

PATENT SPECIFICATION

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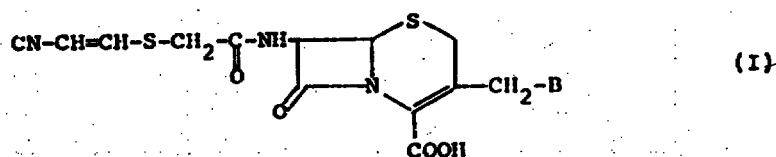


(54) UNSATURATED-THIO-DERIVATIVES OF
 7-ACETAMIDO-3-CEPHEM-4-CARBOXYLIC ACID AND
 PROCESS FOR THEIR PREPARATION

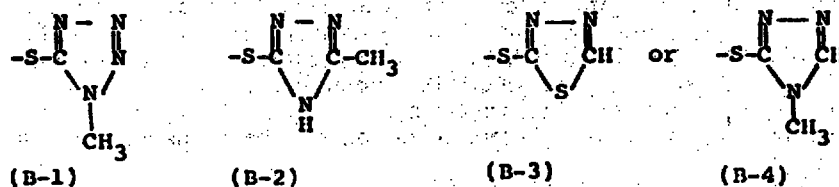
(71) We, FARMITALIA CARLO ERBA S.p.A., formerly known as
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 Milan, Italy, do hereby declare the invention for which we pray that a patent may
 be granted to us, and the method by which it is to be performed, to be particularly
 described in and by the following statement:—

The present invention relates to unsaturated-thio-derivatives of 7-acetamido-
 3-cephem-4-carboxylic acid, to a process for their preparation and to
 pharmaceutical and veterinary compositions containing them. The present
 application is a divisional of No. 33418/77 (Serial No. 1582295).

The derivatives of the invention are certain compounds falling within the
 general formula:



wherein
 the —CH=CH— group is *cis* or *trans*; and
 B represents one of the following groups:



and the pharmaceutically and veterinarily acceptable salts of the compounds of
 formula (I), metabolites thereof having antibacterial activity and bioprecursors of
 the compounds of formula (I).

The present invention provides certain specific compounds within formula (I)
 namely the following:

1) 7 - [β - cyano - ethylene(*trans*) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetra-
 zol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;

- 2) 7 - [β - cyano - ethylene(*trans*) - thio - acetamido] - 3 - [(1,3,4 - thiadiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 3) 7 - [β - cyano - ethylene(*cis*) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 5 4) 7 - [β - cyano - ethylene(*cis*) - thio - acetamido] - 3 - [(1,3,4 - thiadiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 5) 7 - [β - cyano - ethylene(*cis*) - thio - acetamido] - 3 - [(5 - methyl - 1,3,4 - thiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 10 6) 7 - [β - cyano - ethylene(*cis*) - thio - acetamido] - 3 - [1 - methyl - 1,3,4 - thiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 10 7) 7 - [β - cyano - ethylene(*trans*) - thio - acetamido] - 3 - [1 - methyl - 1,3,4 - thiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid;
 15 as well as the pharmaceutically and veterinarily acceptable salts thereof, preferably the alkali metal, most preferably sodium and potassium, salts, metabolites thereof having antibacterial activity and their bioprecursors. The structural formulae of the above-defined acids are set out below in Table 1 with reference to formula (I); 15

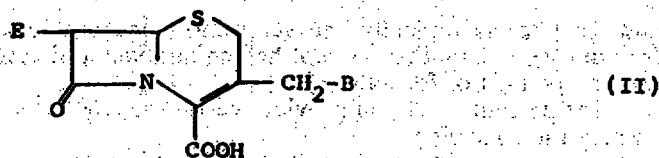
TABLE 1

Compound	Geometric isomer	Formula of "B" group
1	<i>trans</i>	B-1
2	<i>trans</i>	B-3
3	<i>cis</i>	B-1
4	<i>cis</i>	B-3
5	<i>cis</i>	B-2
6	<i>cis</i>	B-4
7	<i>trans</i>	B-4

20 The pharmaceutically and veterinarily acceptable salts of the compounds of formula (I) comprise those with inorganic bases, e.g. sodium, potassium, calcium, aluminium hydroxides and alkali metal and alkaline earth metal carbonates or bicarbonates, or with organic bases, e.g. organic amines, especially lysine, triethylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, N,N'-dibenzyl-ethylenediamine, dehydroabietylamine, N-ethylpiperidine, diethanolamine, N-methylglucamine or tris(hydroxymethyl)aminomethane. Alkali metal, especially sodium and potassium, salts are preferred. 20

25 The compounds of the present invention can be prepared by a process comprising:

(a) reacting a compound of formula (II)



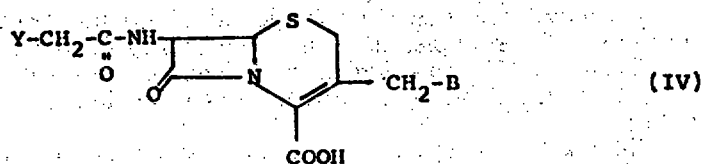
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wherein

B is as defined above and E represents an amino, $-\text{N}-\text{C}=\text{O}$ or $-\text{N}-\text{C}=\text{S}$ group, or a reactive derivative thereof, with an acid of formula (III)

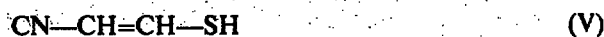
or a reactive derivative thereof;

(b) reacting a compound of formula (IV)



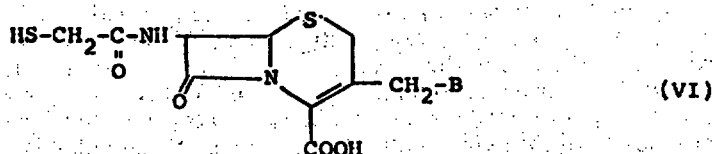
wherein

B is as defined above and Y represents a halogen atom, or a salt thereof, with a compound of formula (V)



or a reactive derivative thereof;

(c) reacting a compound of formula (VI)



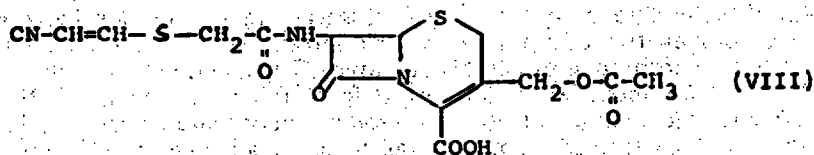
wherein

B is as defined above, or a reactive derivative thereof, with a compound of formula (VII)

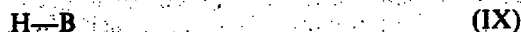


wherein

Y' represents a halogen atom or the residue of an active ester of an alcohol; and (d) reacting a compound of formula (VIII)



or a salt thereof, with a compound of formula (IX)



wherein

B is as defined above, or a reactive derivative thereof, and if desired, converting the product compound 1-7 into a pharmaceutically or veterinarily acceptable salt and/or, if desired, obtaining a free compound 1-7 from a salt and/or, if desired, converting a product compound 1-7 or a salt thereof into another product compound 1-7 or a salt thereof.

