

# PATENT SPECIFICATION

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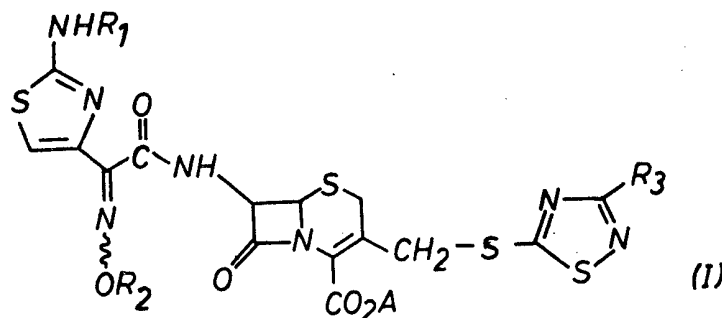
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(54) NEW OXIME DERIVATIVES OF 3-THIADIAZOLYL  
 THIOMETHYL-7-AMINOTHIAZOLYLACETAMIDO-  
 CEPHALOSPORANIC ACID, PROCESSES FOR  
 PREPARING THEM AND PHARMACEUTICAL  
 COMPOSITIONS CONTAINING THEM

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7<sup>eme</sup>, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new oxime derivatives of 3 - thiadiazolylthiomethyl - 7 - aminothiazolylacetamido - cephalosporanic acid, processes for preparing them and pharmaceutical compositions containing them.

In one aspect this invention provides the new 3 - thiadiazolylthiomethyl - 7 - aminothiazolylacetamido - cephalosporanic acid oxime derivatives of the general formula:



wherein R<sub>1</sub> represents a hydrogen atom, a group removable by acid hydrolysis or by hydrogenolysis, or a chloroacetyl group, R<sub>2</sub> represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, R<sub>3</sub> represents an alkyl radical having from 1 to 4 carbon atoms or an alkoxy radical having from 1 to 4 carbon atoms, A represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom, an equivalent of a substituted ammonium group or an ester-forming group removable by acid hydrolysis or by hydrogenolysis, with the proviso that A does not represent an ester-forming group removable by acid hydrolysis or by hydrogenolysis when R<sub>1</sub> represents a hydrogen atom, the compound being in the form of the *syn* or the *anti* isomer.

It is to be understood that the wavy line in general formula I and other formulae hereinafter indicates that the group OR<sub>2</sub> can be in either of the *syn* and *anti* positions.

The term "a group removable by acid hydrolysis or by hydrogenolysis" is used to mean a group that can be readily cleaved from the remainder of the molecule. Examples of such groups that R<sub>1</sub> can represent include the *t*-butoxycarbonyl, trityl, benzyl, benzhydryl, trichloroethyl, carbobenzyloxy, formyl, trichloroethoxycarbonyl and 2 - tetrahydropyranyl groups. R<sub>1</sub>, preferably

represents a *t*-butoxycarbonyl, trityl, benzhydryl, trichloroethyl or carbobenzyloxy group.

$R_2$  may *inter alia* represent an alkyl, alkenyl or alkynyl group, and thus, for example, may represent a methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *sec*-butyl, *t*-butyl, vinyl, propenyl, butenyl, ethynyl or propargyl radical.

The compounds of general formula I may be acids (when A represents a hydrogen atom), salts thereof with alkali metals, alkaline-earth metals, magnesium or organic amines or esters thereof. The salts are a preferred group of compounds of the invention. When the compounds are in the form of salts formed with polyvalent cations A represents an equivalent of the cation—that is to say, the fraction of the cation corresponding to a single valence. Preferred salts of general formula I are those wherein A represents a sodium, potassium or lithium atom, an equivalent of a calcium or magnesium atom or a substituted ammonium group derived from trimethylamine, triethylamine, methylamine, propylamine, N,N-dimethylethanolamine or tris-(hydroxymethyl)-aminomethane - [2-amino - 2-hydroxymethyl - 1,3-propanediol].

A preferred group of esters are those compounds of general formula I wherein A represents a benzhydryl, *t*-butyl, benzyl, *p*-methoxybenzyl or trichloroethyl radical.

$R_3$  may, for example, represent a methyl, ethyl, propyl, *isopropyl*, *n*-butyl, *sec*-butyl, *t*-butyl, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *sec*-butoxy or *t*-butoxy radical.

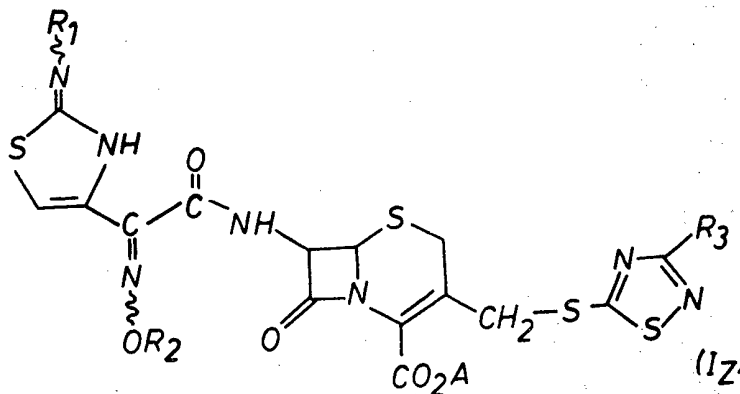
Particularly preferred compounds of general formula I are those wherein the  $OR_2$  group is in the *syn* position; and those wherein  $R_1$  represents a trityl group or a hydrogen atom,  $R_2$  represents a methyl radical,  $R_3$  represents a methyl or methoxy radical and A represents a hydrogen atom or a sodium atom.

The compounds of general formula I described hereinafter in the examples are especially preferred and particularly:

7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - 3 - [(3 - methyl - 1,2,4 - thiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, and salts thereof formed with alkali metals, alkaline-earth metals, magnesium or organic amines; and

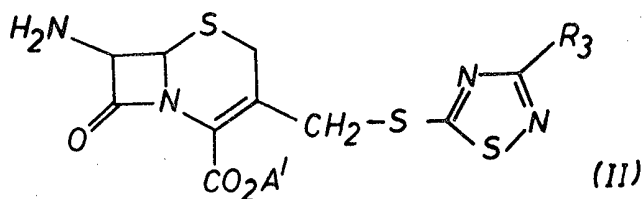
7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - 3 - [(3 - methoxy - 1,2,4 - thiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, and salts thereof formed with alkali metals, alkaline-earth metals, magnesium or organic amines.

