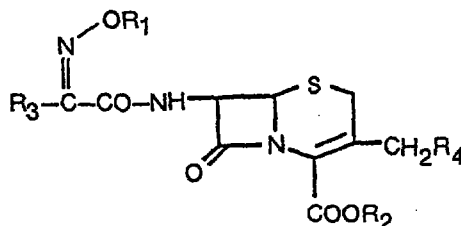


Description

The invention relates to a new process for the production of *syn*-isomers of formula I,



in which

R_1 is hydrogen, alkyl, phenalkyl, carbalkoxyalkyl, acyl or carboxyalkyl,

R_2 is hydrogen, pivaloyloxymethyl or a carboxy protecting group,

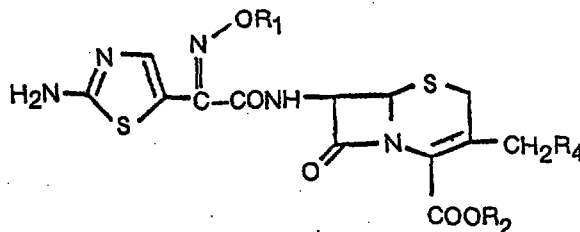
R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino or azido, and

R_4 is hydrogen, acetoxy, carbamoyloxy or $-S-Y$, in which Y is a heterocyclic ring which may be substituted.

The compounds of formula I represent a known class of valuable cephalosporin antibiotics disclosed for example in W. German DOS 2,223,375; 2,556,736; 2,702,501; 2,707,565; 2,715,385; 2,992,036; as well as numerous other patent and other publications. This class of antibiotics is characterised by the presence of an oximino group in the 7-acylamido side-chain attached to the cephalosporin nucleus. It is known that this oximo group may have the *syn* or *anti* configuration but that the *syn* isomers are preferred.

The heterocyclic ring in R_3 contains, as indicated, one or more oxygen and/or sulphur atoms as heteroatom(s). It may, however, additionally contain one or more nitrogen hetero atoms. Suitable heterocyclic rings include furyl, thienyl, thiazolyl, thiadiazolyl, oxazolyl and oxadiazolyl. The heterocyclic ring may as indicated be unsubstituted or substituted by amino or azido, preferably amino. Preferably the heterocyclic ring of R_3 is thiazolyl and this is preferably substituted by amino.

A particular preferred group of *syn*-isomers is that of formula Ia,



in which

R_1 , R_2 and R_4 are as defined above.

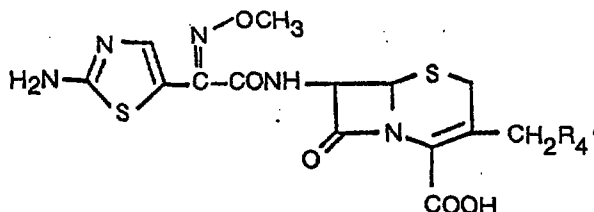
In these structures, the radical R_4 can be hydrogen. It may also be carbamoyloxy. It is, however, preferably, acetoxy or $-S-Y$. Suitable heterocyclic groups which Y may represent are well-known, for example from the numerous publications referred to above. Preferred heterocyclic rings include thiadiazolyl, diazolyl, triazolyl, tetrazolyl, thiazolyl, thiatriazolyl, oxazolyl, oxadiazolyl, triazolylpyridyl, purinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl or thiazinyl. These heterocyclic rings may be unsubstituted or substituted, for example up to three times. Suitable substituents include C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trihalo- C_{1-4} alkyl, hydroxy, oxo, mercapto, amino, carboxyl, carbamoyl, di- (C_{1-4}) alkylamino, carboxymethyl, carbamoylmethyl, sulphomethyl and methoxycarbonylamino. Heterocyclic moieties indicated in the prior art to be particularly preferred include tetrazolyl, in particular 1-methyl-1H-tetrazol-5-yl, and triazinyl, in particular 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl or 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl. Preferably R_4 is acetoxy, 1-methyl-1H-tetrazol-5-yl, or 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl.

In these structures, R_1 may be hydrogen. It may also be C_{1-4} alkyl preferably C_{1-2} alkyl, in particular methyl. Suitable phenalkyl groups include phen- C_{1-4} alkyl, particularly benzyl. R_1 may also be carbalkoxyalkyl, for example carb- (C_{1-2}) alkoxy- (C_{1-4}) alkyl, in particular carb- (C_{1-4}) alkoxymethyl, e.g. carbethoxymethyl. Suitable acyl radicals include C_{2-5} alkanoyl or C_{1-4} alkoxycarbonyl. R_1 may also be carboxyalkyl, in particular carboxy- C_{1-4} alkyl, e.g. carboxymethyl.

As is well known in the cephalosporin field, the compounds may be in the form of free acids

($R_2 = H$) or of salts, for example alkali or alkaline earth metal salts, preferably alkali metal salts, such as sodium salts. Alternatively, the compounds may be in the form of esters, e.g. the pivaloyloxymethyl ester. ($R_2 =$ pivaloyloxymethyl). Other carboxy protecting groups which R_2 may represent are well-known and include acetoxymethyl, 1-acetoxyethyl, 1-ethoxycarbonyloxyethyl, 5-indanoyl or, preferably, hexanoylmethyl, phthalidyl, carbethoxymethoxymethyl or 3-carbethoxy-1-acetonyl.

Particularly preferred compounds are *syn*-isomers having the formula Ib,



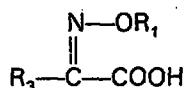
Ib

in which

R_4' is acetoxymethyl, 1-methyl-1H-tetrazol-5-yl, or 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl, and salts thereof.

The compounds of formula Ib are the products known as Cefotaxim ($R_4' =$ acetoxymethyl), SCE—1365 ($R_4' =$ 1-methyl-1H-tetrazol-5-yl) and Ceftriaxone ($R_4' =$ 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl), in the form of sodium salts (Cefotaxim and SCE—1365) or the disodium salt (Ceftriaxone).

As indicated, the compounds of formula I are generally known, and various methods for their production have been proposed. One such method involves acylation of the corresponding 7-aminocephalosporanic acid derivative, which may be protected, with a reactive derivative of the acid of formula A,



A

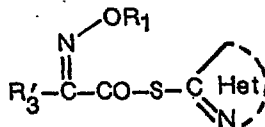
in which R_1 and R_3 are as defined above.

