

PATENT SPECIFICATION

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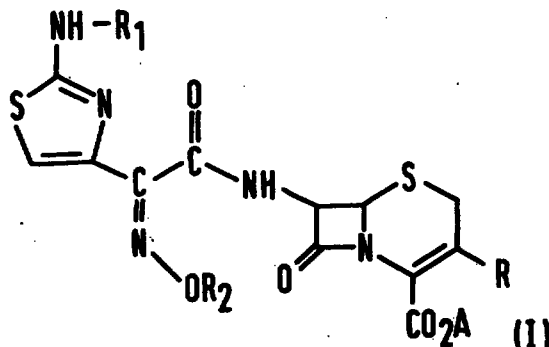
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(54) NEW HYDROCARBYLOXIME DERIVATIVES OF 7-AMINO-THIAZOLYLACETAMIDO-CEPH- 3-EM-4-CARBOXYLIC ACID, PROCESSES FOR PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7eme, 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 hydrocarbyloxime derivatives of 7 - amino - thiazolyl - acetamido - ceph - 3 - em - 4 - carboxylic acid, processes for preparing them and pharmaceutical compositions containing them.

This invention provides the new hydrocarbyloxime derivatives of 7 - amino - thiazolyl - acetamido - ceph - 3 - em - 4 - carboxylic acid syn isomers of the general formula:



wherein R represents an alkyl radical having from 1 to 5 carbon atoms, a cycloalkyl radical having from 3 to 5 carbon atoms, or a radical:



in which R' represents an acyl group having from 2 to 4 carbon atoms, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical; R₁ represents a hydrogen atom or a group removable by acid hydrolysis or by hydrogenolysis; R₂ represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms, and A represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom, a substituted ammonium group, or an ester-forming group removable by acid hydrolysis or by hydrogenolysis with the proviso that A does not represent an ester-forming group removable by acid hydrolysis or by hydrogenolysis when R₁ represents a hydrogen atom.

When R' represents an acyl group it may be an acetyl, propionyl *n*-butyryl or isobutyryl group. When R represents an alkyl or cycloalkyl radical it is preferably a

methyl, ethyl, propyl, *isopropyl*, butyl, *isobutyl*, *t*-butyl, pentyl, cyclopropyl, cyclobutyl or cyclopentyl radical.

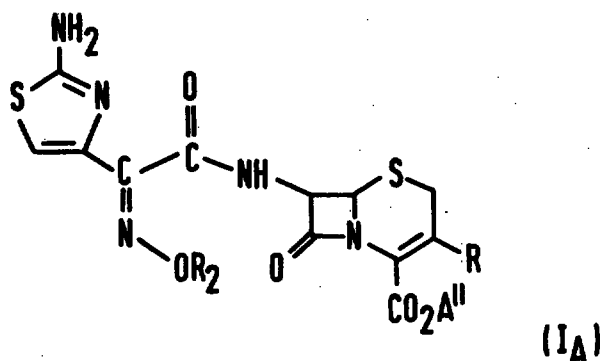
The expression "a group removable by acid hydrolysis or by hydrogenolysis" is used to mean a group that may be cleaved from the remainder of the molecule without otherwise affecting its structure (other than cleaving other groups removable by acid hydrolysis or by hydrogenolysis, where more than one is present). Examples of such groups which R_1 may represent include the *t*-butoxycarbonyl, trityl, benzyl, benzhydryl, trichloroethyl, carbobenzyloxy, formyl, trichloroethoxycarbonyl and 2-tetrahydropyranyl groups.

When R_2 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.

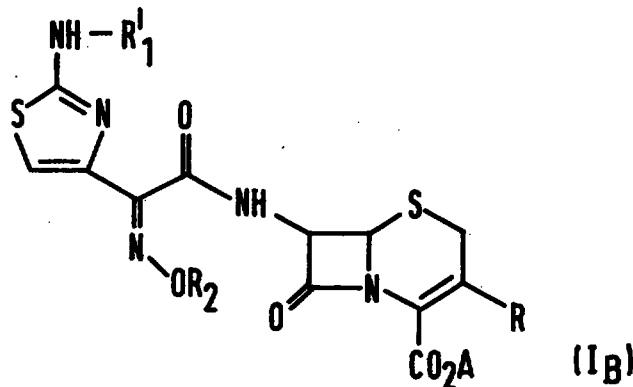
When A represents "an equivalent of an alkaline-earth metal atom" or an "equivalent of a magnesium atom" each molecule of the compound shown in general formula I contains, as A, the fraction of the metal atom corresponding to a single valence.

When A represents a metal atom (and thus the compounds of general formula I are metal salts) A is preferably a sodium, potassium, lithium, calcium or magnesium atom. When A represents a substituted ammonium group A is preferably derived from trimethylamine, triethylamine, methylamine, propylamine, N,N-dimethylethanolamine or tris - (hydroxymethyl) - aminomethane, arginine or lysine. When A represents an ester-forming group removable by acid hydrolysis or by hydrogenolysis it is preferably a benzhydryl, *t*-butyl, benzyl, *p*-methoxybenzyl or trichloroethyl radical.

Thus, the invention extends to the *syn* isomers of the general formula



(wherein A'' represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or a substituted ammonium group) and to the *syn* isomers of the general formula:



wherein R_1 represents a group removable by acid hydrolysis or by hydrogenolysis and A is as defined hereinbefore. In each of general formulae I_A and I_B, R and R_2 are as defined hereinbefore.

Within general formula I there are several preferred sub-groups of

compounds, namely:— the compounds of formula I, wherein A represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or a substituted ammonium group;

5 the compounds of formula I_a wherein A represents a benzhydryl, *t*-butyl, benzyl, *p*-methoxy-benzyl or a trichloroethyl radical;

the compounds of formula I_a wherein R₁' represents a *t*-butoxycarbonyl, trityl, benzhydryl, trichloroethyl or carbobenzyloxy group;

the compounds of formula I wherein R represents the radical:



10 in which R' represents either an acyl group having from 2 to 4 carbon atoms or a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical;

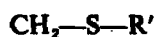
the compounds of formula I wherein R represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 5 carbon atoms;

15 the compounds of formula I wherein R₁ represents a hydrogen atom or a trityl group, R₂ represents a methyl radical, R represents a radical:



in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical and A represents a hydrogen atom;

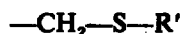
20 the compounds of formula I_a wherein R₂ represents a methyl radical, R represents a radical:



in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical and 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;

25 the compounds of formula I wherein R₁ represents a hydrogen atom or a trityl group, R₂ represents a methyl radical, R represents a methyl or *isopropyl* radical and A represents a hydrogen atom; and

30 the compounds of formula I_a wherein R₂ represents a methyl radical, R represents a radical:



in which R' represents an acyl radical having from 2 to 4 carbon atoms and A represents a hydrogen atom or an alkali metal atom.

35 Amongst the compounds of general formula I the compounds mentioned hereinafter in the Examples are preferred and particularly:

7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

40 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

3 - acetylthiomethyl - 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

45 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - *isopropyl* - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - methyl - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

50 3 - acetylthiomethyl - 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, when prepared according to the process described in Example 6;

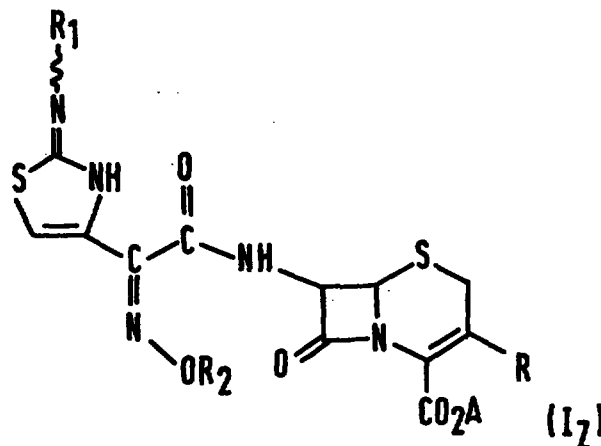
the sodium salt of 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

55 the sodium salt of 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

the sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; and

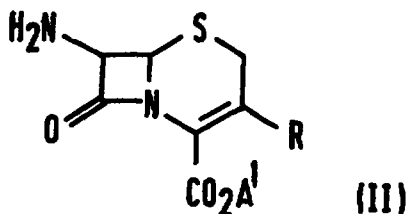
5 the crystalline sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.

It is understood that the compounds of formula I can exist:
either in the form indicated by formula I as set out hereinbefore;
or in the form shown in general formula I₂ set out below;

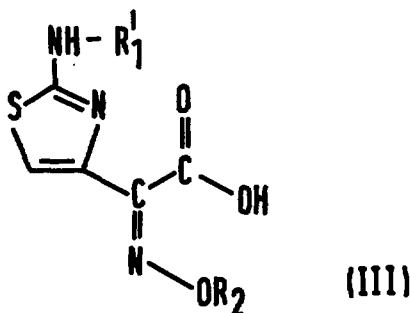


wherein R, R₁, R₂ and A are as defined hereinbefore.

