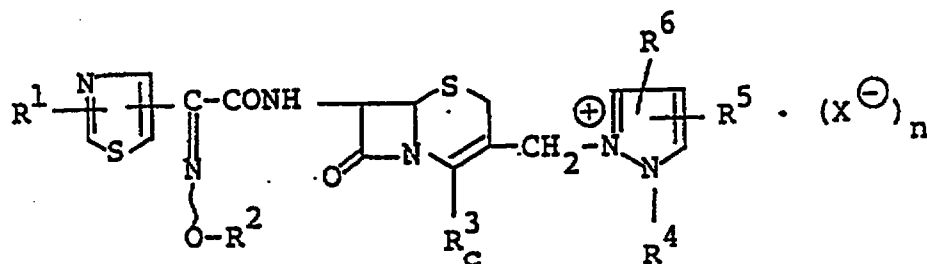
(worin R¹ und R² jeweils wie oben definiert sind, R³, Carboxy oder ein geschütztes Carboxy ist und Y eine Abgangsgruppe ist) oder eines Salzes davon mit einer Verbindung der Formel:



(worin R^4 , R^5 und R^6 jeweils wie oben definiert sind) oder einem Salz davon, oder
iv) Unterwerfen einer Verbindung der Formel:

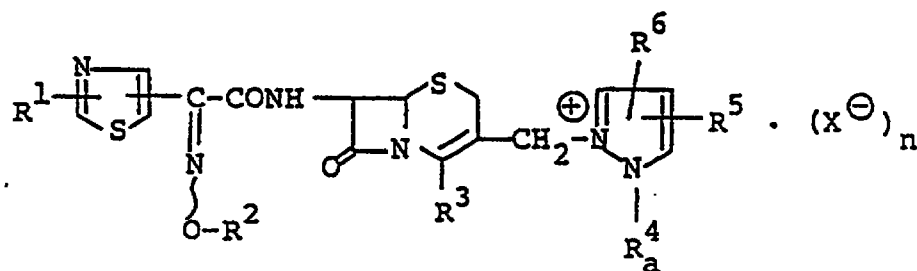


(worin R¹, R², R⁴, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R³_b ein geschütztes Carboxy ist) oder eines Salzes davon der Eliminierungsreaktion der Carboxyschutzgruppe in R³_b, um eine Verbindung der Formel:

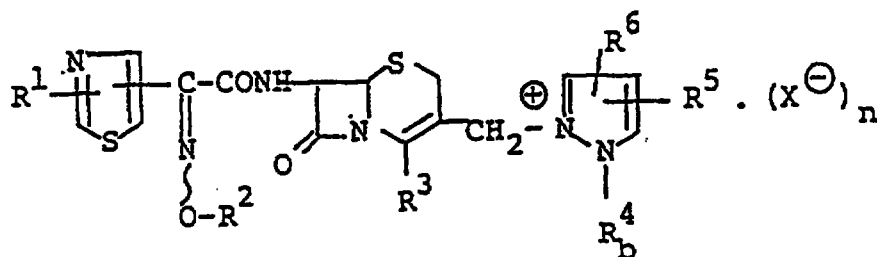


(worin R^1 , R^2 , R^4 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind und R^3 , COO^- oder Carboxy ist) oder ein Salz davon zu erhalten oder

v) Unterwerfen einer Verbindung der Formel:

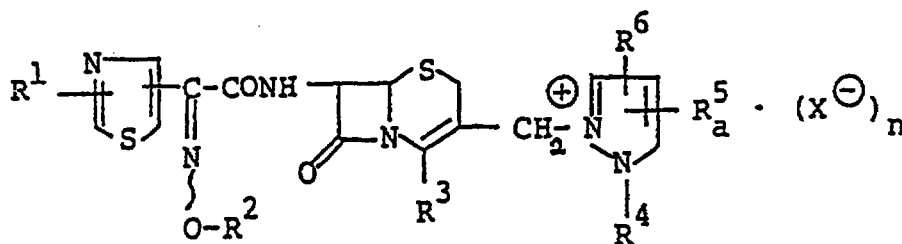


[worin R¹, R², R³, R⁵, R⁶, X⁻ und n jeweils wie oben definiert sind und R⁴_a geschütztes Hydroxy(C₁-C₆)alkyl ist] oder eines Salzes davon der Eliminierungsreaktion der Hydroxyschutzgruppe in R⁴_a, um eine Verbindung der Formel:

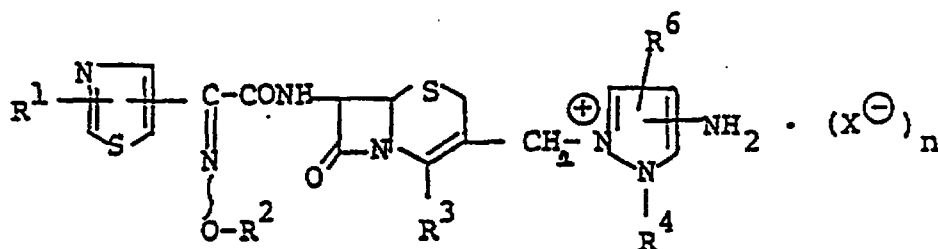


[worin R^1 , R^2 , R^3 , R^5 , R^6 , X^- und n jeweils wie oben definiert sind und R^4 Hydroxy(C_1 - C_6)alkyl ist] oder ein Salz davon zu ergeben oder

vi) Unterwerfen einer Verbindung der Formel:



(worin R^1 , R^2 , R^3 , R^4 , R^5 , X^- und n jeweils wie oben definiert sind, und R^5_a geschütztes Amino ist) oder eines Salzes davon der Eliminierungsreaktion der Aminoschutzgruppe in R^5_a , um eine Verbindung der Formel:



(worin R^1 , R^2 , R^3 , R^4 , R^5 , X^- und n jeweils wie oben definiert sind) oder ein Salz davon zu ergeben.