It is to be understood that the compounds of general formula I may exist either in the form indicated by formula I or in the form of products of the following general formula:

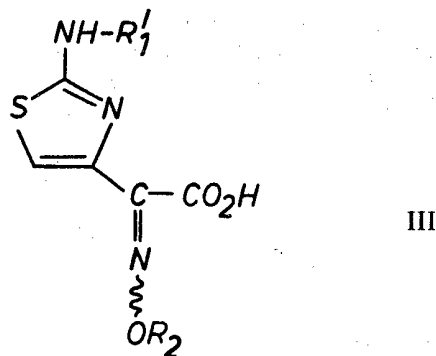


wherein  $R_1$ ,  $R_2$ ,  $R_3$  and A are as defined hereinbefore, and the wavy line to the group  $R_1$  indicates that this group may be in the *syn* or the *anti* position.

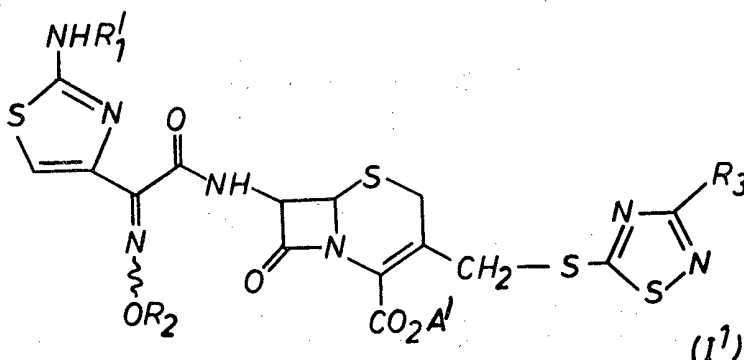
In another aspect this invention provides a process for preparing compounds of general formula I wherein  $R_1$  represents a group removable by acid hydrolysis or by hydrogenolysis or a chloroacetyl radical and A represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or hydrogenolysis, in which process a compound of the general formula:



(wherein  $R_3$  is as defined hereinbefore and  $A'$  represents a hydrogen atom or ester-forming group removable by acid hydrolysis or by hydrogenolysis) is treated with an acid of the general formula:



(wherein  $R_1$  represents a group removable by acid hydrolysis or by hydrogenolysis or a chloroacetyl radical and  $R_2$  is as defined hereinbefore) or with a functional derivative thereof to obtain a product of the general formula:



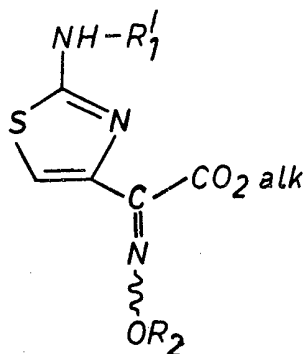
wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $A'$  are as defined hereinbefore.

In a preferred method of carrying out this process the compound of formula II is treated with a functional derivative of the acid of formula III such as the anhydride or the acid chloride. The anhydride of the acid III may be formed *in situ* by the action of *isobutyl* chloroformate or of dicyclohexylcarbodiimide on the acid. It is possible to use other derivatives of the acid III, such as other halides; other anhydrides formed *in situ* by the action of other alkyl chloroformates, of other dicycloalkylcarbodiimides, or of dialkylcarbodiimides; the acid azide; the activated acid amide; or an activated acid ester formed, for example, from hydroxysuccinimide, *p*-nitrophenol or 2,4-dinitrophenol.

When the process comprises reacting a compound of general formula II and a halide of the acid of general formula III or with an anhydride thereof formed with *isobutyl* chloroformate, the reaction is preferably carried out in the presence of a base. The base may be, for example, an alkali-metal carbonate or a tertiary organic base such as *N*-methyl-morpholine, pyridine or a trialkylamine such as triethylamine.

The reaction is preferably carried out in a solvent or a mixture of solvents, and amongst the solvents which may be employed are methylene chloride, chloroform, tetrahydrofuran, acetone or dioxan.



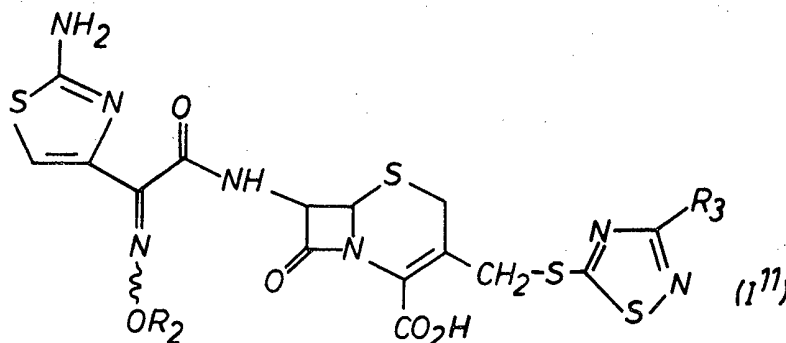


(wherein  $R_1$ ,  $R_2$  and alk are as defined hereinbefore), which product is treated with a base, and then with an acid, to obtain the desired product sought of general formula III. An example of such a preparation is set out hereinafter.

The compounds of general formula B are prepared by the action of diazomethane or of corresponding alkyl halides or sulphates on the ethyl  $\gamma$ -chloro -  $\alpha$  - oxyiminoacetyl acetate described in J. of Medicinal Chemistry 1973, 16 (9), 978.

Compounds of general formula III having the *syn* configuration may be obtained by carrying out the reaction of thiourea on the compound of general formula B a) in an aqueous solvent; b) at ambient temperature using a substantially stoichiometric amount of thiourea and limiting the reaction time to a few hours; or c) using a combination of conditions a) and b).

This invention also provides a process for preparing compounds of general formula I wherein  $R_1$  and A each represent a hydrogen atom, in which process a compound of general formula I' is treated with one or two reagents selected from an acid hydrolysis agent, a hydrogenolysis agent and thiourea so as to convert the substituents  $R_1$  and A' each to a hydrogen atom and thus to obtain a compound of the general formula:



wherein  $R_2$  and  $R_3$  are as defined hereinbefore.