In the above definition of the process, B in formulae (II), (IV), (VI) and the configuration of the geometric isomer in formulae (III), (V) and (VII), i.e. *cis*- or *trans*- $\text{CH}=\text{CH}-$, are selected to be the same as in the compound 1-7 which it is intended to produce. The reactions are stereospecific. The carboxy group is protected, if necessary, in a conventional manner before the reaction takes place. Examples of protecting groups are those usually employed in the synthesis of

peptides, for example, *tert*-butyl, benzhydryl, *p*-methoxybenzyl and *p*-nitrobenzyl. The protecting groups are then removed, at the end of the reaction, in a known manner, e.g. by mild acid hydrolysis.

A reactive derivative of the compound of formula (II) may be, for example, an amine salt, a silyl ester or a metal salt.

A reactive derivative of the compound of formula (III) is, for example, an acyl halide, an anhydride or a mixed anhydride, an amide, an azide, a reactive ester or a salt, such as, for instance, the salts formed with alkali or alkali earth metals, ammonia or an organic base.

A reactive derivative of the compounds of formulae (V) and (VI) is preferably a salt thereof, for example, an alkali metal or alkali earth metal salt.

When Y or Y' are halogen, the halogen is preferably chlorine or bromine. When Y' is the residue of an active ester of an alcohol, it is preferably -O-mesyl or -O-tosyl.

The reaction between the compound of formula (II) or a reactive derivative thereof and the compound of formula (III) or a reactive derivative thereof may be performed either at room temperature or under cooling, in a suitable solvent, e.g. acetone, dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride or dimethylformamide and, if desired, in the presence of a base, e.g. sodium bicarbonate, potassium bicarbonate or a trialkylamine.

When the compound of formula (III) is reacted with the compound of formula (II) wherein E is amino, as a free acid or as a salt, it is desirable that the reaction be performed in the presence of a condensing agent, e.g. N,N'-dicyclohexylcarbodiimide.

The reaction of the compound of formula (IV), or a salt thereof, with the compound of formula (V), or a reactive derivative thereof, for example a salt, is preferably carried out at temperatures ranging from -30°C to +60°C, preferably at room temperature in the presence of an inorganic or organic base, e.g. sodium or potassium hydroxide, sodium carbonate or triethylamine, in a suitable solvent, e.g. acetone, chloroform, methanol, ethanol, methylene chloride or water. When in the compound of formula (V) the -SH group is not salified, it is preferable to carry out the reaction in the presence of a base, e.g. an alkali metal carbonate, an alkali metal hydroxide or triethylamine. The reaction between the compound of formula (VI), or a reactive derivative thereof, e.g. an alkali metal salt, and the compound of formula (VII) may be performed in an aqueous medium and in the presence of an inorganic base or in an organic solvent, preferably in an anhydrous organic solvent, e.g. methylene chloride, chloroform or dioxane, in the presence of an organic base; the reaction temperatures usually range from -20°C to about +50°C.

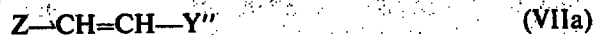
The reaction between the compound of formula (VIII), or a salt thereof, and the compound of formula (IX), or a reactive derivative thereof, e.g. an alkali metal salt, is preferably carried out in an inert organic solvent, e.g. ethanol, dimethylformamide, dioxane, acetone, methylene chloride and chloroform; when a salt of the compound of formula (VIII) is used, then water, a solvent miscible with water, or a mixture of water and organic solvents such as acetone, ethanol, dioxane and tetrahydrofuran is preferably employed. The reaction temperatures range from about 5°C to about 70°C and the pH from about 5 to about 7.5. If necessary, a buffer is used such as, for example, sodium phosphate or acetate. The preferred salts are those formed from an alkali metal or alkaline earth metal hydroxide.

The optional salification of the product compounds 1-7 as well as the optional conversion of a salt into a free compound, may be carried out according to conventional methods, i.e. methods already known in organic chemistry. As stated above, a compound 1-7 or a salt thereof, may be converted into another compound 1-7 or a salt thereof; these optional conversions may be performed by conventional methods.

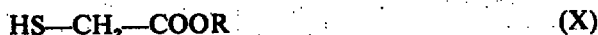
The compound of formula (II), wherein E is amino, may be prepared, for example, by reacting 7-amino-cephalo-sporanic acid or a salt thereof with the compound of formula (IX), using reaction conditions well known in the literature. The compound of formula (II), where E is -N=C=O or -N=C=S may be prepared, e.g. by reacting a compound of formula (II), wherein E is amino, with phosgene or thiophosgene, in the presence of a hydrochloric acid acceptor, using known methods.

The compound of formula (III) may be prepared according to one of the following methods:

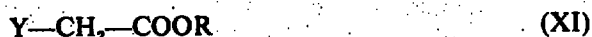
1) Reaction of a compound of formula (VIIa)



wherein Z represents cyano (NC—) or carbamoyl (NH₂CO—) and Y'' represents a halogen atom, preferably chlorine or bromine, or an O-tosyl or O-mesyl group, with a compound of formula (X)



or a compound of formula (V) with a compound of formula (XI)



wherein Y is as defined above

and R represents hydrogen or a C₁—C₈ alkyl group, preferably ethyl or tert-butyl; when R represents a C₁—C₈ alkyl group the reaction product is saponified by known methods. Where Z is carbamoyl, the product is converted into the required corresponding cyano compound by treatment with a dehydrating agent, e.g. phosphorus pentachloride, phosphorus oxychloride or triphenylphosphine in an organic solvent e.g. a mixture of dimethylformamide and diethyl ether, or carbon tetrachloride, triethylamine or N,N'-dicyclohexylcarbodiimide at room temperature or by heating the carbamoyl compound to 30—120°C in an organic solvent, preferably hexamethylphosphorotriamide or dimethyl sulphoxide.