2. Verfahren nach Anspruch 1, worin R^1 Amino, $\text{Ar}(\text{C}_1$ - C_6)alkylamino oder $(\text{C}_1$ - C_6)Alkanoylamino ist, R^2 $(\text{C}_1$ - C_6)Alkyl ist, das 1 bis 3 Halogen-Substituenten aufweisen kann, R^3 COO^- , Carboxy oder $\text{Ar}(\text{C}_1$ - C_6)alkoxycarbonyl ist, R^4 Hydroxy(C_1 - C_6)alkyl, $(\text{C}_1$ - C_6)Alkanoyloxy(C_1 - C_6)alkyl oder Carbamoyloxy(C_1 - C_6)alkyl ist und R^5 Amino oder $(\text{C}_1$ - C_6)Alkanoylamino ist.
3. Verfahren nach Anspruch 2, worin R^1 Amino ist und R^3 COO^- oder Carboxy ist.
4. Verfahren nach Anspruch 3, worin R^2 $(\text{C}_1$ - C_6)Alkyl oder Dihalogen(C_1 - C_6)alkyl ist.
5. Verfahren nach Anspruch 4, worin R^2 Methyl oder Difluormethyl ist, R^4 2-Hydroxyethyl, 2-Formyloxyethyl, 2-Acetoxyethyl oder 2-Carbamoyloxyethyl ist, R^5 Amino, Formamido oder Acetamido ist und R^6 Wasserstoff oder Methyl ist.
6. Verfahren nach Anspruch 5 zur Herstellung von 7 β -[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-amino-2-(2-hydroxyethyl)-1-pyrazolio]methyl-3-cephem-4-carboxylat (Syn-Isomer) oder des Schwefelsäuresalzes davon.

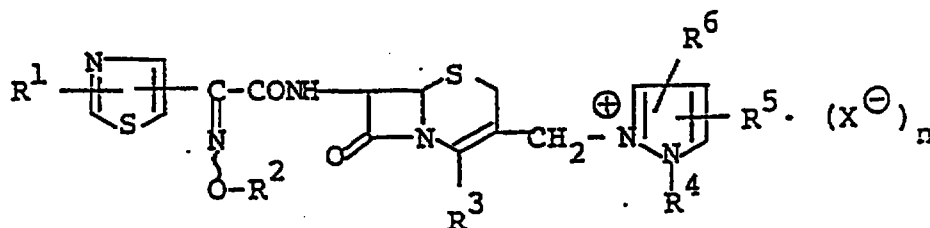


7. Modifizierung des Verfahrens nach Anspruch 1, dadurch charakterisiert, daß eine Verbindung der Formel I oder ein nicht-toxisches Salz davon, hergestellt durch ein Verfahren nach Anspruch 1, durch Zusammenmischung oder Präsentation der genannten Verbindung mit einem pharmazeutisch verträglichen Verdünnungsmittel oder Träger in eine passende pharmazeutische Form gebracht wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Procédé pour préparer un composé céphème de la formule :



dans laquelle :

- R¹ est un amino ou un amino protégé,
- R² est un (C₁-C₆)alkyle qui peut avoir 1 à 3 halogènes comme substituants,
- R³ est un COO⁻, un carboxy ou un carboxy protégé,
- R⁴ est un hydroxy(C₁-C₆)alkyle ou un hydroxy(C₁-C₆)alkyle protégé,
- R⁵ est un amino ou un amino protégé,
- R⁶ est un hydrogène ou un (C₁-C₆) alkyle,
- X est un anion, et
- n est égal à 0 ou 1.

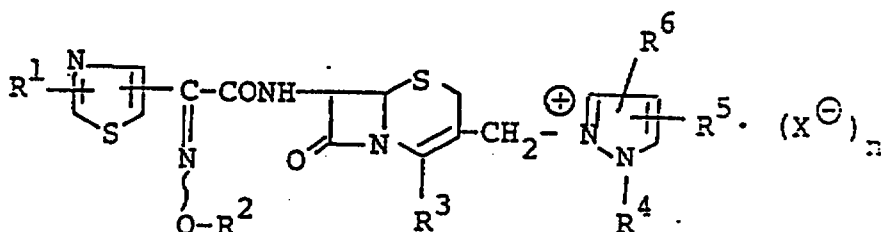
avec comme conditions que :

- (i) lorsque R³ est un COO⁻, alors n est égal à 0 et
 - (ii) lorsque R³ est un carboxy ou un carboxy protégé, alors n est égal à 1,
- ou un sel de celui-ci, acceptable sur le plan pharmaceutique.

2. Composé selon la revendication 1, dans laquelle
- R¹ est un amino, un ar(C₁-C₆)alkylamino ou un (C₁-C₆)alcanoylamino,
 - R² est un (C₁-C₆)alkyle qui peut avoir 1 à 3 halogènes,
 - R³ est un COO⁻, un carboxy ou un ar(C₁-C₆)alcoxycarbonyl,
 - R⁴ est un hydroxy(C₁-C₆)alkyle, un (C₁-C₆)alcanoyloxy(C₁-C₆)alkyle ou un carbamoyloxy(C₁-C₆)alkyle,
 - et
 - R⁵ est un amino ou un (C₁-C₆)alcanoylamino.
3. Composé selon la revendication 2, dans laquelle
- R¹ est un amino et
 - R³ est un COO⁻ ou un carboxy.
4. Composé selon la revendication 3, dans laquelle
- R² est un (C₁-C₆)alkyle ou un dihalo(C₁-C₆)alkyle.
5. Composé selon la revendication 4, dans laquelle
- R² est un méthyle ou un difluorométhyle,
 - R⁴ est un 2-hydroxyéthyle, un 2-formyloxyéthyle, un 2-acétoxyéthyle ou un 2-carbamoyloxyéthyle,
 - R⁵ est un amino, un formamido ou un acétamido et
 - R⁶ est un hydrogène ou un méthyle.
6. Composé selon la revendication 5, qui est le 7β-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-[3-amino-2-(2-hydroxyéthyl)-1-pyrazolio]méthyl-3-céphème-4-carboxylate (isomère syn) ou son sel d'acide sulfurique.