The compounds of general formula I' may be converted into compounds of general formula I'' by choosing the appropriate reagents to replace the substituent  $R_1$  with a hydrogen atom and, when A' is other than a hydrogen atom, also to replace A' with a hydrogen atom.

Thus, the compound of general formula I' is treated with an acid hydrolysis agent when  $R_1$  represents a group removable by acid hydrolysis and when A' represents a hydrogen atom or an ester-forming group removable by acid hydrolysis.

The compound of general formula I' is treated with a hydrogenolysis agent when  $R_1$  represents a group removable by hydrogenolysis and when A' represents a hydrogen atom or an ester-forming group removable by hydrogenolysis.

The compound of general formula I' is treated with both an acid hydrolysis agent and a hydrogenolysis agent when one of substituents  $R_1$  or A' represents a

group removable by acid hydrolysis and the other substituent represents a group removable by hydrogenolysis.

The compound of general formula I' is treated with thiourea alone when R<sub>1</sub>' represents a chloroacetyl radical and when A' represents a hydrogen atom. When R<sub>1</sub>' represents a chloroacetyl radical and A' represents an ester-forming group removable by acid hydrolysis or by hydrogenolysis the compounds of general formula I' are treated with thiourea and with either an acid hydrolysis or a hydrogenolysis agent according to the nature of A'.

The type of reaction taking place in reacting thiourea with a chloroacetyl substituent is similar to that described by Masaki [JACS, 90, 4508 (1968)].

Among the acid hydrolysis agents to which the compounds of formula I' may be subjected, preferred agents are formic acid, trifluoroacetic acid and acetic acid. These acids may be employed in anhydrous form or in aqueous solution. A zinc/acetic acid system may alternatively be used as the acid hydrolysis agent.

Preferably an acid hydrolysis agent such as anhydrous trifluoroacetic acid or aqueous formic or acetic acid is used to eliminate a *t*-butoxycarbonyl or trityl group as substituent R<sub>1</sub>', or to eliminate a benzydryl, *t*-butyl or *p*-methoxybenzyl group as substituent A'.

The zinc/acetic acid system is preferably used to eliminate trichloroethyl groups as substituent R<sub>1</sub>' and/or A'.

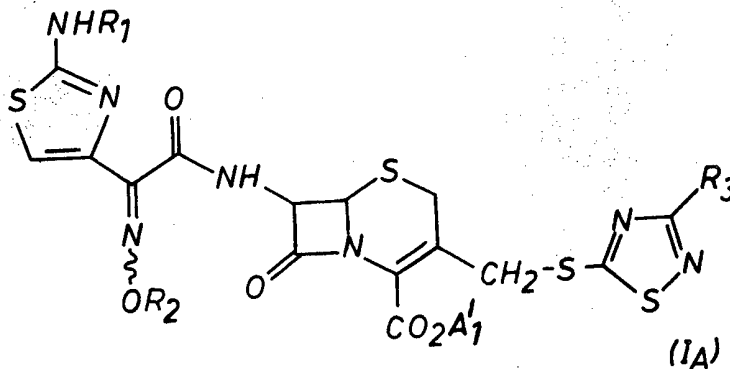
Preferably hydrogen in the presence of a catalyst is used as hydrogenolysis agent to remove a benzydryl or carbobenzyloxy group as substituent R<sub>1</sub>' or to remove benzyl groups as substituent R<sub>1</sub>' and/or A'.

The compounds of general formula I' and I'' may be salified to form compounds of general formula I wherein A represents an alkali metal atom or an equivalent of an alkaline-earth metal atom, a magnesium atom or a substituted ammonium group. This salification may be carried out according to the usual methods employed in forming salts of organic acids. For example, the compounds may be salified by the action on these acids of a mineral base such as sodium or potassium hydroxide, sodium bicarbonate or sodium acetate or of an organic base such as triethylamine.

Obviously the base is chosen having regard to the substituent A which it is desired to introduce. This salification is preferably carried out in a solvent or a mixture of solvents such as water, diethyl ether, methanol, ethanol or acetone. The salts can be obtained from the reaction mixture in amorphous or crystalline form by adopting appropriate separation techniques.

The invention provides a process for the preparation of the compounds of general formula I wherein the OR<sub>2</sub> group is in the *syn* configuration. The process is carried out as described hereinbefore using a compound of general formula III having the OR<sub>2</sub> group in the *syn* position. the compounds I' and I'' obtained in the preparation will then also possess the *syn* configuration.

The invention in a further aspect provides a process for preparing the compounds of the general formula:

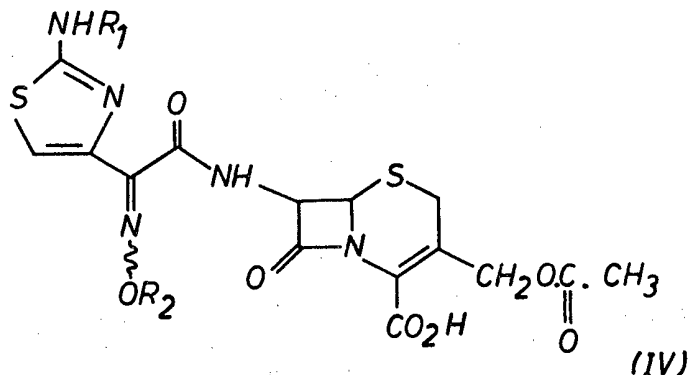


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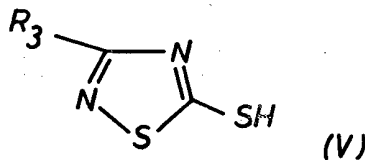
wherein A' represents a hydrogen atom, an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group—being compounds of general formula I wherein A

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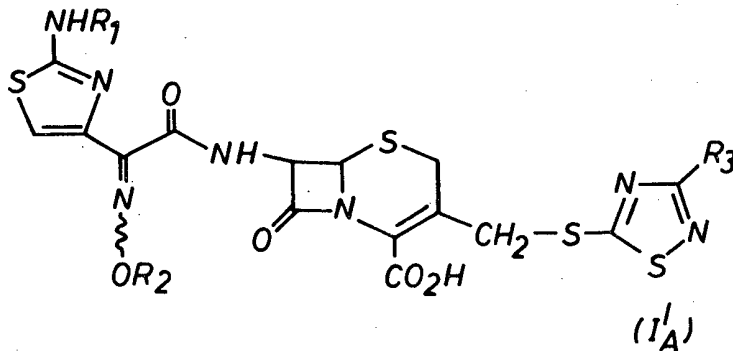
represents  $A'_1$ . Thus, the invention provides a process in which a compound of the general formula:



(wherein  $R_1$  and  $R_2$  are as defined hereinbefore), is treated with a compound of general formula V:



(wherein  $R_3$  is as defined hereinbefore) to give a corresponding compound of the general formula:



(wherein  $R_1$ ,  $R_2$  and  $R_3$  are as defined hereinbefore).