The reaction of the compound of formula (VIIa) with the compound of formula (X) or the reaction of the compound of formula (V) with the compound of formula (XI) are preferably performed in water or in an organic solvent, e.g. tetrahydrofuran, diethyl ether, benzene, or in a mixture of an organic solvent, e.g. one of those mentioned above, with water, in the presence of about 2—2.5 equivalents of a base when R represents hydrogen and about 1—1.5 equivalents of base when R represents C₁—C₈ alkyl, and at temperatures ranging from about -10°C to about +25°C. A suitable base is, for example, sodium hydroxide, sodium bicarbonate or triethylamine.

In the above process, the configuration of the geometric isomer in formula (VIIa), i.e. *cis*-CH=CH— or *trans*-CH=CH— should be the same as that required in the compound of formula (III). In other words the reaction is stereospecific.

2) Reaction of the compound of formula (X) with a compound of formula (XII)



wherein Z is as defined above, thus yielding a compound of formula (III) is *cis* or *trans* form, depending on the reaction conditions. When the reaction between the compound of formula (X) and the compound of formula (XII) is performed in a protic solvent, preferably in an aqueous protic solvent, e.g. water or a lower aliphatic alcohol, e.g. ethanol, in the presence of not more than an equivalent of a base, e.g. triethylamine, an alkali metal bicarbonate, an alkaline hydroxide, and at low temperatures preferably about 0°C, a compound of formula (III) in the *cis*-CH=CH— form is obtained.

When the same reaction is carried out in the same solvents and in the presence of the same bases but at temperatures higher than the room temperature, or with the use of acid catalysts e.g. HCl or an excess of the thiolate anion, a compound of formula (III) is obtained which is a mixture of *cis*-CH=CH— and *trans*-CH=CH— isomers. The separation of the isomers obtained may be carried out by the usual methods employed in organic chemistry for the separation of geometric isomers such as, for example, fractional crystallization from solvents such as, for instance, water or lower aliphatic alcohols, e.g. ethanol, or by chromatographic separation.

Again, when Z is carbamoyl, the product is converted into the corresponding cyano compound as described above.

The compound of formula (IV) may be prepared by reacting the compound of formula (II) with a compound of formula (XI) wherein R is hydrogen or with a halide or a reactive derivative thereof. The reaction between the compound of formula (II) and the compound of formula (XI) wherein R is hydrogen, or a halide or a reactive derivative thereof, is preferably carried out in an aqueous or anhydrous organic solvent such as, e.g. acetone, dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride of dimethylformamide, in the presence of an

organic or inorganic base, such as sodium hydroxide or triethylamine, at temperatures e.g. from about -10°C to about $+25^{\circ}\text{C}$. For instance, an acid halide, anhydride or mixed anhydride, azide, amide, reactive ester or salt may be used as a reactive derivative of the compound of formula (XI) wherein R is hydrogen.

The compound of formula (VI) may be prepared, for example, by reacting the compound of formula (II) with a compound of formula (X) wherein R is hydrogen and using reaction conditions analogous to those employed for the reaction between the compound of formula (II) and the compound of formula (III). The compound of formula (VIII) may be prepared, for example, by reacting 7-aminocephalosporanic acid or a salt thereof with a compound of formula (III), using reaction conditions analogous to those employed for the reaction between the compound of formula (II) and the compound of formula (III).

The compounds of formulae (V), (VII), (VIIa), (IX) as well as the compounds of formulae (X), (XI) and (XII) may be easily prepared by known methods starting from known compounds or, respectively, they are compounds already known in the literature.

The compounds of the present invention show a high antibacterial activity either in animals or in humans against both Gram-positive and Gram-negative bacteria and are therefore useful in the treatment of the infections caused by said microorganisms, such as respiratory tract infections, for example, bronchitis, broncopneumonia, pleurisy; hepatobiliary and abdominal infections, for example, cholecystitis, peritonitis; blood and cardiovascular infections, for example, septicemia; urinary tract infections, for example, pyelonephritis, cystitis; obstetrical and gynecological infections, for instance, cervicitis, endometritis; ear, nose and throat infections, for instance, otitis, sinusitis, parotitis.

The following Table 2 shows the minimal inhibiting concentrations (MIC) in $\mu\text{g/ml}$ of the compounds 3 and 4 of Table 1 against both Gram-positive bacteria and Gram-negative bacteria in comparison with the known compounds coded K 9227 K 10299 (which are the most active compounds among those of the saturated derivatives of British Patent Specification No. 1,478,055) and Cefazolin and Cefamandole.

	Cefazolin	Cefamandole	K 9227	K 10299	3	4
<u>Gram-positive bacteria:</u>						
<i>Staphylococcus aureus</i> Smith	0.05	0.15	0.05	0.075	0.025	0.025
<i>Diplococcus aureus</i> 39/2	0.6	1.2	0.2	0.4	0.14	0.14
<i>Diplococcus pneumoniae</i> ATCC6301	0.05	0.019	0.4	0.2	0.012	<0.006
<i>Streptococcus β-haemolyticus</i> C203	0.05	0.019	0.025	0.037	0.012	<0.006
<u>Gram-negative bacteria:</u>						
<i>Escherichia coli</i> G	1.6	2.35	3.1	0.8	0.14	0.57
<i>Escherichia coli</i> 1507	1.6	0.8	1.6	0.8	0.1	0.57
<i>Klebsiella pneumoniae</i> ATCC 10031	0.8	0.15	0.4	0.2	0.1	0.2
<i>Klebsiella aerogenes</i> 1522E	1.1	0.4	1.6	0.8	0.1	0.28
<i>Enterobacter aerogenes</i> ATCC8308	1.2	1.6	1.2	0.6	0.2	0.4
<i>Enterobacter cloacae</i> 1321E	3.1	1.6	3.1	1.6	0.56	1.6
<i>Salmonella typhi</i> Watson	1.6	0.6	0.8	0.2	0.07	0.2
<i>Shigella sonnei</i> ATCC11060	1.6	2.35	1.6	1.6	0.8	1.6
<i>Proteus mirabilis</i> ATCC9921	6.2	1.6	12.5	6.2	0.4	0.4

Notes to Table

Cefazolin = 7-(1-(1H)-tetrazolylacetamido)-3-[2-(5-methyl-1,3,4-thiadiazolyl)-thiomethyl]-3-cephem-4-carboxylic acid;

Cefamandole = 7-D-mandelamido-3-[(1-methyl-1H-tetrazol-5-yl)-thio]-methyl]-3-cephem-4-carboxylic acid;

K 9227 = 7-[(cyanomethyl-thio)-acetamido]-3-[2-(5-methyl-1,3,4-thiadiazolyl)-thiomethyl]-3-cephem-4-carboxylic acid;

K 10299 = 7-[(cyanomethyl-thio)-acetamido]-3-[5-(1-methyl-1,2,3,4-tetrazolyl)-thiomethyl]-3-cephem-4-carboxylic acid;

As is evident from Table 2, the compounds of the invention show not only a high activity against Gram-positive bacteria but surprisingly they own also a very high activity against Gram-negative bacteria: they are therefore much more useful than the known compounds of the Table, for the treatment of infections caused by Gram-negative such as, for example, urinary tract infections and respiratory tract infections.