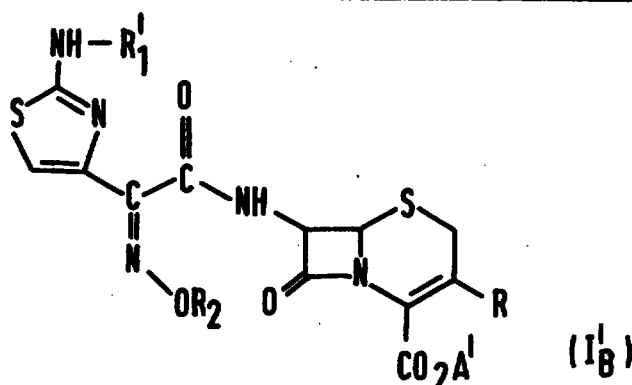
This invention also provides a process for preparing the compounds of formula I₂ wherein A represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or by hydrogenolysis, in which process an appropriate compound of the general formula:



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



(wherein R₁' and R₂ are as defined hereinbefore) or a functional derivative thereof, to give the desired *syn* isomer of the general formula:

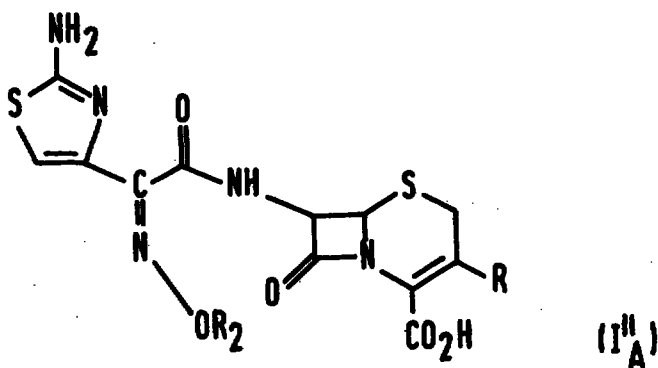


wherein R, R₁', R₂ and A' are as defined hereinbefore.

In a preferred method of carrying out this process, the compound of formula II is reacted with a functional derivative of the acid of formula III such as the anhydride or the acid chloride (the anhydride conveniently being formed *in situ* by the action of isobutyl chloroformate or dicyclohexylcarbodiimide on the acid). Other halides or even other anhydrides (again conveniently formed *in situ* by the action of another alkyl chloroformate, a dialkylcarbodiimide or another dicycloalkylcarbodiimide) can also be used. Yet further acid derivatives such as the acid azide, the acid amide or an activated acid ester-formed, for example, with hydroxysuccinimide, *p*-nitrophenol or 2,4-dinitrophenol can also be used.

In the case where the compound of general formula II is reacted with a halide or with the anhydride formed with an isobutyl chloroformate of the acid of general formula III, the reaction is preferably carried out in the presence of a basic agent. Preferred basic agents include, for example the alkali-metal carbonates and tertiary organic bases such as N-methyl-morpholine, pyridine or a trialkylamine such as triethylamine.

The formed product of general formula I_B' may be treated with one or both of an acid hydrolysis agent and a hydrogenolysis agent, as appropriate, so as to remove the groups R₁' and A', to give a *syn* isomer of the general formula:



(wherein R and R₂ are as defined hereinbefore) — that is, a compound of general formula I_A, wherein A'' represents a hydrogen atom.

Clearly, the conversion of the products of formula I_B' into products of formula I_A involves replacing the substituent R₁' with a hydrogen atom and, in the case when A' is other than a hydrogen atom, also replacing A' with a hydrogen atom.

In order to do this the product of formula I_B' is treated with:

a) an acid hydrolysis agent in the case when R₁' represents a group removable by acid hydrolysis and A' represents a hydrogen atom or a group removable by acid hydrolysis;

b) a hydrogenolysis agent in the case when R₁' represents a group removable by hydrogenolysis and A' represents a hydrogen atom or a group removable by hydrogenolysis; and

c) an acid hydrolysis agent and a hydrogenolysis agent in the case when one of the substituents R₁' or A' represents a group removable by acid hydrolysis and the other of these substituents represents a group removable by hydrogenolysis.

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Preferred acid hydrolysis agents which may be used include formic acid, trifluoroacetic acid or acetic acid, and these acids may be employed either in anhydrous form or in aqueous solution. The zinc-acetic acid system can also be used.

Preferably an acid hydrolysis agent such as anhydrous trifluoroacetic acid or aqueous formic or acetic acid is used to eliminate a *t*-butoxycarbonyl or trityl group as substituent R₁' or to eliminate a benzhydryl, *t*-butyl or *p*-methoxybenzyl group as substituent A'.

The zinc/acetic acid system is preferably used to eliminate trichloroethyl groups as substituents R₁' and A'.

Preferably a hydrogenolysis agent such as hydrogen in the presence of a catalyst is used to eliminate a dibenzyl or carbobenzyloxy group as substituent R₁' or to eliminate benzyl groups as substituents R₁' and A'.

The products of formula I_a' or I_a'' can be salified according to the usual methods. The mineral salts can, for example, be obtained by reacting the formed acids with an appropriate mineral base such as sodium or potassium hydroxide or sodium bicarbonate, or with an appropriate salt of a substituted or unsubstituted aliphatic carboxylic acid — such as diethylacetic acid, ethyl-hexanoic acid or, more preferably, acetic acid.

The particularly preferred salts of the acids of general formula I are the sodium salts.

The substituted ammonium salts may be obtained by reacting the acids with an appropriate organic base such as triethylamine or diethylamine.

In the preparation of the salts the solvates of free acids of general formula I may be used as starting products in place of the free acids.

This salification is preferably carried out in a solvent or a mixture of solvents such as water, diethyl ether, methanol, ethanol or acetone.

The salts are obtained in amorphous or crystalline form according to the reaction conditions employed. The crystalline salts are preferably prepared by reacting the free acids with one of the carboxylic acid salts mentioned hereinbefore, a preferred carboxylic acid salt being sodium acetate.

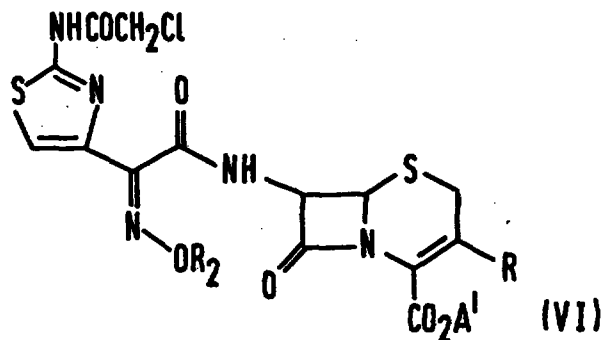
In the preparation of a sodium salt the reaction is conveniently carried out in a suitable organic solvent such as methanol, and this solvent may optionally contain small amounts of water.

This invention also provides a variant of the process for preparing a compound of general formula I_a'' or a salt thereof, in which either a salt of an appropriate compound of general formula I_a' wherein R₁' represents a group removable by acid hydrolysis is treated with an acid to obtain a product of formula I_a'', or a salt of an appropriate compound of general formula I_a' wherein R₁' represents a group removable by hydrogenolysis is subjected to hydrogenolysis, to give the salt of the corresponding compound of general formula I_a'.

The acid used to hydrolyse the substituents R₁' removable by acid hydrolysis is preferably formic acid. Trifluoroacetic acid or acetic acid can, however, be used. These acids can be employed in anhydrous form or in an aqueous solution.

The hydrogenolysis technique used to remove substituents R₁' is preferably catalytic hydrogenation.

A further process for preparing the compounds of formula I_a'' is provided by the invention, in which an appropriate *syn* isomer of the general formula:

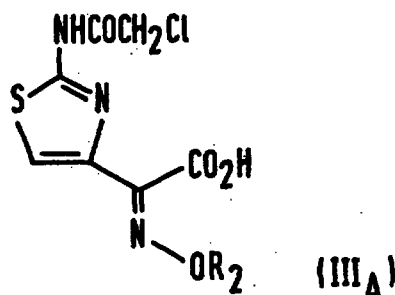


(wherein R₂ and A' are as defined hereinbefore) is treated with thiourea, and when A' does not represent a hydrogen atom also treated with an acid hydrolysis or

hydrogenolysis agent as appropriate, to give the desired product of general formula I_A".

A similar reaction to this treatment of the compound of formula VI with thiourea is described by Masaki in Jacs, 90, 4508 (1968). The reaction may be carried out in a neutral or acidic medium.

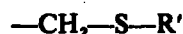
The starting materials of general formula VI may conveniently be prepared by reacting an appropriate compound of general formula II, as defined hereinbefore, with a suitable *syn* isomer of the general formula:



(wherein R₂ is as defined hereinbefore) or a functional derivative thereof.

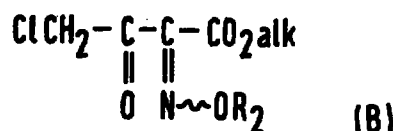
The reaction of the acid of general formula II with the acid of general formula III_A is preferably carried out under the same conditions as those set out hereinbefore for the reaction of the acid of general formula II with the acid of general formula III.

The compounds of general formula II wherein R represents the radical:

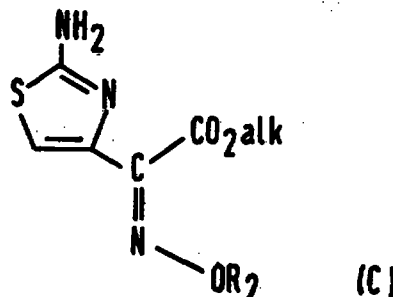


which are not already known may be prepared by a nucleophilic exchange reaction between 7 - amino - cephalosporanic acid and a thiol R'-SH or salt thereof, and an example of such a preparation is set out hereinafter in the Examples.