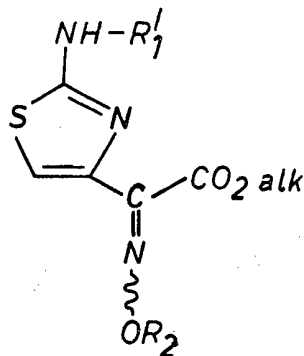
The formed compound  $I'_A$  may be salified to give the compounds of general formula  $I_A$  wherein  $A'_1$  represents an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group.

The reaction of the compound of general formula V with a compound of general formula IV is preferably carried out in a water/acetone mixture, but alternatively other aqueous solvents such as a water/dioxan, water/tetrahydrofuran or water/ethanol mixtures may be used.

The reaction is preferably carried out in the presence of a buffer capable of maintaining a slightly acidic pH, such as a mixture of sodium acid phosphate and sodium bicarbonate, but the reaction may also be carried out without using a buffer.

The salification of the products of formula  $I'_A$  may be carried out according to the usual methods, such as described hereinbefore.

The starting materials of general formula IV may be prepared by the action of an acid of the general formula:



(wherein  $R_1$  and  $R_2$  are as defined hereinbefore) on 7 - aminocephalosporanic acid, this reaction being followed, if necessary, by acid hydrolysis or by hydrogenolysis to give the desired compound of general formula IV. Such a preparation is illustrated by an Example set out hereinafter.

The invention also provides a process for the preparation of compounds of general formula  $I_A$  having the  $OR_2$  group in the *syn* configuration. This process is carried out as described above for the preparation of compound  $I_A$  using a starting material of general formula IV having the  $OR_2$  group in the *syn* position. The products  $I'_A$  and  $I_A$  thus obtained also have the *syn* configuration.

The compounds of general formula I have demonstrated very good antibiotic activity on the one hand against the gram positive bacteria such as the staphylococci and the streptococci, and especially against the penicillin-resistant staphylococci, and on the other hand against the Gram negative bacteria, and especially against the coliform bacteria, the *Klebsiella*, the *Salmonella* and the *Proteus*.

These properties may make the pharmaceutically-acceptable compounds suitable for use as medicaments in the treatment of diseases caused by sensitive microorganisms and especially in the treatment of staphylococcal infections such as staphylococcal septicaemia, malignant facial or skin staphylococcal infections, pyodermitis, septic or suppurating sores, anthrax, phlegmons, erysipelas, acute primary or post-influenza staphylococcal infections, bronchopneumonia and pulmonary suppurations.

These compounds may be also be useful as medicaments in the treatment of colon bacillus infections and associated infections, in infections caused by *Proteus*, by *Klebsiella* and by *Salmonella* and in other diseases caused by Gram negative bacteria.

For use in medicine it is preferred to form the compounds of the invention into pharmaceutical compositions, by combining them with suitable pharmaceutical vehicles.

Accordingly, in a further aspect, this invention provides pharmaceutical compositions containing as active ingredient one or more compounds of general formula I in association with a pharmaceutically-acceptable vehicle.

For use as medicaments, and especially as antibiotic medicaments, the compounds of general formula I wherein A represents a hydrogen atom, an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group, are particularly preferred.

Generally amongst all the compounds of general formula I those wherein the  $OR_2$  group is in the *syn* position have been found preferable over the *anti* isomers.

An especially preferred category of compounds for use as medicaments comprises the compounds of general formula I wherein  $R_1$  represents a hydrogen atom,  $R_2$  represents a methyl radical,  $R_3$  represents a methyl or methoxy radical and A represents a hydrogen atom, as well as the pharmaceutically-acceptable salts of these compounds falling within general formula I, and those compounds having the  $OR_2$  group in the *syn* position are particularly noteworthy. The compounds mentioned specifically in the Examples and particularly those named hereinbefore are most advantageously employed in compositions of this invention.

The description "pharmaceutically acceptable" is used herein to exclude any possibility that the nature of the vehicle, considered of course in relation to the



route by which the composition is to be administered, could be harmful to a patient treated with the composition.

The compositions can be administered orally, rectally, by an intramuscular or parenteral route, or locally by topical application to the skin or mucous membrane. The choice of a suitable vehicle for the route chosen is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations, but the vehicle may, for example, be chosen from the following categories:—

a) the ingestible excipient of a tablet, such as a sublingual or coated tablet; the ingestible container of a capsule or cachet; the ingestible pulverulent solid carrier of a powder or granules; or the ingestible liquid medium of a syrup, solution, suspension or elixir;

b) the solid or liquid medium of a paste, cream, ointment, gel or unguent, or the liquified propellant gas of an aerosol;

c) a sterile injectable liquid solution or suspension medium; or

d) a base material of a suppository.

The particular vehicles employed will generally be formed of one or more of the excipients commonly employed in pharmaceutical compositions. These excipients may be solid or liquid and may include a wide range of organic and inorganic solids, and aqueous and non-aqueous liquids; examples include talc, gum arabic, starch, lactose, magnesium stearate, cocoa butter, paraffin derivatives, glycols or other fatty substances of animal or vegetable origin. These excipients may be compounded with one or more wetting, dispersing or emulsifying agents and/or one or more preservatives.

The dosage of the active ingredient to be administered to a patient will of course vary with the compound concerned, the complaint and the patient being treated and the route of administration chosen. By way of illustration it may be said that a desirable dosage in an adult would be from 0.250 to 4 g when using the product of Example 2 or 4 administered by oral route, or from 0.500 g to 1 g administered three times daily by intramuscular route.

The following Examples and Formulations are now given, though only by way of illustration, to show certain aspects of the invention.