In particular, Table 2 shows that the compound 3 is about 2 times more active than Cefazolin against staphylococci, about 4.2 times more active than Cefazolin against streptococci (including diplococci) and about 9.6 times more active than Cefazolin against Gram-negative bacteria. Furthermore the compound 3 was tested on a series of 60 strains of Gram-negative microorganisms comprising *Klebsiella*, *Escherichia coli*, *Proteus mirabilis* and *Proteus vulgaris* in comparison with Cefazolin and compound 3 was always found to be more active than Cefazolin. Against the *Haemophilus influenzae* (Gram-negative bacterium: 7 strains tested), the compound 3 was about 6 times more active than Cefazolin.

The compounds of the invention may be administered, either to humans or to animals, in a variety of dosage forms, e.g., orally in the form of tablets, capsules, drops or syrups; rectally in the form of suppositories; parenterally e.g. intravenously or intramuscularly (as solutions or suspensions), with intravenous administration being preferred in an emergency situation; by inhalation in the form of aerosols or solutions for nebulizers; intravaginally in the form, e.g. of bougies; or topically in the form of lotions, creams and ointments. The pharmaceutical or veterinary compositions containing the compounds of the invention may be prepared in a conventional way by employing the conventional carriers and/or diluents used for the other cephalosporins. Conventional carriers or diluents are, for example, water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils and cellulose. Daily doses in the range of 1 to 100 mg per kg of body weight may usually be used, in various animal species, the exact dose depending on the age, weight and condition of the subject to be treated and on the frequency and route of administration. A preferred way of administration of the compounds of the invention is the parenteral one: in this case the compounds may be administered, for example to adult humans, in an amount ranging from about 100 mg to about 200 mg per dose preferably about 150 mg per dose, 1—4 times a day, dissolved in a suitable solvent, for example sterile water or lidocaine hydrochloride solution for intramuscular injections, and sterile water, physiological saline solution, dextrose solution or the conventional intravenous fluids or electrolytes, for intravenous injections.

Furthermore, the compounds of the invention may be used as antibacterial agents in a prophylactic manner, e.g. in cleaning or as surface disinfecting compositions, for example, at a concentration of about 0.2 to 1% by weight of such compounds admixed with, suspended or dissolved in conventional inert dry or aqueous carriers for application by washing or spraying. They are also useful as nutritional supplements in animal feeds.

Assessment of melting points was somewhat difficult in some cases, as the compounds tend to retain the solvent. In these cases, after the indication of the melting point, the word "dec." (decomposition) was added.

The I.R. spectra were determined in a solid phase on a Perkin-Elmer 125 spectrophotometer, while the U.V. spectra were usually evaluated in a buffer phosphate solution at pH 7.4 on a Bausch-Lomb (Registered Trade Mark) apparatus. N.M.R. spectra were determined in DMSO (dimethylsulphoxide) with a

Varian (Registered Trade Mark) HA—100 spectrometer with $(\text{CH}_3)_4\text{Si}$ as internal standard.

The invention includes a method of treating a warm-blooded non-human animal comprising administering thereto a medicament having as its active principle a compound according to the invention.

Specific examples of the preparation of compounds according to the invention will now be described.

Example 1.

To a solution containing β -cyano-ethylene(trans)-thio-acetic acid (2.88 g) and triethylamine (2.8 g) in anhydrous acetone (120 ml) some drops of N-methylmorpholine were added. The mixture was cooled at -10°C and then pivaloyl-chloride (2.44 ml) dissolved in anhydrous acetone (30 ml) was added under stirring and then, after stirring for 30 minutes at -10°C , a solution containing 7-amino-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (6.56 g) and triethylamine (2.8 ml) in 50% acetone (240 ml), cooled at -20°C , was added after 30 minutes.

The mixture was then stirred at -20°C for 1 hour and afterwards at room temperature for 2 hours. The acetone was evaporated under vacuum. The residue was taken up with water, stratified with ethyl acetate and the pH of the mixture was brought to 2.5 with 40% H_3PO_4 .

After filtration, the ethyl acetate was separated and the organic phase was washed with water, dried on Na_2SO_4 and evaporated to small volume.

Ethyl ether was added to give a solid, which was filtered and stirred with ethyl ether. The solid was filtered again so obtaining 5.4 g (yield 60%) of 7-[β -cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid, m.p. $118-120^\circ\text{C}$ (dec.);

Analysis:

Found: C 39.83; H 3.42; N 21.31; S 20.87

$\text{C}_{19}\text{H}_{18}\text{N}_6\text{O}_5\text{S}_2$ requires C 39.80; H 3.33; N 21.60; S 21.20;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 267 \text{ m}\mu$; $\epsilon_{\text{cm}}^{1\%} = 411$;

T.L.C.: $R_f = 0.55$ ($\text{CHCl}_3:\text{CH}_3\text{OH}:\text{HCOOH} = 160:40:20$);

I.R. (KBr): ν ($\text{C}\equiv\text{N}$) conjugated 2200 cm^{-1} ;

ν ($\text{C}=\text{O}$) β -lactam 1775 cm^{-1} ;

ν ($\text{C}=\text{O}$ sec. amide 1670 cm^{-1} ;

N.M.R.: ppm ($\text{DMSO}-d_6$);

3.73 (4H, br-s, $-\text{S}-\text{CH}_2-\text{CO}$ and $2-\text{CH}_2$);

3.94 (3H, s, CH_3-N);

4.33 (2H, q, $3-\text{CH}_2$);

5.11 (1H, d, $6-\text{H}$);

5.64 (1H, d, $\text{NC}-\text{CH}=\text{}$);

5.7 (1H, d-d, $7-\text{H}$) $J_{\text{CH}-7\text{H}} = 4.5 \text{ Hz}$;

7.82 (1H, d, $=\text{CH}-\text{S}$) $J_{\text{CH}=\text{CH}(\text{trans})} = 16 \text{ Hz}$;

9.28 (1H, d, $-\text{CONH}$) $J_{7\text{H}-\text{NH}} = 8 \text{ Hz}$.

