

PATENT SPECIFICATION

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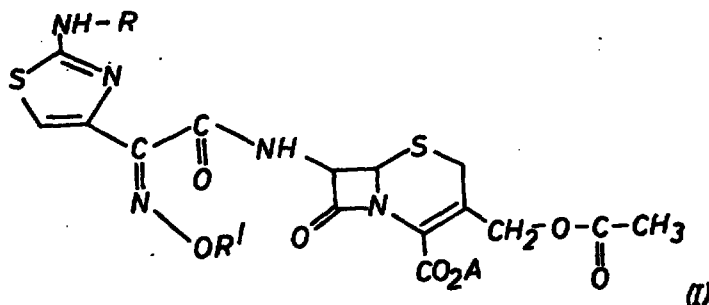


(54) NEW OXIME DERIVATIVES OF 7-AMINO-THIAZOLYLACETAMIDO-CEPHALOSPORANIC ACID, PROCESSES FOR PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS INCORPORATING THEM

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7^{eme}, 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 7-aminothiazolylacetamido - cephalosporanic acid, processes for preparing them and pharmaceutical compositions incorporating them. In particular, it concerns certain derivatives of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid which may be of use in medicine.

Accordingly, this invention provides 7 - aminothiazolylacetamido - cephalosporanic acid oxime derivatives of the general formula:



wherein R represents a hydrogen atom or a group removable by acid hydrolysis or by hydrogenolysis, R' represents a hydrogen atom, a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl 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 or a substituted ammonium group with the provisos that when R' represents a group removable by acid hydrolysis or by hydrogenolysis R represents the same or a different group removable by acid hydrolysis or by hydrogenolysis, and that when R' represents a hydrogen atom R also represents a hydrogen atom, the compounds being in the form of the *syn* isomer.

The expression "a group removable by acid hydrolysis or by hydrogenolysis" is

used to mean a group that may be cleaved from the remainder of the molecule without otherwise affecting its structure (other than cleaving other groups removable by acid hydrolysis or by hydrogenolysis, where more than one is present). Examples of such groups which R and R' can represent include the *t*-butoxycarbonyl, trityl, benzyl, benzylhydryl, trichloroethyl, carbobenzyloxy, formyl, trichloroethoxycarbonyl and 2-tetrahydropyranyl groups.

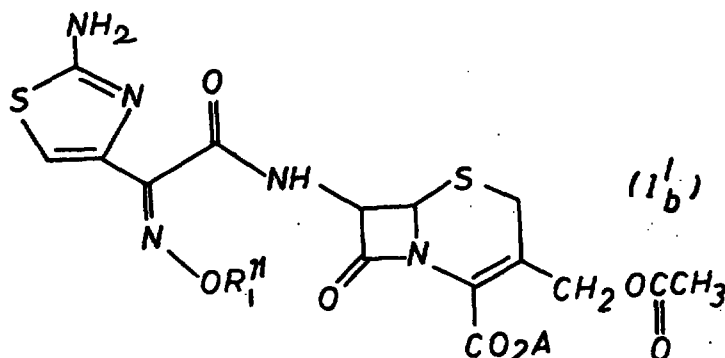
A preferred group of compounds of general formula I are those wherein the groups removable by acid hydrolysis or by hydrogenolysis are selected from the *t*-butoxycarbonyl, trityl, benzylhydryl, trichloroethyl and carbobenzyloxy groups.

When R' represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms it may be an alkyl, alkenyl or an alkynyl group, and examples of suitable groups include the methyl, ethyl, propyl, *isopropyl*, butyl, *sec*-butyl, *t*-butyl, vinyl, propenyl, butenyl, ethynyl and propargyl radicals.

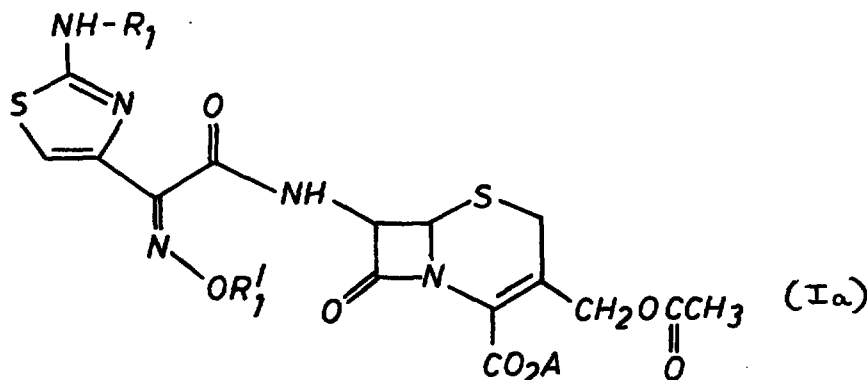
When A represents "an equivalent of an alkaline-earth metal atom" or "an equivalent of a magnesium atom" each molecule of the compound shown in general formula I contains, as A, the fraction of the metal atom corresponding to a single valence.

When A represents a metal atom or equivalent thereof (and thus the compounds of general formula I are metal salts) A is preferably a sodium, potassium or lithium atom or an equivalent of a calcium or magnesium atom. When A represents a substituted ammonium group (and thus the compounds of general formula I are amine salts) A is preferably derived from methylamine, propylamine, trimethylamine, triethylamine, N,N - dimethylethanolamine, tris (hydroxymethyl) aminomethane, arginine or lysine.

The invention provides, as new compounds having antibiotic activity, the *syn* isomers of the general formula:



(wherein R₁' represents a hydrogen atom or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms and A is as defined hereinbefore) and the *syn* isomers of the general formula:



(wherein R₁ represents a group removable by acid hydrolysis or by hydrogenolysis, R₁' represents a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms and

A is as defined hereinbefore), the compounds of general formula I_a' being useful intermediates in preparing compounds of general formula I_b'.

A preferred class of compounds falling within general formula I_b' are those wherein A represents a hydrogen atom, a sodium atom or a diethylammonium group.

The salts falling within general formula I—that is, the compounds wherein A does not represent a hydrogen atom—may be prepared in amorphous or crystalline form. The crystalline salt may be in the form of a hydrate formed with 0.5, 1 or 1.5 molecules of water.

The particularly preferred compounds of general formula I are those compounds prepared in the Examples set out hereinafter and especially:—

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer;

the sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer;

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, as obtained by the process described in Example 4;

the sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, as obtained by the process described in Example 7;

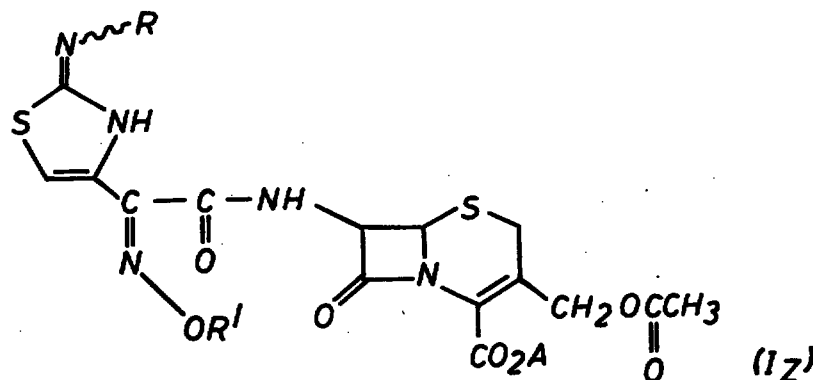
the crystalline sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer;

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - ethoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, and salts thereof formed with alkali metals, alkaline-earth metals, magnesium or organic amines;

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - propenyloxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, and salts thereof formed with alkali metals, alkaline-earth metals, magnesium or organic amines; and

3 - acetoxymethoxy - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - methyl - ethoxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, and salts thereof formed with alkali metals, alkaline-earth metals, magnesium or organic amines.

It is understood that the compound of general formula I can exist: either a) in the form indicated by formula I — as set out hereinbefore, or b) in the form shown in general formula I₂ set out below:—



wherein R, R' and A are as defined hereinbefore. All references to compounds of general formula I should be construed as extending to both these forms, unless otherwise specified.

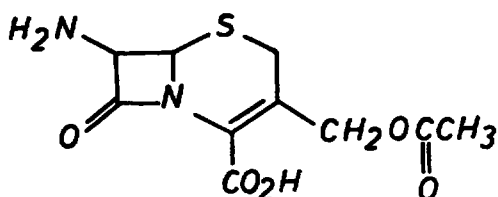
This invention also provides a process for preparing the products of general formula I_a' wherein A represents a hydrogen atom, in which process 7 - amino - cephalosporanic acid of the formula:

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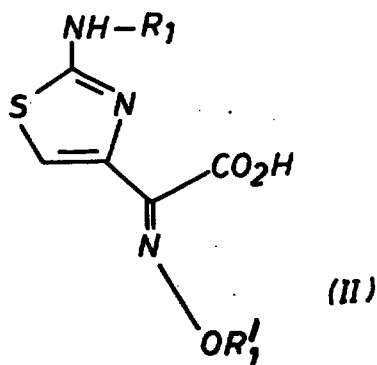
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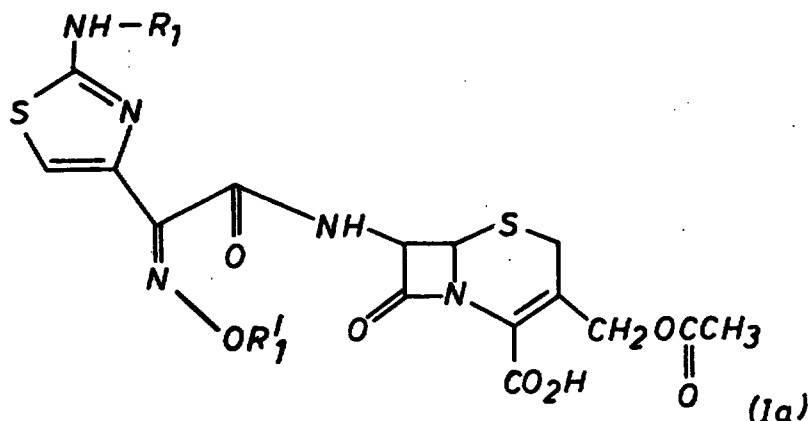
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is reacted with an appropriate acid *syn* isomer of general formula II:



(wherein R₁ and R₁' are as defined hereinbefore) or a functional derivative thereof to obtain the desired compound of general formula Ia:

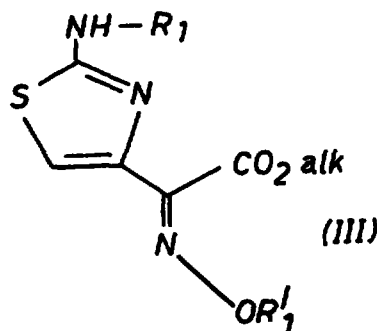


wherein R₁ and R₁' are as defined hereinbefore.

Advantageously, the 7 - amino - cephalosporanic acid is treated with a functional derivative of the acid of formula II, an anhydride or the acid chloride of the acid being preferred. Other acid halides and indeed other acid derivatives such as the acid azide, the activated acid amide, or an activated acid ester formed, for example, with N-hydroxysuccinimide, *para*-nitrophenol or 2,4-dinitrophenol can also be used. The anhydride formed *in situ* by the action of isobutyl chloroformate or dicyclohexylcarbodiimide on the acid II is particularly preferred, although other anhydrides formed *in situ* by the action of other alkyl chloroformates, a dialkylcarbodiimide or other dicycloalkylcarbodiimides can also be used.

When employing a halide of the acid of general formula II or an anhydride formed *in situ* using isobutyl chloroformate, the reaction is preferably carried out in the presence of a base. Preferred bases include alkali metal carbonates, and organic bases such as N-methyl-morpholine, pyridine and trialkylamines — for example, triethylamine.

The starting material of general formula II is conveniently prepared by treating an appropriate *syn* isomer of the general formula:



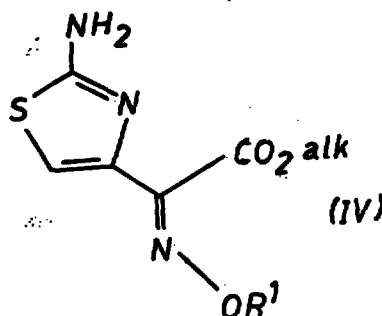
(wherein R_1 and R_1' are as defined hereinbefore and alk represents an alkyl radical having from 1 to 4 carbon atoms) first with a base and then with an acid to form the desired product of general formula II.

The compounds of general formula III above have been described and claimed in our copending Application for Letters Patent No. 79-15561 (Serial No. 1,580,623) of even date herewith.

The base, which is used to saponify the product of formula III is preferably sodium hydroxide, but other bases such as potassium or barium hydroxide can also be used.

The acid which is used to isolate the acid of formula II is preferably dilute hydrochloric acid, but other acids such as acetic acid or formic acid can also be used.

The compounds of general formula III are in turn conveniently prepared by protecting the amino groups, and where appropriate the oxime groups as well, of the corresponding *syn* isomers of the general formula:



wherein R_1' and alky are as defined hereinbefore.

The compounds of general formula IV above have been described and claimed in our copending Application for Letters Patent No. 79-15561 (Serial No. 1,580,623) of even date herewith.

The appropriate compound of general formula IV is treated with a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to form the corresponding product of general formula III.

Naturally the process employs a compound capable of introducing the appropriate group R_1 (and R_1' when R_1' in compound IV is hydrogen) into the compound III and the compound most conveniently employed will depend upon the nature of the group. However, such protecting groups and their introduction into molecules are well known to those skilled in the art. By way of illustration, the trityl group is preferably introduced using trityl chloride, most preferably used in the presence of triethylamine, or another tertiary amine base such as another trialkylamine, N-methylmorpholine or pyridine.

Other compounds capable of introducing groups removable by acid hydrolysis or by hydrogenolysis which may be used include *t*-butyl chloroformate (conveniently prepared *in situ*) or *t*-butyl azidoformate, trichloroethyl or benzyl chloroformate, the mixed formyl-acetic anhydride (prepared *in situ*), benzyl or dibenzyl halides and particularly the chlorides, phthalic anhydride or N-carbathoxyphthalimide.

Certain of the compounds of general formula III, namely those wherein R_1' represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4

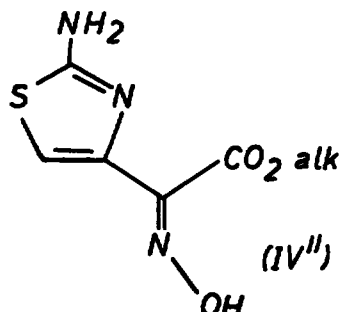
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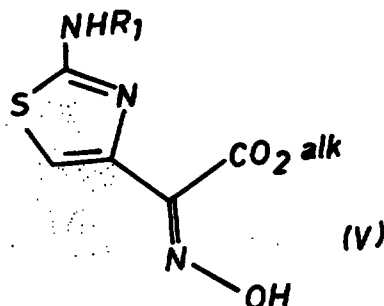
carbon atoms, may be prepared by a process in which an appropriate *syn* isomer of the general formula:



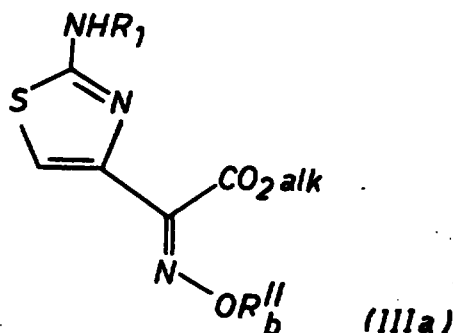
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(wherein alk is as defined hereinbefore) is treated with an equivalent of a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to obtain the corresponding *syn* isomer of general formula:

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(wherein R₁ and alk are as defined hereinbefore) which is then treated with a hydrocarbylating agent to obtain the desired *syn* isomer of the general formula:



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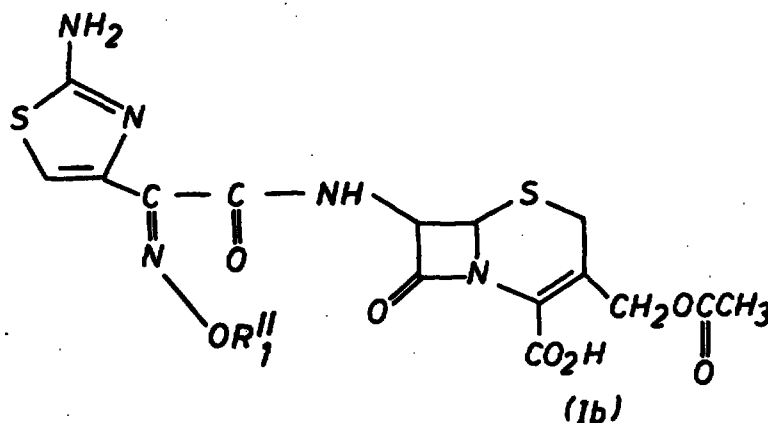
(wherein R₁ and alk are as defined hereinbefore, and R''b represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms.

The compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis is chosen to introduce the desired protecting group, as explained above, and again is preferably trityl chloride. The formation of the product V using trityl chloride is preferably carried out in the presence of a base such as triethylamine. Other bases such as other trialkylamines, N-methylmorpholine or pyridine can also be used.

Other compounds capable of introducing groups removable by acid hydrolysis or hydrogenolysis, such as *t*-butyl chloroformate or azidoformate, trichloroethyl or dibenzyl chloroformate, the mixed formyl acetic anhydride (prepared *in situ*), benzyl or dibenzyl halides (preferably the chlorides), phthalic anhydride or N-carbethoxy-phthalimide can also be used.

The hydrocarbylating agent which is used in the final step of preparing the products of formula IIIa is preferably an alkyl halide such as an alkyl iodide or an alkyl sulphate.

The compounds of general formula Ia may be converted into further compounds falling within general formula I by hydrolysis. Thus, this invention also provides a process for the preparation of compounds of general formula Ib' wherein A represent a hydrogen atom, in which process an appropriate compound of general formula Ia' wherein A represents a hydrogen atom — that is, a compound of general formula Ia — is hydrolysed in an acidic medium or hydrogenolysed to obtain the desired product of the general formula:



wherein R₁' is as defined hereinbefore.

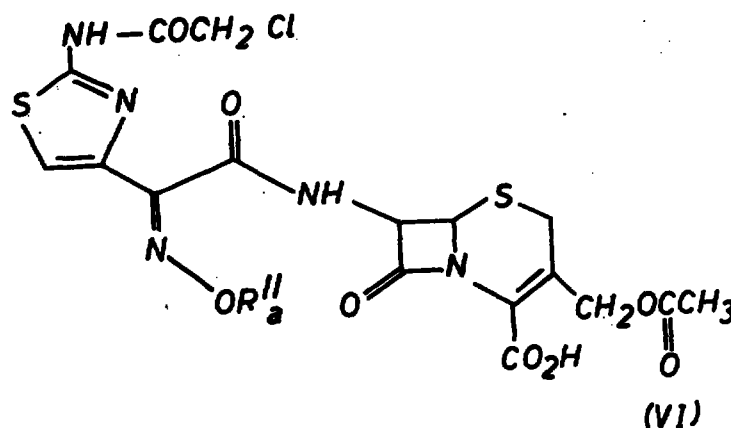
When acid hydrolysis is effected preferred agents which may be used include formic acid, trifluoroacetic acid or acetic acid. These acids can be employed in anhydrous form or in aqueous solution.

When hydrogenolysis is carried out, a preferred agent is the zinc/acetic acid system.

Preferably an acid hydrolysis agent such as anhydrous trifluoroacetic acid or aqueous formic or acetic acid is used to remove *t*-butoxycarbonyl or trityl groups.

Preferably the zinc/acetic acid system is used to remove trichloroethyl groups, while catalytic hydrogenation is preferably used to remove benzyl, benzylhydriyl and carbobenzyloxy groups.

This invention further provides an alternative process for preparing compounds of general formula Ib, in which an appropriate *syn* isomer of general formula:

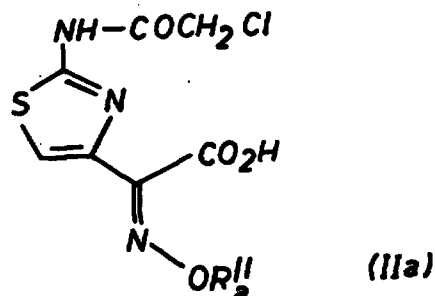


(wherein R''a is a chloroacetyl group or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms) is treated with thiourea to obtain the desired compound of general formula Ib.

This reaction with thiourea is preferably carried out in a neutral or acidic medium, and it has been found that the reaction may be performed in a similar manner to that described by Masaki in Jacs, 90, 4508, (1968) in relation to different compounds.

The compounds of general formula VI may conveniently be prepared by

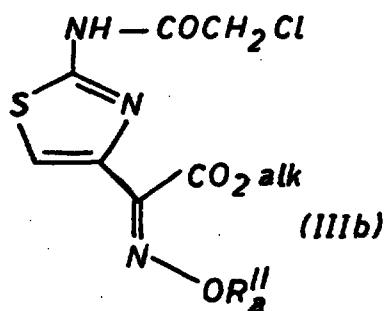
reacting 7-amino-cephalosporanic acid with an appropriate acid *syn* isomer of the general formula:



(wherein R''a is as defined hereinbefore) or a functional derivative thereof, to form the desired compound of general formula VI.

This reaction with 7-amino-cephalosporanic acid is preferably carried out under the same conditions as those described above in relation to the reaction of 7-amino-cephalosporanic acid with the acid of general formula II.

The compounds of general formula IIa may in turn be prepared by treating an appropriate *syn* isomer of the general formula:

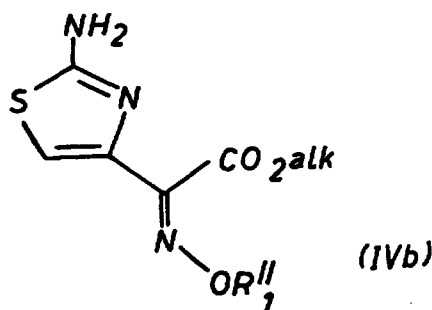


(wherein R''a and alk are as defined hereinbefore) first with a base, and then with an acid, to obtain the desired compound of general formula IIa.

The base which is used to saponify the product of formula IIIb is preferably sodium hydroxide but other bases such as potassium or barium hydroxide can also be used.

The acid which is used to isolate the acid of general formula IIa is, preferably, dilute hydrochloric acid, but acetic acid or formic acid can also be used.

The compounds of general formula IIIb are conveniently prepared by reacting a compound capable of introducing the chloroacetyl group with a *syn* isomer of the general formula:



(wherein R'' and alk are as defined hereinbefore) so as to form the desired N-chloroacetyl compound of general formula IIIb.

The compound capable of introducing the chloroacetyl group is preferably chloroacetic anhydride or a halide such as monochloroacetyl chloride.

In the case where the reaction is carried out with a chloroacetyl halide, work is preferably carried out in the presence of a basic agent such as those described

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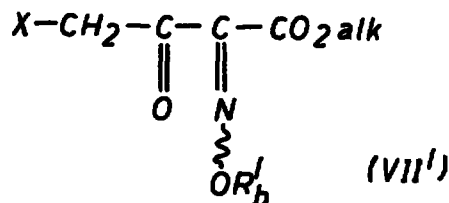
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above for use in the conversion of the compound of general formula IV to compounds of general formula III.

The *syn* isomer compounds of general formula IV, which include the compounds of general formulae IVb and IV'', may conveniently be prepared by reacting thiourea with an appropriate compound of the general formula:



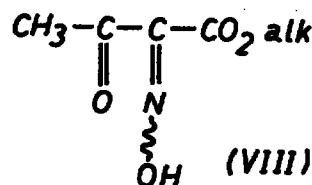
(wherein X represents a chlorine atom and R_b' represents a hydrogen atom, a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, or X represents a bromine atom and R_b' represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms) which process is characterised in that a) the reaction is carried out in an aqueous solvent; or b) the reaction is carried out at ambient temperature in the presence of a substantially stoichiometric amount of thiourea and with a reaction time of from 1 to 3 hours; or c) the reaction is carried out observing both of conditions a) and b).

It has been established that the *syn* configuration of the products of formula I formed by the processes of this invention is governed by the configuration of the products of formula IV, since their configuration can be maintained during the steps of the synthesis from compounds of general formula IV to the desired products. This also applies, of course, to the products obtained from the compounds of formulae IVb and IV'', since these latter compounds all fall within general formula IV.

The configuration of the products of formula IV depends upon a certain number of parameters concerned with their preparation, and thus under the conditions defined above the desired *syn* isomer is formed.

Thus, the compounds of general formula IV prepared in Examples 3, 8, 10, 12 and 21 all have *syn* configuration.

The compounds of general formula VII' wherein X represents a bromine atom and R_b' represents a hydrogen atom may be obtained by treatment of the products of formula:



with a brominating agent.

The brominating agent is preferably bromine itself.

The compounds of formula VII' wherein X represents a chlorine atom which are not known may be prepared from ethyl - γ - chloro - α - oximinoacetylacetate (described in J. of Medicinal Chemistry 1973, Vol. 16, No. 9). The compounds of general formula VII' wherein X represents a chlorine atom and R_b' represents a group removable by acid hydrolysis or by hydrogenolysis may be obtained by standard protecting reactions using functional derivatives of the removable groups. The compounds of general formula VII' wherein X represents a chlorine atom and R_b' represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms may be obtained by reacting ethyl - γ - chloro - α - oximinoacetylacetate with an appropriate alkyl halide or sulphate.

Naturally, to obtain the desired substituent alkyl in the compound of general formula VII' appropriate saponification and re-esterification or trans-esterification may be used.

The compounds of general formulae Ia and Ib, which are free acids, may be salified, and the salification may be carried out according to the usual methods. To form the metal salts the free acid is preferably reacted with a mineral base such as

sodium or potassium hydroxide or sodium bicarbonate, or with a salt of a substituted or unsubstituted aliphatic carboxylic acid, such as diethylacetic acid, ethyl-hexanoic acid or, more usually, acetic acid.

The preferred salts of these acids are the sodium salts.

A preferred amine salt is produced by the action of triethylamine on the appropriate free acid.

The starting material for the preparation of the salts may be the free acid of general formula Ia or Ib or a solvate of the appropriate free acid can equally be used. The solvates formed with water, with formic acid or with an alcohol are those most usually employed.

The solvates with alcohols, and particularly that formed with ethanol may be produced, for example, by treating the corresponding solvate formed with formic acid with a mixture of the alcohol and water, this treatment being followed by concentration of the solution.

This salification is preferably carried out in one or more solvents such as water, ethyl ether, methanol, ethanol or acetone.

The salts are obtained in amorphous or in crystalline form dependent upon the reaction conditions employed in their preparation.

The crystalline salts are preferably prepared by reacting the free acids of general formulae Ia and Ib, or their solvates (for example, those formed with formic acid or with ethanol), with one of the salts of a substituted or unsubstituted aliphatic carboxylic acid, mentioned hereinbefore, and preferably with sodium acetate.

In the preparation of a sodium salt, the reaction is conveniently carried out in an appropriate organic solvent which is capable of containing small amounts of water. Methanol is an example of a suitable solvent.

It is, moreover, possible to transform amorphous salts into their crystalline form. To effect that transformation in the case of an amorphous sodium salt, which can be in the form of a hydrate with, for instance, 0.5, 1 or 1.5 molecule(s) of water, the amorphous salt is dissolved in an appropriate organic solvent — preferably an alcohol of low molecular weight (containing from 1 to 5 carbon atoms), such as methanol — and the crystallization then brought about either directly or indirectly by the addition of one or more other organic solvents such as ethanol, isopropanol, *n*-butanol, acetone and ethers.

If either the starting material or the solvent(s) or both these materials contain any water, the crystalline salt may be obtained in the form of a hydrate. For example, the crystalline sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, may be isolated as a hydrate containing 0.5, 1 or 1.5 molecule(s) of water.

This invention provides a further process for preparing the compounds of general formula I_b', in which a salt of general formula I_b' is either treated with an acid to obtain the corresponding compound of general formula Ib, or subjected to hydrogenolysis to obtain the corresponding salt of general formula Ib'.

The acid used to hydrolyse the salts of formula Ia' is preferably formic acid. However, trifluoroacetic acid or acetic acid can be used. These acids can be employed in anhydrous form or in aqueous solution.

The hydrogenolysis used in the above process is preferably effected by catalytic hydrogenation.

The *syn* isomer compounds of general formula I and particularly those of general formula I_b' possess interesting antibiotic activity, on the one hand against Gram-positive bacteria such as staphylococci and streptococci, and especially the penicillin-resistant staphylococci, and on the other hand against Gram-negative bacteria, and especially the coliform bacteria, Klebsiella, Salmonella and Proteus.

These properties may make the pharmaceutically-acceptable compounds of general formula I_b' and their pharmaceutically-acceptable salts useful as medicaments in the treatment of infections caused by sensitive micro-organisms, 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 primitive or post-influenza staphylococcal infections, bronchopneumonia, and pulmonary suppurations.

The pharmaceutically-acceptable compounds may also be useful as medicaments in the treatment of colibacillosis and associated infections, in

infections caused by *Proteus*, by *Klebsiella* and by *Salmonella* and in other complaints caused by Gram-negative bacteria.

However, before any of the compounds of this invention are used in medicine, they are preferably formed into pharmaceutical compositions by association with suitable pharmaceutical vehicles.

The terms "pharmaceutical" and "pharmaceutically-acceptable" are used herein to exclude any possibility that the vehicle or the active material, as appropriate, considered in relation to the route by which the composition is intended to be administered, could result in the composition being harmful rather than beneficial. The choice of a suitable mode of presentation, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

Accordingly, in yet another aspect this invention provides pharmaceutical compositions containing as active material one or more pharmaceutically-acceptable compounds of general formula I_b', in association with a suitable pharmaceutical vehicle.

Preferred active materials for use in the compositions are those of *syn* configuration, especially those described in the following Examples.

Particularly preferred pharmaceutical compositions are those containing, as active principle, at least one compound of general formula I_b' wherein A represents a hydrogen or sodium atom.

Specific preferred pharmaceutical compositions are those containing, as active material, one of:—

the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid (this product is described in Examples 4, 6, 20 and 22 hereinafter);

the sodium salt of the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid (this product is described in Example 7 hereinafter); and

the crystalline sodium salt of the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid, optionally in the form of a hydrate or solvate or at least one of:—

the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - ethoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid and its pharmaceutically-acceptable salts with alkali metals, alkaline-earth metals, magnesium and amines;

the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - propenyl - oxymino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid and its pharmaceutically-acceptable salts with alkali metals, alkaline-earth metals, magnesium and amines; and

the *syn* isomer of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - methyl - ethoxy) - imino]acetamido] - ceph - 3 - em - 4 - carboxylic acid and its pharmaceutically-acceptable salts with alkali metals, alkaline-earth metals, magnesium and amines.

The compositions of this invention may be administered by buccal, rectal or parenteral routes, or by local route by topical application to the skin or mucous membranes, and thus the pharmaceutical vehicle is preferably:—

a) the ingestible excipient of a tablet, coated tablet, sublingual tablet or pill, 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, lotion, salve, ointment, cream, gel or unguent;

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

d) a base material of a suppository.

Whilst the modes of presentation and vehicles just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The compositions may thus be in the form of a solid or liquid and the preferred pharmaceutical forms currently used in human medicine in which they may be presented are as plain or sugar-coated compressed tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams or gels. The vehicle is typically one or more of the excipients conventionally employed in these pharmaceutical compositions such as talc, gum arabic, lactose, starch magnesium stearate, cocoa butter and aqueous or non-aqueous liquid vehicles including fatty

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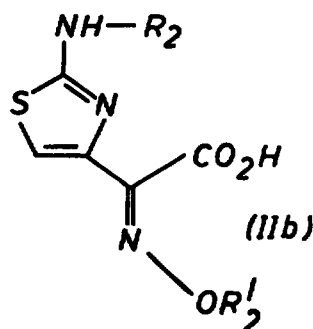
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substances of animal or vegetable origin, paraffin derivatives and glycols. The composition may also include one or more wetting, dispersing or emulsifying agents, and/or one or more preservatives.

The dose of active material administered will vary according to the complaint treated, the person concerned, the route of administration and the product under consideration. However, it may be, for example, between 0.250 g and 4 g per day for administration by oral route in man with the product described in Example 4 or 7 hereinafter, or between 0.500 g and 1 g, taken three times daily, for administration by intramuscular route.