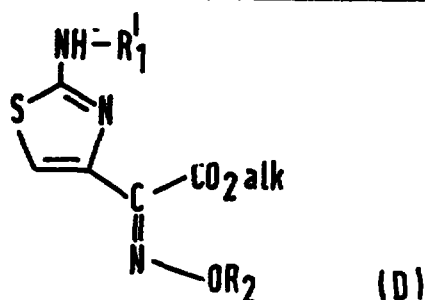
The *syn* isomer compounds of general formula III may be prepared by a process in which thiourea is reacted with a product of the general formula:



(wherein R₂ is as defined hereinbefore and alk represents an alkyl radical having from 1 to 4 carbon atoms) under the conditions defined hereinafter and then treated with a base to give a *syn* isomer of the general formula:



(wherein R₂ and alk are as defined hereinbefore) which is thereafter treated with a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to give a *syn* isomer of the general formula:



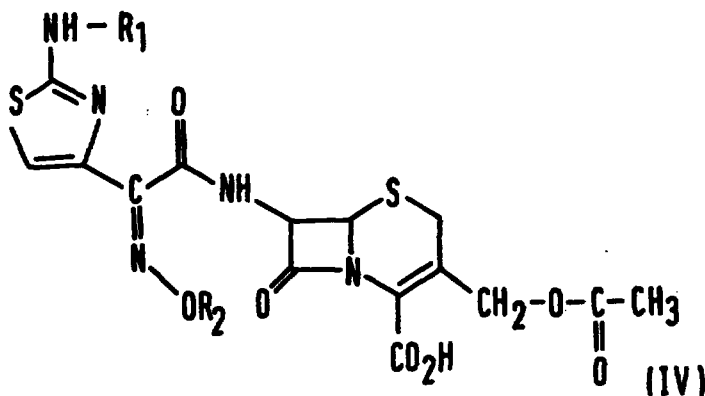
(wherein R_1 , R_2 and alk are as defined hereinbefore) which is in turn treated first with a base and then with an acid, to give the desired *syn* isomer of general formula III. An example of such a preparation is set out hereinafter in the Examples.

The *syn* configuration of the products of general formula III is obtained by reacting thiourea with the compound of formula B a) in an aqueous solvent, such as aqueous acetone or aqueous ethanol; b) at ambient temperature, using a substantially stoichiometric amount of thiourea for a short period, and preferably for from 1 to 3 hours; or c) using a combination of conditions a) and b), to give the *syn* configuration to products (C) which can then be preserved in products (D) and III.

The compounds of general formula B may be prepared by the action of diazomethane or suitable alkyl halides or sulphates on ethyl γ -chloro- α -oxyiminoacetylacetate described in J. of Medicinal Chemistry 1973, 16 (9), 978.

The products of formula III_A may be prepared by reacting a compound capable of introducing the chloroacetyl group — preferably a halide or chloroacetic anhydride — with the appropriate *syn* isomer of general formula C, and treating the product first with a base and then with an acid.

This invention in a further aspect provides a process for preparing the compounds of general formula I_A or I_B wherein R represents the group $-\text{CH}_2\text{S}-\text{R}'$ and A represents A'' (as defined hereinbefore) in which process an appropriate *syn* isomer of general formula:



(wherein R_1 and R_2 are as defined hereinbefore) is treated with a product of the general formula:



(wherein R' is as defined hereinbefore) to obtain an acid *syn* isomer of general formula I_A or I_B wherein R represents the group $-\text{CH}_2\text{S}-\text{R}'$ and A represents a hydrogen atom, which is optionally salified to give the corresponding salts, being compounds of general formula I_A or I_B wherein A represents an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom or a substituted ammonium group.

The action of the compound of general formula V on the compound of general formula IV is preferably carried out in a water-acetone mixture but other aqueous solvents such as water-dioxane, water-tetrahydrofuran and water-ethyl alcohol mixtures may be used.

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

5 The salification of the formed acid may of course be carried out according to the usual methods described hereinbefore.

10 The compounds of general formula IV may be prepared by reacting an appropriate acid of general formula III (as defined hereinbefore) with 7 - amino - cephalosporanic acid, and optionally subjecting the product to acid hydrolysis or hydrogenolysis. An example of such a preparation is set out hereinafter. The compounds of general formula IV preserve the *syn* configuration of the acids of general formula III.

15 The products of general formula I and particularly those of general formula I_A possess very good antibiotic activity on the one hand against the Gram positive bacteria such as the staphylococci and the streptococci and especially against the penicillin-resistant staphylococci, and on the other hand against the Gram negative bacteria, especially against the coliform bacteria, the Klebsiella, and Salmonella and the Proteus.

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

25 The pharmaceutically-acceptable compounds may also be of use as medicaments in the treatment of colibacillosis and associated infections, in infections caused by Protues, Klebsiella or Salmonella, and in other diseases caused by Gram negative bacteria. However, before any of the compounds of this invention are used in medicine, they should preferably be formed into pharmaceutical compositions by association with suitable pharmaceutical vehicles.

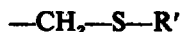
30 The terms "pharmaceutical" and "pharmaceutically-acceptable" are used herein to exclude any possibility that the vehicle or active compound, as appropriate, considered in relation to the route by which the composition is intended to be administered, could be harmful. The choice of a suitable mode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

40 Accordingly, in yet another aspect this invention provides pharmaceutical compositions containing as active principle one or more of the pharmaceutically-acceptable compounds of general formula I_A or I_B in association with a suitable pharmaceutical vehicle.

45 The pharmaceutical compositions preferably contain as the active principle the pharmaceutically-acceptable compounds of general formula I_A.

Other preferred compositions are those containing as active principle one or more of the pharmaceutically-acceptable compounds falling within one of the following categories:—

compounds of general formula I wherein R represents a radical:



50 and R' represents either an acyl group having from 2 to 4 carbon atoms, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical;

compounds of general formula I wherein R represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 5 carbon atoms;

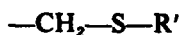
55 compounds of general formula I wherein R₁ represents a hydrogen atom or a trityl group, R₂ represents a methyl radical, R represents a methyl or isopropyl radical and A represents a hydrogen atom; and

especially, compounds of general formula I_A wherein R₂ represents a methyl radical and R represents a radical:



60 in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical.

A further category of preferred pharmaceutical compositions are those containing as active principle one or more of the compounds of general formula I_A wherein R₂ represents a methyl radical, R represents a radical:



5 in which R' represents an acyl radical having from 2 to 4 carbon atoms, and A'' represents a hydrogen atom or an alkali metal atom. 5

Specific preferred compounds for use in the pharmaceutical compositions of the invention include:—

10 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; 10

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

15 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; 15

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - isopropyl - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer;

20 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - methyl - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; 20

3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, as obtained according to the process described in Example 6;

25 the sodium salt of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; 25

30 the sodium salt of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; 30

the sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer; and

35 the crystalline sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer. 35

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

40 a) the ingestible excipient of a tablet such as a coated tablet or sublingual tablet or of a pill; the ingestible container of a capsule or catchet; the ingestible solid carrier of a powder or of granules; or the ingestible liquid medium of a syrup, solution, suspension or elixir, 40

b) the solid or liquid medium of a cream, lotion, salve, ointment or gel,

45 c) a sterile injectable liquid solution or suspension medium, or 45

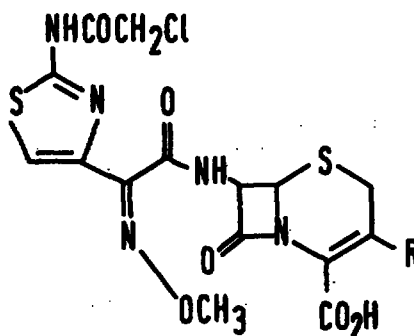
d) a base material of a suppository.

The compositions can thus be in solid or liquid form and are conveniently presented as, for example, plain or sugar-coated compressed tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams or gels, prepared according to the usual methods. The vehicles generally employed will be those conventionally employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, paraffin derivatives, glycols, and other aqueous or non-aqueous vehicles and fatty substances of animal or vegetable origin. The compositions may also contain wetting, dispersing or emulsifying agents, and/or preservatives.

55 The dose administered can be varied according to the disease treated, the person concerned, the route of administration and the active principle employed. By way of illustration, it may be between 0.250 g and 4 g per day by oral route in man for the products described in Examples 4, 6 and 10, or between 0.500 g and 1 g three times daily for compounds administered by intramuscular or intravenous route. 55

Certain of the compounds of general formula VI are themselves new, and this 60

invention provides these compounds *per se*. Thus, this invention extends to the *syn* isomer compounds of the general formula:



wherein R is as defined hereinbefore as well as the process described hereinbefore for its preparation.

These new compounds also possess antibiotic activity and may be useful in treating the same diseases as the compounds of general formula I.

The compounds of general formula III, C and D employed in the process described herein are themselves described and claimed in our Patent Application No. 79-15561 (Serial No. 1,580,623) which was divided out of our Patent Application No. 2640/77 (Serial No.).

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

Example 1

7 - [(2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic Acid

One mixes 2.5 g of the sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxy imino acetic acid with 40 cm³ of methylene chloride and 5 cm³ of 2 N hydrochloric acid. One decants, washes with water, dries and concentrates.

The crude acid is dissolved in 30 cm³ of dry tetrahydrofuran. One adds 0.7 g of dicyclohexylcarbodiimide, agitates for 45 minutes at ambient temperature, vacuum-filters the dicyclohexyl-urea formed, cools to -5°C and adds the solution of 0.895 g of 7 - amino - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid in 10 cm³ of water and 0.9 cm³ of triethylamine (previously cooled to 0°C). One allows to return to ambient temperature over one hour thirty minutes, dries off the tetrahydrofuran, adds 40 cm³ of methylene chloride, washes with dilute hydrochloric acid then with water, dries and concentrates to dryness.

One dissolves the residue in 8 cm³ of dioxane and adds, drop by drop, 3 cm³ of saturated solution of sodium bicarbonate, agitates for 30 minutes, filters, washes with ether, recovers 0.554 g of starting product in the form of sodium salt, drives off the dioxane, takes up with methylene chloride, washes with N hydrochloric acid, then with water, dries and concentrates to dryness. One triturates in ether, vacuum-filters, washes and obtains 1.9 g of crude product.