β -cyano-ethylene(trans)-thio-acetic acid used as starting material was prepared according to the following methods:

method A — to a solution of 70% thioglycolic acid (2.1 ml) and triethylamine (5.6 ml) in water (50 ml, cooled at $+5^\circ\text{C}$, a solution of trans- β -chloro-acrylonitrile (1.73 g) in tetrahydrofuran (7 ml) was added dropwise. The mixture was stirred for 30 minutes at room temperature, acidified with 20% H_2SO_4 . The obtained precipitate was extracted with ethyl acetate; the extracts were washed with a saturated solution of NaCl, dried on Na_2SO_4 , treated with charcoal and evaporated so obtaining an oil which solidifies to give β -cyano-ethylene(trans)-thio-acetic acid (2.5 g; yield 88%), m.p. $= 81-86^\circ\text{C}$;

Analysis:

Found: C 41.81; H 3.57; N 9.71; S 22.31

$\text{C}_5\text{H}_5\text{NO}_2\text{S}$ requires C 41.94; H 3.52; N 9.78; S 22.39;

I.R. (KBr): ν ($\text{C}\equiv\text{N}$) conjugated 2220 cm^{-1} ;

ν ($\text{C}=\text{O}$) acid 1720 cm^{-1} ;

ν ($\text{C}=\text{C}$) conjugated 1575 cm^{-1} ;

ν ($\text{C}-\text{H}$): $\text{C}=\text{C}$ trans 930 cm^{-1} ;

N.M.R. ($\text{DMSO}-d_6$): 5.56 δ (d, $\text{NC}-\text{CH}=\text{}$), 7.78 δ (d, $=\text{CH}-\text{S}$);

$J_{\text{CH}=\text{CH}(\text{trans})} = 16 \text{ Hz}$;

method B) — to a solution of 70% thioglycolic acid (0.5 ml) and NaHCO_3 (0.84 mg) in water (50 ml), β -tosyl-acrylonitrile (1.03 g) was added under stirring. The mixture was stirred for 3 hours at room temperature and filtered. The solution was acidified with 20% H_2SO_4 and extracted with ethyl acetate. The organic phase was dried on Na_2SO_4 and evaporated to dryness so obtaining β -cyano-ethylene(trans)-thio-acetic acid (0.65 g; yield 91%).

By purification through the formation of dicyclohexylamine salt a product identical to that prepared according to method A was obtained.

β -tosyl-acrylonitrile used as starting material was prepared by reacting sodium salt of p-toluenesulphinic acid and β -chloro-acrylonitrile in a mixture of dioxane, water and boric acid according to a known method.

Example 2.

By proceeding according to Example 1 and reacting β -cyano-ethylene(trans)-thio-acetic acid with 7-amino-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid, 7-[β -cyano-ethylene(trans)-thio-acetamido]-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid, yield 68%, m.p. = 100°C(dec.) was obtained;

Analysis:

Found: C 39.66; H 2.91; N 15.25; S 28.05

$\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_4\text{S}_4$ requires C 39.54; H 2.87; N 15.37; S 28.15;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 267 \text{ m}\mu$; $E_{1\text{cm}}^{1\%} = 569.8$;

T.L.C.: $R_f = 0.54$ ($\text{CHCl}_3:\text{CH}_3\text{OH}:\text{HCOOH} = 160:40:20$);

I.R. (KBr): ν (C=N) conjugated 2215 cm^{-1} ;

ν (C=O) β -lactam 1775 cm^{-1} ;

ν (C=O) sec. amide 1675 cm^{-1} .

Example 3.

To a solution of β -cyano-ethylene(cis)-thio-acetic acid (1.44 g) and triethylamine (1.4 ml) in anhydrous acetone (80 ml), some drops of N-methylmorpholine were added. The solution was cooled at 0°C and then pivaloylchloride (1.22 ml) dissolved in anhydrous acetone (20 ml) was added under stirring. The mixture was stirred at 0°C for 30 minutes, then a solution containing 7-amino-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (3.28 g) and triethylamine (1.4 ml) in 50% acetone (160 ml) was added.

After the addition the solution was stirred for 1 hours at 0°C and afterwards for 2 hours at room temperature. The acetone was evaporated under vacuum. The residue was taken up with water and washed with ethyl acetate. After separation, the aqueous phase was stratified with ethyl acetate and brought to pH = 2 with 20% H_2SO_4 .

The residue was filtered off and the organic phase was separated, dried on anhydrous Na_2SO_4 and evaporated to small volume; the residue was taken up with ethyl ether so obtaining 7-[β -cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (2.7 g; yield 60%), m.p. = 113–115°C(dec.);

Analysis:

Found: C 39.78; H 3.43; N 21.40; S 20.78;

$\text{C}_{18}\text{H}_{15}\text{N}_7\text{O}_5\text{S}_3$ requires C 39.80; H 3.33; N 21.60; S 21.20;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 273 \text{ m}\mu$; $E_{1\text{cm}}^{1\%} = 463$;

T.L.C.: $R_f = 0.60$ ($\text{CHCl}_3:\text{CH}_3\text{OH}:\text{HCOOH} = 160:40:20$);

I.R. (KBr): ν (CH=N) conjugated 2210 cm^{-1} ;

ν (C=O) β -lactam 1775 cm^{-1} ;

ν (C=O) amide 1680 cm^{-1} ;

ν (C—N)+ δ (N—H) sec. amide 1540 cm^{-1} ;

N.M.R. ppm ($\text{DMSO}-d_6$):

3.68 (2H, q, 2— CH_2);

3.73 (2H, s, —S— CH_2 —CO);

3.94 (3H, s, CH_3 —N);

4.31 (2H, q, 3— CH_2);

5.10 (1H, d, 6—H);

5.63 (1H, d-d, 7—H);

5.72 (1H, d, NC—CH=);

7.63 (1H, d, =CH—S) $J_{\text{CH—CH(cis)}} = 11 \text{ Hz}$;

9.2 (1H, d, —CONH).

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β -cyano-ethylene(cis)-thio-acetic acid used as starting material was prepared as follows:

To a solution of β -carboxamide-ethylene(cis)-thio-acetic acid (4 g) in dimethyl-formamide/ethyl ether (3:2; 100 ml), cooled at 0°C, phosphorus pentachloride (5.2 g) was added under stirring, maintaining the temperature between 8 and 10°C. The solution was then stirred for 2 hours between 0 and 10°C.