#### Example 1

7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyiminoacetamido] - 3 - [(3 - methoxy - 1,2,4 - thiaziazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer

60 cm<sup>3</sup> of methylene chloride and 10 cm<sup>3</sup> of 2N hydrochloric acid were added to 3.36 g of the sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyiminoacetic acid, *syn* isomer, and the mixture decanted, washed with water, dried and brought to dryness to yield the free acid.

The residue obtained above was dissolved in 30 cm<sup>3</sup> of methylene chloride and 950 mg of dicyclohexylcarbodiimide was added. The mixture was agitated for one hour and the precipitate obtained (750 mg of dicyclohexylurea) then vacuum-filtered off. The filtrate was cooled to -10°C and to it was added, all at once, a solution of 1.3 g of 7 - amino - 3 - [(3 - methoxy - 1,2,4 - thiaziazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid in 12 cm<sup>3</sup> of chloroform and 1.3 cm<sup>3</sup> of triethylamine. This mixture was allowed to return to ambient temperature, washed with 2N hydrochloric acid and then with water, dried, filtered, and brought to dryness to obtain 4.8 g of a crude product. This product was purified by chromatography on 500 g of silica, eluting with a mixture of acetone and water (90:10). 1.6 g of purified product was isolated, R<sub>f</sub>=0.45, and this was further purified by chromatographing a second time on 160 g of silica to give 1.1 g of pure product.

The sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyiminoacetic acid, *syn* isomer, used at the start of this Example 1, is described in Belgian Patent 850,662. It was prepared as follows:

Stage A: ethyl  $\gamma$ -chloro- $\alpha$ -methoxyiminoacetylacetate:

22.5 g of ethyl  $\gamma$ -chloro- $\alpha$ -oximinoacetylacetate was added to 100 cm<sup>3</sup> of methylene chloride, and the mixture was cooled in an ice bath and slowly under agitation 275 cm<sup>3</sup> of a fresh solution of diazomethane (containing 21.6 g/l) was added. This was left in contact for five minutes and then the excess diazomethane was destroyed with a little alumina. The mixture was then concentrated, and

purified by eluting on silica with methylene chloride to give 11.93 g of the desired product.

State B: ethyl 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetate:

1 g of ethyl  $\gamma$ -chloro- $\alpha$ -methoxyiminoacetylacetate, 3 cm<sup>3</sup> of absolute ethanol and 0.42 g of crushed thiourea were mixed and then agitated at ambient temperature for about two hours. The reaction mixture was diluted with 60 cm<sup>3</sup> of ether, and the hydrochloride obtained was crystallised out. The mixture was agitated, and the hydrochloride was vacuum-filtered off, washed with ether, and dried to obtain 685 mg of hydrochloride. This was dissolved in 4 cm<sup>3</sup> of water at 50°C, potassium acetate was added until pH 6 was reached and the amine released crystallised out. The whole was cooled, vacuum-filtered, washed with water and dried to obtain 270 mg of the desired product. M.Pt.=161°C.

The product had the *syn* configuration.

NMR (CDCl<sub>3</sub>, 60 MHz): 4 ppm (NOCH<sub>3</sub>); 6.7 ppm (proton of the thiazole ring).

Stage C: ethyl 2-(2-tritylamino-4-thiazolyl)-2-methoxyiminoacetate, *syn* isomer:

4.6 g of the product prepared according to the previous Stage were dissolved, at 30°C, in 92 cm<sup>3</sup> of the methylene chloride. The solution was cooled to -10°C, 2.9 cm<sup>3</sup> of triethylamine were added, the solution was cooled again to -35°C, then over 15 minutes 6.1 g of trityl chloride were added and the mixture was allowed to return to ambient temperature—that is, after two hours thirty minutes in all. The whole was washed with water, then with 0.5N hydrochloric acid and finally with sodium acetate in water, then it was dried, concentrated, taken up with ether, concentrated again, dissolved in methanol, and water and ether then added. Crystallisation was allowed to take place, and after vacuum-filtering, washing with ether, 6.15 g of the desired product were obtained. M.Pt.=120°C.

State D: sodium salt of 2-(2-tritylamino-4-thiazolyl)-2-methoxyiminoacetic acid, *syn* isomer:

7.01 g of the ester obtained in Stage C were dissolved in 35 cm<sup>3</sup> of dioxan. The solution was heated to 110°C in an oil bath and over 5 minutes 9 cm<sup>3</sup> of 2N sodium hydroxide were added and the solution left for 30 minutes at reflux under agitation. The sodium salt crystallised out. The mixture was cooled and the salt vacuum-filtered off, washed with dioxan and then with ether to obtain a first yield of 5.767 g of salt. The mother liquor was concentrated to obtain a second yield of 1.017 g—that is, 6.784 g of sodium salt in all.

The 7-amino-3-[(3-methoxy-1,2,4-thiadiazol-5-yl)-thiomethyl]-ceph-3-em-4-carboxylic acid was prepared as follows:

Stage A: 3-methoxy-5-mercapto-1,2,4-thiadiazole

A suspension of 6.16 g of crushed sodium hydrosulphide in 300 cm<sup>3</sup> of ethanol was cooled to 0°C and drop by drop 15 g of 3-methoxy-5-chloro-1,2,4-thiadiazole were added. The mixture was agitated for 3 hours at 0°C, then maintained for one night in an ice box, after which it was filtered and washed with methylene chloride to obtain 13.6 g of a crystalline mixture. This was chromatographed on silica with an eluant constituted by chloroform and methanol (95:5) to obtain 3 g of the product sought (Rf=0.35). This product was dissolved in 150 cm<sup>3</sup> of methylene chloride, with heating, then filtered and concentrated until crystallisation occurred.

The whole was left for one night in the ice box, then the crystals were vacuum-filtered off, washed with methylene chloride and dried to obtain 2.6 g of the desired product in all. M.Pt.=146°C.

Stage B: 7-amino-3-[(3-methoxy-1,2,4-thiadiazol-5-yl)-thiomethyl]-ceph-3-em-4-carboxylic acid

Under nitrogen, 2.72 g of 7-aminocephalosporanic acid, 27 cm<sup>3</sup> of distilled water, 840 mg of sodium bicarbonate and 1.48 g of 3-methoxy-5-mercapto-1,2,4-thiadiazole were mixed, and the mixture was agitated for 5 hours at 60°C. Then 0.74 g more of 3-methoxy-5-mercapto-1,2,4-thiadiazole were added and the whole agitated for 2 hours at 60°C, acidified to pH 4 with acetic acid, vacuum-filtered, washed with water, then with acetone and dried to obtain 2.2 g of crude product.