One agitates this product in 5 cm³ of ethyl acetate adds 5 cm³ of ether, agitates, vacuum-filters and washes. One obtains 1.47 g of partially purified product which one dissolves in 2 cm³ of methylene chloride and precipitates with 25 cm³ of ether. After vacuum-filtration and washing one obtains 1.4 g of expected product.

One thus obtains 7 - [(2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid which has the *syn* configuration.

The sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid, *syn* isomer, used at the start of the above Example 1 was prepared as follows:

Stage A

Ethyl *p* - chloro - α - methoxyimino - acetylacetate

One places 22.5 g of ethyl *p* - chloro - α - oximino - acetylacetate in 100 cm³ of methylene chloride.

One places on a bath of ice and slowly adds, under agitation, a fresh solution of diazomethane (containing 21.6 g/l) that is 275 cm³. One leaves in contact for five minutes and destroys the excess diazomethane with a little alumina. One concentrates, then purifies by eluting on silica with methylene chloride. One obtains 11.93 g of expected product.

Stage B

Ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate

One places 1 g of ethyl γ - chloro - α - methoxyimino - acetylacetate, 3 cm³ of absolute ethanol and 0.42 g of ground thiourea. One agitates at ambient temperature for about two hours. One dilutes with 60 cm³ of ether, the hydrochloride obtained crystallises out, one agitates, vacuum-filters, washes, dries and obtains 685 mg of hydrochloride. One dissolves them in 4 cm³ of water at 50°C, adds potassium acetate until pH 6 and the amine released crystallises out. One cools, vacuum-filters, washes with water, dries and obtains 270 mg of expected product. M.Pt.=161°C.

The product obtained has the *syn* configuration. NMR (CDCl₃, 60 MHz) p.p.m.: 4.0 (N—OCH₃), 6.7 (proton of the thiazole ring).

Stage C

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. One cools to -10°C, adds 2.9 cm³ of triethylamine, cools again to -35°C, adds, over 15 minutes, 6.1 g of trityl chloride and allows to return to ambient temperature, that is in all two hours thirty minutes. One washes with water, then 0.5 N hydrochloric acid and with sodium acetate in water. One dries, concentrates, takes up with ether, concentrates again, dissolves in methanol, adds water and ether, allows to crystallize vacuum-filters, washes with ether and obtains 6.15 g of expected product. M.Pt.=120°C.

The product obtained has the *syn* configuration.

Stage D

Sodium Salt of 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. One takes to 110°C in an oil bath and adds, over 5 minutes, 9 cm³ of 2 N sodium hydroxide, then leaves for 30 minutes under agitation at reflux. The sodium salt crystallizes out. One cools, vacuum-filters, washes with dioxane then with ether and obtains a first yield of 5.767 g of salt. One concentrates the mother solution and obtains a second yield of 1.017 g, that is in all 6.784 g of sodium salt.

The product obtained has the *syn* configuration.

Example 2

7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic Acid

The 1.4 g of product obtained in Example 1 are taken, under agitation in 5 cm³ of 50% aqueous formic acid, to 57°C for 15 minutes. One adds 5 cm³ of water, cools to ambient temperature, vacuum-filters, adds 5 cm³ of ethanol, concentrates to dryness, triturates the residue in 5 cm³ of ethanol, vacuum-filters, washes with ethanol and with ether and obtains 0.687 mg of crude product.

The product is dissolved in 7 cm³ of water and 0.2 cm³ of triethylamine, and one vacuum-filters, rinses and acidifies with 0.2 cm³ of 50% formic acid. One agitates, vacuum-filters, washes with alcohol and with ether. One obtains a first yield of 0.275 g.

Analysis:	C ₁₇ H ₁₇ O ₅ N ₅ S ₄ (0.5 EtOH)
Calculated:	C% 39.25 H% 3.66 N% 17.80 S% 23.28
Found:	C% 39.3 H% 3.5 N% 17.9 S% 23.1

The product obtained has the *syn* configuration. NMR (DMSO, 60 MHz) p.p.m.: 3.85 (N—OCH₃), 6.76 (proton of the thiazole ring).

Example 3

7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetal] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic Acid

5 One uses 2.33 g of the sodium salt of 2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid and, operating as in Example 1, obtains the crude acid which one dissolves in 30 cm³ of methylene chloride. One adds 0.7 g of dicyclohexylcarbodiimide and leaves for 50 minutes at ambient temperature under agitation and under inert gas. One vacuum-filters the dicyclohexyl urea formed, 10 cools to -5°C and adds, in one dose, the solution of 0.854 g of 7 - amino - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid in 10 cm³ of methylene chloride and 0.75 cm³ of triethylamine. One allows to return to ambient temperature, adds 1 cm³ of acetic acid, vacuum-filters after 10 minutes, 15 washes with water to which hydrochloric acid has been added, dries, concentrates, takes up with 8 cm³ of dioxane and adds 2.5 cm³ of saturated solution of sodium bicarbonate. One vacuum-filters off the sodium salt of the initial tritylated acid and rinses with 1:1 ether-dioxane mixture, then with ether. One drives off the dioxane, 20 takes up with methylene chloride, washes with water to which hydrochloric acid has been added, dries and concentrates. One triturates in ether, vacuum-filters, washes with ether and obtains 2.29 g of crude product. One then agitates the product for one hour at 10°C in ethanol, vacuum-filters, washes with ether and obtains 1.42 g of purified product.

The product obtained has the *syn* configuration.

Example 4

25 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic Acid 25

30 One places 1.4 g of product prepared in Example 3 in 5 cm³ of 50% aqueous formic acid in a water bath at 55°C. After 15 minutes one adds 5 cm³ of water, cools, vacuum-filters, and concentrates the filtrate after having added thereto 5 cm³ of ethanol. One takes up with 5 cm³ of alcohol, triturates, vacuum-filters, washes with ethanol then with ether, vacuum-filters, dries, makes into a paste in a 1:1 methylene chloride-ether mixture, vacuum-filters, washes and obtains 0.557 g of pure product.

35 Analysis: C₂₈H₂₇O₅N₉S₃ (0.5 EtOH) 35
Calculated: C% 38.19 H% 3.77 N% 23.58 S% 18.00
Found: C% 38.1 H% 3.9 N% 22.5 S% 17.7

The product obtained has the *syn* configuration. NMR (DMSO, 60 MHz) p.p.m.: 3.83 (N—OCH₃) 6.73 (proton of the thiazole ring).

Example 5

40 3 - acetyl - thiomethyl - 7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic Acid 40

45 Starting with 3.1 g of sodium salt of 2 - [(2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino] - acetic acid in 40 cm³ of methylene chloride and 6.5 cm³ of 2 N hydrochloric acid one prepares, as in Example 1, the corresponding acid. This acid is dissolved in 30 cm³ of methylene chloride. One adds 0.8 g of dicyclohexylcarbodiimide and agitates for 1 hour 30 minutes in a water bath and chills. One vacuum-filters the dicyclohexyl-urea formed, cools to -5°C and adds, in 50 one dose, a solution of 1.1 g of 7 - amino - 3 - acetyl - thiomethyl - ceph - 3 - em - 4 - carboxylic acid in 13 cm³ of methylene chloride and 0.9 cm³ of triethylamine (at 0°C). One allows to return to ambient temperature, adds 1 cm³ of acetic acid, vacuum-filters the insoluble matter, washes with water to which hydrochloric acid has been added, then with water, concentrates, takes up the residue in dioxane, adds 3.5 cm³ of a saturated solution of sodium bicarbonate, 55 vacuum-filters after 30 minutes, washes with a dioxane-ether mixture and recovers 0.64 g of sodium salt of the initial tritylated acid. One drives off the dioxane, takes up with 30 cm³ of methylene chloride, washes with water to which hydrochloric acid has been added (10 cm³ of water and 10 cm³ of 2 N hydrochloric acid), then 60 with water and concentrates. One triturates with 25 cm³ of ether, vacuum-filters, washes and obtains 1.89 g of crude product.

One reprecipitates twice by dissolving in 3 cm³ of ethyl acetate and adding 25 cm³ of ether. One obtains 0.89 g of expected product.

The product obtained has the *syn* configuration.

The 7 - amino - 3 - acetyl - thiomethyl - ceph - 3 - em - 4 - carboxylic acid used at the start of Example 5 was prepared as follows:—

One places 5.44 g of 7 - amino - cephalosporanic acid and 50 cm³ of water containing 1% of hydroquinone under an inert gas. One agitates and adds 1.7 g of sodium bicarbonate, then adds, after dissolution, 3 g of potassium thioacetate. One agitates for 3 hours at 60°C, cools and acidifies with acetic acid. One agitates at ambient temperature, vacuum-filters, washes, dries and obtains 4.9 g of expected product.

Example 6

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

The product obtained in Example 5 is agitated for 15 minutes in a bath at 55°C with 5 cm³ of 50% aqueous formic acid. One adds 5 cm³ of water, cools to ambient temperature, vacuum-filters, adds 5 cm³ of alcohol to the filtrate and concentrates to dryness. One disintegrates in 5 cm³ of alcohol and obtains, in two yields, 440 mg of product which one dissolves in 6 cm³ of 50% aqueous acetone. One adds 20 mg of carbon black, vacuum-filters and partially drives off the acetone. One obtains, after vacuum-filtration, 0.265 g of pure product.

Analysis:	C ₁₈ H ₁₇ O ₈ N ₅ S ₃ (0.25 CH ₃ COCH ₃)
Calculated:	C% 41.39 H% 3.83 N% 14.41 S% 19.78
Found:	C% 41.2 H% 3.8 N% 14.4 S% 19.8

The product obtained has the *syn* configuration. NMR (DMSO 60 MHz) 3.83 (N—OCH₃); 6.73 (proton of the thiazole ring).

Example 7

ter - butyl - 7 - [(2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - isopropyl - ceph - 3 - em - 4 - carboxylate

One acidifies 1.65 g of sodium salt of 2 - [(2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino] - acetic acid as indicated in Example 1.