The solution was poured into ice and the ethereal layer was separated; the aqueous layer was extracted four times with ethyl acetate (4 x 50 ml). The combined extracts were dried on Na_2SO_4 and then evaporated to dryness at a temperature not higher than 40°C, so obtaining a yellowish oil which was dissolved in methanol (10 ml). To the resulting solution the stoichiometric amount of dicyclohexylamine was added, so obtaining the precipitation of dicyclohexylamine salt of β -cyano-ethylene(cis)-thio-acetic acid which, after filtration, was repeatedly washed with ethyl ether (m.p. = 180—183°C).

The salt was dissolved in water/ethyl acetate (5:7; 120 ml) at 5°C; the solution was acidified by dropwise addition of 40% H_3PO_4 (10 ml). The resulting solution was extracted three times with ethyl acetate and the combined organic extracts were washed with water saturated with NaCl, dried on Na_2SO_4 and evaporated to dryness under vacuum to obtain β -cyano-ethylene(cis)-thio-acetic acid (2.76 g; yield 77%; m.p. = 90—92°C).

Analysis:

Found: C 41.70; H 3.63; N 9.64; S 22.25

$\text{C}_5\text{H}_5\text{NO}_2\text{S}$ requires: C 41.94; H 3.52; N 9.78; S 22.39

I.R. (KBr): ν (C=N) conjugated 2220 cm^{-1} ;

ν (C=O) acid 1720 cm^{-1}

N.M.R. ($\text{DMSO}-d_6$): 5.4 δ (d, NC—CH=), 7.4 δ (d, =CH—S) $J_{\text{CH}=\text{CH}(\text{cis})} = 10$ Hz.

Example 4.

By proceeding according to Example 3 and reacting β -cyano-ethylene(cis)-thio-acetic acid with 7-amino-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid, 7-[β -cyano-ethylene(cis)-thio-acetamido]-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid (yield 63%), m.p. 93—95°C(dec.) was obtained:

Analysis:

Found: C 39.33; H 2.94; N 15.22; S 27.93;

$\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_4\text{S}_4$ requires C 39.54; H 2.87; N 15.37; S 28.15;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 273 \text{ m}\mu$; $E_{1\%}^{1\text{cm}} = 504$;

T.L.C.: $R_f = 0.56$ (CHCl_3 : CH_3OH : $\text{HCOOH} = 160:40:20$);

I.R. (KBr): ν (C=N) conjugated 2220 cm^{-1} ;

ν (C=O) β -lactam 1775 cm^{-1} ;

ν (C=O) sec. amide 1715 cm^{-1} ;

ν (C—N)+ δ (N—H) sec.amide 1540 cm^{-1} .

Example 5.

To a solution containing β -cyano-ethylene(cis)-thio-acetic acid (1.44 g) and triethylamine (1.4 ml) in anhydrous acetone (80 ml) some drops of N-methylmorpholine were added. After cooling at 0°C, a solution of pivaloyl-chloride (1.22 ml) in anhydrous acetone (20 ml) was added under stirring. The mixture was stirred for 30 minutes at 0°C and then a solution of 7-amino-3-[(1-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid (3.26 g) and triethylamine (1.4 ml) in 50% acetone (160 ml) was added. After the addition, the solution was stirred for 1 hour at 0°C and then for 2 hours at room temperature.

The acetone was evaporated under vacuum, the residue was taken up with water and washed with ethyl acetate.

After separation of the phases, the aqueous phase was stratified with ethyl acetate and the pH brought to 2 with 20% H_2SO_4 .

The residue was filtered off and the organic phase dried on anhydrous Na_2SO_4 and evaporated to small volume; the residue was taken up with ethyl ether. By filtration, 7-[β -cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid (2.5 g; yield 55%), m.p. 125—130°C(dec.) was obtained;

Analysis:

Found: C 42.77; H 3.96; N 18.27; S 20.87;

$\text{C}_{18}\text{H}_{16}\text{N}_6\text{O}_4\text{S}_3$ requires C 42.50; H 3.56; N 18.60; S 21.20;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 267 \text{ m}\mu$; $E_{1\%}^{1\text{cm}} = 458$;

T.L.C.: $R_f = 0.32$ ($\text{CHCl}_3\text{:CH}_3\text{OH:HCOOH} = 160:40:20$);

I.R. (KBr): ν ($\text{C}\equiv\text{N}$) conjugated 2215 cm^{-1} ;

ν (C=O) β -lactam 1775 cm^{-1} ;

ν (C=O) sec.amide 1675 cm^{-1} .

5 Analogously the following compounds were obtained:

7 - [β -cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid, m.p. $127\text{--}131^\circ\text{C}(\text{dec.})$;

Analysis:

Found: C 42.82; H 3.67; N 18.33; S 20.73;

10 $\text{C}_{16}\text{H}_{16}\text{N}_8\text{O}_4\text{S}_3$ requires C 42.50; H 3.56; N 18.60; S 21.20;

U.V. (pH 7.4 buffer phosphate): $\lambda_{\text{max}} = 267\text{ m}\mu$; $E_{1\%}^{1\text{cm}} = 444$;

T.L.C.: $R_f = 0.28$ ($\text{CHCl}_3\text{:CH}_3\text{OH:HCOOH} = 160:40:20$);

I.R. (KBr): ν ($\text{C}\equiv\text{N}$) conjugated 2215 cm^{-1} ;

ν (C=O) β -lactam 1775 cm^{-1} ;

15 ν (C=O) sec.amide 1675 cm^{-1} .

7 - [β -cyano-ethylene(cis)-thio-acetamido]-3-[(5-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid;

Analysis:

Found: C 42.63; H 3.73; N 18.40; S 20.91;

20 $\text{C}_{16}\text{H}_{16}\text{N}_8\text{O}_4\text{S}_3$ requires C 42.50; H 3.56; N 18.60; S 21.20.

Example 6.

To a solution of 7-amino-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (3.28 g) and NaHCO_3 (2g) in 50% aqueous acetone (60 ml), cooled at 0°C , a solution of 2.18 g of β -cyano-ethylene(trans)-thio-acetic acid chloride (obtained from the acid by reaction with oxalyl chloride in dimethylformamide at 0°C) in acetone (30 ml) was added under stirring. The mixture was stirred for 20 minutes at a temperature between 0°C and 5°C . The acetone was evaporated, ethyl acetate was added to the resulting aqueous solution which was then acidified with 8% hydrochloric acid to pH 2. The organic phase was washed with water, dried and evaporated under vacuum. The residue was treated with ethyl ether and filtered so obtaining 7-[β -cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (2.3 g), m.p. $118\text{--}120^\circ\text{C}(\text{dec.})$; microanalysis, U.V., T.L.C., I.R. and N.M.R. data of this compound were identical to those already reported in Example 1. By proceeding analogously, also the other compounds of this invention mentioned in the preceding Examples were prepared.