Certain of the intermediate compounds used in the preparation of the compounds of general formula I and related compounds are new, and in another aspect this invention provides certain of these useful intermediates *per se*.

The *syn* isomers of the general formula:

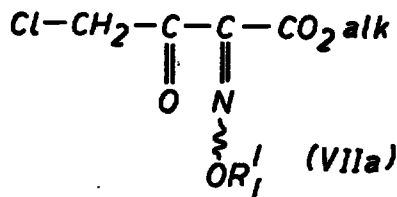


(wherein R_2 represents a hydrogen atom or a group removable by acid hydrolysis or by hydrogenolysis and R'_2 represents a hydrogen atom, a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, with the proviso that R'_2 does not represent a hydrogen atom when R_2 represents a group removable by acid hydrolysis or by hydrogenolysis) are described and claimed *per se* in our Application for Letters Patent No. 79-15561 (Serial No. 1,580,623) divided out of this Application and hence of even date herewith.

Those compounds of general formula IIb that also fall within general formula II may be prepared by a process as described hereinbefore.

Those compounds of general formula IIb wherein R_2 and/or R'_2 represent(s) a hydrogen atom may be prepared by subjecting the corresponding compounds of general formula II wherein R_1 and/or R'_1 represent(s) a group removable by acid hydrolysis or by hydrogenolysis to acid hydrolysis or hydrogenolysis, as appropriate, so as to form the desired compound of general formula IIb.

The compounds of the general formula:



(wherein alk and R'_1 are as defined hereinbefore) are new. These compounds all fall within general formula VII' and may thus be prepared in the manner described hereinbefore in relation to those compounds.

In another aspect this invention provides the compounds of general formula VI as defined hereinbefore, together with processes for their preparation, also defined hereinbefore.

Like the products of formula I, the compounds of general formula VI have been found to possess antibiotic activity and may be useful in treating the same complaints.

The following Examples and Formulations are now given by way of illustration. The Examples show preferred aspects of the preparation of compounds of the invention and the preparations of related *anti* isomers. The Formulations show certain preferred aspects of pharmaceutical compositions of the invention.

Example 1

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - tritylhydroxyimino - acetamido] - cephalosporanic Acid, *Anti* Isomer

5 Stage A: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - hydroxyimino - acetate 5
2 g of ethyl γ - chloro - α - oximinoacetylacetate are placed in 5 cm³ of ethanol and 0.76 g of thiourea and the whole is agitated at ambient temperature for sixteen hours in all, the hydrochloride crystallises out, the whole is diluted with 5 cm³ of ether, vacuum-filtered, rinsed with 1:1 ethanol-ether then with ether, and 1.55 g of hydrochloride are obtained. 10

The 1.55 g of hydrochloride obtained are dissolved at 40—50°C in 8 cm³ of water, then neutralised to pH 5—6 by the addition of sodium acetate. The free amine crystallises out. The whole is chilled then vacuum-filtered, washed with water and dried, and 1.22 g of the *anti* isomer are obtained, M.Pt.=154°C. 15

The mother liquors and washing waters from several experiments are collected, concentrated, taken up with water and washed with ether, sodium acid carbonate is added, the whole is vacuum-filtered and washed with water, and 1.9 g of product giving two spots in thin layer chromatography are obtained and purified by chromatography on silica by eluting with ether. The pure fractions of the *syn* isomer are collected, concentrated, made into a paste with ether, vacuum-filtered and dried, and 50 mg of this isomer are obtained. 20

Stage B: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - tritylhydroxyiminoacetate, *Anti* Isomer

25 To a solution of 5.4 g of the *anti* isomer prepared in stage A in 54 cm³ of chloroform and 7.5 cm³ of triethylamine there is added, at +10°C, a solution of 15 g of trityl chloride in 30 cm³ of chloroform. After standing for one hour, the whole is washed with 40 cm³ of water, then 20 cm³ of water containing 4 cm³ of normal hydrochloric acid, decanted, dried and concentrated to dryness. 25

The residue is taken up with 10 cm³ of ether, 50 cm³ of methanol are added, the whole is agitated, vacuum-filtered and washed with methanol, and 14.2 g of expected product are obtained in two yields. 30

Stage C: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - tritylhydroxyimino Acetic Acid, *Anti* Isomer

35 10.5 g of ester obtained in stage B are put into suspension, close to reflux, in 55 cm³ of dioxane. 17 cm³ of 2 N soda are added slowly. Gentle refluxing is continued, the whole is cooled and the salt is vacuum-filtered. the salt is taken up with 60 cm³ of methylene chloride, 20 cm³ of water and 2 cm³ of acetic acid. The acid is vacuum-filtered and washed with water, and a first yield of 7 g of acid is obtained. 35

The dioxane is evaporated from the mother solution, and 20 cm³ of methylene chloride, 10 cm³ of water and 1 cm³ of acetic acid are added. A second yield of 1.5 g of the same product is isolated. In all there are 8.5 g. 40

Analysis:	C ₄₂ H ₃₂ O ₃ N ₃ S 0.5 H ₂ O
Calculated:	C 75.85 H 5.03 N 6.17 S 4.7
Found:	C 75.8 H 4.9 N 5.9 S 4.6

45 Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - tritylhydroxyimino - acetamido]cephalosporanic Acid, *Anti* Isomer 45

A suspension of 8.5 g of acid prepared in stage C in 50 cm³ of methanol is agitated and 5 cm³ of N-methylmorpholine are added. The whole is agitated for ten minutes at 30°C, 30 cm³ of methylene chloride are added, the whole is concentrated, 100 cm³ of ether are added, the whole is disintegrated, vacuum-filtered, washed with ether and dried, and a first yield of 7.2 g of salt is obtained. It is concentrated to dryness, taken up with ether and a second yield of the same product is obtained. 50

55 4.24 g of the morpholine salt above are put into suspension, under agitation and under inert gas, in 60 cm³ of methylene chloride. 55

The whole is agitated for five minutes, then cooled to -5°C and 6 cm³ of a molar solution of isobutyl chloroformate in methylene chloride are added. The whole is left under agitation at -5°C for fifteen minutes, then cooled to -20°C, and a solution of 1.36 g of 7-amino-cephalosporanic acid in 25 cm³ of methylene chloride and 1.4 cm³ of triethylamine is added. The whole is left for one hour at 60

ambient temperature, washed with 50 cm³ of water containing 10 cm³ of N hydrochloric acid, vacuum-filtered, decanted, washed with water and concentrated to dryness. It is triturated in ether, vacuum-filtered and washed with ether, and 4.5 g of crude product are obtained.

The crude product is agitated for one hour at +10°C in 10 cm³ of methylene chloride. The insoluble matter is vacuum-filtered and rinsed with methylene chloride. 50 cm³ of ether are added to the filtrate, this is agitated, the precipitate is vacuum-filtered and washed with ether, and 2.29 g of expected product are obtained.

Further, a second yield of 0.856 g is obtained, that is 3.146 g of expected product.

Example 2

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - hydroxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Anti* Isomer

2.29 g of product obtained in Example 1 are put into suspension in 18.4 cm³ of 50% aqueous formic acid. The whole is taken under brisk agitation for fifteen minutes to 55°C.

It is cooled, 10 cm³ of water are added, the whole is vacuum-filtered, washed with water and concentrated under vacuum, acetone is added, the whole is vacuum-filtered, 30 cm³ of ether are added, the whole is agitated, vacuum-filtered and washed with ether, and 0.665 g of product is obtained. Further, a second yield of 0.123 g of product which crystallises out is obtained, that is 0.788 g.

0.735 g of the product is dissolved in 7.5 cm³ of ethanol and 7.5 cm³ of acetone. 70 mg of carbon black are added, the whole is vacuum-filtered, the solvents are driven off, the residue is disintegrated in ethanol, and washed with ethanol, and 0.450 g of a first yield, then 0.105 g in a second yield are obtained.

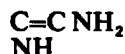
Infra Red



1774 cm⁻¹ (β-lactam)

1740 cm⁻¹

1676 cm⁻¹



1630 cm⁻¹

1520 cm⁻¹

Example 3

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid

Stage A: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate

1 g of ethyl γ - chloro - α - methoxyimino - acetylacetate, 3 cm³ of absolute ethanol and 0.42 g of crushed thiourea are placed together. The whole is agitated at ambient temperature for about two hours. It is diluted with 60 cm³ of ether, the hydrochloride obtained crystallises out, the whole is agitated vacuum-filtered, washed and dried, and 685 mg of hydrochloride are obtained. They are dissolved in 4 cm³ of water at 50°C, potassium acetate is added until pH 6, and the amine released crystallises out. The whole is cooled and vacuum-filtered, the residue being washed with water and dried, and 270 mg of expected product are obtained. M.Pt.=161°C. The product obtained has the *syn* configuration.

NMR (CDCl₃, 60 MHZ) p.p.m.: 4 (N—OCH₃), 6.7 (proton of the thiazole ring).

Stage B: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetate

4.6 g of product prepared according to the previous stage are dissolved at 30°C in 92 cm³ of methylene chloride. The solution is cooled to -10°C, 2.9 cm³ of triethylamine are added, the whole is cooled to -35°C, 6.1 g of trityl chloride are added over fifteen minutes, and the whole is left to return to ambient temperature, in all taking two hours thirty minutes. It is washed with water, then with 0.5 N hydrochloric acid and with sodium acetate in water. It is dried, concentrated, taken up with ether, concentrated again, then dissolved in methanol, water and ether are added, the whole is left to crystallise out, vacuum-filtered, then washed with ether, and 6.15 g of expected product are obtained. M.Pt.=120°C. the product obtained has the *syn* configuration.

Stage C: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic Acid

7.01 g of ester obtained in stage B are dissolved in 35 cm³ of dioxane. The solution is taken to 110°C in an oil bath and 9 cm³ of 2 N soda are added over five

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minutes, then the whole is left for thirty minutes at reflux under agitation. The sodium salt crystallises out. The whole is cooled, vacuum-filtered, washed with dioxane, then with ether, and a first yield of 5.767 g of salt is obtained. The mother solution is concentrated and a second yield of 1.017 g is obtained, that is 6.784 g of salt in all.

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3.06 g of salt are placed in 65 cm³ of methylene chloride and 6.5 cm³ of 2 N hydrochloric acid, and the whole is washed with water, dried and concentrated to dryness to obtain the free acid quantitatively. The product obtained has the *syn* configuration.

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NMR (DMSO, 60 MHZ) p.p.m.: 3.68 (N—OCH₃) 6.6 (proton of the thiazole ring).

Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporanic Acid

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The dry acid obtained in stage C is dissolved in 30 cm³ of dry methylene chloride. 0.78 g of dicyclohexylcarbodiimide is added and the whole is agitated for one hour at ambient temperature. The dicyclohexylurea formed is vacuum-filtered, and the filtrate is cooled to -10°C, and a solution of 1.01 g of 7-aminocephalosporanic acid in 13 cm³ of methylene chloride and 0.9 cm³ of triethylamine is added. The whole is left to return to ambient temperature, 1 cm³ of acetic acid is added, the whole is vacuum-filtered, the residue is washed with water containing hydrochloric acid, washed with water, dried, concentrated to dryness, and taken up with 10 ml of dioxane, and 1 cm³ of water and 3 cm³ of saturated solution of sodium acid carbonate are added. The whole is agitated, vacuum-filtered, washed and concentrated to dryness. It is taken up with methylene chloride, washed with 10 cm³ of water and 5 cm³ of normal hydrochloric acid, decanted, washed with water, dried and disintegrated in ether, and 1.747 g of crude product are obtained and purified by dissolving in ethyl acetate followed by precipitating with ether. 1.255 g of pure product are obtained.

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The product obtained has the *syn* configuration.

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The ethyl γ - chloro - α - methoxyimino - acetylacetate used at the start of Example 3 was prepared as follows:

22.5 g of ethyl γ - chloro - α - oximino - acetylacetate is placed in 100 cm³ of methylene chloride.

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The whole is placed in an ice bath and a fresh solution of diazomethane (containing 21.6 g/l), that is 275 cm³, is added slowly under agitation. The whole is left in contact for five minutes and the excess diazomethane is destroyed with a little quantity of alumina. The remainder is concentrated then purified by eluting on silica with methylene chloride. 11.93 g of expected product are obtained.

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The ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate used in Example 3 was also prepared as follows:

Stage α : Ethyl 2 - acetyl - 2 - methoxyimino - acetate

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180 g of crude ethyl 2 - acetyl - 2 - hydroxyimino - acetate are introduced into 900 cm³ of pure acetone. 234 g of potassium carbonate are added at 10°C under nitrogen; 103 cm³ of dimethyl sulphate are then introduced. The whole is agitated for 3 hours at ambient temperature, ice is added, the whole is poured into 4 litres of water, extracted with methylene chloride, washed with water and dried, and the solvents are distilled off. 185 g of expected product are obtained.

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Stage β : Ethyl 4 - bromo - 2 - methoxyimino - acetylacetate

197 g of product obtained as in stage α are placed in 1 litre of methylene chloride and 200 mg of para-toluene sulphonic acid are added. 1/10th of the solution of 191 g of pure bromine in 200 cm³ of methylene chloride are introduced at 20°C. When the reaction has started, the rest of the bromine solution is introduced over one hour at about 20°C. The whole is then left to rise to 25°C to complete the reaction. It is washed with iced water, extracted with methylene chloride and dried, and the solvent is distilled off. 268 g of expected product are obtained.

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Stage γ : Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate

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80 g of thiourea are introduced into 270 cm³ of ethanol and 540 cm³ of water. 268 g of product obtained in stage β are introduced, under nitrogen over half-an-hour, into 270 cm³ of ethanol. The whole is agitated for one hour at about 20°C. It is cooled to about 15°C and potassium acid carbonate is introduced in small

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portions until pH 5. The whole is vacuum-filtered, washed with water and dried, and 133.8 g of expected product are obtained. The product obtained is identical to that obtained in stage A.

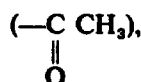
Example 4

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

0.975 g of the product obtained in Example 3 is agitated for ten minutes at 55°C in 4 cm³ of 50% aqueous formic acid. 4 cm³ of water are added, and the whole is vacuum-filtered and concentrated to dryness under vacuum. It is disintegrated in 2 cm³ of ethanol, vacuum-filtered and washed with ethanol, then with ether, and 0.428 g of pure product is obtained.

Analysis:	C ₁₈ H ₁₇ O ₇ N ₅ S ₂		
Calculated:	C% 42.19	H% 3.76	N% 15.37 S% 14.08
Found:	C% 42.3	H% 4.1	N% 15.2 S% 13.8

The product obtained has the *syn* configuration, NMR (DMSO 60 MHZ) p.p.m. 2.03



doublet at 9.58 J=8 HZ (CONH) 6.76 (proton thiazole ring).

Example 5

Diethylamine Salt of 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (methoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

The crude 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (methoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid obtained as indicated in Example 3 from the condensation of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid in the form of the anhydride prepared using dicyclohexyl carbodiimide and 40.8 g of 7-amino-cephalosporanic acid, is put into solution in 350 cm³ of dioxane. 350 cm³ of diethyl ether, then 33 cm³ of diethylamine are added slowly under agitation. The whole is agitated for 20 minutes, and the diethylamine salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid which has crystallised out is vacuum-filtered. This salt is washed twice with 30 cm³ of the above dioxane-ether mixture and 62.6 g of the salt are obtained. the filtrate is concentrated to a syrupy consistency and about 2 and a half litres of diethyl ether are added. The whole is agitated and vacuum-filtered. 110.3 g of expected diethylamine salt are obtained. The product obtained has the *syn* configuration.

Example 6

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (methoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

36 g of product obtained in Example 5 are added to 180 cm³ of 50% aqueous formic acid maintained at 50°C. The whole is agitated for 20 minutes at 50°C, and the triphenyl carbinol formed is vacuum-filtered. 180 cm³ of ethanol are added, and the whole is concentrated to dryness under reduced pressure. The residue is taken up with a mixture of 100 cm³ of water and 20 cm³ of ethanol and it is concentrated again. It is taken up with 100 cm³ of water, agitated for 15 minutes at 15°C, vacuum-filtered and washed with water, then with ether, and 15.6 g of expected product are obtained.

The product is identical to that obtained in Example 4.

Example 7

Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (methoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid
45.55 g of pure 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (methoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid obtained according to the processes of Examples 4 or 6 are mixed with 100 cm³ of distilled

water. 8 g of sodium acid carbonate are added progressively, whilst adding about 20 cm³ of ethanol.