The various reactive derivatives that have been proposed include activated esters. For the production of the *syn*-isomers of formula I the reactive derivatives of the acid of formula A should also be in *syn*-isomeric form in as high a purity as possible, and the *syn*-configuration should as far as possible be unaffected by the subsequent steps, in particular the acylation step. Various reactive derivatives that have previously been proposed, in particular activated esters, suffer from the disadvantage that the *syn*-configuration is somewhat unstable during production or use thus leading to increased formation of the *anti*-isomer and consequential reduction of the yields of the desired *syn*-isomers.

A further difficulty that arises in the production of the preferred compounds of formula Ia is that in practice it is essential to protect the amino substituent in the thiazolidine ring of the side-chain prior to the acylation step. Otherwise competing reactions can occur leading to greatly reduced yields of the final products. The introduction, however, of suitable protecting groups prior to the acylation step, and their subsequent removal is in general accompanied by reduced yield and purity of the desired final product and not insubstantial additional reaction time, energy, effort and cost.

The present invention provides a method by which the desired *syn*-isomers may be obtained in high purity and yield; in particular, the *syn*-isomers of formula Ia may be obtained in high purity and yield without the necessity to protect the amino substituent in the thiazolidine ring of the side-chain.

More particularly, the present invention provides a process for the production of *syn*-isomers of formula I and salts thereof, comprising reacting a *syn*-isomer of formula II,

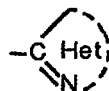


II

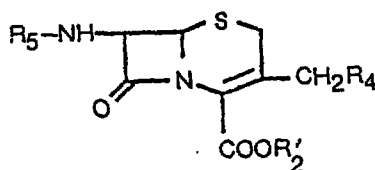
in which

R_1 is as defined above,

R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino, protected amino, or azido, and



represents a 5- or 6-membered heterocyclic ring, which may contain in addition to the nitrogen atom, one or two further hetero atoms, selected from oxygen, nitrogen and sulphur, and which may be substituted or fused to a benzene ring which may itself be substituted, with a compound of formula III.



III

in which

R_2 and R_4 are as defined above, and

R_5 is hydrogen or an amino protecting group,

where required, deprotecting the resulting product, and, where required, converting a resulting product in which R_2 is hydrogen into a salt thereof or *vice versa*.

The process is suitably carried out in an inert organic solvent, such as a chlorinated hydrocarbon, e.g. methylene dichloride, or an ether, e.g. ethyl acetate, or in a mixture of such solvents with water. The reaction temperature is suitably from -40° to $+60^\circ\text{C}$, in particular -15° to $+25^\circ\text{C}$, especially 0° to 20°C , and the reaction time may typically vary from 1/2 to 48 hours. The reactants of formula II or III may conveniently be employed in stoichiometric quantities. Alternatively, an excess of up to 25% of the compound of formula II is conveniently employed.

As indicated, the production of compounds in which R_2 is hydrogen (as well as salts thereof), the carboxylic acid group in the starting materials of formula II, is conveniently protected. Suitable protecting groups are well known and include not only those referred to above as possible significances for R_2 , but also silyl ester protecting groups, in particular the trimethylsilyl protecting groups, which may for example be introduced by reaction of the free acid with N,O-bis-trimethylsilylacetamide.

The 7-amino group of the starting material of formula III may, as indicated, also be protected. Again, suitable protecting groups are well-known and include for example the trimethylsilyl group, which may for example be introduced simultaneously when protecting the carboxylic acid group.

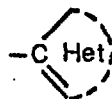
When R_3 in the desired product contains an amino substituent in the heterocyclic ring, the corresponding starting material of formula II may have this amino substituent in free or in protected form. As discussed, in general protection is not necessary. If protection is nevertheless desired, this may be accomplished in conventional manner, suitable protecting groups being well-known.

After reaction of the compounds of formula II and III, any subsequent deprotection steps may be effected in conventional manner. Likewise, interconversion of the free acid ($R_2 = \text{H}$) and salts thereof may be accomplished in well-known manner.

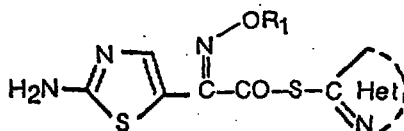
The resulting products may be isolated and purified using conventional techniques.

The process of the invention thus employs as reactive derivatives of the acid of formula A, heterocyclic thioesters. It has been surprisingly found that these esters may be prepared and employed with virtually complete control of the geometry of the —C=N— *syn*-configuration. Furthermore, it has surprisingly been found that when there is an amino group in the heterocyclic ring of these esters, the esters are not self-reacting. Accordingly, protection of this amino group in the subsequent acylation is not essential (although of course not ruled out if for any reason desired).

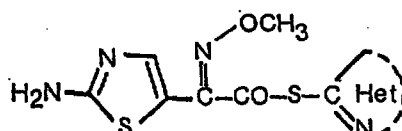
The *syn*-isomers of formula II are novel. The nature of the



ring therein is not critical, the preferred compounds being determined by such factors as ease of formation and availability of starting materials. Preferably, this signifies 2-pyridyl, or, especially, 2-benzthiazolyl. It may also be pyrimidinyl, triazolyl or thiazolyl, however. The preferred compounds of formula II correspond to the preferred end products, namely *syn* isomers of formula IIa and IIb,

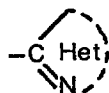


IIa



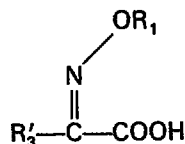
IIb

in which R₁ and



are as defined above.

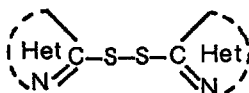
The *syn*-isomers of formula II may be prepared by esterification of a *syn*-isomer of formula IV,



IV

in which R₁ and R₂ are as defined above.

The esterification may for example be accomplished by reaction with a compound of formula V,



V

in which the two groups



are the same and are as defined above.

The reaction is suitably effected in the presence of a tri-(lower alkyl)- or tri(aryl) phosphine or phosphite, in particular triphenylphosphine. The reaction temperature may for example be from -30° to $+50^{\circ}\text{C}$, in particular -20° to $+25^{\circ}\text{C}$, preferably -5° to $+5^{\circ}\text{C}$. The reaction is suitably effected in an inert, non-hydroxy-containing, organic solvent, for example a chlorinated hydrocarbon, such as methylene chloride. Where a compound of formula II in which R₃ is a protected-amino-substituted heterocycle is desired, the amino protecting group may of course be introduced prior to or subsequent to the esterification reaction.

The *syn*-isomers of formula I are as indicated in general known antibiotics. In particular they are indicated for use as antibacterial agents as indicated *in vitro* in the series dilution test, at a concentration for example of 0.01 to 50 $\mu\text{g/ml}$, and *in vivo* in the mouse at a dosage level of for example from 0.1 to 100 mg/kg of animal body weight, against a wide variety of strains, such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus faecalis*, *E. coli*, *Proteus vulgaris*, *Proteus mirabilis*, *Proteus morganii*, *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, *Alcaligenes faecalis*, *Klebsiella aerogenes*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Salmonella Heidelberg*, *Salmonella typhimurium*, *Salmonella enteritidis* and *Neisseria gonorrhoeae*.