Example 7.

To a solution containing 7-(bromo-acetamido)-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (4.45 g) in CH_2Cl_2 (50 ml), triethylamine (2.8 ml) was added.

After stirring for 30 minutes at room temperature, trans-1-cyano-2-mercapto-ethylene (0.85 g) was added and the mixture was stirred for 6 hours at room temperature.

The obtained precipitate was filtered off; the organic solution was washed with water, dried and evaporated to dryness under vacuum. The residue was taken up with ethyl ether so obtaining 7-[β -cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (3.8 g), m.p. $118\text{--}120^\circ\text{C}(\text{dec.})$; microanalysis, U.V., T.L.C., I.R. and N.M.R. data of this compound were identical to those already reported in Example 1.

By proceeding analogously, also the other compounds of the invention mentioned in the preceding Examples were obtained.

7-(bromo-acetamido)-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid used as starting material was prepared by reacting, using a known method, bromoacetyl bromide with 7-amino-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

Example 8.

To a solution containing 7-(mercapto-acetamido)-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (4.22 g) in CH_2Cl_2 (70 ml), triethylamine (2.8 ml) was added.

The mixture was stirred for 30 minutes at room temperature and then trans- β -chloroacrylonitrile (0.87 g) dissolved in CH_2Cl_2 (15 ml) was added. After stirring for 4 hours at room temperature, the obtained precipitate was filtered off and the

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organic solution was washed with water, dried and evaporated to dryness under vacuum; the residue was taken up with ethyl ether, so obtaining 7- [β - cyano - ethylene(trans) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (3.6 g), m.p. 118—120°C(dec.); microanalysis, U.V., T.L.C., I.R. and N.M.R. data of this compound were identical to those already reported in Example 1.

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By proceeding analogously, also the other compounds of the invention mentioned in the preceding Examples were obtained.

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Example 9.

To a solution of sodium salt of 7 - [β - cyano - ethylene(cis) - thio - acetamido] - cephalosporanic acid (4.19 g) in acetone (40 ml) and pH 7 buffer phosphate (200 ml), 5 - mercapto - 1 - methyl - 1,2,3,4 - tetrazole (1.3 g) and NaHCO₃ (1.84 g) were added and the mixture was stirred for 6 hours at 60°C.

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After cooling, stratification with ethyl acetate and acidification with 10% hydrochloric acid, the pH was brought to 2. The two phases system was filtered and the organic phase separated. The aqueous phase was brought to pH = 4.5 with 10% ammonium hydrate and extracted with ethyl acetate; the extracts were washed with water, dried and evaporated to dryness, so obtaining 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (yield 65%), m.p. 113—115°C(dec.); microanalysis, U.V., T.L.C., I.R. and N.M.R. data of this compound were identical to those already reported in Example 3.

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By proceeding analogously, also the other compounds of the invention mentioned in the preceding Examples were obtained.

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Example 10.

To a solution of β - cyano - ethylene(cis) - thio - acetic acid (1.44 g) in anhydrous tetrahydrofuran (50 ml), dicyclohexylcarbodiimide (2.1 g) was added and the mixture was stirred for 30 minutes at room temperature. To this mixture, a solution of 7 - amino - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (3.28 g) and NaHCO₃ (0.84 g) in tetrahydrofuran/water (1:1, 60 ml) was added. After stirring for 3 hours at room temperature the tetrahydrofuran was evaporated under vacuum; the residue was taken up with water and the dicyclohexyl-urea was filtered off.

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The filtrate was stratified with ethyl acetate, acidified with 20% H₂SO₄ to pH 2.5; the organic layer was separated, washed with water, evaporated to small volume and then ethyl ether was added to give a solid which was filtered and then stirred with ethyl ether so obtaining 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid, m.p. 113—115°C(dec.); microanalysis, U.V., T.L.C., I.R. and N.M.R. data were identical to those already reported in Example 3.

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By proceeding analogously, also the other compounds of the invention mentioned in the preceding Examples were obtained.

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Example 11.

To an aqueous suspension of 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (4.53 g) in water (80 ml), the stoichiometric amount of NaHCO₃ was added, so obtaining the complete solution of the compound. This solution was then lyophilized so obtaining the sodium salt of 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

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Example 12.

To a solution of 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (1.13 g) in ethyl acetate (30 ml), the stoichiometric amount of a 30% solution of sodium 2 - ethyl - hexanoate in isopropyl alcohol was added.

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After stirring for 30 minutes at room temperature, the mixture was diluted with petroleum ether and the obtained precipitate was filtered to give the sodium salt of 7-[β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

Example 13.

To a suspension of the sodium salt of 7- β -cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid (2.38 g) in acetone (40 ml), a 10% solution of sodium iodide in water (0.4 ml) and chloromethylpivalate (0.72 ml) was added.

The suspension was heated for 3 hours under reflux and after cooling at 5°C, the solid was filtered off and the resulting solution evaporated under vacuum. The oily residue was dissolved in ethyl acetate (50 ml), the resulting solution washed with a 5% solution of NaHCO₃ in water and then with water, dried and evaporated to dryness so obtaining the pivaloyloxymethyl ester of 7- β -cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

Example 14.

An injectable pharmaceutical composition was prepared by dissolving 100—500 mg of sodium 7- β -cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylate in sterile water or steril normal saline solution (1—2 ml).

WHAT WE CLAIM IS:—

1. 7- β -Cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

2. 7- β -Cyano-ethylene(trans)-thio-acetamido]-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

3. 7- β -Cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

4. 7- β -Cyano-ethylene(cis)-thio-acetamido]-3-[(1,3,4-thiadiazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

5. 7- β -Cyano-ethylene(cis)-thio-acetamido]-3-[(5-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

6. 7- β -Cyano-ethylene(cis)-thio-acetamido]-3-[(1-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

7. 7- β -Cyano-ethylene(trans)-thio-acetamido]-3-[(1-methyl-1,3,4-triazol-2-yl)-thiomethyl]-3-cephem-4-carboxylic acid.

8. A pharmaceutically or veterinarily acceptable salt of any one of the compounds according to claims 1 to 7.

9. A salt according to claim 8 which is an alkali metal salt.

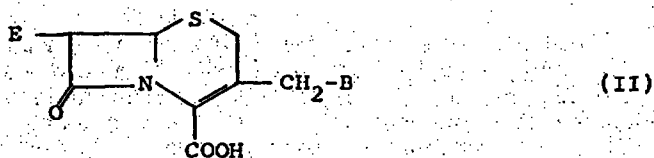
10. A salt according to claim 9 which is the sodium salt.