80 cm³ of ethanol and 4.5 g of active charcoal are added thereto, the whole is agitated for 5 minutes, filtered, rinsed with ethanol and concentrated to dryness under vacuum. It is taken up with 100 cm³ of ethanol and concentrated to dryness, and the residue is dissolved in 100 cm³ of methanol. 2 litres of acetone are added, and the whole is agitated violently, vacuum-filtered, and rinsed with acetone, then with ether. After drying under vacuum, there are obtained 43.7 g of a white product which rehydrates in air to reach a final weight of 45.2 g. $[\alpha]_D^{20} = +55^\circ \pm 2^\circ$ (0.8% in water).

Analysis:

Calculated: C% 40.24 H% 3.38 N% 14.67 S% 13.43 Na% 4.81
Found: C% 40.3 H% 3.8 N% 14.4 S% 13.3 Na% 4.84

The product obtained has the *syn* configuration, NMR (60 MHZ D₂O) p.p.m.: 2.01 (COCH₃) doublet at 9.53 J=8 HZ (NHCO) 6.75 (thiazole proton).

Example 8

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetamido] - cephalosporanic Acid
Stage A: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetate

a) 9.7 g of ethyl 2 - hydroxyimino - 4 - chloro - acetylacetate, 30 cm³ of acetone and 9.15 cm³ of 3-iodopropene are cooled in ice and 27.5 cm³ of 2 N soda are added, then the whole is left for an hour-and-a-half at ambient temperature;

b) 3.8 g of thiourea are added to the reaction mixture, then this is maintained at 60°C for 15 minutes and then for 45 minutes at ambient temperature, the acetone is driven off, methylene chloride is added, then water, then potassium carbonate, the whole is agitated, decanted, extracted with methylene chloride, dried and concentrated to dryness, 9.75 g of residue are obtained which is chromatographed on silica, eluting with ether, 2.7 g of product are isolated and taken up with isopropyl ether, and the crystals are vacuum-filtered, rinsed and dried. 783 mg of expected product are obtained. M.Pt.=100°C. The product obtained has the *syn* configuration.

Stage B: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetate

511 mg of product prepared in stage A, 0.92 cm³ of dimethyl-formamide, 1.8 cm³ of methylene chloride and 0.29 cm³ of triethylamine are mixed. The mixture is cooled to -15°C and 615 mg of trityl chloride are added. The whole is left at ambient temperature for an hour-and-a-half, 2 cm³ of 1 N hydrochloric acid then 5 cm³ of water are added, the whole is decanted, dried and concentrated to dryness, and 1.28 g of crude product are obtained. The product obtained has the *syn* configuration.

Stage C: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetic Acid

1.28 g of product obtained in stage B, 6.2 cm³ of dioxane and 3 cm³ of 2 N soda are mixed and heated at 120°C. The whole is taken to reflux for one hour, the sodium salt crystallises out and is vacuum-filtered, rinsed with an ether-dioxane mixture, then dried and 805 mg of product are isolated.

This is taken up in 10 cm³ of methylene chloride and 3 cm³ of 1 N hydrochloric acid, agitated until obtaining a solution which is decanted, dried, concentrated to dryness, taken up with ether and vacuum filtered, and 715 mg of expected product are obtained. M.Pt.=170°C. The product obtained has the *syn* configuration.

Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetamido] - cephalosporanic Acid

470 mg of product prepared in stage C, 5 cm³ of methylene chloride and 130 mg of dicyclohexylcarbodiimide are mixed, rinsed with a little methylene chloride and left under agitation for one hour at ambient temperature, the dicyclohexylurea formed is vacuum-filtered, the filtrate is cooled and, under inert gas, 136 mg of 7-amino-cephalosporanic acid in solution in 2.4 cm³ of methylene chloride and 0.14

cm³ of triethylamine are added. The whole is left for an hour-and-a-half at ambient temperature, 2 cm³ of 1 N hydrochloric acid and water are added, the whole is agitated, decanted, washed with water, dried and concentrated, and 610 mg of crude product are obtained. The product obtained has the *syn* configuration.

Example 9

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - ((2 - propenyl) - oxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

The 610 mg of product obtained in Example 8 and 3 cm³ of 50% aqueous formic acid are heated at 60°C for 15 minutes, 4 cm³ of water are added, the whole is agitated, the triphenyl carbinol is vacuum-filtered, rinsed with water, the filtrate is concentrated to dryness under vacuum, taken up with water, disintegrated, vacuum-filtered and rinsed, and 120 mg of expected acid are obtained. M.Pt.≈160°C.

Ultra-Violet Spectrum

In ethanol: max 236 nm E₁¹=375 ε=18 000

inflection 252 nm E₁¹=316

inflection 295 nm E₁¹=138 ε=6 600

In an N/10 ethanol-hydrochloric acid mixture:

max 263 nm E₁¹=380 ε=18 300

inflection 280 nm E₁¹=317.

NMR (DMSO 90 MHZ) p.p.m.: 2.02 (OAc) 6.68 (thiazole proton). The product, therefore, has the *syn* configuration.

Example 10

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (ethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

Stage A: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - ethoxyimino - acetate

a) 19.4 g of ethyl γ - chloro - α - oxyimino - acetoacetate are placed in 60 cm³ of acetone and 14.3 cm³ of diethyl sulphate. The whole is cooled for 10 minutes in an ice bath and 55 cm³ of 2 N soda are added over 30 minutes, then the whole is agitated for 40 minutes;

b) 7.6 g of thiourea are added to the reaction medium, this is heated at 55°C for 20 minutes, the acetone is driven off, the remainder is taken up with ethyl acetate, 6.9 g of potassium carbonate are added, and the whole is agitated, decanted, extracted with ethyl acetate, dried and concentrated to dryness. 17.4 g of residue are isolated and chromatographed on silica, eluting with ether. The expected product is recovered, taken up with isopropyl ether, vacuum-filtered, rinsed and dried, and 2.8 g of expected product are obtained. M.Pt.=129°C. The product obtained has the *syn* configuration.

Stage B: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetate

3.16 g of product obtained in stage A, 6 cm³ of dry dimethyl-formamide, 12 cm³ of methylene chloride and 1.89 cm³ of triethylamine are placed under an inert gas. The mixture is cooled to -15°C and 3.98 g of trityl chloride are slowly added. The whole is left to stand for half-an-hour, the temperature is raised to +10°C, then the whole is maintained for three-and-a-half hours at ambient temperature. 13 cm³ of 1 N hydrochloric acid are added, and the whole is agitated, decanted, washed with 1 N hydrochloric acid, then with water. It is extracted with methylene chloride, dried and concentrated to dryness, and 7.89 g of crude residue are obtained. The product obtained has the *syn* configuration.

Stage C: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetic Acid

A mixture of 7.89 g of product obtained in stage B, 40 cm³ of dioxane and 19.5 cm³ of 2 N soda is heated at 110°C for one hour. The mixture is vacuum-filtered, rinsed with an ether-dioxane mixture, then with ether alone and dried. 6.25 g of sodium salt are obtained and taken up in 60 cm³ of methylene chloride and 20 cm³ of 1 N hydrochloric acid, the two phases are agitated, 20 cm³ of methanol are added, the whole is decanted, washed with water, extracted with a methylene chloride-methanol mixture, dried and concentrated, and 5.85 g of pure 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetic acid are isolated. The product obtained has the *syn* configuration.

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Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (ethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

3.43 g of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetic acid prepared in stage C are placed in 34 cm³ of methylene chloride, the suspension is cooled and 970 mg of dicyclohexyl carbodiimide are added, and the whole is rinsed with methylene chloride and agitated for one hour at ambient temperature. The dicyclohexyl-urea is vacuum-filtered.

The filtrate is cooled to -20°C and a solution (cooled at -2°C) of 1.02 g of 7-amino-cephalosporanic acid in 18 cm³ of methylene chloride and 1.06 cm³ of triethylamine is added in one go.

The whole is allowed to heat up for an hour-and-a-half, 1.8 cm³ of acetic acid are added, 9 cm³ of 1 N hydrochloric acid are added, the whole is agitated, decanted, washed with water, extracted with methylene chloride, dried and concentrated, and 4.56 g of expected product are obtained. The product obtained has the *syn* configuration.

Example 11

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (ethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

The 4.56 g of product obtained in Example 10 are placed in 23 cm³ of 50% aqueous formic acid, heated at 55°C for 15 minutes, then diluted with water (30 cm³), and the triphenyl carbinol is vacuum-filtered. The filtrate is concentrated to dryness, taken up with water, agitated, vacuum-filtered, rinsed and dried, and 116 mg of impure product are obtained. A second yield of 674 mg of crystalline product is obtained by concentrating the filtrate, that is in all 790 mg.

The following purification is carried out:

1.063 g of crude product are made into a paste in 5 cm³ of water, heated at 70°C for 5 minutes, cooled, agitated for half-an-hour, vacuum-filtered, rinsed and dried, and 815 mg of purified product are isolated. These 815 mg are taken up in 2 cm³ of water and 3 cm³ of acetone, and after slightly heating, the insoluble matter is vacuum filtered, 3 cm³ of water added, and the whole is heated to 60°C and the acetone is driven off by bubbling in nitrogen, the grains formed are vacuum-filtered, rinsed with water, then with ether, and 438 mg of expected product are isolated.

Analysis:	C ₁₇ H ₁₉ O ₇ N ₅ S ₂
Calculated:	C% 43.49 H% 4.08 N% 14.92 S% 13.66
Found:	C% 44.5 H% 4.4 N% 14.8 S% 13.3

The product has the *syn* configuration NMR (60 MHZ DMSO) p.p.m.: 2.05 (OAc) 6.75 (proton of the thiazole ring).

Example 12

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methylethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

Stage A: Ethyl 2 - acetyl - 2 - (1 - methyl - ethoxyimino) - acetate

39.8 g of ethyl 2 - acetyl - 2 - hydroxyimino - acetate are placed in 200 cm³ of pure acetone. The whole is cooled in an ice bath and 52 g of potassium carbonate are added then, over half-an-hour, 25 cm³ of 2-iodopropane. The whole is then agitated for 2 hours, 800 cm³ of water and 500 cm³ of methylene chloride are added, the whole is agitated, decanted, extracted with methylene chloride, dried, vacuum-filtered and concentrated, and 41.5 g of expected product are isolated.

Stage B: Ethyl 4 - bromo - 2 - (1 - methyl - ethoxyimino) - acetylacetate

The 41.5 g of product obtained in the previous stage are placed in 190 cm³ of methylene chloride with traces of *para*-toluene-sulphonic acid. The whole is agitated and a solution of 11.9 cm³ of bromine in 50 cm³ of methylene chloride is introduced, over one hour, at ambient temperature. the whole is agitated, iced water is added, the whole is decanted, extracted with methylene chloride, washed with iced water, dried and concentrated, and 55 g of expected derivative are isolated.

Stage C: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - (1 - methyl - ethoxyimino) - acetate

14.9 g of thiourea are placed in 55 cm³ of ethanol and 105 cm³ of water and a solution of the 55 g of product prepared in stage B in 55 cm³ of ethanol is added

over 40 minutes. The whole is agitated for two-and-a-half hours at ambient temperature, 220 cm³ of 10% sodium acid carbonate in water are added, the whole is agitated, vacuum-filtered, rinsed and dried, and 42.15 g of crude product are isolated and chromatographed on silica eluting with ether, the fractions rich in expected product are recovered, then concentrated, the crystals are taken up with isopropyl ether, vacuum-filtered and rinsed, and 10.75 g of expected product are obtained. The product obtained has the *syn* configuration.

Stage D: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methyl - ethoxyimino) - acetate

11 g of product obtained in stage C are placed in 20 cm³ of dry dimethyl-formamide, 40 cm³ of methylene chloride and 6.2 cm³ of triethylamine. The mixture is cooled and 13.2 g of trityl chloride are slowly added, the whole is agitated for two-and-a-half hours, 43 cm³ of normal hydrochloric acid are added, the whole is agitated, decanted, washed with 40 cm³ of water, extracted with methylene chloride, dried, vacuum-filtered and concentrated to dryness, and 27.7 g of expected product are obtained. The product obtained has the *syn* configuration.

Stage E: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methyl - ethoxyimino) - acetic Acid

A mixture of 27.7 g of product obtained in stage D, 150 cm³ of dioxane and 65 cm³ of 2 N soda are refluxed for two hours. The sodium salt crystallises, the mixture is cooled, vacuum-filtered, rinsed with a 1:1 ether-dioxane mixture and dried, and 16.85 g of crude sodium salt are obtained. 15.9 g of this sodium salt are dissolved in 15.9 g of dimethyl-formamide, 100 cm³ of water and about 500 cm³ of methanol. 30 cm³ of 2 N hydrochloric acid are added, the methanol is driven off, the remainder is diluted with water, vacuum-filtered, rinsed and dried, the 9.8 g of viscous product obtained are taken up in 220 cm³ of a 50:50 methylene chloride-methanol mixture, concentrated to dryness, taken up with ether and disintegrated, and the crystals are vacuum-filtered, rinsed and dried. 4.9 g of expected acid are obtained. M.Pt. $\approx$ 170°C.

An analytical sample is obtained by dissolving 300 mg of crude product in 2 cm³ of methylene chloride and 1 cm³ of methanol, the whole is diluted with water and methylene chloride, then agitated, the crystals are vacuum-filtered, rinsed with methylene chloride and with water, then dried and 230 mg of pure product are isolated for the analysis.

Analysis:

Calculated: C% 68.77; H% 5.34; N% 8.91; S% 6.8

Found: C% 68.6 H% 5.5 N% 8.8 S% 6.8

The product obtained has the *syn* configuration.

Stage F: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methyl - ethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid

Under argon, 4.89 g of acid obtained in stage E are placed in 13.5 cm³ of dimethyl-formamide. After dissolution, the solution is cooled in an ice bath and 1.62 g of dicyclohexylcarbodiimide in 16 cm³ of methylene chloride are added. The dicyclohexylurea crystallises. The mixture is agitated in an ice bath, vacuum-filtered, rinsed with methylene chloride and dried, and 1.424 g of dicyclohexylurea are isolated. The filtrate is cooled in a methanol-ice bath and a solution of 1.41 g of 7-amino-cephalosporanic acid in 30 cm³ of methylene chloride and 1.45 cm³ of triethylamine is added. The whole is agitated for 3 hours at ambient temperature, 20 cm³ of normal hydrochloric acid are added, the whole is agitated, decanted, extracted with methylene chloride, dried and vacuum-filtered, and 9.05 g of expected product-initial product mixture are obtained.

This is taken up in methylene chloride, initiated and allowed to crystallise under agitation, the crystals are vacuum-filtered, rinsed and dried, 1.6 g of pure initial product are obtained; the filtrate is concentrated to dryness, residue is taken up in isopropyl ether with vigorous agitation and 4.91 g of insoluble viscous product which is the expected product are isolated. The product obtained has the *syn* configuration.

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1,580,621

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Example 13

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1 - methyl - ethoxyimino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid

4.91 g of crude product obtained in Example 12 are placed in 30 cm³ of 50% aqueous formic acid. The whole is agitated in a bath of water at 60°C and diluted with water, the triphenylcarbinol formed is vacuum-filtered, rinsed with water and dried and 1.39 g of triphenylcarbinol are isolated. The filtrate is concentrated to dryness, taken up with water, disintegrated, vacuum-filtered, rinsed with water and dried, and 800 mg of expected product are obtained.

A sample for analysis is obtained by dissolving 972 mg of crude product in 4 cm³ of methanol, this is diluted with 20 cm³ of ether, the insoluble matter is vacuum-filtered, rinsed, dried and 404 mg of pure expected acid are obtained. M.Pt. ≈ 200°C.

Analysis:

Calculated: C% 44.71; H% 4.38; N% 14.48; S% 13.26
Found: C% 44.5 H% 4.5 N% 14.1 S% 13.2

The product has the *syn* configuration NMR (60 MHz DMSO) p.p.m.: 2.01 (CH₃CO); doublet at 9.46 J=8 HZ) CONH); 6.7 (proton of the thiazole ring).