The compounds are therefore useful as bacterially active antibiotics. For this usage, the dosage will of course vary depending on the compound employed, mode of administration and treatment desired. However, in general, satisfactory results are obtained when administered at a daily dosage of from 1 to 6 g conveniently given in divided dosages of from about 0.25 to about 3 g of the compound two to four times daily, or in sustained release form.

The compounds in which R₂ is hydrogen may be employed in free acid form or in the form of their physiologically acceptable salts, which salt forms have the same order of activity as the free acid forms. Suitable salt forms include alkali metal and alkaline earth metal salt forms, in particular alkali metal, such as sodium salt forms. The compounds may be admixed with conventional pharmaceutically acceptable diluents and carriers and optionally other excipients and administered in such forms as capsules or injectable preparations.

The following Examples in which all temperatures are in degrees Centigrade, illustrate the invention.

Example 1

7-[(2-(2-Aminothiazol-4-yl)-2-*syn*-methoximino]acetamido]cephalosporanic acid [Cefotaxim]

2.72 g of 7-Aminocephalosporanic acid are suspended in 50 ml of methylene dichloride. 3.5 ml of N,O-bis-(trimethylsilyl)acetamide are added and the mixture is stirred at room temperature until a clear solution is obtained. 3.5 g of 2-(2-aminothiazol-4-yl)-2-*syn*-methoximino acetic acid and 2-benthiazolyl thioester are added and the mixture is stirred for 15 hours at room temperature. The solution is then extracted with 2 g of KHCO_3 and 40 ml of water and the phases are separated. The aqueous phase is extracted with a mixture of ethyl acetate/*n*-butanol (8/2) at pH 2 and before phase separation, the aqueous phase is saturated with $(\text{NH}_4)_2\text{SO}_4$. The organic phase is washed twice with 100 ml of NaCl solution and evaporated to dryness. The crystalline residue is shaken with 100 ml of diethyl ether,

filtered and washed with ether. The title product is obtained. M.P. 205° (decomp.). Yield 4.2 g; 92% of theory based on pure *syn* isomer.

Example 2

5 7-(2-(2-Aminothiazol-4-yl)-2-*syn*-methoximino)acetamido cephalosporanic acid [Cefotaxim]

2.72 g of 7-Aminocephalosporanic acid are suspended in 40 ml of methylene dichloride and 2.75 ml of N,O-bis-(trimethylsilyl)acetamide are added, dropwise. The mixture is stirred until a clear solution is obtained. 2.9 g of 2-(2-aminothiazol-4-yl)-2-*syn*-methaminoacetic acid 2-pyridyl thioester are added, the mixture is cooled to 10° and stirred at this temperature for 24 hours. 2 g of KHCO₃ in 40 ml of water
10 are added and the mixture is stirred for 30 minutes and the aqueous phase is separated. This is layered with a mixture of *n*-butanol/ethyl acetate and the pH of the mixture is adjusted to 2. The organic phase is evaporated *in vacuo* and the residue is mixed with ether. The precipitated crystalline heading compound is filtered off, washed with ether and dried. M.P. 205° (decomp.). Yield 4.1 g; 90% of theory based on pure *syn* isomer.

15

Example 3

7-[[2-(2-Aminothiazol-4-yl)-2-*syn*-methoximino]acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-a,s-triazin-3-yl)-thio]methyl]-3-cephem-4-carboxylic acid Ceftriaxon

3.71 g of 7-Amino-3-(2,5-dihydro-2-methyl-6-hydroxy-5-oxo-a,s-triazin-3-yl)thiomethyl-3-
20 cephem-4-carboxylic acid are suspended in 50 ml of dry methylene chloride under an inert gas atmosphere. 8 ml of N,O-bis-trimethylsilyl)acetamide are added, with stirring, and the mixture is stirred for 30 minutes when a clear solution is formed which is then cooled to +15°C. 4 g of 2-(2-aminothiazol-4-yl)-2-*syn*-methoximino acetic acid 2-benzthiazolyl thioester are added and the mixture is stirred for 5 hours at 15 to 20°, whereupon a clear solution is formed. The mixture is then cooled to
25 0°C and poured into a solution of 3 ml of methanol in 120 ml of acetonitrile, pre-cooled to 0°. From the resulting initially clear solution, a light precipitate is formed on further stirring at 0° to 5° and this is filtered off and washed with acetonitrile. After drying in vacuum at 50°C, 4.7 g. (85%) of substantially pure title compound are obtained, in the form of the free acid, m.p. >120°C (decomp.).

30

Example 4

7-[[2-Aminothiazol-4-yl)-2-*syn*-methoximino]-acetamido]-3-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid [SCE 1365]

In manner analogous to that of any one of Examples 1 to 3, employing appropriate starting materials in approximately equivalent amounts, the heading compound may be obtained.

35

Example 5

2-(2-Aminothiazol-4-yl)-2-*syn*-methoximino-acetic acid 2-pyridyl thioester [Compound II]

26 g of triphenylphosphine are dissolved in 130 ml of methylene dichloride and 22 g of 2,2-dithiopyridine are added. The mixture is stirred at room temperature for 15 minutes and then cooled to
40 0°C. 10g of finely powdered 2-(2-aminothiazol-4-yl)-2-*syn*-methoximinoacetic acid are then added in portions over 1 hour. the mixture is seeded and cooled for 3 hours at 0°, whereby the heading compound crystallises out. This is filtered and washed with cold methylene chloride; m.p. 112°; yield 16.4 g — 98% of theory based on pure *syn* isomer.

45

Example 6

2-(2-Aminothiazol-4-yl)-2-*syn*-methoximino acetic acid 2-benzothiazolyl thioester [Compound II]

3.93 g of Triphenylphosphine and 5 g of bis[benzthiazolyl-(2)]disulphide are suspended in 50 ml of methylene dichloride and the suspension is stirred for 30 minutes at room temperature. After cooling to 0°, 2 g of 2-(2-aminothiazol-4-yl)-2-*syn*-methoximinoacetic acid are added and the mixture is stirred
50 for 3 to 4 hours at 0°. The insolubles are filtered off and washed with a little cold methylene chloride. The solid is suspended in 25 ml of ethyl acetate and the suspension is stirred for 30 minutes at 0°, filtered and washed with ethyl acetate to obtain the heading compound, m.p. 128°—130° (from tetrahydrofuran/methylene dichloride).