11. A salt according to claim 9 which is the potassium salt.

12. Metabolites having antibacterial activity and bioprecursors of a compound claimed in any preceding claim.

13. A process for the preparation of a compound according to any one of claims 1—11, said process comprising:

(a) reacting a compound of formula (II)



wherein

B represents a (1-methyl-1,2,3,4-tetrazol-5-yl)thio, (1,3,4-thiadiazol-2-yl)thio, (5-methyl-1,3,4-triazol-2-yl)thio or (1-methyl-1,3,4-triazol-2-yl)thio group and E is amino or a —N—C=O or —N—C=S group, or a reactive derivative thereof, with an acid of formula (III)



or with a reactive derivative thereof; or

Example 13.

To a suspension of the sodium salt of 7- [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid (2.38 g) in acetone (40 ml), a 10% solution of sodium iodide in water (0.4 ml) and chloromethylpivalate (0.72 ml) was added.

The suspension was heated for 3 hours under reflux and after cooling at 5°C, the solid was filtered off and the resulting solution evaporated under vacuum. The oily residue was dissolved in ethyl acetate (50 ml), the resulting solution washed with a 5% solution of NaHCO₃ in water and then with water, dried and evaporated to dryness so obtaining the pivaloyloxymethyl ester of 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

Example 14.

An injectable pharmaceutical composition was prepared by dissolving 100—500 mg of sodium 7 - [β - cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylate in sterile water or steril normal saline solution (1—2 ml).

WHAT WE CLAIM IS:—

1. 7 - [β - Cyano - ethylene(trans) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

2. 7 - [β - Cyano - ethylene(trans) - thio - acetamido] - 3 - [(1,3,4 - thiadiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

3. 7 - [β - Cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,2,3,4 - tetrazol - 5 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

4. 7 - [β - Cyano - ethylene(cis) - thio - acetamido] - 3 - [(1,3,4 - thiadiazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

5. 7 - [β - Cyano - ethylene(cis) - thio - acetamido] - 3 - [(5 - methyl - 1,3,4 - triazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

6. 7 - [β - Cyano - ethylene(cis) - thio - acetamido] - 3 - [(1 - methyl - 1,3,4 - triazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

7. 7 - [β - Cyano - ethylene(trans) - thio - acetamido] - 3 - [(1 - methyl - 1,3,4 - triazol - 2 - yl) - thiomethyl] - 3 - cephem - 4 - carboxylic acid.

8. A pharmaceutically or veterinarily acceptable salt of any one of the compounds according to claims 1 to 7.

9. A salt according to claim 8 which is an alkali metal salt.

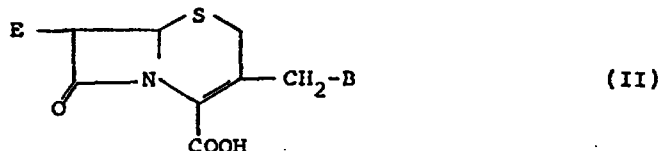
10. A salt according to claim 9 which is the sodium salt.

11. A salt according to claim 9 which is the potassium salt.

12. Metabolites having antibacterial activity and bioprecursors of a compound claimed in any preceding claim.

13. A process for the preparation of a compound according to any one of claims 1—11, said process comprising:

(a) reacting a compound of formula (II)



wherein

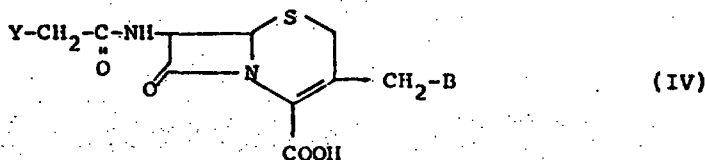
B represents a (1 - methyl - 1,2,3,4 - tetrazol - 5 - yl)thio, (1,3,4 - thiadiazol - 2 - yl)thio, (5 - methyl - 1,3,4 - triazol - 2 - yl)thio or (1 - methyl - 1,3,4 - triazol - 2 - yl)thio group and E is amino or a —N—C=O or —N—C=S group, or a reactive derivative thereof, with an acid of formula (III)



or with a reactive derivative thereof; or



(b) reacting a compound of formula (IV)

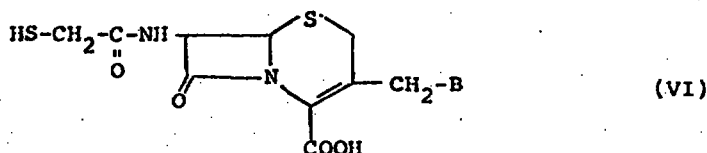


wherein

B is as defined above and Y represents a halogen atom or a salt thereof, with a compound of formula (V)



or with a reactive derivative thereof; or (c) reacting a compound of formula (VI)



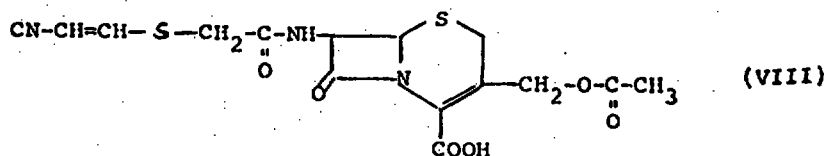
wherein

B is as defined above, or a reactive derivative thereof, with a compound of formula (VII)



wherein Y' represents a halogen atom or the residue of an active ester of an alcohol; or

(d) reacting a compound of formula (VIII)



or a salt thereof, with a compound of formula (IX)



wherein

B is as defined above or a reactive derivative thereof, and, if desired, converting a compound claimed in any one of claims 1—7 into a pharmaceutically or veterinarily acceptable salt and/or, if desired, obtaining a free compound claimed in any one of claims 1—7 from a salt and/or, if desired, converting a compound claimed in any one of claims 1—7 or a salt thereof into another compound claimed in any one of claims 1 to 7 or a salt thereof.

14. A process according to claim 13 substantially as described in any one of the foregoing Examples 1 to 14.

15. A compound according to claim 1 when prepared by a process according to claim 13 or 14.

16. A pharmaceutical or veterinary composition comprising a compound according to any one of claims 1 to 11 and 15 and a pharmaceutically or veterinarily acceptable carrier or diluent.

17. A method of treating a warm-blooded non-human animal comprising administering thereto a medicament having as its active principle a compound according to any one of Claims 1 to 11 and 15.



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