The residual acid is dissolved in 25 cm³ of dry methylene chloride. One adds 0.71 g of dicyclohexylcarbodiimide, agitates for 10 minutes in a bath of iced water and adds 0.965 g of *t*-butyl ester of 7 - amino - 3 - isopropyl - ceph - 3 - em - 4 - carboxylic acid. One leaves under agitation for two hours at ambient temperature, vacuum-filters the dicyclohexyl urea, washes with water (10 cm³) containing 2 cm³ of 2 N hydrochloric acid, then with water, then with 10 cm³ of water containing 5 cm³ of saturated solution of sodium bicarbonate. One dries and concentrates to dryness. One dissolves the residue in ether, vacuum-filters, washes with isopropyl ether and obtains 1.66 g of expected product.

The product obtained has the *syn* configuration.

Example 8

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

The 1.66 g of product obtained in Example 7 are agitated for 15 minutes at ambient temperature with 6 cm³ of trifluoroacetic acid. One adds 60 cm³ of isopropyl ether, vacuum-filters, washes with isopropyl ether and obtains 0.825 g of product in the form of salt in trifluoroacetic acid.

One dissolves this product in 6 cm³ of water and a 4 cm³ of acetone. One adds 0.2 cm³ of pyridine and drives off the acetone. One obtains a first yield of 0.232 g.

One concentrates the filtrate, takes up with 3 cm³ of water and isolates a further 0.194 g of the same product, that is in all 0.426 g.

Analysis:	C ₁₈ H ₁₉ O ₈ N ₅ S ₃ (0.25 CH ₃ COCH ₃)
Calculated:	C% 46.23 H% 4.88 N% 15.41 S% 14.10
Found:	C% 46.1 H% 4.7 N% 15.5 S% 14.1

The product obtained has the *syn* configuration. NMR (DMSO 60 MHz) p.p.m.: 3.83 (N—OCH₃); 6.78 (proton of the thiazole ring).

Example 9

t - butyl - 7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - methyl - cephalosporanic acid - 3 - em - 4 - carboxylate

One acidifies 2.3 g of sodium salt of 2 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino] - acetic acid according to the product indicated in Example 1.

The residual crude acid is dissolved in 30 cm³ of methylene chloride, one adds 1.1 g of dicyclohexylcarbodiimide then, after 5 minutes, 1.35 g of *t*-butyl ester of 7 - amino - disacetoxy - cephalosporanic acid. One agitates for two hours, vacuum-filters, washes with water, with water acidified with hydrochloric acid, with water and finally with a saturated solution of sodium bicarbonate, dries, concentrates, takes up with ether, vacuum-filters, concentrates to dryness and obtains 2.8 g of pure product.

The product obtained has the *syn* configuration.

Example 10

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - methyl - cephalosporanic acid - 3 - em - 4 - carboxylic Acid

To 2.3 g of product prepared in Example 9 there are added 8 cm³ of trifluoroacetic acid. One agitates for 15 minutes at ambient temperature and adds 80 cm³ of isopropyl ether. One agitates, vacuum-filters and washes with isopropyl ether. One obtains 1.12 g of product in the form of the salt of trifluoroacetic acid. One takes them up with 10 cm³ of ethanol at 40°C. One completes crystallisation by adding 0.2 cm³ of pyridine, cools to +10°C, vacuum-filters, washes with ethanol and with ether and obtains 0.531 g of pure product.

Analysis:	C ₁₄ H ₁₅ O ₅ N ₅ S ₂ (0.25 EtOH)
Calculated:	C% 42.6 H% 4.06 N% 17.13 S% 15.68
Found:	C% 42.2 H% 3.9 N% 16.6 S% 15.5

The product obtained has the *syn* configuration. NMR (DMSO, 60 MHz) p.p.m.: 3.85 (N—OCH₃); 6.78 (proton of the thiazole ring).

Example 11

7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [[(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - cephalosporanic acid - 3 - em - 4 - carboxylic Acid

One places 2.7 g of 3 - acetoxy - methyl - 7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporanic acid, 0.624 g of monosodium phosphate, 1.51 g of sodium bicarbonate, 1.32 g of 1 - methyl - 5 - mercapto - tetrazole, 40 cm³ of water and 20 cm³ of acetone. One leaves for one night at 48°C and one hour at 60°C. After purification one obtains the product expected, *syn* isomer, identical to that described in Example 3.

Example 12

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [[(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - cephalosporanic acid - 3 - em - 4 - carboxylic Acid

Starting with 1.7 g of 3 - acetoxy - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporanic acid, 0.624 g of monosodium phosphate, 1.51 g of sodium bicarbonate, 1.32 g of 1 - methyl - 5 - mercapto - tetrazole, 40 cm³ of water and 20 cm³ of acetone and leaving for one night at 48°C and one hour at 60°C, one obtains the product expected, *syn* isomer, identical of that described in Example 4.

The 3 - acetoxy - methyl - 7 - [[2 - (2 - tritylamino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporanic acid, *syn* isomer, used at the start of Example 11 and 3 - acetoxy - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporanic acid, *syn* isomer, used at the start of Example 12 were prepared as follows:

a) 3 - acetoxy - methyl - 7 - [[2 - (2 - trityl - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporanic acid - 3 - em - 4 - carboxylic Acid
One places 3.06 g of sodium salt of 2 - (2 - trityl - amino - 4 - thiazolyl) - 2 - methoxyimino - acetic acid in 65 cm³ of methylene chloride and 6.5 cm³ of 2 N

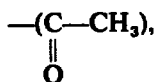
hydrochloric acid, washes with water, dries and concentrates to dryness, to obtain quantitatively the free acid.

5 The free acid obtained is dissolved in 30 cm³ of dry methylene chloride. One adds 0.78 g of dicyclohexylcarbodiimide and agitates for one hour at ambient temperature. One vacuum-filters the dicyclohexyl-urea formed, cools to -10°C and adds a solution of 1.01 g of 7 - amino - cephalosporanic acid in 13 cm³ of methylene chloride and 0.9 cm³ of triethylamine. One allows to return to ambient temperature, adds 1 cm³ of acetic acid, vacuum-filters, washes with water to which hydrochloric acid has been added then with water, dries, concentrates to dryness, takes up with 10 ml of dioxane, and adds 1 cm³ of water and 3 cm³ of saturated solution of sodium acid carbonate. One agitates, vacuum-filters, washes and concentrates to dryness. One takes up with methylene chloride, washes with 10 cm³ of water and 5 cm³ of normal hydrochloric acid, decants, washes with water, dries, disintegrates in ether and obtains 1.747 g of crude product which one purifies by dissolution in ethyl acetate followed by precipitation with ether. One obtains 1.255 g of pure product. 10 15

The product obtained has the *syn* configuration.

20 b) 3 - acetoxy - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic Acid 0.975 g of product obtained above are agitated for ten minutes at 55°C in 4 cm³ of 50% aqueous formic acid. One adds 4 cm³ of water, vacuum-filters and concentrates to dryness under vacuum. One disintegrates in 2 cm³ of ethanol, vacuum-filters, washes with ethanol, then with ether and obtains 0.428 g of pure product.

25 The product obtained has the *syn* configuration. NMR (DMSO, 60 MHz) p.p.m.: 2.03 25



doublet 9.58, J=8 Hz (CONH); 6.76 (proton of the thiazole ring).

Example 13

30 3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer 30

35 One puts into solution 4.55 g of 3 - acetoxy - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, 1.7 g of potassium thioacetate, 2 g of dehydrated monosodium phosphate, 1.05 g of sodium bicarbonate and 20 cm³ of distilled water. One takes to 70°C for 1 hour 30 minutes. One acidifies with 2 cm³ of formic acid and extracts with 4 times 60 cm³ of methyl acetate (one vacuum-filters an insoluble substance). 35

40 One washes the organic solution with water, one dries and concentrates to dryness. One dissolves the residue obtained in 20 cm³ of acetone containing 10% of water. One adds 0.5 g of active charcoal. One agitates for 5 minutes, vacuum-filters the charcoal, washes it with acetone containing 10% of water and concentrates the filtrate to dryness. The residue is treated with absolute ethanol, one vacuum-filters, washes with alcohol then with ether. One obtains 1.9 g of pure product by TLC. 40 45

NMR (DMSO, 60 MHz) 3.85 (N—OCH₃); 6.75 (proton of the thiazole ring).

The product is identical to that obtained in Example 6.

Example 14

50 Sodium Salt of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thio - methyl] - ceph - 3 - em - 4 - carboxylic Acid, *Syn* Isomer 50

55 One adds to a solution of 2.3 g of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thio - methyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer prepared according to Example 2 in 5 cm³ of acetone, an aqueous solution of sodium acid carbonate so as to obtain a pH of 7. One adds 0.4 g of animal charcoal, agitates for 5 minutes, vacuum-filters the charcoal and washes it with 1:1 aqueous acetone. 55

One adds 50 cm³ of ethanol to the decoloured filtrate and concentrates to dryness under vacuum at 30°C. One takes up the residue with 5 cm³ of ethanol, triturates the crystals, vacuum-filters, and washes with ethanol, then with ether. One obtains 1.3 g of expected product.

5

Analysis:

Na: Calculated: 4.18% Found: 4.70

5

Ultra Violet in ethanol:

Max. 235 nm E₁¹=360 ε=19 800

265 nm E₁¹=322 ε=17 700

10

Inflection 280 nm E₁¹=295

in ethanol containing N/10 hydrochloric acid.