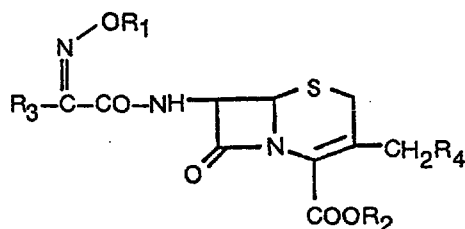
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Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A process for the production of *syn*-isomers of formula I,



15 in which

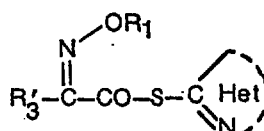
R_1 is hydrogen, alkyl, phenalkyl, carbalkoxyalkyl, acyl or carboxyalkyl,

R_2 is hydrogen, pivaloyloxymethyl or a carboxy protecting group,

R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino or azido, and

20 R_4 is hydrogen, acetoxy, carbamoyloxy or $-S-Y$, in which Y is a heterocyclic ring which may be substituted;

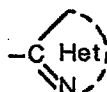
and pharmaceutically acceptable salts thereof, which comprises reacting a *syn*-isomer of formula II,



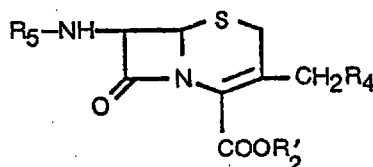
in which

30 R_1 is as defined above,

R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino, protected amino, or azido, and



represents a 5- or 6-membered heterocyclic ring, which may contain in addition to the nitrogen atom, one or two further hetero atoms, selected from oxygen, nitrogen and sulphur, and which may be substituted or fused to a benzene ring which may itself be substituted, with a compound of formula III,



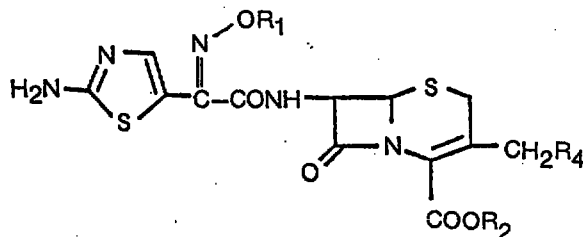
in which

50 R_2 and R_4 are as defined above, and

R_5 is hydrogen or an amino protecting group

where required, deprotecting the resulting product, and, where required, converting a resulting product in which R_2 is hydrogen into a salt thereof or *vice versa*.

2. A process according to Claim 1 for the production of *syn*-isomers of formula Ia,



in which

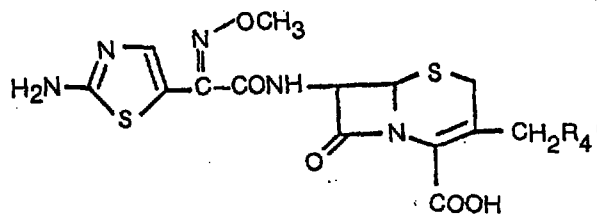
65 R_1 , R_2 and R_4 are as defined and pharmaceutically acceptable salts thereof.



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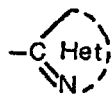
3. A process according to Claim 1, for the production of *syn*-isomers of formula Ib,



10 in which

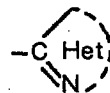
R_4 is acetoxy, 1-methyl-1H-tetrazol-5-yl, or 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl, and pharmaceutically acceptable salts thereof.

4. A process according to any one of Claims 1 to 3, in which, in the *syn*-isomer of formula II,



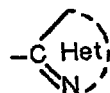
is 2-pyridyl.

5. A process according to any one of Claims 1 to 3, in which, in the *syn*-isomer of formula II,

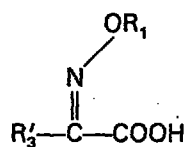


25 is 2-benzthiazolyl.

6. A process for the production of a *syn*-isomer of formula II, stated in Claim 1, in which



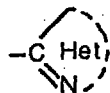
is 2-pyridyl or 2-benzthiazolyl, comprising esterifying a *syn*-isomer of formula IV,



40 in which R_1 and R_3 are as defined in Claim 1.

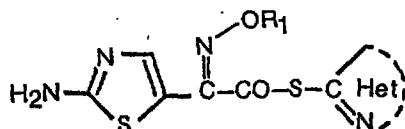
7. A process according to Claim 6, in which the esterification is effected by reaction with 2,2'-dithiopyridine or bis[benzthiazolyl-(2)]disulphide.

8. *Syn*-isomers of formula II, stated in Claim 1, in which

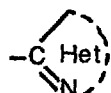


50 is 2-pyridyl or 2-benzthiazolyl.

9. *Syn*-isomers of Claim 8 of formula IIa,



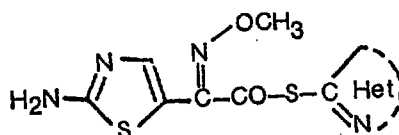
in which R_1 is as defined in claim 1, and



65 is 2-pyridyl or 2-benzthiazolyl.

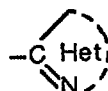


10. *Syn*-isomers of Claim 8 of formula IIb,



IIb

in which



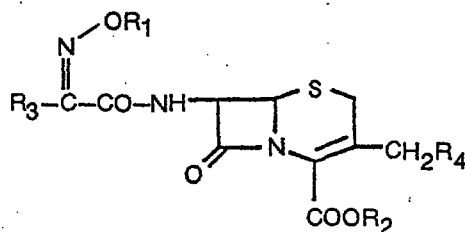
is 2-pyridyl or 2-benzthiazolyl.

11. The compounds of Claim 8 which is 2-(2-aminothiazol-4-yl)-2-*syn*-methoximinoacetic acid 2-pyridyl thioester.

12. The compound of Claim 8 which is 2-(2-aminothiazol-4-yl)-2-*syn*-methoximinoacetic acid 2-benzthiazolyl thioester.

Claims for the Contracting State: AT

1. A process for the production of *syn*-isomers of formula I,



in which

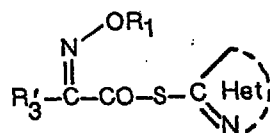
R_1 is hydrogen, alkyl, phenalkyl, carbalkoxyalkyl, acyl or carboxyalkyl,

R_2 is hydrogen, pivaloyloxymethyl or a carboxy protecting group,

R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino or azido, and

R_4 is hydrogen, acetoxy, carbamoyloxy or $-S-Y$, in which Y is a heterocyclic ring which may be substituted;

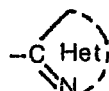
and pharmaceutically acceptable salts thereof, which comprises reacting a *syn*-isomer of formula II,