Example 14

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid

Stage A: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - hydroxyimino - acetate, *Anti* Isomer

32.2 g of ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - hydroxyimino - acetate, anti isomer prepared according to stage A of Example 1, 90 cm³ of dried dimethyl-formamide and 24 cm³ of triethylamine are placed together. Then 47.6 g of trityl chloride are introduced at -30°C in small portions over half-an-hour, the whole is left to heat up spontaneously for two-and-a-half hours, and 150 cm³ of 2 N hydrochloric acid and 600 cm³ of water are added. The whole is agitated for 15 minutes, vacuum filtered made into a paste 3 times with ether, taken up with a mixture of methanol, triethylamine and water, agitated, vacuum, filtered, rinsed with aqueous methanol and dried, and 60.2 g of expected product are isolated, 3.4 g of crude product are recrystallised from a methylene chloride-methanol mixture and 3 g of pure product are obtained. M.Pt. = 260°C.

Stage B: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetate, *Anti* Isomer

11.5 g of product obtained in stage A above, 5.85 g of potassium carbonate and 25 cm³ of dry dimethyl-formamide are placed together. The whole is cooled to 15°C and 16.7 cm³ of ethyl sulphate are added, the whole is left for 4 hours at ambient temperature, 420 cm³ of water and 250 cm³ of ethyl acetate are added, the whole is agitated, decanted, washed with water, extracted with ethyl acetate, dried, filtered evaporated to dryness, taken up with ethanol, left to crystallise, rinsed with ethanol, made into a paste with petroleum ether and dried, and 6.6 g of expected product are obtained. M.Pt. = 165°C. This product can be recrystallised as follows:

797 mg are dissolved in a 50:50 mixture of methylene chloride and ethanol, the solution is vacuum-filtered, concentrated to evaporate off the methylene chloride and the product is left to recrystallise; the mixture is vacuum-filtered, mixed with ethanol and dried, and 596 mg of pure product are isolated. M.Pt. 260°C.

Stage C: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetic Acid, *Anti* Isomer

7.29 g of product prepared in stage B above are placed in 45 cm³ of dioxane and 9 cm³ of 2 N soda. The whole is heated to 50°C in a bath of water under agitation for 1 hour 50 minutes, then cooled, crystallisation is initiated in iced water, the crystals are vacuum-filtered and rinsed with ether and 4.2 g of sodium salt are obtained. The salt is taken up in 50 cm³ of methylene chloride, 40 cm³ of water and 11 cm³ of normal hydrochloric acid, then agitated, decanted, extracted with methylene chloride, washed with water, dried, vacuum-filtered and concentrated to dryness, the residue is taken with 50 cm³ of ether and agitated, the crystals are vacuum-filtered and rinsed with ether, and 3.27 g of expected product are obtained.

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M.Pt.=about 200°C with decomposition.

N.M.R. (60 MHZ CDCl₃) p.p.m.=7.66 (proton of the thiazole ring).
7.36 (protons of the trityl group).

Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - ethoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Anti Isomer*

4.1 g of acid obtained in stage C above, 36 cm³ of tetrahydrofuran, 27 cm³ of methylene chloride and 0.99 cm³ of N-methyl morpholine are placed under inert gas. The mixture is cooled to -20°C and 1.17 cm³ of isobutyl chloroformate are introduced, drop by drop. The whole is left for 3 minutes at this temperature, cooled to -35°C and a solution of 2.45 g of 7-amino-cephalosporanic acid in 4.5 cm³ of methylene chloride and 2.52 cm³ of triethylamine is added. The whole is left to heat up spontaneously for 2-and-a-half hours, the solvents are driven off, and the remainder is taken up with a mixture of methylene chloride, water and normal hydrochloric acid until pH 1-2. The whole is extracted with methylene chloride, rinsed with water, dried, vacuum-filtered, concentrated, taken up with ethyl acetate, diluted with isopropyl ether, agitated, vacuum-filtered, rinsed with isopropyl ether and dried, and 4.87 g of expected product *anti isomer* are obtained. Purification is obtained as follows:

The 4.87 g of product above are dissolved in 10 cm³ of ethyl acetate while heating, the solution is diluted slowly with isopropyl ether, agitated, vacuum-filtered, rinsed and dried, and 4.53 g of purified product are obtained.

Example 15

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - ethoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Anti Isomer*

The 4.27 g of purified product obtained in Example 14 are placed in 20 cm³ of 50:50 aqueous formic acid. The mixture is heated to 60°C in a bath of water, agitated for 20 minutes, cooled and diluted with water, and agitated for 10 minutes, then the triphenyl carbinol is vacuum-filtered, rinsed with water and 1.44 g thereof are obtained. Ethanol is added to the filtrate and the whole is concentrated under vacuum. The residue is taken with ethanol which is driven off again under vacuum, 30 cm³ of water are added to the residue, the mixture formed is agitated for one hour in a bath of iced water, vacuum-filtered, rinsed with water and dried, and 2.06 g of expected product are obtained.

Purification is obtained as follows:

The 2.06 g above are dissolved in 5 cm³ of 10% aqueous sodium bicarbonate and 5 cm³ of water. The cloudy liquid is vacuum-filtered and rinsed with water, pure formic acid is added, drop by drop, until pH 3-4, the crystals obtained are vacuum-filtered after 12 hours at ambient temperature, rinsed with water and dried, and 1.73 g of pure product are obtained.

M.Pt.=about 200°C with decomposition.

N.M.R. (60 MHZ DMSO) p.p.m.=2.04 (CH₃CHO); 7.5 (proton of the thiazole ring).

Example 16

3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methylethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Anti Isomer*

Stage A: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methylethoxy - imino) - acetate, *Anti Isomer*

6.86 g of ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - hydroxyimino - acetate, the anti isomer prepared according to stage A of Example 14, 3.51 g of potassium carbonate in 15 cm³ of dimethyl-formamide and 7.7 cm³ of isopropyl iodide are placed under an inert gas. The mixture is left under agitation for 4-and-a-half hours, 250 cm³ of distilled water and 150 cm³ of ethyl acetate are added, the whole is agitated, decanted, washed with water, extracted with ethyl acetate, dried, vacuum-filtered, concentrated to dryness, taken up with ethanol, left to crystallise after initiation, vacuum-filtered, rinsed with ethanol and made into a paste with isopropyl ether, and 3.26 g of expected product are obtained. M.Pt.=182°C.

23	1,580,621	23
	Stage B: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methylethoxy - imino) - acetic Acid, <i>Anti</i> Isomer	
5	6.8 g of product obtained in stage A above are placed in 41 cm ³ of dioxane and 8.15 cm ³ of 2 N soda. The whole is heated at 55°C for 2 hours in a bath of water, then cooled, 9.5 cm ³ of 2 N hydrochloric acid are added, a pH of 2—3 is obtained, the dioxane is driven off, the remainder is left to crystallise, diluted with water, agitated, vacuum-filtered, rinsed with ether, made into a paste with ether and dried, and 5.87 g of expected product are obtained.	5
10	M.Pt.=240°C with decomposition. N.M.R. (CDCl ₃ 60 MHZ) p.p.m.=7.66 (proton of the thiazole ring), 7.31 (trityl group).	10
	Stage C: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (1 - methylethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, <i>Anti</i> Isomer	
15	5.66 g of acid obtained in stage B above are placed in a mixture of 48 cm ³ of tetrahydrofuran, 48 cm ³ of methylene chloride and 1.32 cm ³ of N-methylmorpholine. the whole is heated to dissolution, cooled to -20°C and 1.56 cm ³ of isobutyl chloroformate are added, the whole is left for 10 minutes between -20°C and -10°C, then cooled to -35°C and 3.26 g of 7-amino-cephalosporanic acid in 60 cm ³ of methylene chloride and 3.36 cm ³ of dry triethylamine are introduced in one go. The whole is left to heat up and agitated for 3 hours 30 minutes, the solvents are driven off, the remainder is taken up with ethyl acetate, total dissolution is observed, the whole is diluted with isopropyl ether, agitated, vacuum-filtered, rinsed with petroleum ether and dried and 5.42 g of expected product are obtained.	15
20		20
25	The product is purified by dissolving with heating 5.82 g of product obtained according to the process above in 20 cm ³ of ethyl acetate and this is diluted with 200 cm ³ of isopropyl ether, vacuum-filtered and dried, and 4.82 g of expected product are isolated.	25
	Example 17	
30	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1 - methylethoxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, <i>Anti</i> Isomer	30
35	3.62 g of product obtained in Examples 16 and 16 cm ³ of 50—50 aqueous formic acid are placed together. The mixture is heated to 60°C for 20 minutes, then cooled to 20°C, 16 cm ³ of water are added, the whole is agitated, the triphenyl carbinol formed is vacuum-filtered, rinsed with water and dried, and 1.23 g thereof are obtained.	35
40	This is concentrated to dryness under vacuum, taken up with ethanol which is then driven off under vacuum, taken up with water, and agitated, crystallisation is initiated by cooling, the crystal-gum mixture obtained is vacuum-filtered, rinsed with water and dried, and 1.68 g of crude expected product are isolated.	40
45	A pure sample is obtained by operating as follows: 2 g of product are dissolved in 5 cm ³ of 10% aqueous sodium bicarbonate and 5 cm ³ of water, the solution is agitated for 10 minutes, vacuum-filtered and rinsed with water, formic acid is added until pH=3, the whole is agitated for one hour in an ice bath, vacuum-filtered and rinsed with water, and the gum is dissolved in 10 cm ³ of ethanol while heating, cooled in ice water, vacuum-filtered, and rinsed with ethanol, then with ether. 748 mg of purified product are obtained. In addition, the formation of a crystalline deposit is observed in the filtrate, which is diluted with ether without causing precipitation, the crystals are vacuum-filtered and rinsed with an ethanol-ether mixture, then with ether. 177 mg of pure crystalline product, the <i>anti</i> isomer, are thus obtained.	45
50	M.Pt.=about 200°C with decomposition. N.M.R. (DMSO 60 MHZ) p.p.m.=7.46 (proton of the thiazole ring); 4.43 (tertiary proton of the isopropyl group).	50
55		55
	Example 18	
60	3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (2 - propenyloxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, <i>Anti</i> Isomer	60
	Stage A: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (2 - propenyloxy - imino) - acetate, <i>Anti</i> Isomer	
	6.86 g of ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - hydroxyimino - acetate, the <i>anti</i> isomer prepared according to stage A of Example 14, 3.51 g of	

potassium carbonate, 15 cm³ of dimethyl formamide and 7 cm³ of allyl iodide are placed under inert gas. The whole is agitated for 5 hours at ambient temperature, 250 cm³ of water and 150 cm³ of ethyl acetate are added, the whole is agitated, decanted, washed with water extracted with ethyl acetate, dried, vacuum-filtered, concentrated to dryness and taken up with ethanol, crystallisation is initiated, the whole is cooled in iced water, left to crystallise under agitation for half-an-hour and vacuum-filtered, the crystals are rinsed with ethanol and 4.72 g of expected product are obtained.

The product is purified in the following manner:

215 mg of above product are dissolved in 2 cm³ of ethanol and 2 cm³ of methylene chloride. The filtrate is concentrated, diluted with ethanol and left to crystallise in iced water, vacuum-filtered, rinsed with ethanol and dried, and 70 mg of purified product are obtained.

M.Pt.=90°C (pasty); M.Pt.=160°C (clear).

Stage B: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (2 - propenyloxy - imino) - acetic Acid, *Anti* Isomer

3.71 g of product obtained in stage A above are placed in 22 cm³ of dioxane and 4.5 cm³ of 2 N soda. The mixture is heated to 55°C in a bath of water for 1 hour 50 minutes, then cooled, 5.25 cm³ of 2 N hydrochloric acid are added until pH=2, the dioxane is driven off, a gum is obtained which is diluted with water, cooled in iced water, vacuum-filtered, rinsed with water, then made 3 times into a paste with ether. 2.85 g of expected product are obtained.

M.Pt.=198°C (decomposition).

N.M.R. (CDCl₃, 90 MHz) p.p.m.=7.64 (proton of the thiazole ring), 7.27 (protons of the trityl).

Stage C: 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - (2 - propenyloxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Anti* Isomer

2.82 g of acid obtained in stage B above, 24 cm³ of dry tetrahydrofuran, 24 cm³ of methylene chloride and then, after dissolution, 0.66 cm³ of N-methyl morpholine are placed together. The whole is cooled to -20°C and 0.78 cm³ of isobutyl chloroformate is added.

The whole is agitated for 3 minutes at -20°C, then cooled to -35°C and a solution of 1.63 g of 7-amino-cephalosporanic acid in 30 cm³ of methylene chloride and 1.68 cm³ of triethylamine is added. The whole is left to heat up for 3 hours, the solvents are driven off, and the remainder is taken up with methylene chloride, 50 cm³ of water are added and 15 cm³ of normal hydrochloric acid. The whole is agitated, decanted, washed with water, extracted with methylene chloride, dried, vacuum-filtered, rinsed with methylene chloride, concentrated to dryness, taken up with ethyl acetate, diluted with isopropyl ether, agitated, vacuum-filtered and rinsed with isopropyl ether, and 3.08 g of expected product are obtained.

Purification is obtained as follows:

3.59 g of product obtained as above are dissolved in 15 cm³ of ethyl acetate, diluted with isopropyl ether and agitated, the precipitate is vacuum-filtered and rinsed with isopropyl ether, and 3.33 g of purified product are isolated.

Example 19

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2 - propenyloxyimino) - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Anti* Isomer

2.53 g of product obtained in Example 18 are placed in 11.5 cm³ of 50—50 aqueous formic acid.

The mixture is heated to 60°C for 20 minutes, diluted with water, cooled to ambient temperature, vacuum-filtered and rinsed with water, and the triphenyl carbinol formed is dried and 963 mg thereof are obtained.

The mother liquors are concentrated to dryness under vacuum, ethanol is added, then driven off, the gum is taken up in 15 cm³ of water, disintegrated, vacuum-filtered, rinsed with water and dried, and 1.275 g of expected product are obtained.

The product is purified as follows:

1.63 g of crude product are suspended in 15 cm³ of ethanol, the whole is heated to reflux, vacuum-filtered and rinsed with ethanol, and 877 mg of insoluble product are recovered. 20 cm³ of ether are added to the filtrate, the insoluble matter is

vacuum-filtered, rinsed with a 1:1 ethanol-ether mixture and dried, and 97 mg of a second insoluble part are isolated. The filtrate is concentrated to half, crystallisation of the product is observed, and this product is vacuum-filtered, rinsed first with ethanol, then with ether and dried, and 162 mg of pure product, the anti-isomer, are isolated, M.Pt.=180°C (pasty).

N.M.R. (DMSO 60 MHz) p.p.m.=7.48 (proton of the thiazole ring); 2.04 (protons of the acetyl group).

Example 20

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, Syn Isomer

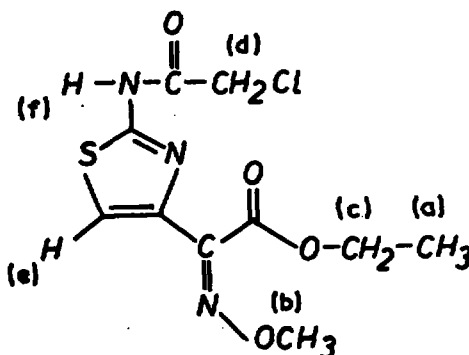
Stage A Ethyl 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxy - iminoacetate, Syn Isomer

45.8 g of ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate, the *syn* isomer prepared according to stage A of the Example 3 are placed in 200 cm³ of methylene chloride. 20 cm³ thereof are distilled off to dry the mixture, which is then cooled to 10°C and 50 cm³ of pyridine are added. 41 g of monochloroacetic anhydride are added and the whole is heated slightly to dissolution. It is left for 6 hours at 20°C under nitrogen, 5 cm³ of water are added, and the whole is agitated and poured into 300 cm³ of iced 2 N hydrochloric acid. The whole is decanted, extracted with methylene chloride, washed with water, with sodium acid carbonate, and with water dried, passed over charcoal, and concentrated, and 300 cm³ of isopropyl ether are added. This product crystallises. It is concentrated until a thick paste is obtained, chilled, vacuum-filtered, washed with isopropyl ether and dried, and 45.4 g of product are obtained. M.Pt.=113°C.

A pure sample is obtained by recrystallisation from a mixture of methylene chloride and isopropyl ether.

M.Pt.=118°C.

N.M.R. (CDCl₃, 60 MHz).



(a) triplet centred on 1.38 p.p.m. J=7 Hz;

(b) singlet 4.05 p.p.m.;

(c) quadruplet centred on 4.44 p.p.m. J=7 Hz;

(d) singlet 4.33 p.p.m.;

(e) singlet 7.27 p.p.m.;

(f) singlet 9.95 p.p.m.