The product was purified by dissolving it in a solution of sodium acid carbonate, then treating it with charcoal and filtering. The filtrate was acidified with acetic acid, vacuum-filtered, washed with water and with acetone and then dried to obtain 1.3 g of the desired product.

5 Example 2 5  
7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyiminoacetamido] - 3 - [(3 - methoxy - 1,2,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer

10 5.5 cm<sup>3</sup> of 50% aqueous formic acid were heated to 55°C. 1.1 g of the product obtained in Example 1 were added and the whole was heated for 25 minutes at 55—60°C. The precipitate of triphenylcarbinol (390 mg) was vacuum-filtered off. 10

15 The filtrate was brought to dryness, and then made into a paste with ethanol, vacuum-filtered, washed with ethanol and dried to obtain 470 mg of a product, which was again made into a paste this time with water, then vacuum-filtered and dried to obtain 330 mg of the desired product. 15

Microanalysis: C<sub>17</sub>H<sub>17</sub>N<sub>7</sub>O<sub>6</sub>S<sub>4</sub>

calculated:	C% 37.56	H% 3.15
found:	37.4	3.2

Ultra-violet spectrum (in ethanol and N/10 hydrochloric acid):

20 inflexion: 240 nm E<sub>1</sub><sup>1</sup>=310 ε=17,000 20  
max: 270 nm E<sub>1</sub><sup>1</sup>=423 ε=23,000  
inflexion: 280 nm E<sub>1</sub><sup>1</sup>=403

25 Example 3 25  
7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - 3 - [(3 - methyl - 1,2,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer

30 60 cm<sup>3</sup> of methylene chloride were added to 2.7 g of the sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyaminoacetic acid, *syn* isomer. The whole was decanted, washed with water, dried and brought to dryness. 30

35 The formed oily residue was dissolved in 30 cm<sup>3</sup> of methylene chloride and 690 mg of dicyclohexylcarbodiimide were added, and the whole was agitated for one hour at ambient temperature, then the dicyclohexylurea precipitate formed (570 mg) was vacuum-filtered off. 35

40 The filtrate was cooled to -10°C and to it was added, all at once, 1 g of 7 - amino - 3 - [(3 - methyl - 1,2,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid in 10 cm<sup>3</sup> of methylene chloride and 1 cm<sup>3</sup> of triethylamine. The whole was allowed to return to ambient temperature over one hour thirty minutes, then washed with normal hydrochloric acid, washed with water, dried, filtered and brought to dryness. The residue was taken up in 10 cm<sup>3</sup> of dioxan and 1 cm<sup>3</sup> of water and to this solution 3 cm<sup>3</sup> of sodium bicarbonate in saturated solution were added. This was left for 30 minutes under agitation and part of the starting sodium salt of the acid precipitated out, and was vacuum-filtered off and dried to obtain 580 mg of the salt. The filtrate was brought to dryness, taken up with 20 cm<sup>3</sup> of methylene chloride, washed with water, then with normal hydrochloric acid, dried, filtered and brought to dryness to obtain 1.95 g of the desired product. This product was made into a paste in ether, vacuum-filtered and dried to obtain 1.7 g of purified product. The product was chromatographed on 450 g of silica using an eluant of acetone containing 10% of water to obtain 1.2 g of the desired product which was dissolved in 4 cm<sup>3</sup> of ethyl acetate. The product was finally precipitated by adding a few cubic centimeters of ether to obtain 940 mg of pure product. 45

50 The 7 - amino - 3 - [(3 - methyl - 1,2,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid used at the start of Example 3 was prepared as follows: 50

55 Under nitrogen, 2.72 g of 7 - aminocephalosporanic acid, 27 cm<sup>3</sup> of distilled water and 0.84 g of sodium acid carbonate were mixed. Partial dissolution was obtained, then 1.45 g of 3 - methyl - 5 - mercapto - 1,3,4 - thiadiazole were added, and the whole agitated for 4 hours 30 minutes at a temperature of 60—70°C. The reaction mixture was then acidified with acetic acid to pH 4, and vacuum- 55



hydrocarbyl radical having from 1 to 4 carbon atoms,  $R_3$  represents an alkyl radical having from 1 to 4 carbon atoms or an alkoxy radical having from 1 to 4 carbon atoms, A represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom, an equivalent of a substituted ammonium group or an ester-forming group removable by acid hydrolysis or by hydrogenolysis, with the proviso that A does not represent an ester-forming group removable by acid hydrolysis or by hydrogenolysis when  $R_1$  represents a hydrogen atom, the compound being in the form of the *syn* or the *anti* isomer.

2. A compound as claimed in Claim 1, wherein  $R_1$  represents a *t*-butoxycarbonyl, trityl, benzhydryl, trichloroethyl or carbobenzyloxy group.

3. A compound as claimed in Claim 1 or Claim 2, wherein A represents a hydrogen atom, an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group.

4. A compound as claimed in Claim 3, in which A represents an equivalent of a substituted ammonium group derived from trimethylamine, triethylamine, methylamine, propylamine, N,N - dimethylethanolamine or tris - (hydroxymethyl) - aminomethane.

5. A compound as claimed in Claim 1 or Claim 2, wherein A represents a benzhydryl, *t* - butyl, benzyl, *p* - methoxybenzyl or trichloroethyl radical.

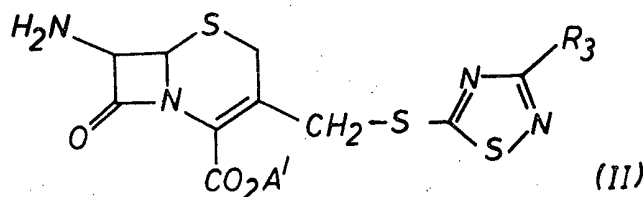
6. A compound as claimed in any of Claims 1 to 5, wherein the  $OR_2$  group is in the *syn* position.