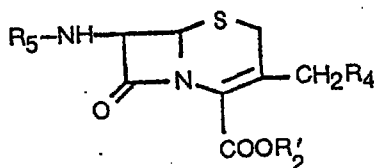
in which

R_1 is as defined above,

R_3 is a 5-membered oxygen- or sulphur-containing heterocyclic ring, which may be substituted by amino, protected amino, or azido, and



represents a 5- or 6-membered heterocyclic ring, which may contain in addition to the nitrogen atom, one or two further hetero atoms, selected from oxygen, nitrogen and sulphur, and which may be substituted or fused to a benzene ring which may itself be substituted, with a compound of formula III,



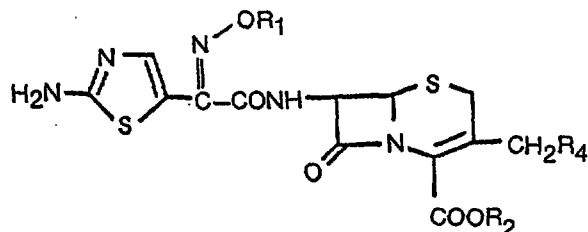
in which



19

R_2 and R_4 are as defined above, and
 R_5 is hydrogen or an amino protecting group,
 where required, deprotecting the resulting product, and, where required, converting a resulting product
 in which R_2 is hydrogen into a salt thereof or *vice versa*.

2. A process according to Claim 1 for the production of *syn*-isomers of formula Ia,

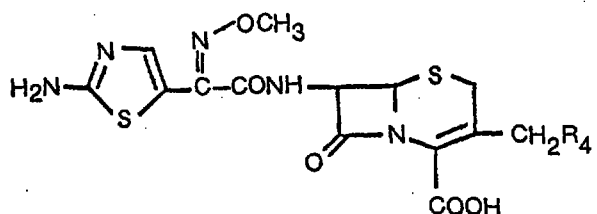


Ia

in which

R_1 , R_2 and R_4 are as defined and pharmaceutically acceptable salts thereof.

3. A process according to Claim 1, for the production of *syn*-isomers of formula Ib,

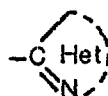


Ib

in which

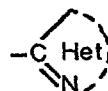
R_4' is acetoxy, 1-methyl-1H-tetrazol-5-yl, or 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl, and pharmaceutically acceptable salts thereof.

4. A process according to any one of Claims 1 to 3, in which, in the *syn*-isomer of formula II,



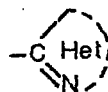
is 2-pyridyl.

5. A process according to any one of Claims 1 to 3, in which, in the *syn*-isomer of formula II,

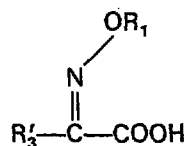


is 2-benzthiazolyl.

6. A process for the production of a *syn*-isomer of formula II, stated in Claim 1, in which



is 2-pyridyl or 2-benzthiazolyl, comprising esterifying a *syn*-isomer of formula IV,



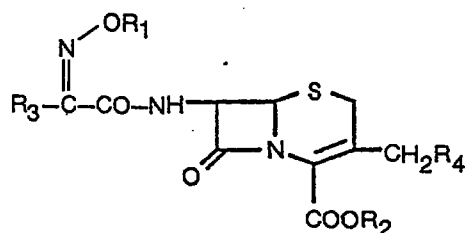
IV

in which R_1 and R_3' are as defined in Claim 1.

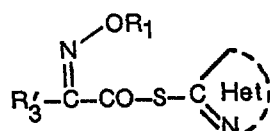
7. A process according to Claim 6, in which the esterification is effected by reaction with 2,2'-dithiopyridine or bis[benzthiazolyl-(2)]disulphide.



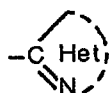
1. Verfahren zur Herstellung von syn-Isomeren der Formel I,



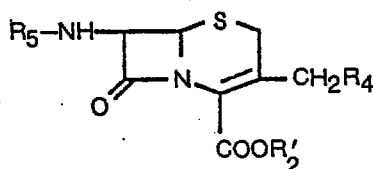
- 15 worin R_1 für Wasserstoff, eine Alkyl-, eine Phenalkyl-, eine Carbalkoxyalkyl-, eine Acyl- oder eine Carboxyalkylgruppe, R_2 für Wasserstoff, die Pivaloyloxymethyl- oder eine Carboxylschutzgruppe, R_3 für einen Sauerstoff oder Schwefel enthaltenden, gegebenenfalls durch die Amino- oder Azidogruppe substituierten 5-gliedrigen Heterocyclus und R_4 für Wasserstoff, die Acetoxy-, die Carbamoyloxy- oder eine S—Y-Gruppe stehen, wobei Y einen gegebenenfalls substituierten Heterocyclus bedeutet, und
20 ihrer pharmazeutisch verträglichen Salze, bestehend aus Umsetzung eines syn-Isomeren der Formel II,



worin R_1 obige Bedeutung besitzt, R'_3 für einen Sauerstoff oder Schwefel enthaltenden 5-gliedrigen Heterocyclus, der durch Amino, geschütztes Amino oder Azido substituiert sein kann, und

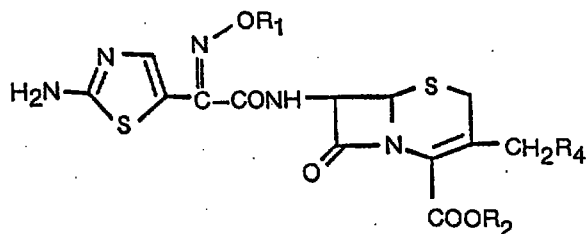


- 35 für einen 5- oder 6-gliedrigen Heterocyclus steht, der neben dem Stickstoffatom noch weitere oder 2 Heteroatome (ausgewählt aus O, N und/oder S) enthalten und der substituiert oder mit einem gegebenenfalls substituierten Benzolring kondensiert sein kann, mit einer Verbindung der Formel III,



worin R_2 und R_4 obige Bedeutung besitzen und R_5 für Wasserstoff oder eine Aminoschutzgruppe steht, und gewünschtenfalls Entschützung des Endprodukts und gewünschtenfalls Umwandlung von Endprodukten, worin R_2 für Wasserstoff steht, in ihre Salze und umgekehrt.