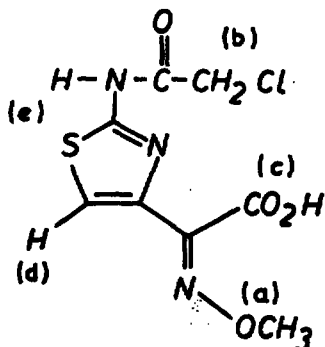
Stage B: 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetic Acid, Syn Isomer

46 g of product obtained in stage A above are placed in 230 cm³ of absolute ethanol. 30 cm³ of pure concentrated aqueous sodium hydroxide solution are added at 20°C under nitrogen. The product dissolves, the sodium salt begins to crystallise out, then the medium congeals into a mass. After 16 hours it is vacuum-filtered and washed with ethanol. The salt obtained is dissolved in water and chilled, 100 cm³ of 2 N hydrochloric acid are added, the whole is saturated with sodium chloride, and extracted with ethyl acetate containing 10% of ethanol. The whole is dried, passed over charcoal, distilled under vacuum, the water is entrained with benzene, the remainder is taken up with methylene chloride, distilled to dryness, taken up with methylene chloride, chilled, vacuum-filtered, washed with methylene chloride and dried, and 34.5 g of expected product are obtained.

32

M.Pt.=about 200°C. The product is purified by recrystallisation from an acetone-isopropyl ether mixture.

Analysis: $C_9H_8O_4N_2ClS$ = 277.68
 Calculated: C% 34.60 H% 2.90 N% 15.13 Cl% 12.77 S% 11.55
 Found: C% 34.8 H% 2.8 N% 14.8 Cl% 12.6 S% 11.5
 N.M.R. (DMSO 60 MHz).



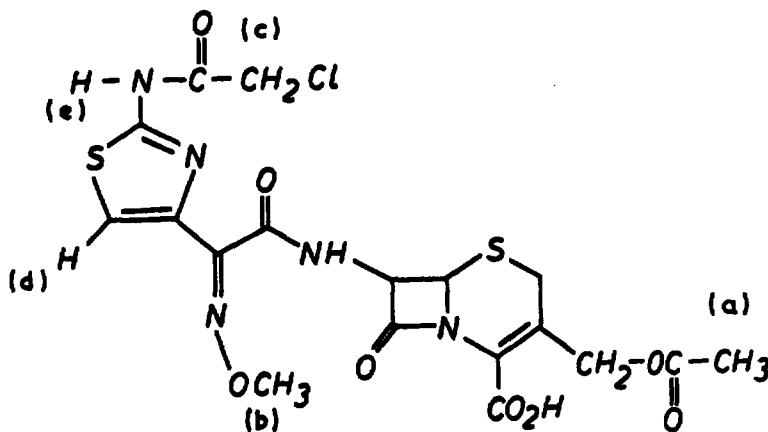
(a) singlet 3.92 p.p.m.; (d) singlet 7.58 p.p.m.;
 (b) singlet 4.38 p.p.m.; (e) singlet 12.6 p.p.m.
 (c) singlet about 5 p.p.m.;

State C: 3 - acetoxymethyl - 7 - [2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

15.3 g of product obtained in stage B above are placed in 80 cm³ of methylene chloride. At 5°C, 8 cm³ of triethylamine are added. At 0°C under nitrogen, 3.8 cm³ of thionyl chloride and 26 cm³ of methylene chloride are introduced. The whole is left for 15 minutes at 0°C, then 7 cm³ of triethylamine are added. 13.6 g of 7-aminocephalosporanic acid in 100 cm³ of methylene chloride and 14 cm³ of triethylamine are introduced at 0°C under nitrogen. The whole is left to return to 20°C, then agitated for one hour. This solution is distilled to dryness under vacuum at about 30—35°C. The residue is dissolved in 250 cm³ of water and passed over charcoal, and 50 cm³ of 2 N hydrochloric acid are added. The precipitate is vacuum-filtered and washed with water. The crude product obtained is put into suspension in 80 cm³ of ethanol. At +5°C, 7 cm³ of triethylamine are added. 15 cm³ of 4 N sulphuric acid are added in a single lot under agitation at +5°C, and after 15 minutes the crystallised product is vacuum-filtered, washed with ethanol by pasting, then with ether, and dried under vacuum, and 18.6 g of expected product are obtained.

$[\alpha]_D^{20} = +26 \pm 1^\circ$ (at 1% in dimethyl formamide).

N.M.R. (DMSO 60 MHz).



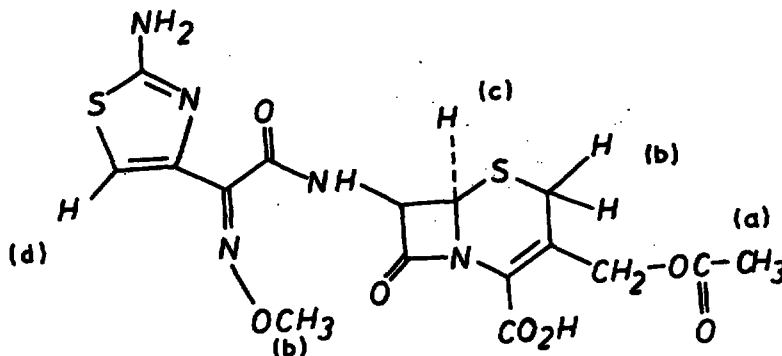
(a) singlet 2.03 p.p.m.; (c) singlet 4.38 p.p.m.;
 (b) singlet 3.90 p.p.m.; (d) singlet 7.45 p.p.m.

Stage D: 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido]ceph - 3 - em - 4 - carboxylic Acid; *Syn* Isomer

5.32 g of acid obtained in stage C above are put into suspension in 10.6 cm³ of water and 912 mg of thiourea. At 20°C, 1 g of potassium acid carbonate is added. After dissolution, the whole is agitated for 6 hours at about 20°C under nitrogen. Gummy precipitation begins after about an hour-and-a-half. 30 cm³ of water and 3 cm³ of formic acid are then added. The whole is cooled to 5°C. It is vacuum filtered and washed with water containing 10% of formic acid. The residue is dissolved at about 5°C in 30 cm³ of water containing triethylamine. At 5°C, 3 cm³ of formic acid are added, and the precipitate is vacuum-filtered and washed by making into a paste with water containing formic acid. The dark brown gum is eliminated. The aqueous phases are collected and treated with charcoal. A clear yellow solution is obtained which is saturated with ammonium sulphate. The precipitate is vacuum-filtered, made into a paste with water, vacuum-filtered and washed with water, and a precipitate A is obtained.

The mother liquors are saturated with ammonium sulphate, which gives a precipitate which is vacuum-filtered and washed 3 times with a minimum of water, and precipitate B is obtained.

The precipitates A and B are put together. They are taken up with ethanol, agitated for one hour at 20°C and left for 16 hours at 0°C. They are vacuum-filtered, washed with ethanol, then with ether and dried under vacuum, and 3.47 g of expected product, the *syn* isomer, are obtained.



N.M.R. (DMSO 60 MHz).

- (a) singlet 2.03 p.p.m.;
- (b) singlet 3.55 p.p.m.;
- (c) doublet 5.19 p.p.m. J=5 Hz;
- (d) singlet 6.8 p.p.m.

This product is identical to that obtained in Examples 4 and 6.

Example 21

Diethylamine Salt of 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

Stage A: Ethyl 2 - acetyl - 2 - methoxyiminoacetate

4.69 kg of ethyl 2 - acetyl - 2 - hydroxyimino - acetyl - acetate corresponding to 4.21 kg of pure product are introduced into 21 litres of pure anhydrous acetone. At 20—25°C, 6.1 kg of potassium carbonate are added. The suspension is agitated for 10 minutes, then, at 20—25°C, 3.72 kg of dimethyl sulphate are added. The whole is agitated for 3 hours at 20—25°C. It is then poured into 126 litres of demineralised water, and extracted using 4 times 5 litres, then 2 litres of methylene chloride. The whole is washed with 10 litres of demineralised water. It is dried, vacuum-filtered and rinsed with 2 litres of methylene chloride. It is distilled under vacuum and 4.88 kg of expected product are obtained.

R_f=0.7 (in thin layer chromatography on silica; eluant: 9:1 methylene chloride-ethyl acetate).

The product is identical to that obtained in stage α of Example 3.

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Stage B: Ethyl 4 - bromo - 2 - methoxyimino - acetylacetate

3.53 kg of product obtained in stage A above are placed in 18.6 litres of methylene chloride and 3.5 g of *para*-toluene sulphonic acid. A solution of 2.96 kg of bromine in 3.5 litres of methylene chloride is added to the above solution over 30 minutes, the temperature being maintained at $22^{\circ}\text{C} \pm 1^{\circ}\text{C}$. A release of hydrobromic acid gas is observed 15 minutes after the introduction. The whole is agitated for 45 minutes at 22°C , then poured in another flask and washed with 2 times 14 litres of chilled demineralised water. The washings are extracted with 2 times 3.5 litres of methylene chloride. They are dried, filtered, rinsed with methylene chloride and distilled under vacuum. 4.73 kg of expected product are obtained.

This product is identical to that obtained in stage β of Example 3.

Stage C: Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate, *Syn Isomer*

1.43 kg of thiourea are introduced into 3.55 litres of ethanol and 7.1 litres of demineralised water. The whole is agitated for 10 minutes at 20°C , then, at $20-25^{\circ}\text{C}$, 4.730 kg of product prepared in stage B above in 3.55 litres of ethanol are added. The whole is agitated for 3 hours at $20-25^{\circ}\text{C}$. It is cooled to $15-20^{\circ}\text{C}$ and neutralised to pH 7 with about 1.6 litres of 22°Bé ammonia.

The whole is agitated for a further 15 minutes at $20-25^{\circ}\text{C}$. It is vacuum-filtered, and washed with 5 times 1.8 litres of demineralised water and dried. 2.947 kg of expected product are obtained. M.Pt. = 162°C .

The product is identical to that obtained in stages A and γ of Example 3.

Stage D: Ethyl 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetate, *Syn Isomer*

3.41 kg of product obtained in stage C above are placed in 17 litres of methylene chloride and 2.275 litres of triethylamine. The whole is agitated for 15 minutes, and 4.55 kg of trityl chloride are added over one hour under agitation and nitrogen at $20-25^{\circ}\text{C}$. The whole is agitated for 20 hours at $20-25^{\circ}\text{C}$ under nitrogen, crystallisation of triethylamine hydrochloride takes place.

The liquid is poured in another flask and washed with 10.2 litres of chilled 0.5 N hydrochloric acid and twice 10.2 litres of iced demineralised water. The washings are extracted with 1.7 litres of methylene chloride. They are dried, filtered and rinsed with 1.7 litres of methylene chloride. They are distilled to dryness under vacuum at a temperature below 50°C .

8.425 kg of crude product are obtained.

This product is redissolved at $20-25^{\circ}\text{C}$ in 8.4 litres of methanol, and 2.8 litres of demineralised water are added over one hour at $20-25^{\circ}\text{C}$ under agitation, crystallisation being initiated. The whole is agitated for a further hour, vacuum-filtered, made into a paste with twice 1.7 litres of methanol containing 25% of water, and dried at 40°C , and 7.165 kg of expected product are obtained.

The product is identical to that obtained in stage B of Example 3.

Stage E: Sodium Salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic Acid, *Syn Isomer*

4.175 kg of product obtained in stage D above are introduced into 20.9 litres of ethanol. The whole is taken to reflux under agitation and nitrogen. Total dissolution is obtained at temperatures above 55°C .

5.235 litres of approximately 2 N soda are introduced at reflux under nitrogen. Rapid crystallisation takes place. The whole is agitated for one hour at reflux under nitrogen. It is brought to $20-25^{\circ}\text{C}$ and maintained for two hours at this temperature. It is vacuum-filtered, washed with 4 times 2.1 litres of ethanol and dried, and 4.02 kg of expected product are obtained.

Stage F: 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic Acid, *Syn Isomer*

500 g of product obtained in stage E above corresponding to 440 g of dry product are placed in 2.5 litres of methylene chloride. 2 litres of approximately normal hydrochloric acid are added over 2 minutes at $20-25^{\circ}\text{C}$ under agitation and nitrogen. The whole is agitated for two hours at $20-25^{\circ}\text{C}$ under nitrogen. The chloromethylenic phase is decanted off and washed with 3 times 2 litres of demineralised water. The washings are extracted with 1 litre of methylene chloride. It is dried, 25 g of charcoal are added, it is vacuum-filtered, rinsed with methylene

chloride and distilled to dryness, and 481 g of crude product are obtained. They are taken up with 2.1 litres of isopropyl ether. They are vacuum-filtered and washed with twice 420 cm³ of isopropyl ether. They are dried under vacuum until constant weight, and 424.6 g of expected product are obtained.

5 The product is identical to that obtained in stage C of Example 3. 5

Stage G: Diethylamine Salt of 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

200 g of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid
10 obtained in stage F above, then 1200 cm³ of methylene chloride are placed in a flask. The suspension is heated to reflux under agitation under inert gas, then at ordinary pressure 600 cm³ of methylene chloride are distilled off. The remainder is brought to 18—20°C, then 54 g of dicyclohexyl carbodiimide in 54 cm³ of methylene chloride are introduced, this temperature being maintained. The whole
15 is agitated for one hour at 18—20°C under an inert gas then at this temperature a solution prepared extemporaneously of 61.4 g of 7-amino-cephalosporanic acid in 900 cm³ of methylene chloride and 63 cm³ of triethylamine is added over 15 minutes. The whole is agitated for one hour thirty minutes at 20°C (pH=6.5—7). 50 cm³ of acetic acid are then added, and the whole is left for 15 minutes under
20 agitation at 20°C, then vacuum-filtered to eliminate the initial 7-amino-cephalosporanic acid. The whole is rinsed with 4 times 200 cm³ of methylene chloride. The organic solution is washed with 3 times 400 cm³ of demineralised water, then dried over magnesium sulphate. It is vacuum-filtered, rinsed with twice 200 cm³ of methylene chloride and distilled to dryness under vacuum and under an
25 inert gas. The dry oily residue is dissolved at 20—25°C under agitation and under inert gas in 700 cm³ of dioxane. 300 cm³ of a dioxane-methylene chloride mixture are distilled off under vacuum and under inert gas at a temperature below 30°C. The remainder is brought to 20°C±2°C, then 500 cm³ of sulphuric ether are added. 52 cm³ of diethylamine are added. After about 10 minutes, the diethylamine salt of
30 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid crystallises out. It is left for one hour under inert gas at 20°. It is vacuum-filtered, and rinsed with 3 times 100 cm³ of a solution of dioxane-ethyl ether. The diethylamine salt recovered is dried and 113.6 g thereof are obtained. The organic solution is precipitated over 30 minutes under agitation in 3.25 litres of isopropyl ether. It is
35 left for 15 minutes under agitation, then vacuum-filtered under vacuum. It is rinsed with twice 400 cm³ of isopropyl ether and dried under vacuum, and 182 g of product identical to that obtained in Example 5 is obtained.

Example 22

40 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer 40

182 g of the product obtained in Example 21 above are introduced under agitation and under an inert gas at 28—30°C, into 347 cm³ of formic acid and 87 cm³ of demineralised water. Total dissolution and crystallisation of the triphenyl carbinol take place. The whole is left under agitation under an inert gas for 2 hours
45 30 minutes at 28—30°C, then precipitated over 15 minutes under agitation in 1740 cm³ of demineralised water and 847 g of ammonium sulphate. The whole is left for 30 minutes under agitation. It is vacuum-filtered, rinsed with twice 174 cm³ of demineralised water and dried under vacuum at 25—30°C, and 147 g of a mixture
50 of expected product and triphenyl carbinol is obtained. The crude product is made into a paste in 735 cm³ of ethyl ether for one hour at 18—20°C. It is vacuum-filtered, rinsed with twice 147 cm³ of ethyl ether and dried at 25—30°C, and 89 g of expected product are obtained.

55 This product is made into a paste, under agitation and under nitrogen, in 445 cm³ of ethanol. The suspension is brought to 45—50°C under agitation and maintained for one hour under these conditions. It is then agitated for one hour at 18—20°C. It is vacuum-filtered, rinsed with twice 45 cm³ of ethanol and dried under vacuum at 20°C, and 76.85 g of expected product are obtained.