10

Inflection 218 nm E₁¹=244

Max=266—267 nm E₁¹=406 ε=22 300

Inflection 280 nm E₁¹=363

15

Example 15

15

Sodium Salt of 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - cephalosporin - 3 - em - 4 - carboxylic Acid,

Syn Isomer

20

One places 3.35 g of 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thio - methyl] - cephalosporin - 3 - em - 4 - carboxylic acid, *syn isomer*, prepared according to Example 4, in 7 cm³ of methanol and 7 cm³ of aqueous molar solution of sodium bicarbonate. One agitates for 5 minutes at ambient temperature, vacuum-filters the insoluble portions and rinses them twice with a 1:1 methanol-water mixture.

20

25

One adds, whilst agitating, 85 cm³ of ethanol and the sodium salt crystallizes out. One then adds 170 cm³ of ether agitates for 10 minutes, vacuum-filters, washes with 1:1 ethanol-ether, then with ether and dries. One obtains 3.26 g of expected product.

25

30

The product is purified as follows:

30

One dissolves the above salt in 40 cm⁴ of water, adds 0.6 cm³ of acetic acid to return to pH 6.8—7, one dilutes with ethanol and drives off the solvents under reduced pressure at a temperature below 35°C. One takes up with ethanol to eliminate the water and brings to dryness.

35

The residue is taken up in 16 cm³ of methanol, then one dilutes with 160 cm³ of acetone and the salt crystallizes out. One agitates for 5 minutes, vacuum-filters and washes with acetone and then with ether.

35

One obtains 2.3 g of expected product.

[α]_D²⁰=-13.5°±1 (at 1%, in water).

40

Analysis:

Na: Calculated: 4.31% Found: 4.8%

40

Example 16

Sodium Salt of 3 - acetyl - thio - methyl - 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn Isomer*

45

One places at ambient temperature 4.5 g of 3 - acetyl - thiomethyl - 7 - [(2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl) - amino] - cephalosporin - 3 - em - 4 - carboxylic acid, *syn isomer*, prepared according to Example 6, in 9 cm³ of methanol and 9 cm³ of a molar solution of sodium bicarbonate in water. One agitates for five minutes at ambient temperature, vacuum-filters the insoluble portions, and rinses with a 1:1 mixture of methanol and water. One adds, under agitation, 110 cm³ of ethanol and the sodium salt crystallizes out. One dilutes with 220 cm³ of ethyl ether, agitates, vacuum-filters and washes with a 1:1 ethanol-ether mixture then with ether. One dries and obtains the expected product.

45

50

The sodium salt obtained is purified as follows:

50

One dissolves the product in 40 cm³ of water and brings the pH to 6.8—7 by the addition of a few drops of acetic acid. One dilutes with 100 cm³ of ethanol, then drives off the solvents under reduced pressure at a temperature below 35°C. One takes up the concentrate, disintegrates twice with 50 cm³ of ethanol and brings to dryness a second time. One dissolves the residue in 15 cm³ of methanol, filters off the insoluble matter, then dilutes the methanolic solution with 150 cm³ of acetone.

60

60

The sodium salt crystallizes out, one agitates for 5 minutes, then vacuum-filters and washes with acetone, then with ether. One dries under reduced pressure. One obtains 1.8 g of expected product.

$[\alpha]_D^{20} = -31 \pm 2$ (at 0.6% in water).

5

Analysis:

Na: Calculated: 4.65% Found: 4.9%

5

Ultra Violet

in ethanol:

Max. 235 nm $E_1^1 = 419$

10

Inflection 260 nm $E_1^1 = 343$

Inflection 300 nm $E_1^1 = 122$

10

in ethanol — N/10 hydrochloric acid.

Inflection 230 nm $E_1^1 = 280$

Max. 263 nm $E_1^1 = 391$ $\epsilon = 19,700$

15

Example 17

15

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

20

One agitates 471.5 mg of 3 - acetyl - thiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic acid, *syn* isomer, prepared according to Example 6, with 1.5 cm³ of molar solution of anhydrous sodium acetate in anhydrous methanol. One adds 0.5 cm³ of ethanol, vacuum-filters a slightly insoluble substance, adds 2 cm³ of ethanol and the sodium salt crystallises out. One vacuum-filters, washes with ethanol, then dries in the oven at 45°C under vacuum.

20

25

One obtains 0.25 g of non-hygroscopic salt.

25

Analysis:

Na: Calculated: 4.66% Found: 4.6%

30

Example 18

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3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

Stage A

35

3 - acetyl - thio - methyl - 7 - [[2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

35

One places 15.3 g of 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetic acid, *syn* isomer, in 80 cm³ of methylene chloride. At 5°C one adds 8 cm³ of triethylamine. At 0°C under nitrogen one introduces 3.8 cm³ of thionyl chloride and 26 cm³ of methylene chloride. One leaves for 15 minutes at 0°C then adds 7 cm³ of triethylamine. One introduces, at 0°C under nitrogen, 14.4 g of 7 - amino - 3 - acetyl - thio - methyl - cephalosporin - 3 - em - 4 - carboxylic acid into 100 cm³ of methylene chloride and 14 cm³ of triethylamine. One allows to return to 20°C then agitates for one hour. This solution is distilled to dryness under vacuum at about 30—35°C. One dissolves the residue in 250 cm³ of water, passes over charcoal and adds 50 cm³ of 2 N hydrochloric acid. One vacuum-filters the precipitate and washes with water. The crude product obtained is put into suspension in 80 cm³ of ethanol. At +5°C one adds 7 cm³ of triethylamine. One adds, in one dose under agitation at +5°C, 15 cm³ of 4 N sulphuric acid and the product crystallizes out after 15 minutes. One vacuum-filters, washes with ethanol by making into a paste, then with ether, dries under vacuum and obtains the expected product.

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Stage B

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3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic Acid, *Syn* Isomer

55

One puts 5.48 g of acid obtained in Stage A above into 10.6 cm of water and 912 mg of thiourea. At 20°C one adds 1 g of potassium acid carbonate. After dissolution one agitates for 6 hours at about 20°C under nitrogen. Gummy

precipitation begins after about 1 hour and a half. One then adds 30 cm³ of water and 3 cm³ of formic acid. One cools to 5°C. One vacuum-filters and washes with water containing 10% of formic acid. One dissolves the residue at about 5°C in 30 cm³ of water containing triethylamine. At 5°C one adds 3 cm³ of formic acid, one vacuum-filters the precipitate and washes by making into a paste with water containing formic acid. One eliminates the dark brown gum. The aqueous phases are collected and treated with charcoal. One obtains a pale yellow solution which one saturates with ammonium sulphate. One vacuum-filters the precipitate, makes into a paste with water, vacuum-filters, washes with water and obtains a precipitate A.

The mother liquors are saturated with ammonium sulphate, which gives a precipitate which one vacuum-filters, washes 3 times with water and obtains the precipitate B.

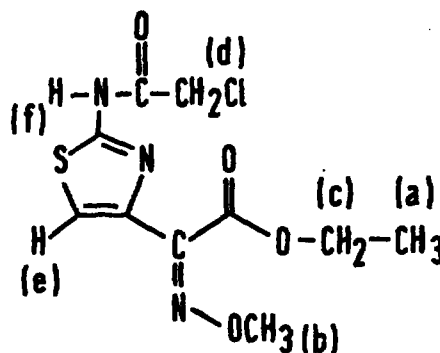
The precipitates A and B are put together. One takes up with ethanol, agitates for one hour at 20°C and leaves for 16 hours at 0°C. One vacuum-filters, washes with ethanol, then with ether, dries under vacuum and obtains the expected product, the *syn* isomer. The product is identical to that obtained in Examples 6 and 13.

The 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetic acid, *syn* isomer, used at the start of Example 18, was prepared as follows:

a) Ethyl 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetate, *Syn* Isomer

One places 45.8 g of ethyl 2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetate, *syn* isomer in 200 cm³ of methylene chloride. One distills 20 cm³ thereof to dry them, cools to 10°C and adds 50 cm³ of pyridine. One adds 41 g of monochloroacetic anhydride and heats lightly until dissolution. One leaves for six hours at 20°C under nitrogen, adds 5 cm³ of water, agitates and pours into 300 cm³ of chilled 2 N hydrochloric acid. One decants, extracts with methylene chloride, washes with water, with sodium acid carbonate, and with water, dries, passes over active charcoal, concentrates and adds 300 cm³ of isopropyl ether. The product crystallizes out. One concentrates until a thick paste is obtained, chills, vacuum-filters, washes with isopropyl ether, dries and obtains 45.4 g of product. M.Pt.=113°C.

One obtains a pure sample by recrystallization 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.

b) 2 - (2 - chloroacetamido - 4 - thiazolyl) - 2 - methoxyimino - acetic Acid, *Syn* Isomer

One places 46 g of product obtained in stage a) above in 230 cm³ of absolute ethanol. At 20°C under nitrogen one adds 30 cm³ of pure sodium hydroxide solution. The product dissolves, the sodium salt begins to crystallize out, then the medium congeals. After sixteen hours one vacuum-filters and washes. The salt obtained is dissolved in water, one chills, adds 100 cm³ of 2 N hydrochloric acid,

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5 saturates with sodium chloride, and extracts with ethyl acetate containing 10% of ethanol. One dries, passes over charcoal, distills under vacuum, entrains the water with benzene, takes up with methylene chloride, distills to dryness, takes up with methylene chloride, chills, vacuum-filters, washes, dries and obtains 34.5 g of expected product. M.Pt.=about 200°C. One purifies the product by recrystallization from an acetone-isopropyl ether mixture.

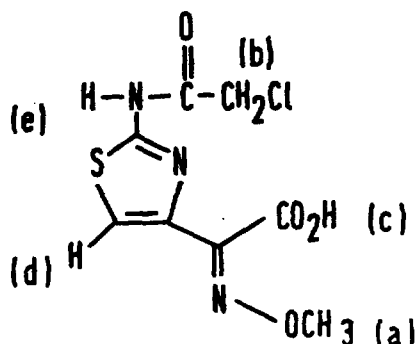
5

Analysis: $C_8H_8O_4N_3ClS=277.68$
 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

10

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

10



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

15

15

Example 19

One made up a preparation for injection of formula:

20

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thio - methyl] - cephalosporin - 3 - em - 4 - carboxylic acid

20

Sterile aqueous excipient q.s.v.