7. Procédé pour préparer un composé céphème de la formule :



dans laquelle :

R¹ est un amino ou un amino protégé,

R² est un (C₁-C₆)alkyle qui peut avoir 1 à 3 halogènes comme substituants,

R³ est un COO⁻, un carboxy ou un carboxy protégé,

R⁴ est un hydroxy(C₁-C₆)alkyle ou un hydroxy(C₁-C₆)alkyle protégé,

R⁵ est un amino ou un amino protégé,

R⁶ est un hydrogène ou un (C₁-C₆)alkyle,

X⁻ est un anion, et

n est égal à 0 ou 1.

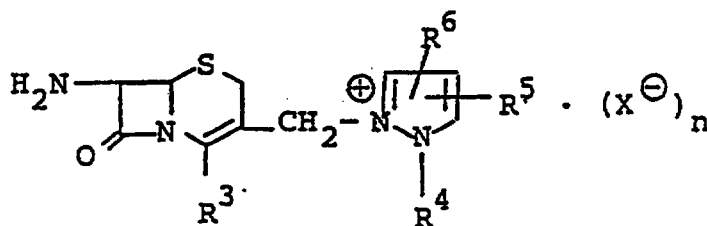
avec comme conditions que :

(i) lorsque R³ est un COO⁻, alors n est égal à 0 et

(ii) lorsque R³ est un carboxy ou un carboxy protégé, alors n est égal à 1,

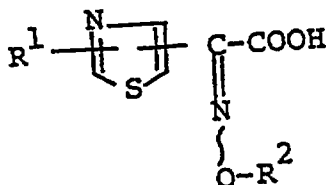
ou un sel de celui-ci qui comprend

i) de faire réagir un composé de la formule :



(dans laquelle R³, R⁴, R⁵, R⁶, X⁻ et n sont chacun comme défini ci-dessus),

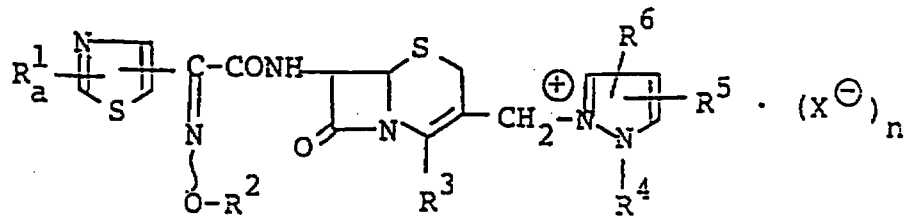
ou son dérivé réactif au groupe amino ou un sel de celui-ci, avec un composé de la formule :



(dans laquelle R¹ et R² sont chacun comme défini ci-dessus), ou son dérivé réactif au groupe carboxy ou un sel de celui-ci, ou

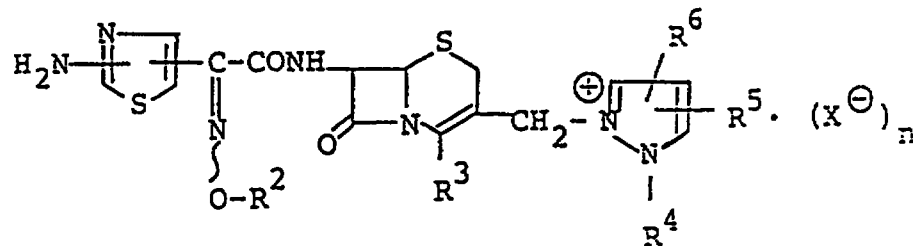


ii) de soumettre un composé de la formule :



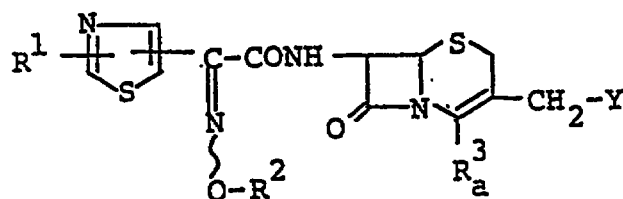
(dans laquelle R^2 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus, et R^1_{a} est un amino protégé)

ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de R^1_{a} , pour donner un composé de la formule :



(dans laquelle R^2 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus) ou un sel de celui-ci, ou

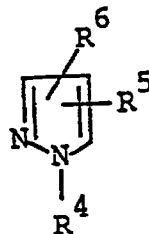
iii) de faire réagir un composé de la formule :



(dans laquelle R^1 et R^2 sont chacun comme défini ci-dessus R^3_{a} est un carboxy ou un carboxy protégé et

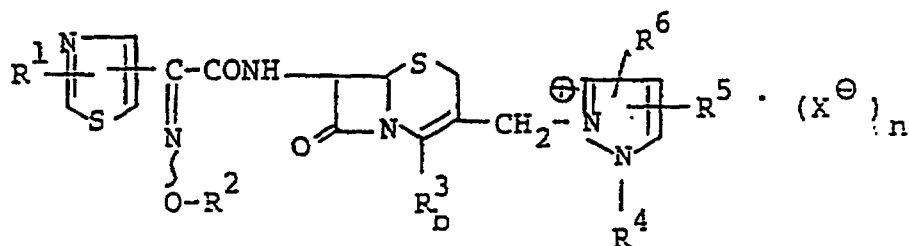
Y est un groupe qui part)

ou un sel de celui-ci, avec un composé de la formule :

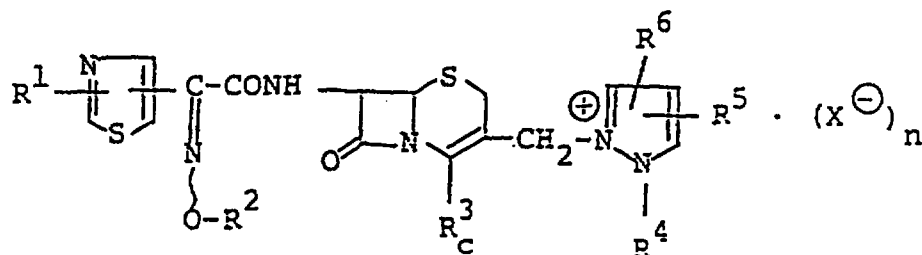


(dans laquelle R^4 , R^5 et R^6 sont chacun comme défini ci-dessus) ou un sel de celui-ci, ou