60 This product is introduced into 230 cm³ of acetic acid. The whole is agitated for 15 minutes under nitrogen, then 77 cm³ of demineralised water are added. 700 cm³ of water are then added to this solution. The whole is left for one hour under agitation at 18—20°C, then 269 g of ammonium sulphate are added over about 10 minutes, the whole is left for 15 minutes, then 3.85 g of charcoal are added. The

whole is left for 15 minutes under agitation, vacuum-filtered and rinsed with 77 cm³ of demineralised water containing 25% of acetic acid. 154 cm³ of formic acid are added at 18—20°C under agitation, an initiating amount of final product is added, then crystallisation is assisted by scratching. The whole is left for 2 hours under agitation at 18—20°C, then for two hours at 0°, +5°C. It is vacuum-filtered, and washed with 4 times 77 cm³ of demineralised water containing 5% of formic acid. It is dried at 20—25°C under vacuum. 49.45 g of product are obtained in the form of the formate.

The formate obtained is made into a paste, under agitation for one hour at 45—50°C, in 250 cm³ of ethanol, then left for one hour at 18—20°C. It is vacuum-filtered, and rinsed with twice 50 cm³ of ethanol. It is dried at 20°C under vacuum, then for 10 to 15 hours at 35—40°C. 45.45 g of expected product are obtained. $[\alpha]_D^{20} = +64.5^\circ$ (at a concentration of 0.5% in water containing 0.5% of NaHCO₃).

The product is identical to that obtained in Examples 4, 6 and 20.

Example 23

Crystalline Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

19.8 g of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid, the *syn* isomer obtained according to Example 4, 6, 20 or 22 are dissolved in 65 cm³ of molar solution of sodium acetate in methanol. The whole is left to crystallise for 35 minutes at ambient temperature, 40 cm³ of ethanol are added over one hour, the agitation is continued for 2 hours 30 minutes in a bath of iced water, the whole is vacuum-filtered and washed twice using 10 cm³ of a 1:1 methanol-ethanol mixture, twice using 10 cm³ of ethanol, then twice using 20 cm³ of ether. After drying for 2 hours at 45°C under vacuum and 48 hours in a dessicator under sulphuric vacuum, 16.191 g of crystalline product are obtained.

Operating with avoidance of all contact with atmospheric humidity, a product is obtained whose physical constants are given hereunder:

H₂O (Karl Fischer)=0.2%

Methanol ≤ 0.1%

Ethanol 0.45%

Determination by Vapour-Phase Chromatography

Analysis: C₁₆H₁₆O₇N₅S₂Na=477.5

Calculated: C% 40.24 H% 3.38 N% 14.67 S% 13.43 Na% 4.81

Found: C% 39.9 H% 3.5 N% 14.5 S% 13.1 Na% 4.8

Left out in the air, the product rehydrates.

The X-ray spectrum (Debye Scherrer) has enabled the crystalline nature of the product obtained to be confirmed.

It is equally possible to use isopropanol in place of ethanol so as to bring about crystallization of the expected product.

Example 24

Crystalline Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

Stage A: Solvate Between 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer, and Formic Acid

In small quantities and with agitation 87.2 g of the diethylamine salt of 3 - acetoxymethyl - 7 - [2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid, prepared according to Example 5, are added to a mixture of 220 cm³ of pure formic acid and 220 cm³ of water. The whole is agitated for 30 minutes at 50°C, cooled, and 30.1 g of triphenyl carbinol are eliminated by filtration. 450 cm³ of water are poured into the filtrate, a slight precipitate is eliminated with carbon, and the whole is concentrated at 40°C under a vacuum until a precipitate forms. 200 cm³ of anhydrous ethanol are added, the whole is cooled with ice, filtered, washed with ethanol and with ether, and dried under a vacuum.

31.1 g of the expected product are obtained.

Analysis: C₁₆H₁₇N₅O₇S₂, HCO₂H.H₂O=541.5

Calculated: C% 39.3 H% 4.08 N% 13.48 S% 12.34 H₂O% 3.46

Found: C% 39.2 H% 4.1 N% 13.2 S% 12.8 H₂O% 4.15

Stage B: Crystalline Sodium Salt

15 g of the freshly-prepared solvate obtained according to Stage A are dissolved in 75 cm³ of methanol, and the solution is treated with 4.5 g of sodium acetate and 3 g of active carbon. After filtration, 5 cm³ of isopropanol are added while agitating. After 16 hours at 0°C, the crystals are isolated, washed with ethanol and with ether and dried for two hours under a forced vacuum at 50°C.

7.95 g of the expected product are obtained.

The product then remains briefly in the open air. The following analysis is obtained:



Calculated:	C% 38.78	H% 3.66	N% 14.14	Na% 4.64	S% 12.94
Found:	C% 38.6	H% 3.7	N% 13.8	Na% 4.6	S% 13.2

Example 25

Amorphous Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

A) Solvate Between 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer, and Ethanol

52 g of the solvate with formic acid obtained in Stage A of Example 24 were dissolved in a mixture of 3 litres of 96% ethanol and 350 cm³ of water. The whole is concentrated under vacuum until it attains a volume of about 300 cm³.

The solvate starts to crystallize out during the course of the concentration. The whole is cooled for one hour in an ice-bath, filtered, washed with a little ethanol and dried under vacuum at ambient temperature in the presence of concentrated sulphuric acid.

44 g of the expected product are obtained.

Analysis: $C_{16}H_{17}N_6O_7S_2 \cdot 0.8 \text{ mole } C_2H_5OH = 492.3$

Calculated:	C% 42.94	H% 4.46	N% 14.23	S% 13.02
Found:	C% 43.0	H% 4.4	N% 14.1	S% 12.9

B) Amorphous Sodium Salt

3 g of the solvate with ethanol obtained in Stage A are put into 60 cm³ of water at 0°C and 0.504 g of sodium acid carbonate dissolved in 6 cm³ of water are added while agitating. The neutral solution is filtered and immediately lyophilised. The product then remains briefly in the open air.

The following analysis is obtained:



Calculated:	C% 38.09	H% 3.8	N% 13.88
Found:	C% 38.2	H% 3.9	N% 13.6

Example 26

Crystalline Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

To 4.95 g of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid, the *syn* isomer, obtained according to Example 4, 6, 20 or 22, there are added 5 cm³ of ethanol, then under agitation in a bath of iced water 10 cm³ of a molar aqueous solution of sodium acid carbonate. After dissolution, 15 cm³ of ethanol are added and the whole is concentrated at 30°C under vacuum, taken up with ethanol and dried to constant weight. A powder is obtained which is taken up with 15 cm³ of methanol. Crystallisation is initiated and the whole is left for one night in the refrigerator. 3.407 g of crystalline product are isolated.

Example 27

Crystalline Sodium Salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

0.5 g of the amorphous sodium salt obtained according to Example 25 is dissolved in 2 cm³ of methanol, 0.25 cm³ of *n*-butanol is added slowly under

agitation, and the whole is cooled for 48 hours in the refrigerator at about 6°C. The crystals are washed with a little cold methanol and dried for 3 hours under a vacuum at 40°C in the presence of concentrated sulphuric acid.

0.2 g of the crystalline product is obtained.

5. The product then remains briefly in the open air.

5

Analysis:	$C_{16}H_{16}N_5NaO_7S_2 \cdot 1.5 H_2O = 504.47$			
Calculated:	C% 38.09	H% 3.8	N% 13.88	O% 26.96
Found:	C% 38.4	H% 3.8	N% 13.8	O% 27.1

10 Working under similar operating conditions, only slightly different crystalline forms are obtained, containing, for example, 0.5 molecule of water or 1 molecule of water and 1 molecule of methanol.

10

The X-ray spectra (Debye Scherrer) of the products obtained above confirm the crystalline nature of the products obtained.

Examples 28—42.

15 In a similar manner to that described in the foregoing Examples, the following compounds of general formula I and their salts may be prepared.

15

Compounds

20 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - propyloxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, alkaline-earth metals, magnesium and amines;

20

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - butyloxyimino - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

25 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2 - methylpropyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

25

30 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1',1' - dimethyl - ethoxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

30

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - butenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, alkaline-earth metals, magnesium and amines;

35 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (3' - butenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

35

40 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - butenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

40

45 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (3' - butenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

45

3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (vinylloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

50 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - propenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

50

55 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - propenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

55

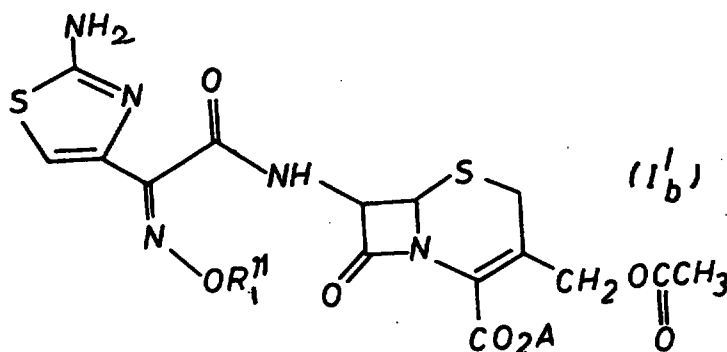
60 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - butenyloxy - imino) - acetamido] - cephalosporin - 3 - em - 4 - carboxylic acid *syn* isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;

60

33	1,580,621	33
	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - ethynyloxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid <i>syn</i> isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines;	
5	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - propynyloxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid <i>syn</i> isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines; and	5
10	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - butynyloxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid <i>syn</i> isomer, and its salts with the alkali metals, the alkaline-earth metals, magnesium and amines.	10
	Formulation 1	
	A preparation for injection was made up, comprising:	
15	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - hydroxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid	15
	Sterile aqueous excipient q.s.v.	500 mg 5 cm ³
	Formulation 2	
20	A preparation for injection was made up, comprising:	20.
	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid	
	Sterile aqueous excipient q.s.v.	500 mg 5 cm ³
	Formulation 3	
25	A preparation for injection was made up, comprising:	25
	Sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid	
30	Sterile aqueous excipient q.s.v.	500 mg 5 cm ³ 30
	Formulation 4	
	A preparation for injection was made up, comprising:	
35	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - methylethoxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid	35
	Sterile aqueous excipient q.s.v.	500 mg 5 cm ³
	Formulation 5	
	Gelatin capsules were made up, comprising:	
40	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid	40
	Excipient q.s. for one gelatin capsul up to	250 mg 400 mg
	Formulation 6	
	Gelatin capsules were made up, comprising:	
45	Sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid	45
	Excipient q.s. for one gelatin capsule up to	250 mg 400 mg
	Formulation 7	
50	Gelatin capsules were made up, comprising:	50
	3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - methyl - ethoxy - imino) - acetamido] - ceph - 3 - em - 4 - carboxylic acid	
	Excipient q.s. for one gelatin capsule up to	250 mg 400 mg

WHAT WE CLAIM IS:—

1. A 7 - aminothiazolyl - acetamido - cephalosporanic acid oxime derivative of the general formula:



wherein R_1' represents a hydrogen atom or a saturated or unsaturated hydrocarbyl 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 or a substituted ammonium group, the compound being in the form of the *syn* isomer.

2. A compound as claimed in Claim 1, wherein R_1' represents a methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *t*-butyl, vinyl, propenyl, butenyl, ethynyl or propargyl radical.

3. A compound as claimed in Claim 1 or Claim 2, wherein A represents a sodium, potassium, or lithium atom or an equivalent of a calcium or a magnesium atom.

4. A compound as claimed in Claim 1 or Claim 2, wherein A represents a substituted ammonium group derived from methylamine, propylamine, trimethylamine, triethylamine, N,N-dimethylethanolamine, tris (hydroxymethyl) aminomethane, arginine or lysine.

5. A compound as claimed in Claim 1, wherein A represents a hydrogen atom, a sodium atom or a diethylammonium group.

6. A salt as claimed in any of the preceding claims, in the form of a crystalline hydrate formed with 0.5, 1 or 1.5 molecules of water.

7. 3 - Acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer.

8. The sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer.

9. The crystalline sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, and optionally in the form of a hydrate or solvate.

10. 3 - Acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, as obtained by the process described in Example 4.

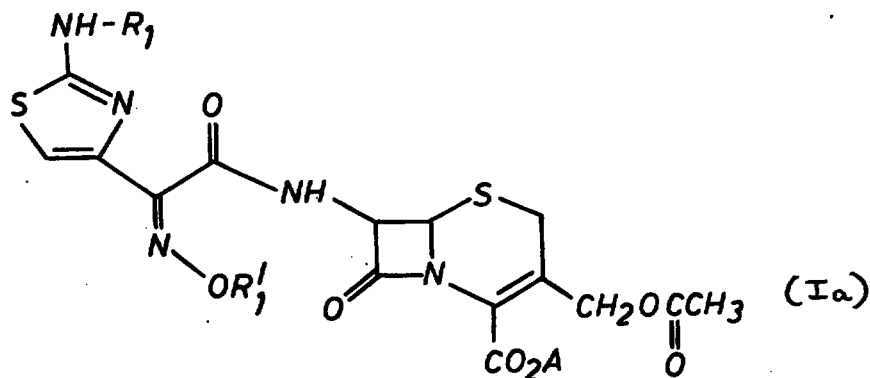
11. The sodium salt of 3 - acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - methoxy - imino - acetamido] - ceph - 3 - em - 4 - carboxylic acid in the form of its *syn* isomer, as obtained by the process described in Example 7.

12. 3 - Acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - ethoxy - imino - acetamido] - 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.

13. 3 - Acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (2' - propenyloxyimino) - acetamido] - 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.

14. 3 - Acetoxymethyl - 7 - [2 - (2 - amino - 4 - thiazolyl) - 2 - (1' - methylethoxy - imino) - acetamido] - 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.

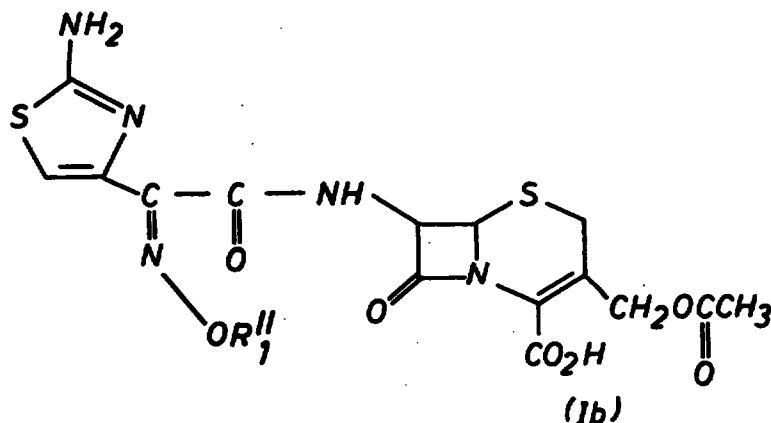
15. A protected 7 - aminothiazolyl - acetamido - cephalosporanic acid oxime derivative of the general formula:



wherein R_1 represents a group removable by acid hydrolysis or by hydrogenolysis, R_1' represents a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, and A is as defined in Claim 1, the compound being in the form of the *syn* isomer.

16. A compound as claimed in Claim 15, wherein one or each of R_1 and R_1' represent a *t*-butoxycarbonyl, trityl, benzhydryl, trichloroethyl or carbobenzyloxy group.

17. A process for the preparation of a compound of general formula I_b' , shown in Claim 1, wherein A represents a hydrogen atom, in which process an appropriate compound of general formula Ia', shown in Claim 15, wherein A represents a hydrogen atom is either hydrolysed in an acidic medium or hydrogenolysed to obtain, as the *syn* isomer, the desired product of the general formula:



wherein R_1'' is as defined in Claim 1.

18. A process as claimed in Claim 17, in which the compound of general formula Ia' is a compound wherein one or each of R_1 and R_1' represents a *t*-butoxycarbonyl or trityl group, which compound is hydrolysed using anhydrous trifluoroacetic acid or aqueous formic or acetic acid.

19. A process as claimed in Claim 17, in which the compound of general formula Ia' is a compound wherein one or each of R_1 and R_1' represents a trichloroethyl group, which compound is subjected to hydrogenolysis using a zinc/acetic acid system.

20. A process as claimed in Claim 17, in which the compound of general formula Ia' is a compound wherein one or each of R_1 and R_1' represents a benzyl, benzhydryl or carbobenzyloxy group, which compound is subjected to catalytic hydrogenation.