2. Verfahren nach Anspruch 1 zur Herstellung von syn-Isomeren der Formel Ia,

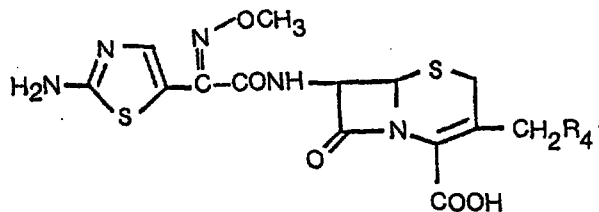


worin R_1 , R_2 und R_4 obige Bedeutung besitzen, und ihrer pharmazeutisch verträglichen Salze.

3. Verfahren nach Anspruch 1 zur Herstellung von syn-Isomeren der Formel Ib,



(21)

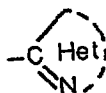


Ib

10 worin R_4 für Acetoxy, 1-Methyl-1H-tetrazol-5-yl oder 2,5-Dihydro-6-hydroxy-2-methyl-5-oxo-as
triazin-3-yl steht, und ihrer pharmazeutisch verträglichen Salze.

4. Verfahren nach einem der Ansprüche 1 bis 3, worin im syn-Isomeren der Formel II

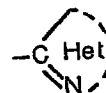
15



für 2-Pyridyl steht.

5. Verfahren nach einem der Ansprüche 1 bis 3, worin im syn-Isomeren der Formel II

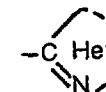
20



für 2-Benzthiazolyl steht.

25

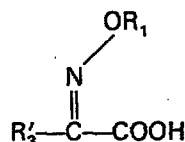
6. Verfahren zur Herstellung eines syn-Isomeren der Formel II, wie im Anspruch 1 angegeben, worin



30

für 2-Pyridyl oder 2-Benzthiazolyl steht, bestehend aus Veresterung eines syn-Isomeren der Formel IV,

35



IV

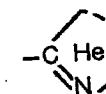
40

worin R_1 und R_3' die im Anspruch 1 angegeben Bedeutung besitzen.

7. Verfahren nach Anspruch 6, worin die Veresterung durch Reaktion mit 2,2'-Dithiopyridin oder bis[Benzthiazol-(2)]disulfid durchgeführt wird.

8. Syn-Isomere der Formel II wie im Anspruch 1 angegeben, worin

45

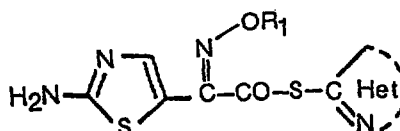


für 2-Pyridyl oder 2-Benzthiazolyl steht.

50

9. Syn-Isomere des Anspruchs 8 der Formel IIa,

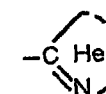
55



IIa

worin R_1 die im Anspruch 1 angegebene Bedeutung besitzt und

60

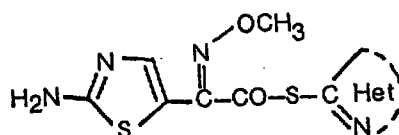


für 2-Pyridyl oder 2-Benzthiazolyl steht.

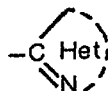
65

10. Syn-Isomere des Anspruchs 8 der Formel IIb,





worin



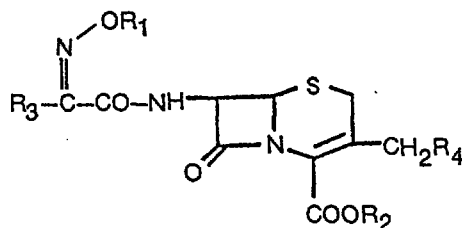
für 2-Pyridyl oder 2-Benzthiazolyl steht.

11. Die Verbindung des Anspruchs 8, welche 2-(2-Aminothiazol-4-yl)-2-syn-methoximino-essigsäure-2-pyridyl-thiolester ist.

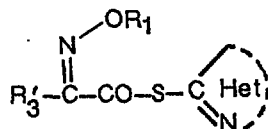
12. Die Verbindung des Anspruchs 8, welche 2-(2-Aminothiazol-4-yl)-2-syn-methoximino-essigsäure-2-benzthiazolyl-thiolester ist.

Patentansprüche für den Vertragsstaat: AT

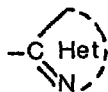
1. Verfahren zur Herstellung von syn-Isomeren der Formel I,



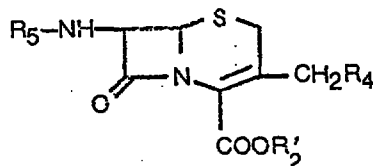
worin R_1 für Wasserstoff, eine Alkyl-, eine Phenalkyl-, eine Carbalkoxyalkyl-, eine Acyl- oder eine Carboxyalkylgruppe, R_2 für Wasserstoff, die Pivaloyloxymethyl- oder eine Carboxylschutzgruppe, R_3 für einen Sauerstoff oder Schwefel enthaltenden, gegebenenfalls durch die Amino- oder Azidogruppe substituierten 5-gliedrigen Heterocyclus und R_4 für Wasserstoff, die Acetoxy-, die Carbamoyloxy- oder einen S—Y-Gruppe stehen, wobei Y einen gegebenenfalls substituierten Heterocyclus bedeutet, und ihrer pharmazeutisch verträglichen Salze, bestehend aus Umsetzung eines syn-Isomeren der Formel II,



worin R_1 obige Bedeutung besitzt, R_3' für einen Sauerstoff oder Schwefel enthaltenden 5-gliedrigen Heterocyclus, der durch Amino, geschütztes Amino oder Azido substituiert sein kann, und



für einen 5- oder 6-gliedrigen Heterocyclus steht, der neben dem Stickstoffatom noch weitere oder 2 Heteroatome (ausgewählt aus O, N und/oder S) enthalten und der substituiert oder mit einem gegebenenfalls substituierten Benzolring kondensiert sein kann, mit einer Verbindung der Formel III,

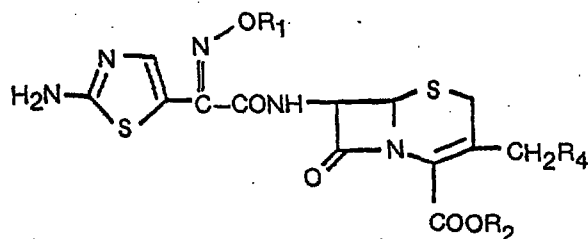


worin R_2 und R_4 obige Bedeutung besitzen und R_5 für Wasserstoff oder eine Aminoschutzgruppe steht, und gewünschtenfalls Entschützung des Endprodukts und gewünschtenfalls Umwandlung von Endprodukten, worin R_2 für Wasserstoff steht, in ihre Salze und umgekehrt.