7. A compound as claimed in Claim 1, wherein  $R_1$  represents a trityl group or a hydrogen atom,  $R_2$  represents a methyl radical,  $R_3$  represents a methyl or methoxy radical and A represents a hydrogen atom or a sodium atom.

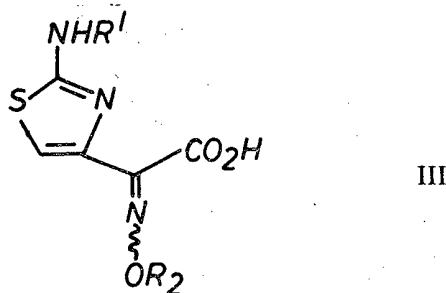
8. 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - 3 - [(3 - methyl - 1,2,4 - thiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid *syn* isomer, or a salt thereof formed with an alkali metal, an alkaline-earth metal, magnesium or an organic amine.

9. 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - 3 - [(3 - methoxy - 1,2,4 - thiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid *syn* isomer, or a salt thereof formed with an alkali metal, an alkaline-earth metal, magnesium or an organic amine.

10. A process for preparing a compound of general formula I as defined in Claim 1, wherein  $R_1$  represents a group removable by acid hydrolysis or by hydrogenolysis or a chloracetyl radical and A represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or hydrogenolysis, in which process a compound of the general formula:

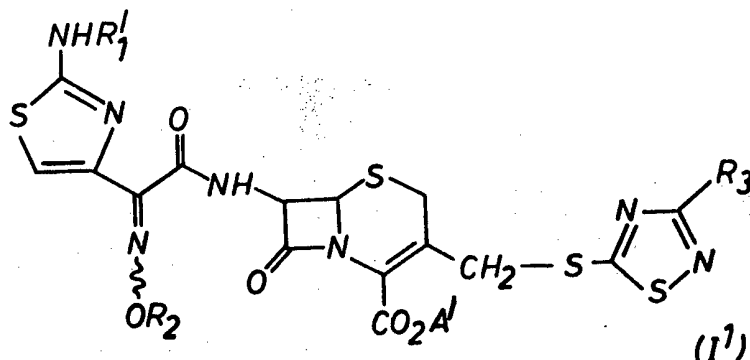


(wherein  $R_3$  is as defined in Claim 1 and  $A'$  represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or by hydrogenolysis) is treated with an acid of the general formula:



(wherein  $R_1$  represents a group removable by acid hydrolysis or by hydrogenolysis

or a chloroacetyl radical and  $R_2$  is as defined in Claim 1) or with a functional derivative thereof to obtain a product of the general formula:



wherein  $R_1$  and  $A'$  are as defined herein, and wherein  $R_2$  and  $R_3$  are as defined in Claim 1.

11. A process as claimed in Claim 10, in which the compound of formula II is treated with an anhydride or an acid chloride of the acid of formula III.

12. A process as claimed in Claim 11, in which the anhydride is formed *in situ* by the action of *isobutyl* chloroformate or of dicyclohexylcarbodiimide on the acid.

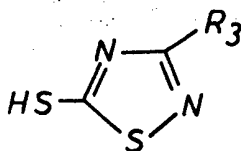
13. A process as claimed in Claim 10, in which a compound of general formula II is reacted with a halide of the acid of general formula III or with an anhydride thereof formed with *isobutyl* chloroformate, and in which the reaction is carried out in the presence of a base.

14. A process as claimed in Claim 13, in which the base is an alkali-metal carbonate, N - methyl - morpholine, pyridine or a trialkylamine.

15. A process as claimed in any of Claims 10 to 14, in which the reaction is carried out in one or more solvents.

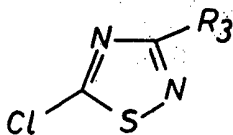
16. A process as claimed in Claim 15, in which the or each solvent is selected from methylene chloride, chloroform, tetrahydrofuran, acetone or dioxan.

17. A process as claimed in any of Claims 10 to 16, in which the starting material of general formula II is prepared by an exchange reaction, in which 7 - amino - cephalosporanic acid is reacted with a compound of the general formula:



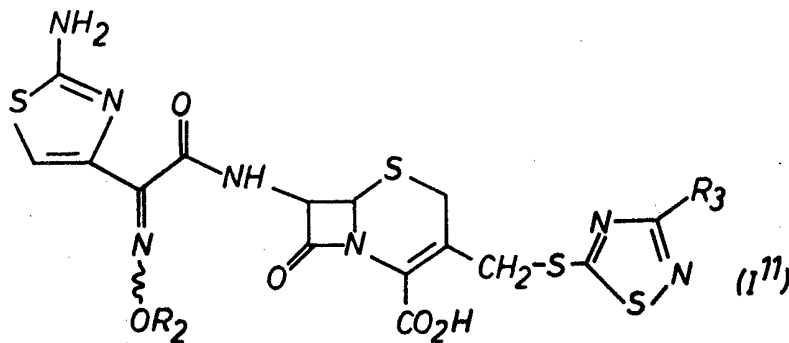
wherein  $R_3$  is as defined in Claim 1.

18. A process as claimed in Claim 17, in which the compound of general formula V is prepared by the action of sodium hydrosulphide or thiourea in the presence of potassium hydroxide on a product of the general formula:



wherein  $R_3$  is as defined in Claim 1.

19. A process for preparing a compound of general formula I as defined in Claim 1, wherein  $R_1$  and  $A'$  each represent a hydrogen atom, in which process a compound of general formula I' is treated with one or two reagents selected from an acid hydrolysis agent, a hydrogenolysis agent and thiourea so as to convert the substituents  $R_1$  and  $A'$  each to a hydrogen atom and thus to obtain a compound of the general formula:



wherein  $R_2$  and  $R_3$  are as defined in Claim 1.

20. A process as claimed in Claim 19, in which the compound of general formula I' is reacted with formic acid, trifluoroacetic acid, acetic acid, or a zinc/acetic acid system.

21. A process as claimed in Claim 20, in which the compound of general formula I' is reacted with anhydrous trifluoroacetic acid or aqueous formic or acetic acid when  $R_1$  represents a *t*-butoxycarbonyl or trityl group or  $A'$  represents a benzhydryl, *t*-butyl or *p*-methoxybenzyl group.

22. A process as claimed in Claim 20, in which the compound of general formula I' is reacted with a zinc/acetic acid system when  $R_1$  and/or  $A'$  represents a trichloroethyl group.