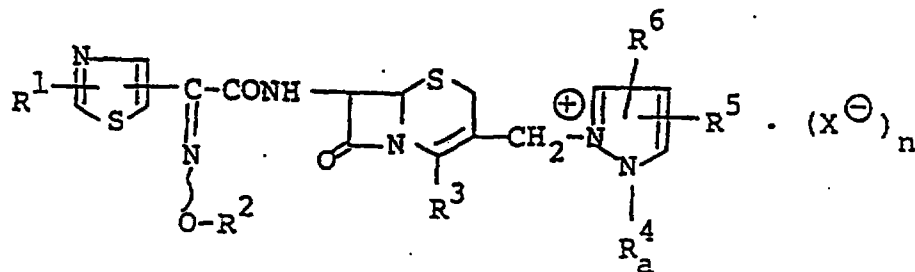
iv) de soumettre un composé de la formule :



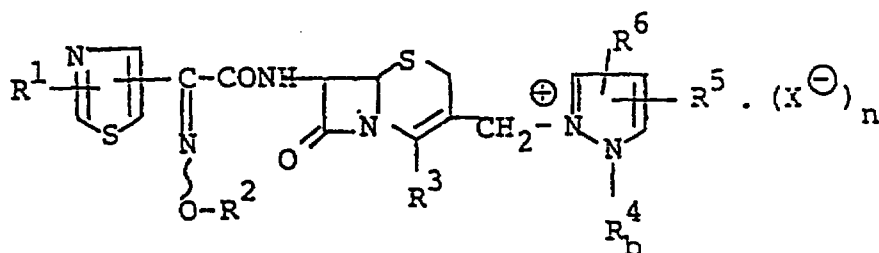
(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^3_b est un carboxy protégé) ou un sel de celui-ci, à une réaction d'élimination du groupe carboxy protecteur de R^3_b , pour donner un composé de la formule :



(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^3_c est un COO^- ou un carboxyle) ou un sel de celui-ci, ou v) de soumettre un composé de la formule :



[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4_a est un hydroxy (C_1 - C_6)alkyle protégé] ou un sel de celui-ci à une réaction d'élimination du groupe hydroxy protecteur de R^4_a , pour donner un composé de la formule :

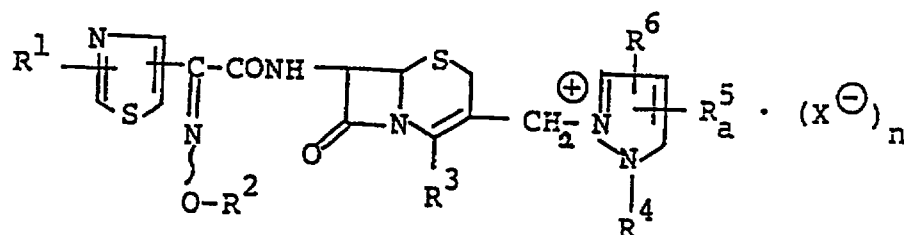


[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4_b est un hydroxy (C_1 - C_6)alkyle]



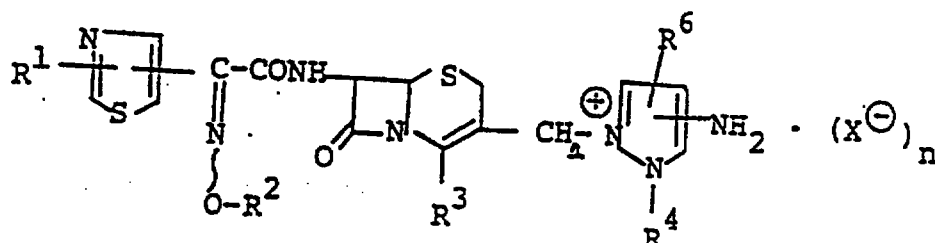
ou un sel de celui-ci, ou

vi) de soumettre un composé de la formule :



(dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , X^- et n sont chacun comme défini ci-dessus et R^5_a est un amino protégé)

ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de R^5_a , pour donner un composé de la formule :

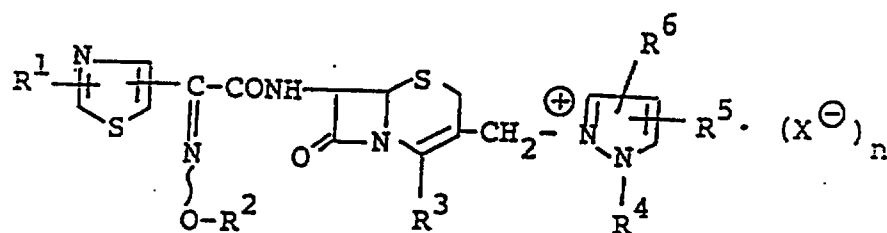


(dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , X^- et n sont chacun comme défini ci-dessus) ou un sel de celui-ci.

8. Composition pharmaceutique qui comprend, comme ingrédient actif, un composé selon la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique en mélange avec des vecteurs acceptables sur le plan pharmaceutique.
9. Composé selon la revendication 1 ou les sels de celui-ci acceptables sur le plan pharmaceutique pour une utilisation en tant que médicament.
10. Composé selon la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique pour une utilisation en tant qu'agent antimicrobien.
11. Utilisation d'un composé selon la revendication 1 et du sel de celui-ci acceptable sur le plan pharmaceutique pour la fabrication d'un médicament pour le traitement thérapeutique de maladies infectieuses,

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour préparer un composé céphème de la formule :





dans laquelle :

R^1 est un amino ou un amino protégé,

R^2 est un (C_1-C_6) alkyle qui peut avoir 1 à 3 halogènes comme substituants,

R^3 est un COO^- , un carboxy ou un carboxy protégé,

5 R^4 est un hydroxy (C_1-C_6) alkyle ou un hydroxy (C_1-C_6) alkyle protégé,

R^5 est un amino ou un amino protégé,

R^6 est un hydrogène ou un (C_1-C_6) alkyle,

X^- est un anion, et

n est égal à 0 ou 1.