O 037 380

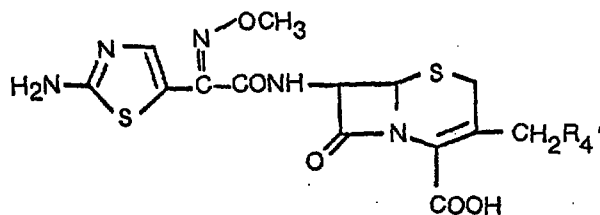
2. Verfahren nach Anspruch 1 zur Herstellung von syn-Isomeren der Formel Ia,



Ia

worin R_1 , R_2 und R_4 obige Bedeutung besitzen, und ihrer pharmazeutisch verträglichen Salze.

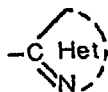
3. Verfahren nach Anspruch 1 zur Herstellung von syn-Isomeren der Formel Ib,



Ib

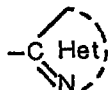
worin R_4' für Acetoxy, 1-Methyl-1H-tetrazol-5-yl oder 2,5-Dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl steht, und ihrer pharmazeutisch verträglichen Salze.

4. Verfahren nach einem der Ansprüche 1 bis 3, worin im syn-Isomeren der Formel II



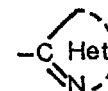
für 2-Pyridyl steht.

5. Verfahren nach einem der Ansprüche 1 bis 3, worin im syn-Isomeren der Formel II

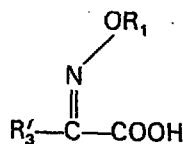


für 2-Benzthiazolyl steht.

6. Verfahren zur Herstellung eines syn-Isomeren der Formel II, wie im Anspruch 1 angegeben, worin



für 2-Pyridyl oder 2-Benzthiazolyl steht, bestehend aus Veresterung eines syn-Isomeren der Formel IV,



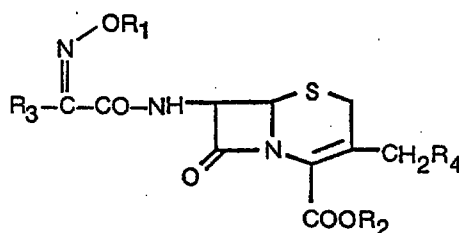
IV

worin R_1 und R_3 die im Anspruch 1 angegebene Bedeutung besitzen.

7. Verfahren nach Anspruch 6, worin die Veresterung durch Reaktion mit 2,2'-Dithiopyridin oder bis[Benzthiazol-(2)]disulfid durchgeführt wird.



1. Un procédé de préparation des isomères syn de formule I



dans laquelle

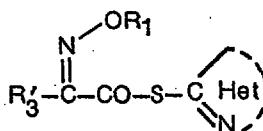
R_1 est l'hydrogène, alkyle, phénalkyle, alcoxycarbonylalkyle, acyle ou carboxyalkyle,

R_2 est l'hydrogène, pivaloyloxyméthyle ou un groupe protecteur du groupe carboxy,

R_3 est un noyau hétérocyclique à 5 chaînons contenant de l'oxygène ou du soufre, qui peut être substitué par amino ou azido, et

R_4 est l'hydrogène, acétoxy, carbamoyloxy de $-S-Y$, dans lequel Y est un noyau hétérocyclique qui peut être substitué;

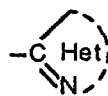
et de leurs sels pharmaceutiquement acceptables, qui comprend la réaction d'un isomère syn de formule II



dans laquelle

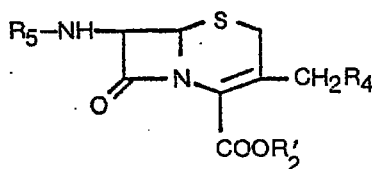
R_1 est tel que défini plus haut,

R_3 est un noyau hétérocyclique à 5 chaînons contenant de l'oxygène ou du soufre, qui peut être substitué par amino, amino protégé, ou azido, et



représente un noyau hétérocyclique à 5 ou 6 chaînons, qui peut contenir en plus de l'atome d'azote, un ou deux autres hétéroatomes choisis parmi l'oxygène, l'azote et le soufre, et qui peut être substitué ou condensé à un noyau benzénique qui peut lui-même être substitué.

avec un composé de formule III

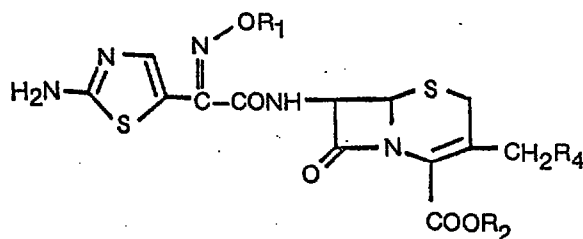


dans laquelle

R_2 et R_4 sont tel que définis plus haut, et

R_5 est l'hydrogène ou un groupe protecteur du groupe amino, lorsque cela est nécessaire, la déprotection du produit résultant, et, si nécessaire, la transformation d'un produit résultant dans lequel R_2 est l'hydrogène en un sel de ce composé ou vice versa.

2. Un procédé selon la revendication 1 de préparation d'isomères syn de formule Ia

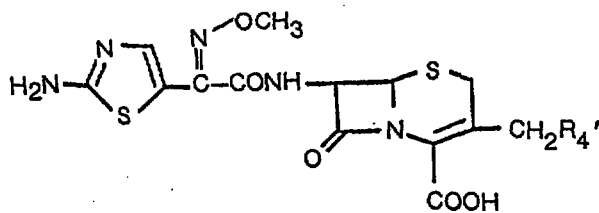


dans laquelle R_1 , R_2 et R_4 sont tels que définis et de leurs sels pharmaceutiquement acceptables.



23

3. Un procédé selon la revendication 1 de préparation d'isomères syn de formule Ib

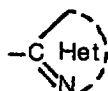


Ib

dans laquelle

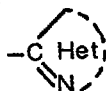
R_4' est acétoxy, 1-méthyl-1H-tétrazole-5-yle, ou 2,5-dihydro-6-hydroxy-2-méthyl-5-oxo-as-triazine-3-yle, et de leurs sels pharmaceutiquement acceptables.

4. Un procédé selon l'une quelconques des revendications 1 à 3, dans lequel, dans l'isomère syn de formule II,



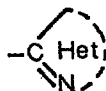
est 2-pyridyle.

5. Un procédé selon l'une quelconque des revendications 1 à 3, dans lequel, dans l'isomère syn de formule II,

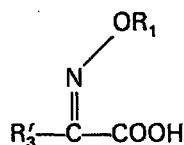


est 2-benzothiazolyle.

6. Un procédé de préparation d'un isomère syn de formule II, indiqué à la revendication 1, dans lequel



est 2-pyridyle ou 2-benzothiazolyle, lequel procédé comprend l'estérification d'un isomère syn de formule IV

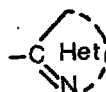


IV

dans laquelle R_1 et R_3 sont tels que définis à la revendication 1.