500 mg
 5 cm³

Example 20

25

One made up a preparation for injection of formula:

25

3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic acid

Sterile aqueous excipient q.s.v.

500 mg
 5 cm³

Example 21

30

One made up a preparation for injection of formula:

30

Sodium salt of 3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - cephalosporin - 3 - em - 4 - carboxylic acid

35

Sterile aqueous excipient q.s.v.

500 mg
 5 cm³

Example 22

One made up gelatin capsules corresponding to the formula:

40

7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thio - methyl] - cephalosporin - 3 - em - 4 - carboxylic acid

40

Excipient q.s. for one gelatin capsule up to

250 mg
 400 mg

Example 23

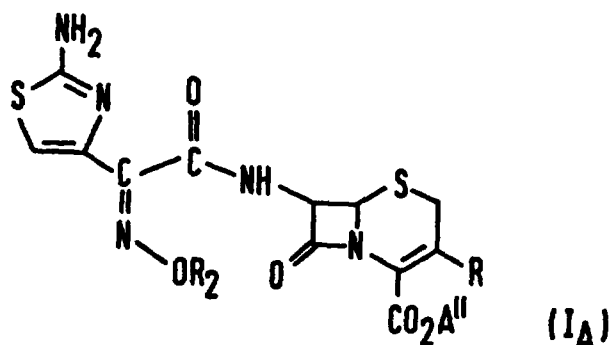
One made up gelatin capsules corresponding to the formula:

5	3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid	250 mg	5
	Excipient q.s. for one gelatin capsule up to	400 mg	

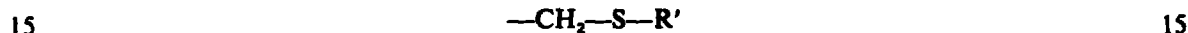
In the following, unless indicated otherwise, the substituents in the general formulae are as first defined.

WHAT WE CLAIM IS:—

- 10 1. A hydrocarbyloxime derivative of 7 - amino - thiazolyl - acetamido - ceph - 3 - em - 4 - carboxylic acid *syn* isomer of the general formula: 10



(wherein R represents an alkyl radical having from 1 to 5 carbon atoms, a cycloalkyl group having from 3 to 5 carbon atoms or a radical:



in which R' represents an acyl group having from 2 to 4 carbon atoms, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical; R₂ represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms; and 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.

20 2. A compound as claimed in Claim 1, wherein R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$.

25 3. A compound as claimed in Claim 1, wherein R represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 5 carbon atoms.

4. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical and R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$ in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical.

30 5. A compound as claimed in Claim 4, wherein A'' represents a hydrogen atom.

6. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical, R represents a methyl or isopropyl radical and A'' represents a hydrogen atom.

35 7. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical, R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$ in which R' represents an acyl radical having from 2 to 4 carbon atoms, and A'' represents a hydrogen atom or an alkali metal atom.

40 8. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.

9. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.

45 10. 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer. 45



Example 23

One made up gelatin capsules corresponding to the formula:

3 - acetyl - thio - methyl - 7 - [[2 - (2 - amino - 4 -
thiazolyl) - 2 - methoxyimino - acetyl] - amino] -
ceph - 3 - em - 4 - carboxylic acid

Excipient q.s. for one gelatin capsule up to

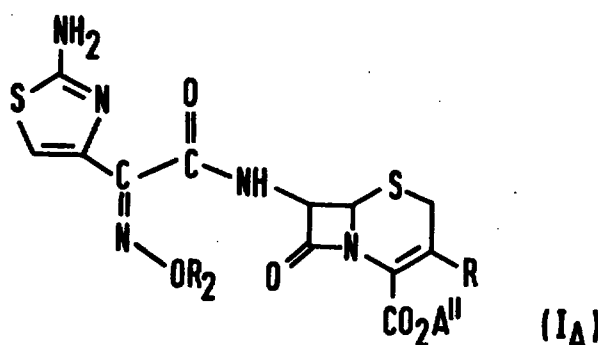
250 mg

400 mg

In the following, unless indicated otherwise, the substituents in the general formulae are as first defined.

WHAT WE CLAIM IS:—

1. A hydrocarbyloxime derivative of 7 - amino - thiazolyl - acetamido -
ceph - 3 - em - 4 - carboxylic acid *syn* isomer of the general formula:



(wherein R represents an alkyl radical having from 1 to 5 carbon atoms, a cycloalkyl group having from 3 to 5 carbon atoms or a radical:



in which R' represents an acyl group having from 2 to 4 carbon atoms, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical; R₂ represents a saturated or unsaturated hydrocarbyl radical having from 1 to 4 carbon atoms; and 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.

2. A compound as claimed in Claim 1, wherein R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$.

3. A compound as claimed in Claim 1, wherein R represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 5 carbon atoms.

4. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical and R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$ in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical.

5. A compound as claimed in Claim 4, wherein A'' represents a hydrogen atom.

6. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical, R represents a methyl or isopropyl radical and A'' represents a hydrogen atom.

7. A compound as claimed in Claim 1, wherein R₂ represents a methyl radical, R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$ in which R' represents an acyl radical having from 2 to 4 carbon atoms, and A'' represents a hydrogen atom or an alkali metal atom.

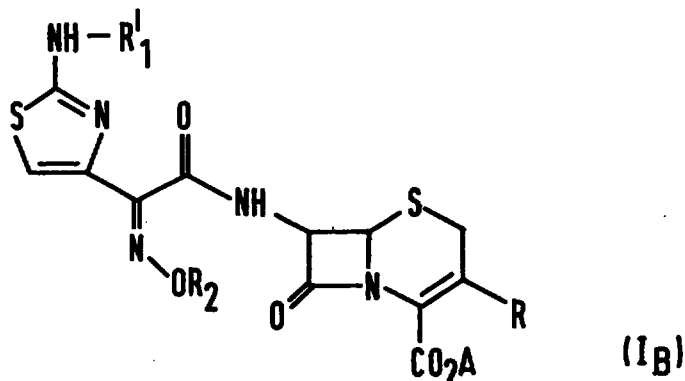
8. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [[(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.

9. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [[(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.

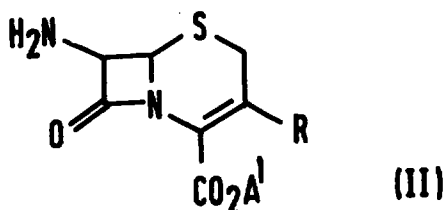
10. 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.



11. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - *isopropyl* - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
12. 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - methyl - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
13. 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, when obtained according to the process described in Example 6.
14. The sodium salt of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(2 - methyl - 1,3,4 - thiadiazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
15. The sodium salt of 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - 3 - [(1 - methyl - tetrazol - 5 - yl) - thiomethyl] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
16. The sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
17. The crystalline sodium salt of 3 - acetylthiomethyl - 7 - [[2 - (2 - amino - 4 - thiazolyl) - 2 - methoxyimino - acetyl] - amino] - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer.
18. A hydrocarbyloxime derivative of 7 - (protected amino) - thiazolyl - acetamido - ceph - 3 - em - 4 - carboxylic acid, *syn* isomer, of the general formula:



- wherein R_1' represents a group removable by acid hydrolysis or by hydrogenolysis, A represents a hydrogen atom, an alkali metal atom, an equivalent of an alkaline-earth metal atom, an equivalent of a magnesium atom, a substituted ammonium group or an ester-forming group removable by acid hydrolysis or by hydrogenolysis.
19. A compound as claimed in Claim 18, wherein A represents a benzhydryl, *t*-butyl, benzyl, *p*-methoxy-benzyl or trichloroethyl radical.
20. A compound as claimed in Claim 18 or Claim 19, wherein R_1' represents a trityl group, *t*-butoxy-carbonyl, trityl, benzhydryl, trichloroethyl or carbobenzyloxy group.
21. A compound as claimed in Claim 18, wherein R_1' represents a trityl group, R_2 represents a methyl radical, R represents a radical $-\text{CH}_2-\text{S}-\text{R}'$ in which R' represents an acetyl radical, a 2 - methyl - 1,3,4 - thiadiazolyl radical or a 1 - methyl - tetrazolyl radical and A represents a hydrogen atom.
22. A compound as claimed in Claim 18, wherein R_1' represents a trityl group, R_2 represents a methyl radical, R represents a methyl or *isopropyl* radical and A represents a hydrogen atom.
23. A process for preparing a compound of formula I, as claimed in Claim 18, wherein A represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or by hydrogenolysis, in which process an appropriate compound of the general formula:





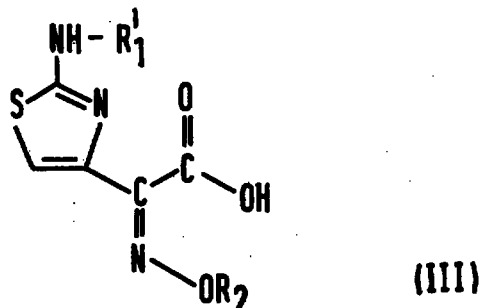
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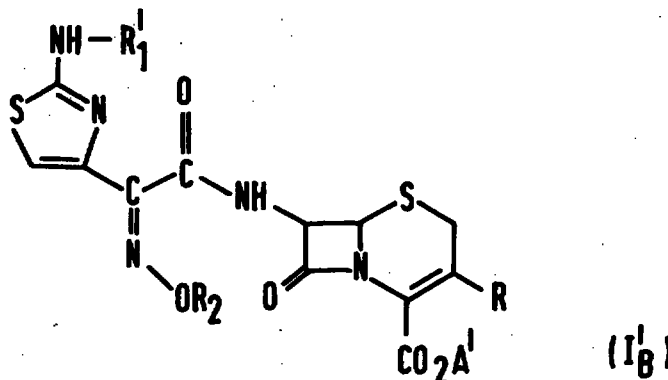
(wherein A' represents a hydrogen atom or an ester-forming group removable by acid hydrolysis or by hydrogenolysis) is treated with a *syn* isomer of the general formula:



5

or a functional derivative thereof, to give the desired *syn* isomer of the general formula:

5



10

24. A process as claimed in Claim 23, in which the acid of formula III is employed in the form of an anhydride or acid halide.