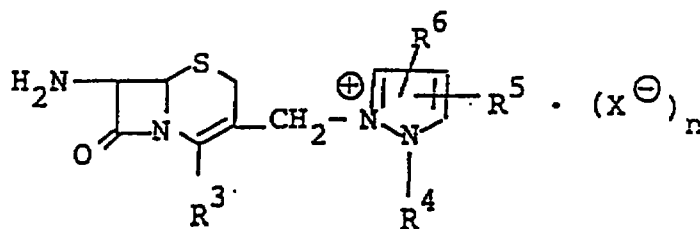
10 avec comme conditions que :

(i) lorsque R^3 est un COO^- , alors n est égal à 0 et

(ii) lorsque R^3 est un carboxy ou un carboxy protégé, alors n est égal à 1 ,
ou un sel de celui-ci qui comprend

i) de faire réagir un composé de la formule :

15



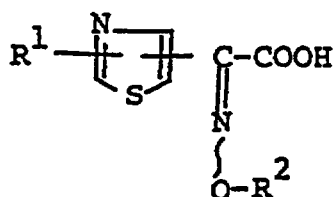
20

25

(dans laquelle R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus),

ou son dérivé réactif au groupe amino ou un sel de celui-ci, avec un composé de la formule :

30

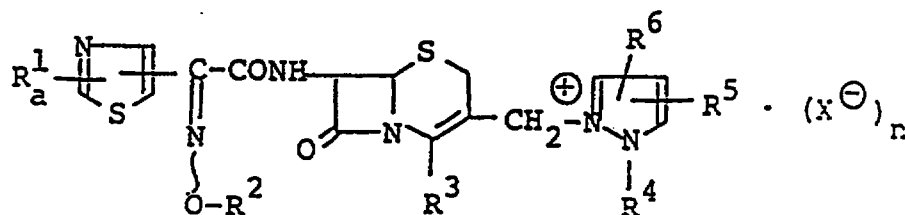


35

(dans laquelle R^1 et R^2 sont chacun comme défini ci-dessus), ou son dérivé réactif au groupe carboxy ou un sel de celui-ci, ou

ii) de soumettre un composé de la formule :

40



45

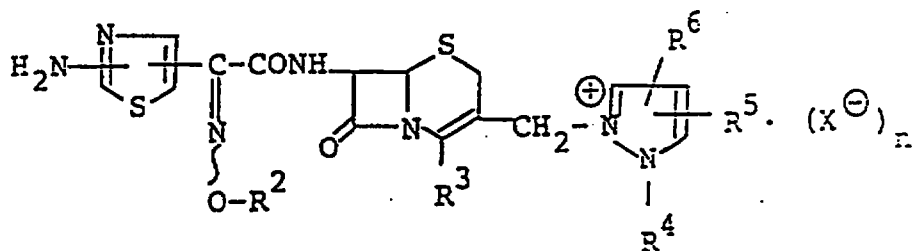
50

(dans laquelle R^2 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus, et

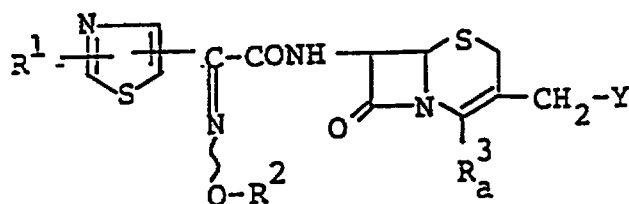
R^1_a est un amino protégé)

ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de R^1_a , pour donner un composé de la formule :

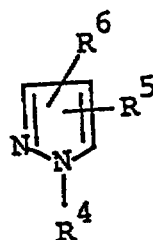
55



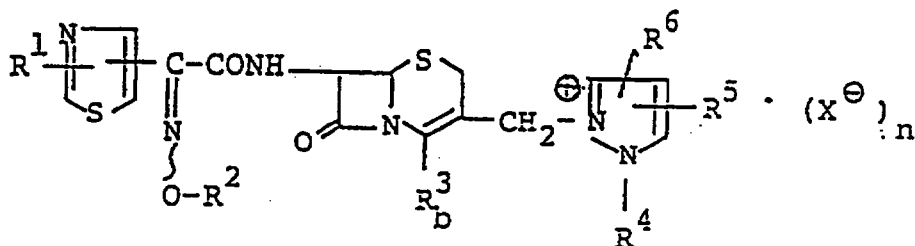
(dans laquelle R^2 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus)
ou un sel de celui-ci, ou
iii) de faire réagir un composé de la formule :



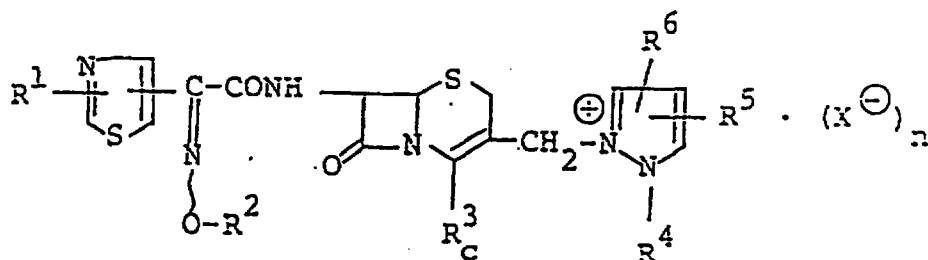
(dans laquelle R^1 et R^2 sont chacun comme défini ci-dessus
 R^3_a est un carboxy ou un carboxy protégé et
 Y est un groupe qui part)
ou un sel de celui-ci, avec un composé de la formule :



(dans laquelle R^4 , R^5 et R^6 sont chacun comme défini ci-dessus)
ou un sel de celui-ci, ou
iv) de soumettre un composé de la formule :

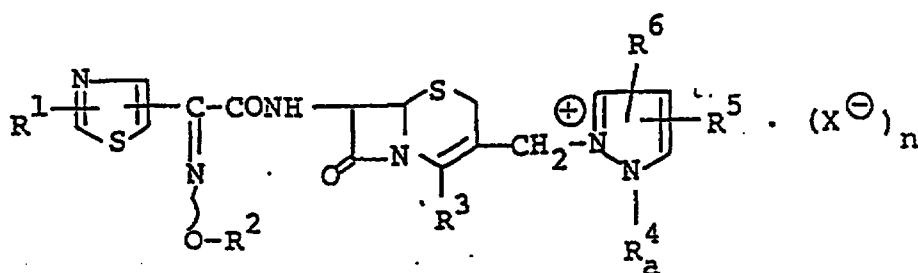


(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et
 R^3_b est un carboxy protégé)
ou un sel de celui-ci, à une réaction d'élimination du groupe carboxy protecteur de R^3_b ,
pour donner un composé de la formule :