23. A process as claimed in Claim 19, in which hydrogen in the presence of a catalyst is used as a hydrogenolysis agent to remove a benzhydryl or carbobenzyloxy group as substituent  $R_1$  or to remove benzyl groups as substituent  $R_1$  and/or  $A'$ .

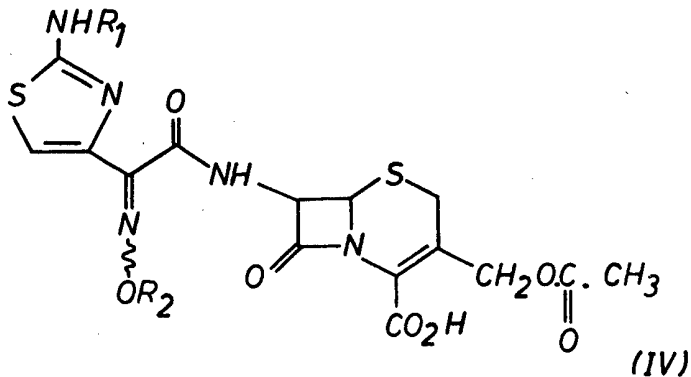
24. A process as claimed in any of Claims 10 to 23, in which the formed compound of general formula I' or I'' is salified to form a corresponding compound of general formula I wherein A represents an alkali metal atom or an equivalent of an alkaline earth metal atom, a magnesium atom or a substituted ammonium group.

25. A process as claimed in Claim 24, in which the salification is carried out in a solvent or a mixture of solvents.

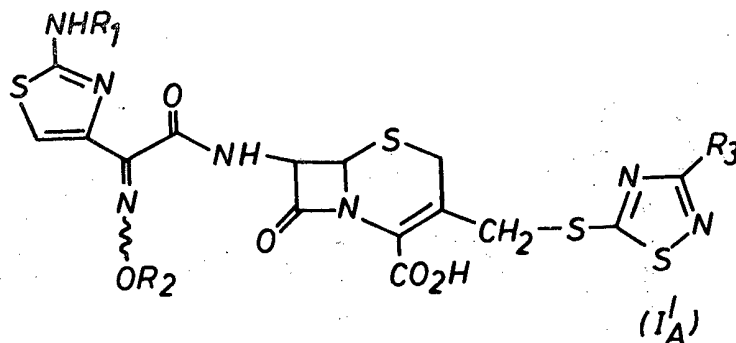
26. A process as claimed in Claim 25, in which the or each solvent is selected from water, diethyl ether, methanol, ethanol and acetone.

27. A process for the preparation of a compound of general formula I as defined in Claim 1 wherein the  $OR_2$  group is in the *syn* configuration, being a process as claimed in any of Claims 10 to 26 and employing a compound of general formula III having the  $OR_2$  group in the *syn* position.

28. A process for preparing a compound of general formula I as defined in Claim 1 wherein A represents a hydrogen atom, in which a compound of the general formula:



(wherein  $R_1$  and  $R_2$  are as defined in Claim 1), is treated with a compound of general formula V (as defined in Claim 17) to give a corresponding compound of the general formula:



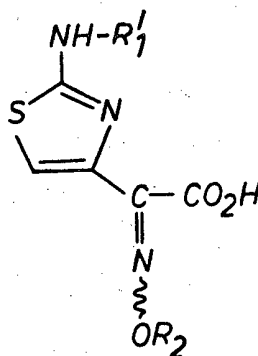
wherein  $R_1$ ,  $R_2$  and  $R_3$  are as defined in Claim 1.

29. A process as claimed in Claim 28, in which the formed compound  $I_A$  is salified to give a compound of general formula I wherein A represents an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group.

30. A process as claimed in Claim 28 or Claim 29, in which the reaction of the compound of general formula V with the compound of general formula IV is carried out in a water/acetone, water/dioxan, water/tetrahydrofuran or water/ethanol mixture.

31. A process as claimed in any of Claims 28 to 30, in which the reaction of the compound of general formula V with the compound of general formula IV is carried out in the presence of a mixture of sodium acid phosphate and sodium bicarbonate.

32. A process as claimed in any of Claims 28 to 31, in which the starting material of general formula IV is prepared by the action of an acid of the general formula:



(wherein  $R_1$  is as defined in Claim 10 and  $R_2$  is as defined in Claim 1) on 7-amino - cephalosporanic acid, this reaction being followed, if necessary, by acid hydrolysis or by hydrogenolysis to give the desired compound of general formula IV.

33. A process for the preparation of a compound of general formula I wherein A represents a hydrogen atom, an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group, and having the  $OR_2$  group in the *syn* configuration, being a process as claimed in any of Claims 28 to 32 using a starting material of general formula IV having the  $OR_2$  group in the *syn* position.

34. A process for the preparation of a compound of general formula I, as defined in Claim 1, substantially as described herein with reference to any one of the Examples.

35. A compound of general formula I, whenever prepared by a process as claimed in any of Claims 10 to 34.

36. A pharmaceutical composition containing an active ingredient of one or more compounds of general formula I, as defined in Claim 1, in association with a pharmaceutically-acceptable vehicle.

37. A composition as claimed in Claim 36, in which the active ingredient comprises one or more compounds of general formula I wherein A represents a



hydrogen atom, an alkali-metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or an equivalent of a substituted ammonium group.

5 38. A composition as claimed in Claim 36 or Claim 37, in which the OR<sub>2</sub> group in the or each compound of general formula I is in the *syn* position. 5

39. A composition as claimed in Claim 36, in which the active ingredient comprises one or more compounds of general formula I wherein R<sub>1</sub> represents a hydrogen atom, R<sub>2</sub> represents a methyl radical, R<sub>3</sub> represents a methyl or methoxy radical and A represents a hydrogen atom, and/or one or more pharmaceutically-acceptable salts thereof falling within general formula I. 10 10

40. A composition as claimed in Claim 39, in which the or each compound of general formula I has the OR<sub>2</sub> group in the *syn* position.

41. A composition as claimed in Claim 36, containing as active ingredient one or more compounds as claimed in Claim 8 or Claim 9. 15

42. A composition as claimed in Claim 36 and substantially as described herein with reference to any one of the Formulations. 15

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