10

25. A process as claimed in Claim 24, in which the anhydride is formed *in situ* by the action of *isobutyl* chloroformate or dicyclohexylcarbodiimide on the acid.

26. A process as claimed in Claim 24, in which the acid halide is the acid chloride.

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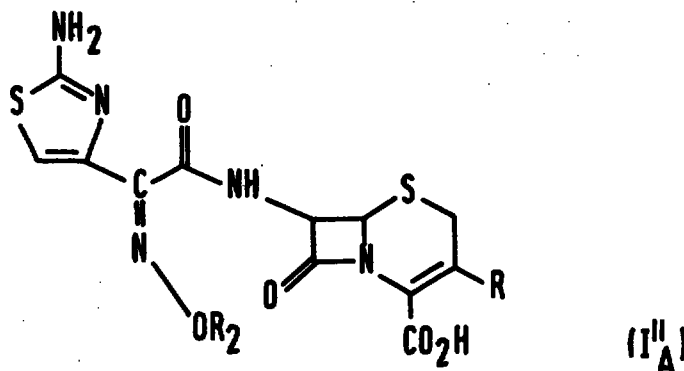
27. A process as claimed in Claim 26, in which the reaction is carried out in the presence of an alkali-metal carbonate, N-methyl-morpholine, pyridine or a trialkylamine.

15

20

28. A process as claimed in any of Claims 23 to 27, in which the formed product of general formula I_B' is treated with one or both of an acid hydrolysis agent and a hydrogenolysis agent, as appropriate, so as to remove the groups R₁' and A', to give a *syn* isomer product of the general formula:

20



29. A process as claimed in Claim 28, in which the acid hydrolysis agent employed is formic acid, trifluoroacetic acid, acetic acid or a zinc/acetic acid system.

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30. A process as claimed in Claim 28 or Claim 29, in which hydrogenolysis is carried out with hydrogen in the presence of a catalyst.

31. A process as claimed in any of Claims 23 to 30, in which the product of formula I_b' or I_a'' is thereafter salified to form a salt as claimed in Claim 1 or Claim 18.

32. A process as claimed in Claim 31, in which a mineral salt is obtained by reacting the formed acid with an appropriate mineral base or with an appropriate salt of a substituted or unsubstituted aliphatic carboxylic acid, or in which a substituted ammonium salt is obtained by reacting the formed acid with an appropriate organic base.

33. A process as claimed in Claim 31, or Claim 32, in which a solvate of the free acid is used as the starting material in the salification.

34. A process as claimed in Claim 33, in which the salification is carried out in a solvent comprising one or more of water, diethyl ether, methanol, ethanol and acetone.

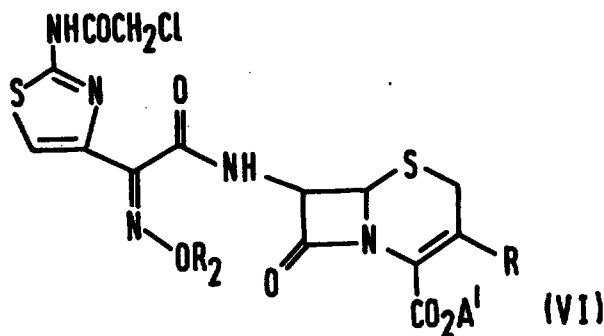
35. A process for preparing a compound as claimed in Claim 1, being a compound of general formula I_a'' (as defined in Claim 28) or a salt thereof, in which either a salt of an appropriate compound of general formula I_b' (as defined in Claim 23) wherein R_1' represents a group removable by acid hydrolysis is treated with an acid to obtain a compound of general formula I_a'' , or a salt of an appropriate compound of general formula I_b' wherein R_1' represents a group removable by hydrogenolysis is subjected to hydrogenolysis to give the corresponding salt of a compound of general formula I_a'' .

36. A process as claimed in Claim 35, in which the acid used to hydrolyse the substituent R_1' is formic acid, trifluoroacetic acid or acetic acid.

37. A process as claimed in Claim 35, in which the substituent R_1' is removed by catalytic hydrogenation.

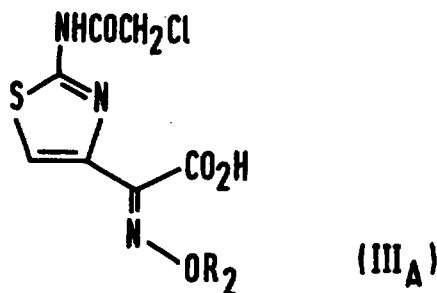
38. A process as claimed in any of Claims 35 to 37, in which the compound of general formula I_b' is prepared by a process as claimed in any of Claims 23 to 27.

39. A process for preparing a compound of general formula I_a'' , (as defined in Claim 28, in which an appropriate *syn* isomer of the general formula:



is treated with thiourea, and when A' does not represent a hydrogen atom also treated with an acid hydrolysis or hydrogenolysis agent as appropriate, to give the desired product of general formula I_a'' .

40. A process as claimed in Claim 39, in which the compound of general formula VI is prepared by reacting an appropriate compound of general formula II (as defined in Claim 23) with a suitable *syn* isomer of the general formula:

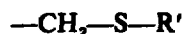


or a functional derivative thereof.



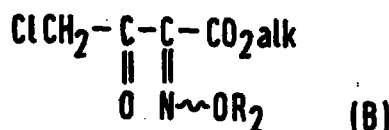
41. A process as claimed in Claim 40, in which the reaction of the compounds of general formulae II and III_A is carried out under the conditions defined in any of Claims 24 to 27 for the reaction of the compounds of general formulae II and III.

42. A process as claimed in Claims 23 to 27, 40 and 41, in which the starting material is a compound of general formula II wherein R represents the radical:

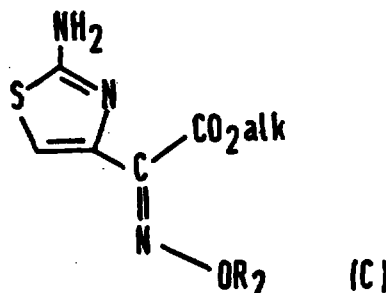


which is prepared by a nucleophilic exchange reaction between 7-aminocephalosporanic acid and a thiol of the formula R'—SH or a salt thereof.

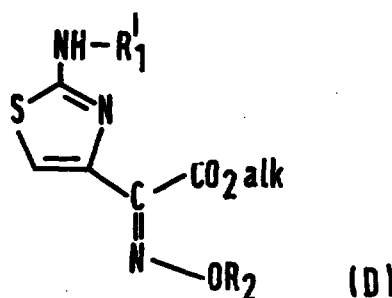
43. A process as claimed in any of Claims 23 to 27, in which the compound of general formula III is prepared by reacting a compound of the general formula:



(wherein alk represents an alkyl radical having from 1 to 4 carbon atoms) with thiourea a) in an aqueous solvent; b) at ambient temperature, using a substantially stoichiometric amount of thiourea for from 1 to 3 hours; or c) using a combination of conditions a) and b), and thereafter with a base to give a *syn* isomer of the general formula:



which is thereafter treated with a compound capable of introducing a group removable by acid hydrolysis or by hydrogenolysis to give a *syn* isomer of the general formula:



which is in turn treated first with a base and then with an acid, to give the *syn* isomer of general formula III.

44. A process as claimed in any of Claims 40 to 42 in which the compound of formula III_A is prepared by reacting a compound capable of introducing the chloroacetyl group with an appropriate *syn* isomer of general formula C (as defined in Claim 43) and treating the formed product first with a base and then with an acid.

45. A process as claimed in Claim 44, in which the compound capable of introducing the chloroacetyl group is a chloroacetyl halide or chloroacetic anhydride.

46. A process for preparing a compound of general formula I_A (as claimed in Claim 1), wherein R represents the group —CH₂S—R' or a compound of general formula I_B (as claimed in Claim 18), wherein R represents the group —CH₂S—R'

*Nc1nc(C2C(=O)NC3C(=O)N(C3C(=O)O)SCC3C(=O)OC(=O)C)cc1S (IV)

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58. A compound of the general formula:

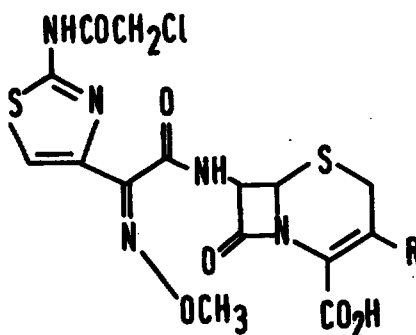


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59. A process for preparing a compound as claimed in Claim 58, as defined in any of Claims 40 to 42, 44 and 45.

For the Applicants,
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Reference has been directed in pursuance of Section 9, Subsection (1) of the Patents Act 1949, to Patent No. 1,536,281.

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ERRATUM

SPECIFICATION No. 1,581,184

Page 1, heading (54), *for* HYDROCARBYL-
OXIDE *read* HYDROCARBYLOXIME

THE PATENT OFFICE

8th March, 1982

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