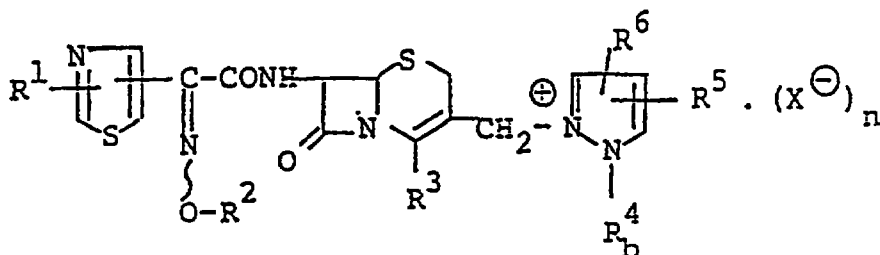


(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^3 est un COO^- ou un carboxyle) ou un sel de celui-ci, ou

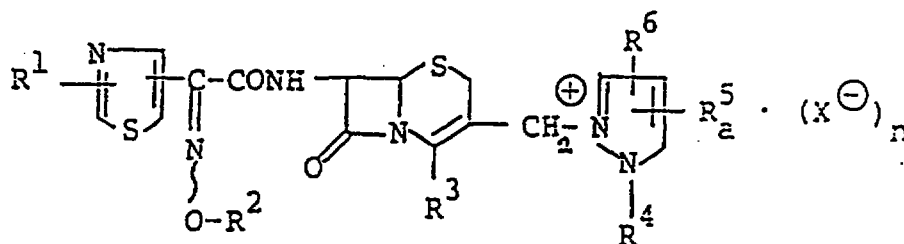
v) de soumettre un composé de la formule :



[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4 est un hydroxy (C_1-C_6)alkyle protégé] ou un sel de celui-ci à une réaction d'élimination du groupe hydroxy protecteur de R^4 , pour donner un composé de la formule :



[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4 est un hydroxy (C_1-C_6)alkyle] ou un sel de celui-ci, ou
vi) de soumettre un composé de la formule :

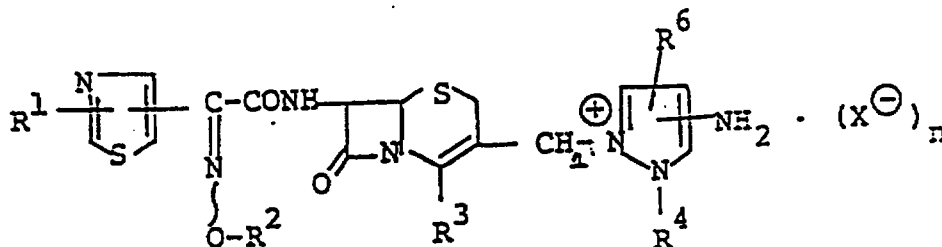


(dans laquelle R^1 , R^2 , R^3 , R^4 , R^6 , X^- et n sont chacun comme défini ci-dessus et



$R^5_{a,}$ est un amino protégé)

ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de $R^5_{a,}$ pour donner un composé de la formule :



(dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , X^- et n sont chacun comme défini ci-dessus) ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans laquelle

R^1 est un amino, un ar(C_1-C_6)alkylamino ou un (C_1-C_6)alcanoylamino,

R^2 est un (C_1-C_6)alkyle qui peut avoir 1 à 3 halogènes,

R^3 est un COO^- , un carboxy ou un ar(C_1-C_6)alcoyloxycarbonyl,

R^4 est un hydroxy(C_1-C_6)alkyle, un (C_1-C_6)alcanoyloxy(C_1-C_6)alkyle ou un carbamoyloxy(C_1-C_6)alkyle, et

R^5 est un amino ou un (C_1-C_6)alcanoylamino.

3. Procédé selon la revendication 2, dans laquelle

R^1 est un amino et

R^3 est un COO^- ou un carboxy.

4. Procédé selon la revendication 3, dans laquelle

R^2 est un (C_1-C_6)alkyle ou un dihalo(C_1-C_6)alkyle.

5. Procédé selon la revendication 4, dans laquelle

R^2 est un méthyle ou un difluorométhyle,

R^4 est un 2-hydroxyéthyle, un 2-formyloxyéthyle, un 2-acétoxyéthyle ou un 2-carbamoyloxyéthyle,

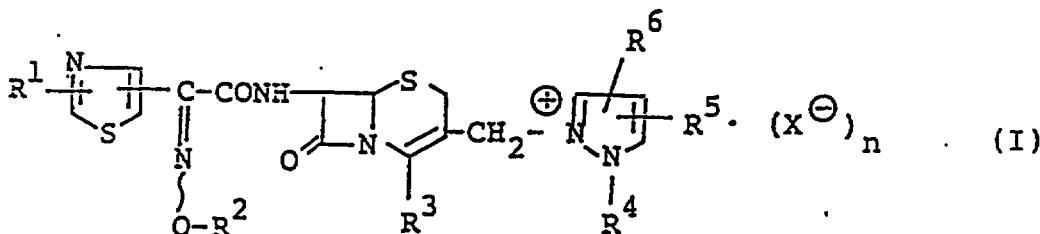
R^5 est un amino, un formamido ou un acétamido et

R^6 est un hydrogène ou un méthyle.

6. Procédé selon la revendication 5, concernant le 7 β -[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-[3-amino-2-(2-hydroxyéthyl)-1-pyrazolio]méthyl-3-céphème-4-carboxylate (isomère syn) ou son sel d'acide sulfurique.