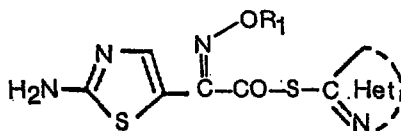
7. Un procédé selon la revendication 6, dans lequel l'estérification est effectuée par réaction avec la 2,2'-dithiopyridine ou le disulfure de bis(2-benzothiazolyle).

8. Des isomères syn de formule II, indiqués à la revendication 1, dans lesquels



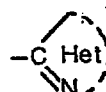
est 2-pyridyl ou 2-benzothiazolyle.

9. Des isomères syn de la revendication 8 de formule IIa



IIa

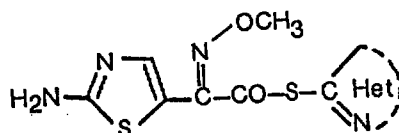
dans laquelle R_1 est tel que défini à la revendication 1, et



est 2-pyridyle ou 2-benzothiazolyle.

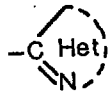


10. Des isomères syn de la revendication 8 de la formule IIb



IIb

dans laquelle



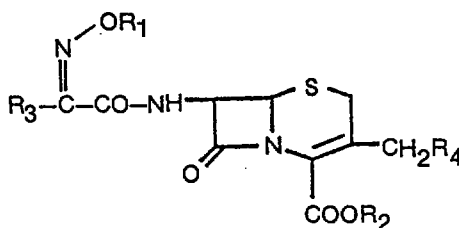
est 2-pyridyle ou 2-benzothiazolye.

11. Le composé de la revendication 8 qui est le thioester 2-pyridylique de l'acide 2-(2-aminothiazole-4-yl)-2-syn-méthoximinoacétique.

12. Le composé de la revendication 8 qui est le thioester 2-benzothiazolique de l'acide 2-(2-aminothiazole-4-yl)-2-syn-méthoxyiminoacétique.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation des isomères syn de formule I



dans laquelle

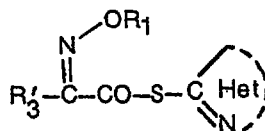
R₁ est l'hydrogène, alkyle, phénalkyle, alcoxycarbonylalkyle, acyle ou carboxyalkyle,

R₂ est l'hydrogène, pivaloyloxyméthyle ou un groupe protecteur du groupe carboxy,

R₃ est un noyau hétérocyclique à 5 chaînons contenant de l'oxygène ou du soufre, qui peut être substitué par amino ou azido, et

R₄ est l'hydrogène, acétoxy, carbamoyloxy de —S—Y, dans lequel Y est un noyau hétérocyclique qui peut être substitué;

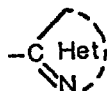
et de leurs sels pharmaceutiquement acceptables, qui comprend la réaction d'un isomère syn de formule II



dans laquelle

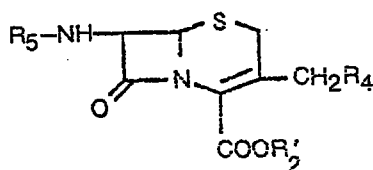
R₁ est tel que défini plus haut,

R₃ est un noyau hétérocyclique à 5 chaînons contenant de l'oxygène ou du soufre, qui peut être substitué par amino, amino protégé, ou azido, et



représente un noyau hétérocyclique à 5 ou 6 chaînons, qui peut contenir en plus de l'atome d'azote, un ou deux autres hétéroatomes choisis parmi l'oxygène, l'azote et le soufre, et qui peut être substitué ou condensé à un noyau benzénique qui peut lui-même être substitué.

avec un composé de formule III



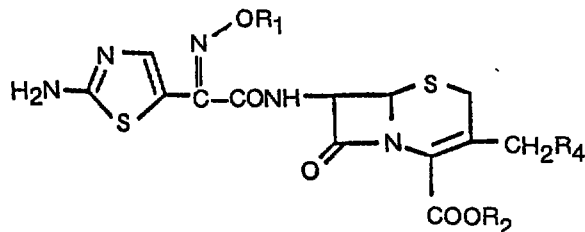
dans laquelle

R_2 et R_4 sont tel que définis plus haut, et

R_5 est l'hydrogène ou un groupe protecteur du groupe amino, lorsque cela est nécessaire, la déprotection du produit résultant, et, si nécessaire, la transformation d'un produit résultant dans lequel

5 R_2 est l'hydrogène en un sel de ce composé ou vice versa.

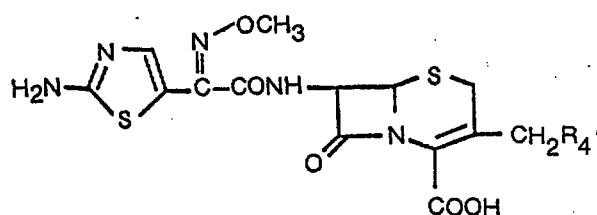
2. Un procédé selon la revendication 1 de préparation d'isomères syn de formule Ia



Ia

dans laquelle R_1 , R_2 et R_4 sont tels que définis et de leurs sels pharmaceutiquement acceptables.

3. Un procédé selon la revendication 1 de préparation d'isomères syn de formule Ib

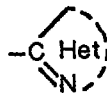


Ib

dans laquelle

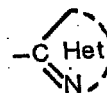
30 R_4' est acétoxy, 1-méthyl-1H-tétrazole-5-yle, ou 2,5-dihydro-6-hydroxy-2-méthyl-5-oxo-as-triazine-3-yle, et de leurs sels pharmaceutiquement acceptables.

4. Un procédé selon l'une quelconque des revendications 1 à 3, dans lequel, dans l'isomère syn de formule II,



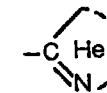
est 2-pyridyle.

5. Un procédé selon l'une quelconque des revendications 1 à 3, dans lequel, dans l'isomère syn de formule II,

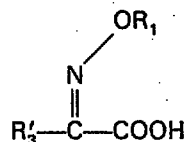


est 2-benzothiazolylo.

6. Un procédé de préparation d'un isomère syn de formule II, indiqué à la revendication 1, dans lequel



est 2-pyridyle ou 2-benzothiazolylo, lequel procédé comprend l'estérification d'un isomère syn de formule IV



IV

dans laquelle R_1 et R_3 sont tels que définis à la revendication 1.

7. Un procédé selon la revendication 6, dans lequel l'estérification est effectuée par réaction avec la 2,2'-dithiopyridine ou le disulfure de bis(2-benzothiazolylo).