21. A process for the preparation of a compound of general formula Ia', shown in Claim 15, wherein A represents a hydrogen atom, in which process 7-aminocephalosporanic acid is reacted with an appropriate acid *syn* isomer of the general formula:

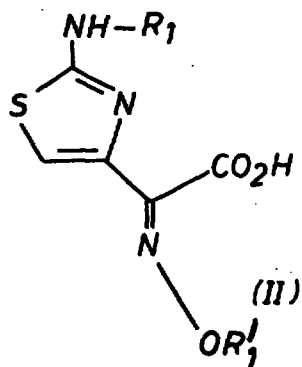
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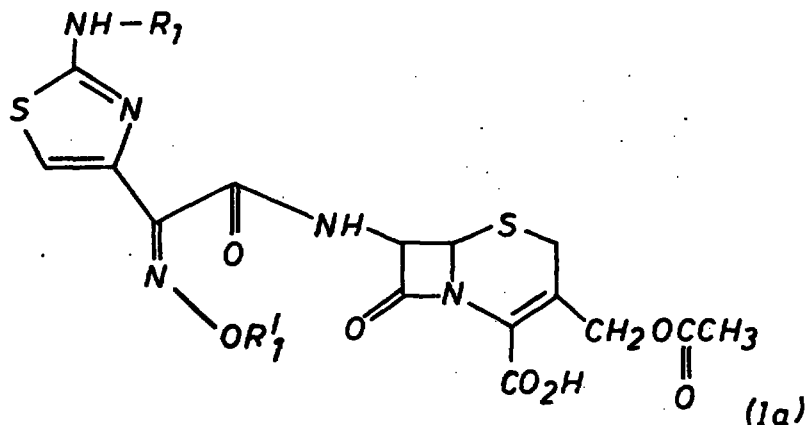
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(wherein R_1 and R_1' are as defined in Claim 15) or a functional derivative thereof to obtain the desired compound of the general formula:



wherein R_1 and R_1' are as defined in Claim 15.

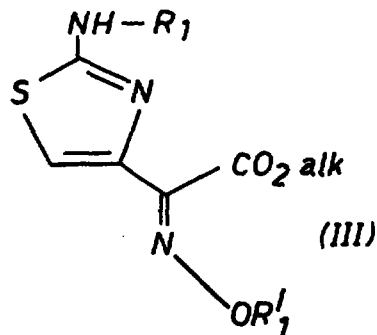
22. A process as claimed in Claim 21, in which an anhydride or the acid chloride of the acid of formula II is employed.

23. A process as claimed in Claim 22, in which the anhydride formed *in situ* by the action of isobutyl chloroformate or dicyclohexylcarbodiimide on the acid II is employed.

24. A process as claimed in Claim 21, in which the functional derivative of the acid II is an acid halide or the acid anhydride formed *in situ* by the action of isobutyl chloroformate and the reaction is carried out in the presence of a base.

25. A process as claimed in Claim 24, in which the base is N-methylmorpholine, pyridine or a trialkylamine.

26. A process as claimed in any of Claims 21 to 25, in which the starting material of general formula II is prepared by treating an appropriate *syn* isomer of the general formula:



(wherein R_1 and R_1' are as defined in Claim 15 and alk represents an alkyl radical having from 1 to 4 carbon atoms) first with a base and then with an acid to form the desired product of general formula II.



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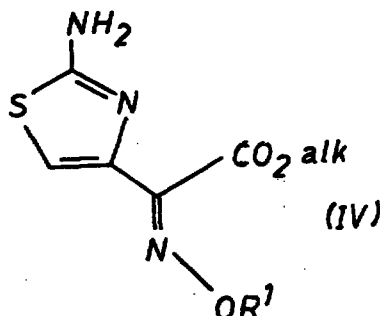
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27. A process as claimed in Claim 26, in which the base is sodium hydroxide.

28. A process as claimed in Claim 26 or Claim 27, in which the acid is dilute hydrochloric acid.

5 29. A process as claimed in any of Claims 26 to 28, in which the compound of general formula III is prepared by treating the corresponding *syn* isomer of the general formula:

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(wherein R' represents a hydrogen atom or a group R₁' and alk is as defined in Claim 26) with a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to form the desired product of general formula III.

10

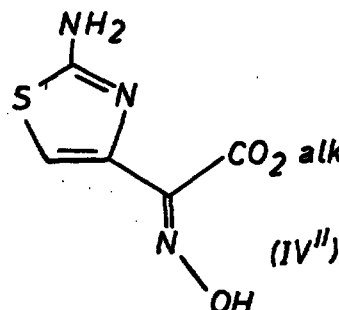
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30. A process as claimed in Claim 29, in which the compound of general formula IV is treated with trityl chloride in the presence of a trialkylamine, N-methylmorpholine or pyridine.

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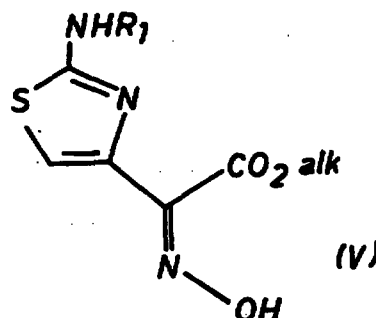
31. A process as claimed in any of Claims 26 to 28, in which a compound of general formula III wherein R₁' represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms is prepared by a multi-step process in which an appropriate *syn* isomer of the general formula:



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(wherein alk is as defined in Claim 26) is treated with an equivalent of a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to obtain the corresponding *syn* isomer of general formula:



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(wherein R₁ is as defined in Claim 15 and alk is as defined in Claim 26) which is then treated with a hydrocarbylating agent to obtain the desired *syn* isomer of the general formula:

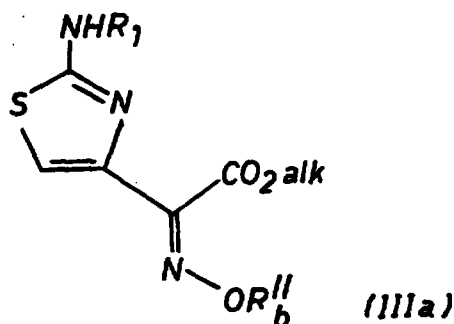
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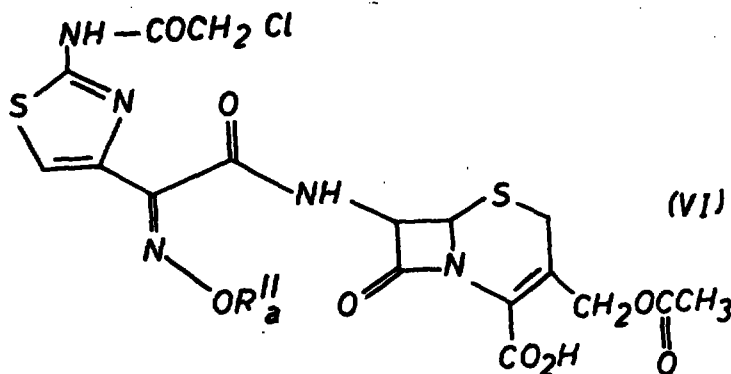
wherein R₁ is as defined in Claim 15, alk is as defined in Claim 26 and R''_b represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms.

32. A process as claimed in Claim 31, in which the compound of general formula IV'' is treated with trityl chloride in the presence of a trialkylamine, N-methyl-morpholine or pyridine.

33. A process as claimed in Claim 31 or Claim 32, in which the hydrocarbylating agent is an alkyl halide or an alkyl sulphate.

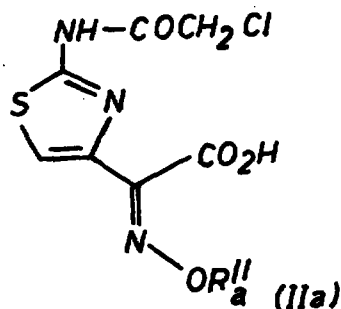
34. A process as claimed in any of Claims 17 to 20, in which the compound of general formula Ia' wherein A represents a hydrogen atom is prepared by a process as claimed in any of Claims 21 to 33.

35. A process for preparing a compound of general formula Ib, shown in Claim 17, in which an appropriate *syn* isomer of general formula:



(wherein R''_a is a chloroacetyl group or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms) is treated with thiourea to obtain the desired compound of general formula Ib.

36. A process as claimed in Claim 35, in which the compound of general formula VI is prepared by reacting 7-amino-cephalosporanic acid with an appropriate acid *syn* isomer of the general formula:

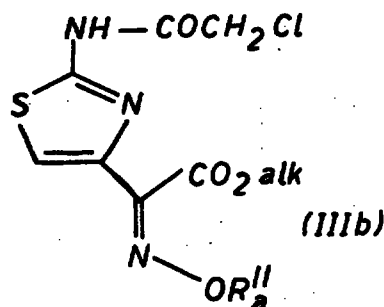


(wherein R''_a is as defined in Claim 35) or a functional derivative thereof, to form the desired compound of general formula VI.



37. A process as claimed in Claim 36, in which the reaction with 7-amino-cephalosporanic acid is carried out under the same conditions as those defined in any of Claims 22 to 25 in relation to the reaction of 7-amino-cephalosporanic acid with the acid of general formula II.

38. A process as claimed in Claim 36 or Claim 37, in which the compound of general formula IIa is prepared by treating an appropriate *syn* isomer of the general formula:

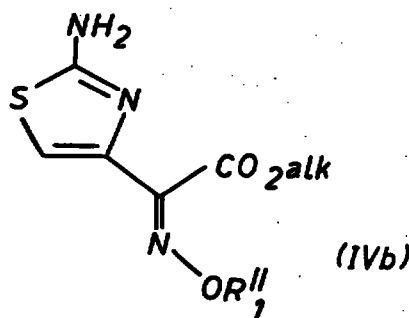


(wherein R''_a is as defined in Claim 35 and alk is as defined in Claim 26) first with a base, and then with an acid, to obtain the desired compound of general formula IIa.

39. A process as claimed in Claim 38, in which the base is sodium hydroxide.

40. A process as claimed in Claim 38 or Claim 39, in which the acid is dilute hydrochloric acid.

41. A process as claimed in any of Claims 38 to 40, in which the compound of general formula IIIb is prepared by reacting a compound capable of introducing the chloroacetyl group with a *syn* isomer of the general formula:

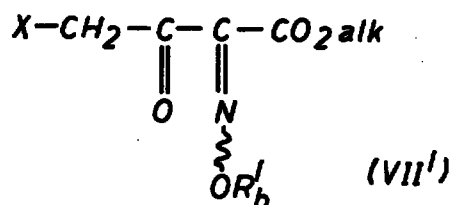


(wherein R''_b is as defined in Claim 1 and alk is as defined in Claim 26) so as to form the desired N-chloroacetyl compound of general formula IIIb.

42. A process as claimed in Claim 41, in which the compound capable of introducing the chloroacetyl group is chloroacetic anhydride or monochloroacetyl chloride.

43. A process as claimed in Claim 41, in which the compound capable of introducing the chloroacetyl group is a chloroacetyl halide and the reaction is carried out in the presence of a base as defined in Claim 30.

44. A process as claimed in any of Claims 29 to 33 and 41 to 43, in which the *syn* isomer of general formula IV, IVb or IV'' as appropriate is prepared by reacting thiourea with an appropriate compound of the general formula:



(wherein X represents a chlorine atom and R'_b represents a hydrogen atom, a group removable by acid hydrolysis or by hydrogenolysis or a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, or X represents a

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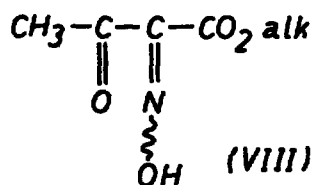


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bromine atom and R_b' represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms) which process is characterised in that a) the reaction is carried out in an aqueous solvent; or b) the reaction is carried out at ambient temperature in the presence of a substantially stoichiometric amount of thiourea and with a reaction time of from 1 to 3 hours; or c) the reaction is carried out observing both of conditions a) and b).

45. A process as claimed in Claim 44, in which the compound of general formula VII' wherein X represents a bromine atom and R_b' represents a hydrogen atom is obtained by treatment of the appropriate compound of general formula:



(wherein alk is as defined in Claim 26) with a brominating agent.

46. A process as claimed in Claim 45, in which the brominating agent is bromine itself.

47. A process as claimed in any of Claims 17 to 46, in which the formed compound of general formula Ia or Ib is thereafter salified to form an alkali metal salt thereof, an alkaline-earth metal salt thereof, a magnesium salt thereof or a substituted ammonium salt thereof.

48. A process as claimed in Claim 47, in which to form a metal salt the compound of general formula Ia or Ib is reacted with an appropriate mineral base or with a salt of a substituted or unsubstituted aliphatic carboxylic acid.

49. A process as claimed in Claim 48, in which the salt of the carboxylic acid is a salt of diethyl-acetic acid, of ethyl-hexanoic acid or acetic acid.

50. A process as claimed in any of Claims 47 to 49, in which a solvate of the compound of general formula Ia or Ib is first formed and is then salified.

51. A process as claimed in Claim 50, in which the solvate formed with water, with formic acid or with an alcohol is employed.

52. A process as claimed in Claim 51, in which the solvate with an alcohol is formed by treating the corresponding solvate formed with formic acid with a mixture of the alcohol and water, this treatment being followed by concentration of the solution.

53. A process as claimed in any of Claims 48 to 52, in which a crystalline salt is formed by reacting the compound of general formula Ia or Ib or a solvate thereof with a salt of a substituted or unsubstituted aliphatic carboxylic acid.

54. A process as claimed in Claim 53, in which the crystalline sodium salt is prepared by reacting sodium acetate with a solvate of a compound of general formula Ia or Ib formed with formic acid or with ethanol.

55. A process as claimed in any of Claims 47 to 54, in which the salification is carried out in one or more of water, ethyl ether, methanol, ethanol and acetone, as solvent.

56. A process as claimed in any of Claims 47 to 53, in which the sodium salt is prepared in an amorphous form and is thereafter converted to the crystalline form by a process in which the amorphous salt is dissolved in an organic solvent and the crystallization then brought about either directly or indirectly by the addition of one or more other organic solvents.

57. A process as claimed in Claim 56, in which the amorphous salt is dissolved in methanol, and crystallization is brought about by addition of one or more of ethanol, isopropanol, *n*-butanol, acetone and ethers.

58. A process for preparing a compound of general formula Ib', shown in Claim 1, in which a salt of general formula Ia', shown in Claim 15, is either treated with an acid to obtain the corresponding compound of general formula Ib, or subjected to hydrogenolysis to obtain the corresponding salt of general formula Ib'.

59. A process as claimed in Claim 58, in which the acid used to hydrolyse the salt of general formula Ia', is formic acid, trifluoroacetic acid or acetic acid.

60. A process as claimed in Claim 58, in which the hydrogenolysis is effected by catalytic hydrogenation.

61. A process as claimed in any of Claims 58 to 60, in which the salt of general formula Ia' is prepared by a process as claimed in any of Claims 47 to 55.



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62. A process for preparing a compound of general formula Ib', shown in Claim 1, or of general formula Ia', shown in Claim 15, substantially as described herein with reference to any one of the Examples 3 to 13 and 20 to 42.

5 63. A compound of general formula Ia' or Ib' whenever prepared by a process as claimed in any of Claims 17 to 62. 5

64. A pharmaceutical composition containing, as active material, one or more pharmaceutically-acceptable compounds of general formula Ib', shown in Claim 1, in association with a suitable pharmaceutical vehicle.

10 65. A composition as claimed in Claim 64, in which the active material comprises at least one compound of general formula Ib' wherein A represents a hydrogen or sodium atom. 10

66. A composition as claimed in Claim 64, in which the active material is a compound as claimed in Claim 7.

15 67. A composition as claimed in Claim 64, in which the active material is a compound as claimed in Claim 8. 15

68. A composition as claimed in Claim 64, in which the active material is a compound as claimed in Claim 9.

20 69. A composition as claimed in Claim 64, in which the active material is a compound as claimed in Claim 10. 20

70. A composition as claimed in Claim 64, in which the active material is a compound as claimed in Claim 11.

71. A composition as claimed in Claim 64, in which the active material comprises at least one of the compounds claimed in any of Claims 12 to 14.

25 72. A composition as claimed in Claim 64, and substantially as described herein with reference to any one of the Formulations. 25

73. A compound of general formula VI as defined in Claim 35.

74. A process for preparing a compound of general formula VI as defined in any of Claims 36 to 43.

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