Revendications pour l'Etat contractant suivant : GR

1. Procédé pour préparer un composé céphème de la formule I :



dans laquelle :

R^1 est un amino ou un amino protégé,

R^2 est un (C_1-C_6)alkyle qui peut avoir 1 à 3 halogènes comme substituants,

R^3 est un COO^- , un carboxy ou un carboxy protégé,



R^4 est un hydroxy(C_1-C_6)alkyle ou un hydroxy(C_1-C_6)alkyle protégé,

R^5 est un amino ou un amino protégé,

R^6 est un hydrogène ou un (C_1-C_6) alkyle,

X^- est un anion, et

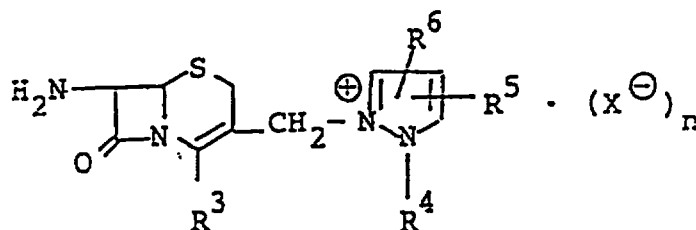
n est égal à 0 ou 1.

avec comme conditions que :

(i) lorsque R^3 est un COO^- , alors n est égal à 0 et

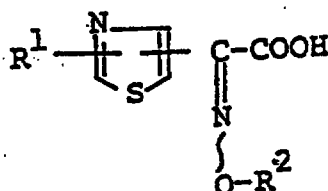
(ii) lorsque R^3 est un carboxy ou un carboxy protégé, alors n est égal à 1 ,
ou un sel de celui-ci qui comprend

i) de faire réagir un composé de la formule :



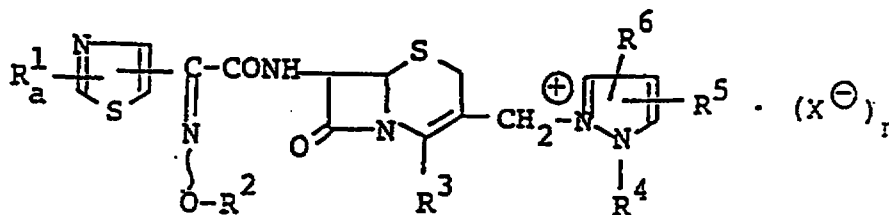
(dans laquelle R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus),

ou son dérivé réactif au groupe amino ou un sel de celui-ci, avec un composé de la formule :



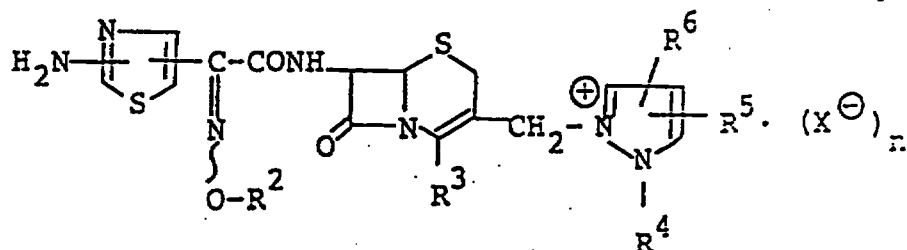
(dans laquelle R^1 et R^2 sont chacun comme défini ci-dessus), ou son dérivé réactif au groupe carboxy ou un sel de celui-ci, ou

ii) de soumettre un composé de la formule :

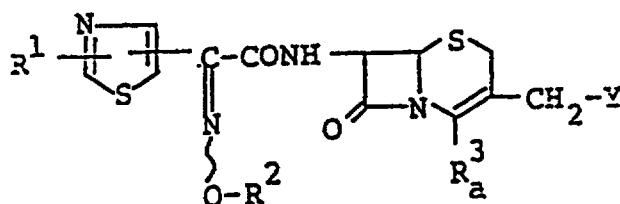


(dans laquelle R^1 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus, et R^1_a est un amino protégé)

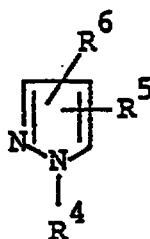
ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de R^1_a , pour donner un composé de la formule :



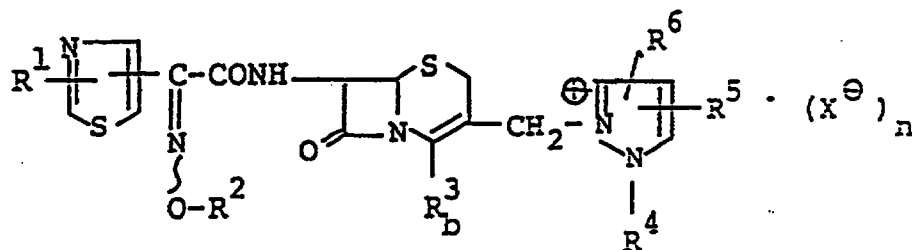
(dans laquelle R^2 , R^3 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus)
ou un sel de celui-ci, ou
iii) de faire réagir un composé de la formule :



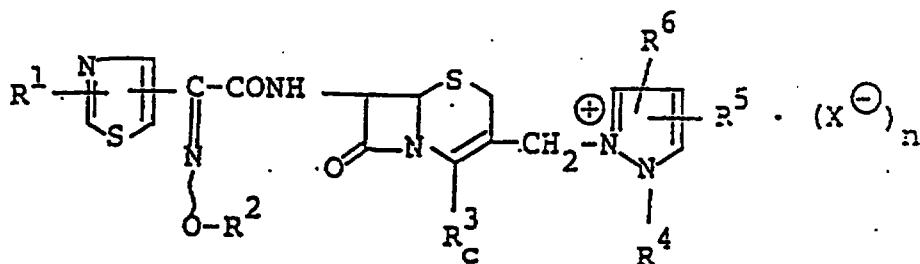
(dans laquelle R^1 et R^2 sont chacun comme défini ci-dessus
 R^3_a est un carboxy ou un carboxy protégé et
 Y est un groupe qui part)
ou un sel de celui-ci, avec un composé de la formule :



(dans laquelle R^4 , R^5 et R^6 sont chacun comme défini ci-dessus)
ou un sel de celui-ci, ou
iv) de soumettre un composé de la formule :

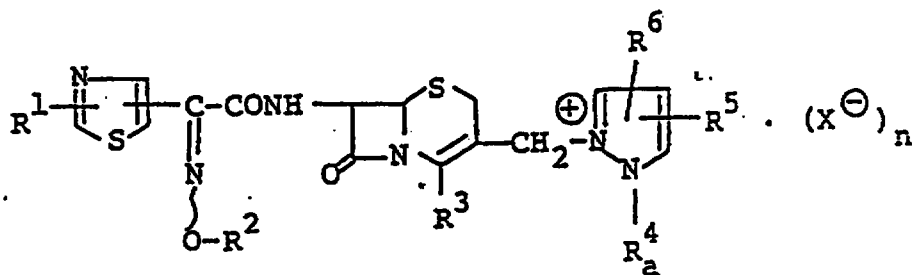


(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et
 R^3_b est un carboxy protégé)
ou un sel de celui-ci, à une réaction d'élimination du groupe carboxy protecteur de R^3_b ,
pour donner un composé de la formule :



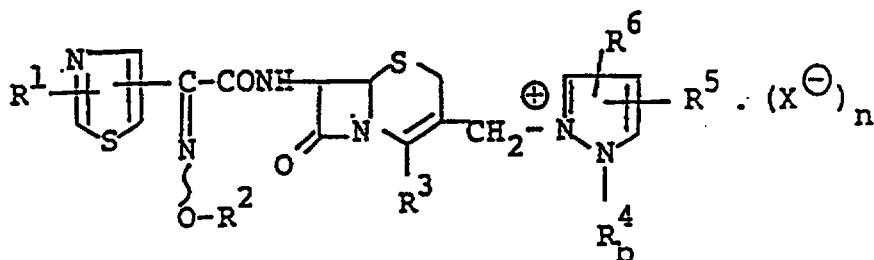
(dans laquelle R^1 , R^2 , R^4 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^3_c est un COO^- ou un carboxyle) ou un sel de celui-ci, ou

v) de soumettre un composé de la formule :



[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4_a est un hydroxy (C_1 - C_6)alkyle protégé]

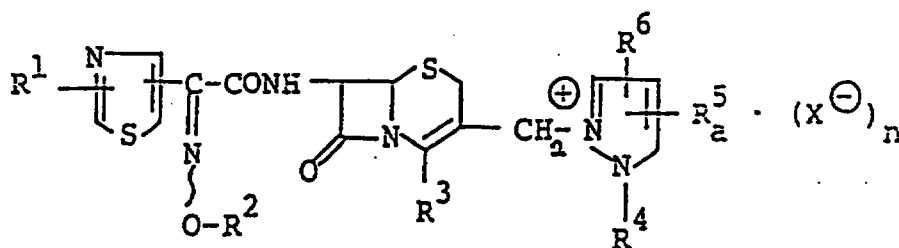
ou un sel de celui-ci à une réaction d'élimination du groupe hydroxy protecteur de R^4_a , pour donner un composé de la formule :



[dans laquelle R^1 , R^2 , R^3 , R^5 , R^6 , X^- et n sont chacun comme défini ci-dessus et R^4_b est un hydroxy (C_1 - C_6)alkyle]

ou un sel de celui-ci, ou

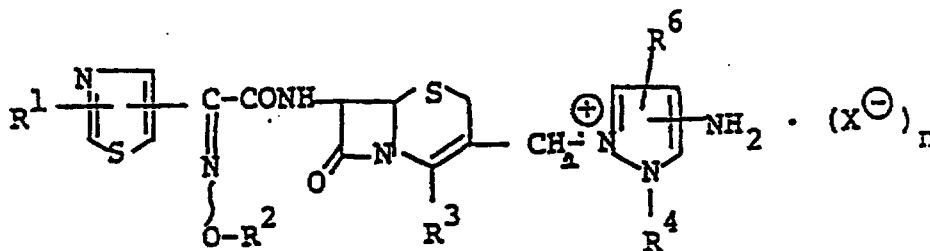
vi) de soumettre un composé de la formule :



(dans laquelle R^1 , R^2 , R^3 , R^4 , R^5 , X^- et n sont chacun comme défini ci-dessus et R^5_a est un amino protégé)



ou un sel de celui-ci, à une réaction d'élimination du groupe amino protecteur de R⁵, pour donner un composé de la formule :



(dans laquelle R¹, R², R³, R⁴, R⁵, X⁻ et n sont chacun comme défini ci-dessus) ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans laquelle

R¹ est un amino, un ar(C₁-C₆)alkylamino ou un (C₁-C₆)alcanoylamino,

R² est un (C₁-C₆)alkyle qui peut avoir 1 à 3 halogènes,

R³ est un COO⁻, un carboxy ou un ar(C₁-C₆)alcoyloxycarbonyl,

R⁴ est un hydroxy(C₁-C₆)alkyle, un (C₁-C₆)alcanoyloxy(C₁-C₆)alkyle ou un carbamoyloxy(C₁-C₆)alkyle, et

R⁵ est un amino ou un (C₁-C₆)alcanoylamino.

3. Procédé selon la revendication 2, dans laquelle

R¹ est un amino et

R³ est un COO⁻ ou un carboxy.

4. Procédé selon la revendication 3, dans laquelle

R² est un (C₁-C₆)alkyle ou un dihalo(C₁-C₆)alkyle.

5. Procédé selon la revendication 4, dans laquelle

R² est un méthyle ou un difluorométhyle,

R⁴ est un 2-hydroxyéthyle, un 2-formyloxyéthyle, un 2-acétoxyéthyle ou un 2-carbamoyloxyéthyle,

R⁵ est un amino, un formamido ou un acétamido et

R⁶ est un hydrogène ou un méthyle.

6. Procédé selon la revendication 5, concernant le 7β-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-[3-amino-2-(2-hydroxyéthyl)-1-pyrazolio]méthyl-3-céphème-4-carboxylate (isomère syn) ou son sel d'acide sulfurique.

7. Modification du procédé revendiqué dans la revendication 1, qui est caractérisé en ce que l'on met un composé de la formule I, ou un sel non toxique de celui-ci, produits par un procédé revendiqué dans la revendication 1, sous une forme acceptable sur le plan pharmaceutique, par mélange ou par formulation dudit composé avec un diluant ou un vecteur acceptable sur le plan pharmaceutique.